International Journal of Psychological Research
ISSN: 2011-2084
ISSN: 2011-7922
Facultad de Psicología. Universidad de San Buenaventura, Medellín

Valencia-Florez, Kenji Baruch; Sánchez-Castillo, Hugo;
Vázquez, Priscila; Zarate, Pavel; Paz, Diana Berenice

Stress, a Brief Update

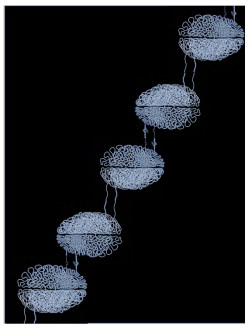
International Journal of Psychological Research,
vol. 16, no. 2, 2023, July-December, pp. 105-121
Facultad de Psicología. Universidad de San Buenaventura, Medellín

DOI: https://doi.org/10.21500/20112084.5815

Available in: https://www.redalyc.org/articulo.oa?id=299075997010

International Journal of PSYCHOLOGICAL RESEARCH

REVIEW ARTICLE



Vol 16, N° 2
https://revistas.usb.edu.co/index.php/IJPR
ISSN 2011-2084
E-ISSN 2011-7922

Stress, a Brief Update

Estrés, una breve actualización

Kenji Baruch Valencia-Florez[1], Hugo Sánchez-Castillo[1,⋆], Priscila Vázquez[1], Pavel Zarate[2], Diana Berenice Paz[3].

[1] *Neuropsychopharmacology Lab. Psychobiology and Neurosciences Department. Psychology School National University of Mexico (UNAM).*

[2] *Iberoamerican Society of Applied Neurosciences (SINA).*

[3] *Neuropsychopharmacology Lab. Psychobiology and Neurosciences Department. Sistema de Universidad Abierta y a Distancia (SUAyD), Psychology School, National University of Mexico (UNAM).*

Abstract.
Stress is fundamental for health and adaptation; it is an evolutionarily conserved response that involves several systems in the organism. The study of the stress response could be traced back to the end of the nineteenth century with George Beard's or Claude Bernard's work and, from that moment on, several studies that have allowed the elucidation of its neurobiology and the consequences of suffering from it were consolidated. In this theoretical review, we discuss the most relevant researches to our knowledge on the study of stress response, from the concept of stress, its neurobiology, the hormonal response during stress, as well as its regulation, the effects of acute and chronic stress, stress from cognition, the different stress responses during life, as well as its relationship with different psychiatric disorders. Taken together, the reviewed research updates the classic perspective on stress, increasing the factors that should be considered in research to explore the effects of stress on health.

Resumen.
El estrés es fundamental para la salud y la adaptación; es una respuesta conservada evolutivamente que implica a varios sistemas del organismo. El estudio de la respuesta de estrés se remonta a finales del siglo XIX con los trabajos de George Beard o Claude Bernard y a partir de ese momento se consolidaron diversos estudios que han permitido dilucidar su neurobiología y las consecuencias de padecerlo. En esta revisión teórica, abordamos lo más relevante para nuestro conocimiento sobre el estudio de la respuesta de estrés, desde el concepto de estrés, su neurobiología, la respuesta hormonal durante el estrés, así como su regulación, los efectos del estrés agudo y crónico, el estrés desde la cognición, las diferentes respuestas de estrés a lo largo de la vida, además de su relación con diferentes trastornos psiquiátricos. En conjunto, las investigaciones revisadas actualizan la perspectiva clásica sobre el estrés, incrementando los factores que deben tenerse en cuenta en la investigación para explorar los efectos del estrés sobre la salud.

Keywords.
Stress; Neurobiology; Cognition; Depression; Resilience; Coping; Glucocorticoids.

Palabras Clave.
Estrés, neurobiología, cognición, depresión, resiliencia, afrontamiento, glucocorticoides.

OPEN ACCESS

Manuscript received: 22-08-2022
Revised: 26-09-2022
Accepted: 06-06-2023

⋆**Corresponding author**:
Hugo Sánchez-Castillo.
Email: hugosancas@comunidad.unam.m

Declaration of data availability: All relevant data are within the article, as well as the information support files.

Conflict of interests: The authors have declared that there is no conflict of interest.

How to Cite:
Valencia-Florez, K. B., Sánchez-Castillo, H., Baruch, K., Vázquez, P., Zarate, P., & Paz, D. B. (2023). Stress, a Brief Update. *International Journal of Psichologycal Research*, *16*(2), 105–121. https://doi.org/10.21500/20112084.5815

1. Introduction

According to WHO, stress has been considered the epidemic of the XXI century (Fink, 2016). Between 1983 and 2020, the perception of stress increased among the general population due to an increment in stressors in the United States of America (American Psychological Association, 2020) and Mexico (Mexican Institute of Social Security, 2017). One of the first sources of stress was Covid-19 pandemic, which disrupted work, education, health care, economy, and relationships. In fact, cumulative stress has been associated with an increased probability of heart disease and hypertension (Albert et al., 2017), addictions (Roeckner et al., 2017), anxiety, depression (Trucco, 2002), acute stress disorder, post traumatic stress disorder (PTSD) (Sánchez-Castillo et al., 2014), Alzheimer's disease, which is less reported, and in the case of stress occurring twice in life (pregnancy and puberty), and schizophrenia (Sarkar et al., 2019).

Stress is a highly personal phenomenon. It changes between subjects (Hammen, 2005), depending on their vulnerability, resilience (Couto-Pereira et al., 2019), and behavioral and cognitive resources to cope with adversity (Lehrer & Woolfolk, 2007). Chronic stress has been associated with the beginning, maintenance, and aggravation of the symptomatology of many psychiatric disorders such as anxiety (Martin et al., 2010) and major depression (Yin et al., 2016). Recently, there has been an increase in the number of psychological and behavioral research (Willner, 2015), investigations focused on the neurobiology of stress, its mechanisms, and consequences in animal models (Stanton et al., 2018), and improved technology for a better understanding that helps us to treat and prevent stress consequences (Fink, 2016).

2. Stress

It is hard to establish a precise moment when the history of stress concept begins. There are some predecessors like Beard "neurasthenia" or Cannon "homeostasis" (Hutmacher, 2021). Neither Beard nor Cannon properly defined the term stress, but their contributions allowed the construction of this concept. The concept of stress has changed among scientists since the first definition by Selye (1936), who defined it as "the non-specific response of the body to any demand" (1976, p. 137). However, researchers like Pacák (2001) show that different stressors cause specific responses measured by cFos activity in the brain, and these responses were also accompanied by neurotransmitter specifical changes. Selye's definition could change to "body response to any demand". Over this definition, McEwen and Akil (2020) proposed stress was the body's response to any real or perceived threat that enhances physiological and psychological activity to cope with the stressor. Also in the study of the stress response, the concept of allostasis and allostatic load were included, in which allostasis represents stability across change and allostatic load refers to the price the body pays for being forced to adapt to adverse psychosocial or physical situations. These concepts are important because they explain the systemic mechanisms that protect the system when it adapts and those that damage the system when it is overloaded (McEwen & Akil, 2020). Considering this, stress could be defined as a systemic response triggered by a stimulus potentially harmful to an organism (Migliaro et al., 2020).

Stress is highly associated with fear and anxiety. Craske et al. (2009) define fear as "an alarm response to imminent danger" (p. 1067) and anxiety as "the anticipatory response to a possible threat" (p. 1067). This conceptualization has remained and is approved by the American Psychiatric Association (2013). Even though those definitions represent a human state, they are useful in animal models either, for describing freezing and immobility behavior respectively (Fink, 2016).

The stress response begins when a stimulus is considered threatening and alters homeostasis (McCarty, 2016). If a stimulus is capable of initiating the stress response, it is considered a stressor (Sapolsky, 2019). However, although it seems that the stress response only begins in the face of high-intensity stressors, such as a predator attack, a natural disaster, or violence, the stress response also participates in the moments in which the body must deal with daily experiences such as social interaction, physical activity, and work (McEwen & Akil, 2020). When the brain senses a stimulus as a threat, it commands a response controlled by two large neuroendocrine systems, the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adrenomedullary (SAM), which is part of the autonomic nervous system (ANS) (Fink, 2017). Understanding the neurobiological mechanisms that regulate the stress response is important to attend to the mental, behavioral, and somatic state of patients with stress-related illnesses (Fink, 2016).

3. Neurobiology of Stress

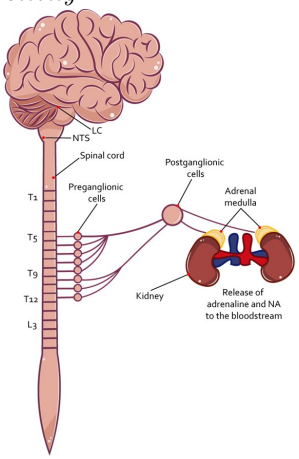
The stress response involves a complex and evolutionarily conserved system where the central nervous system (CNS) mainly participates (Lovejoy & Michalec, 2017). To initiate the stress response, the system must first perceive a stressor. Stressors can be physical or psychological. Physical stressors must alter the physiological state of the system —bleeding, infection, pain, etc.—, while the psychological ones should be interpreted as aversive or challenging —dangerous environments, work demands, social disapproval, harassment, etc.— (Godoy et al., 2018). Although the nature of the stressor is different, it triggers a neuroendocrine response mediated by the activation of SAM and the HPA (Radley et al., 2017).

The SAM axis is the first to be activated when the stress response begins (Sharpley, 2009). The activation initiates in the brain stem, specifically the nucleus of

the solitary tract (NTS) (see Figure 1), as well as the circumventricular organs because they process information related to blood pressure, respiration, somatic and visceral pain, and inflammation (Herman et al., 2003). Deregulation of these processes by some stressor signals the NTS and consequently activates the Locus Coeruleus (LC) that modulates the sympathetic response of the preganglionic sympathetic nuclei of the intermediolateral column of the spinal cord (Kandel et al., 2013). This allows the release of adrenaline and noradrenaline (NA), which increases the function of organs such as the heart, lungs, viscera, bladder, and adrenal glands, elevating blood pressure and respiratory rate, decreasing intestinal motility, promoting fluid retention, modulating glucocorticoid release, and releasing epinephrine and norepinephrine peripherally (Smeets, 2010). To regulate the sympathetic response, the NTS also activates the parasympathetic branch by activating the postganglionic nuclei of the spinal cord, and through the release of acetylcholine (Ach), they decrease sympathetic activity and return to a state of rest to start again (Ulrich-Lai & Herman, 2009).

Figure 1

SAM Axis Activity

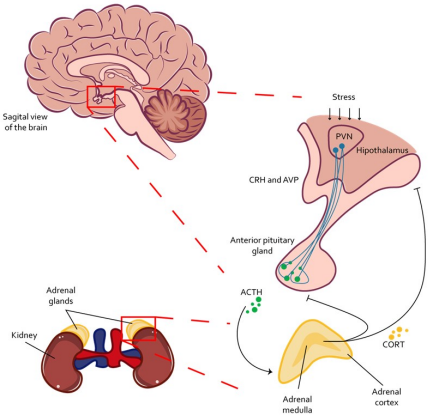


Note. The stress response begins with the activity of the SAM axis. First, the NTS signals to the LC the physiological dysregulations in the organism, which leads to the activation of the sympathetic branch at the level of the spinal cord. Then, through the preganglionic cells signals to the postganglionic cells, releasing NA, which promotes activation of the organs that innervate, for example, the adrenal medulla, promoting the release of adrenaline and NA peripherally. LC - Locus coeruleus; NTS - Nuclei of the solitary tract; NA - Noradrenaline.

