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Translation of “Cardiología molecular. Módulo 3: Diabetes Mellitus tipo 2” by Jonatan Navarro Solano from Spanish to English and “The Next Fifty Years” by John Brockman from English to Spanish for the Hospital Mexico Library

Thesis Submitted to Obtain the Bachelor´s Degree in English

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Dedication

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Abstract

This thesis explores the challenges and outcomes associated with applying translation procedures to medical documents for Hospital Mexico Library, focusing on achieving accuracy, clarity, and cultural relevance when translating from Spanish and English and vice versa. The central research question investigates how these challenges impact the quality of medical translations and what strategies best address them. Conducted by Akysha Santamaría using a qualitative methodology, the study involved translating two key documents *Cardiología Molecular. Módulo 3: Diabetes Mellitus Tipo 2* and *The Next Fifty Years* with the analysis of the translation processes applied. The research included a thorough text analysis based on Christiane Nord's functionalist model and the application of specific translation procedures such as modulation, transposition, and explicitation. One of the main findings revealed that accuracy and readability often depend on the translator's ability to balance technical precision with audience accessibility. The creation of specialized glossaries significantly contributed to maintaining terminological consistency. The study concludes that effective medical translation not only enhances communication within healthcare environments but also fosters better patient outcomes. Culturally relevant and linguistically accurate translations are essential in multilingual healthcare settings like Hospital Mexico, where bridging language gaps can have direct implications on health equity and patient safety.

Keywords: Medical translation, accuracy, clarity, cultural relevance, glossary, qualitative research.

Resumen

Esta tesis explora los desafíos y resultados asociados con la aplicación de procedimientos de traducción en documentos médicos para la Biblioteca del Hospital México, centrándose en lograr precisión, claridad y relevancia cultural al traducir entre español e inglés. La pregunta central de investigación analiza cómo estos desafíos afectan la calidad de las traducciones médicas y qué estrategias son más eficaces para enfrentarlos. Desarrollado por Akysha Santamaría mediante una metodología cualitativa, el estudio consistió en traducir dos documentos clave: *Cardiología Molecular. Módulo 3: Diabetes Mellitus tipo 2* y *The Next Fifty Years* junto con el análisis de los procedimientos de traducción utilizados. La investigación incluyó un análisis detallado de textos basado en el modelo funcionalista de Christiane Nord y la aplicación de procedimientos específicos como la modulación, transposición y explicitación. Uno de los principales hallazgos fue que la precisión y legibilidad dependen en gran medida de la capacidad del traductor para equilibrar el rigor técnico con la accesibilidad del público. La creación de glosarios especializados contribuyó significativamente a mantener la consistencia terminológica. Se concluye que una traducción médica eficaz no solo mejora la comunicación en entornos de salud, sino que también promueve mejores resultados para los pacientes. Las traducciones culturalmente relevantes y lingüísticamente precisas son esenciales en contextos sanitarios multilingües como el del Hospital México, donde cerrar brechas lingüísticas tiene implicaciones directas en la equidad y seguridad del paciente.

Palabras clave: Traducción médica, precisión, claridad, relevancia cultural, glosario, investigación cualitativa.

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Chapter I

Introductory Framework

In an increasingly interconnected world, the demand for effective communication between diverse languages and cultures has never been more critical, especially in the medical field. Medical translation is crucial in ensuring that healthcare information is accessible to non-English speaking patients, physicians, and researchers. This thesis explores the nuances and complexities involved in translating medical documents from English into Spanish, emphasizing the importance of accuracy, cultural sensitivity, and contextual appropriateness in the translation process.

The main objective of this research is to highlight the importance of accurate medical translation in improving patient outcomes and promoting effective healthcare delivery. Translation errors in medical documents can lead to severe consequences, such as misunderstandings about diagnoses, medication instructions, and treatment plans. Therefore, this study will investigate best practices in medical translation, including compliance with medical terminology, understanding idiomatic expressions, and the impact of cultural context on the translation process.

Finally, this thesis will develop a glossary to confirm and maintain clarity and understanding of the various medical terms used around translated documents that enhance patient care in populations. Through this comprehensive analysis, the research will demonstrate that effective translation is an indispensable component of contemporary healthcare practices.

1.1. Problem Statement

What are the challenges and outcomes associated with applying translation procedures to medical documents for the Hospital Mexico Library, particularly in achieving accuracy, clarity, and cultural relevance when translating from Spanish to English and vice versa?

Translating medical documents is a critical task, especially for institutions like the Hospital Mexico Library, where the accuracy, clarity, and cultural relevance of information can significantly impact patient care outcomes. The challenges of applying specialized translation procedures to medical documents are multifaceted and require a nuanced understanding of both language and medical practice.

One of the foremost challenges is ensuring translation accuracy. Medical terminology is not only complex but also varies substantially between Spanish and English. Even minor inaccuracies can lead to misunderstandings that affect patient safety, treatment plans, and overall healthcare quality. As healthcare increasingly becomes a global endeavor, translators must not only be proficient in both languages but also possess a deep knowledge of the medical concepts and terminologies inherent to each language. This necessitates a level of expertise that often requires ongoing education and collaboration with healthcare professionals.

Clarity is another substantial concern in medical translations. Medical documents, such as patient records, consent forms, and treatment protocols, are laden with technical jargon and intricate concepts. The challenge lies in ensuring that while the translation remains true to the original text in terms of accuracy, it must also be easily comprehensible to a diverse audience including healthcare providers, patients, and potentially non-medical

professionals. This requires an understanding of the target audience's knowledge base and cultural context, ensuring that the language used resonates effectively and avoids any potential for misinterpretation.

Moreover, cultural relevance plays a pivotal role in medical translations. Healthcare practices and beliefs about medicine can differ greatly across cultures, which can affect how medical information is perceived and understood. Translators face the challenge of conveying concepts that may not have direct equivalents in the target language or that might carry different connotations. For instance, certain diseases may have local names or cultural understandings that are not fully aligned with clinical terminology in another language. Therefore, translators are tasked with not just finding the right words but also ensuring that the cultural context is preserved to avoid confusion or miscommunication.

In order to effectively address these challenges, translators are encouraged to collaborate with subject matter experts and engage in continuous professional development to stay updated with evolving medical knowledge and terminologies. Developing standardized glossaries and reference materials can help ensure terminological consistency and reliability, thus facilitating better communication across language barriers.

The implications of successful medical translation extend far beyond mere comprehension; they play a significant role in improving patient care and fostering a cooperative healthcare environment. When translations are both accurate and culturally sensitive, they bridge crucial communication gaps between healthcare professionals and patients, enhancing understanding of medical instructions and ultimately impacting treatment outcomes positively. By prioritizing accuracy, clarity, and cultural relevance in medical translations, institutions like the Hospital Mexico Library can significantly enhance the

effectiveness of healthcare delivery, ensuring that all patients receive appropriate and competent medical care regardless of their language proficiency.

In conclusion, the challenges of translating medical documents for the Hospital Mexico Library necessitate a strategic, multifaceted approach that embraces the complexities of language, medicine, and culture. Addressing these issues not only enhances translation quality but also contributes to a more inclusive and effective healthcare system. Therefore, continued exploration and improvement of translation practices are essential for ensuring the delivery of high-quality care to diverse patient populations.

1.2. Investigation Objectives

1.2.1. General Objective

To analyze the use of translation procedures to translate some documents from Spanish-English and English-Spanish for the Hospital Mexico Library

1.2.2. Specific Objectives

- To translate “Cardiología molecular. Módulo 3: Diabetes Mellitus tipo 2" by Jonatan Navarro Solano and "The Next Fifty Years" by John Brockman for Hospital Mexico to achieve accurate and natural target texts.
- To apply translation techniques for ensuring linguistic clarity, readability, and alignment with industry standards in medical translation
- To create a glossary with the most relevant terminology found in both texts, ensuring consistency and accuracy for the Hospital Mexico Library.
- To evaluate the effect of the translation techniques applied to the documents

1.3. Justification of the Study

The motivation for this thesis lies in the critical need for effective medical translation services, particularly in healthcare institutions such as the Hospital Mexico Library. As populations become increasingly diverse, including a substantial number of non-English-speaking patients, the need for accurate and culturally relevant medical translations becomes essential. Miscommunication in medical contexts can lead to misdiagnosis, inappropriate medication administration, and compromised patient safety, underscoring the urgency of addressing these issues through dedicated research.

The healthcare industry operates in a landscape dominated by complex medical terminology and jargon that requires accurate translation. Any discrepancies in this translation process can have detrimental results not only for patients but also for healthcare professionals, who depend on clear and understandable information to assist patients effectively. This thesis aims to address this challenge by exploring specialized translation procedures that focus on maintaining the integrity and clarity of medical documents while ensuring their accessibility to the speaking audiences.

Furthermore, the essence of this research goes beyond mere linguistic translation; it encompasses cultural considerations vital to effectively transmitting medical information. Different cultures have unique health beliefs, practices, and terminologies that affect how medical information is perceived and understood. Failure to account for these differences can result in ineffective communication and health disparities among diverse populations. By prioritizing cultural relevance in medical translation, this thesis aims to improve understanding and trust between healthcare professionals and patients, fostering an environment conducive to positive health outcomes.

In conclusion, this thesis addresses pressing needs within the Mexico Hospital Library and contributes to the broader field of medical translation. By investigating the impact of

specialized translation techniques, this research will provide insights that can help improve communication and patient care, ultimately demonstrating that effective medical translation is an essential component of high-quality healthcare delivery.

1.4. Antecedents

Translation of some documents from Spanish into English and from English into Spanish. - Triani Yuan Argüello (December, 2023).

The paper is a thesis on translating for two websites, the User Way website translating from English to Spanish, and the SLL website that translates from Spanish to English. In this following study, the results on these websites are studied when translating both sites with different types of strategies used not to let them get translated and also gives you information on ways to ensure your translation is correct.

This project in a multilingual environment like the Hospital Mexico Library highlights the importance of precise and culturally appropriate translations to bridge the language gap, facilitate communication, as well as improve user experience. Translation theory could be well developed in the theoretical aspect, however, in the practical part, which is literary translation, especially for library work that requires accuracy and flow readability, it is equally important as a thesis the application of polyglot interpretation such as literal translation, modulation technique transposition, and omission technique to some methods.

In essence, this document provides a detailed framework and analysis of translation techniques, which could inform and guide the translation of documents for the Hospital Mexico Library, ensuring the translations are both accurate and culturally adapted.

Translation and Analysis of the Documents Propuesta dique de cierre sector este from Spanish into English and Standard Test Methods for Particle-Size Distribution (Gradation) of Soils Using Sieve Analysis from English into Spanish for Insuma.- Andrés Gutiérrez López (2022).

This document is closely related to the task of translating documents for the Hospital Mexico Library because translation techniques such as transposition, modulation, omission, amplification, and exploitation, to enhance the accuracy and fluency of translations, are techniques used mainly for medical and administrative texts, the key to ensure precision and clarity.

Before translating any text, the document also points out the importance of understanding the difference between certain text styles and functions, like informative, expressive, and evocative. This process is essential in hospital-related documents, as erroneous communication of values like patient instructions and policies can result in miscommunication which the rigorous method can avoid. The paper also highlights the need for glossary development, particularly in technical terminology. This is especially true in the case of the Hospital Mexico Library, which might benefit from creating glossaries for medical, administrative, and technical terms to obtain a more consistent and accurate translation.

A crucial point in this document is how focusing on good translation accuracy also produces more natural ones. Hospital documents must be accurate to communicate that everything has been completed; a failure here would lead to possible patient harm. In general, it is a down-to-earth approach to translation methods for the translation of Hospital Mexico Library materials, addressed through common translation practice together with specialized

insights into some translating techniques and challenges such as terminology work or the tight-rope walk between remaining very close to the source text while at other times letting go excessively.

Translation Project: Learning Environments and Concepts. - Carla Obando Campos (August 19, 2011).

The document "Translation Project: Learning Environments and Concepts" translates academic articles about learning environments and concepts from English to Spanish. This comes in handy when translating materials for the Hospital Mexico Library; it discusses a theory on various translation techniques and strategies compatible with formal or informal learning situations.

On the part of the translation process, before anything, the document mentions the proper preparation, including knowledge of the author's background, knowledge of the target audience, and knowledge of the purpose of the text. This is important because that is how one ensures that the translation is correct and proper. Such methods can be used in translating medical documents and information going out of the hospital to keep the same meaning while catering to either Spanish or English-speaking audiences.

Further, the document emphasizes clarity and coherence in translating specialized terminology into the medical and administrative languages in the overall hospital documentation. The techniques and strategies discussed, such as handling idiomatic expressions and technical language, are directly connected to translation in a healthcare setting to provide access to both languages in patient-related critical information.

Medical Translation: Analysis of Non-specialized Texts to Formulate Guidelines for Beginner Translators- Inge Groenewoud (July 2011)

The document "Traducción Médica: Análisis de textos no especializados con el fin de formular directrices para el traductor principiante" offers a thorough examination of medical translation, focusing on non-specialized medical texts as a basis for developing guidelines for beginner translators. Although the analyzed texts are less complex than highly specialized medical materials, the study provides valuable insights into the foundational aspects of translating medical documents. It emphasizes the importance of mastering medical terminology, ensuring terminological consistency, and addressing cultural and linguistic nuances in translation work. The document identifies the challenges translators face, such as the lack of direct equivalents for some medical terms, and highlights strategies to maintain the integrity and clarity of the original content.

Moreover, the study underscores the critical role of glossaries and other reference tools in achieving accuracy and coherence in translations. By standardizing medical terms across documents, glossaries ensure a high level of precision and reduce the risk of misinterpretation. The research also explores the balance between technical accuracy and readability, emphasizing that translations must be accessible to their target audiences while preserving the meaning and intent of the original text.

The document’s emphasis on building foundational skills for translators and addressing practical challenges in medical translation resonates with your objectives of creating a specialized glossary and applying consistent translation techniques. It serves as a complementary resource, offering strategies and theoretical insights that could strengthen your framework for addressing the complexities of specialized medical translation.

Medical Translation from the Perspective of User Needs of Medical Professionals - Zuzana Ševčíková (2021)

The thesis "Medical Translation from the Perspective of User Needs of Medical Professionals" by Zuzana Ševčíková delves into the intricate relationship between medical translation and its end users, primarily healthcare professionals such as physicians, dentists, and medical students. It focuses on understanding the specific needs of these users by addressing critical translation aspects such as terminology usage, abbreviations, grammatical structures like the passive voice, and the formatting of bibliographical references. By surveying medical professionals and translators, the research identifies the varying expectations and preferences in medical texts, emphasizing the lack of uniform guidelines provided by clients and the diverse approaches translators adopt to address these gaps.

This study is particularly relevant to your thesis on translating specialized medical documents for the Hospital Mexico Library. It highlights the importance of tailoring translations to meet the practical and linguistic needs of medical practitioners, ensuring clarity, accuracy, and usability. For example, the study reveals preferences for combining Latin terms with localized explanations, a practice that resonates with your objective of maintaining cultural sensitivity while preserving technical accuracy. The exploration of terminological consistency and the creation of glossaries align directly with your goal of developing resources to standardize translations. Moreover, Ševčíková’s emphasis on addressing the end-user’s needs supports your focus on ensuring that translated texts are both comprehensible and professionally credible.

Furthermore, the research underscores the challenges translators face in balancing technical precision with readability, a core concern in your thesis. It also draws attention to

the collaborative role between translators and medical professionals, advocating for a feedback-driven process to refine translations.

1.5. Scope

This thesis focuses on translating medical documents from English to Spanish and vice versa, explicitly targeting materials prepared for the Hospital Mexico Library. The scope encompasses a detailed examination of specialized translation procedures to enhance accuracy, clarity, and accessibility within medical communication. The critical phases of the research are:

1. **Document Selection:** The thesis will analyze selected medical texts, including "Cardiología molecular. Módulo 3: Diabetes Mellitus tipo 2" by Jonatan Navarro Solano and "The Next Fifty Years" by John Brockman. These documents are chosen for their relevance to current medical practice and patient care within the population.
2. **Translation Techniques:** The research will investigate various specialized medical translation techniques that ensure the correct use of medical terminology, cultural relevance, and comprehensibility. This includes studying best practices in translating technical jargon, idiomatic expressions, and culturally specific health concepts.
3. **Challenges in Medical Translation:** The thesis will delve into the difficulties experienced by medical translators, such as the rapid evolution of medical knowledge, varying dialects within the Spanish and English languages, and the necessity of maintaining message integrity while ensuring clarity for a diverse audience.
4. **Cultural Considerations:** An integral part of the study will focus on cultural relevance and appropriateness in translation. This involves analyzing how different health beliefs, practices, and terminologies can impact the translation process and the target audience's understanding of medical content.

5. **Glossary Development:** The creation of a standardized glossary of medical terms will be a crucial aspect of this research. It will serve as a reference tool to ensure consistency and clarity in translation efforts.

By focusing on these elements, the thesis aims to provide a comprehensive understanding of the role and impact of medical translation in improving healthcare access and quality for patients within the context of the Hospital Mexico Library. The research will contribute to the ongoing discourse on best practices in medical translation and serve as a foundation for future studies in the field.

Chapter II

Theoretical Framework

A theoretical framework for a thesis serves as a structure that guides research by providing a clear rationale and context for the study. It encompasses the theories, concepts, and definitions that underpin the research topic, allowing the study to be anchored in existing literature and knowledge. Researchers can situate their work within a well-defined academic landscape by establishing this framework. The framework serves several key purposes. First, it provides a solid foundation for research by outlining the theoretical basis of the study and detailing the principles and ideas that will be explored. This foundational aspect is crucial for grounding the research in established scholarship and theories.

Additionally, the theoretical framework is important in formulating research questions and hypotheses. It ensures that these inquiries are rooted in established theories, enhancing their relevance and significance within the academic discourse. Researchers can engage more deeply with their chosen topics by grounding questions in theoretical concepts. Furthermore, the framework contextualizes the study by referencing relevant theories, which situates the research within the broader academic dialogue. This connection demonstrates how the current work builds on or challenges existing knowledge, highlighting its contribution to the field.

The theoretical framework also informs the methodology by influencing the choice of research methods and analytical approaches. By aligning these methods with the theoretical perspectives introduced, researchers can ensure consistency and coherence throughout their study. Finally, a solid theoretical framework aids in interpreting research findings. It allows for a more nuanced understanding of the results by providing a lens through which to analyze and contextualize the data in light of the theoretical underpinnings.

Overall, a well-defined theoretical framework enhances the credibility and depth of the research, offering a coherent perspective for analyzing the topic at hand.

2.1. Text Analysis

Christiane Nord's (1991) concept of text analysis in translation is a cornerstone of her functionalist approach to translation theory. It emphasizes the need for a systematic examination of the source text to guide translation decisions, ensuring the final product fulfills its intended function in the target culture. Nord’s approach is deeply rooted in the principle that translation is not just a linguistic transfer but also a communicative act, shaped by the purpose of the translation and the needs of the target audience.

At the heart of Nord's concept is the idea of functionality, where the purpose (or skopos) of the translation determines how the text should be rendered. This functionalist perspective requires the translator to consider the specific communicative situation of the target text rather than adhering rigidly to the source text's form. As a result, the translator's primary task is to adapt the content and style of the source text to align with the expectations, cultural context, and communicative needs of the target audience.

Nord's text analysis framework is divided into two main dimensions: extratextual and intratextual factors. The extratextual factors encompass the external context of the text, such as the sender (who wrote the text), the receiver (the intended audience), the medium (how the text is delivered), and the purpose (why the text was written). These elements help the translator understand the broader communicative context and the sociocultural environment in which the text operates. On the other hand, the intratextual factors focus on the internal characteristics of the text, including its content, structure, style, and use of non-verbal

elements like images or formatting. This dual focus allows translators to make informed decisions about what aspects of the text to prioritize or adapt.

Overall, Christiane Nord's text analysis provides a structured, purpose-driven approach to translation. It equips translators with the tools to analyze and adapt texts effectively, ensuring that the translation fulfills its communicative function while maintaining ethical integrity. This concept has proven particularly useful in fields where cultural, contextual, and functional nuances significantly impact the success of a translation.

2.1.1. Text Styles

Jean Boase-Beier's Translation and Style (2019) provides an in-depth examination of the concept of text style in translation, particularly in the realm of literary works. Boase-Beier defines style as the unique way in which meaning is expressed in a text, shaped by the author's linguistic and literary choices. Style encompasses various elements, such as tone, rhythm, syntax, word choice, and figurative language, all of which contribute to a text's deeper meaning and emotional resonance. In translation, style is not merely about replicating the surface features of the source text but also about interpreting and conveying the author's intent, cultural context, and aesthetic values in a way that resonates with the target audience.

A central theme in the book is the idea that style is inherently interpretive. Translators must first identify and analyze the stylistic features of the source text, understanding their purpose and effect, before deciding how to render them in the target language. This involves not only linguistic considerations but also an awareness of the source text's cultural and literary context. For Boase-Beier, the translator's task is to faithfully reproduce the intended meaning and stylistic impact of the original text while adapting to the linguistic norms and expectations of the target culture.

The book places particular emphasis on the challenges of translating literary style. Literary texts are often defined by their unique stylistic identity, making the preservation of tone, voice, and aesthetic quality a central concern for translators. Boase-Beier argues that literary translation requires a deep sensitivity to the author's voice and the text's stylistic nuances, including rhythm, imagery, and sound. Translators must balance fidelity to the source text's style with the need for naturalness and readability in the target language, often finding creative solutions to bridge linguistic and cultural differences.

Despite all this information, in Nida's classification of texts, it can be found that different types are narrative, description, discussion, and dialogue, as cited by Newmark (1988), it reflects an analytical framework that highlights the distinct linguistic and functional features of both literary and non-literary texts. Each category emphasizes specific linguistic structures and stylistic elements that define its communicative purpose and mode of expression:

- **Narrative Texts:** Narrative texts are characterized by a dynamic sequence of events, focusing on verbs that convey action and movement. In English, this includes the use of "dummy" verbs, verb-nouns, or phrasal verbs, such as in the examples "He made a sudden appearance" or "He burst in." These constructions are common in storytelling and serve to drive the plot forward. The prominence of action verbs aligns with the narrative's function to recount events and create engagement through progression.
- **Descriptive Texts:** Description, by contrast, is static, emphasizing linking verbs, adjectives, and adjectival nouns. This type of text focuses on portraying details, attributes, and settings rather than actions. The static nature of descriptive texts supports their primary goal: to paint vivid pictures or provide detailed explanations that help the audience visualize or understand a subject more deeply.

- **Discussion Texts:** Discussion texts involve the treatment of ideas, characterized by abstract nouns (concepts), verbs of mental activity (e.g., “consider,” “argue”), logical arguments, and connectives. These texts are analytical and intellectual, designed to explore, debate, or explain complex ideas. The focus on abstraction and logic makes this text type highly structured, requiring clarity and coherence for effective communication.
- **Dialogue Texts:** Dialogue emphasizes colloquialisms and phatic expressions (phrases used to establish or maintain social interaction, such as “How are you?”). This type captures the natural flow of conversation and interpersonal communication. Dialogue texts aim to reflect spoken language, making them essential in contexts like plays, interviews, or narrative segments with direct speech.

Nida’s classification is valuable for understanding how linguistic elements are adapted to serve specific communicative purposes. For translators, recognizing these text types is crucial for selecting appropriate translation strategies. Newmark (1988) integrates this framework into his broader discussion of functional text types, underscoring how the translator must adapt their approach based on the linguistic and functional characteristics of the text. This classification also serves as a guide for linguistic analysis, aiding in the identification of stylistic features and their intended effects within both source and target languages.

2.1.2. Stylistic Scales

Stylistic scales in translation refer to the spectrum of linguistic and rhetorical styles a translator must navigate to ensure that the translation appropriately reflects the tone, register, and stylistic choices of the original text. These scales are critical in determining how a text’s

emotional, formal, or casual elements are conveyed in the target language, ensuring that the translated message resonates similarly with the target audience.

According to Vinay and Darbelnet (2000), stylistic scales in translation are influenced by various factors, including the intended audience, the purpose of the text, and the specific nuances that define its emotional or intellectual appeal. For instance, in literary translation, the translator must work within a stylistic scale that ranges from formal, high-register language to informal, colloquial expressions. The goal is to preserve the emotional and aesthetic qualities of the source text while making it culturally appropriate for the target language. This can involve significant shifts, such as adapting metaphors, idiomatic expressions, or even sentence structure to reflect the style and tone of the original work.

Baker (1992) further elaborates on stylistic scales by discussing how to register, the combination of formality, subject matter, and language function; affects the translation process. In technical and scientific translations, the scale of formality is often high, requiring precise and unambiguous language. In contrast, casual conversations or marketing texts may employ a more dynamic and engaging tone, adapting stylistic choices to the target audience's expectations. This adaptability is crucial for achieving the desired effect, whether it be conveying technical accuracy or emotional depth.

Munday (2016) also addresses the importance of stylistic choices in translation, emphasizing how translators must be attuned to shifts in tone, style, and register across different types of texts. Whether translating a legal document, a novel, or a dialogue, understanding where a text falls on the stylistic scale helps the translator make informed decisions about word choice, syntax, and tone. For example, translating a legal text requires a

formal, precise style, while a literary text may require more creativity and interpretative flexibility to capture the nuances of the original's emotional resonance.

In essence, stylistic scales in translation highlight the complexity of balancing formal, neutral, and informal styles within the linguistic and cultural frameworks of the source and target languages. Translators must be sensitive to these scales to ensure that the style, tone, and register of the original text are faithfully reflected, whether the text is technical, literary, or conversational. By understanding these stylistic nuances, translators ensure that the target audience receives a translation that maintains the integrity and intent of the original text.

2.1.2.1. Scale of Formality

The scale of formality in translation refers to the degree of politeness, tone, and linguistic sophistication required to faithfully reflect the source text's intent and adapt it appropriately for the target audience. Translators must navigate this scale carefully, balancing the original text's function and tone with the cultural and social expectations of the target language. Formality in language spans a continuum from highly formal (e.g., legal documents or academic texts) to informal (e.g., casual conversations or personal letters). As noted by Baker and Saldanha (2020) and Newmark (1988), the translator's task is to manage this spectrum of formality, ensuring the translation aligns with the communicative function and cultural norms of the target audience. This careful calibration contributes to producing a translation that feels both authentic and appropriate to its context.

Formality is closely tied to the concept of register, which varies based on context, audience, and purpose of communication. As Baker and Saldanha (2020) highlight, formal language often emphasizes structured and precise terminology, while informal language is characterized by conversational tone and colloquialisms. Translators must analyze the field

(subject matter), tenor (relationship between writer and reader), and mode (medium of communication) to determine the appropriate tone and style. Nida and Taber (1982) note that a casual tone in the source text might need adjustment to a more neutral or formal tone in the target language to better suit the expectations of the audience, particularly in cultural contexts like Japanese or French, which rely heavily on hierarchical forms of address and politeness. This kind of adaptation ensures that the translation remains culturally respectful and functionally effective.

The type of text being translated plays a significant role in determining the level of formality. For instance, legal, scientific, and medical documents demand strict adherence to formal conventions, ensuring accuracy and professionalism. In contrast, marketing materials, novels, or dialogues require a more dynamic approach, with informal or colloquial tones often being necessary to engage the audience effectively, as noted by Reiss (1981). To navigate these differences, translators may employ various strategies, such as literal translation to preserve the original tone in formal texts, or dynamic equivalence to adapt informal or emotionally driven texts for cultural resonance (Nida, 1964). These choices not only reflect linguistic skill but also cultural awareness, which is crucial for producing effective and contextually appropriate translations.

The challenges of maintaining formality arise from linguistic and cultural differences between source and target languages. For example, languages like French and Spanish distinguish between formal and informal pronouns (e.g., "tu" and "vous" in French), which have no direct equivalents in English. As Newmark (1988) explains, translators often compensate by adding contextual elements or rephrasing sentences to convey politeness levels accurately. This strategy helps preserve the intended tone of the original while

respecting the norms of the target language, which is essential for achieving culturally appropriate translations.

To summarize, the Routledge Encyclopedia of Translation Studies and other sources emphasize the importance of understanding how formality intersects with register, cultural norms, and audience expectations. Translators must carefully manage the scale of formality across different text types and contexts, ensuring that their translations are both linguistically accurate and culturally appropriate (Baker & Saldanha, 2020). Recognizing this dynamic continuum enables translators to adapt effectively, producing texts that resonate with the intended audience while remaining true to the source material.

2.1.2.2. Scale of Generality or Difficulty

The scale of generality or difficulty in translation, as outlined by Newmark (1988), categorizes texts based on their vocabulary complexity, which influences how translators approach and handle translation tasks. The scale ranges from simple texts that require minimal linguistic effort to highly specialized texts that demand in-depth knowledge and expertise. This scale also intersects with key translation theories, such as those discussed in The Cambridge Handbook of Translation (Malmkjær & Windle, 2021), which examines how the specificity of a source text influences the translator's approach. Newmark's Scale categorizes texts as follows:

- **Simple:** These texts use basic, everyday vocabulary that is easy to understand and translate with little complexity. An example is, "the floor of the sea is covered with rows of big mountains and deep pits," where the vocabulary is plain and direct.

- **Popular:** These texts employ more current or colloquial vocabulary but remain accessible. For instance, "the floor of the oceans is covered with great mountain chains and deep trenches" is a popular-level description that uses familiar language.
- **Neutral:** While still based on basic vocabulary, neutral texts may incorporate more abstract or scientific terms straightforwardly, like "a graveyard of animal and plant remains lies buried in the earth's crust."
- **Educated:** These texts are meant for those with a certain level of education, containing terms and ideas suited to university-level audiences, like "the last step in vertebrae evolution was the tool-making man."
- **Technical:** Highly specialized texts, such as "Critical path analysis is an operational research technique used in management," that requires a deep understanding of a specific field. Translators working with technical texts must be familiar with the jargon and terminology of the subject matter.
- **Opaquely Technical:** This type is highly specialized and only comprehensible to experts in the field, such as "neuraminic acid in the form of its alkali-stable methoxy derivative was first isolated by Klenk from gangliosides."

The scale of generality or difficulty directly impacts the translation strategies employed. Simpler texts require a focus on clarity and accessibility, while more complex or technical texts demand precision, specialized knowledge, and careful consideration of the target audience’s understanding. This complexity is further influenced by the cultural and linguistic context of the translation, where even the most technical text must be adjusted to ensure that the translated message is both accurate and culturally appropriate. For example, technical terms must be precisely translated, but when no equivalent exists, the translator

must balance faithfulness to the source with clarity in the target language (Malmkjær & Windle, 2021).

In summary, the scale of generality or difficulty in translation is a crucial concept that shapes how translators approach texts of varying complexity. From simple, everyday language to highly technical and specialized texts, understanding this scale enables translators to apply the right strategies for each context. As demonstrated in the works of Newmark (1988) and further explored in The Cambridge Handbook of Translation (Malmkjær & Windle, 2021), this scale not only influences vocabulary but also guides the level of formality, accuracy, and cultural adaptation required in the translation process. Ultimately, the ability to assess the generality or difficulty of a text allows translators to balance fidelity to the original with clarity and accessibility for the target audience, ensuring that the message is effectively conveyed regardless of its complexity or subject matter.

2.1.2.3. Scale of Emotional Tone

The book Emotion in Discourse, edited by J. Lachlan Mackenzie and Laura Alba-Juez (2019), explores how emotional tones are expressed through language and how they are conveyed in different discourse contexts, including translation. It examines how emotions, which are typically complex and multidimensional, are integrated into language through lexical, syntactic, and pragmatic devices. The work emphasizes that emotional tone is not merely an additive feature of discourse but is intricately woven into how meaning is constructed and interpreted. In translation, maintaining an emotional tone is crucial as it shapes the reader's or listeners' emotional response to the text. This is particularly challenging because emotional expressions in language extend beyond direct emotional vocabulary and can include subtler forms, such as intonation, humor, and irony. Translators must not only

find equivalent words but also account for the socio-cultural, cognitive, and emotional dimensions that influence how a message is received across different languages and contexts. The challenge lies in balancing the emotional resonance of the original discourse while adapting it to the target language, ensuring that the tone matches the intent and impact of the original text.

Concerning this, Newmark (1988) categorizes emotional tones into three distinct types, intense, factual, and understatement, each requiring different approaches in translation. For instance, an intense emotional tone is marked by the use of intensifiers like “absolutely wonderful,” “enormously successful,” and “heart-warming melodies,” which necessitate careful attention to how emotional intensity is preserved in the target language. Translators must use equivalent intensifiers in the TL that carry the same emotional weight. On the other hand, a factual tone, which is neutral and “cool,” uses terms like “significant,” “exceptionally well-judged,” and “personable.” Translating this tone involves ensuring that the neutrality and objectivity of the original message are preserved without emotional excess. Understatement involves downplaying emotions, such as using the phrase “not undignified” to express a sense of modesty or restraint. Translators must ensure that this subtlety is maintained without altering the original intent or introducing unintended emphasis.

The analysis of emotional tone is further supported by Baker (1992), who discusses how register and formality are closely linked to emotional tone. In the case of literary translation or narrative discourse, the emotional tone is often intertwined with style, register, and the intended emotional impact. For example, translating an intense emotional tone into a language that does not have the same expressive range as intensifiers may require creative strategies, such as modifying sentence structure or adding descriptive elements to capture the original emotion. Similarly, the scale of formality and generality in a text, as described by

Newmark (1988), affects how emotional tone is conveyed. A text with a formal register may need to be translated with a more restrained emotional tone, while an informal text might embrace a more relaxed and expressive tone.

Ultimately, translating emotional tone is not a straightforward task, as it involves much more than transferring words from one language to another. As emphasized by Mackenzie and Alba-Juez (2019), translators must navigate the cultural and emotional contexts of both the source and target languages to ensure that the emotional essence of the original text is faithfully conveyed. Balancing between accuracy, clarity, and emotional fidelity, translators play a critical role in adapting texts to maintain the intended emotional impact across linguistic and cultural boundaries.

2.1.3. Text Function

2.1.3.1. Informative

The informative function in translation prioritizes the accurate and clear communication of factual information, ensuring that the essence of the original text is preserved and accessible to the target audience. Central to this function is the commitment to accuracy and clarity, as the translator must carefully handle details and specialized terminology to uphold the integrity of the source material (Wu, 2022). Precision in language use helps maintain the original's intent and prevents misinterpretation of critical information. Adopting techniques from communicative translation theory, translators aim to make the content as understandable as possible, employing methods like part-of-speech conversion, voice transformation, and sentence restructuring to adapt the text to the target audience's linguistic norms.

Meanwhile, functionalist approaches, such as Reiss's text typology and Vermeer's skopos theory, highlight the importance of purpose in translation. For informative texts, this purpose typically involves delivering straightforward and content-focused translations that align with the audience's expectations and needs. Translators also utilize various translation techniques, such as simplifying overly complex sentences, using culturally and contextually familiar terminology, and ensuring logical coherence throughout the text. In some cases, adding or omitting minor details can enhance clarity and ensure the translation effectively serves its intended function. Together, these strategies ensure the informative function is maintained, providing the target audience with a clear and reliable reflection of the source text.

2.1.3.2. Expressive

Peter Newmark's theory on expressive text function emphasizes the significance of the author's voice, emotions, and creative expression in translation. Expressive texts, such as literary works, autobiographies, or personal essays, prioritize the preservation of the original style and emotive impact. According to Newmark (1988), semantic translation is particularly suited for these types of texts because it aims to stay faithful to the original meaning, nuance, and aesthetic quality. This contrasts with communicative translation, which is more focused on ensuring the message is understood by the target audience, often at the expense of stylistic elements.

In expressive texts, the translator's role is to replicate the author's voice and stylistic features as closely as possible. This involves maintaining cultural and linguistic elements of the source text that contribute to its artistic value. Newmark argues that achieving equivalent effects in these cases requires a balance between literal fidelity and interpretative creativity.

For example, translating poetry or metaphors demands sensitivity to the emotional and cultural layers embedded in the text to ensure the target audience receives a similar aesthetic and emotive experience as the source audience.

