SO FAR CHI Sociedad de Farmacología de Chile

ARTÍCULO DE REVISIÓN

WHAT WE KNOW ABOUT THE LONG-TERM CONSEQUENCES OF EARLY MATERNAL SEPARATION AND NEUROENDOCRINE RESPONSE TO STRESS

(Qué sabemos sobre las consecuencias a largo plazo de la separación materna temprana y la respuesta neuroendocrina al estrés)

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ABSTRACT

Adverse conditions during early life are a risk factor for stress-related diseases. How this early adversity induce long-term effects is not well understood, however there are several evidence that the stress hormones play a determining role. Here we will focus on evidence obtained from the long-term consequences of prolonged maternal separation procedures.
The purpose of this article is to review the literature about the influence of early experiences on the hypothalamic-pituitary-adrenal (HPA) axis function and endocrine stress responses in rodents. Early experiences have long-term influences on the behavioral and endocrine responses to stress and the alterations depend mostly on environment conditions and the interaction between mother and offspring. In the rodent, brief periods of separation result in an attenuated adrenal response to stress (reduced secretion of corticosterone). In contrast, longer periods of separation result in an exaggerated response. Besides, it is known that the prevalence of affective and anxiety disorders are significantly higher in women than in men. Emotional reactivity to stress and abnormalities in HPA axis activity have been implicated in the etiology of both depression and anxiety disorders. Therefore sexually dimorphic effects of maternal separation on the HPA axis function are discussed since gender is an important factor influencing the response to stress.
The literature clearly demonstrates that early experiences trigger long-term changes in the stress system that may permanently alter brain and behaviour.

Keywords: *maternal separation, stress, hypothalamic-pituitary-adrenal axis, corticosterone, sex differences.*

Published by the Chilean Society of Pharmacology

INTRODUCTION

The accumulation of stressful life events has been reported to be a particularly efficient factor to precipite pathological outcomes. Separation from parents and maltreatment during childhood is associated with increased prevalence of adult psychiatric illness, including depression and anxiety disorders (De Bellis 2005, Nemeroff 2004) and alterations in neuroendocrine response to stress (McEwen 2003).

Maternal separation in rodents is an animal model used to study different childhood experiences that could induce psychiatric illness during life. Neonatal rats and mice go through a period of time during which the absence of stress is crucial for the normal development of the nervous and endocrine system. This period has been termed the "Stress hyporesponsive period" (SHRP) and the characteristics are discussed below. A substantial part of brain development happens after birth, and consequently is subject to environmental influences, such as maternal separation (MS), hypothermia or food deprivation, some of which may negatively affect brain maturation (Kuhn and Schanberg, 1998; Zhang et al., 2002).

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The present article focuses on rodent models of prolonged MS during postnatal period that induced changes in neuroendocrine parameters. Several lines of evidence from rodent MS studies support the notion that the early-life rearing conditions have long-term consequences for stress response as adults. The emphasis is on the alterations in the hypothalamic-pituitary-adrenal (HPA) axis and neuropeptides as CRF and AVP and alterations in extra hypothalamic areas of the brain that regulate the HPA axis. The article provides a mini review that is focused on data from experimental studies that investigated the impact of early-life conditions on neuroendocrine parameters. The neuroendocrine parameters are known to be crucial for normal social, emotional, and neurobiological development.

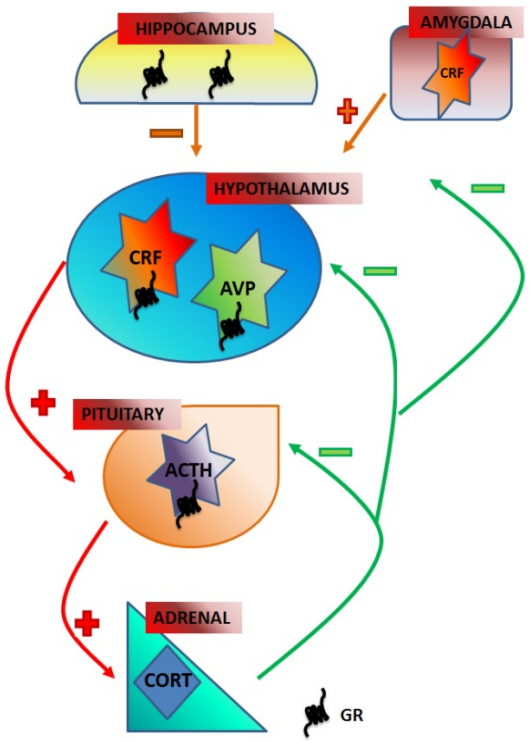
HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The major neuroendocrine axis mediating the hormonal stress response is the HPA axis. The HPA axis activation is triggered by a cascade of signals beginning with the release into the hypophyseal-portal system of the neuropeptides corticotropin-releasing factor (CRF) along with a second secretagogue, arginine vasopressin (AVP), from the paraventricular nucleus of the hypothalamus (PVN). During stress response CRF and AVP bring about the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. Circulating ACTH is the key regulator of glucocorticoid secretion by the adrenal gland (cortisol in primates and corticosterone (CORT) in rodent). The hormones secreted by the HPA axis control their own secretion through a neuroendocrine negative feedback loop by acting not only at the hypothalamus and the pituitary gland but also at extrahypothalamic centers (i.e. hippocampus, amygdala and prefrontal cortex), to inhibit the further release of hypothalamic CRF and AVP (Fig. 1) (Herman et al. 2003, Tsigos & Chrousos 2002, Romeo 2010, De Kloet et al. 1998).