In addition to the activity of the SAM axis, the HPA axis is also activated during the response to physical stressors (see Figure 2). This occurs by the peripheral release of adrenaline and NA, which, through stimulation of the vagus nerve, promote the activity of the paraventricular nucleus of the hypothalamus (PVN) (Raison et al., 2006). This allows the synthesis and release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which travel through the pituitary portal blood to the anterior pituitary (Fink, 2017), promoting the synthesis and release of adrenocorticotropic hormone (ACTH) by binding to the CRH1 and CRH2 receptors (Faught et al., 2016). Once ACTH is released into the bloodstream, it travels until it reaches the adrenal gland, where, through the proopiomelanocortin (POMC) receptors, promotes the synthesis and release of glucocorticoids such as cortisol —main glucocorticoid in humans, dogs, hamsters, and fish— or corticosterone —main glucocorticoid in rats, mice, birds, and reptiles— (Faught et al., 2016; Doczy et al., 2009).

Figure 2

HPA Axis Activity



Note. Once a stressor is interpreted, the HPA axis initiates its response through the PVN at the level of the hypothalamus, where it secretes CRH and AVP to the median eminence. Once it reaches the anterior pituitary, it synthesizes and releases ACTH to the bloodstream. When ACTH reaches the adrenal cortex, it signals for CORT to be produced and released. PVN - Hypothalamic Paraventricular Nucleus; CRH - Corticotropin Releasing Hormone; AVP - Arginine Vasopressin; ACTH - Adrenocorticropic Hormone; CORT - Glucocorticoids (cortisol or corticosterone).

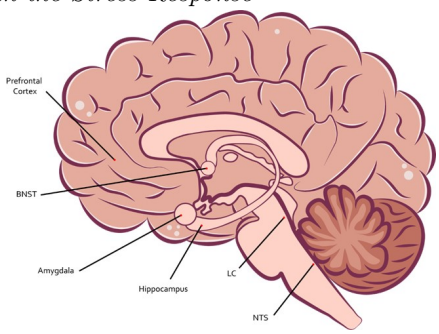
In addition to signaling through the NTS for physical stressors, other kinds of stressors, such as psychological ones, initiate the stress response if the stressor is compared with past experiences and is interpreted as aversive or challenging (Skoluda et al., 2015). This activity is compared at the hippocampal and caudate nucleus level for the modulation of memory information and subsequently signals towards the basolateral amygdala (BLA), which transmits this information through the lateral amygdala (LA) and to the central nucleus of the amygdala (CeA) (Pruessner et al., 2010). Also, the basal amygdala (BA), which is part of the BLA complex, signals towards CeA or the medial amygdala (MeA) (Roozendaal et al., 2009). CeA and MeA control the autonomic and PVN response. However, CeA is the main source of efferent connections with the autonomic and endocrine systems to promote the physiological and behavioral response to the stressor (Vyas et al., 2003). Also, this response can be sensitized if exposure to stress is repeated (Radley et al., 2017). It should be noted that connections of CeA to PVN to control

the endocrine response are scarce, the activation of the HPA axis is carried out through the inhibition of the bed nucleus of the stria terminalis (BNST), since BNST promotes the inhibition of PVN by activation of perihypothalamic GABAergic interneurons (Vyas et al., 2003).

Currently, the study of the neurobiology of stress is very complex, since it involves various structures of the CNS as well as the adrenal glands in the periphery (see Figure 3). The connection and proper functioning of these structures allow the adaptation of physiological and behavioral responses to increase the possibility of survival of the organism in the face of stressors (Sánchez-Castillo et al., 2014).

Figure 3

Scheme of Structures at the CNS Level that Participate in the Stress Response



Note. The stress response begins with the SAM axis response, which involves signaling from the NTS to the LC, which increases sympathetic activity in the spinal cord. On the other hand, projections of the amygdala towards the BNST increase the activity of the HPA axis. initially in PVN, which signals to the anterior pituitary and later to the adrenal glands, promoting the release of glucocorticoids, epinephrine, and NA to deal with a stressful condition. In addition, structures such as the hippocampus and the prefrontal cortex modulate the activity of the HPA axis downward. BNST - Bed nuclei of stria terminalis; LC - Locus coeruleus; NTS - Nuclei of the solitary tract.

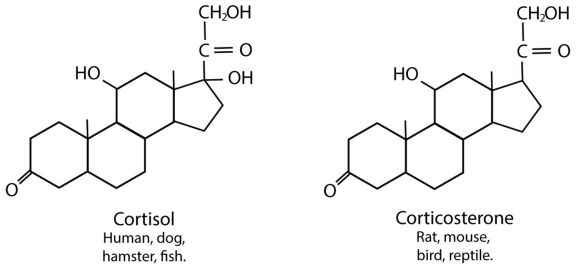
4. Glucocorticoids

The activation of the HPA axis is the release of glucocorticoids (cortisol or corticosterone) through the adrenal cortex, which cause a wide variety of transcriptional and non-transcriptional effects in the body (Doczy et al., 2009). These effects are related to metabolism (Jaszczyk & Juszczak, 2021), sodium and water balance (de Kloet, 2013), immune response (Raison et al., 2006), increased growth factors (Juszczak & Stankiewicz, 2018), cardiovascular function (Grippo et al., 2005), reproduction (Sánchez Castillo et al., 2014), mood, and cognitive functions (Timmermans et al., 2019), being its release and signaling of vital importance for the proper functioning of organisms (Becker, 2013).

Their synthesis begins with cholesterol and ends with the production of mineralocorticoids, glucocorticoids, and androgens (Murison, 2016). Aldosterone is the main mineralocorticoid, and its function is related to the conservation of sodium and water. Cortisol is the main glucocorticoid in humans, dogs, hamsters, and fish, as well as corticosterone is the main glucocorticoid in rats, mice, birds, and reptiles, and its function is associated with gluconeogenesis (Faught et al., 2016; Doczy et al., 2009), as it can be seen in Figure 4, and dehydro-epiadrosterone (DHEA), which is the precursor of testosterone and estrogens (Timmermans et al., 2019).

Figure 4

Structure Diagram of the Main Endogenous Glucocorticoids (Cortisol and Corticosterone) in Different Species



Its release is mainly mediated by the hypothalamus and to a lesser extent by the sympathetic branch of the autonomic nervous system (ANS), the thymus, the vasculature, and the epithelial barriers (Timmermans et al., 2019). Under normal conditions, glucocorticoids are released into the bloodstream in a circadian (rhythmicity in periods of approximately 24 hours) and ultradian (rhythmicity in periods of 20 hours or less), having their peak concentration during the active phase of the organism and decreasing towards the inactive phase (Dean & Keshavan, 2017). Around 10-20 mg are secreted daily unless the cycle is altered by stimulation of its release due to stress (Becker, 2013).

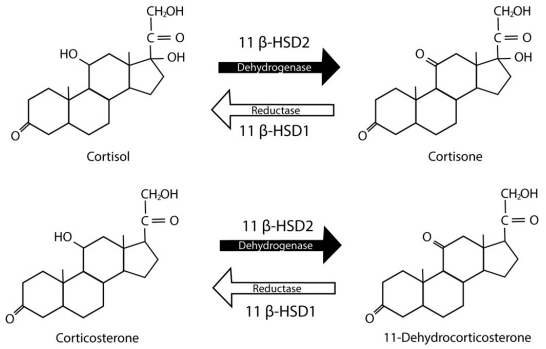
Glucocorticoids are highly lipophilic and when they are released into the bloodstream, they can pass through the cell membrane (Doczy et al., 2009). However, because they are highly lipophilic, to travel in the bloodstream, they are also coupled to proteins such as albumin (low affinity) and with high affinity to the globulin coupling protein (CBG) or transcortin, so that the glucocorticoids coupled to CBG are not free to cross the membranes of all cells (Schaaf & Meijer, 2017). The proportion of free glucocorticoids to bind to their receptors will depend on the amount of GBG available (Spencer & Deak, 2017).

On the other hand, glucocorticoids have a short half-life (<15 min in rodents and humans), due to their rapid metabolism by the enzyme 11β Hydroxysteroid dehydrogenase 2 (11β-HSD2) that converts corticosterone or cortisol into Deohydro corticosterone or cortisone, two hormones that have a very low affinity for glucocorticoid receptors and mineralocorticoid receptors, while 11β-HSD1 converts metabolites to active steroids (Hammond, 2016), as shown in Figure 5. The expression of 11β-HSD2 is

higher in the kidneys and in the placenta, in pregnant women, protecting the fetus from the passage of glucocorticoids. Another important aspect is that the expression of 11β-HSD1 is higher in the hippocampus. Therefore, this is possibly one of the reasons why this structure is highly affected by stress (Spencer & Deak, 2017).

Figure 5

Diagram of the Activity of 11β HSD Type 1 or Type 2 on Cortisol and Corticosterone



Note. β HSD, Beta hydroxysteroid dehydrogenase.

5. Glucocorticoid and Mineralocorticoid Receptors

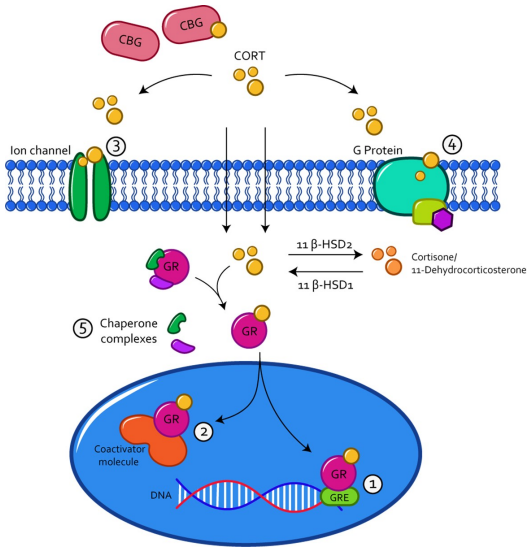
Once glucocorticoids are uncoupled from CBG or albumin, they can either bind to membrane receptors and promote non-genomic effects or cross the cell membrane to promote their genomic effects (Dejean & Richard, 2013). To generate these changes, they require binding to two types of receptors (Hammond, 2016): glucocorticoid receptors (GR), where they bind with an affinity of 5–10 nM, and mineralocorticoid receptors (MR), with which they have an affinity of 0.5–1 nM (Doczy et al., 2009), that is, a higher concentration of glucocorticoids present is required to occupy the GRs, while in small concentrations, binding to MRs is possible (Schaaf & Meijer, 2017).

