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Review

Disruptions of the mother–infant relationship and stress-related behaviours: Altered corticosterone secretion does not explain everything

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ABSTRACT

The hypothalamic–pituitary–adrenal (HPA) axis is the main neuroendocrine system of response to stress, and an imbalance of this system's activity is believed to be at the core of numerous psychiatric pathologies. During the neonatal period, the glucocorticoid response to stress is maintained at low levels by specific maternal behaviours, which is essential for proper brain development. Effective evaluation of the impact of increased secretion of corticosterone during an essentially anabolic developmental period on adulthood behaviour involved separation of the neonate from its mother for periods ranging from 3 to 24 h. It has been shown that disinhibition of the stress response is achieved by such procedures. The pioneering studies by Seymour Levine set the stage for a prolific and promising field of study that may help neuroscientists unveil the neurobiological underpinnings of stress-related disorders. Based on a series of studies, we propose that maternal separation and maternal deprivation change stress-related behaviours, but that corticosterone seem to be only partially involved in these changes in adulthood. It appears that extra-hypothalamic corticotrophin-releasing factor and neurotransmitter systems may be the primary mediators of these behavioural outcomes.

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1. Introduction

A growing body of data points to a fundamental interaction between genetic factors and early environmental experiences as determinants of later vulnerability to psychopathology and many stress-related disorders (Caspi et al., 2003; Plotsky et al., 1998). One of the most robust risk factors for the development of anxiety and depressive disorders in adulthood is a history of severe childhood stress. The risk of developing depression and anxiety is higher in children exposed to family violence (especially when there is police involvement or same-sex parent victimization), insecure attachment or inconsistent rearing attitudes, than in children who had no such experiences (Penza et al., 2003). Epidemiological data also show that parental neglect and early maltreatment are risk factors for later psychopathologies (Gutman and Nemeroff, 2003). For instance, there is a greater likelihood of developing major depression with a history of emotional abuse during childhood, and of anxiety disorders and post-traumatic stress disorder (PTSD) in the context of a history of emotional

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abuse in addition to physical or sexual abuse (Gibb et al., 2007; Springer et al., 2007).

Pre-clinical research may help to shed light on the neurobiological consequences of early life adversity, although modelling of human conditions is extremely difficult and sometimes unfeasible. As discussed in Loman and Gunnar (2009) review, children are rarely submitted to a single type of adversity, as is the case in animal studies. Therefore, pre-clinical studies may be more helpful in establishing cause and effect relationships than clinical studies.

The development of the rat brain includes a spurt of development of specialized astrocytes and pyramidal cells before birth, whereas peak brain growth, myelination and the emergence of granule cells of the dentate gyrus and cells of the olfactory bulb and cerebellum takes place from postnatal days (PNDs) 7–14 (Morgane et al., 2002). This period of intense cellular change occurs during a time when the activity of the hypothalamic–pituitary–adrenal (HPA) axis, the most important neuroendocrine system involved in the stress response, exhibits a peculiar maturational profile known as the stress hyporesponsive period (SHRP). The SHRP extends from PNDs 4 to 14 and consists of a period of low activity of the adrenocortical system and refractory responsiveness to stressors that would normally induce a robust stress response in adult animals (Rosenfeld et al., 1992a). This period is considered a highly adaptive phase in development because the maintenance of low and stable levels of corticosterone (CORT) is required for normal growth and development of the central nervous system (CNS) during ontogeny (Ballard et al., 1979; Doupe et al., 1985; Meyer and Fairman, 1985; Meyer and Joy, 1985; Sawano et al., 1969). Although very well-characterized in rats, the SHRP is less well-understood in children, although the establishment of salivary cortisol assays has allowed for a breakthrough in the study of this system in very young humans and has revealed the existence of such a period in children raised by responsible and caring parents (Gunnar and Donzella, 2002). Although some studies have sought to determine the long-term consequences of disturbances in the activity of the HPA axis during this period in humans, such investigation is easier in animals, especially due to the much faster rate of maturation in rodents.