GLUCOCORTICOID RECEPTORS

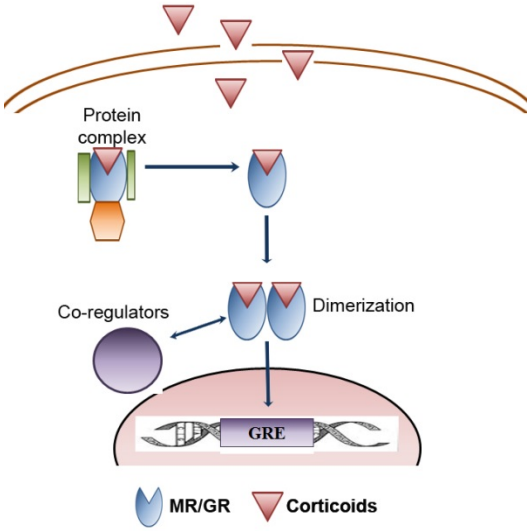
The actions of glucocorticoids in the central nervous system are mediated by two receptors: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) which are abundantly expressed and colocalized in neurons from several areas of the brain. These steroid receptors are found in relatively high concentrations throughout the neural–pituitary network that controls both negative feedback and activation of the HPA axis (Sapolsky 2000, Romero & Buttler 2007). Corticoids receptors act as transcription factors activated by ligand, altering, by various mechanisms, the expression of genes. Inactivated receptors reside in the cytosol as multimeric protein complexes. After ligand binding, the receptors dissociate from the rest of the complex, dimerize and translocate to the nucleus. In nucleus, they exert their action on DNA by binding to specific sequences of bases called glucocorticoids response element (GRE) and recruite co-repressors or co-activators. Activated receptors activate or inhibit the transcriptional activity of certain genes (Fig. 2) (Chrousos 1998; de Kloet et al. 2005). The affinity of MR for corticosteroids is high and is typically saturated under basal glucocorticoid levels, while the low-affinity GR are activated with high plasma corticosteroid levels (de Kloet et al. 1998). Therefore, when glucocorticoid levels rise during the peak ultradian pulses and in response to stressors, the negative feedback on the HPA axis is primarily mediated by the GR (Fig.1) (de Kloet et al. 1998), having an established function in the response to and recovery from stress. However, the MR also appears to play a role in glucocorticoid-mediated negative feedback under mildly stressful conditions (Pace & Spencer, 2005). The balance between MR and GR mediated actions is thought to determine the stress responsiveness of an individual. Disturbance of this balance can dysregulate the stress system and enhance vulnerability to stress-related disorders (de Kloet et al. 2005, Oitzl et al. 2010, Harris et al. 2013).

Figure 1



Simplified representation of the integrated stress response emphasizing in HPA axis activation and glucocorticoid-mediated feedback. **CRF:** corticotrophin realising factor; **AVP:** arginine-vasopressin; **ACTH:** adrenocorticotrophin; **CORT:** corticosterone; **GR:** glucocorticoid receptor.

Figure 2



Representation of the mechanism of action of corticoids receptors. **GRE**: glucocorticoid responsive element, **GR**: glucocorticoid receptor; **MR**: mineralocorticoid receptor.