Under physiological conditions, during the inactive phase of organisms (at night for humans and during the day for rodents), the receptors most occupied by the release of glucocorticoids are the MR (Reul & De Kloet, 1986). While the glucocorticoid release peak occurs during the active phase, the GR's most occupied (Becker, 2013). Both GR and MR exert primary biological actions through gene transcription or non-genomic mechanisms (O'Connor et al., 2000). Both are members of the steroid hormone receptor superfamily, possessing DNA-binding domains that are available after ligand binding (Doczy et al., 2009).

Receptors found in the cytosol as monomers are coupled to available glucocorticoids, associated with a complex of chaperones that include heat shock proteins (HSP) and immunophilipins such as FKBP51 and FKBP52 (Faught et al., 2016), as shown in Figure 6. When this is achieved, a translocation signal to the nucleus is activated through the activity of HSP (Pratt et al., 2004). Once in the nucleus, the GR and MR have an affinity to DNA for immunophilipins (Kirschke et al., 2014). Mediating cellular activity, coupling directly to DNA response elements such as homodimers (GR-GR) or heterodimers (GR-MR) (1), or interacting with other transcription factor complexes (2) (Timmermans et al., 2019).

Figure 6

Genomic and Non-genomic Action of Glucocorticoids



Note. Glucocorticoids that uncouple from CBG or albumin can cross the cell membrane and couple within the cytosol to their GR receptors and translocate to the cell nucleus. In there they can have direct effects on gene expression by coupling to GREs in DNA (1) or indirectly through coupling to a coactivator molecule (2). Among the genomic effects is the modulation of cell signaling, through the activation of ion channels (3), or G protein-coupled receptors (4), as well as the dissociation of the chaperone complexes from the GR receptors. (5). CBG - globulin coupling protein; CORT - cortisol or corticosterone; β HSD, Beta hydroxysteroid dehydrogenase; GR - Glucocorticoid receptor; GRE - Glucocorticoid response element.

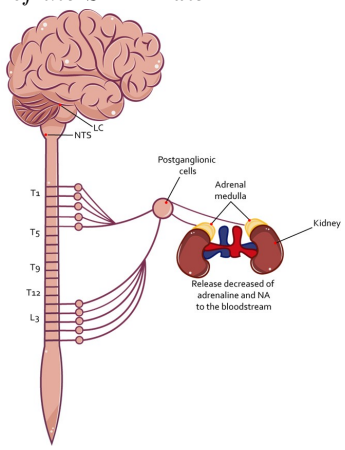
GR and MR have a differential distribution in the body (Dejean & Richard, 2013). While GR is widely distributed in most cells of the body, at the CNS level they are expressed in large quantities in the hippocampus, amygdala, PVN, and prefrontal cortex (PFC), while MR has a more restricted expression. They are mainly expressed in the limbic system, with high expression in the hippocampus, and moderate expression in the amygdala and PFC (Koning et al., 2019), as well as in the kidneys (Spencer & Deak, 2017). GR and MR control various processes such as neuronal differentiation (Fitzsimons et al., 2013), neuron excitability (Joëls et al., 2017), as well mood and cognitive processes such as memory (de Kloet et al., 2005). However, its effects are not only limited to the brain, at the peripheral level, but they can also modulate the immune response, where MR receptors promote the pro-inflammatory response and GR, the anti-inflammatory response (Chantong et al. , 2012).

6. Terminating the Physiological Stress Response

The SAM axis is the first to decrease its activity, after a stressor exposure (see Figure 7). This regulation occurs by the activation of the NTS that stimulates the parasympathetic branch and allows the release of Ach (Ulrich-Lai & Herman, 2009), which decreases the activity of the heart, lungs, viscera, bladder, and adrenal glands, decreasing blood pressure, respiratory rate, fluid retention, the release of glucocorticoids, restoring intestinal activity, and reducing the release of adrenaline and noradrenaline (Smeets, 2010).

Figure 7

Regulation of the SAM Axis



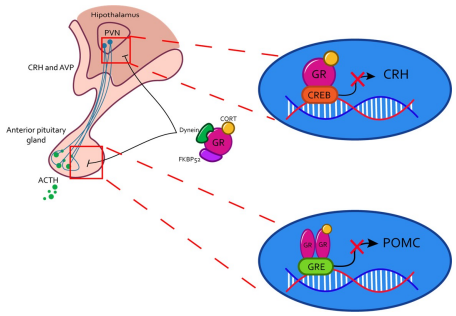
Note. Once the activity of the SAM axis begins, the NTS activates the parasympathetic branch of the autonomic nervous system. That, through the cervical and sacral region, signals the preganglionic cells that communicate to the postganglionic cells releasing Ach, which promotes the inhibition of the organs that innervate, for example, the adrenal medulla, decreasing the release of adrenaline and NA peripherally. LC - Locus coereleus; NTS - Nuclei of the solitary tract: NA - Noradrenaline.

On the other hand, the activity of the HPA axis, by a stressor, decreases due to the activity of the limbic system and glucocorticoid activity (Pruessner et al., 2010). Glucocorticoids released into the bloodstream, when the stress response is triggered, generate a phenomenon known as negative feedback. This phenomenon occurs when a system regulates itself, in this case, the release of glucocorticoids decreases the activity of the HPA axis at different levels, reducing the release of corticotropins through coupling to the GR and MR (Doczy et al., 2009). These effects are generated by signaling at the level of the anterior pituitary gland and hypothalamus due to that these structures present large amounts of GR (Mizoguchi et al., 2001).

Negative feedback regulation occupies genomic and non-genomic mechanisms (Gjerstad et al., 2018) to decrease the HPA axis response (Osterlund et al., 2016). The genomic mechanisms occur through the repression of the transcription of the CRH and POMC genes, which decreases the translation into proteins of CRH and ACTH (Myers et al., 2012), as shown in Figure 8. However, regulation of HPA axis activity can also be regulated by non-genomic mechanisms by promoting endocannabinoid release from CRH-releasing neurons and inhibiting glutamate release from excitatory presynaptic neurons (Timmermans et al., 2019), as it can be seen in Figure 9. Regulation of the stress response by non-genomic GR signaling lasts approximately seconds or minutes (Groeneweg et al., 2012), while genomic mechanisms of GR take approximately 45 to 60 min (Malham et al., 2002). It is a slow regulation; however, this delay protects the system from constantly responding to stressful events (Willner, 2017).

Figure 8

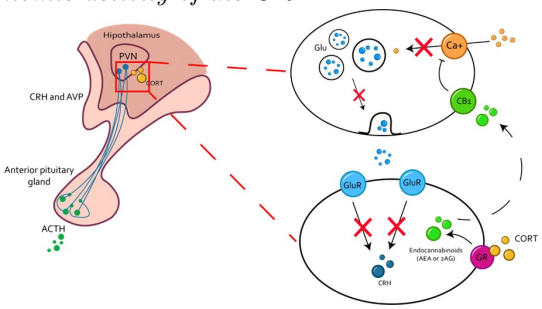
Regulation of the stress response by genomic activity of the GR



Note. This process can occur in the PVN or in the pituitary gland. In both, CORT translocates to the nucleus coupled to a GR and inhibit the transcription of CRH and ACTH genes, decreasing the signal to continue the stress response. PVN - Paraventricular nucleus of the hypothalamus; CRH - Corticotropin releasing hormone; AVP - Arginine vasopressin; ACTH - Adrenocorticotropic hormone; GR - Glucocorticoid receptor; CREB - cAMP response element-binding protein; GRE - Glucocorticoid response element; POMC - Proopiomelanocortins.

Figure 9

Regulation of the stress response by the non-genomic activity of the GR



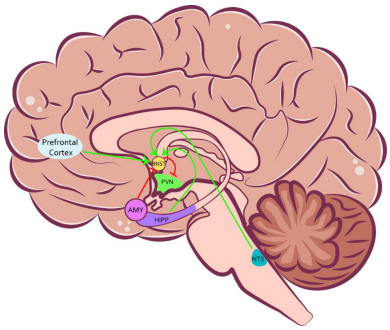
Note. CORT can regulate endocannabinoid signaling, from postsynaptic cell to presynaptic cell and reduces calcium flux decreasing Glu release from excitatory presynaptic neurons, therefore CRH signaling is downregulated. PVN - Paraventricular nucleus of the hypothalamus; CRH - Corticotropin releasing hormone; AVP - Arginine vasopressin; ACTH - Adrenocorticotropic hormone; GR - Glucocorticoid receptor; Ca+ - Calcium; Glu - glutamate; GluR - Glutamate receptor.

Also, limbic system structures related to emotional processing participate in the regulation of the HPA axis (Pruessner et al., 2010). Neurons of the PVN of the hypothalamus receive GABAergic inputs from BNST

and excitatory inputs from various nuclei of the brain stem, including neurons of the NTS (Radley et al., 2017; Ulrich-Lai & Herman, 2009). GABAergic circuits of the BNST receive glutamatergic inputs from the hippocampus (in the region of the ventral subiculum) and the PFC (i.e., the medial PFC, the anterior cingulum, and the prelimbic PFC), resulting in inhibition of the activity of the PVN and completion of the stress response (Vyas et al., 2003), as shown in Figure 10. However, BNST receives GABAergic inputs from structures such as the amygdala (in its medial and central region), which decreases the inhibition of the PVN (by the BNST), and stress response can be initiated or maintained for a longer time. On the other hand, the PFC (in its infralimbic region) signals through its glutamatergic connections to the PVN of the hypothalamus, which would also increase or maintain the stress response (Doczy et al., 2009).

Figure 10

Control of the PVN response by limbic system structures



Note. PVN - paraventricular nucleus of the hypothalamus; BNST - bed nucleus of the stria terminalis; AMY - amygdala; HIPP hippocampus; NTS - nucleus of the solitary tract; (green arrows) Glutamatergic inputs; (red lines) GABAergic inputs.

7. Acute and Chronic Stress

One of the main controversies in stress research is the temporality of exposure to one or more stressors. Short exposures to stress have been understood as acute stress, while prolonged exposures are called chronic stress (Stoney, 2017). Initially, the acute stress response was defined as exposure to a stressor that does not exceed a short time from minutes to hours (Dickerson & Kemeny, 2004), while the chronic stress response was defined as exposure to a stressor that lasts for days, weeks, or even years (Joëls & Baram, 2009).

Different situations have the potential to become stressors and we deal with them multiple times a day (e.g., work stressors and social stressors). The first exposure to them would provoke an acute stress response that would allow us to deal with the situation in a potentially successful way. If the stressful situation were repeated several times (the same day, during the week, during the month, or the year), it would at some point become a chronic stressor (Rohleder, 2019). However, one question arises when we consider this problem: When does acute stress become chronic?

Authors such as Katz et al. (1981) conducted experiments testing stress batteries in rats to study the possible relationship between stress exposure and altered behavior. Their results indicated that exposure to stress for 21 days had greater effects on behavior than exposure to stress for 1 hr. As their stress batteries reached 21 days of exposure, and when replicating their studies many other authors found similar results (Beck & Luine, 1999; Guo et al., 2009; Zlatković et al., 2014), the chronic stress response was believed to only achievable up to 21 days. However, over the years, it was detected that, in addition to the temporality, the intensity of the stress, the predictability, as well as its nature were important factors to achieve the altered behavioral phenotype (Willner, 2017). Currently, several studies called their protocols chronic when the exposure lasts 10 days (Valencia-Flores, 2018), 14 days (Tseilikman et al., 2020), 21 days (Roohi-Azizi et al., 2018), and 56 days (Chen et al., 2016).

