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REVIEW PAPER

Brief review of pathophysiological disorders as consequence of psychological stress

Breve revisión de los trastornos fisiopatológicos como consecuencia del estrés psicológico

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ABSTRACT
Background: Psychological stress is a reaction to an unexpected situation that favours adaptation and response to the event. However, when psychological stress is chronic or very intense, it can induce changes in various systems and tissues, causing diseases or aggravating existing ones. **Objective:** To briefly analyse the pathophysiological conditions caused by psychological stress. **Method:** A narrative review of the scientific literature on pathophysiological conditions as a consequence of psychological stress was performed. **Results:** Psychological stress can induce various conditions at the gastrointestinal, immune and cardiovascular levels. This is mainly due to the neurobiological and endocrine response because when faced with a stressful stimulus, a deregulated release of glucocorticoids and catecholamines is generated, altering the normal physiology of the organism. Gastrointestinal disorders are mainly due to goblet cell dysfunction, resulting in intestinal hyperpermeability, inflammation and infection. Changes at the immune level lead to an increase in inflammatory responses but a decrease in the protective activities of the immune system. Finally, cardiovascular conditions include atherosclerosis, increased blood pressure and stroke. **Conclusion:** Psychological stress can induce real physiological pathologies and, in some cases, fatal ones. Some of the molecular mechanisms involved in these pathologies have already been studied and identified. Knowledge of these molecular mechanisms can help clinicians and therapists to improve the treatment and therapy of patients.
Keywords: Psychological Stress, Glucocorticoids, Immunity, Cardiovascular Diseases, Brain-gut Axis.

RESUMEN
Introducción: El estrés psicológico es una respuesta a una situación inesperada que favorece la adaptación y la respuesta ante dicho evento. Sin embargo, cuando el estrés psicológico es crónico o muy intenso, se pueden desencadenar afecciones en diversos sistemas y tejidos, generando enfermedades o empeorando las ya existentes. **Objetivo:** Analizar brevemente las afecciones fisiopatológicas causadas por el estrés psicológico. **Método:** Se realizó una revisión narrativa con la literatura científica sobre las afecciones fisiopatológicas debidas al estrés psicológico. **Resultados:** El estrés psicológico puede desencadenar diversas afecciones a nivel gastrointestinal, inmunitario y cardiovascular. Esto se debe principalmente a la respuesta neurobiológica y endócrina, ya que ante estímulos estresores, se genera una liberación desregulada de glucocorticoides y catecolaminas que alteran la fisiología normal del organismo. Las afecciones a nivel gastrointestinal se deben principalmente a la disfunción de las células caliciformes, dando como consecuencia hiperper-

meabilidad intestinal, inflamación e infecciones. Las alteraciones a nivel inmunitario generan un aumento en las respuestas inflamatorias pero una reducción en las actividades protectoras del sistema inmune. Por último, las afecciones cardiovasculares incluyen ateroesclerosis, aumento de la presión arterial y derrames cerebrales, entre otros. **Conclusión**: El estrés psicológico puede causar patologías fisiológicas reales y, en algunos casos, mortales. Algunos de los mecanismos moleculares implicados en estas patologías ya han sido estudiados y establecidos. Conocer estos mecanismos moleculares puede ayudar a los médicos y terapeutas a mejorar el tratamiento y la terapia del paciente.

Palabras claves: Estrés Psicológico, Glucocorticoides, Inmunidad, Enfermedades Cardiovasculares, Enfermedades Inflamatorias del Intestino.

BACKGROUND

Throughout the life of the human being, events occur that do not turn out as expected; sometimes they are better, but at other times, they are worse, and can lead to psychological stress and frustration. Psychological stress is a physiological response to an unexpected or unfavorable event for the person who perceives it. This response favors an adaptation for a better action and response to the situation (Piqueras Rodríguez et al., 2009). Therefore, stress may have a protective effect in the short run, during minutes or hours, when the individual needs to stay alert (Antoni y Dhabhar, 2019). However, when this response is very intense or chronic, it may lead to negative emotions such as fear, anxiety, anger, and sadness (Piqueras Rodríguez et al., 2009).

Since the human being is predisposed to adaptation, the emotional perception to adverse situations and the intensity and duration of their reaction to them depends, among other factors, on the discrepancy between what has been achieved and what is expected based on previous experiences and learning (Mustaca, 2018). When these states are very intense or chronic, they can affect the person's quality of life by contracting mental illness or physical disorders (Piqueras Rodríguez et al., 2009).