THE STRESS HYPORESPONSIVE PERIOD

As alluded above, the HPA axis during the early development is remarkably different from the adult, both in structure and function. A large body of evidence has accumulating supporting that during the first 2 weeks of the early postnatal development in rats and mice, the pituitary-adrenal axis of the pups is hyporesponsive to most stimuli. This period has been termed the stress hyporesponsive period (SHRP) and extends from postnatal day 4 to 14 approximately. The main characteristics of this period are very low basal CORT levels and an inability of many stressors to elicit a CORT response (Levine et al. 2007, Sapolsky & Meaney 1986, Walker et al. 2001). Data indicate that maternal factors are responsible for actively inhibiting the endocrine responses to stress postnatally. Thus, during development, most of the peripheral and central stress-responsive systems are capable of being activated. However, under conditions of normal dam-pup interactions, these responses are mostly suppressed by the dam's behavioral interaction with the pups. It has been suggested that this is an important mechanism in protecting the neonatal rat from prolonged episodes of glucocorticoid secretion during this critical period of brain development (Faturi et al. 2010). High levels of glucocorticoids in this period can have damaging effects on the brain, since it is a period of major axonal growth, synaptogenesis and myelinitation of the main brain circuit (Lehmann & Feldon 2000). The mother influences as diverse physiological responses such as heart rate, the sleep-wake cycle and the production of growth hormone (Levine 1994).

MATERNAL SEPARATION

Adverse events in early life affect wide physiologic and behavioral responses and contribute to the development of different kinds of disease in adult life.

In laboratory rats, the chronic effects of postnatal manipulation of the infant-mother relationship have been studied experimentally for more than 50 years. The alterations depend mostly on environment conditions and the interaction between mother and offspring. In order to study the effects and possible alterations by adverse experiences in early life was developed an animal model of early life stress called maternal separation (MS). There is a large number of MS procedures, however is well known that, either 24h or repeated shorter periods of neonatal MS, is considered one of the most potent stressors during development.

In the literature, there are major the inconsistencies and contradictory findings for almost all parameters investigated. Even subtle variations in methodological procedures such as differences in frequency, duration, age, gender could account for these discrepancies (Lehman & Feldom 2000).

Although results are not consistent within the MS paradigm, it has been shown that the MS manipulation affects a large number of behavioral and neurobiological variables in the offspring that persist into adulthood.
It has been shown that generally short-term MS (usually 15 min or less) appeared to reduce anxiety-like behaviors, decreased HPA-axis tone and reduced the response to stress (Plotsky et al. 2005, Ladd et al. 2005, Levine 2005) in adulthood. These short-term separation periods, called early-handled (EH), could emulate the natural period of time in which the mother leaves her pups for short periods of time to collect food. Thus, short-term MS might be considered as a more natural environment (Nishi et al. 2013). Whereas the effects of EH have been well documented and replicated, the long-term effects of prolonged MS are more controversial. This could be due in part to the different procedures of maternal separation that the laboratories used. However, several works have demonstrated that separation of pups from their mother during prolonged periods could lead hyper reactivity of the HPA axis to stress at the adult stage (Aisa et al. 2008, Lippmann et al. 2007, Milde et al. 2004, Ladd et al. 2004).

In the next section we discussed more in detail the different responses of the HPA axis among the different protocols of prolonged MS used between laboratories.

MATERNAL SEPARATION AND THE HPA AXIS

The response of an organism to stress involves various systems such as the nervous, endocrine and immune. Indeed, the connections between brain circuits and peripheral systems form the basis of adaptive or maladaptive responses of an organism to stressful stimuli. One of the major pathways that are activated against stress is the HPA axis.

Usually, different protocols of maternal separation did not produce any change in the basal plasma levels of CORT or ACTH. Following daily 4.5 and 3 h MS in the first 3 weeks of life, no significant differences in basal plasma CORT and ACTH levels were observed (Ogawa et al. 1994, Ladd et al. 2005). However, it has been shown in female rats that MS from postnatal day (PND) 1 to 21 during 4,5 h decreased ACTH levels and increased CORT plasma levels in adulthood (Suárez et al. 2001).

As stated above, MS increase the risk to develop different disease as adult. It has been demostrated that MS increase adulthood vulnerability to stress and produce a heightened HPA axis hormonal response (Plotsky & Meaney 1993, Suchecki et al. 1995, Ladd et al. 2004, Milde et al. 2004). However, different results it has been shown.