Further, authors like Rohleder (2019) define acute stress as stressors of limited time, brief, low intensity, and a very similar environment (Rohleder, 2019), while chronic stress is defined as sequences of stressful events, in which an initial stressor leads to a series of repeated stressful events. Chronic stressors are considered high-intensity and have a negative effect in the short or long term (Rohleder, 2019). Furthermore, authors like Nursey and Phelps (2016) added a category that includes traumatic stressors: these are acute high-intensity stressors that directly threaten life, which occurred in the past, and do not occur again in the present, but have long-term consequences in the psychological health of the individual.

In summary, acute stress occurs in a short time (less than 24 hours) but has no short or long-term consequences, and chronic stress is made up of acute events, but sequenced, which continue for a certain time (more than 24 hours) and produce short or long-term consequences. Finally, traumatic stressors are events that directly threaten the life of the body and have long-term health consequences.

8. Cognition, Brain Plasticity, and Stress

The stress response not only involves the source of stress, the mobilization of energy resources, and the physiological regulation of the organism, but it also has an important cognitive component for its triggering, as well as its regulation (Lehrer & Woolfolk, 2007). This cognitive control is used in therapeutics to reduce the physiological symptoms of people with stress-related disorders (Dwyer et al., 2016). From a psychological perspective, authors like Lazarus and Folkman (1984) mention that the stress response involves the relationship between the

subject and its environment, where the demands of the environment are perceived as uncontrollable for the individual. Although this theory of cognitive control of the stress response was raised in the 1980s, it is still used today as a central tool in therapeutic research (Berenguera et al., 2020). Classification of the event as a potential stressor falls on the evaluation, as a cognitive process that allows evaluating an event and giving it significance for the individual. Thus, psychological stressors to trigger the stress response must be interpreted as threatening (Calvo & Gutiérrez-García, 2010).

The cognitive evaluation of the stressor can be of two types: primary and secondary (Carver & Connor-Smith, 2010). In turn, as Calvo and Gutiérrez-García (2010) reported, the primary evaluation can be of three types: (1) irrelevant, the situation is evaluated as neutral for the individual and does not have a stressful consequence; (2) benign, the situation is evaluated as positive and is not stressful; and (3) stressful, the situation is assessed as relevant to the organism (Calvo & Gutiérrez-García, 2010). If seemed stressful, the secondary assessment begins with the resources, capabilities, and options to deal with the demand considered. In this evaluation, the stressor can be considered (a) threatening, an event that may have negative consequences is perceived; (b) harmful, the perception that something negative has occurred; (c) loss, access to something has been lost which is positive; and (d) challenging, is evaluated as an opportunity to make a profit (Calvo & Gutiérrez-García, 2010).

The evaluation of the stimulus is not always directed, as in many cases this evaluation works automatically (Carver & Connor-Smith, 2010). In addition, the perception of a stressful event is modulated by unpredictability and uncontrollability. These two perceptions are triggered by any situation. However, during the stress response, the inability to predict what, when, where, how, and with what intensity or the perception of not being able to deal with the stressful situation increases the intensity of the stress response, its duration, as well as the consequences (Calvo & Gutiérrez-García, 2010).

On the other hand, the stress response, depending on whether it is acute or chronic, modulates cognitive functions such as attention, memory, learning, and executive functions (Kim & Diamond, 2002). Specifically, during the acute stress response, attentional processes improve and focus on the stressor, and emotional memory processing for negative events, as well as learning for negative emotional events, improve (Sánchez-Castillo et al., 2014). Cognitive flexibility decreases and increases rigid responses such as habits and decision-making oriented towards riskier choices (Calvo & Gutiérrez-García, 2010; Marin et al., 2019).

During the chronic stress response, the effects on cognitive functions can be modulated up or down (Orsetti et al., 2007; Wolf, 2017). Attention can decrease or stay increased, memory and learning are affected downwards, cognitive flexibility decreases, and decision-making is also altered towards higher risk options, in addition, the reinforcing value of stimuli decreases (Calvo & Gutiérrez-García, 2010; Marin et al., 2019).

These cognitive changes, the product of exposure to stress, are associated with structural and functional changes in regions of the limbic system such as the hippocampus, prefrontal cortex (PFC), and amygdala (Pêgo et al., 2009; Qiao et al., 2016). In the hippocampus, exposure to chronic stress produces neuronal atrophy and reduces neurogenesis. These alterations have been associated with an increase in the presence of glucocorticoids, which reduces the number, dendritic length, and quantity of new neurons. These changes have been associated with increased glutamatergic signaling of N-methyl aspartate (NMDA) receptors (McEwen et al., 2016).

In contrast to atrophy and reduced hippocampal neurogenesis, exposure to chronic stress promotes hypertrophy of amygdala neurons (Vyas et al., 2002). Chronic stress increases the dendritic arborization of pyramidal neurons in the BLA, as well as glucocorticoid and CRH levels in this region. This effect is associated with an increase in glutamatergic signaling by NMDA receptors and a decrease in GABAergic signaling (Radley et al., 2017). Hippocampal atrophy, together with the hypertrophy of the amygdala, promotes a state of hyperactivity of the HPA axis, which promotes cognitive alterations in attention, memory, and anxiety-like and depression-like behavior (Willner, 2017).

The plasticity of neurons in the PFC, mainly in the regions of the anterior cingulate, prelimbic cortex, and infralimbic cortex, are altered by exposure to chronic stress mostly by reduction of the length, density, and arborization of dendritic spines of pyramidal neurons in the apical region. In addition, these changes have been associated with increased levels of glucocorticoids (McEwen & Morrison, 2013).

9. Stress and Ageing

Throughout our lives, we experience situations or environmental demands in which we adjust our response to this dynamic environment, so the stress response is of utmost importance. However, we must consider that the stress response is different during the various stages of our life, from fetal development to old age. This is because the organism, during the first stages of life, begins its development, and as time passes it goes maturing and adjusting the responses to maintain heterostasis (e.g., personal communication). Furthermore, when we become older (ageing), we suffer a gradual functional decline process (McHugh & Gil, 2018) that affects every way in which we respond to stress. Although its biological causes remain largely unknown, studies in the past few decades have identified common cellular and

molecular traits associated with aging (López-Otín et al., 2013). For example, senescence refers to a cellular response that limits the proliferation of aged or damaged cells. Although senescence plays physiological roles in normal development, it has also been implicated as a major cause of age-related changes (McHugh & Gil, 2018).

The first stage of development is the prenatal stage. In humans, this stage lasts about 9 months, and in rodents, it lasts about 3 weeks (McCormick & Hodges, 2017). During this stage, the brain continues to develop, and the main processes that occur during this stage are neuronal differentiation and myelination (Conrad, 2011). Once the third week of gestation in rats ends, and by the second trimester in humans, the HPA axis becomes functional (Walker & McCormick, 2009). Although their regulation is not fully mature, the neurons of the PVN begin to respond to physical stress and glucocorticoids start to secrete from the adrenal gland (McCormick & Hodges, 2017).

During this stage, the placenta plays a very important role in regulating the mother's stress and its effects on the fetus (Krontira et al., 2020). It has a large amount of NE and adrenaline transporters, as well as enzymes such as 11β-HSD2, to break down glucocorticoids to their inactive metabolites and reduce the impact of stress on the developing body (Piquer et al., 2017). However, it also has high amounts of the enzyme 11β-HSD1 that converts metabolites to active glucocorticoids, since its presence is vital for the development of the fetus to the neonate (McCormick & Hodges, 2017).

The second stage of development is the neonatal stage. In humans, it lasts approximately up to 4-5 years of age, while in rodents it lasts approximately 21-25 days (Rice & Barone, 2000). This stage is characterized by being a relatively long period of great parental care because humans, such as rodents, are altricial organisms, that is, they are born helpless, without the ability to support themselves (Conrad, 2011). During this period, neurogenesis decreases considerably, while gliogenesis remains in the process (Rice & Barone, 2000). In addition, the maturation of the cortex, as well as the cerebellum and hippocampus, continues for about 3 weeks later in rodents and the first 4 years in humans (McCormick & Hodges, 2017).

In the neonatal stage, the regulation of the stress response is highly dependent on the mother, the release of glucocorticoids begins to adjust at a rate, around the first two weeks (Spiga et al., 2014), MR and GR reach their peak of expression around 2 and three weeks, respectively. In addition, the response of the HPA axis shows resistance to activation during the first two weeks and is known as the hyporesponsive period of stress (McCormick & Hodges, 2017).

The third stage of development is adolescence. This period ranges from 11 to 16-17 years in humans and from 21 to 60 days approximately in rodents (Romeo, 2014). During adolescence, the puberty period becomes present; it begins earlier in females (the vaginal canal opens) and in males (the balanopreputial separation). The regulation by gonadal steroids (estradiol or testosterone) begins to promote differences in regulation of the HPA axis and the brain (Spear, 2000). During this stage, neurogenesis decreases in the hippocampus, but remains even higher compared to adulthood. Cell proliferation is noticeable in the amygdala, locus coeruleus, nucleus accumbens, and prefrontal cortex (Andersen & Teicher, 2008). Furthermore, it increases synaptic pruning and cell reorganization (Glover & Clinton, 2016).

During this period, sexual differences appear due to the release of gonadal steroids, testosterone modulates the response of the HPA axis downward, while estradiol increases its activity (Juraska et al., 2013). However, the development of PVN, the expression of GR and MR, and the basal glucocorticoid levels are very similar to those of adults (McCormick & Hodges, 2017). The difference is that, during adolescence, the release of glucocorticoids is more prolonged, as well as the effectiveness of CRH, which is greater compared to adults (McCormick & Mathews, 2010).

The fourth stage of development is adulthood. This period ranges in humans from 17-18 years to approximately 65 years and in rodents from 60 days to approximately 24 months (Conrad, 2011). In adults, neurogenesis declines to its lowest peak, without completely disappearing. The cortex and hippocampus, as well as other structures, have reached their peak of maturation. Hormone levels stabilize and risky behaviors as well as gambling behavior decrease (Chaby et al., 2017).

During this stage, the release of glucocorticoids in the face of a stressor decreases, since the better negative feedback of the HPA axis is achieved, and the circadian rhythmicity is consolidated, having release peaks at the beginning of the activity phase and decreasing towards the inactivity phase of the organism (Steptoe & Serwinski, 2016). In turn, during adulthood, the consequences of exposure to stress do not have long-term effects as in previous periods; adults show recovery from stress in approximately 10 days (Conrad, 2011).

The last period of an organismṫs life is aging. This stage includes humans from 65 years of age and rodents from approximately 2 years of age (McCormick & Hodges, 2017). Aging is associated with the selective loss of mental abilities and a high risk for the development of neurodegenerative disorders. However, aging is experienced in different ways depending on the care taken during the previous stages (Conrad, 2011).