An important aspect of Newmark's approach is the understanding that each expressive text carries its unique context, including historical and cultural connotations, which should be taken into account during translation. This context helps to shape the reader's understanding and appreciation of the work. Therefore, a skilled translator must not only possess linguistic proficiency but also an in-depth knowledge of both source and target cultures.

Additionally, Newmark's insights highlight the ethical responsibility of the translator in preserving the author's original intent while navigating the creative aspects of language. This balance can be particularly challenging in expressive texts, as any misrepresentation can dilute the originality and emotional resonance of the work. Thus, translators often engage in a creative process that requires intuition, empathy, and a deep understanding of both languages involved, ultimately aiming to craft a translated piece that feels authentic and emotionally engaging for the new audience. In summary, Newmark's theory underlines the complexities of translating expressive texts, advocating for a nuanced approach that prioritizes both fidelity to the original work and the creative elements necessary to resonate with a new audience.

2.1.3.3. Vocative

The vocative function in translation is characterized by its focus on engaging the reader directly and prompting them to act, think, or feel in a specific way. This function is most commonly seen in texts such as advertisements, instructions, and public notices, where

the goal is to persuade or motivate the audience (Cojocaru, 2014). A key element of vocative texts is their reader-centric approach, which prioritizes addressing the reader directly and intentionally. This requires the translator to understand not only the language but also the psychology behind the communication, ensuring that the text appeals effectively to the target audience.

The effectiveness of communication in vocative texts is crucial, as the success of the message depends on how compelling and clear it is to the reader. The translator must focus on eliciting the desired response, whether it is to encourage the purchase of a product, adherence to instructions, or a behavior change. To achieve this, they may need to restructure or rephrase elements of the original text to make it resonate more strongly with the target audience.

Another critical aspect is cultural adaptation, as vocative texts often rely on cultural nuances, idiomatic expressions, and references. Translators must adapt these elements to ensure they are meaningful and relatable to the target culture. This process might involve modifying examples, metaphors, or even the tone of the text to suit the cultural context without losing the original intent or emotional impact.

Finally, the language and style of vocative texts play a significant role in their effectiveness. These texts require engaging and persuasive language that retains the original's impact while aligning with the preferences and expectations of the target audience. The translator’s task is to strike a balance between maintaining the persuasive force of the original and adapting the style to meet the cultural and linguistic norms of the target readership. By carefully addressing these elements, translators can ensure that the vocative text achieves its intended purpose and creates the desired impact on the target audience.

2.1.4. Translation Methods

2.1.4.1. Semantic translation

According to Mohamed (2022), semantic translation focuses on achieving a faithful representation of the source text's original meaning and form, this means that the translator must not only translate the words but also capture the underlying emotions and messages conveyed within the text. This method aims to preserve the cultural and linguistic nuances of the source language, including idiomatic expressions, metaphors, and stylistic features by providing footnotes, explanations, or equivalent phrases that maintain the intended meaning. For example, a specific cultural reference would be explained rather than omitted, offering the target audience insight into the original context.

It emphasizes the author's voice and intent, ensuring that the translation reflects their thought processes and specific language choices. Semantic translation is particularly suited for expressive texts, such as literary works, philosophical essays, and technical writings, where the preservation of tone and detail is critical. However, this approach can result in translations that are more complex, detailed, and occasionally less natural in the target language, as it prioritizes fidelity over readability. It is considered ideal for contexts where the authenticity of the original message outweighs the need for audience adaptability.

In summary, semantic translation is a crucial method employed by translators who aim to maintain fidelity to the original text while also making it accessible to a new audience. By emphasizing meaning, structure, and cultural nuances, this approach enriches the reading experience and fosters a greater understanding of diverse literary and academic works.

2.1.4.2. Communicative translation

Communicative translation, as described by Mohamed (2022), centers on ensuring that the target audience fully understands the message of the source text. This method adapts the original content to make it clear, accessible, and culturally relevant for the reader, often modifying idiomatic expressions or general terms for greater resonance because translators often find themselves faced with idiomatic expressions, cultural references, or humor that may not have a direct equivalent in the target language. It emphasizes the social function of communication and prioritizes the audience's comprehension and reaction to the text. This approach is particularly effective for practical or functional texts such as advertisements, instructions, and public notices, where the intended outcome is to inform, persuade, or instruct. In this case, a translator may adapt slogans or promotional messages to evoke desired emotions, ensuring that they align with the cultural values and preferences of the target market. This strategic adaptation can significantly enhance the effectiveness of marketing campaigns across different regions.

In summary, communicative translation transcends mere word-for-word translation. It embodies a thoughtful, culturally aware approach that prioritizes audience understanding. By allowing for creativity and flexibility, this method enhances communication across languages and cultures, making texts not only readable but relatable.

2.2. Translation Procedures

2.2.1. Transposition

Transposition is a translation procedure identified by Vinay and Darbelnet (2000) that involves replacing one part of speech with another without altering the meaning of the

original message. This technique is particularly valuable when the source language (SL) and the target language (TL) have different syntactic structures, requiring adjustments for the translation to flow naturally and feel fluent in the TL. There are two main types of transposition: obligatory transposition, which occurs when the linguistic structures of the source and target languages necessitate a shift (such as translating a noun phrase from French into a verb phrase in English), and optional transposition, which allows the translator to make stylistic adjustments for readability or to convey specific nuances (e.g., shortening a phrase for smoother expression).

In addition to these, other types of transposition are used depending on the context of the translation. Adjectival to noun conversion is a common example, where an adjective is turned into a noun, an example is translating French “la politique sociale” into English as “social policy”. Another example is the verb to-noun (nominalization), which involves converting a verb into a noun for syntactic fluidity, such as translating “il a annoncé son départ" (He announced his departure) into "He announced his departure." Active to passive voice shifts, where the sentence changes from active to passive or vice versa, are also forms of transposition; for example, "Le livre a été écrit" (The book was written) is a passive construction in French, which is translated into English similarly. Additionally, changing word order can be necessary in translation, such as transforming the French "l’homme avec qui j’ai parlé” into “the man I spoke with” in English. Lastly, tense and aspect modulation occurs when the tense or aspect of a verb needs to be altered to align with the target language’s grammatical conventions (e.g., converting "Dès son lever" into “As soon as he gets up”).

These types of transposition are important for handling the syntactic differences between languages, ensuring that the translated message remains clear, accurate, and

idiomatic while retaining the original meaning. They also offer opportunities to enhance the literary quality of the translation, as some types of transposition, such as verb-to-noun conversion or word order adjustments, can make a translation more dynamic or appropriate for the target audience's stylistic norms. By carefully selecting and applying these techniques, translators can achieve the right balance between the form and content of the original text and its natural flow in the target language.

2.2.2. Modulation

Modulation is a key translation procedure described by Vinay and Darbelnet, referring to the variation of the form of the message in translation by changing the point of view, cognitive category, or expression. This adjustment is often necessary when a direct, literal translation would result in an awkward, unidiomatic, or even grammatically incorrect translation in the target language (TL). Modulation essentially alters the perspective or approach to the original message, ensuring that it remains natural and clear in the TL, aligning with the linguistic and cultural norms of the target audience.

According to Molina (2002), there are two primary types of modulation: obligatory and free modulation. Obligatory modulation occurs when the SL requires a grammatical or structural change in the TL. For instance, certain expressions in English require a change in word order or phrasing when translated into languages like French. The phrase “the time when” is often translated as “Le moment où,” where the structure of the TL forces this shift.

Free modulation, on the other hand, is more flexible and can be applied to enhance clarity, emphasis, or natural flow. A common example is turning a negative expression into a positive one. For instance, “It is not difficult to show” might be modulated into “Il est facile de démontrer” in French, which shifts the negative phrasing to a positive form to make the

sentence sound more fluid and less cumbersome in the target language. This type of modulation is often based on the translator's judgment and understanding of the context, allowing for a more dynamic translation that fits the cultural and communicative needs of the target audience.

Modulation is particularly valuable when a literal translation would either lack nuance or produce a sentence that feels foreign or awkward. For instance, in literary translations, modulation can be used to adjust metaphors, idioms, and expressions that would not resonate with the target audience, ensuring the translation feels authentic and engaging. Free modulation, when used effectively, translates seem more natural, allowing it to resonate with readers on a cultural and emotional level.

Thus, modulation is not just about shifting grammatical structure but also about fine-tuning the translation to ensure that the message is conveyed in the most idiomatic, culturally appropriate, and clear way possible.

2.2.3. Omission

Omission is a translation procedure in which certain elements of the source text are deliberately left out when translated into the target language. This technique can be employed for a variety of reasons, such as cultural differences, the absence of equivalent concepts in the target language, or to avoid redundancy in the translation. Vinay and Darbelnet (2000) discuss omission as a procedure that often results from the communicative situation of the text. When the source text contains cultural references, idiomatic expressions, or specific terms that would not resonate with the target audience, these elements may be omitted for clarity and simplicity. For example, the Arabic greeting "صباحكم الله بالخير" (literally, "may God give you goodness this morning") can be omitted in English, simply translating it

as "good morning." The original phrase would not be well-understood in the target language, and simplifying it ensures the translation feels natural and culturally appropriate.

Omission is also a way to avoid over-translation, which can complicate the message and potentially confuse the target audience. When certain terms, concepts, or references from the source culture do not have direct equivalents in the target language, leaving them out can prevent the translation from becoming unnecessarily verbose. In some cases, the target audience would be better served by omitting details that would otherwise require lengthy explanations or footnotes. Ivir (2013) highlights how translators might choose to omit certain terms to maintain fluency in the target language, ensuring the translation remains smooth and concise. For example, if an Arabic text mentions "هيئة الإذاعة البريطانية" (BBC), a translator might omit the full Arabic term and simply use "BBC" in the English translation, knowing that the English-speaking audience will recognize the abbreviation.

Moreover, the choice of omission can also reflect the translator's judgment about what is culturally relevant. For instance, a translator may omit a culturally specific term that is understood in the source culture but is irrelevant or meaningless to the target audience. According to Molina and Hurtado Albir (2002), this decision is based on the context and function of the translation, aiming to preserve the text's effectiveness without introducing unnecessary foreign elements. When applied thoughtfully, omission can enhance the clarity and accessibility of the translation while still respecting the original intent.

Thus, omission is a critical procedure for ensuring that translations remain both faithful and functional. It helps to maintain the clarity of the message while avoiding unnecessary confusion or distortion, ensuring that the translation is culturally appropriate and easily understood by the target audience. By using omission, translators can balance between

staying true to the original text and adapting it to fit the linguistic and cultural norms of the target language.

2.2.4. Amplification

Amplification in translation is a procedure where additional information is introduced to ensure clarity or to adapt the message to the target language and culture. This technique is often used when a concept or term in the source language (SL) does not have a direct equivalent in the target language (TL). The translator may add explanations, details, or context to help the target audience understand the full meaning of the original text, especially when the SL term might be unfamiliar or too vague for the TL reader.

For instance, when translating culturally specific terms or phrases, the translator might need to provide additional context or a more detailed description to make the text comprehensible. This procedure is particularly common when translating cultural references, metaphors, or idiomatic expressions that require further clarification. For example, a term like “kung fu” in English is often used as it is, but it may sometimes require additional description in certain contexts to explain its cultural and historical significance (Vinay & Darbelnet, 2000; Ivir, 2013). Similarly, an Arabic greeting like "صباح الخير" might be translated simply as "Good morning" in English, as the cultural context does not require the more elaborate literal translation in the TL (Ivir, 2013). These examples illustrate how translation often involves not just linguistic conversion, but also cultural adaptation to ensure the message is both clear and appropriate for the intended audience.

Amplification can also be used when translating metaphors or figurative language that might not translate smoothly. For example, the English metaphor “to save face” may be translated into Arabic with added context, such as "حفظ ماء الوجه" (literally "to save one’s

water face"), to preserve its cultural and figurative meaning (Ivir, 2013). This helps make the expression more accessible and meaningful to the target audience.

In short, amplification is a valuable translation technique that allows the translator to ensure the message remains accurate, clear, and culturally appropriate while enhancing the overall readability and understanding of the target text.

2.2.5. Explicitation

Explicitation in translation refers to the process of making implicit information in the source text more explicit in the target text. This technique involves adding elements to the translation to clarify meaning, resolve ambiguity, or provide additional context that may be implied but not directly stated in the source language. According to Vinay and Darbelnet, explicitation is especially useful when translating between languages with different syntactic or semantic structures, where certain details might be implicit in the source but need to be made more overt for the target audience to understand fully.

There are two primary types of explicitation: obligatory and optional. Obligatory explicitation arises from the structural and syntactic differences between languages, where certain elements must be added in the target language for the translation to be grammatically or culturally correct. For example, English often requires articles ("the," "a"), while other languages, like Russian, do not have definite articles, necessitating their addition in English translations (Vinay & Darbelnet, 2000). Optional explicitation, on the other hand, is influenced by the translator's choice, driven by stylistic or clarity considerations. For instance, when translating from a language like French, which has fewer explicit conjunctions than English, a translator might add connecting words in English to improve coherence and readability (Séguinot, 1988). In both cases, explicitation plays a key role in ensuring that the

target text is both grammatically accurate and accessible to the reader, reinforcing the importance of context-sensitive decision-making in translation.

Explicitation also occurs in response to cultural differences, where implicit cultural knowledge in the source text needs to be made explicit for the target audience. For example, translating a local reference in the source text might involve adding explanatory phrases or cultural context to make the meaning clear to readers unfamiliar with the source culture (Baker, 1992). This approach helps bridge cultural gaps and ensures that the target audience fully understands the significance or nuance of the original reference, thereby enhancing the overall communicative effectiveness of the translation.

This technique is crucial for ensuring that the target text is not only grammatically accurate but also culturally and contextually relevant for the audience. By explicitly conveying underlying meanings that might otherwise remain unclear, explicitation helps to make translations more accessible and faithful to the intent of the original message.

2.2.6. Literal Translation

Literal Translation is a translation procedure that involves transferring a text from the source language (SL) into the target language (TL) as directly as possible, maintaining its grammatical structure and meaning. According to Vinay and Darbelnet (2000), this procedure is most commonly applied when translating between languages of the same family, where structural similarities allow for a relatively straightforward word-for-word translation. The primary goal is to stay as close as possible to the original text, preserving the verbatim meaning and transparency of the SL expression in the TL.

However, while literal translation may be useful in certain contexts, it has limitations, especially when dealing with languages that have significant structural differences or cultural nuances. It is particularly effective in legal or technical translations where accuracy and consistency are paramount. In such cases, a literal translation ensures that the precise terminology and concepts are preserved, even if the translation is less stylistically polished. According to Ivir (2013), terms like "the Cold War" or "the black market" may remain the same across different languages, as they are universally understood. Nevertheless, this approach can fall short when translating cultural or idiomatic expressions that require adaptation to convey the intended meaning accurately. Therefore, literal translation must be applied selectively and with consideration of both linguistic fidelity and cultural relevance.

Despite its apparent simplicity, literal translation can sound unnatural in the target language if applied indiscriminately, especially when dealing with idiomatic expressions or culturally specific references. In those instances, the translator must decide whether a more dynamic or free translation method is needed to capture the intended meaning without distorting the message. For example, translating a metaphor or idiomatic phrase literally may result in an awkward or unclear translation that does not convey the same nuance in the TL.

To sum up, literal translation is an essential procedure for ensuring accuracy, but its application must be done thoughtfully to avoid producing rigid, unnatural translations. It is most effective in contexts where the source and target languages share similar structures and cultural backgrounds.

2.2.7. Punctuation changes

Punctuation changes in translation refer to the adjustments made to the punctuation marks of the source language (SL) when translating into the target language (TL). These

changes are essential for ensuring the translated text reads smoothly and adheres to the grammatical norms of the TL, which may differ from those in the SL. As Vinay and Darbelnet (2000) point out, punctuation marks such as commas, periods, and quotation marks can vary significantly between languages, and their placement often requires adaptation to match the stylistic and syntactic rules of the target language. Making these adjustments ensures that the translated text maintains both clarity and natural flow, enhancing its readability for the intended audience.

The document explains that punctuation is a crucial tool for enhancing clarity and meaning. Incorrect punctuation can change or even obscure the intended meaning of a sentence. Therefore, translators must carefully manage punctuation when translating to preserve the clarity and effectiveness of the message. Specific types of punctuation, such as commas or semicolons, can help separate clauses or phrases in a way that improves readability and ensures the intended message is communicated accurately.

Additionally, certain punctuation practices might be unique to particular languages, requiring the translator to make specific changes to adapt to the target audience's expectations. For example, while English often uses commas to separate clauses, other languages might use different punctuation marks or structures, making these adjustments vital for an idiomatic and fluent translation.

2.3. Glossaries

2.3.1. Relevance for the translator

Glossaries are highly relevant for translators as they serve as essential tools for maintaining consistency, ensuring accuracy, and improving efficiency in translation projects.

According to sources on translation practices, glossaries provide a centralized repository of terms and their equivalents in different languages, which is particularly important when dealing with specialized or technical texts (Pym, 2015). This ensures that terminology is consistently translated across documents, reducing the likelihood of errors and discrepancies.

For translators, glossaries are especially valuable when working in domains such as legal, medical, or scientific translation, where precision and adherence to established terms are critical. By referencing a glossary, translators can save time and ensure the uniformity of their work, which is crucial for documents that are part of a larger project or intended for professional use. Furthermore, glossaries can help translators navigate cultural and linguistic nuances, offering explanations or alternative terms to fit the context of the target language.

Additionally, glossaries serve as a bridge between translators and their clients or organizations. They help clarify expectations and align terminology preferences, particularly for businesses that operate in global markets. With a glossary, translators can better meet client's needs by adhering to preferred terms and stylistic conventions, which enhances the quality and professionalism of the translation.

2.3.2. Relevance for the translation process

Glossaries play a critical role in the translation process, ensuring accuracy, consistency, and efficiency. As Snell-Hornby (1988) highlights, they are particularly relevant in technical, legal, and specialized fields, where precise terminology is essential. Glossaries help translators maintain uniformity across projects by providing pre-defined equivalents for terms, phrases, and industry-specific jargon. This prevents ambiguity and ensures that the translation aligns with the expectations of the target audience.

Additionally, glossaries facilitate cultural and linguistic adaptation, ensuring that terms resonate appropriately within the context of the target language. As Gao (2013) notes, a glossary might include localized terms or cultural references that provide clarity and relevance, improving the overall quality of the translation. By reducing the time spent researching terminology, glossaries also enhance productivity, allowing translators to focus on the nuanced aspects of the translation process.

2.3.3. How to create a glossary

Creating a glossary for translation involves several key steps that ensure it serves as an effective tool for accuracy, consistency, and efficiency. First, it's important to define the purpose of the glossary, whether it's for technical, legal, medical, or creative translation; so that the scope and depth of terms can be tailored accordingly (Gao, 2013). The next step is to collect the relevant terms from the source text, focusing on specialized vocabulary, frequently used phrases and culturally specific references. For each term, providing clear definitions and context is essential, particularly for ambiguous terms that might have multiple meanings or require clarification (Snell-Hornby, 1988). The glossary should also include target language equivalents for each term, being mindful of cultural and contextual differences, and offering explanations where direct equivalents are not available.

Additionally, incorporating notes on industry-specific jargon or cultural nuances ensures that the glossary bridges linguistic and cultural gaps. To maximize usability, the glossary should be well-organized, either alphabetically or categorically, and formatted for easy reference, with digital tools such as Excel or translation-specific software being useful for this purpose (Gao, 2013). Finally, the glossary should undergo a review process involving subject matter experts to ensure accuracy and relevance, with periodic updates to keep it aligned with evolving contexts. By following these steps, translators can create a glossary

that enhances consistency and aids in producing high-quality, culturally appropriate translations.

Chapter III

Methodological Framework

The Methodological Framework chapter of this thesis outlines the research approach and strategies used to analyze and translate the texts under consideration. This chapter is designed to provide a clear and structured overview of the translation methodology applied throughout the study, ensuring that the process adheres to established theoretical principles while maintaining flexibility to address the specific challenges posed by the texts. Translation methodology is central to achieving fidelity to the source text while ensuring the translation resonates with the target audience. According to Nida (1964), translation is both a science and an art, requiring systematic procedures and creative adaptation. In the context of this study, the methodology will be rooted in functionalist translation theory, which emphasizes the purpose (or "skopos") of translation as the key determinant in decision-making processes (Vermeer, 2004). This approach allows for a nuanced understanding of how the function of the source text influences the translation strategies employed. Additionally, dynamic equivalence (Nida, 1964) will guide the analysis of how meaning, tone, and style are conveyed, ensuring that the translation effectively communicates the original's intended message while adapting to cultural and linguistic differences.

The framework will also incorporate semantic translation (Newmark, 1988) for certain cases, particularly in texts where accuracy and direct representation of the source material are paramount. This will be balanced with communicative translation techniques (Newmark, 1988), which prioritize the clarity and accessibility of the translation for the target audience. The application of these approaches will be analyzed in specific case studies, illustrating how different translation strategies are selected depending on the text type and the

goals of the translation. By employing a mixed-methods approach that combines theoretical analysis with practical application, this chapter provides the necessary foundation for understanding the translation choices made throughout the thesis. It will also establish the criteria for evaluating the success of the translations, ensuring that each decision is justified by the linguistic, cultural, and communicative demands of the target language.

In summary, the Methodological Framework is a guide to the theoretical approach used in this study and a roadmap for how the translator navigates the intricate balance between linguistic accuracy and cultural adaptation in translation. This chapter sets the stage for a deeper exploration of the challenges and solutions involved in translating complex texts across different languages and cultures.

3.1. Research Approach

This research explores the translation of specialized medical and scientific materials for the Hospital Mexico Library, focusing on the qualitative aspects of the process. This approach allows for a deep understanding of the complexities involved in ensuring accurate, coherent, and culturally relevant translations. The research delves into the cultural nuances present in the texts. Christiane Nord's functionalist framework guides this examination, emphasizing factors such as the text's purpose, target audience, and cultural context, alongside internal elements like syntax, vocabulary, and mood (Nord 1991). This is crucial, as it highlights the importance of producing translations that meet the communication needs of the intended audience while preserving the text's integrity.

This research examines the translation process of two distinct texts: "Molecular Cardiology Module 3; Type 2 Diabetes Mellitus" and "The Next Fifty Years." Through a close analysis of these texts, the research uncovers obstacles such as navigating medical

jargon, colloquial sayings, and cultural subtleties. It also focuses on developing a list of essential medical terms to maintain consistency in current and future translations. This approach is chosen for its capacity to offer in-depth perspectives on the translation process, facilitating a nuanced understanding of the choices and tactics used to address linguistic and cultural challenges.

In translation studies, qualitative analysis is often used to comprehensively examine various aspects of the translation process. This research analyzes the effectiveness of different translation approaches by categorizing and evaluating them based on their impact on the quality of translations. This qualitative assessment considers how well the translations convey meaning and achieve their intended purpose.

This qualitative approach is particularly valuable as it offers rich insights into the complexities of medical translation. By focusing on the linguistic and cultural hurdles encountered in these tasks, the research aims to understand the nuances of effective communication in healthcare settings. This approach, as recommended by Molina and Hurtado Albir (2002), is essential for gaining a complete grasp of the translation process.

This research is well-suited to the goals of improving translation practices for the Hospital Mexico Library in the field of medicine. By focusing on qualitative analysis, the research aims to understand and optimize the translation of medical texts. This research strategy underscores the importance of understanding cultural nuances, ensuring technical precision, and promoting readability in enhancing healthcare communication and services.

3.2. Research Design

This research design provides a structured framework for investigating the translation of specialized medical documents, focusing on a qualitative approach informed by

phenomenology. It outlines the methods, strategies, and processes used to achieve the study's objectives, detailing how data will be collected, analyzed, and interpreted to address the research questions (Creswell, 2014). This design is particularly suitable for exploring the complexities of medical translation, emphasizing the lived experiences and interpretations of both the translators and the target audience.

The research plan involves three distinct phases, each targeting a specific aspect of the translation process. The first phase focuses on qualitative analysis, using Christiane Nord's text analysis model to examine both extratextual and intratextual factors of the source texts (Nord, 1991). Extratextual factors include elements such as the purpose of the text, its intended audience, and the cultural context, while intratextual factors analyze linguistic features, style, and tone. This phase will be further enriched by exploring the phenomenology of translation, considering the translators' experiences, interpretations, and decision-making processes as they engage with the texts. This includes examining their understanding of the medical concepts, their navigation of linguistic and cultural nuances, and their reflections on the impact of their translation choices.

The second phase involves the translation of two selected documents, "Cardiología molecular. Módulo 3: Diabetes Mellitus Tipo 2" and "The Next Fifty Years." During this phase, key medical terms will be identified and standardized, culminating in the creation of a specialized glossary to ensure terminological accuracy and consistency. The phenomenological lens will continue to be applied, exploring the translators' lived experience of the translation process: the challenges they encounter, the strategies they employ, and their reflections on the meaning-making during translation.

The third phase involves a qualitative evaluation of the translation techniques employed, this phase will focus on the "why" and "how" of their application. The analysis

will delve into the translators' rationale for choosing specific techniques, exploring how these choices shape the meaning and impact of the translated text. This qualitative evaluation will also consider the potential impact of the translations on the target audience, exploring how different translation choices might be perceived and understood by medical professionals and lay readers. The phenomenological perspective will be crucial here, examining how the translated texts are experienced and interpreted by their intended recipients.

The research strategy aligns the theoretical and practical aspects of translation. The first strategic element is text analysis, guided by Nord's functionalist approach, which ensures that the translations fulfill their communicative purpose while respecting the cultural and contextual needs of the target audience (Nord, 1991). The second strategy focuses on glossary creation, addressing the challenges of maintaining consistency and accuracy in medical terminology (Groenewoud, 2011). The use of case studies as the third strategic element allows for a detailed examination of the translation process for the two selected documents, highlighting specific challenges and solutions. Finally, the strategy of qualitative evaluation explores the effectiveness of translation techniques, providing rich insights into the complexities of the translation process.

Furthermore, the use of Christiane Nord's functionalist model ensures that the analysis is purpose-driven, focusing on the communicative intent of the texts. This is particularly important for medical translation, where accuracy and clarity are critical to patient care and communication among healthcare professionals (Groenewoud, 2011). The glossary development component addresses the need for consistency in medical terminology, a factor emphasized in studies of medical translation as essential for reducing ambiguity and errors (Molina & Hurtado Albir, 2002). The phenomenological perspective adds another

layer of depth, exploring the subjective experiences and interpretations that shape the translation process and its outcomes.

In conclusion, this research design provides a comprehensive framework for investigating and addressing the challenges of translating specialized medical documents. By integrating a qualitative approach with a phenomenological lens, the study captures the full spectrum of linguistic, cultural, technical, and experiential considerations, contributing to best practices in medical translation for the Hospital Mexico Library.

3.3 Information Sources

In a translation thesis, **information sources** are the materials and references that support the research, translation processes, and theoretical framework. These sources form the foundation for analysis, guide decisions during translation, and validate research findings. Information sources are typically divided into three categories: **primary, secondary, and tertiary sources** (Creswell, 2014). Each category plays a distinct role in the research process, contributing to a well-rounded and evidence-based thesis.

3.3.1. Primary Sources

Primary sources are original, firsthand materials that are the main subject of analysis or investigation. In translation research, primary sources refer to the documents or texts undergoing translation, as these are the foundation of the study (Nord, 1991). They represent the unaltered texts that require interpretation and linguistic adaptation. For this thesis, the **primary sources** are:

- *Cardiología molecular. Módulo 3: Diabetes Mellitus tipo 2* by Jonatan Navarro Solano.
- *The Next Fifty Years* by John Brockman.

These texts are the central focus of the research, providing the basis for analyzing the translation process and developing specialized techniques.

3.3.2. Secondary Sources

Secondary sources analyze, critique, or interpret primary sources. A translation thesis, includes theoretical works, academic articles, and previous theses that discuss translation methods, theories, and relevant concepts (Creswell, 2014). These sources offer context and a theoretical foundation for the translation strategies applied in this research. The **secondary sources** for this thesis include:

- Christiane Nord's *Text Analysis in Translation: Theory, Methodology, and Didactic Application* (1991), informs the functionalist approach used in this study.
- Vinay and Darbelnet's *Comparative Stylistics of French and English: A Methodology for Translation* (2000), which outlines the translation techniques such as modulation, transposition, and omission.
- Molina and Hurtado Albir's (2002) article, *Translation Techniques Revisited: A Dynamic and Functionalist Approach,* provides a framework for analyzing the effectiveness of various translation procedures.
- Groenewoud's (2011) thesis, *Traducción Médica: Análisis de Textos no Especializados,* emphasizes the importance of terminological consistency in medical translation.

These sources support the methodological choices in the thesis, validating the translation process and ensuring alignment with established practices in the field of translation studies.

3.3.3. Tertiary Sources

Tertiary sources compile and summarize information from primary and secondary sources. In a translation thesis, they serve as reference tools for verifying terms, concepts, and stylistic conventions (Creswell, 2014). These include glossaries, dictionaries, style guides, and tools for evaluating readability. For this thesis, the **tertiary sources** include:

- Medical dictionaries and glossaries are essential for ensuring accuracy in the translation of specialized terminology.
- Style guides for academic and scientific writing, which help maintain consistency and professionalism in the translated documents.
- Readability tools, such as Flesch Reading Ease, are used to assess the accessibility of translated texts.

These tertiary sources are indispensable for maintaining terminological precision and ensuring that the translations meet professional standards.

The classification of sources into primary, secondary, and tertiary categories helps organize the research materials and ensures a structured approach to the thesis. The primary sources form the core of the research, as they are the texts being translated and analyzed. Secondary sources provide theoretical insights and frameworks that justify the translation strategies used. Tertiary sources act as reference tools to ensure accuracy, consistency, and readability in the final translations. By understanding and leveraging these categories effectively, this thesis ensures a solid foundation for achieving its objectives of accurate and culturally sensitive translations for the Hospital Mexico Library.

3.4 Analysis Categories

In a translation thesis, the term "Analysis Categories" refers to the specific criteria or dimensions used to evaluate and interpret the translation process and its outcomes. These categories play a crucial role in systematically examining the translation work, providing a structured framework for analysis. By defining these categories, researchers can ensure a thorough and consistent evaluation of the translations being studied (Munday, 2016). Within a qualitative framework, these categories can be derived from established translation methods, offering a lens through which to examine translator practices. These analytical categories facilitate the identification and analysis of translator approaches and strategies, leading to a richer comprehension of the translation process and its inherent challenges. While numerous methods exist, as outlined by Newmark (1988), such as word-for-word, literal, faithful, semantic, adaptation, and free translation, this particular study will employ the following analytical categories: translation, translation procedures, glossary, and text analysis. These specific category definitions will inform the development of more precise and detailed research instruments, allowing for a nuanced exploration of the translator's decision-making process.

Furthermore, these categories will serve as a framework for interpreting the qualitative data collected, enabling a deeper understanding of how translators navigate the complexities of meaning transfer, cultural adaptation, and target audience considerations. By focusing on these key areas, the act of translation itself, the specific procedures employed, the development and utilization of glossaries, and the comprehensive analysis of the source and target texts; the research aims to uncover the intricate interplay of factors that contribute to effective and meaningful translation. This focused approach will provide valuable insights into the strategies employed by translators to achieve accuracy, fluency, and cultural

appropriateness in their work, ultimately contributing to the broader field of translation studies.

3.5. Data Collection Instruments

In this part of the research, data collection instruments are developed and described to support the analysis and interpretation of the translation process. These instruments serve as tools to collect and organize relevant information systematically, ensuring a comprehensive evaluation of the translated texts. Each instrument is tailored to address the specific needs of the study, ensuring that the translation process is thoroughly analyzed and documented.

The first instrument is the **"Text Analysis Framework"**. This framework allows for a structured comparison of the source and translated texts by analyzing factors such as text style, function, and stylistic scale (e.g., formality, complexity, and emotional tone). Its purpose is to assess the linguistic and functional equivalence between the texts, ensuring that the translation aligns with the communicative purpose. For instance, the framework can be applied to analyze the selected texts, documenting stylistic and functional shifts.

Table 1. Text Analysis Framework

Text Analysis	"The Next Fifty Years" by John Brockman	"Cardiología Molecular. Módulo 3: Diabetes Mellitus Tipo 2" by Jonatan Navarro
Text Style		
Text Function		
Formality		
Generality or Difficulty		
Emotional Tone		

Table 1 Illustrate one of the data collection instruments.

Another crucial instrument is the **terminology glossary development**, which is designed to ensure consistency in translating specialized medical terms. The glossary includes entries for each source term, its target language equivalent, a definition or context, and the source of verification (e.g., medical dictionaries or peer-reviewed articles). This tool is particularly valuable in a medical translation project, where terminological precision is critical. The glossary is developed alongside the translation process and verified using references.

The last instrument is the color coding. Color coding is a method used to visually organize and highlight different aspects of the translation process, making it easier to identify and analyze key elements during research. In a translation thesis, color coding is often applied to categorize observations, challenges, techniques, and decisions systematically. This technique enhances readability and provides a clear framework for reviewing the translation process. Color coding involves assigning specific colors to different categories or types of information. For example, the ones that are going to be used in this work are going to be:

Table 2. Color Coding Chart

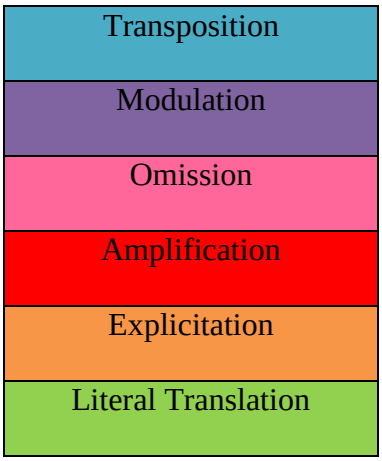

Table 2 Illustrate the color and its meaning for the color coding instrument.

Together, these instruments provide a robust framework for collecting and analyzing data throughout the translation process. They ensure that the study captures both the linguistic features of the texts and the translator's strategies, offering a comprehensive evaluation of the translation project. This approach reflects the mixed-method design of the research and supports the development of a well-rounded, systematic analysis of the translations.

3.6. Collection data process and data analysis

The data collection process for this translation thesis involves gathering relevant texts, resources, and feedback to analyze the quality, techniques, and challenges in translating medical documents between Spanish and English. This comprehensive process includes several crucial steps aimed at ensuring the accuracy and effectiveness of medical translations.

First, the selection of source texts plays a key role. Two medical texts were chosen for translation: "Cardiología Molecular. Módulo 3: Diabetes Mellitus Tipo 2" (Spanish-English) and "The Next Fifty Years"(English to Spanish). These texts were selected due to their technical nature, relevance to medical terminology, and significance for bilingual medical professionals, patients, and other translators in the area. The choice of texts is essential as it ensures that the translation process effectively addresses the complexities and nuances inherent in medical documentation.

Following the selection, a text analysis framework is employed. Each text is scrutinized for its linguistic and stylistic features, including text type, function, formality, and tone. This analysis serves to guide the translation process. A structured evaluation, similar to an established table, will be utilized to assess the differences in style, function, and difficulty between the two texts. This categorization helps in determining the appropriate translation approach for each text's unique characteristics.

Additionally, a detailed translation process logbook is maintained throughout the project. This logbook documents translation decisions, challenges encountered, strategies applied, and the rationale behind specific choices. To enhance clarity and systematic tracking, the logbook is color-coded, allowing for easier navigation through the various stages of the translation process.

Finally, a bilingual glossary is created during the translation process to standardize recurring medical terms, ensuring consistency across the translations. This glossary is continuously updated based on findings and vocabulary encountered during the translation work, providing a reliable reference for both source and target languages.

In conclusion, the data collection process also includes a document analysis framework that examines the texts for equivalence, fidelity, and naturalness in the target language. This comparative analysis focuses on specialized terminology and readability, contributing to a thorough understanding of how effectively medical documents are translated from one language to another. Through these systematic steps, the thesis aims to contribute valuable insights into the translation of medical texts between Spanish and English.

Chapter IV

Translated Texts

4.1. Translation from Spanish to English

Molecular Cardiology. Module 3: Diabetes Mellitus Type 2

Jonatan Navarro Solano

About the Author

Jonatan Navarro Solano, a Costa Rican born in San José, is a general practitioner who currently works in the private sector. He is the principal investigator for observational studies endorsed by the Ministry of Health of Costa Rica and has made several specific scientific publications in the field of Cardiology.

