ARTICULO DE REVISIÓN

MAPPING THE NEURAL PATHWAYS OF STRESS: A PSYCHOCHEMICAL INVESTIGATION

MAPEO DE LAS VÍAS NEURONALES DEL ESTRÉS: UNA INVESTIGACIÓN PSICO QUÍMICA

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RESUMEN

Con el paso de los años, la sociedad ha ido desarrollándose, esto ha traído como resultado que la manera de pensar y actuar de los seres humanos se haya ido transformando, todo ello debido a su capacidad adaptativa ante los cambios del medio. Sin embargo, debido a los ritmos acelerados y cambiantes que hoy enfrenta el mundo en los contextos de la ciencia y la tecnología, se ha evidenciado como la vida de las personas se ha diversificado, experimentando cada vez más afecciones como el estrés, el cual, actualmente, ocupa un lugar destacado en el ámbito investigativo de la salud. En este sentido, el estudio tuvo como propósito indagar en la importancia que tiene hoy en día el estudio de las vías neuronales del estrés para contribuir a el mejoramiento de la calidad de vida de la sociedad. Para su logro, se llevó a cabo una revisión sistemática de variados artículos derivados de la base de datos indexada de Scopus en español e inglés. De esta forma, se muestra como en los últimos cinco años, un porcentaje elevado de la población mundial ha sufrido o sufre de situaciones de estrés. Así, se evidencia la necesidad imperante de ejecutar nuevos estudios que estén orientados hacia esta problemática, y donde se expongan elementos que contribuyan positivamente a la concientización sobre una de las afecciones que más incidencia posee actualmente en la sociedad.

PALABRAS CLAVE: vías neuronales, estrés, psico químico, revisión documental.

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ABSTRACT

Over the years, society has developed, this has resulted in the way of thinking and acting of human beings having been transformed, all due to their adaptive capacity in the face of changes in the environment. However, due to the accelerated and changing rhythms that the world faces today in the contexts of science and technology, it has been evident how people's lives have diversified, experiencing more and more conditions such as stress, which, Currently, it occupies a prominent place in the field of health research. In this sense, the purpose of the study was to investigate the importance that the study of the neural pathways of stress has today to contribute to the improvement of the quality of life of society. To achieve this, a systematic review of various articles derived from the Scopus indexed database in Spanish and English was conducted. In this way, it is shown that in the last five years, a high percentage of the world's population has suffered or is suffering from stressful situations. Thus, the prevailing need to conduct new studies that are oriented towards this problem is evident, and where elements that contribute positively to raising awareness about one of the conditions that currently have the greatest incidence in society are exposed.

KEYWORDS: neural pathways, stress, psychochemical, document review.

INTRODUCTION AND BACKGROUND

At present, there are various psychological and biological factors that directly influence the functioning of individuals, both at the physical and emotional levels. These factors have persisted over time and have been addressed through various approaches in the fields of science, health, and psychology, among others (Bonet, 2019; Rodríguez-Bermejo, 2019; Pérez Pereda, 2022). Similar to this, the relationship between context and health preservation is also important. It should be noted that not all researchers, but many of them at some point in their careers have had to deal with complex phenomena when it comes to their resolution and explanation in physical and emotional aspects.

Authors such as Epel *et al*. (2018), Justice (2018), Sánchez-Valle & Méndez-Sánchez (2018), Portilla-Flores *et al*. (2019), Khatri *et al*. (2018), Wohleb *et al*. (2018), Belleau *et al*. (2019), Jacques *et al*. (2019), Hernández Espinosa *et al*. (2019), Konovalova *et al*. (2019), Díaz-Soto

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& Calderín-Miranda (2020), Labanski *et al*. (2020), Eynard (2021), and Romero Romero *et al*. (2021) have approached the topic neural pathways of stress from various perspectives, and how their development is determined by sub-processes that involve biological and chemical aspects specific to the anatomy of the human body. In general, these authors agree that both animals and humans are currently affected by and suffer from stress, which results in not only negative effects on them but also on the environment they live in.

Due to the advancements in science and technology, it is possible to explain how life can be sustained through a constant and dynamic equilibrium known as homeostasis. However, this equilibrium is repeatedly challenged by unfavorable causes, which can be intrinsic or extrinsic, real, or perceived, and can be considered stressors (Lu *et al*., 2021). Thus, stress is an element that is present in people's daily lives.

