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Impact of stress in childhood: Psychobiological alterations

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Abstract

Background: An extremely high percentage of children worldwide are exposed to stress from the first months of life. The aim of this review is to bring together the experimental results related to chronic early-life stress in both human and experimental models. **Methods:** We aimed to achieve our objective via a thorough review of the literature. **Results**: Early-life stress is a challenge for the developing organism and leads to negative effects in the medium and long term. The emotional, cognitive, and behavioral domains are compromised due to alterations produced in the nervous system, with some of the most important being related to the main neurotransmission systems. **Conclusions**: By using experimental models, it is possible to address the study of the structural and functional changes resulting from early-life stress and, thus, plan intervention and prevention alternatives.

Key words: Development, early-life stress, neurotransmission, child abuse, maternal separation, neglect.

Resumen

Impacto del estrés en la infancia: alteraciones psicobiológicas. **Antecedentes:** un porcentaje realmente elevado de niños en todo el mundo se encuentran expuestos al estrés desde los primeros meses de vida. El objetivo es compendiar e integrar los resultados experimentales relacionados con el estrés temprano crónico ya sea en humanos o en modelos experimentales. **Métodos**: a través de la revisión bibliográfica intentamos conseguir el objetivo propuesto. **Resultados**: el estrés temprano supone un desafío para el organismo en desarrollo y da lugar a efectos negativos a medio y largo plazo. Los dominios emocional, cognitivo y conductual se ven comprometidos debido a las alteraciones que se producen en el sistema nervioso, siendo algunas de las más relevantes relacionadas con los principales sistemas de neurotransmisión. **Conclusiones**: mediante modelos experimentales, se puede abordar el estudio de los cambios estructurales y funcionales a los que da lugar el estrés temprano y de este modo plantearse alternativas de intervención y prevención.

Palabras clave: desarrollo, estrés temprano, neurotransmisión, maltrato infantil, separación maternal, negligencia.

More than 50% of the children in the world are exposed to stress (Fenoglio, Brunson, & Baram, 2006). Every year, 1 in 10 children born in the west experiences emotional abuse (van Harmelen, de Jong et al., 2010) and 8 million children live in institutions all over the world (Malter Cohen et al., 2013).

Neglect is the most prevalent form of child abuse in the United States (Spratt et al., 2012; Widom, 2013). The child abuse rate varies depending on the country, but it ranges between 3 and 32% of the entire population (van Harmelen, de Jong et al., 2010). In Spain 4.54% of boys and 3.94% of girls between 8 and 17 years old claim to have suffered abuse by a member of their family, according to a study carried out by the Reina Sofia center (Ordóñez-camblor et al., 2016). In addition, the Spanish Childhood Observatory report (2013) pointed out that there were 42,569 minors with open files due to protective measures.

The abuses that children can suffer can differ in duration and type. There is physical, sexual and psychological abuse, as well as neglect in the care that parents or guardians should provide. These types of abuses can occur in a combined way, and efforts have been made to distinguish the differential effects produced by the different types of abuse (Trickett & McBride-Chang, 1995). Just as abuse within the family leads to negative consequences, attentional deficits and academic difficulties are also found in institutionalized children (De Bellis, Woolley, & Hooper, 2013; Desmarais, Roeber, Smith, & Pollak, 2012; Fox, Almas, Degnan, Nelson, & Zeanah, 2011; Merz, McCall, Wright, & Luna, 2013; Sheridan, Drury, McLaughlin, & Almas, 2010; Spratt et al., 2012). This review aims to provide a view of the alterations caused by early-life stress in human populations. The effects reviewed will be behavioral, affective, and cognitive, and tentative explanations will be provided about the cerebral base for these effects, with the neurotransmission systems emphasized as one of the possible keys. The paper will also review studies in animal models of early-life stress, such as the maternal separation stress (MS) model.

Effects of early-life stress: Affective, cognitive and behavioral

Early-life stress is defined as a period of severe and/or chronic trauma, as well as environmental/social deprivation or neglect, in pre/postnatal care (Hedges & Woon, 2011). Psychosocial stress factors, especially when occurring in early stages of life, contribute to the development of anxiety and depression disorders. In fact,

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patients who suffer from affective disorders show higher levels of the corticotropin release factor (CRH) in the cerebrospinal fluid (Brunson, Avishai-Eliner, Hatalski, & Baram, 2001; Coplan et al., 1996; De Bellis et al., 2013; Fishbein et al., 2009; Koizumi & Takagishi, 2014; Marin et al., 2011; Spratt et al., 2012; Trickett & McBride-Chang, 1995; van Harmelen, de Jong et al., 2010).