Since 2019 he has been dedicated to the research and study of cardiac molecular function, as he considers it of extreme importance to unveil more and more an understandable and useful way this subjects at the clinical level, for the development of future molecules that have a therapeutic role in cardiovascular pathology.

Introduction

Type 2 diabetes mellitus (T2DM) plays a very relevant role in the development of cardiovascular disease, due to its metabolic actions in the myocardium, which affect its diastolic and systolic function.

The pathophysiological processes of type 2 diabetes mellitus in the heart are produced by the different molecular pathways, which are stimulated by the new adaptation of the myocardium, generating other cardiac pathologies, such as atrial fibrillation.

To learn more about this topic, which is currently relevant, this module will analyze the behavior of cardiac molecules in type 2 diabetes mellitus, so that the information can serve as a guide for the therapeutic management of cardiovascular disease.

Based on this objective, the action of the cardiac biomarkers ST2 and galectin-3 in T2DM, the function of the type 1 sodium-glucose receptor in the myocardium, the molecular actions of ISGLT2 in the myocardium, and, finally, the relationship of the atrial fibrillation with T2DM are specifically explained.

Chapter 1. The Cardiac Biomarkers Activity in Type 2 Diabetes Mellitus

Introduction

Type 2 diabetes mellitus (T2DM) currently affects about 62 million people in the Americas, making this disease a major public health problem that needs attention. Recent studies have shown that the global annual death rate from type 2 diabetes mellitus is 1.5 million and an additional 2.2 million deaths are related to cardiovascular disease.

This last fact takes on greater relevance if we consider that prediabetes and T2DM have been associated with the development of direct myocardial damage, microvascular inflammation, and endothelial dysfunction, factors that contribute to an increased risk of cardiovascular clinical events. This is influenced by the elevation in T2DM of the biomarkers ST2 and galectin-3, which act on cardiac tissue. Hence, the importance of knowing these two biomarkers in greater depth.

ST2 (Suppression of Tumorigenicity 2)

Action of ST2 in the Myocardium

The suppression of Tumorigenicity 2 (ST2) is a protein that is part of IL-1 (interleukin 1). This biomarker is finding multiple isoforms at the tissular level, including the transmembrane known as ST2 ligand (ST2L) and the soluble circulating one (sST2).

In cardiac tissue, fibroblasts produce interleukin 33, which forms a complex together with ST2L (IL-33/ST2L), to stimulate nuclear factor (NF)-kB, to prevent detrimental actions in the myocardium, such as oxidative stress and cell apoptosis. Thus, this complex exerts cardioprotective effects, such as the reduction of myocardial fibrosis and cardiomyocyte hypertrophy, and decreases cell apoptosis, improving myocardial function.

However, the high concentration of the soluble ST2 isoform blocks the favorable effects of the IL-33/ST2L complex, increasing cardiac remodeling, with a negative impact on clinical outcomes.

Investigations of the Cardiac ST2 Biomarker in T2DM

In recent years, multiple studies have been carried out in which the relationship between the ST2 biomarker and T2DM has been analyzed. Some of them are summarized below:

- In one study, the levels and the relationship of cardiac ST2 were analyzed in three groups of people: a control group (without T2DM), a group with prediabetes, and a group with T2DM. The results showed that the concentrations of the biomarker were 37.9 ng/ml in the T2DM group, 26.1 ng/ml in the prediabetes group, and 19.3 ng/ml in the control group. On the other hand, it was determined that the risk of presenting prediabetes in the control group concerning the ST2 values did not have a statistically significant difference ($p>0.05$). However, the development of T2DM was demonstrated in the control group as ST2 values increased ($p<0.001$). In conclusion,

cardiac ST2 values are higher in T2DM, generating myocardial injury. To this day, the exact mechanism that produces this involvement is not known, although it is likely that it develops from the sST2/IL pathway.

- A group of researchers evaluated the effect of ST2 on both cardiovascular and all-cause mortality in atherosclerotic disease in a group of patients from the To Vergata Atherosclerosis Registry. Study participants were divided into four groups based on glycemic levels: the first with normal glycemic values, the second with altered glycemic levels, the third with newly diagnosed T2DM, and the fourth with an established diagnosis of diabetes. In the groups of people with diabetes, the presence of higher levels of ST2 was demonstrated, being statistically significant compared to the other groups. It was also found that elevated glycemic and glycosylated hemoglobin levels were related to increased ST2 levels (p=0.002). Finally, this biomarker was associated with higher mortality due to cardiovascular causes in diabetic patients; however, it did not present a significant risk in all-cause mortality. From this study, we conclude that ST2 is elevated in glycemic alterations, but the specific biochemical or molecular mechanism by which this molecule acts in the myocardium affected by diabetes is not very clear.
- A study in heart failure with reduced and preserved ejection fraction analyzed ST2 and BNP levels. Among the participants, 58 had T2DM, and 63 had normal glycemia levels. Higher ST2 levels were evident in the diabetic group compared to non-diabetics (72 ± 42 ng/ml vs. 59 ± 33 ng/ml; p = 0.04). In addition, elevated ST2 levels were shown to be an independent prognostic factor in diabetes and, thus, to be related to a higher incidence of T2DM.

Galectina-3

Physiological Action of Galectin-3

Galectin-3 is a protein secreted into the extracellular matrix and is translocated into the circulation by several cell types, mainly macrophages that mediate acute and chronic inflammation, as well as innate and adaptive immunity.

At the extracellular level, galectin-3 is involved in allergic and infectious processes and stimulates cell adhesion; while at the intracellular level, it acts as a pre-mRNA splicing factor and regulates the cell cycle, modulating cell proliferation, cell differentiation, and programmed cell death.

In general, galectin-3 regulates different cellular functions, such as diffusion, compartmentalization, endocytosis of plasma membrane glycoproteins and glycolipids, receptor kinase signaling, and cell membrane receptor functionality.

The increased expression of this biomarker has a major impact on cardiac remodeling, due to its adhesive and growth-regulating effects.

Investigations of cardiac galectin-3 in T2DM

Several studies have confirmed the relationship between galectin-3 and T2DM. Some of them are summarized below:

- In the Dallas Heart study it was shown that a higher incidence and prevalence of diabetes increases galectin-3 levels ($p<0.001$). In addition, it was found that this biomarker has a significant relationship with other cardiac biomarkers, such as ICAM-1 (intercellular adhesion molecule) and VCAM (vascular cell adhesion molecule), increasing their pathological actions in the myocardium.

- In a study of people with T2DM, the relationship between galectin-3 levels and cardiovascular events was analyzed. The participants were divided into two groups; the first group had primary cardiovascular outcomes (non-fatal myocardial infarction, coronary revascularization, non-fatal stroke, cardiovascular mortality); whereas the second group had none of the above cardiovascular outcomes. The results showed an elevation of galectin-3 in the first group compared to the second group ($p<0.01$). On the other hand, an increase in the biomarker of cardiovascular mortality was demonstrated. In conclusion, elevated galectin-3 was found to be associated with adverse cardiovascular outcomes in persons with T2DM, independently of traditional risk factors.
- In an investigation in which galectin-3 levels were evaluated in persons with prediabetes and T2DM, divided into three groups (a control group without T2DM, a prediabetes group, and two subgroups in group 3 with T2DM), based on the percentage of glycosylated hemoglobin (group I <7% and group II >7%), the cardiac biomarker showed values of 13.3 ng/ml ± 3.42 in the control group; 14.28 ng/ml ± 3.45 in the prediabetes group; 15.71 ng/ml ± 4.22 in subgroup I and 15.65 ng/ml ± 3.31 in subgroup II; showing that galectin-3 values increase in metabolic disease. It is remarkable that between the control group and group II (HbA1c>7%), galectin-3 showed a statistically significant elevation ($p=0.002$). In conclusion, galectin-3 can be considered an independent marker of prognosis and cardiovascular complications in T2DM.
- In an observational study conducted to evaluate the post-infarction prognostic value of galectin-3, 23.6% of the participants were found to have T2DM, and a significant relationship was demonstrated between increased galectin-3 levels and the prevalence

of T2DM. At the same time, it was shown the elevation of the biomarker is associated with post-infarction mortality, over a five-year period.

General Comments

T2DM generates myocardial involvement from glycotoxicity and lipotoxicity, causing diabetic cardiomyopathy and, from this, diastolic and systolic dysfunction, related to the elevation and compensatory mechanisms of cardiac biomarkers.

Several studies have shown that in the presence of T2DM soluble ST2 is elevated; however, the exact direct pathophysiological mechanism between the effect of diabetes and the release of the biomarkers is not yet known. It could be thought to be related to the following mechanisms, which should be evaluated in future research:

a. The direct effect of hyperglycemia in the myocardium causes glucotoxicity and lipotoxicity, generating inflammatory processes (activation of cytokines), oxidative stress (activation of reactive oxygen species), and cell apoptosis.
b. The common pathway between the toxic causes of hyperglycemia and the action of ST2 stimulates the nuclear factor (NFkB), activating inflammatory cytokines.
c. The blockade of the action of ST2L and interleukin-3 by soluble ST2 produces interstitial fibrosis, myocyte hypertrophy, and apoptosis in the myocardium, generating diastolic dysfunction.

Regarding galectin-3, studies have also shown that its levels are elevated in T2DM, causing myocardial involvement, mainly in preexisting cardiovascular disease.

It is expected that in the coming years, based on clinical and experimental studies, therapeutic development based on these biomarkers on the myocardium will be very useful,

as has been the case with the drug valsartan, which stimulates the beneficial effects of natriuretic peptides.

Summary

A summary of the effects of T2DM on cardiac ST2 and galectin-3 biomarkers is shown in Figure 1.

Figure 1. Summary of the Effect of T2DM on Cardiac ST2 and Galectin-3

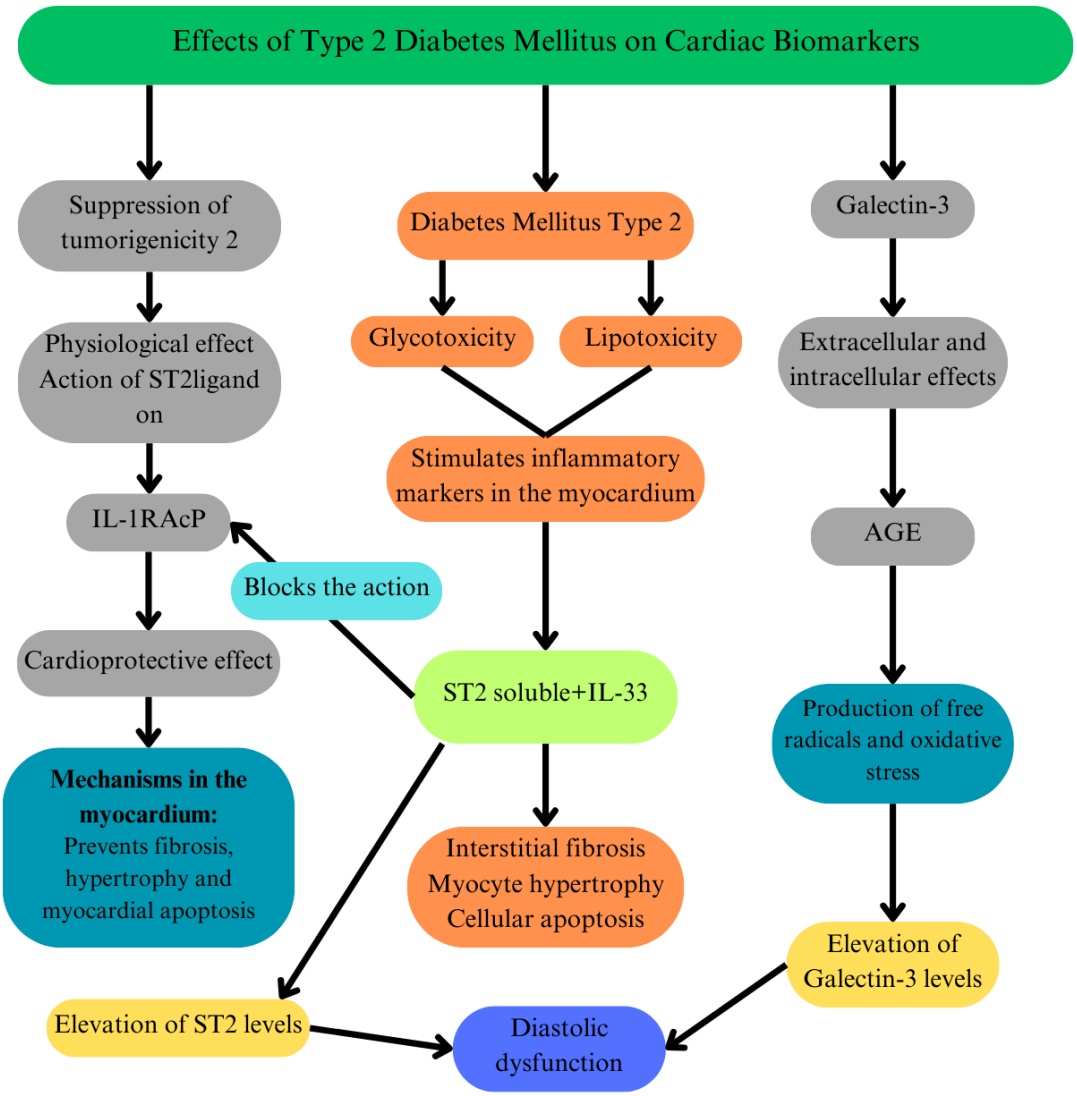

Figure 1 Biomarker effects in type 2 diabetes mellitus and cardiovascular disease. *Hyperglycemia produces toxic effects on the myocardium through glucotoxicity and lipotoxicity, stimulating inflammatory markers in the myocyte and thus generating elevation in the levels of the biomarkers ST2 and galectin-3.ST2 ligand together with interleukin 33 stimulates interleukin 1, producing a cardioprotective effect that prevents myocardial fibrosis, hypertrophy, and apoptosis; however, the binding of soluble ST2 to interleukin 33 blocks this protective action and generates interstitial fibrosis, myocyte hypertrophy, and cell apoptosis. Galectin-3, for its part, stimulates the end products of advanced glycosylation, producing oxidative stress in the mitochondrial myocyte, with the consequent elevation of biomarker levels. All this is encompassed in myocardial diastolic dysfunction.*

Chapter 2. Molecular Action of SGLT2 Inhibitors in Diabetic Myocardium

Introduction

The sodium-glucose cotransporter type 2 (iSGLT2) inhibitors reduce rates of hyperglycemia in type 2 diabetes mellitus (T2DM) by decreasing the glucose via renal reabsorption, leading to increased glucose excretion (glycosuria) and urinary sodium (natriuresis).

At the cardiac level, these drugs produce a decrease in blood pressure and in scientific studies have been shown to reduce cardiovascular mortality in various clinical scenarios (heart failure with or without T2DM).

The following sections describe the action of canagliflozin and empagliflozin on some specific molecules involved in harmful processes in the myocardium, based on scientific studies and research in patients with T2DM.

Effect of the Canagliflozin on the Myocardium

In an experimental study with a group of mice without T2DM, which underwent coronary artery occlusion to evaluate the effects of canagliflozin, specifically on oxidative stress and cell apoptosis, as well as other actions in the process of coronary ischemia/ reperfusion, it was found this iSGLT2 decreased the Bax/Bcl2 ratio, reducing cardiomyocyte apoptosis. In addition, a reduction in the expression of genes related to nitro-oxidative stress was identified, including phosphorylated p47, SOD2 (dismutase), and catalase.

On the other hand, canagliflozin demonstrated increased phosphorylation in coenzyme A carboxylase and AMPK, reducing the synthesis and accumulation of fatty acids in the cardiac cell, thus improving myocardial functionality.

The drug also stimulated the phosphorylation of eNOS (endothelial isoform of nitric oxide synthase) and increased the production of oxydonitric oxide with greater arterial vasodilatation, improving coronary perfusion.

Effect of the Empagliflozin on the Myocardium

In an experimental study performed in a group of diabetic mice, the action of empagliflozin on cardiomyocyte oxidative stress was analyzed, specifically on the Nrf2 (nuclear factor erythroid-related factor 2)/ARE (antioxidant response element) pathway and on the molecules lipid hydroperoxide (the free radical of lipid peroxidation), glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and malondialdehyde (MDA); The action of the drug on myocardial fibrosis was also analyzed in the TGF-β/Smad signaling pathway and on molecules such as TGF-β1, p-Smad2 and p-Smad3. The results showed that empagliflozin decreases lipid hydroperoxide and MDA levels, and increases superoxide dismutase and Nrf2 values; molecular actions that reduce oxidative stress. On the other hand, empagliflozin was found to suppress the TGF-β/Smad pathway, which in turn stimulates the Smad7 molecule, reducing myocardial fibrosis ($p<0.05$). Thus, we conclude that empagliflozin reduces oxidative stress in the cardiomyocyte and cardiac tissue fibrosis, improving ventricular function.

In another experimental study performed in type 2 diabetic mice with myocardial infarction, the effects of empagliflozin on the myocardium were evaluated. The results showed that this drug preserves ATP levels, generating greater availability of energy in the cardiomyocyte, and increases superoxide dismutase 2 and sirtuin 3, two molecules that decrease the production of reactive oxygen species and improve mitochondrial function in the cardiac cell.

Another experimental investigation analyzed the action of empagliflozin on cardiac microvascular endothelial cells (CEMC) following tumor necrosis factor-alpha (TNF-alpha) exposure. Physiologically, CEMC increases sarcomere length shortening and generates a faster rate and shorter time of myocardial relaxation; however, the binding of these cells to TNF-alpha decreases these effects. In this circumstance, it was determined that iSGLT2 preserves CMEC function, improving cardiomyocyte contraction and diastolic function, with an increase in relaxation velocity. A reduction of TNF-alpha in endothelial cells and a decrease in reactive oxygen species in both cytoplasm and mitochondria were also demonstrated. Based on the above, it is concluded that empagliflozin restores the physiological function of the microvascular endothelial cell, improving myocardial contraction and relaxation; in addition, it reduces tumor necrosis factor levels and the accumulation of reactive oxygen species.

On the other hand, in a study performed on endothelial cells of coronary arteries, with the objective of analyzing the effect of empagliflozin on the reduction of TNF-alpha levels, it was demonstrated that the drug decreases TNF-alpha activity and, therefore, reduces the production of reactive oxygen species, with statistically significant results (empagliflozin $p<0.05$), in addition to restoring the availability of nitric oxide, improving endothelial function of the coronary arteries.

In another experimental investigation in heart failure mice with reduced ejection fraction, were divided into two groups (one without diabetes and the other with diabetes) in order to establish the molecular mechanism of empagliflozin at the cardiac level in both groups. It was found that this inhibitor is related to the mechanism of the sodium/hydrogen exchanger type 1 (NHE1).

Physiologically, the heart of this exchanger starts with the entry of sodium into the cell and the mobilization of hydrogen ions to the extracellular space, which activates the molecule AKT1, which induces BIRC2 (baculoviral IAP repeat-containing protein 2), which degrades XIAP (X-linked inhibitor of apoptosis mediated by proteasome), and BIRC5. Subsequently, NHE1 activates NOS2 (nitric oxide synthase), stimulating inflammation and cardiac cell hypertrophy. To avoid this situation, empagliflozin inhibits NHE1, AKT 1-3, and BIRC2, allowing the expression of anti-apoptotic mediators XIAP and BIRC5; it also reduces the progression of heart failure with and without type 2 diabetes. In addition to the above, it could further decrease cardiomyocyte cell death by inhibiting the AKT-dependent protein mTOR (RAPTOR) and down-regulating the actions of NOS2.

Summary

A summary of the main actions performed by iSGLT2 in the myocardium, according to research carried out, is shown in Table 1.

Table 1. Molecular Action of iSGLT2s

Drug	Molecules Related to iSGLT2	Molecular Action
Canagliflozin	Bax (proapoptotic) Bcl2 (anti-apoptotic)	Decreased Bax/Bcl2 ratio, with reduced apoptosis.
	phosphorylated p47 SOD2 (dismutase) Catalase	Reduced expression of oxidative stress genes.
	Hydroxynonenal molecule	Reduction of oxidative stress.
Empagliflozin	Lipid hydroperoxide	Reduction of oxidative stress.

	Malondialdehyde MDA	
	Dismutase superoxide	Increased antioxidant action.
	NoX4	Reduction of its effect.
	Via Nrf2/ARE	Elevation of their levels to regulate oxidative stress.
	Via TFG-Beta/Smad	Decreased pathway and myocardial fibrosis.
	Smad 7	Increased levels and inhibition of the TFG-Beta/Smad pathway.
	SOD 2 SIRT3	Reduction of oxidative stress.
	Tumor necrosis factor-alpha (TNF-alpha)	Reduction of this molecule; decreased inflammation and improved myocardial contractility.

Chapter 3. Relationship between Type 2 Diabetes Mellitus and Atrial Fibrillation

Introduction

As mentioned in previous chapters, type 2 diabetes mellitus (T2DM) produces glycotoxicity and lipotoxicity in the myocardium, which generate deleterious effects such as oxidative stress, inflammation, and cell apoptosis. These effects give rise to fibrosis and

hypertrophy in atrial cardiomyocytes, leading to structural and electrical remodeling in the atria.

On the other hand, chronic hyperglycemia has been shown to be related to the pathogenesis of cardiac autonomic neuropathy by altering the blood perfusion of nerve structures, which produces sympathetic stimulation at the myocardial level and generates a shortening of the refractory period in the atrial cells, thus contributing to the development of atrial fibrillation.

From this context, the molecular processes generated by T2DM in the atria and the development of atrial fibrillation due to mitochondrial dysfunction and atrial electrical and structural remodeling are described below. As a complement, the action of iSGLT2 in atrial fibrillation is mentioned.

Detrimental Effects of T2DM on the Atrium

Mitochondrial Oxidative Stress in Atrial Cardiomyocytes Atrial

Reactive oxygen species (ROS) produce proarrhythmic effects, due to the modulation of regulatory domains in mitochondria, which are sensitive to the reduction-oxidation of multiple mitochondrial proteins in the atria involved in excitation-contraction coupling, including sodium channels, potassium channels, L-type calcium channels, ryanodine receptors, and the sodium/calcium exchanger.

Based on the above and considering that in T2DM there is usually oxidative stress and damage due to high levels of reactive species of high oxidative potential and a decrease in antioxidants, it is clear that this pathology leads to mitochondrial dysfunction, causing structural remodeling in the atria, including atrial tissue elongation and an increase in lipid deposits in cardiac cells and interstitial fibrosis in the atrial muscle.

In turn, this process activates proinflammatory cytokines, which cause a delay in the electrical transport of the atria. Likewise, an increase in interstitial collagen is generated, which produces an alteration of cellular coupling and propagation of the action potential.

On the other hand, T2DM in conjunction with atrial fibrillation increases nuclear transcription factor kappa B (NF-kB) signaling, involved in atrial myocyte inflammatory processes. Specifically, this molecule acts in the reduction-oxidation signaling pathway and the angiotensin cascade, improving conduction heterogeneity by promoting atrial reentry. When hyperglycemia is present, it determines the overproduction of reactive oxygen species in the vessels and decreases the availability of nitric oxide, leading to a positive regulation of NF-kB that mediates the transcription of proinflammatory genes (e.g., encoding adhesion molecules), thus perpetuating the inflammatory state.

A study by Raposeiras et al. demonstrated elevated levels of advanced glycation end products in T2DM and atrial fibrillation. This increase generates structural rigidity and loss of atrial elasticity; consequently, activation of the receptor for advanced glycation end product produces distension of the left atrium, altering its structural configuration. In addition, this activation causes an increase in the production of proinflammatory cytokines.

In addition to the above, it has been reported that another pathway involved in the pathophysiology of T2DM is the activation of the molecule transforming growth factor beta 1 (TGF-β1) in the atrium, which increases interstitial fibrosis, altering the function of ion channels, with the risk of developing atrial fibrillation.

Atrial Electrical Remodeling

The atrial electrical remodeling that occurs due to T2DM includes:

- Increase in conduction velocity.
- Heterogeneity of conduction velocity.
- Prolongation of action potential duration (APD).
- Increased incidence of APD.
- Decreased sodium channel currents.
- Increased calcium channel currents.
- Increased interatrial conduction time.

Structural Remodeling

Remodeling in the atrial structure is mainly due to diffuse interstitial fibrosis and is the main substrate of type 2 diabetes to generate atrial fibrillation; this is related to the activation of connective tissue growth factor (CTGF), which produces collagen accumulation and interferes with atrial contractility.

Other molecules involved in profibrotic signaling in the atria include angiotensin II and TGF-β1, which increase fibroblast proliferation and promote their differentiation into collagen-secreting myofibroblasts.

On the other hand, an experimental study in T2DM demonstrated that atrial fibrosis produces an increase in the dispersion of the effective refractoriness period, a decrease in sodium channel current, and an increase in calcium channels over the action potential.

Studies on the Action of iSGLT2 in Atrial Fibrillation

In a meta-analysis on the use of iSGLT2 in cardiovascular disease and T2DM, a significant reduction in the incidence of atrial fibrillation was demonstrated. Also, an increase

in mitochondrial function and a reduction in oxidative stress in atrial cardiomyocytes was documented, improving electrical action in atrial fibrillation.

On the other hand, in a cohort study in which the risk of mortality from cardiac causes and the risk of developing arrhythmias in T2DM with the use of iSGLT2 was evaluated, it was determined that iSGLT2 reduced both mortality from cardiovascular causes and cardiac events due to atrial fibrillation.

Empagliflozin

A substudy of the EMPA-REG OUTCOME trial evaluated the efficacy of empagliflozin in atrial fibrillation, as well as cardiovascular outcomes (cardiovascular mortality, hospitalization for heart failure, and all-cause mortality) and renal outcomes (worsening renal function) in two groups: one with patients with atrial fibrillation and the other with patients without atrial fibrillation.

In the group with atrial fibrillation, empagliflozin showed a greater reduction in cardiovascular events, including death from this cause, and a decrease in the worsening of nephropathy; the number of events prevented was greater in this group than in those without atrial fibrillation. Based on these results, the investigators considered the use of this drug beneficial in patients with diabetes, cardiovascular events, and atrial fibrillation.

Dapagliflozin

A substudy of DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58), evaluated the effect of dapagliflozin on the development of atrial fibrillation in persons with T2DM. The results demonstrated a 19% reduction in arrhythmia generation with the use of dapagliflozin compared to placebo. In

addition, this iSGLT2 generated a significant reduction in the number of cardiovascular events due to atrial fibrillation compared to placebo ($p=0.005$); specifically, this decrease was 12.4 % with dapagliflozin and 15.2 % with placebo.

Molecular Effect of iSGLT2 on Atrial Fibrillation

In an experimental study of mice with induced T2DM, divided into four groups (control; without the use of drugs; with low doses of empagliflozin; and with high doses of empagliflozin for eight weeks), the effect of this drug on atrial remodeling caused by diabetes mellitus was evaluated based on echocardiographic parameters, metabolic and inflammatory factors, oxidative stress and others. Regarding echocardiographic parameters, it was determined that both left atrial diameter and left ventricular posterior wall stiffness were elevated in the non-drug group ($p<0.005$), while in the high-dose empagliflozin group there was a reduction in the values of both parameters ($p<0.05$).

Regarding biochemical markers, a reduction in total cholesterol and glycemia was identified in the fourth study group compared to the second group ($p<0.03$).

In the case of inflammatory markers, a reduction in high-sensitivity C-reactive protein levels was observed in the empagliflozin groups.

At the molecular level, an increase in SOD (superoxide dismutase) molecule levels was observed in the groups using empagliflozin ($p<0.05$), increasing its antioxidant action. It was also observed that empagliflozin reduced the levels of the molecule MDA (malondialdehyde), related to oxidative stress, compared to the no-drug diabetes group ($p<0.05$).

In addition to the above, several mitochondrial molecules were analyzed, such as PGC-1a (peroxisome proliferator-activated receptor c coactivator 1a), which promotes mitochondrial biogenesis and is regulated by AMPK (adenosine monophosphate kinase), which has metabolic effects. At the same time, Tfam (mitochondrial transcription factor A) and NRF-1 (nuclear respiratory factor 1), which activates nuclear genes for mitochondrial respiration, transcription, and mitochondrial DNA replication, were evaluated. The values of these molecules remained reduced in the diabetes group, whereas in the empagliflozin group, they were elevated, increasing mitochondrial function. Other molecules analyzed were Mfn-1 (mitofusin 1) and OPA-1 (optic atrophy 1), which generate mitochondrial fusion; in this case, all their values increased with the use of empagliflozin, regulating and improving mitochondrial function.

On the other hand, empagliflozin showed a reduction in interstitial fibrosis compared to the drug-free diabetes mellitus group ($p<0.05$). In the case of atrial fibrillation, its development was significantly reduced (up to 36.8%) with high doses of this iSGLT2.

Conclusion

Based on the above, it is concluded that mitochondrial dysfunction is related to atrial remodeling caused by diabetes mellitus, through the production of reactive oxygen species, which damage the mitochondrial membrane and affect its action in the function of atrial cardiomyocytes. They also alter calcium consumption, promote cellular respiratory dysfunction, and produce cardiomyocyte apoptosis. Mitochondrial damage generates an increase in the extracellular matrix, causing altered contractility, hypertrophy, and fibrosis in the left atrium. This leads to electrical alterations in conduction or repolarization in both ventricles and atria.

Summary

T2DM is a cause of atrial fibrillation and participates in pathophysiology such as oxidative stress, and structural and electrical remodeling.

The iSGLT2s, such as empagliflozin and dapagliflozin, have demonstrated clinical benefits such as reduction in cardiovascular mortality and atrial fibrillation-related events. Future scientific studies are expected to indicate the specific management of these drugs in atrial fibrillation with and without the presence of T2DM.

A summary of the main effects of these iSGLT2 at the atrial level is shown in Table N° 1.

Table 1. Effects of iSGLT2 at the Atrial Level

Metabolic	They reduce glycotoxicity and lipotoxicity, leading to a decrease in oxidative stress.
Structural	Reduce interstitial fibrosis and atrial myocyte hypertrophy
Electric	They optimize calcium consumption; improve conduction velocity by activation of sodium channels; and reduce atrial electrical reentry pathways and interatrial conduction time.
Mitochondrial	Reduce oxidative stress: • Increase of superoxide dismutase molecule. • Reduction of MDA.

	Enhances mitochondrial respiration: • Increases PGC-1α. • Promotes mitochondrial biogenesis. • Upregulation of NRF-1. • Activation of nuclear genes for mitochondrial respiration and DNA replication. • Increased Tfam. • Produces mitochondrial transcription.
	Benefit cell fission and fusion: • Fission: increase DRP-1. • Fusion: increase Mfn-1 and OPA-1.

4.2. Translation from English to Spanish

Los próximos cincuenta años por Jhon Brockman

Parte dos: El futuro en práctica

Mente, cerebro y ser

(Joseph Ledoux)

El joven Sigmund Freud comenzó su carrera científica estudiando el sistema nervioso y creía que los secretos de la vida mental se esclarecerían mediante la comprensión del funcionamiento del cerebro. Como pronto se dio cuenta de que las herramientas disponibles

para estudiar el cerebro no estaban lo suficientemente avanzadas como para poner en práctica su creencia, se decantó por un enfoque puramente psicológico. En los años transcurridos, la neurociencia se ha convertido en una disciplina floreciente, y sus descubrimientos asombrarían a Freud. Aun así, queda mucho por aprender y aquí se describen algunos de los avances que podemos esperar en los próximos años.

Leyendo el cerebro

La investigación neurocientífica ha recorrido un largo camino para revelar cómo ciertos aspectos de la mente, como la percepción, la memoria y la emoción, están mediados por el cerebro. Gran parte de este trabajo ha implicado el estudio de organismos no humanos, especialmente ratas y monos. Aunque este enfoque es adecuado para realizar preguntas acerca de las funciones cerebrales que los humanos comparten con otras criaturas, ha dejado importantes brechas en nuestra comprensión de los aspectos únicos del cerebro humano. La investigación en humanos con lesiones cerebrales ha ayudado a cerrar la brecha pero los estudios en sujetos con lesiones cerebrales tratan tanto de cómo el cerebro compensa la pérdida de la de función como de la función normal.

Las técnicas existentes nos estás proporcionando poderosas herramientas para evaluar lo que ocurre en los cerebros y mentes de las personas. A medida que estas técnicas mejoren, tendremos que preguntarnos como sociedad si estamos preparado para lo que esta investigación nos deparará. Cuando sea posible mirar dentro del cerebro y ver lo que alguien piensa o siente, para predecir, decir, si es probable que alguien sea un asesino, un pederasta o un violador, ¿qué haremos con esta información?

La gestión de la memoria

Cada vez que formas un recuerdo, tú ajustas la escritura, la conectividad sináptica, de tu cerebro. Ya sea algo tan trivial como el color de las calcetas que te pusiste esta mañana o tan significativo como el sonido de la voz de tu madre, la memoria es un proceso de ajuste de conexiones entre neuronas. En términos sencillos, esto es así: Las neuronas que participan activamente durante una experiencia experimentan ciertos cambios químicos que activan genes e inician la síntesis de proteínas en el interior de estas células activas. Las proteínas se envían a las sinapsis activas de las células activas, donde alteran la habilidad de esas sinapsis, únicamente esas, para recibir mensajes de las neuronas que están conectadas. La memoria se materializa en esos cambios. Podemos esperar, dado a lo que ya sabemos, que en el futuro cercano sea posible gestionar la memoria de varias maneras.

Ahora que las personas viven más años, cada vez son más los que sufren problemas de memoria relacionados a la edad. Estos problemas son más evidentes en personas con Alzheimer y otras enfermedades neurológicas, pero la memoria también flaquea en personas mayores sin trastornos cerebrales específicos. Los científicos intentan utilizar la información obtenida en estudios sobre la memoria de animales tan diversos como las babosas marinas, las moscas, las ratas, los conejos y los monos para desarrollar formas para mejorar la memoria humana. Está bien establecido, por ejemplo, que muchas formas de la memoria dependen del neurotransmisor glutamato y de sus receptores. Una estrategia para mejorar la memoria es el desarrollo de fármacos que facilites la transmisión del glutamato. Además, un importante paso en la formación de la memoria en el flujo de iones químicos (especialmente calcio) a través de los receptores de glutamato en las neuronas; el aumento de calcio provoca entonces la activación de moléculas que a su vez activan genes. El desarrollo de fármacos dirigidos a estos procesos dentro de nuestras células cerebrales (Es decir, intentar mejorar su habilidad para activar los genes que fabrican las proteínas que estabilizan el tejido sináptico que subyace a la memoria) ofrece otra estrategia para mejorar la función de la memoria.

Pero, ¿qué hay de arreglar los cerebros de las personas con problemas neurológicos como la enfermedad de Alzheimer? El reciente descubrimiento de que las nuevas neuronas del cerebro en un adulto son hechas en el hipocampo, una región del cerebro de gran importancia para nuestra habilidad de recordar conscientemente, ofrece una nueva esperanza. Si estas células pueden de alguna manera ser alentadas a conectarse con los circuitos degenerativos de la memoria y así participar en ellos, quizás se pueda restaurar la función de la memoria. Y si el gobierno federal desata las manos de los investigadores y les permite proceder con mayor libertad en la investigación con células madre, quizá pueda ser posible evitar condiciones como el Alzheimer se presenten en personas susceptibles de padecerlas.

Otra área donde la ciencia del cerebro podría tener un impacto importante en la creación o eliminación de recuerdos no deseados, especialmente los traumáticos. Estas memorias constituyen el núcleo de enfermedades como el trastorno de estrés postraumático, y si se pueden cortocircuitar, el trastorno podría mejorar en cierta medida. Los investigadores han ideado formas de alterar el destino de los recuerdos mientras estos se están formando y estabilizando; esto podría conducir al desarrollo de fármacos que podrían administrarse poco después de algún acontecimiento muy estresante y así evitar el desarrollo de recuerdo traumáticos. Pero como la estabilización de la formación de la memoria solo tarda unas horas (El tiempo que tardan las proteínas en fabricarse y utilizarse), este método tendrá una aplicación limitada y es posible que exista una alternativa.