In this context, the brain plays a crucial role as the primary controller of interpretations regarding what can or cannot be stressful, as well as the behavioral and physiological responses that are executed (McEwen, 2019).

Consistent with the afore mentioned, stress is seen consequently manifested as a state of homeostasis, whether threatened or perceived. Consequently, individuals, in their structural composition (body and mind), react in various ways to stress, triggering a complex repertoire of the central nervous system (CNS). Therefore, when these responses are somehow inadequate, it can lead to adverse effects on physiological functions such as metabolism, inflammatory response, among others (Lu *et al*., 2021).

A comprehensive review of research documents has revealed that the first finding of an association between stress-related pathologies was made by the author Hans Selye. This researcher explained that non-specific systemic reactions of the body occur after prolonged exposure to stress (Berger *et al*., 2019; Forman & Zhang, 2021).

Today, stress can be defined as the mechanism connecting a stressful agent or stressor to its target organ, resulting in a physiological or behavioral response (Johnson, 2018; Berger *et al*., 2019). On the other hand, stress has been classified into eustress, which refers to certain experiences of a specific duration, and distress, or "being stressed," which refers to experiences characterized by a lack

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of control and dominance, typically lasting, vexing, and physically and mentally threatening (Peltier *et al*., 2019).

Thus, the neural pathways of stress act in various ways, as the stress response is initially led by the stress system (SS) through central and peripheral components within the CNS. The activation of the SS leads to a set of physical and behavioral transformations, which are negative and affect the improvement of quality of life (QoL) (Lempesis *et al*., 2023). Although essential for survival, frequent neurobiological stress responses significantly increase the risk of health conditions, especially when experienced during periods of rapid brain development (O'Connor *et al*., 2021). Therefore, the objective was to describe the importance of studying the neural pathways of stress for improving quality of life.

METHODOLOGY

This systematic review was conducted using a qualitative approach, which is appropriate for synthesizing findings from studies with diverse methodologies on stress neural pathways. The PRISMA guidelines (Page et al., 2022) were followed, as they are the standard for systematic reviews. The methodology includes a structured protocol consisting of four phases: 1) Identification of research questions and eligibility criteria; 2) Systematic search of sources; 3) Study selection; and 4) Data extraction, analysis, and reporting. This method aims to minimize biases and methodological errors, ensuring rigor and transparency.

The research questions that guided the study were as follows:

What is the link between stress and memory?

What are the causes of stress?

What are the general symptoms of stress?

What is the relevance of studying the neural pathways of stress for QoL?

The systematic search was conducted in documents from the Scopus database. Academic search engines such as Google Scholar and PubMed were also used, with the MeSH thesaurus as the controlled vocabulary of MEDLINE to obtain relevant information on the terms "stress," "memory," "neural pathways," "quality of life," and their Spanish equivalents. Additionally, English, and Spanish articles published in academic journals within the last five years were included.

The eligibility criteria were as follows: 1) empirical research articles or systematic reviews; 2) studies on stress and neural pathways; 3) focus on educational contexts, y 4) relation between quality of life and stress. It is important to note that expert opinions, government reports, and texts unrelated to the field of study were excluded.

The initial population consisted of fifty documents, which were categorized according to the corresponding editorials in the Scopus database. However, after an exhaustive analysis of the existing literature on the topic, thirty articles were excluded for not meeting the specified standards of publication date validity, level and quality of methodological resources, and relevance, as indicated by Page et al. (2022). As a result, the sample consisted of twenty documents, including original research articles, case study articles, bibliometric analyses, and systematic review articles. They were further categorized by editorials as follows: Wiley (5), Taylor & Francis (5), Elsevier (5), and Springer (5). The objective was to describe the relevance of the neural pathways of stress for QoL, resulting in both positive contributions and the exploration of new thematic lines, as well as their importance in each conceived stage.

Finally, data extraction and analysis were conducted based on the research questions, identifying relevant concepts and categories through an inductive process. The findings were synthesized into evidence-based practical recommendations, providing a more comprehensive and generalizable understanding of the phenomenon in question.