In the cognitive domain, alterations are also found in children who have experienced chronic early-life stress. These alterations remain even when sociodemographic factors are eliminated, such as the mother's IQ, birth difficulties, gender, ethnic group, and weight at birth (Bosquet Enlow, Egeland, Blood, Wright, & Wright, 2012). The domains affected are language, memory, attention, and the executive functions (Desmarais et al., 2012; Hedges & Woon, 2011; Marin et al., 2011). In addition, infants who experience early-life stress usually have higher cognitive biases than controls. For example, they often interpret social cues as more hostile than non-abused children do (Trickett & McBride-Chang, 1995), and they have worse recognition of positive facial expressions (Fishbein et al., 2009; Koizumi & Takagishi, 2014)

Regarding measures of intelligence and academic performance, these children demonstrate worse academic performance and lower scores on intelligence tests, with lower IQs (Fox et al., 2011; Sheridan et al., 2010). They are twice as likely to repeat a grade in school (Loughan & Perna, 2012; Spratt et al., 2012), and they show poorer working habits and difficulties in developing them independently (De Bellis et al., 2013; Manly, Lynch, Oshri, Herzog, & Wortel, 2013). Furthermore, children who have suffered neglect develop more behavioral problems, (Fishbein et al., 2009; Spratt et al., 2012). Underlying some of these behavioral problems, we could find a reduction in cognitive flexibility. This flexibility is essential in adolescence when individuals are more vulnerable to risk behaviors (Spann et al., 2012).

Psychosocial functioning is also affected (Koizumi & Takagishi, 2014; Loughan & Perna, 2012). These children are evaluated by their teachers as having less behavioral control and being less social, and showing fewer interactions with their classmates (Manly et al., 2013). In addition, other alterations in social behavior are found, such as uninhibited attachment, as they display friendly behaviors with adult strangers (Sheridan et al., 2010).

Effects of early-life stress at the Psychobiological level

Early-life stress leads to different effects depending on when in ontogenetic development it occurs. The cerebral areas that are developing when the stress is experienced are affected to a greater degree (Hedges & Woon, 2011).

Stress effects on the autonomic nervous system (NS) have been widely studied. Attention has been focused on the structures that modulate the activity of the stress axis, such as the amygdala (which increases its activity), or the hippocampus (HC) and the prefrontal cortex (PFC), which inhibit it.

Chronic exposure to glucocorticoids alters the morphology and functional integrity of the HC (neuronal loss, dendritic atrophy). This hippocampal damage could explain learning problems (Brunson, Chen, Avishai-Eliner, & Baram, 2003). Thus, there is a relationship between HC volume, cognitive performance, and stress axis function (Pruessner et al., 2010).

The HC continues to develop in the first weeks of life; therefore, continued stress in this period, which affects the structure, alters normal development (Fenoglio et al., 2006). The HC is completely developed at the age of two, whereas the PFC and the amygdala take longer to develop. Therefore, the HC is the preferred candidate to explain the neural basis for the deficits when stress occurs in the first months of life (Marin et al., 2011).

One of the cerebral keys to understanding how stress affects the HC (and, therefore, learning and memory) consists of the interneurons that express CRH receptors. These interneurons innervate hippocampal pyramidal cells, and the number and activity of these cells are regulated by the amount of CRH. Thus, acute stress levels would improve hippocampal functioning, whereas high levels of continued stress would be harmful (Brunson et al., 2001, 2003; Fenoglio et al., 2006).

Orbitofrontal cortex activity is lower in institutionalized children, as is the integrity of the uncinate fascicule, which connects this area to limbic structures like the amygdala (Sheridan et al., 2010). These alterations in the frontal-limbic network could be responsible for alterations in social behavior (Koizumi & Takagishi, 2014). Less amygdalin inhibition by the PFC is also found in adults who were abused as children (De Bellis et al., 2013; Fishbein et al., 2009). Along the same lines, early-life stress has been shown to be a greater predictor of the reduction in PFC volume than anxiety or depression (van Harmelen, van Tol et al., 2010).

Studying the effects of early-life stress on the main neurotransmitters is one of the most significant aspects in revealing the neural basis of the long-term damage it produces. Evidence for this statement is based on the distribution of the CRH. The CRH and its receptors are found in many regions involved in anxiety and depression disorders (PFC, cingulate, insular, amygdala, HC and periaqueductal gray matter). The neuronal somas that release this substance are also found in the locus coeruleus, tegmental ventral area, and dorsal raphe; which modulate the monoaminergic neurotransmitter systems (Coplan et al., 1996). When faced with chronic stress, the stress axis is altered, and the effects of the different stress hormones will act on the main neurotransmission systems.