MS during 180 min from PND 2 to 14 produced an augmented plasma ACTH and CORT concentrations following an acute stressor, compared to EH animals that were maternally separated during 15 min from PND 2 to 14 (Lippmann et al. 2007). Also, MS during 180 min from PND 1 to 14 produced enhanced stress reactivity responses as shown by elevated CORT levels following the exposure to shock stress. But this response was not observed in rats EH that was maternally separated during 10 min (Milde et al. 2004). MS from PND 2 to 14 during 3 h produced an increase in ACTH levels after different stressors (Liu et al. 2000, Ladd et al., 2004) and produced an increase in CORT levels after exposure to a brief mild handling stress compared to EH (15 min) rats (Kalinichev et al. 2002).
However, contrary response was found, Roman et al. (2006) have been shown that a separation from PND 1 to 21 during 15 minutes increase CORT release after immobilization, but a separation during 6 h did not produce alteration in CORT release induced by stress.

With regards the neuropeptides that regulate the HPA axis it has been found that MS, 3 h daily on PND 1 to 14 showed higher AVP mRNA expression in the PVN and the bed nucleus of the stria terminalis compared with control rats (Veenema & Neumann 2009). Aisa et al 2008 found that MS (180 min/day from PND 2-21) in females produce an increase in CRF mRNA expression in the PVN. Besides, following chronic homotipyc stress, CRF mRNA expression was significantly increased in maternally separated rats (180 min/day during PND 2-14), compared to controls (Babygirija et al. 2012).

The stress peptide CRF by binding to CRF1 and 2 receptors (CRFR1 and CRFR2) is key to persistent changes in central stress circuits induced by MS. In this sense, O'Malley et al (2011) showed that MS during 3 h from PND 2 to 12 produced an increase in the CRFR1 in the hypothalamus.

These studies illustrate that early life perturbations induce persistent changes in the HPA axis function and increased sensitivity to stress, which may contribute to different disease and behavioral changes in adulthood. Most of the data found suggests that the maladaptation in stress response in neonatal maternally separated rats could be due to alterations in the central nervous system, like an upregulated CRF system. In the next section, the discussion is focused in the alterations induced by MS in other brain structures that regulate the HPA axis.

MATERNAL SEPARATION EFFECTS ON EXTRA HYPOTHALAMIC ÁREAS

Hippocampus: The activity of the HPA axis is controlled by different limbic and cortical areas. The hippocampus is a brain region that has an inhibitory influence over the HPA response (Fig. 1) (Jacobson & Sapolsky 1991). This structure is particularly vulnerable to early life adverse experiences for different reasons, in the first place it continues to develop after birth, secondly it shows a remarkable degree of structural and functional plasticity and finally, it contains a high number of GR which makes it susceptible to changes in glucocorticod levels. MS affect a number of structural, molecular and physiological aspects of the hippocampus. For instance, prolonged MS (360 min/day, PND 1-21) alters glutamate receptor expression in the hippocampus (Pickering et al. 2006). Decrease neurogenesis has also been found in adult hippocampus of maternally separated rats, specifically a decrease in cell proliferation and immature neuron production in the dentate gyrus (Mirescu et al. 2004, Huot et al. 2002). Concentrations of neurotrophin also decrease in the hippocampus of the maternally separated rats (Marais et al. 2008). MS leads to a deregulated HPA activity with down-regulation of GR in the hippocampus. This reduced capacity to detect glucocorticoids leads to inefficient negative feedback on the HPA axis and an extended stress response (Meaney 2001).

Extended Amygdala: Various stressors activate different sources of CRF, such as the central nucleus of the amygdala (CeA) and the paraventricular nucleus of the hypothalamus (PVN). Amygdalar CRF may stimulate the hypothalamic CRF release through a feed-forward effect; this represents the limbic activation of the HPA axis (Fig. 1) (Herman et al. 2005, Jankord & Herman 2008).

Maternally separated rats for 180 min daily from PND 2 to 14 showed significantly elevated levels of CRF expression and CRF mRNA in the CeA, in bed nucleus of the stria terminalis and locus coeruleus, compared with EH animals (15 min). Therefore, early rearing conditions can permanently alter the developmental set-point of central CRF systems (Plotsky et al. 2005). Besides, Troakes and Ingram (2009) showed that MS from PND 5 to 21 for 6 h induced a significantly increase in c-fos mRNA expression, after the exposure to the elevated plus maze, in specific brain areas, including medial amygdala. The MS rats displayed greater anxiety behaviour compared to controls undisturbed rats. The region-specific increase in c-fos mRNA reflects activation of neural circuits associated with anxiogenic stress response (Troakes & Ingram 2009). Also, rats that were separated from the dams for 3 h per day from PND 1 to 14 had significantly more restraint stress-induced Fos positive cells, an estimate of neuronal activation, in the central nucleus of the amygdala (CeA), paraventricular nucleus of the hypothalamus (PVN), and the bed nucleus of the stria terminalis (BNST), each of which plays an important role in organizing the biobehavioral response to stress (Sanders & Anticevic 2007).