RESULTS

Table 1

Editorial structuring of articles

Editorials and studies	Year	Relevance Level	Results and Recommendations
Elsevier			
Estrés oxidativo en la asfixia perinatal y la encefalopatía hipóxico-isquémica. *Nuñez et al*. (2018)	2018	Medium	The role of oxidative stress (OS) is highlighted as the main cause of direct damage to the CNS, as well as in the activation of metabolic cascades leading to apoptosis and inflammation. At the same time, the combination of hypothermia with coadjuvant therapies to modulate OS is emphasized for improvement of prognosis.
Avances genéticos en el trastorno por estrés postraumático. Guillén-	2018	High	The importance of studies that explore the relationship between genes and the environment to

Burgos & Gutiérrez-Ruiz (2018)			identify disease-specific phenotypes is emphasized. Furthermore, the genetic advances in understanding the genomics of post-traumatic stress disorder are highlighted.
COVID-19 y salud mental. Rodríguez-Quiroga *et al*. (2020)	2020	High	The study examines the effects of COVID-19 on the general population, particularly in the context of confinement, resulting in increased stress and mental health problems.
El cuerpo duele, y el dolor social… ¿duele también? Martín *et al*. (2020)	2020	High	This study provides a comprehensive review of the concept of social pain and its relationship with physical pain, demonstrating that social pain is processed in the same brain areas involved in the affective dimension of physical pain.
Depresión e inflamación: ¿Una relación más allá del azar? Erazo (2020)	2020	Medium	The research conducts a review of the various connections between clinical phenomena and the interplay of the immune, nervous, and endocrine systems. It delves into the link between depression and systemic inflammatory diseases, with stress playing a determinant role.
Springer			
Silencing of Long Noncoding RNA SOX21-AS1 Relieves Neuronal Oxidative Stress Injury in Mice with Alzheimer's Disease by Upregulating FZD3/5 via the Wnt Signaling Pathway. Zhang *et al*. (2019)	2019	Low	The study investigates the effect of the lncRNA SOX21-AS1 on neuronal OS injury in mice with Alzheimer's disease, specifically via the Wnt signaling pathway targeting FZD3/5.
A Clinical Guide to the Treatment of the Human Stress Response. Everly & Lating (2019)	2019	High	This study highlights the most recent discoveries in various disciplines regarding the treatment of human stress. Likewise, it provides an updated overview of neuroscience, starting with an innovative model that tracks the

			development of stress throughout the human body.
Multiple immune-inflammatory and oxidative and nitrosative stress pathways explain the frequent presence of depression in multiple sclerosis. Morris *et al*. (2018)	2018	High	The study conducts a comprehensive review that presents interesting findings. It demonstrates that patients with multiple sclerosis (MS) and major depressive disorder (MDD) exhibit various neuroimaging abnormalities. MS patients with depressive symptoms show different neuroimaging profiles compared to those without depressive symptoms.
The anatomy and physiology of the human stress response. Everly *et al*. (2019)	2019	High	This study explores the phenomenology of stress as a "linking" mechanism.
Psychoneuroimmunology—developments in stress research. Straub & Cutolo (2018)	2018	High	The study addresses multiple clinical best practices that influence stress responses and outcomes in chronic diseases.
Taylor & Francis			
Sesamin and sesamol attenuate H2O2-induced oxidative stress on human neuronal cells via the SIRT1-SIRT3-FOXO3a signaling pathway. Ruankham *et al*. (2021)	2021	High	This original research article presents highly relevant findings. It suggests that sesamin and sesamol are compounds that protect neuronal cells from OS, which is essential to prevent mental health diseases and, therefore, to live a much healthier life, both physically and mentally.
Neuronal damage and protection in the pathophysiology and treatment of psychiatric illness: stress and depression. Duman (2022)	2022	High	The research yields different results, including the potential for behavioral and therapeutic interventions to reverse structural alterations by stimulating neuroprotective pathways, contributing to resilience, and overcoming stressful situations.
Post-traumatic stress disorder: the neurobiological impact of psychological trauma. Sherin & Nemeroff (2022)	2022	Medium	The research demonstrates how certain pathological features observed in individuals with post-traumatic stress disorder can