The relationship between the main caregiver and the child during sensitive developmental periods has been shown to have long-term effects on the mesolimbic dopaminergic system and on the stress axis (Pruessner et al., 2010). Children with post-traumatic stress disorder (after the abuse) show higher noradrenaline (NA) and dopamine levels, indicating an over-functioning of the sympathetic NS.

The dopaminergic afferents to the PFC are particularly sensitive to stress. This DA mesocortical pathway seems to be in charge of focusing the attention on stressful stimuli in order to deal with them. However, chronic stress alters the PFC function, causing hypervigilance in the developing subjects. In other words, chronic stress biases the attention toward the threatening stimuli (De Bellis et al., 2013).

Other catecholamines such as adrenaline and NA are released immediately as a response to stressful stimuli. Stress produces the activation of the sympathetic NS and the release of NA. The amygdala is stimulated by the NA from the locus coeruleus, which, in turn, activates the stress axis and the medial prefrontal cortex (mPFC) through the dopaminergic routes. NA has been found to be increased in children who had been severely abused and now suffered from a mood disorder.

Finally, serotonin is also modified in response to stress. Serotonin also modulates the mood and participates in both the

anxiolytic and anxiogenic pathways. Low levels of serotonin are related to suicide and aggressiveness. Serotoninergic deregulation could explain the development of anti-social behaviors in adults who experienced early-life stress (De Bellis et al., 2013).

Experimental models for the study of early-life stress

Attachment to the main caregiver has a clear effect on the molding of the developing NS, so that a negative interaction and/or a lack of care are the triggers for cognitive deficits stemming from an alteration in the encephalic structure and its functioning (Bosquet Enlow et al., 2012). This not only occurs in humans, as animal models have shown that subjects deprived of adequate early social contact display atypical social behaviors (Fox et al., 2011).

One of the problems of working with humans is the complexity of finding a sample that has undergone stress at the same stage, with the same intensity, and the same duration. One of the reasons for using animal models of early stress is that we can control the type of abuse, the duration, and the developmental stage of the organism in which it is produced (Trickett & McBride-Chang, 1995).

In rats, the sensitive period of postnatal hippocampal development occurs between days 2 and 10. Maternal contact is fundamental to ideal development in this period (Brunson et al., 2003). Chronically interrupted contact with the mother, or maternal separation (MS), has been used as an animal model, with alterations in recognition memory (Solas et al., 2010; Wei, Simen, Mane, & Kaffman, 2012) and recall (Schmauss, Lee-McDermott, & Medina, 2014; Solas et al., 2010; Wei et al., 2012) found in adult subjects. These functions are mainly sustained by the HC and the associated cortices (Marin et al., 2011).

Child abuse, as pointed out above, leads to a higher predisposition to developing disorders such as anxiety and depression. MS also produces anxious (Li, Xue, Shao, Shao, & Wang, 2013; Marcos, Aisa, & Ramírez, 2008; Schmauss et al., 2014; Spivey, Padilla, Shumake, & González-Lima, 2011) and depressive behaviors (Gracia-Rubio et al., 2016; Marcos et al., 2008; Nishi, Horii-Hayashi, Sasagawa, & Matsunaga, 2013; Schmauss et al., 2014; Solas et al., 2010; Spivey et al., 2011).

These effects of MS on the behavior and NS of animals are analogous to the effects produced by early-life stress in humans; therefore, MS is presented as an adequate model to emulate adverse early experiences. However, not just any type of MS leads to deficits in animals. If the MS is very brief (about 15 minutes), like those used in *Handling* models, early-life stress is not modeled, given that no deficits or even improvements are observed in different dimensions (Loizzo et al., 2012; Nishi et al., 2013).

Early-life stress effects on neurotransmission in animal models

The separated animals show a greater response to a stressor, or cocaine administration, in the dopamine levels of the nucleus accumbens, and they also have less dopamine-transporter density in the accumbens core and in the striatum. In other words, MS changes the reactivity of the mesolimbic DA to stress (Brake, Zhang, Diorio, Meaney, & Gratton, 2004). When extra-cellular levels of DA, their metabolites, and the density of the D1 receptor are measured, findings show that MS induces a reduction in the levels of 3 4-Hydroxyphenylacetic acid (DOPAC) in the mPFC and a reduction in D1 receptor density in the anterior cingulate cortex (Lejeune et al., 2013).

There is a high correlation between noradrenergic activity and stress axis activity (the neurons that secrete CRH in the paraventricular nucleus are stimulated by the NA). When propanol, a β-blocker, is administered, the depressive behavior diminishes, as well as the mnemonic disorders, in the separated subjects (Aisa, Tordera, Lasheras, Del Río, & Ramírez, 2007).