The CRF receptors (CRFR) 1 and 2 are distributed in a region-specific and species-typical pattern, including various cortical laminae, subcortical, limbic, and brainstem structures such as amygdala, bed nucleus of the stria terminalis, raphe nuclei, and locus ceruleus (Chalmers et al. 1996, Wong et al. 1994). CRF mRNA expression has been studied in the PVN in context of maternal separation paradigm, and it has been revealed that there is a rapid induction of heteronuclear and mature mRNA for CRF in both deprived and nondeprived animals within 15 min of an isotonic saline injection (Dent et al. 2000). These findings indicate that during the SHRP, central brain elements are clearly responsive to environmental events, even though adrenal responses may be limited. The expression and distribution of brain CRF receptors changes across animal development (Avishai-Eliner et al. 1996, Eghbal-Ahmadi et al. 1998). Eghbal-Ahmadi et al. (1997) demonstrated that 24-h of MS induced a downregulation of CRFR2 in ventromedial hypothalamus and the basomedial amygdala. On the other hand, MS during 3 h from PND 2 to 12 produced an increase in CRFR2 in the amygdala following acute psycological stressor (O'Malley et al 2011). However little is known about the impact of maternal separation on CRF receptor expression in the brain.

This indicates that the alterations induced by maternal separation in structures that regulate the behavioral response to stress and the HPA axis could be part of the cause of emotional disorders in adulthood.

GENDER DEPENDENT EFFECTS IN MATERNAL SEPARATION MODELS

Sexually dimorphic responses in mammals can be considered as the final outcome of the mutual influences between genes, sex hormones, organizers and activators effects of hormones on the brain, learning, social influences and other environmental influences (Kelly et al. 1999, Palanza 2001). Sex differences have referred, for a long time, only to mating behaviors, sex hormones and the hypothalamus. However, this view has changed because a lot of findings highlight the influence of sex on several brain areas, on different types of behavior, memory, emotions, vision, face processing, perception of fear levels of neurotransmitters and the brain's response to stress hormones (Cahill 2006).

While stress is a common experience to all organisms, many stress responses are sexually dimorphic. It is known that the prevalence of affective and anxiety disorders are significantly higher in women than in men. Emotional reactivity to stress and abnormalities in HPA axis activity have been implicated in the etiology of both depression and anxiety disorders (Gold & Chrousos 2002). Besides, there is a wide body of evidence indicating that sex hormones are involved in the control of the HPA axis. In general, estrogen has excitatory effects, and androgen has inhibitory effects on HPA function (McCormick et al. 2002, Lund et al. 2006).

On the other hand, as stated earlier, the behavior of the mother plays a critical role in the development of the stress response. There is evidence that maternal care is different in males and females (Moore et al., 1997), therefore the offspring of the opposite sex would be exposed to different patterns of maternal care, which could also contribute to sex differences in the development of behavior and stress response.

Wigger and Neumann (1999) found that periodic maternal separation (180 min/day on postnatal day 3-10; PND) induced higher plasma ACTH and CORT concentrations in female than in male rats. This difference might be due in part to a direct stimulatory effect of estrogen on CRH gene expression by interaction with estrogen responsive elements in the promotor area of the gene coding for CRH. Slotten et al. (2006) reported decreased CORT levels for daily 3 h (PND 3-15) maternally separated females compared with non-handled rats. They showed that females had higher corticosterone and ACTH basal levels than males (Slotten et al. 2006). On the other hand, it has been shown that 4.5 h maternal separation during the first 3 weeks of life (PND1-21) did not produce alterations in basal CORT or in basal ACTH levels neither in males nor in females (Renard et al. 2007). However, in front of a stress situation (variable chronic stress) the pituitary-adrenal axis is less active in maternally separated males showing a