			overlap with characteristics of traumatic brain injury patients.
Neural plasticity: consequences of stress and actions of antidepressant treatment. Duman (2022)	2022	Medium	The review study addresses the issue of neuronal plasticity because of a primary mechanism of neuronal function. Thus, further elucidation of the mechanisms underlying neuronal plasticity may lead to the creation of novel drugs, which could assist in effective therapeutic interventions to prevent mental health conditions.
The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Smith & Vale (2022)	2022	Low	This document review highlights the significance of the hypothalamic-pituitary-adrenal axis in integrating adaptive stress responses in animals. Additionally, it provides evidence that stress response is also partly mediated by noradrenergic neurons in the brainstem and parasympathetic systems.
Wiley			
Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease. Trist *et al*. (2019)	2019	High	This review explores the molecular factors contributing to the high steady state of OS in the healthy *substantia nigra* during old age and how this chemical environment renders neurons susceptible to oxidative damage in Parkinson's disease.
Inflammation and post-traumatic stress disorder. Hori & Kim (2019)	2019	High	This study presents findings that suggest mechanisms of inflammation in post-traumatic stress disorder.
The role of astrocytes in oxidative stress of central nervous system: A mixed blessing. *Cell proliferation.* Chen *et al*. (2020)	2020	High	The study demonstrates how the multiple functions of astrocytes indicate that their proper performance is crucial for the normal functioning of the CNS. Additionally, it summarizes the roles of astrocytes in redox regulation and the corresponding mechanisms under both normal and different pathological conditions.

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Emerging roles of ER stress in the etiology and pathogenesis of Alzheimer's disease. Gerakis & Hetz (2018)	2018	Medium	The study addresses the functional role of endoplasmic reticulum stress signaling in Alzheimer's disease, discussing the pathway's complex involvement in the control of neuronal survival, the amyloid cascade, the neurodegeneration, and the synaptic function.
Environmental noise induces the release of stress hormones and inflammatory signaling molecules leading to oxidative stress and vascular dysfunction-Signatures of the internal exposome. Daiber *et al*. (2019)	2019	High	The research conducts a comprehensive review and analyzes the mechanisms of cardiovascular and metabolic consequences induced by non-auditory noise, focusing on the signaling pathways and the neural pathways of stress.

Note: Own elaboration.

What is the link between stress and memory? (Neuronal pathways)

The document review revealed that the study conducted by Bruce McEwen (Peters *et al*., 2021) showed that initially, when a stressful encounter occurred, it was stored in the memory bank (thus being registered and therefore avoidable in the future). However, when stress episodes repeated, this resulted in a gradual decrease in memory over time, as the cells in the hippocampus began to shrink. In this sense, chronic stress leads to the loss of dendritic branches in the apical dendrites residing in the neurons of the CA3 region of the hippocampus, which participate in memory processes, and thus they become shorter in a reversible manner. Likewise, chronic stress impairs neurogenesis in the dentate gyrus (DG) and over time can decrease the number of neurons, as well as the volume in the DG (Colyn *et al*., 2019; Gulyaeva, 2021). On the other hand, this issue also affects memory consolidation, as moderate levels of stress experienced after encoding contribute to memory enhancement (Thomas & Karanian, 2019).

What are the causes of stress?

Table 2
Causes of stress

Physiological level	Emotional level	Cognitive level
Variations in heart rate and blood pressure.	Anxiety issues.	Altered perception.
Abrupt changes in stomach activity	Depression states.	Loss of control and denial.
Transformations in the immune system	Experiencing fear, dread, etc.	Decreased memory and attention, etc.

Note: Own elaboration based on the studies of Espinoza et al. (2018).

What are the general symptoms of stress?

Stress can manifest in various ways. However, among the most common manifestations are headaches, difficulty swallowing (esophageal spasms), heartburn, nausea, dizziness, chest pain, back pain, neck pain, frequent urination, decreased memory, gastric spasms, cold sweats, chronic fatigue, panic attacks, insomnia, constipation, and diarrhea.

Furthermore, other stress-related conditions include:

- Metabolic responses.
- Cardiovascular response.
- Gastrointestinal response.
- Autonomic system functioning.
- Female and male reproductive systems.
- Acceleration of cutaneous aging.

What is the relevance of studying the neural pathways of stress for QoL?