During aging, the HPA axis response is altered, negative feedback is diminished, the response is exacerbated by a stressful condition, and the circadian regulation of glucocorticoid release loses its rhythmicity (Garrido et al., 2012). In addition, exposure to stress during this pe-

riod potentiates the adverse effects of stress, decreases cell proliferation, dendritic density, and synaptic contacts, and even some reports indicate that the possibility of death increases if stress becomes chronic during old age (Van Camp et al., 2018).

10. Psychiatric Illness and Stress

The relationship between stress and psychiatric disorders is widely reported (McEwen & Akil, 2020; Neumann et al., 2011; Nursey & Phelps, 2016). Stress plays a very important role in the onset, maintenance, and worsening of some psychiatric disorders (Chaby et al., 2017). Dysregulation of the stress system and allostatic load are implicated in many psychiatric disorders (McEwen & Akil, 2020). In fact, in the *Diagnostic and Statistical Manual of Mental Disorders 5th Edition* (DSM5, 2013), symptoms associated with stress appear in disorders such as schizophrenia (Corcoran et al., 2002), autism (Derguy et al., 2016), posttraumatic stress disorder (Porter et al., 2016), major depression (Belzung et al., 2015), in substance abuse disorders (Favoretto et al., 2020), and anxiety disorders (Riboni & Belzung, 2017).

Although exposure to stress has been linked to different mental disorders, some of the most studied are anxiety and depression disorders (Pêgo et al., 2009). Studies point to stress as a risk factor that increases allostatic load during life for the development of a psychiatric disorder (Fink, 2016). Anxiety disorders are characterized by excessive fear and avoidance in response to specific objects, situations, or sensations and the absence of true danger (Craske et al., 2017). The relationship between stress and anxiety disorders lies in the similarity of affectations in the neural circuits that are responsible for these responses, such as the limbic system and the hyperactivated sympathetic response (Shin & Liberzon, 2010). One of the most important biomarkers in anxiety disorders is cortisol levels (Roozendaal et al., 2009). In disorders such as post-traumatic stress disorder (PTSD) in generalized anxiety disorder, glucocorticoid levels are chronically decreased (Daskalakis et al., 2016).

One of the vulnerability factors for the development of an anxiety disorder is mainly sex: women have twice the risk of developing an anxiety disorder, and the risk increases during adolescence (McLean et al., 2008). Another factor that is considered a risk for the development of an anxiety disorder is having parents with anxiety or depression; the heritable component has been studied, but remains undetermined (Shimada-Sugimoto et al., 2015). One of the most reported factors is stress in the early stages, such as abuse, parental neglect, and reduced social contact between children and their parents (Uliaszek et al., 2012). Finally, suffering from an anxiety disorder triples the risk of developing another anxiety disorder or doubles the risk of developing a depressive disorder (Lieb et al., 2002).

Depressive disorders are characterized by a lack of interest or pleasure, fatigue, persistent depressed mood, sleep problems, and sexual appetite (American Psychiatric Association, 2013). The relationship between stress and depressive disorders again lies in the similarity of the neural mechanisms that underlie both conditions, mainly the structures of the limbic system, hippocampus, amygdala, and prefrontal cortex (Roy & Roy, 2017).

The vulnerability factors for the development of a depressive disorder involve exposure to stress in the early stages (Slavich et al., 2011), or during adulthood (Willner et al., 2013). Furthermore, the interaction between various genes and the environment (Caspi et al., 2003), as well as the preexistence of a depressive phenotype (Fogel et al., 2006), can be vulnerability factors. Changes possibly enhanced by stress obey the hypothesis of stress diathesis (Willner & Belzung, 2015). This hypothesis indicates that the predisposition (diathesis) to develop depression because of exposure to stress can occur due to genetic predisposition and exposure to stress at different stages of life. The amount of stress required to trigger the disorder will depend on the individual's diathesis and their ability to cope with stress (Willner, 2017). Finally, anxiety disorders and depressive disorders have high comorbidity, sometimes anxiety first, then depression or vice versa; the relationship suggests that neurobiological alterations are shared between both disorders (Shin & Liberzon, 2010).

11. Conclusion

The study of the stress response, its implications, and consequences is very important to understand its relationship with the beginning of different psychiatric disorders (Trucco, 2002). The interplay between stress and life stages highlights the importance of allostatic load and the impact of experience in the development of psychiatric illnesses. Although its conceptualization has not been defined, the similarity in the definition proposals allows us to rescue important aspects to consider when it comes to stress. On the other hand, the description of its neurobiology is well-studied and shows evidence of the possible mechanisms that are involved in its functioning and dysregulation (McEwen, 2000). Even though the stress response involves central systems, such as the limbic system and the HPA axis, it also makes use of peripheral systems as the SAM axis, which is part of the ANS (de Kloet et al., 2005). On the other hand, the release of CORT by the neuroendocrine response has been studied with great attention; its genomic and non-genomic physiological activity, the rhythmicity of its release, and the regulatory role of the stress response are the most common topics in its study.

Finally, an aspect not considered in the study of stress is the regulation or modulation of cognition, both for the triggering of the response and the termination and its therapeutic use. The unpredictability and the

feeling of loss of control stand out within this topic because they worsen or increase the negative effects of exposure to stress. Likewise, the stress response changes depending on the stage of life in which we find ourselves, from the fetal stage to old age, the behavioral dynamics of the HPA axis are different, and the response may be imprecise and increased during the early stages of the development as the latest. Finally, the altered CORT response, a product of exposure to stress, is of utmost importance to understand the changes associated with the triggering of various psychiatric disorders such as anxiety and depression (Doczy et al., 2009). These are mainly because they share neuronal bases associated with the limbic system, the prefrontal cortex, and the brain stem, structures that have a high expression of GR and MR receptors.

12. Funding

This research was supported by Consejo Nacional de Ciencia y Tecnología (CONACYT) CVU-925597 and DGAPA-PAPIIT IN-208722.

References

Albert, M. A., Durazo, E. M., Slopen, N., Zaslavsky, A. M., Buring, J. E., Silva, T., Chasman, D., & Williams, D. R. (2017). Cumulative psychological stress and cardiovascular disease risk in middle aged and older women: Rationale, design, and baseline characteristics. *American Heart Journal*, *192*, 1–12. https://doi.org/10.1016/j.ahj.2017.06.012

American Psychiatric Association. (2020). *Stress in America. A national mental health crisis.* American Psychological Association. https://www.apa.org/news/press/releases/stress/2020/sia-mental-health-crisis.pdf

American Psychiatric Association. (2013). *Dsm 5.*

Andersen, S. L., & Teicher, M. H. (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends in Neurosciences*, *31*(4), 183–191. https://doi.org/10.1016/j.tins.2008.01.004

Beck, K. D., & Luine, V. N. (1999). Food deprivation modulates chronic stress effects on object recognition in male rats: Role of monoamines and amino acids. *Brain Research*, *830*(1), 56–71. https://doi.org/10.1016/S0006-8993(99)01380-3

Becker, D. E. (2013). Basic and clinical pharmacology of Glucocorticosteroids. *Anesthesia Progress*, *60*(1), 25–32. https://doi.org/10.2344/0003-3006-60.1.25

Belzung, C., Willner, P., & Philippot, P. (2015). Depression: From psychopathology to pathophysiology. *Current Opinion in Neurobiology*, *30*, 24–30. https://doi.org/10.1016/j.conb.2014.08.013

Berenguera, A., Coma-Auli, N., Carmona-Terés, V., Pons-Vigués, M., Pujol-Ribera, E., Medina-Perucha, L., Jacques-Aviñó, C., & Moix, J. (2020). Living with knee osteoarthritis is like. The usefulness of metaphors to understand life experience. *Atencion Primaria Practica*, *2*(1–2). https://doi.org/10.1016/j.appr.2019.10.011

Calvo, M., & Gutiérrez-García, A. (2010). Cognition and stress. *Encyclopedia of Stress*, 513–515. https://doi.org/10.1016/B978-0-12-800951-2.00016-9

Carver, C. S., & Connor-Smith, J. (2010). Personality and Coping. *Annual Review of Psychology*, *61*(1), 679–704. https://doi.org/10.1146/annurev.psych.093008.100352

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H. L., McClay, J., Mill, J., Martin, J., BraithWaite, A., & Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, *301*(5631), 386–389. https://doi.org/10.1126/science.1083968

Chaby, L. E., Zhang, L., & Liberzon, I. (2017). The effects of stress in early life and adolescence on posttraumatic stress disorder, depression, and anxiety symptomatology in adulthood. *Current Opinion in Behavioral Sciences*, *14*, 86–93. https://doi.org/10.1016/j.cobeha.2017.01.001

Chantong, B., Kratschmar, D. V., Nashev, L. G., Balazs, Z., & Odermatt, A. (2012). Mineralocorticoid and glucocorticoid receptors differentially regulate NF-kappaB activity and pro-inflammatory cytokine production in murine BV-2 microglial cells. *Journal of Neuroinflammation*, *9*, 1–14. https://doi.org/10.1186/1742-2094-9-260

Chen, J., Wang, Z.-Z., Zuo, W., Zhang, S., Chu, S.-F., & Chen, N.-H. (2016). Effects of chronic mild stress on behavioral and neurobiological parameters - Role of glucocorticoid. *Hormones and Behavior*, *78*, 150–159. https://doi.org/10.1016/j.yhbeh.2015.11.006

Conrad, C. (2011). The Handbook of Stress: Neuropsychological Effects on the Brain. John Wiley & Sons Ltd. https://doi.org/10.1002/9781118993811

Corcoran, C., Mujica-Parodi, L., Yale, S., Leitman, D., & Malaspina, D. (2002). Could stress cause psychosis in individuals vulnerable to schizophrenia? *CNS Spectrums*, *7*(1), 33–42. https://doi.org/10.1017/S1092852900022240

Couto-Pereira, N. de S., Lampert, C., Vieira, A. dos S., Lazzaretti, C., Kincheski, G. C., Espejo, P. J., Molina, V. A., Quillfeldt, J. A., & Dalmaz, C. (2019). Resilience and Vulnerability to Trauma: Early Life Interventions Modulate Aversive Memory Reconsolidation in the Dorsal Hippocampus.