Psychological stress was already frequent worldwide, but this and other mental disorders have increased because of the COVID-19 pandemic (Cooke et al., 2020; Nochaiwong et al., 2021), affecting general population, including health professionals as well (Mathur et al., 2020), and some opinions suggest that COVID-19 related stress may continue even after the pandemic is over (Łaskawiec et al., 2022).

However, and unfortunately, due to modern lifestyles and social demands and expectations, the impacts of psychological stress are greatly underestimated (Güler et al., 2019; Izawa et al., 2016; Nakamura-Taira et al., 2018), and there is an urge to raise greater awareness in this regard. Therefore, it is important to inform the population about the importance of psychological stress and the influence it can have on people's health. Among these pathologies are gastrointestinal conditions (He et al., 2018), immune system affections (Ilchmann-Diounou & Menard, 2020) and cardiovascular conditions (Vancheri et al., 2022), which can have an important clinical impact on people. Therefore, we consider it necessary to carry out a brief narrative review on this topic aimed at psychologists, doctors, community pharmacists and even patients or anyone interested in the topic.

This review aims to briefly describe pathophysiological disorders such as gut, cardiovascular, and immune system affections as consequence of psychological stress and some of the involved mechanisms according to recent scientific research.

METHODS

This article is a brief narrative review on the pathophysiological consequences of psychological stress. To this end, a non-systematized bibliographic search of specialized scientific literature was carried out in databases such as PubMed, Google Scholar and SciELO using key words such as "psychological stress", "pathophysiological disorders", "stress and stressors", "gut health", "immune system", "cardiovascular system" and "neurobiology of stress". Only refereed scientific publications were considered. Those in English language published in the last five years (from 2018 to March 2023) were prioritized, although the inclusion of some older articles and in Spanish language was also allowed as they were previously identified. Original research articles were included, as well as other narrative and systematic reviews. Likewise, to complement some definitions, sources were consulted from official websites such as the World Health Organization (WHO) site.

RESULTS

Stress and stressors

According to the World Health Organization, stress is "a state of worry or mental tension generated by a difficult situation" (World Health Organization, 2023). This typically occurs when an individual feels unable to cope with an adverse situation or negative environmental stimulus (Epel et al., 2018; Huh et al., 2021). Each individual has a different response to these situations, so it is important to take into account the concept of "perceived stress", which is the way in which an individual understands the amount of stress to which they are exposed (Huh et al., 2021) so that the individual produces psychological and emotional responses to these situations, such as the appearance of overwhelming sensations, anxiety or a feeling of loss of control and insufficiency (Epel et al., 2018).

Therefore, psychological stress response is subjective and its measurement and perception complex, because it involves external stressors and the individual`s abilities to cope with them, which varies among individuals (Vancheri et al., 2022). So, an individual may have a response against a real or perceived (but not real) threat to the well-being which may be exacerbated (van der Sluis & Hoekstra, 2020). This response is acute when the experience it is brief but intense, or chronic when it is constant in time. Acute psychological stress may be a result of quick events, such as an interview, an accident, or natural disasters such as earthquakes and hurricanes, among others, whereas chronic stress is the result of long term or repetitive exposure to stressors or stressful situations, such as prolonged family or job-related problems, low socioeconomic status, diseases, or loneliness, among others (Vancheri et al., 2022). Therefore, acute stress may be beneficial in some situations because its response may help the individual to adapt to an adverse situation in a moment of need, but chronic stress is considered harmful because it can produce some pathophysiological disorders as a result (Antoni & Dhabhar, 2019).

Sex and age differences against psychological stress

Regarding sex and age differences, it is difficult to establish a correlation with psychological stress because it depends on very personal or specific circumstances. For example, COVID-19 pandemic increased psychological stress in general population; a study conducted in China during the pandemic stablished that unemployment increased psychological stress, but it was also found that people under 45 years old and females were found to be more affected by this circumstance (Yan et al., 2021). In another study conducted also in China, it was shown that psychological stress was correlated with an increase for hypertension in women, but not in men (Hu et al., 2015).

Altogether, this suggest that women are more vulnerable against psychological stress than men. However, as it was mentioned before, it is difficult to establish a clear general correlation, as it was shown in a review study in which the authors concluded that despite many research articles suggest that there is in indeed a stronger link in women between stress and sleep with inflammation because of hormone differences, in some cases, methodologies of measurement are poor and the results are largely mixed (Dolsen et al., 2019). The same can be said about age differences, as different events affect people differently. For example, in a study, it was established that young adults were indeed more vulnerable to stress during COVID-19 pandemic due to isolation (Birditt et al., 2021), but other situations or circumstances in life such as retirement can cause great stress to older people, and it has been established that men are more vulnerable to it (Berezina et al., 2019).