The serotonin level in the nucleus of the raphe and the HC is lower in subjects that have been separated, which could be responsible for the depression-related behaviors found in these animals. (Lee et al., 2007). Along the same lines, recent studies have found reduced serotonin metabolism in the PFC of these subjects (Gracia-Rubio et al., 2016). However, other authors have found an increase in serotonin activity (greater quantity of neurotransmitters and metabolites) in the HC and hypothalamus in separated subjects (Rentesi et al., 2010) and an increase in serotonin and its metabolites in the nuclei of the dorsal raphe and the accumbens in separated females when they reach 15 months old (Arborelius & Eklund, 2007).

Regarding the serotoninergic receptors and their functioning, MS does not seem to produce alterations in the 5-HT6 receptor in the HC or the PFC; however, the serotonin levels in the PFC are higher in separated subjects. Moreover, the administration of a selective inhibitor of the 5-HT6 receptor (SB271046) has been shown to revert the cognitive deficits associated with MS (Marcos et al., 2008). The 5-HT6 receptors do not seem to be affected by MS, as the injection of its agonist, 8-hydroxy-2-(di-n-propylamin) tetralin (8-OH-DPAT), which has anxiolytic and antidepressant effects, does not manage to improve the anxious and depressive behaviors that separated adult animals display (Lambás-Señas et al., 2009). However, in very young subjects, an increase has been found in the mRNA levels of the 5-HT1A receptor in CA1 and of the 5-HT2A in the parietal cortex. That is, the cortical and hippocampal serotonin receptors seem to be sensitive to MS in early childhood (Shikanai, Kimura, & Togashi, 2013; Vázquez, López, Van Hoers, Watson, & Levine, 2000) and adolescence (Li et al., 2013).

Some behavioral results, such as deficits in object recognition after MS, have led to the study of acetylcholine. Based on these deficits, an increase can be found in acetylcholinesterase (an enzyme that participates in the degradation of acetylcholine) in the HC and perirrinal cortex of the separated subjects. Proof of this is that when galantamine (an acetylcholinesterase blocker) is administered to them, the memory alterations revert (Benetti et al., 2009).

Finally, studies that analyze glutamate and GABA have found that, after MS, in separated males the hippocampal glutamate levels increase, whereas females show GABA reduction (Barbosa Neto et al., 2012). Reductions have been found in the PFC parvalbumin of adolescent separated subjects. These reductions correlate with behaviors related to depression, which could indicate a decrease in GABAergic neurotransmission because parvalbumin is one of the proteins present in GABAergic interneurons (Leussis, Freund, Brenhouse, Thompson, & Andersen, 2012).

It is possible that the depressive behaviors displayed by separated subjects that are maintained until senescence are related to the down-regulation of the vesicular transporters of glutamate and GABA in the HC. This modulation of the neurotransmission of glutamate and GABA could be caused by an increase in the circulating corticosterone levels (Martisova et al., 2012). MS has also been shown to have an effect on the development of the

GABAergic receptors because separated subjects show an increase in $GABA_A$ receptors (Kinkead et al., 2008).

Conclusions

It is clear that chronic early-life stress has affective, cognitive, and behavioral consequences. The negative outcomes of this stress could be mitigated, or even eliminated, if we uncovered all the processes that underlie the deficits described. Studying this in human beings is a very complex for several reasons. First of all, there is great variability in when the stress starts, when it ends, the duration, the type of stress, the intensity, and so on. Second, conducting longitudinal studies entails very high costs in terms of human resources, time, and expense. Third, we depend on the subjects' memory of events that occurred in childhood, with false memories being very common, especially related to emotional memories. For all of these reasons, it is essential to develop good animal models of early adverse experience.

Animal models are more effective, and we are able to control the duration, intensity, and type of stressor, allowing us to make comparisons. In addition, the ontogenetic development of rodents is shorter, making it less expensive to study medium- and long-term effects of early-life stress in the subjects and their descendants. One of the most widely-used chronic-early-stress models is MS. MS adequately models neglect, which is the most frequent type of abuse, but we also need to homogenize early-life stress models, even within MS. Regarding the monoamines, there are contradictory results that can be due to differences between the models used. Not all the neuronal systems and networks develop at the same time, and this is equally true for the neurotransmission systems. Therefore, it would be interesting to compare several time windows for early-life stress in the near future. Moreover, discovering the genetic, physiological, and neural bases of resilience to early-life stress, in order to reveal the keys to this resilience, would allow the population to have tools to minimize or eliminate the deleterious effects of early-life stress. Thus, there is a need for future studies in this line of research.

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