Nuevos estudios en ratas han demostrado que determinadas memorias bien formadas pueden verse alteradas si se interfiere con las proteínas en el lugar de la memoria en el cerebro durante el proceso de rememoración de la experiencia. Pero para ser útil en el desmantelamiento de recuerdos traumáticos en humanos mientras se mantienen intactos otros recuerdos, el fármaco operativo tendrá que dirigirse a las áreas implicadas en los

recuerdos traumáticos. Esto, a su vez, requerirá que encontremos el lugar de formación de la memoria traumática en el trastorno de estrés postraumático, así como alguna forma de restringir el fármaco en esa región. Consideraremos este punto más adelante.

Por supuesto, aunque sea posible debilitar o no eliminar los recuerdos perturbadores de los humanos, no es algo que debamos tomar a la ligera. Imagine a una víctima del Holocausto que ha vivido durante décadas con los recuerdos de los campos de concentración. Sin duda, estos recuerdos se han arraigado como parte de la personalidad de la víctima. Aunque la persona pueda sentirse gravemente perturbada por esos recuerdos, ¿qué ocurriría con el tejido de su personalidad si se eliminara un conjunto de episodios que se han convertido en una parte central de su vida?

Los avances científicos a veces se convierten en parte de la vida diaria. Así pues, podríamos llegar a ver el día en que se utilicen medicamentos sin receta para dar una experiencia concreta y una representación especialmente fuerte en el cerebro. Supongamos que desea recordar un cumpleaños o aniversario de bodas en particular. Justo antes de la fiesta, tome una pastilla que haga que el glutamato y otra molécula funcionen de forma más eficiente y todo lo que ocurra se grabará en su cerebro con todo lujo de detalles.

El recableado recreativo no es tan descabellado como parece. Nosotros organizamos situaciones todo el tiempo para aumentar el impacto emocional de las experiencias y hacer que nuestros recuerdos de ellas sean vívidos y duraderos. Tomar un medicamento para conseguirlo es sólo una forma diferente de hacer lo mismo. Es menos romántico regalar a su cónyuge una pastilla en su aniversario que un ramo de flores, pero la píldora puede conseguir el resultado deseado (una velada memorable) de forma más eficaz. O puedes arriesgarte y probar tanto la píldora como el ramo de flores.

Medicamentos inteligentes

Macbeth anhelaba por “algún dulce antídoto ignorante” contra la tristeza. En la actualidad disponemos de una serie de fármacos que ayudan con bastante éxito a tratar la depresión y otros trastornos psiquiátricos pero los fármacos tienen un precio: los efectos secundarios. Dentro de cincuenta años, o antes, los fármacos tratarán las redes problemáticas del cerebro sin afectar a otras. Para crear esos fármacos, tendrán que producirse varios avances.

Primero tendremos que aprender más sobre cuáles son exactamente las redes que presentan problemas en trastornos específicos. Las técnicas de imagen cerebral ya empiezan a ser útiles en este sentido. Los estudios están mostrando en qué se diferencian los cerebros de las personas con depresión, trastornos de ansiedad o esquizofrenia de los de las personas que no padecen estas afecciones. Pero para entender estas diferencias, necesitamos saber más sobre el funcionamiento normal de las áreas identificadas.

Por ejemplo, es una suposición razonable, dados los datos existentes sobre animales y humanos, que los trastornos relacionados con el miedo (ataque de pánico, trastorno de estrés postraumático, ansiedad generalizada, fobia, esquizofrenia paranoide) son el resultado de alteraciones en la forma en que las redes cerebrales del miedo funcionan normalmente e interactúan con otras redes. Dado que la amígdala, como hemos visto, es una parte clave de estas redes, las alteraciones en el funcionamiento de la amígdala podrían explicar ciertos aspectos de la ansiedad. En concreto, el miedo excesivo e inapropiado podría producirse porque la amígdala es hipersensible, detectando el peligro y respondiendo a la defensiva ante una situación que otra persona ignoraría; o la amígdala podría ser demasiado reactiva, respondiendo con una defensa más enérgica de lo que lo haría otra persona ante el mismo grado de amenaza. Cualquiera de estas condiciones puede deberse a la genética, a

experiencias traumáticas o estresantes, o a una combinación de ambas. Además, cualquiera de estos efectos puede verse acentuado por la forma en que otras regiones cerebrales conectadas con la amígdala regulan su funcionamiento. Y las distintas condiciones pueden explicarse por diferentes alteraciones de los circuitos dentro de la amígdala, o entre la amígdala y otras áreas. Si los estudios de imagen determinan que la amígdala (o cualquier otra área) se ve afectada en los trastornos de ansiedad, la aclaración de la función de la región y su interacción con los estudios son otros sistemas que serán fundamentales para inventar nuevas estrategias de tratamiento. Pero incluso ahora, cuando las imágenes demuestran la implicación de determinadas regiones cerebrales en trastornos humanos como la ansiedad, los estudios con animales siguen siendo importantes para comprender los mecanismos neuronales detallados a nivel de células y sinapsis en esa región; en última instancia, el desarrollo de nuevos y mejores medicamentos depende de este nivel de conocimiento.

Una vez que los estudios de imagen en humanos indiquen la implicación de redes específicas en una enfermedad concreta y los estudios en animales esclarezcan la organización detallada de esas redes, podremos buscar fármacos dirigidos a los circuitos afectados. Una estrategia consistiría en aprovechar los avances de la genética molecular: Si podemos identificar alguna molécula que sólo se manifieste en la amígdala, o que se manifieste allí de alguna manera concreta, podría ser posible utilizar esa molécula como clave para descubrir un fármaco. Es decir, el fármaco seguiría tomándose por vía oral y seguiría viajando ampliamente por el torrente sanguíneo hasta muchas regiones cerebrales; sin embargo, debido al empaquetamiento molecular del fármaco, sería inerte en la mayoría de las regiones cerebrales. Sólo cuando encuentra la clave molecular, que en este ejemplo hipotético sólo está presente en la amígdala, la droga se activa. Un fármaco de este tipo podría ayudar a corregir la función anormal de la amígdala sin afectar a otras regiones cerebrales, reduciendo así los efectos secundarios psicológicos no deseados causados por la acción generalizada del

fármaco. Pero como la amígdala también participa en funciones cerebrales “normales”, el verdadero reto será encontrar alguna forma de atacar selectivamente las funciones alteradas.

La defensa de la amígdala

La amígdala, como muchas otras regiones cerebrales, trabaja fuera de nuestra conciencia. Podemos darnos cuenta de las consecuencias de la activación de la amígdala, pero no tenemos acceso consciente a su funcionamiento interno. Dado que se puede provocar a la amígdala para que exprese respuestas emocionales controladas inconscientemente, se plantea la posibilidad de que la amígdala pueda cometer inconscientemente un delito que la persona consciente nunca aprobaría voluntariamente.

Esta posibilidad no ha escapado de los abogados. El sistema jurídico reconoce desde hace tiempo los "crímenes pasionales", en los que una persona razonable y respetuosa de la ley comete un delito durante un lapso de racionalidad o cordura. La “defensa de la amígdala” añade un fundamento neurológico a este tipo de argumentos. A medida que conozcamos mejor el funcionamiento del cerebro y los abogados sepan más sobre lo que se ha descubierto, las defensas con base neurológica serán cada vez más comunes. Así que echemos un vistazo rápido a lo que quiero decir con la defensa de la amígdala.

En primer lugar, la defensa de la amígdala no debe confundirse con una problemática relacionada, que podemos denominar defensa del cerebro patológico. En esta última, el argumento es que la persona cometió un delito debido a alguna alteración física en su cerebro. La defensa de la amígdala, por el contrario, se basa en la noción de que la amígdala normalmente controla el comportamiento emocional de forma inconsciente y, como resultado, es posible que la amígdala cometa un delito independientemente del pensamiento consciente. Está claro que es posible que la amígdala controle un acto agresivo independientemente del control consciente en determinadas circunstancias provocativas; sin

embargo, para que la defensa de la amígdala funcione, tendrían que cumplirse varios criterios.

Una tarea importante de la amígdala es iniciar rápidamente respuestas protectoras ante un peligro repentino. Pero si el estímulo ha estado presente durante algún tiempo y se ha percibido conscientemente, el comportamiento tiende a estar bajo el control de procesos superiores, mediados por el córtex. Además, los tipos de respuestas dirigidas por la amígdala son respuestas rápidas, sencillas e innatas (programadas) que se ejecutan de forma estereotipada, es decir, de forma similar en todos los miembros de la especie. Así pues, si un acto es deliberado, se expresa con relativa lentitud (a lo largo de segundos en lugar de milisegundos), implica una secuencia compleja de movimientos y se llevará a cabo de forma diferente en distintas personas, es probable que no esté controlado directamente por la amígdala. La amígdala puede influir o modular indirectamente estas respuestas más complejas, pero, al final, son asunto de otros sistemas cerebrales. Estos hechos sugieren que para que la defensa de la amígdala tenga éxito, el delito tendría que implicar una respuesta estereotipada, innata y relativamente simple, ejecutada instantáneamente y sin premeditación al producirse la provocación.

Sospecho que pocos delitos cumplirán los criterios necesarios para que la defensa de la amígdala tenga éxito. Sin embargo, cada vez es más evidente que muchos sistemas cerebrales distintos de la amígdala funcionan de forma inconsciente, e incluso que la propia conciencia es producto del funcionamiento inconsciente de las redes cerebrales, lo que plantea la posibilidad de que, aunque la defensa de la amígdala sea errónea de nombre, siga siendo válida en espíritu. Sin embargo, que tengamos que reconsiderar la naturaleza y los límites de la responsabilidad humana dependerá de futuros descubrimientos sobre el

equilibrio entre el control consciente e inconsciente del cerebro. También es probable que se produzcan en los próximos cincuenta años.

Fármacos, ADN y el diván del analista

(Samuel Barondes)

En 1950, un químico en Rhône-Poulenc, una compañía francesa farmacéutica, modificó la estructura de un antihistamínico y accidentalmente creó un fármaco que podía eliminar el pensamiento psicótico de las personas con esquizofrenia. Dentro de unos años, el nuevo fármaco se convirtió famoso mundialmente como clorpromazina (Largactil), la primera medicación verdaderamente efectiva para un trastorno mental incapacitante. Debido a su efecto impactante, la clorpromazina establece un nuevo camino para la psiquiatría por el resto del siglo veinte.

El gran éxito de la clorpromazina estimuló una vigorosa competencia por parte de otras empresas farmacéuticas. En los años cincuenta, la búsqueda de más medicamentos antipsicóticos condujo a un descubrimiento accidental de otros dos tipos de fármacos psiquiátricos. Primero Geigy, una compañía farmacéutica suiza, surgió con una versión de uno de sus antihistamínicos que, aunque fuera inservible contra la psicosis, probó ser un valioso tratamiento para la depresión severa. Nombrada imipramina (Tofranil), pavimentando el camino para muchos antidepresivos contemporáneos. Luego Hoffman-La Roche, otra compañía suiza, creó el clordiazepóxido (Librium), el cual tampoco ayuda a la psicosis pero alivia la ansiedad. Fue seguido prontamente por otro benzodiacepínico, el diazepam (Valium), el cual se convierte en el fármaco más vendido en América durante aproximadamente una década, a partir de mediados de los sesentas.

A la expectación generada por estos fármacos se sumó una avalancha de descubrimientos sobre sus efectos en los neurotransmisores, una clase de químicos cerebrales que transmiten señales entre las células nerviosas. Por los años setenta fue descubierto que el clorpromazina bloquea ciertas acciones de un neurotransmisor llamado dopamina; la imipramina aumenta la acción de varios neurotransmisores, incluyendo la norepinefrina (Noradrenalina) y la serotonina; y el diazepam amplifica los efectos de otro neurotransmisor llamado ácido gamma-aminobutírico (GABA, por sus siglas en inglés). En cada caso, el resultado neto es un cambio en el señalamiento de los circuitos cerebrales que controlan los aspectos emocionales del comportamiento.

Estos descubrimientos incitaron una búsqueda por otros químicos que pudieran tener efectos similares en la neurotransmisión pero con menos indeseables efectos secundarios que los originales. La búsqueda dio sus frutos con un flujo de nuevos medicamentos que los pacientes prefieren. El más famoso, fluoxetina (Prozac), fue inicialmente identificado como un químico que prolongaba la neurotransmisión por la serotonina; posteriormente se demostró que era un tratamiento eficaz tanto para la depresión severa y la moderada. Llamada un ISRS (inhibidores selectivos de la recaptura de serotonina), prolongando los efectos de la serotonina inhibiendo su recaptación por los nervios que la liberan, la cual es la forma normal en el que la señalización de la serotonina se termina. En los fármacos relacionados se incluyen sertralina (Zoloft), paroxetina (Paxil), fluvoxamina (Luvox) y citalopram (Celexa), seguidos rápidamente.

A medida que aumentaba la experiencia con los ISRS, los psiquiatras se dieron cuento que estos medicamentos también podrían ayudar a la gente que no está depresiva. Las ISRSs se han convertido en un tratamiento establecido para los ataques de pánico no provocados (trastorno de pánico) y de preocupación incontrolable (trastorno de ansiedad generalizado)-

efectos beneficiosos confirmados por comparaciones formales con placebos en ensayos controlados.

La eficacia de estos y de otros nuevos medicamentos transformaron la psiquiatría. Antes de que aparecieran estos fármacos, la mayoría de los psiquiatras pensaban en sus pacientes en términos puramente psicológicos y se interesaban sobre todo por tratarlos con psicoterapia. Ahora la atención se ha desviado hacia el cerebro y que el tratamiento psiquiátrico frecuentemente incluye al menos una medicación. Diez millones de americanos toman fármacos psiquiátricos.

Pero, por valioso que sean, los fármacos que sustituyeron la clorpromazina, imipramina y clordiazepóxido son simples versiones modificadas de los originales. Ninguno de ellos es sustancialmente más efectivo y todos ellos tienen algunos indeseables efectos secundarios. A pesar del extensivo conocimiento acerca de sus efectos en neurotransmision, el desarrollo de nuevos fármacos continua basándose en un método de prueba y error similar al utilizado en los años cincuenta.

No es probable que el próximo gran paso de la psiquiatría consista en seguir perfeccionando los fármacos y las psicoterapias que definen el campo en la actualidad. Vendrá, en cambio, de los descubrimientos sobre las variaciones genéticas humanas y la forma en que afectan al cerebro. Del mismo modo que las historias reveladoras de los divanes de los psicoanalistas guiaron la psiquiatría en la primera mitad del siglo veinte, y los productos de los malolientes laboratorios de química la guiaron en la segunda mitad, los conocimientos sobre las diferencias genéticas individuales guiarán la psiquiatría en los próximos cincuenta años.

El conocimiento de las diferencias genéticas individuales es tan prometedor para la psiquiatría porque ayudará a responder a una pregunta fundamental: ¿Qué determina la

susceptibilidad individual al comportamiento pertubado? Las experiencias pasadas de una persona juegan claramente un papel escencial. Pero ¿por qué una persona trasciende las dificultades mentales repetidas, mientras que otra cae fácilmente en un estado de angustia? y ¿por qué una persona sucumbe a la depresión, otra a la ansiedad sostenida y una tercera al retraimiento y los delirios de la esquizofrenia?

La mejor pista que tenemos es que todos estos patrones de comportamiento perturbado se dan en familias. Considere, por ejemplo, el riesgo de volverse esquizofrénico. La mayoría de las personas tiene una posibilidad entre cien de desarrollar el patrón característico de síntomas. Pero si usted tiene uno de los padres o hermanos que es esquizofrénico, su riesgo de por vida es ocho veces mayor. Lo mismo ocurre con la otra causa principal de psicosis, la enfermedad maníaco-depresiva, también conocida como trastorno bipolar. De nuevo, el riesgo general es de uno por cada cien, pero el riesgo es ocho veces mayor si uno de los padres o hermanos padece este transtorno. La depresión y los desórdenes de ansiedad son tambien familiares.

No hace mucho tiempo, estos estudios de familias provocaron explosivos debates entre quienes los consideraban pruebas de la existencia de patrones familiares aprendidos de comportamiento anormal y quienes los consideraban pruebas de la existencia de una predisposición hereditaria a los trastornos mentales. Ahora la mayoría de las personas estan de acuerdo en que tanto el entorno como la herencia juegan algún papel. Tambien coinciden en que el mejor paso siguiente para evaluar la importancia de la herencia es tratar de encontrar las formas alternativas de los genes implicados.

El principal catalizador de este acuerdo ha sido el desarrollo de potentes técnicas para la examinación completa de las formas alternativas de los genes humanos, llamados alelos, o variantes genéticas. Estas variantes que surgen por cambios aleatorios en la estructura del

ADN son responsables de gran parte de la diversidad humana, incluidas las diferencias en susceptiblidad a determinadas enfermedades pero hasta hace poco su existencia sólo podía inferirse. Las nuevas tecnicas hacen posible de identificar las variantes genéticas específicas que contribuyen a un atributo humano. En lugar de discutir acerca de la importancia relativa de la naturaleza y la crianza, ahora podemos centrar nuestra atención en la búsqueda de varantes genéticas que contribuyan a la prdisposición individual a una enfermedad.

Una manera de encontrarlos es comparando el ADN de los miembros de la famiilia que padecen la enfermedad con aquellos que no la padecen. Si solamente esos que padecen la enfermedad tienen una determinada variante de un gen en particular, es probable que la correlación sea significativa. Si la misma variante es también encontrada solamente en los miembros afectados de otras familias, el caso se refuerza. En algún momento la probabilidad llega a ser tan alta que se establece un rol para la variante. En la década de los noventa, a medida que se iban conociendo los detalles acerca de la estructura genética humana, se identificaron algunas variantes genéticas que afectaban a la sucsceptibilidad a determinadas enfermedades. Ejemplos famosos incluyen la variante de tres genes diferentes que cada uno incrementa en gran medida el riesgo de desarrollar tipos raros de la enfermedad de Alzheimer que empieza antes de los cincuenta años. En un grupo de familias el culpable fue una variante de un gen llamado APP; en otra era PS1 y en una tercera fue el PS2.

El descubrimiento de variaciones genéticas que incrementan el riesgo de padecer tipos raros de Alzheimer ha estimulado los estudios genéticos de la esquizofrenia, la depresión, la depresión maníaca y de otros trastornos psiquiátricos. El inmenso atractivo de estos estudios es que no dependen de conjeturas acerca de qué genes podrían estar implicados, porque pueden diseñarse para detectar una correlación entre el trastorno y una variante de cualquier gen humano. Aunque muchos de los estudios se centraron en genes específicos,

especialmente en los que influyen en la neurotransmision, sabemos tan poco del control genético de los procesos mentales que no sería sorprendente que estuvieran implicados otros tipos de genes. Desafortunadamente, a pesar de años de esfuerzo, nadie ha encontrado una variante genética que aumente definitivamente el riesgo de padecer alguna de estas enfermedades mentales. Tampoco ha habido mucho éxito en los estudios genéticos de otros trastornos comunes, como la diabétes y la presión arterial elevada. Una razón para la falta de progreso es que la susceptibilidad a todos estos males está determinada por las acciones combinadas de variantes de múltiples genes y no por variantes de un único gen. A pesar de que la tecnología actual ha hecho relativamente simple de identificar las variantes extrañas de los genes individuales que si tienen un efecto importante en el riesgo, como el APP, el PS1 o el PS2, sigue siendo muy difícil encontrar aquellas variantes genéticas que aumentan el riesgo sólo si se heredan en conjunto con otras.

Esta dificultad disminuirá pronto debido al continuo crecimiento de los conocimientos sobre el genoma humano. La reciente publicación dde la estructura detallada del ADN humano es un primer paso fundamental. Ahora el ADN de muchas personas esta siendo examinado para identificar y catalogar las variantes comunes de cada uno de los aproximadamente treinta mil genes humanos. Esto simplificará enormemente la búsqueda de las numerosas variantes genéticas que pueden operar conjuntamente para influir en la vulnerabilidad a los transtornos mentales. La búsqueda también se está simplificando debido al desarrollo de nuevas técnicas eficaces para el examen detallado del ADN de cualquie individuo. Estas técnicas están en continuo desarrollo, lo que recuerda el desarrollo permanente de los chips informáticos. Lo mismo ocurre con los métodos computacionales utilizados para analizar la gran cantidad de información procedente de estos estudios del ADN.

Con la evolución de la tecnología de recopilación y evaluación de grandes cantidades de datos de ADN pronto será posible realizar una búsqueda masiva de los grupos de variantes genéticas que influyen en la susceptibilidad a determinados trastornos mentales. A medida que los costes de los análisis de ADN sigan bajando, podriamos ir más allá de los estudios de familias relativamente pequeñas y analizar muestras de ADN de miles de personas no emparentadas con un trastorno en particular. Dicha investigación debe identificar las variantes genéticas relevantes de las cuales solo algunas se encontrarán en cada individuo afectado.

Para utilizar adecuadamente esta masa de datos sobre variantes genéticas será necesario correlacionarlos no solo con patrones de conducta desordenada, sino también con propiedades del cerebro. Se están empezando a utilizar diversos métodos nuevos, como la resonancia magnética funcional, para evaluar las funciones de regiones específicas de cerebros humanos individuales. La correlación de los patrones de variantes genéticas con los resultados de estos y otros estudios permitirá identificar subtipos de trastornos que actualmente se agrupan en categorías diagnósticas, como la esquizofrenia o la depresión.

La combinación de información genética y estudios funcionales proveerá objetivos para medicamentos realmente novedosos, un método que ya se utiliza para encontrar nuevos tratamientos contra el Alzheimer. Actualmente, los principales fármacos para el Alzheimer mejoran el funcionamiento del cerebro prolongando las acciones del neurotransmisor llamado acetilcolina, un mecanismo similar a las acciones de otros fármacos contemporáneos, como los ISRSs. La identificación de variantes de APP, PS1 y PS2 en casos raros de Alzheimer ha contribuido a centrar la atención en objetivos farmacológicos alternativos. Llamadas secretasas, son las enzimas que forman parte en la producción de una proteína tóxica fragmentada llamada beta amiloide, cuya acumulación es también afectada por las

variaciones genéticas de diferentes maneras. Muchas de las compañías farmacéuticas están estudiando fármacos que inactiven las secretasas, que esperan utilizar para reducir la acumulación de beta amiloide y detener así la degeneración cerebral.

Además de encontrar nuevos objetivos farmacológicos, los estudios de ADN pueden identificar variantes genéticas que distinguen a las personas que se benefician de los fármacos disponibles, como los ISRSs, de los que no. Tales distinciones pueden ser causadas por las variantes particulares que predisponen un individuo a padecer un trastorno mental y a otras que determinan cómo la droga afecta al cerebro. Lo mismos datos del ADN también pueden revelar variantes genéticas que influyen en la vulnerabilidad individual a determinados efectos secundarios de los fármacos. Toda esta información genética va a guiar la selección de tratamientos para cada paciente.

Los datos del ADN pueden ayudar a redefinir los límites entre las diferentes enfermedades mentales que a menudo se superponen. También lo hacen los límites entre los patrones de comportamiento que llamamos normal y aquellos que clasificamos como trastornos. Combinando la información acerca de las variantes genéticas con estudios del funcionamiento del cerebro, pruebas psicológicas formales, y una historia de vida detallada hará posible remplazar categorías diagnósticas tradicionales con un rico perfil individual para cada paciente.

Dentro de 50 años, los motivos de una consulta psiquiátrica no habrán cambiado. Algunos pacientes quedarán incapacitados por delirios de inutilidad u omnipotencia, o por inexplicables ataques de pánico, o por voces amenazadoras que resuenan en sus cabezas. Otros se sentirán sin alegría, sin ánimo, pesimistas, crónicamente preocupados. Otros simplemente querrán dar un paso más en su vida.

Pero dentro de 50 años, todo el que visite un psiquiatra traerá consigo una nueva fuente de información, una contraseña que de acceso a su archivo personal de ADN en el ordenador del Servicio Nacional de Salud. En ese archivo estará la secuencia de cada uno de sus genes junto con una anotación que llamando la atención sobre las variantes y combinaciones de genes en ese individuo que influyen en la vulnerabilidad a una variedad de trastornos y otros que influyen en las acciones de los fármacos.

La primera consulta tomará una hora. Un tercio de ese tiempo será reservado para rellenar un cuestionario formal acerca del desarrollo personal, historia familiar, síntomas específicos. El resto será un intercambio informal. Al final de la sesión, el psiquiatra ofrecerá una evaluación, sugerirá algunas pruebas diagnósticas y solicitará acceso al expediente de ADN del paciente.

La solicitud de dicho acceso no parecerá descabellada. La legislación que estableció un depósito nacional de archivos de ADN para garantizar su privacidad también habrá reservado fondos para dar a conocer las ventajas de ponerlos a disposición de los profesionales adecuados. Muchas personas que consultan a psiquiatras estarán deseosas de acceder. Esto es especialmente cierto en el caso de quienes proceden de familias afectadas por determinados trastornos mentales; pueden solicitar una evaluación de su nivel de riesgo y averiguar si puede tomar alguna medida preventiva. Quienes busquen medicación pueden optar por ser guiados por el conocimiento de su combinación particular de variantes genéticas.

Esta orientación será especialmente valiosa, porque habrá cientos de medicamentos entre los que elegir. Algunos serán versiones mejoradas de los actuales, con efectos más selectivos sobre la neurotransmisión. Otras se habrán desarrollado a partir de nuestros nuevos

conocimientos sobre el funcionamiento del cerebro. Otras se habrán desarrollado a partir de la identificación de variantes genéticas que aumentan el riesgo de trastornos mentales.

La disponibilidad de información genética sobre los trastornos mentales no sólo cambiará las prácticas diagnósticas y terapéuticas de los psiquiatras, sino que también aumentará su contribución a la forma en que pensamos sobre nosotros mismos. En la primera mitad del siglo XX, la psiquiatría nos ayudó a darnos cuenta de que todos estamos muy influenciados por poderosas pasiones innatas y nos beneficia tomar conciencia de ellas. En la segunda mitad, nos proporcionó fármacos para mitigar comportamientos incontrolables y demostró lo dependientes que somos todos de simples sustancias químicas cerebrales, como la serotonina y la dopamina. La identificación de variantes genéticas que influyen en las diferencias de comportamiento completará algunos detalles importantes sobre la biología única de cada persona. Aunque puede resultar difícil interpretar el significado de muchas de estas variantes genéticas, algunas de ellas se convertirán sin duda en herramientas útiles para contemplar y construir nuestra narrativa vital individual.

Chapter V

Data Analysis

This chapter presents a detailed analysis of the data collected during the translation process of the selected documents for the Hospital México Library. It aims to examine the translation decisions made, identify recurring patterns or challenges, and assess how theoretical frameworks and strategies were applied in practice. Through this analysis, the study seeks to validate the proposed methodology and highlight areas for improvement or further exploration.

Data analysis is a crucial stage in any research process, as it allows the researcher to interpret the results in light of the objectives and theoretical concepts previously discussed. As Hurtado Albir (2001) emphasizes, the analysis of translation data offers insights into the translator's decision-making and the dynamics between source and target texts, shedding light on the complexity of the translation act. Therefore, this chapter not only contributes to answering the research questions but also provides evidence to support the conclusions and recommendations presented in the final chapter.

5.1. Analysis and interpretation of the results

This section presents a detailed analysis and interpretation of the translation process carried out for the selected documents from the Hospital México Library. The aim is to reflect on the translator's decision-making by examining the procedures, challenges, and solutions identified throughout the project. In doing so, the analysis offers insight into how the theory was applied in practice, especially in the context of specialized medical translation, where precision, clarity, and consistency are essential. The interpretation of the results is

directly aligned with the research objectives and seeks to demonstrate how translation problems were addressed with specific strategies grounded in translation theory.

To carry out this analysis, a set of tools and methods were implemented, each contributing to a clearer understanding of the translation process. First, a textual analysis of the source documents helped identify linguistic and terminological features that required particular attention. Following this, a color coding system was applied to visually categorize and analyze the translation procedures used, such as literal translation, transposition, modulation, amplification, explanation, and reduction. This system allowed for a clearer representation of where and why certain strategies were chosen, helping to trace patterns and justify translation decisions. Additionally, a glossary was created to maintain terminological coherence and to document the most relevant medical terms encountered during the translation. The glossary served not only as a reference tool but also as a product of the translation process itself, reflecting the effort to ensure consistency and accuracy. Finally, other supporting instruments may be included to clarify decisions further and illustrate the problem-solving process.

As Hurtado Albir (2001) emphasizes, translation is a complex cognitive operation that requires not only linguistic competence but also analytical reasoning and strategic decision-making. This section, therefore, is essential to understanding how the translator navigated between the source and target languages and how theoretical knowledge was transformed into practical solutions. The tools applied here contribute significantly to the overall evaluation of the translation and support the conclusions drawn in the final chapter.

5.1.1. Text Analysis

This section presents a detailed analysis of the selected source and target text paragraphs, focusing on key textual features that influence the translation process. The

analysis is centered on five specific elements: text style, text function, formality level, generality or difficulty, and emotional tone. These elements are examined to determine how the original message was conveyed and how effectively it was rendered in the translated version.

Understanding these textual characteristics is essential for identifying potential translation challenges and evaluating the translator's decisions. For example, shifts in emotional tone, variations in formality, or differences in the level of generality may require specific strategies to preserve the intended meaning and impact of the original text. By comparing the source and translated versions, this analysis aims to highlight areas where adaptation was necessary and to provide insight into the rationale behind those choices. The findings from this section also contribute to the broader interpretation of the translation techniques applied, as discussed in subsequent sections.

Table 3. Text Analysis

Text Analysis	"The Next Fifty Years" by John Brockman	"Cardiología Molecular. Módulo 3: Diabetes Mellitus Tipo 2" by Jonatan Navarro
Text Style	Descriptive/ Discussion Text	Discussion Text
Text Function	Informative	Informative
Formality	Formal	Formal
Generality or Difficulty	Educated	Opaquely Technical
Emotional Tone	Factual	Factual

Table 3 illustrates the text analysis of both translated texts. Source: Researcher's creation

5.1.2. Color Coding

The color-coding system is a tool for collecting data, highlighting the different translation techniques applied within each translated paragraph. A total of 15 paragraphs were analyzed, each ranging from 120 to 150 words, and taken from both the source and the translated texts. The method involves aligning each source paragraph with its corresponding translation. The color coding is applied specifically to the translated segments to indicate the techniques used. Notably, “omission” is the only technique identified in the source text. In total, six distinct translation techniques are employed in this study, with each one represented by a different color. This visual system allows for easier identification and analysis of the methods used in each paragraph.

Table 4. Color-Coding Chart

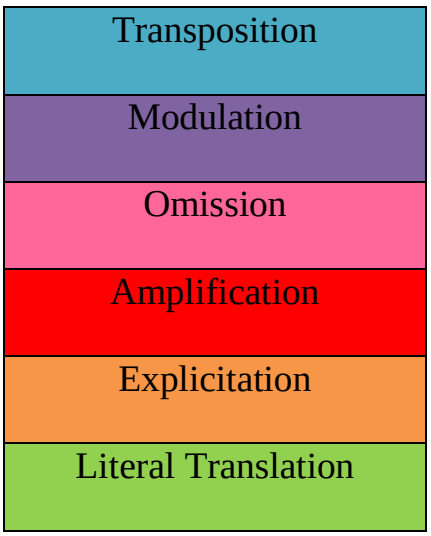

Table 4 Illustrate the colors and its meaning for the color coding chart

5.1.2.1. Color Coding of "Cardiología Molecular. Módulo 3: Diabetes Mellitus Tipo 2" by Jonatan Navarro.

1. **Original Text**

La diabetes mellitus tipo 2 (DM2) desempeña un papel muy relevante en el desarrollo de la enfermedad cardiovascular, debido a sus acciones metabólicas en el miocardio, que afectan su función diastólica y sistólica. Los procesos fisiopatológicos de la DM2 en el corazón se producen por medio de diferentes vías moleculares, las cuales son estimuladas ante las nuevas adaptaciones del miocardio, generando otras patologías cardíacas, como la fibrilación auricular. Para conocer más sobre este tema, que es de gran relevancia en la actualidad, se analizará en este módulo el comportamiento de las moléculas cardíacas ante la diabetes mellitus tipo 2, con el fin de que la información pueda servir de guía para el manejo terapéutico en la enfermedad cardiovascular. Partiendo de ese objetivo, se explican específicamente la acción de los biomarcadores cardíacos ST2 y galectina-3 en la DM2, la función del receptor de sodio-glucosa tipo 1 en el miocardio, las acciones moleculares de los iSGLT2 en el miocardio y, por último, la relación de la fibrilación auricular con la DM2.

Type 2 diabetes mellitus (T2DM) plays a very relevant role in the development of cardiovascular disease, due to its metabolic actions in the myocardium, which affect its diastolic and systolic function. The pathophysiological processes of type 2 diabetes mellitus in the heart are produced by the different molecular pathways, which are stimulated by the new adaptation of the myocardium, generating other cardiac pathologies, such as atrial fibrillation. To learn more about this topic, which is currently relevant, this module will analyze the behavior of cardiac molecules in type 2 diabetes mellitus, so that the information can serve as a guide for the therapeutic management of cardiovascular disease. Based on this objective, the action of the cardiac biomarkers ST2 and galectin-3 in T2DM, the function of

the type 1 sodium-glucose receptor in the myocardium, the molecular actions of ISGLT2 in the myocardium, and, finally, the relationship of the atrial fibrillation with T2DM are specifically explained.

2. **Original Text**

La supresión de tumorigenicidad 2 (ST2) es una proteína que forma parte de la IL-1 (interleucina 1). Este biomarcador se encuentra en múltiples isoformas a nivel tisular, entre ellas la transmembrana conocida como ligando ST2 (ST2L) y la circulante soluble (sST2). En el tejido cardíaco los fibroblastos producen la interleucina 33, que forma un complejo junto a la ST2L (IL-33/ST2L), para estimular el factor nuclear (NF)-kB, con el fin de prevenir acciones perjudiciales en el miocardio, como el estrés oxidativo y la apoptosis celular. De tal forma, este complejo ejerce efectos cardioprotectores, como la reducción de la fibrosis miocárdica y de la hipertrofia del cardiomiocito, y disminuye la apoptosis celular, mejorando la función miocárdica. Sin embargo, la elevada concentración de la isoforma ST2 soluble bloquea los efectos favorables del complejo IL-33/ST2L, aumentando la remodelación cardíaca, con una repercusión negativa sobre los desenlaces clínicos.

The suppression of Tumorigenicity 2 (ST2) is a protein that is part of IL-1 (interleukin 1). This biomarker is found in multiple isoforms at the tissular level, including the transmembrane known as ST2 ligand (ST2L) and the soluble circulating one (sST2). In cardiac tissue, fibroblasts produce interleukin 33, which forms a complex together with ST2L (IL-33/ST2L), to stimulate nuclear factor (NF)-kB, to prevent detrimental actions in the myocardium, such as oxidative stress and cell apoptosis. Thus, this complex exerts cardioprotective effects, such as the reduction of myocardial fibrosis and cardiomyocyte hypertrophy, and decreases cell apoptosis, improving myocardial function. However, the high concentration of the soluble ST2 isoform blocks the favorable effects of the IL-33/ST2L complex, increasing cardiac remodeling, with a negative impact on clinical outcomes.

3. **Original Text**

En los últimos años se han efectuado múltiples estudios en los que se ha analizado la relación existente entre el biomarcador ST2 y la DM2. A continuación, se resumen algunos de ellos:

En un estudio se analizaron los niveles y la relación del ST2 cardíaco en tres grupos de personas: un grupo control (sin DM2), un grupo con prediabetes y un grupo con DM2. Los resultados demostraron que las concentraciones del biomarcador fueron de 37,9 ng/ml en el grupo con DM2, de 26,1 ng/ml en el grupo con prediabetes y de 19,3 ng/ml en el grupo control. Por otro lado, se determinó que el riesgo de presentar prediabetes en el grupo control con respecto a los valores de ST2, no tiene una diferencia estadísticamente significativa ($p>0,05$). Sin embargo, se demostró el desarrollo de DM2 en el grupo control conforme aumentaban los valores de ST2 ($p<0,001$).