Neurobiology and endocrinology of psychological stress

When the human being is exposed to a stressor, acute stress is caused because the nervous systems immediately respond by activating the sympatho-adrenal medullary system (SAMS) which then causes the release of catecholamines (Turner et al., 2020). At the same time, there is also an activation of the limbic-hypothalamo-pituitary adrenal axis (LHPAA), causing a secretion of high levels of corticotropin releasing factor (CRF) from hypothalamus. CRF then binds in the pituitary gland, resulting in the production of adrenocorticotropic hormone (ACTH), which then stimulates the production of stress hormones such as glucocorticoids, including cortisol and corticosterone that affects immunity and hearth health as described later (van der Sluis and Hoekstra, 2020).

Several neurotransmitters are also involved in psychological stress response. One of the most important ones is dopamine. Dopamine is a neuromodulator because it modulates sensitivity to other neurotransmitters. For example, it modulates the influence of glutamate in other neurons (Wise & Robble, 2020). Acute stressors induce a pronounced activation of the dopamine system, and it has been seen that children with traumas have elevated urinary dopamine metabolites and that acute psychosocial stressors induce greater dopamine release in people with low self-reported maternal care. It is interesting that even after a single stress exposure, long-lasting changes in the dopamine system may occur in a similar way to that induced by addictive drugs and that a long-term exposure to psychological adversity is related to a diminished dopaminergic function (Ap Bloomfield et al., 2019).

On the other hand, the excitatory neurotransmitter glutamate, and the inhibitory neurotransmitter gammaaminobutyric acid (GABA) are also important. Basolateral amygdala (BLA) is a region of the brain that plays an important role in fear learning and memory, and it consist of 80% of excitatory neurons (glutamatergic neurons) and 20% of inhibitory neurons (GABAergic neurons). It has been shown that acute stressors induce higher expression of glutamate receptors in BLA and a large increase in excitatory neurotransmitter glutamine pool which can cause acute and chronic nerve cell injuries, causing degeneration and death of glutamatergic neurons. In fact, similarly to what happens with the dopamine system, prolonged stress causes a low expression of glutamine receptors and glutamine response overall, causing a biochemical imbalance and BLA structural changes, therefore causing behavioural disorders (Wang et al., 2021). Interestingly, GABAergenic response seems to be the opposite; a study carried with magnetic resonance spectroscopy method on healthy human subjects showed that prefrontal GABA decreased by 18% in a threat-of-shock condition relative to the safe condition, showing a rapid presynaptic down-regulation of GABAergic neurotransmission in response to acute psychological stress. This makes sense, because GABA is the main inhibitory neurotransmitter and GABA receptor agonists that enhance GABA transmissions such as benzodiazepines are used as anxiolytics (Hasler et al., 2010).

Norepinephrine is another important neurotransmitter involved in psychological stress responses. Locus coeruleus (LC) is the main norepinephrine secretor in the brain. Norepinephrine is secreted by the LC during acute stress which activates BLA and all that it entails, as previously described (Giustino et al., 2020). Furthermore, it has been reported that norepinephrine released by daily stressed young adults induces vasoconstriction, which may lead to cardiopathies (Greaney et al., 2020) as described later.

Overall, this means that the brain transduces the emotional stimuli (stressor) perceived by the person (stress perception) into hemodynamic, neuroendocrine and immune changes to generate a “fight or flight” response (stress response) (Vancheri et al., 2022). However, this response produces an energy expenditure and metabolism for an activity that may not eventuate, which is why the response is considered “metabolically unjustified” (Turner et al., 2020).

Psychological stress measurement

As it was mentioned earlier, psychological stress measurement is complex because it depends on subjective perceptions. However, they are reliable tools available for this purpose. The simplest ones are self-report questionaries, such as the Perceived Stress Scale (PSS-10), the Job Content Questionnaire, the Job Stress Survey, the Coping Strategy Indicator, the Stress and Coping Process Questionnaire, the Coping Inventory for Stressful Situations, among many others. The PSS-10 is the most used tool to measure perception of stress for clinical and research purposes. It was developed by Cohen, Kamarck and Memelstein in 1983, and it contains 10 questions on current levels of perceived stress; six items measure stress itself and four measure coping strategies to it (Frisone et al., 2021).