Frontiers in Molecular Neuroscience, *12*, 134. https://doi.org/10.3389/fnmol.2019.00134

Craske, M. G., Rauch, S. L., Ursano, R., Prenoveau, J., Pine, D. S., & Zinbarg, R. E. (2009). What is an anxiety disorder? *Depression and Anxiety*, *26*(12), 1066–1085. https://doi.org/10.1002/da.20633

Craske, M. G., Stein, M. B., Eley, T. C., Milad, M. R., Holmes, A., Rapee, R. M., & Wittchen, H. U. (2017). Anxiety disorders. *Nature Reviews Disease Primers*, *3*(May). https://doi.org/10.1038/nrdp.2017.24

Daskalakis, N. P., Cohen, H., Nievergelt, C. M., Baker, D. G., Buxbaum, J. D., Russo, S. J., & Yehuda, R. (2016). New translational perspectives for blood-based biomarkers of PTSD: From glucocorticoid to immune mediators of stress susceptibility. *Experimental Neurology*, *284*, 133–140. https://doi.org/10.1016/j.expneurol.2016.07.024

de Kloet, E. (2013). Functional profile of the binary brain corticosteroid receptor system: Mediating, multitasking, coordinating, integrating. *European Journal of Pharmacology, 719*(1–3), 53–62. https://doi.org/10.1016/J.EJPHAR.2013.04.053

de Kloet, E., Joëls, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. *Nature Reviews Neuroscience*, *6*(6), 463–475. https://doi.org/10.1038/nrn1683

Dean, J., & Keshavan, M. (2017). The neurobiology of depression: An integrated view. *Asian Journal of Psychiatry*, *27*, 101–111. https://doi.org/10.1016/j.ajp.2017.01.025

Dejean, C., & Richard, D. (2013). Mécanismes d'action des glucocorticoïdes. *Revue de Medecine Interne*, *34*(5), 264–268. https://doi.org/10.1016/j.revmed.2013.02.021

Derguy, C., M'Bailara, K., Michel, G., Roux, S., & Bouvard, M. (2016). The Need for an Ecological Approach to Parental Stress in Autism Spectrum Disorders: The Combined Role of Individual and Environmental Factors. *Journal of Autism and Developmental Disorders*, *46*(6), 1895–1905. https://doi.org/10.1007/s10803-016-2719-3

Dickerson, S. S., & Kemeny, M. E. (2004). Acute Stressors and Cortisol Responses: A Theoretical Integration and Synthesis of Laboratory Research. *Psychological Bulletin*, *130*(3), 355–391. https://doi.org/10.1037/0033-2909.130.3.355

Doczy, E. J., Seroogy, K., Harrison, C. R., & Herman, J. P. (2009). Hypothalamo-Pituitary-Adrenocortical Axis, Glucocorticoids, and Neurologic Disease. *Immunology and Allergy Clinics of North America*, *29*(2), 265–284. https://doi.org/10.1016/J.IAC.2009.02.003

Dwyer, D. B., Harrison, B. J., Yücel, M., Whittle, S., Zalesky, A., Pantelis, C., Allen, N. B., & Fornito, A. (2016). Stress: Concepts, Cognition, Emotion, and Behavior. *2: Cognition, Emotion, and Behavior*, 177–185. https://doi.org/10.1016/b978-0-12-800951-2.00021-2

Faught, E., Aluru, N., & Vijayan, M. M. (2016). The Molecular Stress Response. In C. B. Schreck, L. Tort., A. Farrell, & C. J. Brauner (Eds.), *Fish Physiology* (pp. 113–166, Vol. 35). https://doi.org/10.1016/B978-0-12-802728-8.00004-7

Favoretto, C. A., Nunes, Y. C., Macedo, G. C., Lopes, J. S. R., & Quadros, I. M. H. (2020). Chronic social defeat stress: Impacts on ethanol-induced stimulation, corticosterone response, and brain monoamine levels. *Journal of Psychopharmacology*, *34*(4). https://doi.org/10.1177/0269881119900983

Fink, G. (2016). Stress, Definitions, Mechanisms, and Effects Outlined: Lessons from Anxiety. In G. Fink (Ed.), *Stress: Concepts, Cognition, Emotion, and Behavior. Handbook of Stress Series* (pp. 3–11, Vol. 1). Elsevier Inc. https://doi.org/10.1016/B978-0-12-800951-2.00001-7

Fink, G. (2017). Stress Neuroendocrinology: Highlights and Controversies. In G. Fink (Ed.), *Stress: Neuroendocrinology and Neurobiology. Handbook of Stress Series* (pp. 1–13, Vol. 2). Elsevier Inc. https://doi.org/10.1016/B978-0-12-802175-0.00001-2

Fitzsimons, C. P., Hooijdonk, L. W. A., Schouten, M., Zalachoras, I., Brinks, V., Zheng, T., Schouten, T. G., Saaltink, D. J., Dijkmans, T., Steindler, D. A., Verhaagen, J., Verbeek, F. J., Lucassen, P. J., Kloet, E. R., Meijer, O. C., Karst, H., Joels, M., Oitzl, M. S., & Vreugdenhil, E. (2013). Knockdown of the glucocorticoid receptor alters functional integration of newborn neurons in the adult hippocampus and impairs fear-motivated behavior. *Molecular Psychiatry*, *18*(9), 993–1005. https://doi.org/10.1038/mp.2012.123

Fogel, J., Eaton, W. W., & Ford, D. E. (2006). Minor depression as a predictor of the first onset of major depressive disorder over a 15-year follow-up. *Acta Psychiatrica Scandinavica*, *113*(1), 36–43. https://doi.org/10.1111/j.1600-0447.2005.00654.x

Garrido, P., de Blas, M., Del Arco, A., Segovia, G., & Mora, F. (2012). Aging increases basal but not stress-induced levels of corticosterone in the brain of the awake rat. *Neurobiology of Aging*, *33*(2), 375–382. https://doi.org/10.1016/j.neurobiolaging.2010.02.015

Gjerstad, J. K., Lightman, S. L., & Spiga, F. (2018). Role of glucocorticoid negative feedback in the regulation of HPA axis pulsatility. *Stress*, *21*(5),

403–416. https://doi.org/10.1080/10253890.2018.1470238

Glover, M. E., & Clinton, S. M. (2016). Of rodents and humans: A comparative review of the neurobehavioral effects of early life ssri exposure in preclinical and clinical research. *International Journal of Developmental Neuroscience*, *51*, 50–72. https://doi.org/10.1016/j.ijdevneu.2016.04.008

Godoy, L. D., Rossignoli, M. T., Delfino-Pereira, P., Garcia-Cairasco, N., & de Lima Umeoka, E. H. (2018). A Comprehensive Overview on Stress Neurobiology: Basic Concepts and Clinical Implications. *Frontiers in Behavioral Neuroscience*, *12,* Article 127. https://doi.org/10.3389/fnbeh.2018.00127

Grippo, A. J., Sullivan, N. R., Damjanoska, K. J., Crane, J. W., Carrasco, G. A., Shi, J., Chen, Z., Garcia, F., Muma, N. A., & Kar, L. D. (2005). Chronic mild stress induces behavioral and physiological changes, and may alter serotonin 1A receptor function, in male and cycling female rats. *Psychopharmacology*, *179*(4), 769–780. https://doi.org/10.1007/s00213-004-2103-4

Groeneweg, F. L., Karst, H., Kloet, E. R., & Joëls, M. (2012). Mineralocorticoid and glucocorticoid receptors at the neuronal membrane, regulators of nongenomic corticosteroid signalling. *Molecular and Cellular Endocrinology*, *350*(2), 299–309. https://doi.org/10.1016/j.mce.2011.06.020

Guo, J. Y., Li, C. Y., Ruan, Y. P., Sun, M., Qi, X. L., Zhao, B. S., & Luo, F. (2009). Chronic treatment with celecoxib reverses chronic unpredictable stress-induced depressive-like behavior via reducing cyclooxygenase-2 expression in rat brain. *European Journal of Pharmacology*, *612*(1–3), 54–60. https://doi.org/10.1016/j.ejphar.2009.03.076

Hammen, C. (2005). Stress and Depression. *Annual Review of Clinical Psychology*, *1*(1), 293–319. https://doi.org/10.1146/annurev.clinpsy.1.102803.143938

Hammond, G. (2016). Plasma Steroid-binding Proteins: Primary Gatekeepers of Steroid Hormone Action. *The Journal of Endocrinology*, *230*(1), 1–36. https://doi.org/10.2174/138161211796197016

Herman, J. P., Figueiredo, H., Mueller, N. K., Ulrich-Lai, Y., Ostrander, M. M., Choi, D. C., & Cullinan, W. E. (2003). Central mechanisms of stress integration: Hierarchical circuitry controlling hypothalapituitary-adrenocortical responsiveness. *Frontiers in Neuroendocrinology, 24*(3), 151–180. https://doi.org/10.1016/j.yfrne.2003.07.001

Hutmacher, F. (2021). Putting Stress in Historical Context: Why It Is Important That Being Stressed Out Was Not a Way to Be a Person 2000 Years Ago. *Frontiers in Psychology*, *12,* Article 539799. https://doi.org/10.3389/fpsyg.2021.539799

Jaszczyk, A., & Juszczak, G. R. (2021). Glucocorticoids, metabolism and brain activity. *Neuroscience and Biobehavioral Reviews*, *126*(March), 113–145. https://doi.org/10.1016/j.neubiorev.2021.03.007

Joëls, M., & Baram, T. Z. (2009). The neuro-symphony of stress. *Nature Reviews Neuroscience*, *10*(6), 459–466. https://doi.org/10.1038/nrn2632

Joëls, M., Sarabdjitsingh, R. A., Boon, F. S., & Karst, H. (2017). Rapid and Slow Effects of Corticosteroid Hormones on Hippocampal Activity. In G. Fink (Ed.), *Stress: Neuroendocrinology and Neurobiology. Handbook of Stress Series* (pp. 327–341, Vol. 2). Elsevier Inc. https://doi.org/10.1016/B978-0-12-802175-0.00033-4

Juraska, J. M., Sisk, C. L., & DonCarlos, L. L. (2013). Sexual differentiation of the adolescent rodent brain: Hormonal influences and developmental mechanisms. *Hormones and Behavior*, *64*(2), 203–210. https://doi.org/10.1016/j.yhbeh.2013.05.010

Juszczak, G. R., & Stankiewicz, A. M. (2018). Glucocorticoids, genes and brain function. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *82*(October 2017), 136–168. https://doi.org/10.1016/j.pnpbp.2017.11.020

Kandel, E., Schwartz, J., Jessell, T., Segelbaum, S., & Hudspeth, A. (2013). *Principles of Neural Science* (5th ed.). McGraw-Hill.

Katz, R. J., Roth, K. A., & Carroll, B. J. (1981). Acute and chronic stress effects on open field activity in the rat: Implications for a model of depression. *Neuroscience & Biobehavioral Reviews*, *5*(2), 247–251. https://doi.org/10.1016/0149-7634(81)90005-1

Kim, J. J., & Diamond, D. M. (2002). The stressed hippocampus, synaptic plasticity and lost memories. *Nature Reviews Neuroscience*, *3*(6), 453–462. https://doi.org/10.1038/nrn849

Kirschke, E., Goswami, D., Southworth, D., Griffin, P. R., & Agard, D. A. (2014). Glucocorticoid receptor function regulated by coordinated action of the Hsp90 and Hsp70 chaperone cycles. *Cell*, *157*(7), 1685–1697. https://doi.org/10.1016/j.cell.2014.04.038

Koning, A.-S. C. A. M., Buurstede, J. C., van Weert, L. T. C. M., & Meijer, O. C. (2019). Glucocorticoid and Mineralocorticoid Receptors in the Brain: A Transcriptional Perspective. *Journal of the Endocrine Society*, *3*(10), 1917–1930. https://doi.org/10.1210/js.2019-00158

Krontira, A. C., Cruceanu, C., & Binder, E. B. (2020). Glucocorticoids as Mediators of Adverse Outcomes of Prenatal Stress. *Trends in Neuroscien-*

ces, *43*(6), 394–405. https://doi.org/10.1016/j.tins.2020.03.008

Lazarus, R., & Folkman, S. (1984). *Stress: Appraisal and coping*. Springer Publishing Company.