In recent years, multiple studies have been carried out in which the relationship between the ST2 biomarker and T2DM has been analyzed. Some of them are summarized below:

In one study, the levels and the relationship of cardiac ST2 were analyzed in three groups of people: a control group (without T2DM), a group with prediabetes, and a group with T2DM. The results showed that the concentrations of the biomarker were 37.9 ng/ml in the T2DM group, 26.1 ng/ml in the prediabetes group, and 19.3 ng/ml in the control group. On the other hand, it was determined that the risk of presenting prediabetes in the control group concerning the ST2 values did not have a statistically significant difference ($p>0.05$). However, the development of T2DM was demonstrated in the control group as ST2 values increased ($p<0.001$).

4. Original Text

Un grupo de investigadores evaluó el efecto del ST2 en la mortalidad tanto por causas cardiovasculares como por todas las causas en la enfermedad ateroesclerótica de un grupo de pacientes del Registro de Ateroesclerosis To Vergata. Los participantes del estudio se dividieron en cuatro grupos, con base en los niveles de glicemia: el primero con valores glicémicos normales, el segundo con alteración en los niveles de glicemia, el tercero con diagnóstico reciente de DM2 y el cuarto con diagnóstico de diabetes ya establecido. En los grupos de personas con diabetes se demostró la presencia de mayores niveles de ST2, siendo estadísticamente significativo en comparación con los demás grupos. También se comprobó que los niveles elevados de glicemia y de hemoglobina glicosilada estaban relacionados con el aumento en los niveles de ST2 (p=0,002). Finalmente, este biomarcador se asoció con mayor mortalidad por causas cardiovasculares en pacientes diabéticos; sin embargo, no presentó un riesgo significativo en la mortalidad por todas las causas. A partir de este estudio se concluye que la ST2 se encuentra elevada en alteraciones de la glicemia, pero no queda muy claro el mecanismo bioquímico o molecular específico por el que esta molécula actúa en el miocardio afectado por diabetes

A group of researchers evaluated the effect of ST2 on both cardiovascular and all-cause mortality in atherosclerotic disease in a group of patients from the To Vergata Atherosclerosis Registry. Study participants were divided into four groups based on glycemic levels: the first with normal glycemic values, the second with altered glycemic levels, the third with newly diagnosed T2DM, and the fourth with an established diagnosis of diabetes. In the groups of people with diabetes, the presence of higher levels of ST2 was demonstrated, being statistically significant compared to the other groups. It was also found that elevated glycemic and glycosylated hemoglobin levels were related to increased ST2 levels (p=0.002).

Finally, this biomarker was associated with higher mortality due to cardiovascular causes in diabetic patients; however, it did not present a significant risk in all-cause mortality. From this study, we conclude that ST2 is elevated in glycemic alterations, but the specific biochemical or molecular mechanism by which this molecule acts in the myocardium affected by diabetes is not very clear.

5. **Original Text**

Diversos estudios han confirmado la relación existente entre la galectina-3 y la DM2. A continuación, se resumen algunos de ellos:

En un estudio en personas con DM2, se analizó la relación de los niveles de galectina-3 y los eventos cardiovasculares. Los participantes se dividieron en dos grupos; el primer grupo cursaba con desenlaces cardiovasculares primarios (infarto de miocardio no fatal, revascularización coronaria, ictus no fatal, mortalidad por causas cardiovasculares) y un desenlace secundario (mortalidad por cualquier causa); mientras que el segundo grupo no presentaba ninguno de los desenlaces cardiovasculares anteriores. Los resultados demostraron una elevación de la galectina-3 en el primer grupo, en comparación con el segundo grupo ($p<0,01$). Por otra parte, se demostró un aumento del biomarcador en la mortalidad cardiovascular. Como conclusión, se determinó que la galectina-3 elevada se asocia con resultados cardiovasculares adversos en personas con DM2, independiente-mente de los factores de riesgo tradicionales.

Several studies have confirmed the relationship between galectin-3 and T2DM. Some of them are summarized below:

In a study of people with T2DM, the relationship between galectin-3 levels and cardiovascular events was analyzed. The participants were divided into two groups; the first

group had primary cardiovascular outcomes (non-fatal myocardial infarction, coronary revascularization, non-fatal stroke, cardiovascular mortality) and a secondary outcome (all-cause mortality); whereas the second group had none of the above cardiovascular outcomes. The results showed an elevation of galectin-3 in the first group compared to the second group ($p<0.01$). On the other hand, an increase in the biomarker of cardiovascular mortality was demonstrated. In conclusion, elevated galectin-3 was found to be associated with adverse cardiovascular outcomes in people with T2DM, independently of traditional risk factors.

6. **Original Text**

En varios estudios se ha demostrado que en presencia de DM2 se eleva el ST2 soluble; sin embargo, aún no se conoce con exactitud el mecanismo fisiopatológico directo entre el efecto de la diabetes y la liberación del biomarcador. Podría pensarse que está relacionada con los siguientes mecanismos, los cuales deben ser valorados en futuras investigaciones:

a. El efecto directo de la hiperglicemia en el miocardio causa la glucotoxicidad y la lipotoxicidad, generando procesos inflamatorios (activación de citoquinas), estrés oxidativo (activación de especies reactivas de oxígeno) y apoptosis celular.
b. La vía en común entre las causas tóxicas de la hiperglicemia y la acción del ST2 estimula al factor nuclear (NFkB), activando las citoquinas inflamatorias.
c. El bloqueo de la acción del ST2L y la interleucina-3 por medio del ST2 soluble, produce a nivel del miocardio fibrosis intersticial, hipertrofia del miocito y apoptosis, generando una disfunción diastólica.

Several studies have shown that in the presence of T2DM soluble ST2 is elevated; however, the exact direct pathophysiological mechanism between the effect of diabetes and

the release of the biomarkers is not yet known. It could be thought to be related to the following mechanisms, which should be evaluated in future research:

d. The direct effect of hyperglycemia in the myocardium causes glycotoxicity and lipotoxicity, generating inflammatory processes (activation of cytokines), oxidative stress (activation of reactive oxygen species), and cell apoptosis.

e. The common pathway between the toxic causes of hyperglycemia and the action of ST2 stimulates the nuclear factor (NFkB), activating inflammatory cytokines.

f. The blockade of the action of ST2L and interleukin-3 by soluble ST2 produces interstitial fibrosis, myocyte hypertrophy, and apoptosis in the myocardium, generating diastolic dysfunction.

7. Original Text

En un estudio experimental con un grupo de ratones sin DM2, a los que se les realizó una oclusión de la arteria coronaria para evaluar los efectos de la canagliflozina, específicamente en el estrés oxidativo y la apoptosis celular, así como otras acciones en el proceso de isquemia/reperfusión coronaria, se encontró que este iSGLT2 disminuyó la relación Bax/Bcl2, reduciendo la apoptosis de los cardiomiocitos. Además, se identificó una reducción en la expresión de genes relacionados con el estrés nitro-oxidativo, entre ellos el p47 fosforilado, la SOD2 (dismutasa) y la catalasa. Por otra parte, la canagliflozina demostró una mayor fosforilación en la coenzima A carboxilasa y la AMPK, reduciendo la síntesis y la acumulación de los ácidos grasos en la célula cardíaca, mejorando así la funcionalidad miocárdica. También el fármaco estimuló la fosforilación de eNOS (isoforma endotelial del óxido nítrico sintasa) y aumentó la producción del óxido nítrico con una mayor vasodilatación arterial, mejorando la perfusión coronaria.

In an experimental study with a group of mice without T2DM, which underwent coronary artery occlusion to evaluate the effects of canagliflozin, specifically on oxidative stress and cell apoptosis, as well as other actions in the process of coronary ischemia/ reperfusion, it was found this iSGLT2 decreased the Bax/Bcl2 relation, reducing cardiomyocyte apoptosis. In addition, a reduction in the expression of genes related to nitro-oxidative stress was identified, including phosphorylated p47, SOD2 (dismutase), and catalase. On the other hand, canagliflozin demonstrated increased phosphorylation in coenzyme. A carboxylase and AMPK, reducing the synthesis and accumulation of fatty acids in the cardiac cell, thus improving myocardial functionality. The drug also stimulated the phosphorylation of eNOS (endothelial isoform of nitric oxide synthase) and increased the production of nitric oxide with greater arterial vasodilatation, improving coronary perfusion.

8. Original Text

En un estudio experimental realizado en un grupo de ratones diabéticos, se analizó la acción de la empagliflozina sobre el estrés oxidativo del cardiomiocito, específicamente sobre la vía Nrf2 (factor nuclear relacionado con el eritroide 2)/ARE (elemento de respuesta antioxidante) y en las moléculas hidroperóxido lipídico (radical libre de la peroxidación lipídica), glutatión peroxidasa (GSH-Px), dismutasa superóxido (SOD) y malondialdehído (MDA); asimismo, se analizó la acción del fármaco sobre la fibrosis miocárdica en la vía de señalización TGF-ß/Smad y en moléculas como TGF-β1, p-Smad2 y p-Smad3. Los resultados demostraron que la empagliflozina disminuye los niveles del hidroperóxido lipídico y del MDA, y aumenta el superóxido dismutasa y los valores de Nrf2; acciones moleculares que reducen el estrés oxidativo. Por otro lado, se encontró que la empagliflozina suprime la vía TGF-B/Smad, que a su vez estimula a la molécula Smad7, reduciendo la fibrosis miocárdica ($p<0,05$). De tal forma, se concluye que la empagliflozina reduce el estrés

oxidativo en el cardiomiocito y la fibrosis del tejido cardíaco, mejorando la función ventricular.

In an experimental study performed in a group of diabetic mice, the action of empagliflozin on cardiomyocyte oxidative stress was analyzed, specifically on the Nrf2 (nuclear factor erythroid-related factor 2)/ARE (antioxidant response element) pathway and on the molecules lipid hydroperoxide (the free radical of lipid peroxidation), glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and malondialdehyde (MDA); The action of the drug on myocardial fibrosis was also analyzed in the TGF-β/Smad signaling pathway and on molecules such as TGF-β1, p-Smad2 and p-Smad3. The results showed that empagliflozin decreases lipid hydroperoxide and MDA levels, and increases superoxide dismutase and Nrf2 values; molecular actions that reduce oxidative stress. On the other hand, empagliflozin was found to suppress the TGF-β/Smad pathway, which in turn stimulates the Smad7 molecule, reducing myocardial fibrosis ($p<0.05$). Thus, we conclude that empagliflozin reduces oxidative stress in the cardiomyocyte and cardiac tissue fibrosis, improving ventricular function.

9. **Original Text**

Otra investigación experimental analizó la acción de la empagliflozina sobre la célula endotelial microvascular cardíaca (CEMC) posterior a la exposición del factor de necrosis tumoral alfa (TNF-alfa). Fisiológicamente, la CEMC aumenta el acortamiento de la longitud del sarcómero y genera una mayor velocidad y un tiempo más corto en la relajación miocárdica; sin embargo, la unión de estas células con el TNF-alfa disminuye dichos efectos. Ante esa circunstancia, se logró determinar que el iSGLT2 preserva la función de la CMEC, mejorando la contracción de los cardiomiocitos y la función diastólica, con un incremento en la velocidad de la relajación. También se demostró una reducción del TNF-alfa en las células

endoteliales y una disminución de las especies reactivas de oxígeno tanto en el citoplasma como en la mitocondria. Con base en lo anterior, se concluye que la empagliflozina restaura la función fisiológica de la célula endotelial microvascular, mejorando la contracción y la relajación miocárdica; además, reduce los niveles del factor de necrosis tumoral y la acumulación de especies reactivas de oxígeno.

Another experimental investigation analyzed the action of empagliflozin on cardiac microvascular endothelial cell (CEMC) following tumor necrosis factor-alpha (TNF-alpha) exposure. Physiologically, CEMC increases sarcomere length shortening and generates a faster rate and shorter time of myocardial relaxation; however, the binding of these cells to TNF-alpha decreases these effects. In this circumstance, it was determined that iSGLT2 preserves CMEC function, improving cardiomyocyte contraction and diastolic function, with an increase in relaxation velocity. A reduction of TNF-alpha in endothelial cells and a decrease in reactive oxygen species in both cytoplasm and mitochondria were also demonstrated. Based on the above, it is concluded that empagliflozin restores the physiological function of the microvascular endothelial cell, improving myocardial contraction and relaxation; in addition, it reduces tumor necrosis factor levels and the accumulation of reactive oxygen species.

10. Original Text

Un subestudio del EMPA-REG OUTCOME trial, evaluó la eficacia de la empagliflozina en la fibrilación auricular, así como en los desenlaces cardiovasculares (mortalidad cardiovascular, hospitalización por insuficiencia cardíaca y mortalidad por todas las causas) y renales (empeoramiento de la función renal) en dos grupos: uno con pacientes con fibrilación auricular y otro con pacientes sin fibrilación auricular. En el grupo con fibrilación auricular, la empagliflozina demostró una mayor reducción de los eventos

cardiovasculares, incluyendo la muerte por esta causa, y una disminución del empeoramiento de la nefropatía; el número de eventos prevenidos fue mayor en este grupo que en el de personas sin fibrilación auricular. Con base en estos resultados, los investigadores consideraron beneficioso el uso de este medicamento en pacientes con diabetes, con eventos cardiovasculares y con fibrilación auricular.

A substudy of the EMPA-REG OUTCOME trial evaluated the efficacy of empagliflozin in atrial fibrillation, as well as cardiovascular outcomes (cardiovascular mortality, hospitalization for heart failure, and all-cause mortality) and renal outcomes (worsening renal function) in two groups: one with patients with atrial fibrillation and the other with patients without atrial fibrillation. In the group with atrial fibrillation, empagliflozin showed a greater reduction in cardiovascular events, including death from this cause, and a decrease in the worsening of nephropathy; the number of events prevented was greater in this group than in those without atrial fibrillation. Based on these results, the investigators considered the use of this drug beneficial in patients with diabetes, cardiovascular events, and atrial fibrillation.

11. Original Text

Adicional a lo anterior, se analizaron diversas moléculas mitocondriales, como el PGC-1a (coactivador del receptor c activado por el proliferador de peroxisomas 1a), el cual promueve la biogénesis mitocondrial y es regulado por la AMPK (quinasa monofosfato de adenosina), que tiene efectos metabólicos. A la vez, se evaluó el Tfam (factor de transcripción mitocondrial A) y el NRF-1 (factor respiratorio nuclear 1), que activa los genes nucleares para la respiración mitocondrial, la transcripción y la replicación del ADN mitocondrial. Los valores de estas moléculas permanecieron reducidos en el grupo de diabetes, mientras que en el grupo de empagliflozina estos se elevaron, incrementando la

función mitocondrial. Otras moléculas analizadas fueron la Mfn-1 (mitofusina 1) y la OPA-1 (atrofia óptica 1), que generan la fusión mitocondrial; en este caso, todos sus valores aumentaron con el uso de la empagliflozina, regulando y mejorando la función mitocondrial.

In addition to the above, several mitochondrial molecules were analyzed, such as PGC-1a (peroxisome proliferator-activated receptor c coactivator 1a), which promotes mitochondrial biogenesis and is regulated by AMPK (adenosine monophosphate kinase), which has metabolic effects. At the same time, Tfam (mitochondrial transcription factor A) and NRF-1 (nuclear respiratory factor 1), which activates nuclear genes for mitochondrial respiration, transcription, and mitochondrial DNA replication, were evaluated. The values of these molecules remained reduced in the diabetes group, whereas in the empagliflozin group, they were elevated, increasing mitochondrial function. Other molecules analyzed were Mfn-1 (mitofusin 1) and OPA-1 (optic atrophy 1), which generate mitochondrial fusion; in this case, all their values increased with the use of empagliflozin, regulating and improving mitochondrial function.

12. Original Text

En un estudio experimental en ratones con DM2 inducida, divididos en cuatro grupos (control; sin uso de fármacos; con dosis bajas de empagliflozina; y con dosis elevadas de empagliflozina durante ocho semanas), se evaluó el efecto de dicho fármaco sobre el remodelado auricular, ocasionado por la diabetes mellitus, con base en los parámetros ecocardiográficos, los factores metabólicos e inflamatorios, el estrés oxidativo y otros. En lo que respecta a los parámetros ecocardiográficos, se determinó que tanto el diámetro de la aurícula izquierda como la rigidez de la pared posterior del ventrículo izquierdo, cursaron con valores elevados en el grupo sin fármacos ($p<0,005$), mientras que en el grupo de empagliflozina a dosis elevadas hubo una reducción en los valores de ambos parámetros

(p<0,05). En cuanto a los marcadores bioquímicos, se identificó una reducción del colesterol total y de la glicemia en el cuarto grupo del estudio en comparación con el segundo grupo (p<0,03).

In an experimental study of mice with induced T2DM, divided into four groups (control; without the use of drugs; with low doses of empagliflozin; and with high doses of empagliflozin for eight weeks), the effect of this drug on atrial remodeling caused by diabetes mellitus was evaluated based on echocardiographic parameters, metabolic and inflammatory factors, oxidative stress and others. Regarding echocardiographic parameters, it was determined that both left atrial diameter and left ventricular posterior wall stiffness were elevated in the non-drug group (p<0.005), while in the high-dose empagliflozin group there was a reduction in the values of both parameters (p<0.05). Regarding biochemical markers, a reduction in total cholesterol and glycemia was identified in the fourth study group compared to the second group (p<0.03).

13. Original Text

Por otra parte, la DM2 en conjunto con la fibrilación auricular aumenta la señalización del factor de transcripción nuclear kappa B (NF-kB), involucrado en procesos de inflamación de los miocitos auriculares. Específicamente, esta molécula actúa en la vía de señalización de reducción-oxidación y en la cascada de angiotensina, mejorando la heterogeneidad de la conducción, al promover la reentrada en la aurícula. Cuando hay hiperglicemia, esta determina la sobreproducción de especies reactivas de oxígeno en los vasos y disminuye la disponibilidad de óxido nítrico, lo que conduce a una regulación positiva del NF-kB que media la transcripción de genes proinflamatorios (por ejemplo, codificación de moléculas de adhesión), perpetuando de esta forma el estado inflamatorio. En un estudio realizado por Raposeiras y colaboradores, se demostró una elevación en los

niveles de los productos finales de la glicosilación avanzada en DM2 y fibrilación auricular. Este aumento genera rigidez estructural y pérdida de la elasticidad de las aurículas; por consiguiente, la activación del receptor de los productos finales de la glicosilación avanzada produce distensión de la aurícula izquierda, alterando su configuración estructural. Además, esta activación ocasiona un incremento en la producción de citoquinas proinflamatorias.

On the other hand, T2DM in conjunction with atrial fibrillation increases nuclear transcription factor kappa B (NF-kB) signaling, involved in atrial myocyte inflammatory processes. Specifically, this molecule acts in the reduction-oxidation signaling pathway and the angiotensin cascade, improving conduction heterogeneity by promoting atrial reentry. When hyperglycemia is present, it determines the overproduction of reactive oxygen species in the vessels and decreases the availability of nitric oxide, leading to a positive regulation of NF-kB that mediates the transcription of proinflammatory genes (e.g., encoding adhesion molecules), thus perpetuating the inflammatory state. A study by Raposeiras et al. demonstrated elevated levels of advanced glycation end products in T2DM and atrial fibrillation. This increase generates structural rigidity and loss of atrial elasticity; consequently, activation of the receptor for advanced glycation end product produces distension of the left atrium, altering its structural configuration. In addition, this activation causes an increase in the production of proinflammatory cytokines.

14. Original Text

Como se mencionó en los capítulos anteriores, la diabetes mellitus tipo 2 (DM2) produce glucotoxicidad y lipotoxicidad en el miocardio, que generan efectos nocivos como estrés oxidativo, inflamación y apoptosis celular. Estos efectos dan origen a la fibrosis y a la hipertrofia en los cardiomiocitos auriculares, lo cual conlleva a remodelaciones estructurales y eléctricas en las aurículas. Por otra parte, se ha comprobado que la hiperglicemia crónica

está relacionada con la patogénesis de la neuropatía autonómica cardíaca, al alterar la perfusión sanguínea de las estructuras nerviosas, la cual produce una estimulación simpática a nivel del miocardio y genera un acortamiento en el período de refractariedad en las células de la aurícula, contribuyendo así al desarrollo de la fibrilación auricular. Partiendo de ese contexto, se describen a continuación los procesos moleculares generados por la DM2 en las aurículas y el desarrollo de la fibrilación auricular a causa de la disfunción mitocondrial y el remodelado eléctrico y estructural auricular. Como complemento, se menciona la acción de los iSGLT2 en la fibrilación auricular.

As mentioned in previous chapters, type 2 diabetes mellitus (T2DM) produces glycotoxicity and lipotoxicity in the myocardium, which generate deleterious effects such as oxidative stress, inflammation, and cell apoptosis. These effects give rise to fibrosis and hypertrophy in atrial cardiomyocytes, leading to structural and electrical remodeling in the atria. On the other hand, chronic hyperglycemia has been shown to be related to the pathogenesis of cardiac autonomic neuropathy by altering the blood perfusion of nerve structures, which produces sympathetic stimulation at the myocardial level and generates a shortening of the refractory period in the atrial cells, thus contributing to the development of atrial fibrillation. From this context, the molecular processes generated by T2DM in the atria and the development of atrial fibrillation due to mitochondrial dysfunction and atrial electrical and structural remodeling are described below. As a complement, the action of iSGLT2 in atrial fibrillation is mentioned.

15. Original Text

Fisiológicamente, en el corazón este intercambiador inicia con el ingreso de sodio a la célula y la movilización de los hidrogeniones al espacio extracelular, lo que activa a la molécula AKT1, que induce a la BIRC2 (proteína 2 que contiene repetición de baculovirales

IAP), la cual degrada al XIAP (inhibidor de la apoptosis ligado al X mediado por proteasoma) y al BIRC5. Por otra parte, AKT1 activa a MAPK1/3 (proteína quinasa activada por mitógeno 1/3) y esta a su vez estimula al RPTOR (proteína reguladora asociada de mTOR), ocasionando hipertrofia y muerte celular del cardiomiocito. Posteriormente, el NHE1 activa a la NOS2 (óxido nítrico sintasa), estimulando la inflamación e hipertrofia de la célula cardíaca. Para evitar esta situación, la empagliflozina inhibe a las moléculas NHE1, AKT 1-3 y BIRC2, permitiendo la expresión de los mediadores antiapoptóticos XIAP y BIRC5; asimismo, reduce la progresión de la insuficiencia cardíaca con y sin diabetes tipo 2. Adicional a lo anterior, podría disminuir aún más la muerte celular de los cardiomiocitos, al inhibir la proteína mTOR que depende de AKT (RPTOR) y disminuye la regulación de las acciones del NOS2.

Physiologically, this exchanger in the heart starts with the entry of sodium into the cell and the mobilization of hydrogen ions to the extracellular space, which activates the molecule AKT1, which induces BIRC2 (baculoviral IAP repeat-containing protein 2), which degrades XIAP (X-linked inhibitor of apoptosis mediated by proteasome), and BIRC5. On the other hand, AKT1 activates MAPK1/3 (mitogen-activated protein kinase 1/3) and this in turn stimulates RPTOR (mTOR-associated regulatory protein), causing cardiomyocyte hypertrophy and cell death. Subsequently, NHE1 activates NOS2 (nitric oxide synthase), stimulating inflammation and cardiac cell hypertrophy. To avoid this situation, empagliflozin inhibits NHE1, AKT 1-3, and BIRC2, allowing the expression of anti-apoptotic mediators XIAP and BIRC5; it also reduces the progression of heart failure with and without type 2 diabetes. In addition to the above, it could further decrease cardiomyocyte cell death by inhibiting the AKT-dependent protein mTOR (RAPTOR) and down-regulating the actions of NOS2.

5.1.2.2. Color Coding of "The Next Fifty Years" by John Brockman

1. **Original Text:**

The future of research on the human brain with fMRI or other approaches, including other ways to record activity, and ways to stimulate selective brain regions and induce activity is likely to be in three broad domains. The first is the most pedestrian: We will learn more about some processes that we already know something about, that is, the neural organization of perception, memory, emotion, language, and working memory. The second entails discovering more about how these processes interact in the brain. This investigation will take us from narrow to broader systems-level concepts of brain function, and toward at least the beginnings of a theory of how the brain makes the mind, as opposed to how specific mental processes function. Work of this type has begun, but is far too rare.

El futuro de la investigación sobre el cerebro humano con IRMf u otros métodos, incluidas otras formas de registrar la actividad y de estimular regiones cerebrales concretas e inducir actividad, se centrará probablemente en tres grandes ámbitos. El primero es el más pedestre: aprenderemos más sobre algunos procesos de los que ya sabemos algo, es decir, la organización neural de la percepción, la memoria, la emoción, el lenguaje y la memoria de trabajo. La segunda implica descubrir más sobre cómo interactúan estos procesos en el cerebro. Esta investigación nos llevará de conceptos limitados a conceptos más amplios de la función cerebral a nivel sistémico, y hacia al menos los inicios de una teoría de cómo el cerebro crea la mente, en contraposición a cómo funcionan los procesos mentales específicos. Ya se han iniciado trabajos de este tipo, pero son demasiado escasos.

2. **Original Text:**

But what about fixing the brains of people with neurological problems like Alzheimer's disease? The recent discovery that in adult brains new neurons are made in the

hippocampus, a brain region of central importance to our ability to consciously remember, offers new hope. If these cells can somehow be encouraged to connect with and thus participate in the degenerating memory circuits, perhaps memory function can be restored. And if the federal government will untie the hands of researchers and allow them to proceed more freely with stem cell research, it may be possible to prevent conditions such as Alzheimer's from being expressed at all in people who are susceptible.

Pero ¿qué hay de arreglar los cerebros de las personas con problemas neurológicos como la enfermedad de Alzheimer? El reciente descubrimiento de que las nuevas neuronas del cerebro en un adulto son hechas en el hipocampo, una región del cerebro de gran importancia para nuestra habilidad de recordar conscientemente, ofrece una nueva esperanza. Si estas células pueden de alguna manera ser alentadas a conectarse con los circuitos degenerativos de la memoria y así participar en ellos, quizás se pueda restaurar la función de la memoria. Y si el gobierno federal desata las manos de los investigadores y les permite proceder con mayor libertad en la investigación con células madre, quizá pueda ser posible evitar que condiciones como el Alzheimer se presenten en personas susceptibles de padecerlas.

3. **Original Text:**

For example, it is a reasonable assumption, given existing animal and human data that fear-related disorders (panic attack, posttraumatic stress disorder, generalized anxiety, phobia, paranoid schizophrenia) result from alterations in the way the brain's fear networks normally function and interact with other networks. Since the amygdala, as we have seen, is a key part of these networks, alterations in amygdala function might account for certain aspects of anxiety. Specifically, excess and inappropriate fear could occur because the amygdala is oversensitive, detecting danger and responding defensively to a situation that would be

ignored by another person; or the amygdala could be too reactive, responding with a more vigorous defense than another person would to the same degree of threat. Either of these conditions could arise from genetic wiring or from traumatic or otherwise stressful experiences, or from some combination of the two.

Por ejemplo, es una suposición razonable, dados los datos existentes sobre animales y humanos, que los trastornos relacionados con el miedo (ataque de pánico, trastorno de estrés postraumático, ansiedad generalizada, fobia, esquizofrenia paranoide) son el resultado de alteraciones en la forma en que las redes cerebrales del miedo funcionan normalmente e interactúan con otras redes. Dado que la amígdala, como hemos visto, es una parte clave de estas redes, las alteraciones en el funcionamiento de la amígdala podrían explicar ciertos aspectos de la ansiedad. En concreto, el miedo excesivo e inapropiado podría producirse porque la amígdala es hipersensible, detectando el peligro y respondiendo a la defensiva ante una situación que otra persona ignoraría; o la amígdala podría ser demasiado reactiva, respondiendo con una defensa más enérgica de lo que lo haría otra persona ante el mismo grado de amenaza. Cualquiera de estas condiciones puede deberse a la genética, a experiencias traumáticas o estresantes, o a una combinación de ambas.

4. **Original Text:**

Once human imaging studies implicate specific networks in a particular condition and animal studies illuminate the detailed organization of those networks, we can look for drugs that will target the afflicted circuits. One strategy would involve capitalizing on advances in molecular genetics: If we can identify some molecule that is expressed only in the amygdala, or is expressed there in some particular way, it might then be possible to use that molecule as a key to unlock a drug. That is, the drug would still be taken orally and would still travel widely in the bloodstream to many brain regions; however, because of the drug's molecular

packaging, it would be inert in most brain regions. Only when it encountered the molecular key, which in this hypothetical example is present only in the amygdala, would the drug become active.

Una vez que los estudios de imagen en humanos indiquen la implicación de redes específicas en una enfermedad concreta y los estudios en animales esclarezcan la organización detallada de esas redes, podremos buscar fármacos dirigidos a los circuitos afectados. Una estrategia consistiría en aprovechar los avances de la genética molecular: si podemos identificar alguna molécula que solo se manifieste en la amígdala o que se manifieste allí de alguna manera concreta, podría ser posible utilizar esa molécula como clave para descubrir un fármaco. Es decir, el fármaco seguiría tomándose por vía oral y seguiría viajando ampliamente por el torrente sanguíneo hasta muchas regiones cerebrales; sin embargo, debido al empaquetamiento molecular del fármaco, sería inerte en la mayoría de las regiones cerebrales. Sólo cuando encuentra la clave molecular, que en este ejemplo hipotético solo está presente en la amígdala, la droga se activa.

5. **Original Text:**

First, the amygdala defense should not be confused with a related issue, which we can call the pathological brain defense. In the latter, the argument is that the person com-mitted a crime because of some physical alteration in his or her brain. The amygdala defense, in contrast, is based on the notion that the amygdala normally controls emotional behavior in an unconscious fashion, and as a result it is possible for a crime to be committed by the amygdala independent of conscious thought. It is clearly possible for the amygdala to control an aggressive act independent of conscious control in certain provocative circumstances; however, in order for the amygdala defense to work, several criteria would have to be met.

En primer lugar, la defensa de la amígdala no debe confundirse con una problemática relacionada, que podemos denominar defensa del cerebro patológico. En esta última, el argumento es que la persona cometió un delito debido a alguna alteración física en su cerebro. La defensa de la amígdala, por el contrario, se basa en la noción de que la amígdala normalmente controla el comportamiento emocional de forma inconsciente y, como resultado, es posible que la amígdala cometa un delito independientemente del pensamiento consciente. Está claro que es posible que la amígdala controle un acto agresivo independientemente del control consciente en determinadas circunstancias provocativas; sin embargo, para que la defensa de la amígdala funcione, tendrían que cumplirse varios criterios.

6. **Original Text:**

An important job of the amygdala is to rapidly initiate protective responses in the face of a sudden danger. But if the stimulus has been present for some time and consciously perceived, behavior tends to be under the control of higher thought processes, mediated by the cortex. Further, the kinds of responses directed by the amygdala are fast, simple, innate (hardwired) responses that are executed in a stereotyped manner -that is, performed similarly in all members of the species. So if an act is deliberate, expressed relatively slowly (over seconds rather than milliseconds), involves a complex sequence of movements, and would be carried out differently in different people, it is probably not directly controlled by the amygdala. The amygdala can indirectly influence or modulate these more complex responses, but they are, in the end, the business of other brain systems. These facts suggest that in order for the amygdala defense to succeed, the crime would have to involve a relatively simple, innate, stereotyped response executed instantaneously and without premeditation upon the occurrence of the provocation.

Una tarea importante de la amígdala es iniciar rápidamente respuestas protectoras ante un peligro repentino. Pero, si el estímulo ha estado presente durante algún tiempo y se ha percibido conscientemente, el comportamiento tiende a estar bajo el control de procesos superiores, mediados por el córtex. Además, los tipos de respuestas dirigidas por la amígdala son respuestas rápidas, sencillas e innatas (programadas) que se ejecutan de forma estereotipada, es decir, de forma similar en todos los miembros de la especie. Así pues, si un acto es deliberado, se expresa con relativa lentitud (a lo largo de segundos en lugar de milisegundos), implica una secuencia compleja de movimientos y se llevará a cabo de forma diferente en distintas personas, es probable que no esté controlado directamente por la amígdala. La amígdala puede influir o modular indirectamente estas respuestas más complejas, pero, al final, son asunto de otros sistemas cerebrales. Estos hechos sugieren que, para que la defensa de la amígdala tenga éxito, el delito tendría que implicar una respuesta estereotipada, innata y relativamente simple, ejecutada instantáneamente y sin premeditación al producirse la provocación.

7. **Original Text:**

The great success of chlorpromazine stimulated vigorous competition from other pharmaceutical companies. In the 1950s the search for more antipsychotic medications led to the accidental discovery of two other types of psychiatric drugs. First Geigy, a Swiss pharmaceutical company, came up with a modified version of one of its antihistamines that, although useless against psychosis, proved to be a valuable treatment for severe depression. Named imipramine (Tofranil), it paved the way for many contemporary antidepressants. Then Hoffman-La Roche, another Swiss company, created chlordiazepoxide (Librium), which doesn't help psychosis either but does relieve anxiety. It was soon followed by another

benzodiazepine, diazepam (Valium), which became the best-selling drug in America for about a decade, beginning in the mid-1960s.

El gran éxito de la clorpromazina estimuló una vigorosa competencia por parte de otras empresas farmacéuticas. En los años cincuenta, la búsqueda de más medicamentos antipsicóticos condujo a un descubrimiento accidental de otros dos tipos de fármacos psiquiátricos. Primero, Geigy, una compañía farmacéutica suiza, surgió con una versión de uno de sus antihistamínicos que, aunque fuera inservible contra la psicosis, probó ser un valioso tratamiento para la depresión severa. Nombrada imipramina (Tofranil), pavimenta el camino para muchos antidepresivos contemporáneos. Luego, Hoffman-La Roche, otra compañía suiza, creó el clordiazepóxido (Librium), el cual tampoco ayuda a la psicosis, pero alivia la ansiedad. Fue seguido prontamente por otro benzodiacepínico, el diazepam (Valium), el cual se convierte en el fármaco más vendido en América durante aproximadamente una década, a partir de mediados de los sesentas.

8. **Original Text:**

These discoveries spurred a search for other chemicals that would have similar effects on neurotransmission but fewer undesirable side effects than the originals. The search paid off in a stream of new medications that patients prefer. The most famous, fluoxetine (Prozac), was initially identified as a chemical that prolongs neurotransmission by serotonin; it was subsequently shown to be an effective treatment for both severe and moderate depression. Called an SSRI (selective serotonin reuptake inhibitor), it pro-longs serotonin's effects by inhibiting its reuptake by the nerves that release it, which is the normal way that serotonin signaling is terminated. Related drugs, including sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and citalopram (Celexa), soon followed.

Estos descubrimientos incitaron una búsqueda por otros químicos que pudieran tener efectos similares en la neurotransmisión, pero con menos indeseables efectos secundarios que los originales. La búsqueda dio sus frutos con un flujo de nuevos medicamentos que los pacientes prefieren. El más famoso, fluoxetina (Prozac), fue inicialmente identificado como un químico que prolongaba la neurotransmisión por la serotonina; posteriormente, se demostró que era un tratamiento eficaz tanto para la depresión severa como la moderada. Llamada un ISRS (inhibidores selectivos de la recaptura de serotonina), prolonga los efectos de la serotonina inhibiendo su recaptación por los nervios que la liberan, la cual es la forma normal en la que la señalización de la serotonina se termina. En los fármacos relacionados se incluyen sertralina (Zoloft), paroxetina (Paxil), fluvoxamina (Luvox) y citalopram (Celexa), seguidos rápidamente.

9. **Original Text:**

The best clue we have is that all these patterns of disturbed behavior run in families. Consider, for example, the risk of becoming schizophrenic. Most people have about one chance in a hundred of developing the characteristic pattern of symptoms. But if you have a parent or sibling who is schizophrenic, your lifetime risk is eight times greater. The same is true of the other major cause of psychosis-manic-depressive illness, also known as bipolar disorder. Again, the general risk is about one in a hundred, but the risk is eight times greater if you have a parent or sibling who suffers from this disorder. Depression and the anxiety disorders are also familial.