However, there are other tools which may be more objective because they rely on technology to measure stress via bio-signals evaluation, imageology or biomarkers and metabolites detection. For example, as it was mentioned before, nuclear magnetic resonance can be useful to measure neurotransmitters related to perceived stress (Hasler et al., 2010). Similarly, heart activity measurement tools such as electrocardiogram, blood volume pressure, heart rate and heart rate variability measurements are useful to detect perceived stress on patients and how stress affects their cardiovascular system. However, electroencephalogram (EEG) is probably the most used technique to detect changes in neuronal activity associated with external stimuli, therefore, it is useful to measure stress responses, especially by measuring the EEG asymmetry index because it reveals emotional arousal; most research studies support the statement that under stress conditions there is generally greater frontal right alpha activity in relation to the left alpha activity (Giannakakis et al., 2022).

However, now days technological advances can be exploited even further in various exciting ways. For example, there is a lot of promising research regarding real-time stress monitoring using wearable devices. Such instruments would be very beneficial, not only for regular patients, but also for people with especially dangerous or stressful occupations such as firefighters, police officers, athletes, soldiers, among others (Parlak, 2021). For example, in a study, scientist developed a wearable instrument to measure EEG asymmetry index in human subjects to study stress in real time. This instrument was built with off-the shelf instruments and dry electrodes. Its response was compared with standardized stress test, observational questionnaires, and performance measurements. It reached more than 90% accuracy (Arpaia et al., 2020). On the other side, one of the most promising approaches in this regard is real-time cortisol measurement. This has been successfully reported in several research works, and it has been reached mainly via development of immune-electrochemical sensors using enzymes or antibodies. These devices detect and measure cortisol on saliva and other human fluids (Parlak, 2021).

Effect of psychological stress on gut

Microbiota is the set of microorganisms that coexist on human surfaces and cavities. These includes bacteria, archaea, bacteriophages, eukaryotic virus, and fungi. These microorganisms, especially bacteria, are mutualistic organism, therefore, they have several important functions that brings benefit to human health; they train host immunity, digest some food, modify drug and toxin structures, regulate gut endocrine action and neurological signalling, among other activities (Fan & Pedersen, 2020).

However, gut microbiota is not directly in contact with gastrointestinal epithelium; it lies on a layer of mucus that creates a coat, protecting intestinal tissue from bacteria and other biological and mechanical stress (Paone & Cani, 2020). In addition, this mucus layer also provides nutrients and adhesion for microbe growth (He et al., 2018). The main constituent of this mucus layer are mucins, which are large, complex, glycosylated proteins produced and secreted by goblet cells (Paone & Cani, 2020).

Goblet cells produce mucins in response of nervous stimuli (via a brain-gut axis), and it has been shown that acute stress increases mucus release (He et al., 2018). This acute stimulus enhances the mucosal barrier and protects a leaky epithelium against microbial infection, but on the long term, it has been shown that exaggerated and prolonged stimulation of goblet cells reduces their numbers and, therefore, decreases mucus secretion (Söderholm et al., 2002). Additionally, the protective function of the mucus layer is also reduced because psychological stress also alters O-glycosylation of mucins, resulting in flattening of the layer and a consequent loss of cohesion (He et al., 2018). All of this results in intestinal hyperpermeability, a consequent intestinal inflammation and possible infection (Söderholm et al., 2002; Wei et al., 2019). That's why psychological stress may produce gastrointestinal symptoms.

Additionally, as it was mentioned before, LHPAA stimulation releases CRF, which increases oxidative damage in the colon, leading to inflammatory responses and increasing intestinal permeability and bacterial translocation. It also causes to microbiota dysbiosis, which leads to gastrointestinal diseases such as irritable bowel syndrome (Zhang et al., 2023).

Effect of psychological stress on immune system

Immune system activates inflammatory response in a hostile environment to preserve cellular and organ integrity. Therefore, it is a natural and necessary response against biotic and abiotic stress. However, alterations of immune system due to diseases may cause an insufficiency or an overactivity. Insufficient response may cause immunodeficiency, resulting in infections and cancer, while an overactivity may lead to autoimmune disorders (Kjekshus, 2015).