Lehrer, P. M., & Woolfolk, R. L. (2007). Research on clinical issue in stress management. In P. M. Lehrer, R. L. Woolfolk, & W. E. Sime (Eds.), *Principles and practice of stress management* (pp. 703–721). The Guilford Press.

Lieb, R., Isensee, B., Höfler, M., Pfister, H., & Wittchen, H. U. (2002). Parental major depression and the risk of depression and other mental disorders in offspring: A prospective-longitudinal community study. *Archives of General Psychiatry*, *59*(4), 365–374. https://doi.org/10.1001/archpsyc.59.4.365

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The Hallmarks of Aging. *Cell*, *153*(6), 1194–1217. https://doi.org/10.1016/j.cell.2013.05.039

Lovejoy, D. A., & Michalec, O. M. (2017). Evolution and Phylogeny of the Corticotropin-Releasing Factor Family of Peptides. In G. Fink (Ed.), *Stress: Neuroendocrinology and Neurobiology. Handbook of Stress Series* (pp. 49–55, Vol. 2). Elsevier Inc. https://doi.org/10.1016/B978-0-12-802175-0.00005-X

Malham, S. K., Lacoste, A., Gélébart, F., Cueff, A., & Poulet, S. A. (2002). A first insight into stress-induced neuroendocrine and immune changes in the octopus eledone cirrhosa. *Aquatic Living Resources*, *15*(3), 187–192. https://doi.org/10.1016/S0990-7440(02)01173-7

Marin, M.-F., Raymond, C., & Lupien, S. J. (2019). Memory and Stress. In G. Fink (Ed.), *Stress: Physiology, Biochemistry, and Pathology. Handbook of Stress Series* (pp. 68–78, Vol. 3). Elsevier Inc. https://doi.org/10.1016/b978-0-12-813146-6.00006-0

Martin, E. I., Ressler, K. J., Binder, E., & Nemeroff, C. B. (2010). The Neurobiology of Anxiety Disorders: Brain Imaging, Genetics, and Psychoneuroendocrinology. *Clinics in Laboratory Medicine*, *30*(4), 865–891. https://doi.org/10.1016/j.cll.2010.07.006

McCarty, R. (2016). Chapter 4 - The Fight-or-Flight Response. In G. Fink (Ed.), *Stress: Concepts, Cognition, Emotion, and Behavior Handbook of Stress Series* (pp. 33–37, Vol. 1). Elsevier Inc. https://doi.org/10.1016/B978-0-12-800951-2.00004-2

McCormick, C. M., & Hodges, T. E. (2017). Stress, Glucocorticoids, and Brain Development in Rodent Models. In G. Fink (Ed.), *Stress: Neuroendocrinology and Neurobiology Handbook of Stress Series* (pp. 197–206, Vol. 2). Elsevier Inc. https://doi.org/10.1016/B978-0-12-802175-0.00019-X

McCormick, Ch., & Mathews, I. (2010). Adolescent development, hypothalamic-pituitary-adrenal function, and programming of adult learning and memory. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(5), 756–765. https://doi.org/10.1016/j.pnpbp.2009.09.019

McEwen, B. S. (2000). Stress, Definitions and Concepts of. In G. Fink (Ed.), *Encyclopedia of Stress* (2nd ed., p. 653). Elsevier Inc. https://doi.org/10.1016/B978-012373947-6.00364-0

McEwen, B. S., & Akil, H. (2020). Revisiting the Stress Concept: Implications for Affective Disorders. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *40*(1), 12–21. https://doi.org/10.1523/JNEUROSCI.0733-19.2019

McEwen, B. S., & Morrison, J. H. (2013). The Brain on Stress: Vulnerability and Plasticity of the Prefrontal Cortex over the Life Course. *Neuron*, *79*(1), 16–29. https://doi.org/10.1016/J.NEURON.2013.06.028

McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress Effects on Neuronal Structure: Hippocampus, Amygdala, and Prefrontal Cortex. *Neuropsychopharmacology*, *41*(1), 3–23. https://doi.org/10.1038/npp.2015.171

McHugh, D., & Gil, J. (2018). Senescence and aging: Causes, consequences, and therapeutic avenues. *Journal of Cell Biology*, *217*(1), 65–77. https://doi.org/10.1083/jcb.201708092

McLean, C., Asnaani, A., Litz, B., & Hofmann, S. (2008). Gender Differences in Anxiety Disorders: Prevalence, Course of Illness, Comorbidity and Burden of Illness. *J. Psychiatr Res*, *23*(1), 1–7. https://doi.org/10.1038/jid.2014.371

Mexican Institute of Social Security. (2017). *Estrés Laboral*. Gobierno de México. http://www.imss.gob.mx/salud-en-linea/estres-laboral

Migliaro, M., Valencia-Flores, K. B., Orizaba-Huerta, C., Sandoval-Flores, N., Benitez-Serratos, F., Galicia-Castillo, O., Paz Trejo, D. B., Zarate González, P., Sanchez-Castillo, H. (2020). Effects on Behavior by Different Exposure Durations of Predator Scent Stress. *Acta de Investigación Psicológica*, *10*(2), 17–26. https://doi.org/10.22201/fpsi.20074719e.2020.2.343

Mizoguchi, K., Yuzurihara, M., Ishige, A., Sasaki, H., Chui, D. H., & Tabira, T. (2001). Chronic stress differentially regulates glucocorticoid negative feedback response in rats. *Psychoneuroendocrinology*, *26*(5), 443–459. https://doi.org/10.1016/S0306-4530(01)00004-X

Murison, R. (2016). The Neurobiology of Stress. In M. Flaten & M. al'Absi (Eds.), *The Neuroscience*

of Pain, Stress, and Emotion: Psychological and Clinical Implications (pp. 29–49). Elsevier Inc. https://doi.org/10.1016/B978012800538500002-9

Myers, B., McKlveen, J. M., & Herman, J. P. (2012). Neural regulation of the stress response: The many faces of feedback. *Cellular and Molecular Neurobiology*, *32*(5), 683–694. https://doi.org/10.1007/s10571-012-9801-y

Neumann, I. D., Wegener, G., Homberg, J. R., Cohen, H., Slattery, D. A., Zohar, J., Olivier, J. D. A., & Mathé, A. (2011). Animal models of depression and anxiety: What do they tell us about human condition? *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(6), 1357–1375. https://doi.org/10.1016/j.pnpbp.2010.11.028

Nursey, J., & Phelps, A. J. (2016). Trauma, and Memory in PTSD. In G. Fink (Ed.), *Stress: Concepts, Cognition, Emotion, and Behavior. Handbook of Stress Series* (pp. 169–176, Vol. 1). Elsevier Inc. https://doi.org/10.1016/B978-0-12-800951-2.00020-0

O'Connor, T. M., O'Halloran, D. J., & Shanahan, F. (2000). The stress response and the hypothalamic-pituitary-adrenal axis: From molecule to melancholia. *QJM : Monthly Journal of the Association of Physicians*, *93*(6), 323–333. http://www.ncbi.nlm.nih.gov/pubmed/10873181

Orsetti, M., Colella, L., Dellarole, A., Canonico, P. L., & Ghi, P. (2007). Modification of spatial recognition memory and object discrimination after chronic administration of haloperidol, amitriptyline, sodium valproate or olanzapine in normal and anhedonic rats. *International Journal of Neuropsychopharmacology*, *10*(3), 345–357. https://doi.org/10.1017/s1461145706006705

Osterlund, C. D., Rodriguez-Santiago, M., Woodruff, E. R., Newsom, R. J., Chadayammuri, A. P., & Spencer, R. L. (2016). Glucocorticoid fast feedback inhibition of stress-induced ACTH secretion in the male rat: Rate independence and stress-state resistance. *Endocrinology*, *157*(7), 2785–2798. https://doi.org/10.1210/en.2016-1123

Pacák, K., & Palkovits, M. (2001). Stressor Specificity of Central Neuroendocrine Responses: Implications for Stress-Related Disorders. *Endocrine Reviews*, *22*(July), 502–548. https://doi.org/10.1210/edrv.22.4.0436

Pêgo, J. M., Sousa, J. C., Almeida, O., & Sousa, N. (2009). Stress and the Neuroendocrinology of Anxiety Disorders. In M. A. Geyer, C. A. Marsden, B. A. Ellenbroek, T. R. E. Barnes, S. L. Andersen, M. P. Paulus, & J. Olivier (Eds.), *Current Topics in Behavioral Neurosciences* (pp. 97–118). https://doi.org/10.1007/7854_2009_13

Piquer, B., Fonseca, J. L., & Lara, H. E. (2017). Gestational stress, placental norepinephrine transporter and offspring fertility. *Reproduction, 153*(2), 147–155. https://doi.org/10.1530/REP-16-0312

Porter, K. E., Cochran, H. M., Richards, S. K. H., & Sexton, M. B. (2016). Combat Stress. In G. Fink (Ed.), *Stress: Concepts, Cognition, Emotion, and Behavior. Handbook of Stress Series* (pp. 365–371, Vol. 1). Elsevier Inc. https://doi.org/10.1016/B978-0-12-800951-2.00046-7

Pratt, W. B., Galigniana, M. D., Harrell, J. M., & DeFranco, D. B. (2004). Role of hsp90 and the hsp90-binding immunophilins in signalling protein movement. *Cellular Signalling*, *16*(8), 857–872. https://doi.org/10.1016/j.cellsig.2004.02.004

Pruessner, J. C., Dedovic, K., Pruessner, M., Lord, C., Buss, C., Collins, L., Dagher, A., & Lupien, S. J. (2010). Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations - 2008 Curt Richter Award Winner. *Psychoneuroendocrinology*, *35*(1), 179–191. https://doi.org/10.1016/j.psyneuen.2009.02.016

Qiao, H., Li, M. X., Xu, C., Chen, H. B., An, S. C., & Ma, X. M. (2016). Dendritic Spines in Depression: What We Learned from Animal Models. *Neural Plasticity*, 20–24. https://doi.org/10.1155/2016/8056370

Radley, J., Morilak, D. A., Vilau, V., & Campeau, S. (2017). Chronic stress and brain plasticity: mechanisms underlying adaptive and maladaptive changes and implications for stress- related CNS disorders. *Physiology & Behavior*, *176*(1), 139–148. https://doi.org/10.1016/j.physbeh.2017.03.040

Radley, J. J., Johnson, S. B., & Sawchenko, P. E. (2017). Limbic Forebrain Modulation of Neuroendocrine Responses to Emotional Stress. In G. Fink (Ed.), *Stress: Neuroendocrinology and Neurobiology. Handbook of Stress Series* (pp. 17–27, Vol. 2). Elsevier Inc. https://doi.org/10.1016/B978-0-12-802175-0.00002-4

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*, *27*(1), 24–31. https://doi.org/10.1016/J.IT.2005.11.006

Reul, J. M. H. M., & Kloet, E. R. (1986). Anatomical resolution of two types of corticosterone receptor sites in rat brain with in vitro autoradiography and computerized image analysis. *Journal of Steroid Biochemistry*, *24*(1), 269–272. https://doi.org/10.1016/0022-4731(86)90063-4