La mejor pista que tenemos es que todos estos patrones de comportamiento perturbado se dan en familias. Considere, por ejemplo, el riesgo de volverse esquizofrénico. La mayoría de las personas tiene una posibilidad entre cien de desarrollar el patrón característico de síntomas. Pero, si usted tiene uno de los padres o hermanos que es

esquizofrénico, su riesgo de por vida es ocho veces mayor. Lo mismo ocurre con la otra causa principal de psicosis: la enfermedad maníaco-depresiva, también conocida como trastorno bipolar. De nuevo, el riesgo general es de uno por cada cien, pero el riesgo es ocho veces mayor si uno de los padres o hermanos padece este trastorno. La depresión y los desórdenes de ansiedad son también familiares.

10. Original Text:

The main catalyst for this agreement has been the development of powerful techniques for direct examination of the alternative forms of human genes, called alleles, or gene variants. These variants, which arose by random changes in DNA structure, are responsible for a great deal of human diversity, including differences in susceptibility to particular illnesses. But until recently their existence could only be inferred. The new techniques make it possible to identify specific gene variants that contribute to a human attribute. Instead of arguing about the relative importance of nature and nurture, we can now turn our attention to a search for gene variants that contribute to individual predisposition to an illness.

El principal catalizador de este acuerdo ha sido el desarrollo de potentes técnicas para la examinación completa de las formas alternativas de los genes humanos, llamados alelos o variantes genéticas. Estas variantes que surgen por cambios aleatorios en la estructura del ADN son responsables de gran parte de la diversidad humana, incluidas las diferencias en susceptibilidad a determinadas enfermedades, pero hasta hace poco su existencia solo podía inferirse. Las nuevas técnicas hacen posible identificar las variantes genéticas específicas que contribuyen a un atributo humano. En lugar de discutir acerca de la importancia relativa de la naturaleza y la crianza, ahora podemos centrar nuestra atención en la búsqueda de variantes genéticas que contribuyan a la predisposición individual a una enfermedad.

11. **Original Text:**

One way to find them is to compare the DNA of family members who have that illness with those who don't. If only those with the illness have a certain variant of a particular gene, the correlation is probably meaningful. If the same variant is also found only in the affected members of a number of other families, the case is strengthened. At some point the likelihood becomes so high that a role for the variant is established. As the details of human genetic structure were being worked out in the 1990s, some gene variants affecting susceptibility to particular illnesses were identified in just this way. Famous examples include the variants of three different genes that each greatly increase the risk of developing rare types of Alzheimer's disease which begin before the age of fifty. In one group of families the culprit was a variant of a gene called APP; in another it was PS1; and in a third it was PS2.

Una manera de encontrarlos es comparando el ADN de los miembros de la familia que padecen la enfermedad con aquellos que no la padecen. Si solamente esos que padecen la enfermedad tienen una determinada variante de un gen en particular, es probable que la correlación sea significativa. Si la misma variante es también encontrada solamente en los miembros afectados de otras familias, el caso se refuerza. En algún momento, la probabilidad llega a ser tan alta que se establece un rol para la variante. En la década de los noventa, a medida que se iban conociendo los detalles acerca de la estructura genética humana, se identificaron algunas variantes genéticas que afectaban a la susceptibilidad a determinadas enfermedades. Ejemplos famosos incluyen la variante de tres genes diferentes que cada uno incrementa en gran medida el riesgo de desarrollar tipos raros de la enfermedad de Alzheimer que empieza antes de los cincuenta años. En un grupo de familias, el culpable fue una variante de un gen llamado APP; en otra, era PS1 y, en una tercera, fue el PS2.

12. Original Text:

The discovery of gene variants that increase the risk of rare types of Alzheimer's disease has stimulated genetic studies of schizophrenia, depression, manic depression, and other psychiatric disorders. The immense appeal of these studies is that they are not dependent on guesses about which genes might be involved, because they can be designed to detect a correlation between the disorder and a variant of any human gene. Although many early studies did focus on specific genes, especially those that influence neurotransmission, we know so little about the genetic control of mental processes that it would not be surprising if other types of genes were implicated. Unfortunately, despite years of effort, no one has yet found a gene variant that definitely increases the risk of any of these mental illnesses. Nor has there been much success in genetic studies of other common disorders, such as diabetes and high blood pressure. One reason for this lack of progress is that susceptibility to all these maladies is determined by the combined actions of variants of multiple genes rather than by variants of a single gene. Although current technology has made it relatively simple to identify the rare variants of single genes that do indeed have a major effect on risk -such as APP, PS1, or PS2- it remains very difficult to find those gene variants that increase risk only if they are inherited in concert with a number of others.

El descubrimiento de variaciones genéticas que incrementan el riesgo de padecer tipos raros de Alzheimer ha estimulado los estudios genéticos de la esquizofrenia, la depresión, la depresión maníaca y de otros trastornos psiquiátricos. El inmenso atractivo de estos estudios es que no dependen de conjeturas acerca de qué genes podrían estar implicados, porque pueden diseñarse para detectar una correlación entre el trastorno y una variante de cualquier gen humano. Aunque muchos de los estudios se centraron en genes específicos, especialmente en los que influyen en la neurotransmisión, sabemos tan poco del control genético de los procesos mentales que no sería sorprendente que estuvieran implicados otros

tipos de genes. Desafortunadamente, a pesar de años de esfuerzo, nadie ha encontrado una variante genética que aumente definitivamente el riesgo de padecer alguna de estas enfermedades mentales. Tampoco ha habido mucho éxito en los estudios genéticos de otros trastornos comunes, como la diabetes y la presión arterial elevada. Una razón para la falta de progreso es que la susceptibilidad a todos estos males está determinada por las acciones combinadas de variantes de múltiples genes y no por variantes de un único gen. A pesar de que la tecnología actual ha hecho relativamente simple de identificar las variantes extrañas de los genes individuales que sí tienen un efecto importante en el riesgo, como el APP, el PS1 o el PS2, sigue siendo muy difícil encontrar aquellas variantes genéticas que aumentan el riesgo solo si se heredan en conjunto con otras.

13. Original Text:

This difficulty will soon be lessened because of the continued growth of knowledge about the human genome. The recent publication of the detailed structure of human DNA is a critical first step. Now DNA specimens from many people are being examined in order to identify and catalog the common variants of each of the approximately thirty thousand human genes. This will greatly simplify the search for the many gene variants that may operate together to influence vulnerability to mental disorders. The search is also being simplified by the development of efficient new techniques for detailed examination of the DNA of any individual. These techniques are in a continual state of improvement, reminiscent of the ongoing development of computer chips. So, too, are the computational methods used to analyze the masses of information from such DNA studies.

Esta dificultad disminuirá pronto debido al continuo crecimiento de los conocimientos sobre el genoma humano. La reciente publicación de la estructura detallada del ADN humano es un primer paso fundamental. Ahora el ADN de muchas personas está siendo examinado

para identificar y catalogar las variantes comunes de cada uno de los aproximadamente treinta mil genes humanos. Esto simplificará enormemente la búsqueda de las numerosas variantes genéticas que pueden operar conjuntamente para influir en la vulnerabilidad a los trastornos mentales. La búsqueda también se está simplificando debido al desarrollo de nuevas técnicas eficaces para el examen detallado del ADN de cualquier individuo. Estas técnicas están en continuo desarrollo, lo que recuerda el desarrollo permanente de los chips informáticos. Lo mismo ocurre con los métodos computacionales utilizados para analizar la gran cantidad de información procedente de estos estudios del ADN.

14. Original Text:

With the evolution of the technology for collecting and evaluating large masses of DNA data, it will soon be possible to mount a massive search for the groups of gene variants that influence susceptibility to particular mental dis orders As the costs of DNA analysis keep falling, we can go beyond relatively small family studies and scrutinize DNA samples from thousands of unrelated people with a particular disorder. Such an investigation should identify the relevant gene variants, only some of which will be found in each affected individual.

To properly use this mass of data about gene variants, it will be necessary to correlate it not only with patterns of disordered behavior but also with properties of the brain. A variety of new methods, such as functional magnetic resonance imaging, are beginning to be used to assess the functions of specific regions of individual human brains. Correlating patterns of gene variants with the results of these and other studies will lead to the identification of subtypes of disorders that are presently lumped together in diagnostic categories, such as schizophrenia or depression.

Con la evolución de la tecnología de recopilación y evaluación de grandes cantidades de datos de ADN, pronto será posible realizar una búsqueda masiva de los grupos de variantes genéticas que influyen en la susceptibilidad a determinados trastornos mentales. A medida que los costos de los análisis de ADN sigan bajando, podríamos ir más allá de los estudios de familias relativamente pequeñas y analizar muestras de ADN de miles de personas no emparentadas con un trastorno en particular. Dicha investigación debe identificar las variantes genéticas relevantes de las cuales solo algunas se encontrarán en cada individuo afectado.

Para utilizar adecuadamente esta masa de datos sobre variantes genéticas, será necesario correlacionarlos no solo con patrones de conducta desordenada, sino también con propiedades del cerebro. Se están empezando a utilizar diversos métodos nuevos, como la resonancia magnética funcional, para evaluar las funciones de regiones específicas de cerebros humanos individuales. La correlación de los patrones de variantes genéticas con los resultados de estos y otros estudios permitirá identificar subtipos de trastornos que actualmente se agrupan en categorías diagnósticas, como la esquizofrenia o la depresión.

15. Original Text:

The combination of genetic information and functional studies will also provide targets for truly novel medications, an approach that is already being used to find new treatments for Alzheimer's disease. Currently the main drugs for Alzheimer's disease improve brain function by prolonging the actions of a neurotransmitter called acetylcholine, a mechanism similar to the actions of some other contemporary drugs, such as the SSRIs. The identification of variants of APP, PS1, and PS2 in rare cases of Alzheimer's disease has helped focus attention on alternative drug targets. Called secretases, these are brain enzymes that play a part in the production of a toxic protein fragment called beta-amyloid, whose

accumulation is also affected by the gene variants in a few different ways. Several drug companies are studying drugs that inactivate the secretases, which they hope to use to reduce beta-armyloid accumulation and thereby stop brain degeneration.

La combinación de información genética y estudios funcionales proveerá objetivos para medicamentos realmente novedosos, un método que ya se utiliza para encontrar nuevos tratamientos contra el Alzheimer. Actualmente, los principales fármacos para el Alzheimer mejoran el funcionamiento del cerebro prolongando las acciones del neurotransmisor llamado acetilcolina, un mecanismo similar a las acciones de otros fármacos contemporáneos, como los ISRS. La identificación de variantes de APP, PS1 y PS2 en casos raros de Alzheimer ha contribuido a centrar la atención en objetivos farmacológicos alternativos. Llamadas secretasas, son las enzimas que forman parte en la producción de una proteína tóxica fragmentada llamada beta amiloide, cuya acumulación es también afectada por las variaciones genéticas de diferentes maneras. Muchas de las compañías farmacéuticas están estudiando fármacos que inactiven las secretasas, que esperan utilizar para reducir la acumulación de beta amiloide y detener así la degeneración cerebral.

5.1.3. Glossary

This section presents the glossaries developed for each of the two translated documents: one translated from English to Spanish and the other from Spanish to English. Each glossary was compiled as a support tool to ensure terminological consistency, accuracy, and clarity throughout the translation process. Given the specialized nature of the texts, particularly in the medical and scientific fields, many terms required careful consideration to preserve their meaning in the target language while maintaining readability for the intended audience.

The creation of two separate glossaries allowed for a focused approach to terminology management in each language direction. Terms were selected based on frequency, technical relevance, and potential ambiguity, and each entry includes the source term, its equivalent in the target language, and, when necessary, explanatory notes or context of use. These glossaries not only supported the translation process itself but also served as a reference for future translations of similar texts. Their inclusion in this chapter contributes to the analysis by highlighting the terminological challenges encountered and the strategies used to resolve them.

5.1.3.1. Glossary of "Cardiología Molecular. Módulo 3: Diabetes Mellitus Tipo 2" by Jonatan Navarro.

To ensure the glossary's accuracy and reliability, definitions were drawn from various authoritative and specialized sources. For medical and scientific terms, references such as Cleveland Clinic, ScienceDirect, MedlinePlus, NCBI (National Center for Biotechnology Information), and National Cancer Institute were used. These platforms provided up-to-date and contextually appropriate definitions, particularly valuable for specialized terminology encountered in medical documents translated from Spanish to English. In cases where conceptual or stylistic terms, such as understatement, were involved. Resources like the Merriam-Webster Dictionary were also consulted to obtain definitions that accurately reflect linguistic and rhetorical usage. By cross-referencing multiple sources, the glossary aimed to include the most precise and contextually relevant definitions possible, helping to preserve both the technical accuracy and the intended tone of the original texts. This methodical approach supports consistency throughout the translation and reinforces the glossary's role as a foundational tool in this project.

Table 4. Glossary from Spanish to English Translation.

Word #	Source Language	Target Language	Grammatical Category	Definition
1.	AMPK	AMPK	Noun	AMP-activated protein kinase (AMPK) is an enzyme that helps maintain cellular energy levels. It's activated when cellular energy is low, and it helps restore energy balance by increasing glucose and fatty acid uptake and oxidation.
2.	Angiotensina	Angiotensin	Noun	Angiotensin is a peptide hormone, specifically angiotensin II that plays a crucial role in regulating blood pressure and fluid balance by causing vasoconstriction and stimulating sodium and water retention.
3.	ARE	ARE	Noun	The antioxidant response element (ARE) is a DNA sequence found in the promoter regions of genes encoding antioxidant and detoxification enzymes, that, when activated, triggers the expression of these protective genes, primarily through the transcription factor Nrf2.
4.	Fibrilación Auricular	Atrial Fibrillation	Noun	Atrial fibrillation (Afib) is an irregular heart rhythm that begins in your heart's upper chambers (atria). Symptoms include fatigue, heart palpitations, trouble breathing and dizziness.
5.	BIRC2	BIRC2	Noun	BIRC2 is a multi-functional protein that regulates apoptosis and plays a role in various cellular processes, including cancer development and immune evasion.
6.	Canagliflozina	Canagliflozin	Noun	Canagliflozin is in a class of medications called sodium-glucose co-transporter 2 (SGLT2) inhibitors. It lowers blood sugar by causing the kidneys to get rid of more glucose in the urine.
7.	Biomarcadores Cardiácos	Cardiac Biomarkers	Noun	Cardiac biomarkers are substances released into the bloodstream when the heart is damaged or stressed, and their measurement helps diagnose, assess risk, and manage conditions like acute coronary syndrome (ACS) and heart failure.

8.	Catalasa	Catalase	Noun	Catalase is a red crystalline enzyme that consists of a protein complex with hematin groups and catalyzes the decomposition of hydrogen peroxide into water and oxygen
9.	Apoptosis Celular	Cell Apoptosis	Noun	Apoptosis, or programmed cell death, is a natural, clean process where cells self-destruct to maintain tissue health and development
10.	Citoquinas	Cytokines	Noun	A type of protein that is made by certain immune and non-immune cells and has an effect on the immune system.
11.	Disfunción Diastólica	Diastolic Dysfunction	Noun	Diastolic dysfunction is a condition where the heart's ventricles (lower chambers) don't relax and fill with blood adequately during the diastolic phase of the cardiac cycle (the period between heartbeats when the heart chambers are filling).
12.	Empagliflozina	Empagliflozin	Noun	Empagliflozin is used to treat type 2 diabetes. It works in the kidneys to prevent absorption of glucose (blood sugar). This helps lower the blood sugar level.
13.	Galectina-3	Galectin-3	Noun	Galectin 3 is a member of the multifunctional galectin family, which is ubiquitously expressed in the heart, the kidney, blood vessels, and macrophages and plays a role in tissue fibrosis, immunity, and the inflammatory response.
14.	Glucotoxicidad	Glucotoxicity	Noun	Glycotoxicity refers to the detrimental effects of chronic exposure to high blood glucose (hyperglycemia) on the function of beta cells, leading to impaired insulin secretion and increased insulin resistance.
15.	IL-1 (interleucina 1)	IL-1 (interleukin 1)	Noun	Interleukin-1 (IL-1) is a family of cytokines, primarily produced by immune cells like macrophages that play a crucial role in the innate immune response, inflammation, and fever, acting as a bridge between innate and acquired immunity.

16.	iSGLT2	iSGLT2	Noun	iSGLT2 stands for inhibitors of the sodium-glucose co-transporter 2. These are a class of medications that work by blocking the reabsorption of glucose in the kidneys, leading to increased glucose excretion in the urine.
17.	Lipotoxicidad	Lipotoxicity	Noun	Lipotoxicity refers to the harmful effects of excess lipids and their metabolites accumulating in non-adipose tissues, leading to cellular dysfunction and potential cell death, often associated with metabolic disorders like obesity and type 2 diabetes.
18.	Malondialdehído	Malondialdehyde	Noun	Malondialdehyde (MDA) is a highly reactive aldehyde, a byproduct of lipid peroxidation (oxidation of lipids), and is used as a marker for oxidative stress and lipid damage in the body.
19.	Miocardio	Myocardium	Noun	The myocardium is the middle muscular layer of the heart. It is the thickest layer which lies between the single-cell endocardium layer, and the outer epicardium, which makes up the visceral pericardium that surrounds and protects the heart.
20.	Nefropatía	Nephropathy	Noun	Nephropathy, also known as kidney disease, refers to any damage or disease of the kidneys, potentially leading to kidney failure and requiring dialysis or a transplant.
21.	Nrf2	Nrf2	Noun	Nrf2, or nuclear factor erythroid 2-related factor 2, is a transcription factor that acts as a master regulator of cellular responses against oxidative stress, regulating the expression of genes involved in antioxidant defense, detoxification, and other stress-related processes.

22.	Estrés oxidativo	Oxidative Stress	Noun	Oxidative stress is an imbalance where the body produces too many reactive oxygen species (free radicals) and doesn't have enough antioxidants to neutralize them, leading to potential cell and tissue damage.
23.	ST2	ST2	Noun	ST2, or soluble interleukin 1 receptor-like 1 (sIL1RL1), is a circulating biomarker, a protein released in response to cardiac stress, that signals the presence and severity of adverse cardiac remodeling and tissue fibrosis, particularly in heart failure.
24.	Dismutasa Superóxido	Superoxide Dismutase	Noun	Superoxide dismutase (SOD) is a metalloenzyme that catalyzes the dismutation of superoxide radicals into oxygen and hydrogen peroxide, playing a crucial role in cellular antioxidant defense.
25.	Sistólica	Systolic	Adjective	Used to describe the phase of the blood pressure cycle when the ventricles of the heart have their strongest contractions against the blood vessel walls.
26.	Type 2 diabetes mellitus (T2DM)	Type 2 diabetes mellitus (T2DM)	Noun	Type 2 diabetes, formerly known as adult-onset diabetes, is a form of diabetes mellitus that is characterized by high blood sugar, insulin resistance, and relative lack of insulin.

Table 5 illustrates the glossary from the translation made of "Cardiología Molecular. Módulo 3: Diabetes Mellitus Tipo 2" by Jonatan Navarro. Source: Researcher's creation

5.1.3.2. Glossary of "The Next Fifty Years" by John Brockman

For the glossary created during the translation of "The Next Fifty Years" by John Brockman, a selection of reliable and scientifically recognized sources was consulted to ensure precise and contextually appropriate definitions, particularly for terms related to neuroscience, genetics, psychiatry, and molecular biology. The glossary entries were informed by references such as the National Cancer Institute, Clínica Universidad de Navarra, the National Human Genome Research Institute, MedlinePlus, and CIMA (Centro

de Investigación Médica Aplicada). To provide academic and research-based definitions, resources from the Universitat Pompeu Fabra (Barcelona) were also used. Additionally, KenHub and the Mayo Clinic supported the glossary with clinically accurate and anatomically grounded explanations. These sources were selected for their relevance, clarity, and scientific credibility, allowing the glossary to serve as a key reference point for ensuring consistency, accuracy, and accessibility throughout the translation of this complex and interdisciplinary scientific text.

Table 5. Glossary from English to Spanish Translation.

Word #	Source Language	Target Language	Grammatical Category	**Definition**
1.	Acetylcholine	Acetilcolina	Noun	La acetilcolina (ACh) es un neurotransmisor fundamental en el sistema nervioso central y periférico, clave en la transmisión de señales nerviosas, la memoria, el aprendizaje y el control muscular.
2.	Gamma-Aminobutyric Acid (GABA)	Ácido Gamma-Aminobutírico (GABA)	Noun	El ácido gamma-aminobutírico (GABA) es un neurotransmisor inhibitorio crucial en el sistema nervioso central, que reduce la excitabilidad neuronal y juega un papel importante en la regulación de la ansiedad, el sueño y el tono muscular.
3.	Alleles	Alelos	Noun	Un alelo es una de las formas o variantes de un gen que se encuentra en el mismo locus (posición) en los cromosomas homólogos, heredando uno de cada progenitor.
4.	Alzheimer	Alzheimer	Noun	La enfermedad de Alzheimer es la forma más común de demencia entre las personas mayores. La demencia es un trastorno cerebral que afecta gravemente las habilidades de pensamiento y memoria.
5.	Antihistamine	Antihistamínico	Noun	Tipo de medicamento que bloquea la acción de la histamina, sustancia que puede causar fiebre, picazón,

				estornudos, mucosidad nasal y lagrimeo. Los antihistamínicos se utilizan para prevenir la fiebre en los pacientes que se someten a transfusiones de sangre y para el tratamiento de alergias, tos y resfriados.
6.	APP	APP	Noun	El gen APP codifica la proteína precursora amiloide (APP, por sus siglas en inglés). Este péptido es el principal componente de las placas amiloides, que son depósitos anormales que se forman en el cerebro de las personas con enfermedad de Alzheimer.
7.	Benzodiaze-pine	Benzodiace-pínico	Noun	Las benzodiacepinas son un grupo de fármacos psicotrópicos usados para tratar trastornos como la ansiedad, el insomnio y las convulsiones, actuando como moduladores alostéricos de los receptores GABA, lo que potencia la acción inhibidora de este neurotransmisor.
8.	Beta Amyloid	Beta Amiloide	Noun	El péptido beta amiloide (Aβ) es un producto natural del metabolismo de la proteína precursora del amiloide (PPA), y su acumulación en placas seniles en el cerebro es un factor clave en la patogénesis de la enfermedad de Alzheimer.
9.	Citalopram (Celexa)	Citalopram (Celexa)	Noun	El citalopram pertenece a una clase de antidepresivos llamados inhibidores selectivos de la recaptación de serotonina (SSRI, selective serotonin reuptake inhibitors). Su acción consiste en aumentar la cantidad de serotonina, una sustancia natural del cerebro que ayuda a mantener el equilibrio mental.
10.	Chlordiazepoxi de (Librium)	Clordiazepó-xido (Librium)	Noun	El clordiazepóxido se utiliza para aliviar la ansiedad y para control la agitación causada por la abstinencia de alcohol. El clordiazepóxido pertenece a una clase de medicamentos llamados benzodiacepinas. Su acción consiste

				en reducir la actividad eléctrica anormal en el cerebro.
11.	Chlorproma-zine (Largactil)	Clorpromazina (Largactil)	Noun	Es un fármaco antipsicótico y neuroléptico perteneciente al grupo de medicamentos denominados fenotiazinas. Su actividad neuroléptica se manifiesta por su capacidad sedante que resulta de utilidad en los estados de agitación, agresividad y angustia de los enfermos mentales.
12.	Cortex	Córtex	Noun	La corteza cerebral (córtex cerebral o corteza del encéfalo) es la capa externa de sustancia gris que cubre por completo la superficie de ambos hemisferios cerebrales. Es en la corteza cerebral donde ocurren la percepción, la imaginación, el pensamiento, el juicio y la toma de decisiones.
13.	Diazepam (Valium)	Diazepam (Valium)	Noun	El diazepam, comercializado como Valium, es una benzodiazepina que se utiliza para tratar la ansiedad, la agitación, la tensión psíquica, los espasmos musculares y, en algunos casos, la abstinencia de alcohol.
14.	Fluoxetine (Prozac)	Fluoxetina (Prozac)	Noun	La fluoxetina se utiliza para tratar la depresión, el trastorno obsesivo-compulsivo (pensamientos molestos que no desaparecen, y la necesidad de realizar ciertas acciones una y otra vez), algunos trastornos de la alimentación y ataques de pánico.
15.	Fluvoxamine (Luvox)	Fluvoxamina (Luvox)	Noun	La fluvoxamina (Luvox) es un medicamento antidepresivo que se utiliza para tratar el trastorno obsesivo-compulsivo (TOC) y, en algunos casos, la depresión, al aumentar la disponibilidad de serotonina en el cerebro.
16.	Human Genome	Genoma Humano	Noun	El genoma humano es la totalidad del material genético (ADN) que contiene un organismo, organizado en 23 pares de cromosomas, y contiene toda la información necesaria para el desarrollo y funcionamiento de un ser humano.

17.	Glutamate	Glutamato	Noun	El glutamato es un aminoácido no esencial que actúa como el principal neurotransmisor excitatorio en el cerebro, crucial para la comunicación entre neuronas, el aprendizaje, la memoria y la plasticidad sináptica, además de ser responsable del sabor umami.
18.	Imipramine (Tofranil)	Imipramina (Tofranil)	Noun	La imipramina en tabletas y cápsulas se usa para tratar la depresión. La imipramina pertenece a una clase de medicamentos denominados antidepresivos tricíclicos.
19.	Norepinephrine (Noradrenalin)	Norepinefrina (Noradrenalina)	Noun	Noradrenalina (norepinefrina) pertenece al grupo de medicamentos llamados “agentes adrenérgicos y dopaminérgicos”, que actúan aumentando la presión de la sangre. Noradrenalina se usa para el tratamiento de las bajadas agudas de tensión arterial (hipotensión aguda).
20.	Paroxetine (Paxil)	Paroxetine (Paxil)	Noun	La paroxetina pertenece a una clase de medicamentos llamados inhibidores selectivos de la recaptación de serotonina (ISRS). Trata la depresión y otras enfermedades mentales aumentando la cantidad de serotonina, una sustancia natural del cerebro que ayuda a mantener el equilibrio mental.
21.	PS1	PS1	Noun	El gen PS1 codifica la proteína presenilina 1. Esta proteína es un componente de un complejo enzimático llamado gamma-secretasa. La gamma-secretasa es responsable de cortar la proteína APP en los fragmentos más pequeños, incluyendo el péptido beta-amiloide.
22.	PS2	PS2	Noun	El gen PS2 codifica la proteína presenilina 2. Esta proteína es similar a la presenilina 1 y también es un componente de la gamma-secretasa.

23.	Sertraline (Zoloft)	Sertralina (Zoloft)	Noun	La sertralina se utiliza para tratar la depresión, el trastorno obsesivo-compulsivo (pensamientos molestos que no desaparecen, y la necesidad de realizar ciertas acciones una y otra vez), los ataques de pánico (ataques repentinos e inesperados de miedo extremo, y la preocupación por estos ataques), etc.
24.	Synaptic Tissue	Tejido Sináptico	Noun	El tejido sináptico, o sinapsis, es el punto de comunicación entre dos células, generalmente neuronas, donde se transmite la información a través de señales químicas o eléctricas, permitiendo la transmisión de impulsos nerviosos.
25.	Bipolar Disorder	Trastorno Bipolar	Noun	El trastorno bipolar, antes denominado depresión maníaca, es una enfermedad mental que causa cambios del estado de ánimo extremos. Estos incluyen subidones emocionales, también conocidos como manía o hipomanía, y bajones, también conocidos como depresión.

Table 6 Illustrates the glossary made from the translation of "The Next Fifty Years" by John Brockman. Source: Researcher's creation

Chapter VI

Conclusions and Recommendations

This chapter aims to synthesize the key findings of the study and outline practical recommendations for future research and practice in the field of medical translation. It begins by clarifying the purpose of the conclusions, emphasizing how the insights gained from this study enhance our understanding of the effectiveness of the translation procedures applied in both the English-to-Spanish and Spanish-to-English projects.

The discussion is structured around the specific objectives of the research, providing a detailed examination of the outcomes associated with each. This allows for a comprehensive reflection on the successes and challenges encountered during the translation processes and how these experiences inform the best practices moving forward. To reaffirm the study's central inquiry, the chapter restates the research question, providing context for the findings and framing them within the broader landscape of medical translation. It is also crucial to address any unexpected results documented throughout the study. This exploration highlights areas that require further investigation, drawing attention to gaps in the current body of knowledge and suggesting avenues for future exploration.

The chapter concludes with targeted recommendations aimed at enhancing translation quality, ensuring terminological consistency, and promoting overall best practices within the field of medical translation. These recommendations are intended not only to guide practitioners in their day-to-day work but also to serve as a foundation for future researchers seeking to build upon the findings of this study. Through these efforts, we can aspire to improve the effectiveness and accuracy of medical translations, benefiting patients and healthcare providers alike.

6.1. Purpose of the Conclusion

The conclusion of this investigation serves two primary purposes. Firstly, it aims to present and consolidate the key findings derived from the translation and analysis of two distinct texts: “Cardiología molecular. Módulo 3: Diabetes Mellitus Tipo 2” and “The Next Fifty Years.” By reflecting on the translation process of these texts, one from Spanish into English and the other from English into Spanish, this section offers a broader understanding of the challenges, strategies, and outcomes associated with translating specialized content in both directions. Secondly, the conclusion functions to evaluate the extent to which the general and specific objectives of the research were successfully met. Through a critical review of the results, the researcher validates the effectiveness of the applied translation techniques, and the methodological tools used, such as text analysis, color coding, and glossary creation. In doing so, this chapter highlights the academic and practical value of the study and contributes to the ongoing development of best practices in medical and scientific translation.

6.2. Conclusions

This section presents the main conclusions of the study, based on the analysis and results obtained throughout the translation and evaluation of two specialized texts. Each subsection corresponds to a specific objective stated in Chapter I and aims to assess how it was fulfilled through the research process.

6.2.1. To translate “Cardiología molecular. Módulo 3: Diabetes Mellitus tipo 2” by Jonatan Navarro Solano and “The Next Fifty Years” by John Brockman for Hospital Mexico to achieve accurate and natural target texts

The translations of both texts, “The Next Fifty Years” by John Brockman and “Cardiología Molecular. Módulo 3: Diabetes Mellitus Tipo 2” by Jonatan Navarro, were

completed with a strong emphasis on linguistic accuracy, fluency, and a natural, engaging flow in the respective target languages. Each translation underwent a meticulous process that prioritized not only the preservation of meaning but also the adaptability of language to cater to the cultural and contextual nuances key to each work.

For Brockman's piece, the translation was crafted specifically for an educated audience. This involved ensuring that the content was both intellectually stimulating and easily comprehensible, preserving the author's intent while making it accessible to a broad readership. The translator paid special attention to the tonal quality of the work, selecting phrases and vocabulary that resonate with an audience familiar with contemporary discussions in science and philosophy. On the other hand, Navarro's work was translated with a focus on individuals with a technical background in the medical field. This required the incorporation of specialized terminology and concepts relevant to molecular cardiology and diabetes research. The translator's expertise allowed for a nuanced rendering of highly specific terms, ensuring that readers with a strong foundational knowledge would find the translation informative and coherent.

This project exemplified the translator's flexibility and skill as it navigated through both directions of translation, from Spanish to English and vice versa. The thoroughness with which cultural context and structural differences were addressed resulted in translations that not only align with the original texts but also feel authentic and relatable to the target audiences. The final versions of both texts reflect high standards of clarity and professionalism. Such quality makes them appropriate for integration into the esteemed resources of the Hospital Mexico Library, contributing valuable insights and knowledge to healthcare professionals and scholars who utilize these materials.

6.2.2. To apply translation techniques for ensuring linguistic clarity, readability, and alignment with industry standards in medical translation.

During the translation process, a variety of well-established techniques were adeptly employed to ensure both accuracy and clarity. Key among these methods were transposition, modulation, amplification, explicitation, omission, and literal translation. Each of these techniques played a distinct role in addressing the unique challenges posed by the medical texts being translated. In the translated texts, literal translation was frequently prioritized as it serves to maintain the integrity of specialized terminology and precise meanings essential in a field where even minor discrepancies can lead to misunderstandings. This focus on accuracy helps to ensure that critical information is conveyed correctly to healthcare professionals and patients alike.

On the other hand, modulation was employed to adapt the message in a way that enhances comprehension without altering the intended meaning. This technique allowed translators to adjust the perspective or tonal quality of the original text, making complex medical concepts more accessible to the target audience. Amplification was also a valuable strategy, particularly for expanding upon terminology that may not have an exact equivalent in the target language. Explicitation was utilized to clarify implicit information and to fill in gaps that might confuse readers unfamiliar with specific medical jargon. Then, the omission was judiciously applied to eliminate redundant or culturally irrelevant elements that could detract from the overall flow and understanding of the text.

Each of these methods was meticulously chosen based on the linguistic and contextual requirements specific to each text. The deliberate application of these strategies contributed significantly to improving the clarity and coherence of complex medical and scientific passages. By adhering to widely accepted industry standards, translations achieved a balance

between precision and readability, two essential pillars for effective medical translation. This careful diligence not only serves the needs of the medical community but also fosters better patient outcomes through enhanced communication.

6.2.3. To create a glossary with the most relevant terminology found in both texts, ensuring consistency and accuracy for the Hospital Mexico Library

Two comprehensive glossaries were meticulously compiled, one for each document involved in the translation process. These glossaries include essential medical and scientific terminology that was encountered during the translation, ensuring that all relevant terms were thoroughly captured and explained. To create these glossaries, definitions were drawn from a range of reputable and authoritative sources, including MedlinePlus, the National Cancer Institute, the Mayo Clinic, and ScienceDirect, among others. This careful selection of sources guarantees that the definitions are not only accurate but also reflect the most current understandings within the medical and scientific communities.

The creation of these glossaries played a crucial role in maintaining consistency in terminology usage throughout the translation process, thereby reducing ambiguity and misinterpretation. Furthermore, they served as valuable resources for decision-making during the translation, allowing translators to reference standardized definitions and ensure that they aligned with the original texts' intents.

In addition to their immediate application in the translation process, these glossaries are designed as practical tools for future translators and professionals who may utilize these texts in various academic or clinical environments. By providing clarity and understanding of specialized terms, the glossaries contribute significantly to the library's long-term resource development, enhancing the quality of knowledge available to its users.

6.2.4. To evaluate the effect of the translation techniques applied to the documents

The evaluation of the translation techniques employed was conducted through a comprehensive methodology that combined meticulous text analysis with a visually engaging color-coded system. This approach was specifically designed to illuminate the various translation procedures utilized in each paragraph of the translated material. By mapping these techniques visually, it became possible to accurately pinpoint the frequency, function, and impact of a range of strategies, including modulation, amplification, and omission. The analysis unveiled that these translation strategies effectively navigated numerous linguistic and cultural challenges, allowing translators to convey meaning more clearly and effectively. Moreover, these techniques played a crucial role in enhancing the overall coherence, tone, and readability of the target texts, making them more accessible to the audience.

Additionally, the evaluation underscored how the careful selection and application of these techniques directly affected the accuracy and accessibility of specialized content, especially in contexts such as institutional and academic settings. The process affirmed the necessity of adopting a systematic and context-sensitive approach to translation, particularly in complex fields like medicine and science, where precision and clarity are of paramount importance.

6.3. Restatement of the Research Question

What are the challenges and outcomes associated with applying translation procedures to medical documents for the Hospital Mexico Library, particularly in achieving accuracy, clarity, and cultural relevance when translating from Spanish to English and vice versa?

The research question guiding this study was: What are the challenges and outcomes associated with applying translation procedures to medical documents for the Hospital Mexico Library, particularly in achieving accuracy, clarity, and cultural relevance when translating from Spanish to English and vice versa? This investigation has demonstrated that translating medical and scientific texts presents a range of challenges, including specialized terminology, differences in syntactic structure, variations in cultural context, and the need for consistent tone and register. However, the application of carefully selected translation techniques, such as modulation, transposition, explicitation, and amplification, proved effective in addressing these challenges. The outcomes of the study confirm that it is possible to produce translations that are not only accurate and clear but also culturally and functionally appropriate for the intended audience. The findings validate the importance of a methodical and context-sensitive approach to medical translation and reinforce the need for linguistic precision and cultural awareness in institutional settings like the Hospital Mexico Library.