When glucocorticoids are released after a stressful situation, they can modulate immune response; it has been established that they attenuate immune responses and inflammatory processes by attenuating signalling pathways of the inflammatory process, diminishing leukocyte transmigration, and decreasing levels and production of chemo-attractants that are important for immune cells to fight infectious agents (Ilchmann-Diounou & Menard, 2020). They also cause apoptosis of B and T lymphocytes, causing adaptive immune deficiency (Xu et al., 2020). This is why glucocorticoids are used as pharmacological agents to treat immune-related disorders, such as autoimmune diseases in which the organism has exaggerated immune responses (Ilchmann-Diounou & Menard, 2020). However, when considering chronic stress, these immune alterations may lead to chronic infection, chronic inflammatory autoimmune diseases or even cancer. Additionally, stress-induced sympathetic adrenergic signalling can inhibit immune responses in infection diseases (Bae et al., 2019).

Nevertheless, it has also been established in animal models and in humans that stressful events and stress-related disorders such as post-traumatic stress disorder is associated with an increase in pro-inflammatory markers, such as various interleukins (Il) and TNFα, among others. This obviously leads to an exaggerated immune response and damage in several tissues, including intestinal barrier which produces intestinal hypopermeability (Ilchmann-Diounou and Menard, 2020), aggravating gut health described in the previous section.

Overall, this means that stress is related to an up-regulation of inflammation and a down regulation of protective immunity; a combination of factors that can lead to serious damage on an individual's health and can also aggravate other preexisting diseases such as cancer, since affected immune cells may not control cancer cells effectively and may act as stromal cells (Antoni & Dhabhar, 2019).

Effect of psychological stress on cardiovascular system

The most common cardiovascular disease (CVD) is atherosclerosis or coronary artery disease (CAD). This disease consists of lipid accumulation and inflammation of large arteries, and can lead to other cardiovascular affections and stroke (Björkegren & Lusis, 2022).

Chronic stress is related to increase of CVD due to acceleration of atherosclerosis. This is because greater amygdala activity caused by stress is associated with carotid artery intima-media thickness, enhanced blood pressure reactions and inflammatory responses. Besides, there is a maladaptation of the neuroendocrine pathways involved in the response to stress (Vancheri et al., 2022).

Additionally, because of the LHPAA stimulation, stress also favours glucocorticoids secretion from adrenal glands, accelerating atherosclerosis (Björkegren & Lusis, 2022). This is because glucocorticoids reduce nitric oxide concentration, which is a key driver of vasodilation. Glucocorticoids can also promote vascular contractility via regulation of various expression factors of enzymes and proteins involved in vascular contractility (Macleod et al., 2021). This also explains why corticosteroid therapy is associated with CAD (Björkegren & Lusis, 2022).

Acute stress can also have cardiovascular consequences; as it was mentioned before, seconds after the exposure to the stressor, a large sympathetic nervous system activity is produced, causing release of catecholamines adrenaline and noradrenaline into circulation, therefore causing an increase in hearth rate and blood pressure and peripheral microvascular constriction. This circumstance also favours atherosclerosis development. Besides, significant acute stress may trigger cardio-pathological events such as angina, arrhythmias, stress cardiomyopathy, myocardial infarction, stroke, or sudden death (Vancheri et al., 2022).

There is also clinical evidence in real patients: in a study carried in Sweden with data from 1987 to 2013, it was observed that stress related disorders are associated with several CVDs independently of family background or psychiatric comorbidities (Song et al., 2018). These findings show the importance of stress related disorders awareness because these pathologies may affect anyone regardless of their family history of diseases.

CONCLUSIONS

Psychological stress can cause real physiological pathologies, and not just psychological perception of somatic symptoms as some people may believe. Some of the molecular mechanisms involved in these physiological pathologies caused by psychological stress have already been studied and established. Knowing these molecular mechanisms may help physicians and therapists to improve patient`s treatment and therapy. This is important because this is a case of a disorder that causes other disorders, and in some cases, fatal ones. This is why psychological stress must not be overlooked or underestimated by patients nor physicians.

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Francisco López-Naranjo: Conceptualization, investigation, writing, review, supervision, and approval of the final version.
Rebeca Córdova-Moreno: Review, supervision, and approval of the final version.
Ivo Heyerdahl-Viau: Conceptualization, methodology investigation, writing, editing, translation, and approval of the final version.

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CONFLICTO DE INTERESES

The authors declare that there were no conflicts of interest in the collection of data, analysis of information, or writing of the manuscript.

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DATA AVAILABILITY STATEMENT

Not applicable.

DISCLAIMER

The authors are responsible for all statements made in this article.

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