decrease in ACTH and CORT levels (Renard et al 2007). This trait is not observed in female rats. The diminutions in plasma ACTH and CORT only in males might be due to a lower sensitivity of the HPA axis to stress in animals subjected to maternal separation. In accordance, Ladd et al. (2005) demonstrated that chronic variable stress decreased the neuroendocrine stress response in prolonged maternally separated (180 min/day, PND 2-14) male rats. Chronic stress may dampen the pituitary-adrenal response in maternally separated rats by enhancing transcription of glucocorticoid receptor in the cortex. Alternatively, they proposed that variable chronic stress may increase regional GABAergic tone, thereby dampening stress responsiveness in maternally separated animals. In contrast, neonatal handling (15 min/day, 1h) during the first 3 weeks of life increase CORT response to stress in male but not in female rats (Papaioannou et al. 2002).
Furthermore, it has been found that the medial parvocellular portion of the paraventricular hypothalamic nucleus has a vasopressinergic activity that is dependent on the animal's sex. Female rats showed higher activity in the AVP neurons than males (Renard et al 2010). Furthermore, the combination of early-life stress and variable chronic stress as adults produced a neuronal activity pattern in vasopressinergic neurons that is opposite in males and females. In males, the activity of AVP neurons turned back to baseline, whereas in females the exposure to both protocols caused a marked increase in such activity (Renard et al. 2010). Since AVP is a hypothalamic hormone that, together with the CRF, stimulates ACTH release from the pituitary gland, a higher activity in AVP neurons in females is in accordance with results showing that female rats exhibited elevated ACTH levels compared to males, evidencing a sexual dimorphism (Renard et al. 2007).

Regarding GR, Xu et al. (2011) found that GRs in the hippocampus were more abundant in females than in males and maternal separation from PND 2 to PND 14 during 3 h increase GR levels only in males. On the other hand, it has been shown that there were no gender-dependent effects in the PVN or in the dorsal hippocampus in animals subjected to maternal separation (4.5 h/day from PND1-21) and males and females showed an increase in GR expression in the CA1, CA2 and CA3 subfields of the hippocampus, when they were subjected to early maternal separation and variable chronic stress as adults (Renard et al 2010). Other investigators have found an increase in GR mRNA density in the frontal cortex of maternally separated male rats subjected to variable chronic stress, but they have not found changes in the hippocampus of males with the same treatment (Ladd et al. 2005). Desbonnet et al. (2008) showed that neonatal maternal separation (3 h/day from PND 2-14) increase CRF expression and the activity of CRF neurons in the PVN after an acute swim stress only in female rats. They did not found differences in CRF in the hypothalamus of maternally separated males, however, maternal separation produce a decrease in AVP expression in the PVN of males. It has also been shown that early postnatal environment affects the differentiation of hippocampal neurons; this effect involves alterations in GR expression in the rat brain, resulting in changes in the sensitivity of the system to the inhibitory effects of glucocorticoids on the synthesis of CRF and AVP in hypothalamic neurons (Meaney et al., 1996). Moreover, these effects of maternal separation have also been shown to be gender-dependent, with greater decreases in GR levels in the PVN of males compared to females, following 24 h of maternal separation (Avishai- Eliner et al. 1999). Aisa et al. 2008 found that maternal separation (180 min/day from PND2 - 21) in females produce an increase in CORT levels and CRF mRNA expression in the PVN. They also showed a decrease in GR expression in the hippocampus and suggest that the altered HPA axis function may be associated to behavioral and cognitive deficits in maternally separated females (Aisa et al. 2007, 2008).

The sexually dimorphic effects of maternal separation on the HPA axis function indicate that gender is an important factor influencing the response to stress. In general, the enhanced response to stress in maternally separated female rats relative to males suggests that maternal separation results in a more reactive neuroendocrinological stress system in females, than in males. The mechanism of this differential gender-specific vulnerability to the same perinatal environment may be related to the perinatal sex steroid milieu (Yoshimura et al. 2003).

CONCLUSIONS

Traumatic experiences in early life or in adulthood alter the ability of an individual to adapt. If coping mechanisms fail a state of distress appear, which is reflected in an altered HPA axis and limbic system function. Evidence shows that stressful events, particularly those occurring during the postnatal period, may cause changes in the development of the nervous system and behavior of animals. These studies all support the notion that prolonged periods of MS are associated with risk to develop different disease associated with alterations in the neuroendocrine response to stress. However, there are several models of MS and they generate different results and the experimental conditions have to be chosen accordingly.
Besides existing sex differences in neuroendocrine responses to stressful situations in early postnatal life and in adulthood could underlie the predisposition of either sex for various disorders such as depression and anxiety. However, still much remains unknown about the different neural mechanisms and functional brain processes that operate in different sexes in situations of stress.

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