6.4. Unexpected Results

Although the study was carefully planned around specific objectives, several unexpected yet insightful findings emerged. One notable result was the high frequency and adaptability of techniques such as amplification and modulation, which proved more useful than initially anticipated, particularly in managing complex and layered meanings in both texts. Additionally, while medical terminology was expected to pose the main challenge, stylistic shifts, and tone preservation, especially in the English-Spanish translation of The Next Fifty Years, presented equally significant demands on the translator. Another unexpected insight was the added benefit of the glossaries, which not only supported terminological consistency but also enhanced the efficiency of the translation process. Finally, the use of the color-coded system, originally intended as a simple tracking method,

revealed itself as a powerful tool for visualizing and evaluating translation decisions, adding a layer of depth to the analysis.

6.5. Recommendations

Based on the findings and outcomes of this study, several recommendations can be made for both experienced translators and those who are new in the profession. The first and most fundamental recommendation is the importance of selecting appropriate translation techniques based on the context, purpose, and audience of the text. Techniques such as modulation, amplification, explicitation, transposition, and literal translation proved highly effective when applied with intention and flexibility. Translators should aim not only to transfer meaning but to ensure that the target text reads, accurately, and naturally within its specialized context.

A second important recommendation is the creation and use of project-specific glossaries. Throughout this research, glossary development played a crucial role in maintaining terminological consistency and improving translation speed. Glossaries should be based on trustworthy and specialized sources. New translators can benefit from building glossaries as they translate, helping them reinforce terminology learning while also enhancing quality control.

In addition, it is highly recommended that translators conduct a textual analysis before translation, considering features such as text function, style, formality, emotional tone, and level of complexity. This preliminary step helps anticipate challenges and informs decisions on how to approach each segment of the text. For example, identifying a high level of formality or emotional nuance will guide the translator toward more appropriate techniques for achieving functional equivalence. New translators are also encouraged to understand the limitations of literal translation, especially in texts with rhetorical or expressive components,

such as those found in The Next Fifty Years. A balance between literal and functional equivalence is key to producing translations that are not only linguistically accurate but also culturally and contextually appropriate.

Finally, this research highlights the value of translating in both directions (Spanish to English and English to Spanish). Doing so enhances the translator's awareness of syntactic and lexical challenges in each language and fosters greater adaptability. Whenever possible, collaboration with subject-matters is also recommended, especially for highly technical or medical texts. Their insights can resolve ambiguities and improve both the reliability and safety of the final product. Together, these recommendations aim to support the development of best practices in specialized translation and provide practical guidance for those working on institutional projects, such as those for the Hospital Mexico Library.

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Annexes

Annex 1. "Cardiología Molecular. Módulo 3: Diabetes Mellitus Tipo 2" by Jonatan Navarro

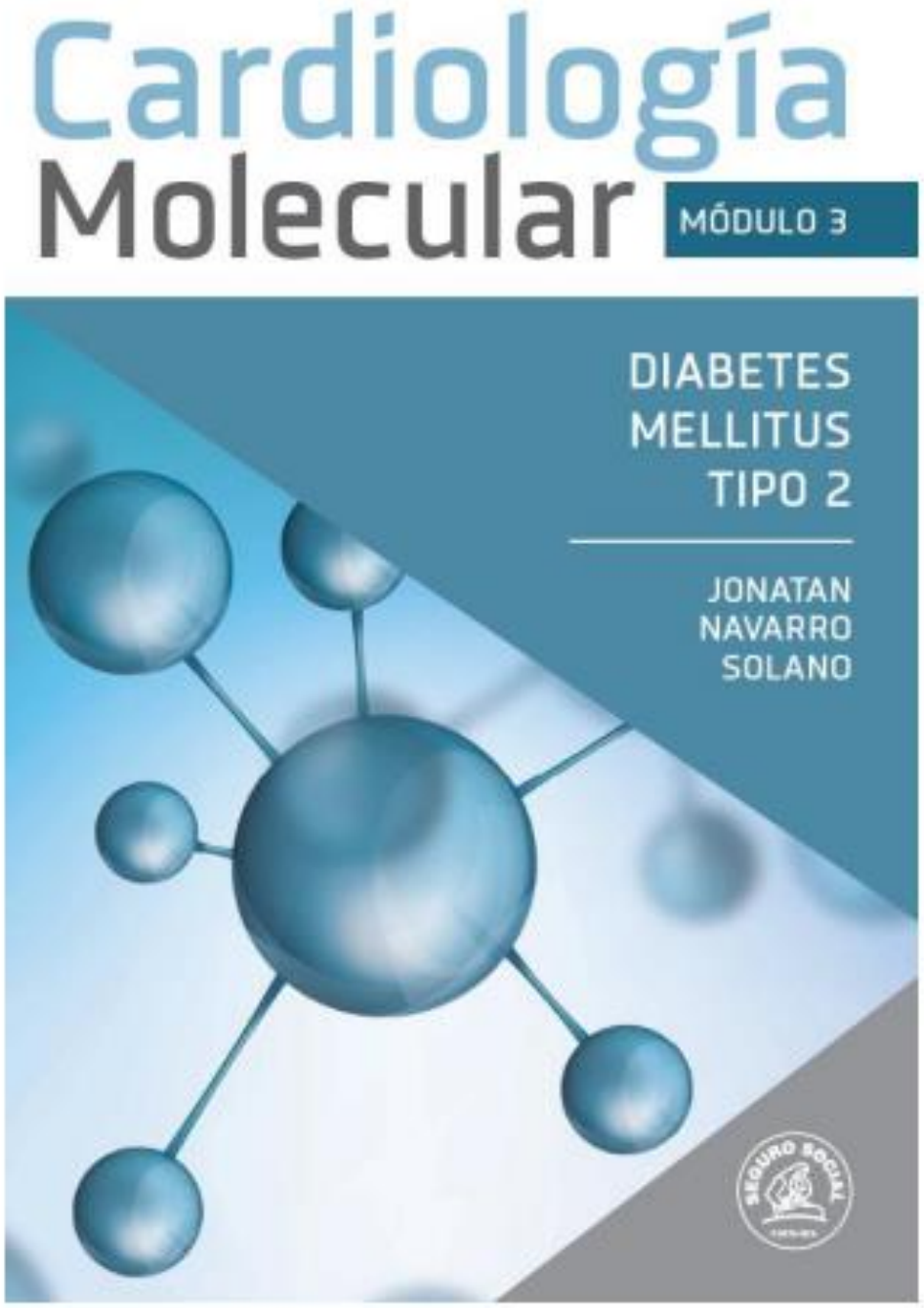

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TABLA DE CONTENIDO

SOBRE EL AUTOR

Jonatan Navarro Solano, costarricense, nacido en San José, es médico general y actualmente labora en el sector privado. Posee el título de investigador principal para estudios observacionales avalado por el Ministerio de Salud de Costa Rica y ha realizado varias publicaciones científicas en el campo de la Cardiología.

Desde el año 2019 se ha dedicado a la investigación y al estudio del funcionamiento molecular cardíaco, por cuanto considera de suma importancia el develar cada vez más y de manera comprensible y útil este tema a nivel clínico, para el desarrollo de futuras moléculas que tengan una función terapéutica en la patología cardiovascular.

INTRODUCCIÓN

La diabetes mellitus tipo 2 (DM2) desempeña un papel muy relevante en el desarrollo de la enfermedad cardiovascular, debido a sus acciones metabólicas en el miocardio, que afectan su función diastólica y sistólica.

Los procesos fisiopatológicos de la DM2 en el corazón se producen por medio de diferentes vías moleculares, las cuales son estimuladas ante las nuevas adaptaciones del miocardio, generando otras patologías cardíacas, como la fibrilación auricular.

Para conocer más sobre este tema, que es de gran relevancia en la actualidad, se analizará en este módulo el comportamiento de las moléculas cardíacas ante la diabetes mellitus tipo 2, con el fin de que la información pueda servir de guía para el manejo terapéutico en la enfermedad cardiovascular.

Partiendo de ese objetivo, se explican específicamente la acción de los biomarcadores cardíacos ST2 y galectina-3 en la DM2, la función del receptor de sodio-glucosa tipo 1 en el miocardio, las acciones moleculares de los iSGLT2 en el miocardio y, por último, la relación de la fibrilación auricular con la DM2.

CAPÍTULO 1. ACTIVIDAD DE LOS BIOMARCADORES CARDÍACOS EN LA DIABETES MELLITUS TIPO 2

INTRODUCCIÓN

La diabetes mellitus tipo 2 (DM2) afecta actualmente a alrededor de 62 millones de personas en las Américas (1), convirtiendo a esta enfermedad en un problema importante de salud pública, al que debe prestársele atención.

Estudios recientes han demostrado que la tasa de mortalidad anual global por diabetes mellitus tipo 2 es de 1,5 millones y adicionalmente se producen 2,2 millones de muertes relacionadas con enfermedades cardiovasculares (2).

Ese último dato toma mayor relevancia si se considera que la prediabetes y la DM2 se han asociado con el desarrollo de daño miocárdico directo, inflamación microvascular y disfunción endotelial, factores que contribuyen a un mayor riesgo de eventos clínicos cardiovasculares (2).

Se ha comprobado que en lo anterior influye la elevación que se produce en la DM2 de los biomarcadores ST2 y galectina-3, los cuales actúan en el tejido cardíaco (2). De ahí la importancia de conocer con mayor profundidad estos dos biomarcadores.

ST2 (SUPRESIÓN DE TUMORIGENICIDAD 2)

Acción del ST2 en el miocardio

La supresión de tumorigenicidad 2 (ST2) es una proteína que forma parte de la IL-1 (interleucina 1). Este biomarcador se encuentra en múltiples isoformas a nivel tisular, entre ellas la transmembrana conocida como ligando ST2 (ST2L) y la circulante soluble (sST2).

En el tejido cardíaco los fibroblastos producen la interleucina 33, que forma un complejo junto a la ST2L (IL-33/ST2L), para estimular el factor nuclear (NF)-kB, con el fin de prevenir acciones perjudiciales en el miocardio, como el estrés oxidativo y la apoptosis celular. De tal forma, este complejo ejerce efectos cardioprotectores, como la reducción de la fibrosis miocárdica y de la hipertrofia del cardiomiocito, y disminuye la apoptosis celular, mejorando la función miocárdica (3-4).

Sin embargo, la elevada concentración de la isoforma ST2 soluble bloquea los efectos favorables del complejo IL-33/ST2L, aumentando la remodelación cardíaca, con una repercusión negativa sobre los desenlaces clínicos (5).

Investigaciones del biomarcador ST2 cardíaco en DM2

En los últimos años se han efectuado múltiples estudios en los que se ha analizado la relación existente entre el biomarcador ST2 y la DM2. A continuación, se resumen algunos de ellos:

- En un estudio se analizaron los niveles y la relación del ST2 cardíaco en tres grupos de personas: un grupo control (sin DM2), un grupo con prediabetes y un grupo con DM2. Los resultados demostraron que las concentraciones del biomarcador fueron de 37,9 ng/ml en el grupo con DM2, de 26,1 ng/ml en el grupo con prediabetes y de 19,3 ng/ml en el grupo control. Por otro lado, se determinó que el riesgo de presentar prediabetes en el grupo control con respecto a los valores de ST2, no tiene una diferencia estadísticamente significativa ($p>0,05$). Sin embargo, se demostró el desarrollo de DM2 en el grupo control conforme aumentaban los valores de ST2 ($p<0,001$). En conclusión, los valores del ST2 cardíaco están más elevados en la DM2, generando lesión miocárdica. Hasta el momento no se conoce con exactitud cuál es el mecanismo que produce esta afectación, aunque es probable que se desarrolle a partir de la vía sST2/IL33 (6).

- Un grupo de investigadores evaluó el efecto del ST2 en la mortalidad tanto por causas cardiovasculares como por todas las causas en la enfermedad ateroesclerótica de un grupo de pacientes del Registro de Ateroesclerosis *To Vergata*. Los participantes del estudio se dividieron en cuatro grupos, con base en los niveles de glicemia: el primero con valores glicémicos normales, el segundo con alteración en los niveles de glicemia, el tercero con diagnóstico reciente de DM2 y el cuarto con diagnóstico de diabetes ya establecido. En los grupos de personas con diabetes se demostró la presencia de mayores niveles de ST2, siendo estadísticamente significativo en comparación con los demás grupos. También se comprobó que los niveles elevados de glicemia y de hemoglobina glicosilada estaban relacionados con el aumento en los niveles de ST2 (p=0,002). Finalmente, este biomarcador se asoció con mayor mortalidad por causas cardiovasculares en pacientes diabéticos; sin embargo, no presentó un riesgo significativo en la mortalidad por todas las causas. A partir de este estudio se concluye que la ST2 se encuentra elevada en alteraciones de la glicemia, pero no queda muy claro el mecanismo bioquímico o molecular específico por el que esta molécula actúa en el miocardio afectado por diabetes (*7*).

- Un estudio en insuficiencia cardiaca con fracción de eyección reducida y preservada, analizó los niveles de ST2 y BNP. Dentro de los participantes, 58 cursaban con DM2 y 63 con niveles normales de glicemia. En el grupo de los diabéticos se evidenciaron mayores niveles de ST2 en comparación con los no diabéticos (72±42 ng/ml vs 59±33 ng/ml; p=0,04). Además, los niveles elevados de ST2 demostraron ser un factor pronóstico independiente en la diabetes y, por ende, estar relacionados con una mayor incidencia de DM2 (8).

GALECTINA-3

Acción fisiológica de la galectina-3

La galectina-3 es una proteína secretada en la matriz extracelular y se traslada hacia la circulación por medio de varios tipos de células, principalmente macrófagos que median la inflamación aguda y crónica, así como la inmunidad innata y adaptativa.

A nivel extracelular, la galectina-3 participa en procesos alérgicos e infecciosos y estimula la adhesión celular; mientras que a nivel intracelular actúa como un factor de empalme pre-ARNm y regula el ciclo celular, modulando la proliferación, la diferenciación celular y la muerte celular programada (9).

En general, la galectina-3 regula diferentes funciones celulares, como la difusión, la compartimentación, la endocitosis de las glucoproteínas y los glucolípidos de la membrana plasmática, la señalización de la quinasa receptora y la funcionalidad de los receptores de la membrana celular (10).

El aumento en la expresión de este biomarcador genera un gran impacto en la remodelación cardíaca, debido a sus efectos adhesivos y reguladores del crecimiento (11).

Investigaciones de la galectina-3 cardíaca en DM2

Diversos estudios han confirmado la relación existente entre la galectina-3 y la DM2. A continuación, se resumen algunos de ellos:

- En el estudio *Dallas Heart* se demostró que una mayor incidencia y prevalencia de la diabetes incrementa los niveles de la galectina-3 ($p<0,001$). Además, se comprobó que este biomarcador tiene una relación significativa con otros biomarcadores cardíacos, como el ICAM-1 (molécula de adhesión intercelular) y el VCAM (molécula de adhesión celular vascular), incrementando sus acciones patológicas en el miocardio (12).

- En un estudio en personas con DM2, se analizó la relación de los niveles de galectina-3 y los eventos cardiovasculares. Los participantes se dividieron en dos grupos; el primer grupo cursaba con desenlaces cardiovasculares primarios (infarto de miocardio no fatal, revascularización coronaria, ictus no fatal, mortalidad por causas cardiovasculares) y un desenlace secundario (mortalidad por cualquier causa); mientras que el segundo grupo no presentaba ninguno de los desenlaces cardiovasculares anteriores. Los resultados demostraron una elevación de la galectina-3 en el primer grupo, en comparación con el segundo grupo ($p<0,01$). Por otra parte, se demostró un aumento del biomarcador en la mortalidad cardiovascular. Como conclusión, se determinó que la galectina-3 elevada se asocia con resultados cardiovasculares adversos en personas con DM2, independientemente de los factores de riesgo tradicionales (13).

- En una investigación en la que se evaluaron los niveles de galectina-3 en personas con prediabetes y DM2, divididas en tres grupos (un grupo control -sin DM2-, un grupo de prediabetes y dos subgrupos en el grupo 3 -con DM2-), con base en el porcentaje de hemoglobina glicosilada (grupo I <7 % y grupo II >7 %), el biomarcador cardíaco cursó con valores de 13,3 ng/ml ± 3,42 en el grupo control; 14,28 ng/ml ± 3,45 en el de prediabetes; 15,71 ng/ml ± 4,22 en el subgrupo I y 15,65 ng/ml ± 3,31 en el subgrupo II; dejando en evidencia que los valores de galectina-3 aumentan en la enfermedad metabólica. Destaca que entre el grupo control y el grupo II (Hb1Ac >7 %) la galectina-3 mostró una elevación estadísticamente significativa ($p=0,002$). En conclusión, la galectina-3 puede ser considerada como un marcador independiente del pronóstico y las complicaciones cardiovasculares en la DM2 (14).

- En un estudio observacional realizado para evaluar el valor pronóstico postinfarto de la galectina-3, se encontró que el 23,6 % de los participantes tenía DM2 y se demostró una relación significativa entre el aumento de los niveles de la galectina-3 y la prevalencia de la DM2. A la vez, se evidenció

que la elevación del biomarcador está asociada con la mortalidad postinfarto, en un lapso de cinco años (15).

COMENTARIOS GENERALES

La DM2 genera una afectación miocárdica a partir de la glucotoxicidad y la lipotoxicidad, ocasionando la cardiomiopatía diabética y, a partir de esta, una disfunción diastólica y sistólica, relacionadas con la elevación y los mecanismos compensatorios de los biomarcadores cardíacos.

En varios estudios se ha demostrado que en presencia de DM2 se eleva el ST2 soluble; sin embargo, aún no se conoce con exactitud el mecanismo fisiopatológico directo entre el efecto de la diabetes y la liberación del biomarcador. Podría pensarse que está relacionada con los siguientes mecanismos, los cuales deben ser valorados en futuras investigaciones:

a. El efecto directo de la hiperglicemia en el miocardio causa la glucotoxicidad y la lipotoxicidad, generando procesos inflamatorios (activación de citoquinas), estrés oxidativo (activación de especies reactivas de oxígeno) y apoptosis celular.
b. La vía en común entre las causas tóxicas de la hiperglicemia y la acción del ST2 estimula al factor nuclear (NFkB), activando las citoquinas inflamatorias.
c. El bloqueo de la acción del ST2L y la interleucina-3 por medio del ST2 soluble, produce a nivel del miocardio fibrosis intersticial, hipertrofia del miocito y apoptosis, generando una disfunción diastólica.

En lo que respecta a la galectina-3, estudios también han demostrado que sus niveles se elevan en la DM2, ocasionando afectación miocárdica, principalmente en la enfermedad cardiovascular preexistente.

Se espera que en próximos años, con base en estudios clínicos y experimentales, se dé un desarrollo terapéutico a partir de estos biomarcadores sobre el miocardio, que sea de gran utilidad, como lo ha sido el fármaco sacubitril/valsartán, que estimula los efectos beneficiosos de los péptidos natriuréticos.

RESUMEN

En la Figura N° 1 se muestra un resumen de los efectos de la DM2 sobre los biomarcadores cardíacos ST2 y galectina-3.

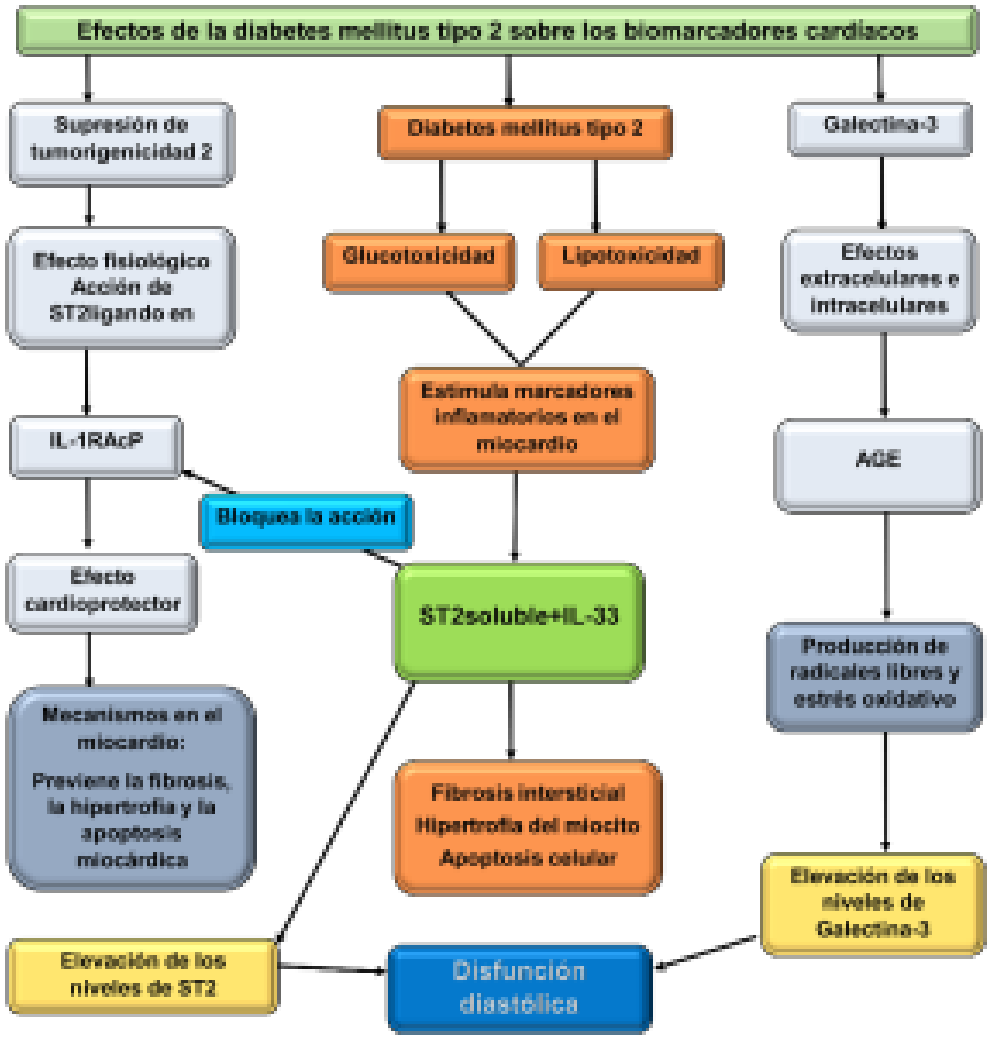

Figura N° 1. Efectos de los biomarcadores en la diabetes mellitus tipo 2 y en la enfermedad cardiovascular. La hiperglicemia produce efectos tóxicos en el miocardio por medio de la glucotoxicidad y la lipotoxicidad, estimulando marcadores inflamatorios en el miocito y generando así la elevación en los niveles de los biomarcadores ST2 y galectina-3. El ST2 ligando junto a la interleucina 33 estimulan a la interleucina 1, produciendo un efecto cardioprotector que previene la fibrosis, la hipertrofia y la apoptosis miocárdica; sin embargo, la unión de la ST2 soluble con la interleucina 33 bloquea esa acción protectora y genera fibrosis intersticial, hipertrofia del miocito y apoptosis celular. La galectina-3, por su parte, estimula a los productos finales de la glicosilación avanzada, produciendo estrés oxidativo en el miocito mitocondrial, con la consecuente elevación de los niveles del biomarcador. Todo esto se engloba en la disfunción diastólica miocárdica.

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CAPÍTULO 2. ACCIÓN MOLECULAR DE LOS INHIBIDORES DEL SGLT2 EN EL MIOCARDIO DIABÉTICO

INTRODUCCIÓN

Los inhibidores del cotransportador de sodio y glucosa tipo 2 (iSGLT2) reducen las tasas de hiperglicemia en la diabetes mellitus tipo 2 (DM2), al disminuir la glucosa por medio de la reabsorción renal, lo cual conlleva a un aumento de la excreción de glucosa (glucosuria) y de sodio urinario (natriuresis).

A nivel cardíaco, estos fármacos producen una disminución de la presión arterial y en estudios científicos han demostrado reducir la mortalidad cardiovascular en diversos escenarios clínicos (insuficiencia cardíaca con o sin DM2).

En los siguientes apartados se describe la acción de la canagliflozina y de la empagliflozina sobre algunas moléculas específicas involucradas en procesos nocivos en el miocardio, con base en estudios e investigaciones científicas en pacientes con DM2.

EFECTO DE LA CANAGLIFLOZINA EN EL MIOCARDIO

En un estudio experimental con un grupo de ratones sin DM2 (1), a los que se les realizó una oclusión de la arteria coronaria para evaluar los efectos de la canagliflozina, específicamente en el estrés oxidativo y la apoptosis celular, así como otras acciones en el proceso de isquemia/reperfusión coronaria, se encontró que este iSGLT2 disminuyó la relación Bax/Bcl2, reduciendo la apoptosis de los cardiomiocitos. Además, se identificó una reducción en la expresión de genes relacionados con el estrés nitro-oxidativo, entre ellos el p47 fosforilado, la SOD2 (dismutasa) y la catalasa.

Por otra parte, la canagliflozina demostró una mayor fosforilación en la coenzima A carboxilasa y la AMPK, reduciendo la síntesis y la acumulación de los ácidos grasos en la célula cardíaca, mejorando así la funcionalidad miocárdica.

También el fármaco estimuló la fosforilación de eNOS (isoforma endotelial de la óxido nítrico sintasa) y aumentó la producción del óxido nítrico con una mayor vasodilatación arterial, mejorando la perfusión coronaria.

EFECTO DE LA EMPAGLIFLOZINA EN EL MIOCARDIO

En un estudio experimental realizado en un grupo de ratones diabéticos (2), se analizó la acción de la empagliflozina sobre el estrés oxidativo del cardiomiocito, específicamente sobre la vía Nrf2 (factor nuclear relacionado con el eritroide 2)/ARE (elemento de respuesta antioxidante) y en las moléculas hidroperóxido lipídico (radical libre de la peroxidación lipídica), glutatión peroxidasa (GSH-Px), dismutasa superóxido (SOD) y malondialdehído (MDA); asimismo, se analizó la acción del fármaco sobre la fibrosis miocárdica en la vía de señalización TGF-β/Smad y en moléculas como TGF-β1, p-Smad2 y p-Smad3. Los resultados demostraron que la empagliflozina disminuye los niveles del hidroperóxido lipídico y del MDA, y aumenta el superóxido dismutasa y los valores de Nrf2; acciones moleculares que reducen el estrés oxidativo. Por otro lado, se encontró que la empagliflozina suprime la vía TGF-β/Smad, que a su vez estimula a la molécula Smad7, reduciendo la fibrosis miocárdica ($p<0,05$). De tal forma, se concluye que la empagliflozina reduce el estrés oxidativo en el cardiomiocito y la fibrosis del tejido cardíaco, mejorando la función ventricular.

En otro estudio experimental realizado en ratones diabéticos tipo 2 con infarto al miocardio (3), se evaluaron los efectos de la empagliflozina sobre el miocardio. Los resultados demostraron que este medicamento preserva los niveles del ATP, generando mayor disponibilidad de energía en el cardiomiocito, y aumenta el superóxido dismutasa 2 y la sirtruina 3, dos moléculas que

disminuyen la producción de especies reactivas de oxígeno y mejoran la función mitocondrial en la célula cardíaca.

Otra investigación experimental analizó la acción de la empagliflozina sobre la célula endotelial microvascular cardíaca (CEMC) posterior a la exposición del factor de necrosis tumoral alfa (TNF-alfa) (4). Fisiológicamente, la CEMC aumenta el acortamiento de la longitud del sarcómero y genera una mayor velocidad y un tiempo más corto en la relajación miocárdica; sin embargo, la unión de estas células con el TNF-alfa disminuye dichos efectos. Ante esa circunstancia, se logró determinar que el iSGLT2 preserva la función de la CMEC, mejorando la contracción de los cardiomiocitos y la función diastólica, con un incremento en la velocidad de la relajación. También se demostró una reducción del TNF-alfa en las células endoteliales y una disminución de las especies reactivas de oxígeno tanto en el citoplasma como en la mitocondria. Con base en lo anterior, se concluye que la empagliflozina restaura la función fisiológica de la célula endotelial microvascular, mejorando la contracción y la relajación miocárdica; además, reduce los niveles del factor de necrosis tumoral y la acumulación de especies reactivas de oxígeno.

Por otro lado, en un estudio realizado en células endoteliales de las arterias coronarias, con el objetivo de analizar el efecto de la empagliflozina en la reducción de los niveles de TNF-alfa (5), se demostró que el fármaco disminuye la actividad del TNF-alfa y, por ende, reduce la producción de las especies reactivas de oxígeno, con resultados estadísticamente significativos (empagliflozina $p<0,05$), además de restaurar la disponibilidad del óxido nítrico, mejorando la función endotelial de las arterias coronarias.

En otra investigación experimental en ratones con insuficiencia cardíaca con una fracción de eyección reducida, divididos en dos grupos (uno sin diabetes y otro con diabetes) con el fin de establecer el mecanismo molecular de la empagliflozina a nivel cardíaco en ambos grupos (6), se encontró que este inhibidor se relaciona con el mecanismo del intercambiador sodio/hidrogenión

tipo 1 (NHE1). Fisiológicamente, en el corazón este intercambiador inicia con el ingreso de sodio a la célula y la movilización de los hidrogeniones al espacio extracelular, lo que activa a la molécula AKT1, que induce a la BIRC2 (proteína 2 que contiene repetición de baculovirales IAP), la cual degrada al XIAP (inhibidor de la apoptosis ligado al X mediado por proteasoma) y al BIRC5. Por otra parte, AKT1 activa a MAPK1/3 (proteína quinasa activada por mitógeno 1/3) y esta a su vez estimula al RPTOR (proteína reguladora asociada de mTOR), ocasionando hipertrofia y muerte celular del cardiomiocito. Posteriormente, el NHE1 activa a la NOS2 (óxido nítrico sintasa), estimulando la inflamación e hipertrofia de la célula cardíaca. Para evitar esta situación, la empagliflozina inhibe a las moléculas NHE1, AKT 1-3 y BIRC2, permitiendo la expresión de los mediadores antiapoptóticos XIAP y BIRC5; asimismo, reduce la progresión de la insuficiencia cardíaca con y sin diabetes tipo 2. Adicional a lo anterior, podría disminuir aún más la muerte celular de los cardiomiocitos, al inhibir la proteína mTOR que depende de AKT (RPTOR) y disminuye la regulación de las acciones del NOS2.

RESUMEN

En el Cuadro N° 1 se encuentra un resumen de las principales acciones realizadas por los iSGLT2 en el miocardio, según investigaciones realizadas.

Cuadro N° 1. Acción molecular de los iSGLT2

Fármaco	Moléculas relacionadas con los iSGLT2	Acción molecular
Canagliflozina	Bax (proapoptótica) Bcl2 (antiapoptótica)	Disminución de la relación Bax/Bcl2, con una reducción de la apoptosis.
	p47 fosforilado SOD2 (dismutasa) Catalasa	Reducción de la expresión de genes del estrés oxidativo.

Cuadro N° 1. Acción molecular de los iSGLT2		
Fármaco	**Moléculas relacionadas con los iSGLT2**	**Acción molecular**
	Molécula hidroxinonenal	Disminución del estrés oxidativo.
Empagliflozina	Hidroperóxido lipídico Malondialdehído MDA	Reducción del estrés oxidativo.
	Superóxido de dismutasa	Aumento de la acción antioxidante.
	NoX4	Reducción de su efecto.
	Vía Nrf2/ARE	Elevación de sus niveles para regular el estrés oxidativo.
	Vía TFG-Beta/Smad	Disminución de la vía y la fibrosis miocárdica.
	Smad 7	Aumento de sus niveles e inhibición de la vía TFG-Beta/Smad.
	SOD 2 SIRT3	Reducción del estrés oxidativo.
	Factor de necrosis tumoral alfa (TNF-alfa)	Reducción de esta molécula; disminución de la inflamación y mejora la contractilidad miocárdica.

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CAPÍTULO 3. RELACIÓN DE LA DIABETES MELLITUS TIPO 2 Y LA FIBRILACIÓN AURICULAR

INTRODUCCIÓN

Como se mencionó en los capítulos anteriores, la diabetes mellitus tipo 2 (DM2) produce glucotoxicidad y lipotoxicidad en el miocardio, que generan efectos nocivos como estrés oxidativo, inflamación y apoptosis celular. Estos efectos dan origen a la fibrosis y a la hipertrofia en los cardiomiocitos auriculares, lo cual conlleva a remodelaciones estructurales y eléctricas en las aurículas.

Por otra parte, se ha comprobado que la hiperglicemia crónica está relacionada con la patogénesis de la neuropatía autonómica cardiaca, al alterar la perfusión sanguínea de las estructuras nerviosas, la cual produce una estimulación simpática a nivel del miocardio y genera un acortamiento en el período de refractariedad en las células de la aurícula, contribuyendo así al desarrollo de la fibrilación auricular (1).

Partiendo de ese contexto, se describen a continuación los procesos moleculares generados por la DM2 en las aurículas y el desarrollo de la fibrilación auricular a causa de la disfunción mitocondrial y el remodelado eléctrico y estructural auricular. Como complemento, se menciona la acción de los iSGLT2 en la fibrilación auricular.

EFECTOS PERJUDICIALES DE LA DM2 EN LA AURÍCULA

Estrés oxidativo mitocondrial de los cardiomiocitos auriculares

Las especies reactivas de oxigeno (ROS) producen efectos proarrítmicos, debido a la modulación de los dominios reguladores en la mitocondria, los cuales son sensibles a la reducción-

oxidación de múltiples proteínas mitocondriales en las aurículas, que participan en el acoplamiento excitación-contracción, incluyendo los canales de sodio, los canales de potasio, los canales de calcio tipo L, los receptores de rianodina y el intercambiador de sodio/calcio (2).

Partiendo de lo anterior y considerando que en la DM2 suele presentarse estrés y daño oxidativo por los niveles elevados de especies reactivas de alto potencial oxidante y la disminución de aquellas antioxidantes (3), es claro que esta patología conlleva a una disfunción mitocondrial, ocasionando un remodelado estructural en las aurículas, que comprende el alargamiento del tejido auricular y un aumento de los depósitos de lípidos en las células cardíacas y de la fibrosis intersticial en el músculo auricular.

A su vez, en este proceso se activan las citoquinas pro-inflamatorias, que causan un retraso del transporte eléctrico de las aurículas. Asimismo, se genera un aumento del colágeno intersticial, que produce una alteración del acoplamiento celular y la propagación del potencial de acción (4).

Por otra parte, la DM2 en conjunto con la fibrilación auricular aumenta la señalización del factor de transcripción nuclear kappa B (NF-kB), involucrado en procesos de inflamación de los miocitos auriculares. Específicamente, esta molécula actúa en la vía de señalización de reducción-oxidación y en la cascada de angiotensina, mejorando la heterogeneidad de la conducción, al promover la reentrada en la aurícula. Cuando hay hiperglicemia, esta determina la sobreproducción de especies reactivas de oxígeno en los vasos y disminuye la disponibilidad de óxido nítrico, lo que conduce a una regulación positiva del NF-κB que media la transcripción de genes proinflamatorios (por ejemplo, codificación de moléculas de adhesión), perpetuando de esta forma el estado inflamatorio (5).

En un estudio realizado por Raposeiras y colaboradores (6), se demostró una elevación en los niveles de los productos finales de la glicosilación avanzada en DM2 y fibrilación auricular. Este

aumento genera rigidez estructural y pérdida de la elasticidad de las aurículas; por consiguiente, la activación del receptor de los productos finales de la glicosilación avanzada produce distensión de la aurícula izquierda, alterando su configuración estructural. Además, esta activación ocasiona un incremento en la producción de citoquinas proinflamatorias.

Adicional a lo anterior, se ha reportado que otra vía involucrada en la fisiopatología de la DM2 es la activación de la molécula factor de crecimiento transformante beta-1 (TGF-β1) en la aurícula, que incrementa la fibrosis intersticial, alterando la función de los canales iónicos, con riesgo de desarrollo de fibrilación auricular (7).