Riboni, F. V., & Belzung, C. (2017). Stress and psychiatric disorders: From categorical to dimensional

approaches. *Current Opinion in Behavioral Sciences*, *14*, 72–77. https://doi.org/10.1016/j.cobeha.2016.12.011

Rice, D., & Barone, S. (2000). Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. *Environmental Health Perspectives*, *108*(SUPPL. 3), 511–533. https://doi.org/10.2307/3454543

Roeckner, A. R., Bowling, A., & Butler, T. R. (2017). Chronic social instability increases anxiety-like behavior and ethanol preference in male Long Evans rats. *Physiology and Behavior*, *173*, 179–187. https://doi.org/10.1016/j.physbeh.2017.02.010

Rohleder, N. (2019). Stress and inflammation - The need to address the gap in the transition between acute and chronic stress effects. *Psychoneuroendocrinology*, *105*, 164–171. https://doi.org/10.1016/j.psyneuen.2019.02.021

Romeo, R. D. (2014). The Teenage Brain: The Stress Response and the Adolescent Brain. *Current Directions in Psychological Science*, *22*(2), 140–145. https://doi.org/10.1177/0963721413475445

Roohi-Azizi, M., Torkaman-Boutorabi, A., Akhondzadeh, S., Nejatisafa, A. A., Sadat-Shirazi, M. S., & Zarrindast, M. R. (2018). Influence of citicoline on citalopram-induced antidepressant activity in depressive-like symptoms in male mice. *Physiology and Behavior*, *195*, 151–157. https://doi.org/10.1016/j.physbeh.2018.08.002

Roozendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nature Reviews Neuroscience*, *10*(6), 423–433. https://doi.org/10.1038/nrn2651

Roy, A., & Roy, R. N. (2017). Stress and Major Depression: Neuroendocrine and Biopsychosocial Mechanisms. In G. Fink (Ed.), *Stress: Neuroendocrinology and Neurobiology. Handbook of Stress Series* (pp. 173–184, Vol. 2). Elsevier Inc. https://doi.org/10.1016/B978-0-12-802175-0.00017-6

Sánchez-Castillo, H. S., Paz-Trejo, D., Vázquez-Ramírez, J. V., Zárate-González, P. Z., & Migliaro, M. (2014). Neurobiology of Posttraumatic Stress Disorder (PTSD) and its Frontostriatal Implications: a short review. *Actualidades en Psicología*, *28*(117), 13–20. https://doi.org/10.15517/ap.v28i117.14131

Sapolsky, R. M. (2019). Stress, Health and Social Behavior. In J. Chun Choe (Ed.), *Encyclopedia of Animal Behavior* (2nd, pp. 163–170, Vol. 1). https://doi.org/10.1016/b978-0-12-809633-8.20762-0

Sarkar, T., Patro, N., & Patro, I. K. (2019). Cumulative multiple early life hits- a potent threat leading to neurological disorders. *Brain Research Bulletin*, *147*(January), 58–68. https://doi.org/10.1016/j.brainresbull.2019.02.005

Schaaf, M. J. M., & Meijer, O. C. (2017). Corticosteroid Receptors. In G. Fonk (Ed.), *Stress: Neuroendocrinology and Neurobiology. Handbook of Stress Series* (pp. 295–302, Vol. 2). https://doi.org/10.1016/B978-0-12-802175-0.00029-2

Selye, H. (1936). A Syndrome produced by Diverse Nocuous Agents. *Nature*, *138*(3479), 32–32. https://doi.org/10.1038/138032a0

Selye, H. (1976). Stress without Distress. In G. Serban (Ed.), *Psychopathology of Human Adaptation* (pp. 137–146). Springer.

Sharpley, C. F. (2009). Neurobiological Pathways between Chronic Stress and Depression: Dysregulated Adaptive Mechanisms? *Clinical Medicine Insights: Psychiatry*, *2*, CMPsy.S3658. https://doi.org/10.4137/cmpsy.s3658

Shimada-Sugimoto, M., Otowa, T., & Hettema, J. (2015). Genetics of anxiety disorders: Genetic epidemiological and molecular studies in humans. *Psychiatry and Clinical Neurosciences*, *69*(7), 388–401. https://doi.org/10.1111/pcn.12291

Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*, *35*(1), 169–191. https://doi.org/10.1038/npp.2009.83

Skoluda, N., Strahler, J., Schlotz, W., Niederberger, L., Marques, S., Fischer, S., Thoma, M. V., Spoerri, C., Ehlert, U., & Nater, U. (2015). Intra-individual psychological and physiological responses to acute laboratory stressors of different intensity. *Psychoneuroendocrinology*, *51*, 227–236. https://doi.org/10.1016/j.psyneuen.2014.10.002

Slavich, G. M., Monroe, S. M., & Gotlib, I. H. (2011). Early parental loss and depression history: Associations with recent life stress in major depressive disorder. *Journal of Psychiatric Research*, *45*(9), 1146–1152. https://doi.org/10.1016/j.jpsychires.2011.03.004

Smeets, T. (2010). Autonomic and hypothalamicpituitaryadrenal stress resilience: Impact of cardiac vagal tone. *Biological Psychology*, *84*(2), 290–295. https://doi.org/10.1016/j.biopsycho.2010.02.015

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience and biobehavioral reviews*, *24*(4), 417–463. https://doi.org/10.1016/s0149-7634(00)00014-2

Spencer, R. L., & Deak, T. (2017). A users guide to HPA axis research. *Physiology and Behavior*, *178*, 43–65. https://doi.org/10.1016/j.physbeh.2016.11.014

Spiga, F., Walker, J. J., Terry, J. R., & Lightman, S. (2014). HPA Axis-Rhythms. *Comprehensive Physiology*,

4(3), 1273–1298. https://doi.org/10.1002/cphy.c140003

Stanton, C. H., Holmes, A. J., Chang, S. W. C., & Joormann, J. (2018). From Stress to Anhedonia: Molecular Processes through Functional Circuits. *Trends in Neurosciences*, *42*(1), 23–42. https://doi.org/10.1016/j.tins.2018.09.008

Steptoe, A., & Serwinski, B. (2016). Cortisol Awakening Response. In G. Fink (Ed.), *Stress: Concepts, Cognition, Emotion, and Behavior. Handbook of Stress Series* (pp. 277–283, Vol. 1). Elsevier Inc. https://doi.org/10.1016/B978-0-12-800951-2.00034-0

Stoney, C. M. (2017). Lipids and Lipoproteins. In G. Fink (Ed.), *Stress: Neuroendocrinology and Neurobiology. Handbook of Stress Series* (pp. 284–294, Vol. 2). Elsevier Inc. https://doi.org/10.1016/B978-0-12-802175-0.00028-0

Timmermans, S., Souffriau, J., & Libert, C. (2019). A general introduction to glucocorticoid biology. *Frontiers in Immunology*, *10*(JULY). https://doi.org/10.3389/fimmu.2019.01545

Trucco, M. (2002). Estrés y trastornos mentales: Aspectos neurobiológicos y psicosociales. *Revista Chilena de Neuro-Psiquiatria*, *40*, 8–19. https://doi.org/10.4067/s0717-92272002000600002

Tseilikman, V., Komelkova, M., Lapshin, M., Alliluev, A., Tseilikman, O., Karpenko, M., Pestereva, N., Manukhina, E., Downey, H. F., Kondashevskaya, M., Sarapultsev, A., & Dremencov, E. (2020). High and low anxiety phenotypes in a rat model of complex post-traumatic stress disorder are associated with different alterations in regional brain monoamine neurotransmission. *Psychoneuroendocrinology*, *117,* Article 104691. https://doi.org/10.1016/j.psyneuen.2020.104691

Uliaszek, A. A., Zinbarg, R. E., Mineka, S., Craske, M. G., Griffith, J. W., Sutton, J. M., Epstein, A., & Hammen, C. (2012). A longitudinal examination of stress generation in depressive and anxiety disorders. *Journal of Abnormal Psychology*, *121*(1), 4–15. https://doi.org/10.1037/a0025835

Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews. Neuroscience*, *10*(6), 397–409. https://doi.org/10.1038/nrn2647

Valencia-Flores, K. B. (2018). *Evaluación de los efectos inducidos por diferentes tiempos de exposición al estrés* [Undergraduate thesis]. Universidad Nacional Autónoma de México. https://repositorio.unam.mx/contenidos/evaluacion-de-los-efectos-inducidos-por-diferentes-tiempos-de-exposicion-al-estres-336367?c=VQ5e7M&d=false&q=*:*&i=2&v=1&t=search_0&as=2

Van Camp, G., Cigalotti, J., Bouwalerh, H., Mairesse, J., Gatta, E., Palanza, P., Maccari, S., & Morley-Fletcher, S. (2018). Consequences of a double hit of stress during the perinatal period and midlife in female rats: mismatch or cumulative effect? *Psychoneuroendocrinology*, *93*, 45–55. https://doi.org/10.1016/J.PSYNEUEN.2018.04.004

Vyas, A., Bernal, S., & Chattarji, S. (2003). Effects of chronic stress on dendritic arborization in the central and extended amygdala. *Brain Research*, *965*(1–2), 290–294. https://doi.org/10.1016/S0006-8993(02)04162-8

Vyas, A., Mitra, R., Shankaranarayana Rao, B. S., & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *Journal of Neuroscience*, *22*(15), 6810–6818. https://doi.org/10.1523/jneurosci.22-15-06810.2002

Walker, C. D., & McCormick, C. M. (2009). Development of the stress axis: Maternal and environmental influences. *Hormones, Brain and Behavior Online*, 1931–1974. https://doi.org/10.1016/B978-008088783-8.00061-9

Willner, P., Scheel-Krüger, J., & Belzung, C. (2013). The neurobiology of depression and antidepressant action. *Neuroscience and Biobehavioral Reviews*, *37*(10), 2331–2371. https://doi.org/10.1016/j.neubiorev.2012.12.007

Willner, P. (2017). The chronic mild stress (CMS) model of depression: History, evaluation and usage. *Neurobiology of Stress*, *6*, 78–93. https://doi.org/10.1016/j.ynstr.2016.08.002

Willner, P., & Belzung, C. (2015). Treatment-resistant depression: are animal models of depression fit for purpose? *Psychopharmacology*, *232*(19), 3473–3495. https://doi.org/10.1007/s00213-015-4034-7

Wolf, O. (2017). Chapter 31-Stress Effects on Learning and Memory in Humans. In G. Fink (Ed.), *Stress: Neuroendocrinology and Neurobiology. Handbook of Stress Series* (pp. 309–315, Vol. 2). Elsevier Inc. https://doi.org/10.1016/B978-0-12-802175-0.00031-0

Yin, X., Guven, N., & Dietis, N. (2016). Stress-based animal models of depression: Do we actually know what we are doing? *Brain Research*, *1652*, 30–42. https://doi.org/10.1016/J.BRAINRES.2016.09.027

Zlatković, J., Todorović, N., Tomanović, N., Bošković, M., Djordjević, S., Lazarević-Pašti, T., & Filipović, D. (2014). Chronic administration of fluoxetine or clozapine induces oxidative stress in rat liver: A histopathological study. *European Journal of Pharmaceutical Sciences*, *59*(1), 20–30. https://doi.org/10.1016/j.ejps.2014.04.010