As mentioned earlier, stress is currently considered one of the most prevalent conditions affecting the global population. Therefore, it is crucial for individuals to be increasingly informed about how to act or what to do to avoid stress situations. The manifestations of stress are as unique as the organism experiencing it. Stress becomes visible through a wide range of physiological, cognitive, and behavioral responses (Konovalova et al., 2019). Signs such as headaches, sleep disorders, compulsive habits, irritability, or hypertension are among the most common responses to this condition.

It is worth noting that two of the most distinguished stress disorders are classified by the Diagnostic and Statistical Manual of Mental Disorders DSM-5: acute stress disorder, post-traumatic stress disorder, and adjustment disorder. Both acute and post-traumatic stress are the consequences of exposure to a traumatic event; however, they mainly differ in the onset and duration of symptoms. These symptoms typically involve a combination of intrusion, negative mood, dissociative symptoms, avoidance symptoms, negative effects on cognition and/or mood, and arousal symptoms (Nuñez et al., 2018).

Currently, society is experiencing rapid changes and transformations that lead people to live their lives differently than they did 20 years ago. As a result, issues like stress have become much more visible, affecting the quality of life of both young and adult populations.

In this sense, the phenomena included in the concept of stress have been related to all aspects of life, the formation of the nervous system, neuronal death due to aging, hormonal, and immune responses to emotional or physical aggression, coping with daily problems, and the biological modulation of cognitive functions. All these fields and many others are important in education, work, daily life, aging, and the optimization of human performance. However, their relationship with diseases has been the aspect that has driven research development and its application (Cambronero Jáuregui, 2022).

Therefore, it is important that both educational institutions and other organizations address the negative consequences that can arise from prolonged exposure to stress, as well as the detrimental elements that may appear and negatively impact people's quality of life, starting from an early age. While it is known that everyone may face difficult situations that can lead to moments of stress, it is also important to know what to do, not only to avoid such situations but also to face and overcome them.

DISCUSSION

The study leads to various specificities, among which it is exposed that stress can be classified according to the intensity and frequency of its origins. In turn, acute stress can be presented as one of its variants; however, when it reaches intense levels following an immediate event, it begins to affect both the physical and psychological levels. This results in an alteration of the biological and chemical processes in the human body, which can lead to problems that affect the improvement of quality of life through diseases such as hypertension and other cardiovascular diseases. The aforementioned is in line with the studies conducted by Casado Urizar *et al*. (2022), who investigate the neuroendocrine pathway of stress.

In this context, the review conducted presents similarities with the studies conducted by Wohleb *et al*. (2018), Casado Urizar *et al*. (2022), and Chen *et al*. (2020). Although stress levels and the intensity of its manifestations may vary in each person, science has shown that the physiological mechanism associated with stress does not vary, and it is the same in all individuals. In this sense, stress can be both a physical and mental manifestation, where during the process of responding to stressful stimuli conducted in the organism, various structures of the CNS are involved, which can be associated with biological, neural, chemical factors, among others. One example of these structures includes the hypothalamus, the pituitary gland, and the adrenal glands. These structures are interconnected, forming an axis called the hypothalamic-pituitary-adrenal axis. In this way, the axis is activated when certain hormones called releasing factors are released, which affect specific structures, and through neural and chemical processes stimulate or inhibit, as the case may be, the secretion of different hormones.

Finally, the most significant limitations of the study lie in the fact that various documents are currently not openly accessible, resulting in the reviews and analyses not being able to be fully executed. Therefore, at times, the necessary theoretical and methodological foundations cannot be fully relied upon for their proper presentation.

CONCLUSIONS

Currently, contexts related to science and technology are experiencing revolutionary changes, which over time have become investigative processes. These processes have shifted their focus to issues revolving around mental health, all due to a considerable number of people worldwide suffering or having suffered from conditions such as stress. In this regard, stress can be caused by internal and external factors, which disrupt the organism's homeostasis, resulting in various psychophysiological manifestations that negatively impact the quality of life of individuals.

Therefore, educating people about the development and functioning of the neuronal pathways of stress, as well as their associated physiological foundations, is a fundamental task that significantly enhances the development of neurocognitive skills. These skills favor both lifestyles and the execution of various self-regulation mechanisms, all with the purpose of achieving an improvement in the ways of thinking and acting in the face of stressful events, situations and moments, elements that contribute favorably to the integral development of individuals.

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