Remodelado eléctrico auricular

El remodelado eléctrico auricular que se produce por la DM2 incluye:

- Aumento en la velocidad de conducción.
- Heterogeneidad de la velocidad de conducción.
- Prolongación de la duración del potencial de acción (DPA).
- Aumento de la incidencia de DPA.
- Disminución de las corrientes en los canales de sodio.
- Aumento de las corrientes en los canales de calcio.
- Mayor tiempo de conducción interauricular.

Remodelado estructural

El remodelado en la estructura auricular se debe principalmente a la fibrosis intersticial difusa y es el principal sustrato de la diabetes tipo 2 para generar fibrilación auricular; esto se relaciona con la activación del factor de crecimiento de tejido conectivo (CTGF), que produce acumulación del colágeno e interfiere en la contractilidad auricular.

Otras moléculas que participan en la señalización profibrótica en las aurículas son la angiotensina II y el TGF-β1, las cuales aumentan la proliferación de fibroblastos y promueven su diferenciación en miofibroblastos secretores de colágeno (8).

Por otro lado, un estudio experimental en DM2 demostró que la fibrosis auricular produce un incremento en la dispersión del período de refractariedad efectivo, una disminución en la corriente de los canales de sodio y un aumento en los canales de calcio sobre el potencial de acción (9).

ESTUDIOS SOBRE LA ACCIÓN DE LOS iSGLT2 EN LA FIBRILACIÓN AURICULAR

En un metaanálisis sobre el uso de los iSGLT2 en enfermedad cardiovascular y DM2, se demostró una reducción significativa en la incidencia de fibrilación auricular. También, se documentó un aumento de la función mitocondrial y una reducción del estrés oxidativo en los cardiomiocitos auriculares, mejorando la acción eléctrica en la fibrilación auricular (10).

Por otra parte, en un estudio cohorte en el que se evaluó el riesgo de mortalidad por causas cardíacas y el riesgo de desarrollo de arritmias en DM2 con el uso de los iSGLT2, se logró determinar que estos disminuyeron tanto la mortalidad por causas cardiovasculares, como los eventos cardíacos por fibrilación auricular (11).

Empagliflozina

Un subestudio del EMPA-REG OUTCOME trial (12), evaluó la eficacia de la empagliflozina en la fibrilación auricular, así como en los desenlaces cardiovasculares (mortalidad cardiovascular, hospitalización por insuficiencia cardíaca y mortalidad por todas las causas) y renales (empeoramiento de la función renal) en dos grupos: uno con pacientes con fibrilación auricular y otro con pacientes sin fibrilación auricular. En el grupo con fibrilación auricular, la empagliflozina demostró una mayor reducción de los eventos cardiovasculares, incluyendo la muerte por esta causa, y una disminución del empeoramiento de la nefropatía; el número de eventos prevenidos fue mayor en este grupo que en el de personas sin fibrilación auricular. Con base en estos resultados, los investigadores consideraron beneficioso el uso de este medicamento en pacientes con diabetes, con eventos cardiovasculares y con fibrilación auricular.

Dapagliflozina

Un subestudio del DECLARE-TIMI 58 (*Dapagliflozin Effect on Cardiovascular Events– Thrombolysis in Myocardial Infarction* 58) (13), evaluó el efecto de la dapagliflozina sobre el desarrollo de la fibrilación auricular en personas con DM2. Los resultados demostraron una reducción del 19 % en la generación de la arritmia con el uso de dapagliflozina en comparación con el placebo. Además, este iSGLT2 generó una reducción significativa en el número de eventos cardiovasculares por fibrilación auricular en comparación con el placebo (p=0,005); en específico, esta disminución fue de 12,4 % con la dapagliflozina y de 15,2 % con el placebo.

EFECTO MOLECULAR DE LOS iSGLT2 EN LA FIBRILACIÓN AURICULAR

En un estudio experimental en ratones con DM2 inducida (14), divididos en cuatro grupos (control; sin uso de fármacos; con dosis bajas de empagliflozina; y con dosis elevadas de empagliflozina durante ocho semanas), se evaluó el efecto de dicho fármaco sobre el remodelado auricular, ocasionado por la diabetes mellitus, con base en los parámetros ecocardiográficos, los factores metabólicos e inflamatorios, el estrés oxidativo y otros. En lo que respecta a los parámetros ecocardiográficos, se determinó que tanto el diámetro de la aurícula izquierda como la rigidez de la pared posterior del ventrículo izquierdo, cursaron con valores elevados en el grupo sin fármacos (p<0,005), mientras que en el grupo de empagliflozina a dosis elevadas hubo una reducción en los valores de ambos parámetros (p<0,05).

En cuanto a los marcadores bioquímicos, se identificó una reducción del colesterol total y de la glicemia en el cuarto grupo del estudio en comparación con el segundo grupo (p<0,03).

En el caso de los marcadores inflamatorios, se observó una reducción en los niveles de la proteína C reactiva de alta sensibilidad en los grupos de empagliflozina.

A nivel molecular, se observó un incremento en los niveles de la molécula SOD (superóxido dismutasa) en los grupos que utilizaron la empagliflozina ($p<0,05$), aumentando su acción antioxidante. También se observó que la empagliflozina redujo los niveles de la molécula MDA (malondialdehído), relacionada con el estrés oxidativo, en comparación con el grupo de diabetes sin fármacos ($p<0,05$).

Adicional a lo anterior, se analizaron diversas moléculas mitocondriales, como el PGC-1a (coactivador del receptor c activado por el proliferador de peroxisomas 1a), el cual promueve la biogénesis mitocondrial y es regulado por la AMPK (quinasa monofosfato de adenosina), que tiene efectos metabólicos. A la vez, se evaluó el Tfam (factor de transcripción mitocondrial A) y el NRF-1 (factor respiratorio nuclear 1), que activa los genes nucleares para la respiración mitocondrial, la transcripción y la replicación del ADN mitocondrial. Los valores de estas moléculas permanecieron reducidos en el grupo de diabetes, mientras que en el grupo de empagliflozina estos se elevaron, incrementando la función mitocondrial. Otras moléculas analizadas fueron la Mfn-1 (mitofusina 1) y la OPA-1 (atrofia óptica 1), que generan la fusión mitocondrial; en este caso, todos sus valores aumentaron con el uso de la empagliflozina, regulando y mejorando la función mitocondrial.

Por otra parte, la empagliflozina mostró una reducción de la fibrosis intersticial en comparación con el grupo de diabetes mellitus sin fármacos ($p<0,05$). En el caso de la fibrilación auricular, se redujo su desarrollo significativamente (hasta un 36,8 %) con dosis elevadas de este iSGLT2.

CONCLUSIÓN

Con base en lo anterior, se concluye que la disfunción mitocondrial se encuentra relacionada con el remodelado auricular ocasionado por la diabetes mellitus, mediante la producción de especies reactivas de oxígeno, los cuales dañan la membrana mitocondrial y afectan su accionar en la función de los cardiomiocitos auriculares. También alteran el consumo

de calcio, promoviendo una disfunción respiratoria celular, y producen apoptosis de los cardiomiocitos. El daño mitocondrial genera un incremento de la matriz extracelular, causando alteración en la contractilidad, hipertrofia y fibrosis en la aurícula izquierda. Esto conlleva a alteraciones eléctricas en la conducción o repolarización en ambos ventrículos y aurículas.

RESUMEN

La DM2 es una causa de la fibrilación auricular y participa en la fisiopatología como estrés oxidativo, remodelado estructural y eléctrico.

Los iSGLT2, como la empagliflozina y la dapagliflozina, han demostrado beneficios clínicos como reducción de la mortalidad cardiovascular y de los eventos relacionados con la fibrilación auricular. Se espera que a futuro estudios científicos indiquen el manejo específico de estos fármacos en la fibrilación auricular con y sin presencia de DM2.

En el Cuadro N° 1 se encuentra un resumen de los principales efectos de estos iSGLT2 a nivel auricular.

Cuadro N° 1. Efectos de los iSGLT2 a nivel auricular

Metabólicos	Reducen la glucotoxicidad y la lipotoxicidad, conllevando a un decremento del estrés oxidativo.
Estructurales	Reducen la fibrosis intersticial y la hipertrofia del miocito auricular.
Eléctricos	Optimizan el consumo de calcio; mejoran la velocidad de conducción por activación de los canales de sodio; y reducen las vías de reentrada eléctrica auricular y el tiempo de conducción interauricular.

Cuadro N° 1. Efectos de los iSGLT2 a nivel auricular	
Mitocondriales	Reducen el estrés oxidativo: • Aumento de la molécula superóxido dismutasa. • Reducción de MDA.
	Mejoran la respiración mitocondrial: • Aumento de la PGC-1α. • Promueve la biogénesis mitocondrial. • Aumento del NRF-1. • Activación de los genes nucleares para la respiración mitocondrial y la replicación del ADN. • Aumento de Tfam. • Produce la transcripción mitocondrial.
	Benefician la fisión y la fusión celular: • Fisión: aumento de DRP-1. • Fusión: aumento Mfn-1 y de OPA-1.

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SEGURO SOCIAL
Cardiología
Molecular
DIABETES MELLITUS TIPO 2

Annex 2. "The Next Fifty Years" by John Brockman

JOSEPH LEDOUX

❑

Mind, Brain, and Self

YOUNG SIGMUND FREUD BEGAN his scientific career by studying the nervous system and believed that the secrets of mental life would be illuminated by an understanding of brain function. Because he soon came to realize that the tools available for studying the brain were not sufficiently advanced to put his belief into practice, he turned to a purely psychological approach. In the intervening years, neuroscience has become a thriving discipline, and its discoveries would astound Freud. Still, there is much left to learn, and some of the developments we can expect in the coming years are described here.

Reading the Brain

Neuroscientific research has gone a long way toward revealing how certain aspects of the mind, like perception, memory, and emotion, are mediated by the brain. Much of this work has involved studies of nonhuman organisms, especially rats and monkeys. While this approach is adequate for asking questions about brain functions that humans share with other creatures, it has left important gaps in our

understanding of the unique aspects of the human brain. Research on humans with brain damage has helped close the gap, but studies of brain-injured subjects are as much about how the brain compensates for lost function as about normal function.

New technologies are enabling us to study normal human brain function, and they promise a new level of understanding of the relation of the human brain to the human mind. Specifically, the emergence of functional magnetic resonance imaging (fMRI) has provided a safe and practical means for researchers to peek into the brain of a human being and observe its activity as the subject performs psychological tasks or has certain experiences. Most of the imaging studies to date have focused on validating the technique, showing that this approach reveals the same picture of brain function as more traditional approaches. Many of the existing findings are thus referenced to studies of brain function in experimental animals. Without this basic grounding in how specific brain systems work, the imaging findings would exist in an intellectual vacuum. For example, studies of rats and other mammals have shown that the amygdala, a small region in the temporal lobe, is a key part of the brain network involved in detecting and responding to danger. Guided by this information, researchers then showed that patients with amygdala damage are impaired in recognizing danger and that regions of the amygdala are activated, as determined by fMRI, when humans are exposed to threatening stimuli. In this and many other areas, animal studies have paved the way.

It is important to match the species studied to the question being asked. For example, working memory, which allows you to hold information in mind and do things with it, is a key process underlying human thought. This process

is known to involve a region of the human brain called the dorsolateral prefrontal cortex. Rats do not have a dorsolateral prefrontal cortex and thus are not appropriate subjects for these kinds of memory studies. Monkeys do have a dorsolateral prefrontal cortex, and much of what has been learned about the role of this region in working memory was discovered through studies of monkeys. But a key aspect of human thought involves verbal working memory, a function that cannot be studied directly in any species but humans. Recent fMRI studies have played an important role in elucidating how verbal working memory functions in the human brain.

The future of research on the human brain with fMRI or other approaches—including other ways to record activity, and ways to stimulate selective brain regions and induce activity—is likely to be in three broad domains. The first is the most pedestrian: We will learn more about some processes that we already know something about—that is, the neural organization of perception, memory, emotion, language, and working memory. The second entails discovering more about how these processes interact in the brain. This investigation will take us from narrow to broader systems-level concepts of brain function, and toward at least the beginnings of a theory of how the brain makes the mind, as opposed to how specific mental processes function. Work of this type has begun, but is far too rare.

The third domain is perhaps the most important. Nearly all studies of brain function focus on the way the brain typically works in most of us most of the time. Each such study includes a great many subjects, in order to produce a norm. Once we have a solid grounding in our understanding of these normative functions, we can ask questions about how variations between individuals determine the unique

qualities that account for the self or personality. These questions require a slightly different approach—one in which a lot of measurements are made in an individual, rather than a single measurement being made in multiple subjects.

Existing techniques are giving us powerful tools for assessing what is going on in the brains, and minds, of people. As these techniques improve, we will have to ask whether we are as a society ready for what this research will tell us. When it becomes possible to look inside the brain and see what someone is thinking or feeling—to predict, say, whether someone is likely to be a murderer, child molester, or rapist—what will we do with this information?

Managing Memory

Every time you form a memory, you adjust the wiring—the synaptic connectivity—of your brain. Be it as trivial as the color of the socks you pulled up this morning or as significant as the sound of your mother's voice, memory is a process of adjusting connections between neurons. In simple terms, it goes like this: Those neurons that are actively engaged during an experience undergo certain chemical changes that activate genes and thereby initiate the synthesis of proteins inside these active cells. The proteins are then shipped to the active synapses on the active cells, where they alter the ability of those synapses, and only those, to receive messages from the neurons they are connected with. Memory is embodied in such changes. We can expect, given what we already know, that in the near future it will be possible to manage memory in various ways.

Now that people are living longer, more of them are suffering from age-related memory problems. These problems are most apparent in people with Alzheimer's disease and

certain other neurological conditions, but memory also falters in older people without specific brain disorders. Scientists are currently attempting to use information gleaned from memory studies of such diverse animals as sea slugs, flies, rats, rabbits, and monkeys to develop ways to improve our human memory. It is well established, for example, that many forms of memory depend on the neurotransmitter glutamate and its receptors. One strategy for memory improvement thus involves the development of drugs that facilitate glutamate transmission. Further, an important step in memory formation is the flow of chemical ions (especially calcium) through glutamate receptors into neurons; the rise in calcium then leads to the activation of molecules that in turn activate genes. The development of drugs targeting these processes within our brain cells—that is, attempting to improve their ability to activate the genes that make the proteins that stabilize the synaptic wiring that underlies memory—offers another strategy for improving memory function.

But what about fixing the brains of people with neurological problems like Alzheimer's disease? The recent discovery that in adult brains new neurons are made in the hippocampus, a brain region of central importance to our ability to consciously remember, offers new hope. If these cells can somehow be encouraged to connect with and thus participate in the degenerating memory circuits, perhaps memory function can be restored. And if the federal government will untie the hands of researchers and allow them to proceed more freely with stem cell research, it may be possible to prevent conditions such as Alzheimer's from being expressed at all in people who are susceptible.

Another area where brain science could have an important impact is in the prevention or elimination of unwanted

memories, especially traumatic ones. Such memories form the core of conditions like posttraumatic stress disorder, and if they can be short-circuited, the disorder might be ameliorated to some extent. Researchers have come up with ways to alter the fate of memories while they are being formed and stabilized; this could lead to the development of drugs that could be administered shortly after some highly stressful event and thus prevent the development of traumatic memories. But because the stabilization of memory formation takes only a few hours—the time it takes for proteins to be made and utilized—this approach will have limited application. An alternative, though, may be available.

New studies in rats have shown that specific well-formed memories can be disrupted if proteins are interfered with at the site of memory in the brain during the process of recalling the experience. But in order to be useful in dismantling traumatic memories in humans while leaving other memories intact, the operative drug would have to target the areas involved in traumatic memory. This in turn will require us to find the site of traumatic-memory formation in posttraumatic stress disorder, as well as some way to restrict the drug to that region. We'll consider these points shortly.

Of course, even if it becomes possible to weaken or remove disturbing memories in humans, it is not something we should do lightly. Imagine a Holocaust victim who lived for decades with memories of death camps. These memories have undoubtedly become ingrained as part of the victim's personality. Although the person may be severely troubled by such memories, what would happen to the fabric of her personality if a set of episodes that had become such a central part of her life were removed?

Scientific advances sometimes become part of daily life. We might therefore see the day when over-the-counter drugs will be used to give a particular experience an especially strong representation in your brain. Suppose you want to remember a birthday or wedding anniversary particularly vividly. Right before the party, pop a pill that gets glutamate or other molecules working more efficiently, and everything that happens will be burned into your circuits in brilliant detail.

Recreational rewiring is not as far-fetched as it sounds. We arrange situations all the time to increase the emotional impact of experiences and make our recollections of them vivid and enduring. Taking a drug to do this is just a different way of doing the same thing. It is less romantic to give your spouse a pill on your anniversary than a bouquet, but the pill may achieve the desired result (a memorable evening) more effectively. Or you can hedge your bets and try both the pill and the bouquet.

Smart Drugs

Macbeth pined for "some sweet oblivious antidote" to sorrow. We now have a number of drugs that are fairly successful at helping to treat depression and other psychiatric disorders. But drugs come with a price—side effects. Fifty years from now, or sooner, drugs will treat troubled networks in the brain without affecting others. To create such drugs, several developments will have to take place.

We will first need to learn more about exactly which networks are troubled in specific disorders. Brain imaging is already beginning to be helpful in this respect. Studies are showing how the brains of people with depression, anxiety disorders, or schizophrenia differ from those of people with-

out such afflictions. But in order make some sense of these differences, we need to learn more about the normal function of the areas identified.

For example, it is a reasonable assumption, given existing animal and human data, that fear-related disorders (panic attack, posttraumatic stress disorder, generalized anxiety, phobia, paranoid schizophrenia) result from alterations in the way the brain's fear networks normally function and interact with other networks. Since the amygdala, as we have seen, is a key part of these networks, alterations in amygdala function might account for certain aspects of anxiety. Specifically, excess and inappropriate fear could occur because the amygdala is oversensitive, detecting danger and responding defensively to a situation that would be ignored by another person; or the amygdala could be too reactive, responding with a more vigorous defense than another person would to the same degree of threat. Either of these conditions could arise from genetic wiring or from traumatic or otherwise stressful experiences, or from some combination of the two. Moreover, either effect can be accentuated by the way other brain regions connected with the amygdala regulate amygdala function. And different conditions may be accounted for by different alterations of circuits within the amygdala, or between the amygdala and other areas. If imaging studies determine that the amygdala (or any other area) is affected in anxiety disorders, clarification of the function of the region and its interaction with other systems will be fundamental to inventing new treatment strategies. But even now, when imaging studies are showing the involvement of certain brain regions in such human conditions as anxiety, animal studies remain important for understanding detailed neural mechanisms at the

level of cells and synapses in that region; ultimately, the development of new and better medications depends on this level of knowledge.

Once human imaging studies implicate specific networks in a particular condition and animal studies illuminate the detailed organization of those networks, we can look for drugs that will target the afflicted circuits. One strategy would involve capitalizing on advances in molecular genetics: If we can identify some molecule that is expressed only in the amygdala, or is expressed there in some particular way, it might then be possible to use that molecule as a key to unlock a drug. That is, the drug would still be taken orally and would still travel widely in the bloodstream to many brain regions; however, because of the drug's molecular packaging, it would be inert in most brain regions. Only when it encountered the molecular key, which in this hypothetical example is present only in the amygdala, would the drug become active. Such a drug could help correct abnormal amygdala function without affecting other brain regions, thus reducing unwanted psychological side effects caused by widespread drug action. But because the amygdala also participates in "normal" brain functions, the real challenge will be to find some way to selectively attack the disordered functions.

The Amygdala Defense

The amygdala, like many brain regions, does its work outside our conscious awareness. We can become aware of the consequences of amygdala activation, but we do not have conscious access to its inner workings. Because the amygdala can be provoked into expressing unconsciously con-

trolled emotional responses, the possibility is raised that the amygdala could unconsciously commit a crime—one that the conscious person would never willfully condone.

This possibility has not escaped lawyers. The legal system has long recognized "crimes of passion," in which an otherwise law-abiding and reasonable person commits a crime during a lapse of rationality or sanity. The "amygdala defense" adds a neurological rationale to this sort of argument. As we learn more about how the brain works, and lawyers learn more about what has been discovered, neurologically based defenses will become more and more common. So let's take a close look at what I mean by the amygdala defense.

First, the amygdala defense should not be confused with a related issue, which we can call the pathological brain defense. In the latter, the argument is that the person committed a crime because of some physical alteration in his or her brain. The amygdala defense, in contrast, is based on the notion that the amygdala normally controls emotional behavior in an unconscious fashion, and as a result it is possible for a crime to be committed by the amygdala independent of conscious thought. It is clearly possible for the amygdala to control an aggressive act independent of conscious control in certain provocative circumstances; however, in order for the amygdala defense to work, several criteria would have to be met.

An important job of the amygdala is to rapidly initiate protective responses in the face of a sudden danger. But if the stimulus has been present for some time and consciously perceived, behavior tends to be under the control of higher thought processes, mediated by the cortex. Further, the kinds of responses directed by the amygdala are fast, simple, innate (hardwired) responses that are exe-

cuted in a stereotyped manner—that is, performed similarly in all members of the species. So if an act is deliberate, expressed relatively slowly (over seconds rather than milliseconds), involves a complex sequence of movements, and would be carried out differently in different people, it is probably not directly controlled by the amygdala. The amygdala can indirectly influence or modulate these more complex responses, but they are, in the end, the business of other brain systems. These facts suggest that in order for the amygdala defense to succeed, the crime would have to involve a relatively simple, innate, stereotyped response executed instantaneously and without premeditation upon the occurrence of the provocation.

I suspect that few crimes would meet the criteria necessary for the amygdala defense to succeed. However, it is becoming increasingly apparent that many brain systems other than the amygdala function unconsciously—and even that consciousness itself is the product of the unconscious workings of brain networks, raising the possibility that while the amygdala defense is wrong in name, it may still be valid in spirit. Whether we will need to reconsider the nature and limits of human responsibility, though, will depend on future discoveries about the balance between conscious and unconscious control in the brain. These, too, are likely to come in the next fifty years.

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SAMUEL BARONDES

Drugs, DNA, and the Analyst's Couch

IN 1950 A CHEMIST AT Rhône-Poulenc, a French pharmaceutical company, modified the structure of an antihistamine and accidentally created a drug that can eliminate the psychotic thinking of people with schizophrenia. Within a few years the new drug became world famous as chlorpromazine (Thorazine), the first truly effective medication for a disabling mental disorder. Because of its dramatic effect, chlorpromazine set a new course for psychiatry for the rest of the twentieth century.

The great success of chlorpromazine stimulated vigorous competition from other pharmaceutical companies. In the 1950s the search for more antipsychotic medications led to the accidental discovery of two other types of psychiatric drugs. First Geigy, a Swiss pharmaceutical company, came up with a modified version of one of its antihistamines that, although useless against psychosis, proved to be a valuable treatment for severe depression. Named imipramine (Tofranil), it paved the way for many contemporary antidepressants. Then Hoffman-La Roche, another Swiss company, created chlordiazepoxide (Librium), which doesn't help psychosis either but does relieve anxiety. It

was soon followed by another benzodiazepine, diazepam (Valium), which became the best-selling drug in America for about a decade, beginning in the mid-1960s.

Adding to the excitement over these drugs were a flurry of findings about their effects on neurotransmitters, a class of brain chemicals that transmit signals between nerve cells. By the 1970s it was discovered that chlorpromazine blocks certain actions of a neurotransmitter called dopamine; imipramine augments the actions of several neurotransmitters, including norepinephrine and serotonin; and diazepam amplifies the effects of yet another neurotransmitter, called gamma-aminobutyric acid (GABA). In each case, the net result is a change in signaling in brain circuits that control emotional aspects of behavior.

These discoveries spurred a search for other chemicals that would have similar effects on neurotransmission but fewer undesirable side effects than the originals. The search paid off in a stream of new medications that patients prefer. The most famous, fluoxetine (Prozac), was initially identified as a chemical that prolongs neurotransmission by serotonin; it was subsequently shown to be an effective treatment for both severe and moderate depression. Called an SSRI (selective serotonin reuptake inhibitor), it prolongs serotonin's effects by inhibiting its reuptake by the nerves that release it, which is the normal way that serotonin signaling is terminated. Related drugs, including sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and citalopram (Celexa), soon followed.

As experience with SSRIs grew, psychiatrists became aware that these medications could also help people who aren't depressed. SSRIs have now become an established treatment for unprovoked attacks of panic (panic disorder) and uncontrollable worrying (generalized anxiety disor-

der)—beneficial effects that have been confirmed by formal comparisons with placebos in controlled trials.

The effectiveness of these and other new medications transformed psychiatry. Before such drugs came on the scene, most psychiatrists thought about their patients in purely psychological terms and were mainly interested in treating them with psychotherapy. Now attention has shifted to the brain, and psychiatric treatment frequently includes at least one medication. Tens of millions of Americans take psychiatric drugs.

But, valuable though they are, the drugs that replaced chlorpromazine, imipramine, and chlordiazepoxide are simply modified versions of the originals. None of them is substantially more effective, and all of them have some undesirable side effects. Despite extensive knowledge about their effects on neurotransmission, the development of new drugs still relies on a trial-and-error approach similar to that used in the 1950s.

The next big step in psychiatry is not likely to come from further refinements of the drugs and psychotherapies that define the field today. It will come, instead, from discoveries about human genetic variations and the ways they affect the brain. Just as eye-opening stories from psychoanalysts' couches guided psychiatry in the first half of the twentieth century, and the products of smelly chemistry laboratories guided it in the second half, so will knowledge about individual genetic differences guide psychiatry over the next fifty years.

Knowledge about individual genetic differences holds out such promise for psychiatry because it will help to answer a fundamental question: What determines individual susceptibility to disturbed behavior? A person's past experi-

ences clearly play a vital role. But why does one person transcend repeated mental hardships, whereas another is readily tipped into a state of distress? And why does one person succumb by lapsing into depression, another into sustained anxiety, and a third into the withdrawal and delusions of schizophrenia?

The best clue we have is that all these patterns of disturbed behavior run in families. Consider, for example, the risk of becoming schizophrenic. Most people have about one chance in a hundred of developing the characteristic pattern of symptoms. But if you have a parent or sibling who is schizophrenic, your lifetime risk is eight times greater. The same is true of the other major cause of psychosis—manic-depressive illness, also known as bipolar disorder. Again, the general risk is about one in a hundred, but the risk is eight times greater if you have a parent or sibling who suffers from this disorder. Depression and the anxiety disorders are also familial.

Not long ago these studies of families sparked explosive debates between those who took them as evidence for learned familial patterns of abnormal behavior and those who took them as evidence for inheritance of a predisposition to mental disorders. Now most people agree that environment and heredity both play some part. They also agree that the best next step in assessing the importance of heredity is to try to find the alternative forms of genes that are involved.

The main catalyst for this agreement has been the development of powerful techniques for direct examination of the alternative forms of human genes, called alleles, or gene variants. These variants, which arose by random changes in DNA structure, are responsible for a great deal of human diversity, including differences in susceptibility

to particular illnesses. But until recently their existence could only be inferred. The new techniques make it possible to identify specific gene variants that contribute to a human attribute. Instead of arguing about the relative importance of nature and nurture, we can now turn our attention to a search for gene variants that contribute to individual predisposition to an illness.

One way to find them is to compare the DNA of family members who have that illness with those who don't. If only those with the illness have a certain variant of a particular gene, the correlation is probably meaningful. If the same variant is also found only in the affected members of a number of other families, the case is strengthened. At some point the likelihood becomes so high that a role for the variant is established. As the details of human genetic structure were being worked out in the 1990s, some gene variants affecting susceptibility to particular illnesses were identified in just this way. Famous examples include the variants of three different genes that each greatly increase the risk of developing rare types of Alzheimer's disease which begin before the age of fifty. In one group of families the culprit was a variant of a gene called APP; in another it was PS1; and in a third it was PS2.

The discovery of gene variants that increase the risk of rare types of Alzheimer's disease has stimulated genetic studies of schizophrenia, depression, manic depression, and other psychiatric disorders. The immense appeal of these studies is that they are not dependent on guesses about which genes might be involved, because they can be designed to detect a correlation between the disorder and a variant of any human gene. Although many early studies did focus on specific genes, especially those that influence neurotransmission, we know so little about the genetic

control of mental processes that it would not be surprising if other types of genes were implicated. Unfortunately, despite years of effort, no one has yet found a gene variant that definitely increases the risk of any of these mental illnesses. Nor has there been much success in genetic studies of other common disorders, such as diabetes and high blood pressure. One reason for this lack of progress is that susceptibility to all these maladies is determined by the combined actions of variants of multiple genes rather than by variants of a single gene. Although current technology has made it relatively simple to identify the rare variants of single genes that do indeed have a major effect on risk—such as APP, PS1, or PS2—it remains very difficult to find those gene variants that increase risk only if they are inherited in concert with a number of others.

This difficulty will soon be lessened because of the continued growth of knowledge about the human genome. The recent publication of the detailed structure of human DNA is a critical first step. Now DNA specimens from many people are being examined in order to identify and catalog the common variants of each of the approximately thirty thousand human genes. This will greatly simplify the search for the many gene variants that may operate together to influence vulnerability to mental disorders. The search is also being simplified by the development of efficient new techniques for detailed examination of the DNA of any individual. These techniques are in a continual state of improvement, reminiscent of the ongoing development of computer chips. So, too, are the computational methods used to analyze the masses of information from such DNA studies.

With the evolution of the technology for collecting and evaluating large masses of DNA data, it will soon be possi-

ble to mount a massive search for the groups of gene variants that influence susceptibility to particular mental disorders. As the costs of DNA analysis keep falling, we can go beyond relatively small family studies and scrutinize DNA samples from thousands of unrelated people with a particular disorder. Such an investigation should identify the relevant gene variants, only some of which will be found in each affected individual.

To properly use this mass of data about gene variants, it will be necessary to correlate it not only with patterns of disordered behavior but also with properties of the brain. A variety of new methods, such as functional magnetic resonance imaging, are beginning to be used to assess the functions of specific regions of individual human brains. Correlating patterns of gene variants with the results of these and other studies will lead to the identification of subtypes of disorders that are presently lumped together in diagnostic categories, such as schizophrenia or depression.

The combination of genetic information and functional studies will also provide targets for truly novel medications, an approach that is already being used to find new treatments for Alzheimer's disease. Currently the main drugs for Alzheimer's disease improve brain function by prolonging the actions of a neurotransmitter called acetylcholine, a mechanism similar to the actions of some other contemporary drugs, such as the SSRIs. The identification of variants of APP, PS1, and PS2 in rare cases of Alzheimer's disease has helped focus attention on alternative drug targets. Called secretases, these are brain enzymes that play a part in the production of a toxic protein fragment called beta-amyloid, whose accumulation is also affected by the gene variants in a few different ways. Several drug companies are studying drugs that inactivate the secretases,

which they hope to use to reduce beta-amyloid accumulation and thereby stop brain degeneration.

In addition to finding new drug targets, DNA studies may identify gene variants that distinguish people who benefit from available drugs, like SSRIs, from those who do not. Such distinctions could be caused by the particular variants that predispose an individual to a mental disorder and by others that determine how the drug affects the brain. The same DNA data may also reveal gene variants that influence individual vulnerability to certain side effects of drugs. All this genetic information will guide the selection of treatments for individual patients.

The DNA data will also help to redefine the boundaries between different mental illnesses, which often overlap. So, too, do the boundaries between the patterns of behavior we call normal and those we classify as disorders. Combining information about gene variants with studies of brain function, formal psychological tests, and a detailed life story will make it possible to replace crude diagnostic categories with a rich individual profile for each patient.

Fifty years from now, the reasons for a psychiatric consultation will not have changed. Some patients will be disabled by delusions of worthlessness or omnipotence, or by inexplicable attacks of panic, or by threatening voices echoing in their heads. Others will feel joyless, lifeless, pessimistic, chronically worried. Still others will just want to take stock of their lives.

But fifty years from now, everyone who visits a psychiatrist will bring with them a new source of information—a password providing access to their personal DNA file on the National Health Service computer. In that file will be the sequence of each of their genes, along with annotations

calling attention to gene variants and combinations in that individual which influence vulnerability to a variety of disorders, and of others that influence the actions of drugs.

The initial consultation will take about an hour. A third of that time will be set aside for the completion of a formal questionnaire about personal development, family history, and specific symptoms. The rest will be an informal interchange. At the end of the session, the psychiatrist will offer an assessment, suggest some diagnostic tests, and request access to the patient's DNA file.

The request for such access will not seem untoward. The legislation that established a national repository of DNA files and ensured their privacy will also have set aside funds to publicize the benefits of making them available to appropriate professionals. Many people who consult psychiatrists will be eager to comply. This will be particularly true of those who come from families that are riddled with certain mental disorders; they may wish to get an assessment of their level of risk and find out if any preventive measures can be taken. Those who seek medication may opt to be guided by knowledge of their particular combination of gene variants.

Such guidance will be especially valuable, because there will be hundreds of medications to choose from. Some will be improved versions of those we have now, with more selective effects on neurotransmission. Others will have been developed on the basis of our new knowledge about brain functions. Still others will have followed from the identification of gene variants that increase the risk of mental disorders.

The availability of genetic information about mental disorders will not only change the diagnostic and therapeutic practices of psychiatrists but also augment psychiatry's

contribution to the way we think about ourselves. In the first half of the twentieth century, psychiatry helped us realize that we are all heavily influenced by powerful innate passions and benefit from becoming aware of them. In the second half, it provided us with drugs for mitigating uncontrollable behaviors and showed how dependent we all are on simple brain chemicals, such as serotonin and dopamine. The identification of gene variants that influence behavioral differences will fill in some important details about each person's unique biology. Although it may prove difficult to interpret the significance of many of these gene variants, some of them will surely become useful tools for contemplating and constructing our individual life narratives.

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Annex 3. Carta de recepción de documentos de parte de la Biblioteca del Hospital México.

15 de abril del 2025

A la atención de la Biblioteca
Hospital México

Estimados señores:

Por medio de la presente, yo Akysha Santamaría Quesada, estudiante de la Universidad Internacional de las Américas, informo que los documentos prestados por el Hospital México para la realización de las traducciones de mi tesis titulada *Translation of "Cardiología molecular. Módulo 3: Diabetes Mellitus tipo 2"* de Jonatan Navarro Solano, y *"The Next Fifty Years"* de John Brockman, han sido entregados y recibidos junto con las traducciones de dichos documentos por la Biblioteca del Hospital México.

Agradezco mucho la colaboración y el apoyo de la biblioteca para facilitar el acceso a estos materiales, lo cual fue fundamental para la realización de dicho trabajo.

Se solicita amablemente que el bibliotecario encargado firme la presente para constatar la recepción de los documentos.

Quedo a su disposición para cualquier consulta adicional.

Atentamente,

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Rec. 15/4/25

Annex 4. Carta de aprobación del lector del trabajo final de graduación

CARTA DE APROBACIÓN DEL LECTOR DEL TRABAJO FINAL DE GRADUACIÓN

Fecha 22/04/2025

Señores
Departamento de Registro
Universidad Internacional de las Américas

Estimados señores:

El suscrito, **Keren Raquel Muñoz Ramirez**, Profesor de la carrera de **Ingles** de la Universidad Internacional de las Américas y en mi condición de ***Lector DEL TRABAJO FINAL DE GRADUACIÓN*** titulado **"Translation of "Cardiología molecular. Módulo 3: Diabetes Mellitus tipo 2" by Jonatan Navarro Solano from Spanish to English and "The Next Fifty Years" by John Brockman from English to Spanish for the Hospital Mexico Library"**. Elaborado por el/la/los estudiantes(s) **AKYSHA NICOLE SANTAMARÍA QUESADA, 118920957**, para optar por el título de bachillerato en inglés.
Considero que dicho trabajo reúne los requisitos exigidos por la universidad, por lo tanto, doy la aprobación para ser sometido a la defensa pública y evaluación por parte del Tribunal Examinador asignado para tal efecto.

KEREN RAQUEL MUÑOZ RAMIREZ (FIRMA)
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