The present paper reviews studies of the short- and long-term effects of two of the most used environmental adversities during development, long maternal separation and maternal deprivation, in rodents. The focus of this review will be on the activity of the HPA axis and on behavioural and physiological processes that may be modulated by this system. In addition, it presents the results of original studies in which the main objectives were to determine whether high circulating levels of corticosterone during the SHRP affected emotional behaviours and whether they correlate with neuroendocrine responses in adulthood.

1.1. The stress hyporesponsive period in the neonate and the influence of maternal behaviours

The SHRP has been proposed to result from factors intrinsic to the pup, such as enhanced negative feedback at the brain and pituitary levels (Walker et al., 1990, 1991) and/or from immaturity of pathways leading to the neonatal hypothalamus (De Kloet et al., 1988). There is currently sufficient evidence, however, to show that negative feedback in the neonate is deficient. More specifically, when a stress response is triggered, CORT and ACTH levels remain elevated for at least 2 h after presentation of the stimulus (Suchecki et al., 1995, 1993b; van Oers et al., 1997).

Factors extrinsic to the pup (e.g., maternal presence) are major determinants of the SHRP. The mother represents a major source of interaction and regulation of physiological and psychological processes. One way to determine how maternal care regulates distinct processes is separation of the dam from her offspring and subsequent evaluation of changes in the course of development of any given system (Hofer, 1987). By using this separation approach, Miron Hofer elaborated his theory of hidden regulators within the mother–infant interaction in which some criteria must be fulfilled. The first criterion states that changes in physiological processes in the neonate should develop slowly over the course of many hours of separation, such that they would be distinguishable from the immediate reaction to separation from the mother, which would reflect a non-specific response to the loss of maternal care. The second criterion states that the replacement of specific maternal behaviours during the separation period should prevent or reverse the effects of maternal removal (Hofer, 1983). According to these criteria, the developing HPA axis is under maternal regulation in a tonic inhibitory fashion; however, the available data indicate that the main *locus* of the SHRP is the adrenal gland. For instance, it has been shown that the neonatal rat is quite capable of responding to stress with increased expression of CRH mRNA in the paraventricular nucleus of the hypothalamus (PVN) at PNDs 6 and 12 (Dent et al., 2000b). Vasopressin (AVP) mRNA is also increased in the PVN of 12-day-old pups, as is c-fos expression, in an age-dependent manner (PND 6 < PND 12 < PND 18) (Dent et al., 2000a). Thus, even before weaning, the central component of the HPA axis is responsive to stress. The adrenal gland, on the other hand, is refractory to both direct and indirect stimulation. This physiological feature is dependent on maternal presence. In normally reared pups, administration of ACTH, which overcomes the neural processing of stress stimuli and the activation of brain mechanisms of the stress response, results in a U-shaped curve with adult-like CORT output at PNDs 1 and 2, followed by a progressive decline until it reaches a nadir between PNDs 8 and 12, only to start increasing again after PND 14 (Witek-Janusek, 1988).

The mechanisms involved in the onset and offset of adrenal insensitivity during the SHRP are not completely understood. Evidence suggests that metabolic signals may be a crucial factor for the SHRP. Feeding results in the maintenance of high plasma levels of leptin. This hormone blocks ACTH-induced steroidogenesis in cultures of adrenal cells from 10-day-old pups, strongly suggesting that it may be a mediator of the SHRP (Salzmann et al., 2004). In mice, however, leptin does not appear to play an important role. Instead, GHrelin and glucose seem to be stronger inhibitors of ACTH and corticosterone responses to 12-h maternal deprivation (Schmidt et al., 2006).

These regulatory factors do not explain why maternally deprived pups, which secrete more CORT in response to stress, do so in a similar age-dependent manner as non-deprived pups, i.e., in a U-shaped curve. One possibility could be that this negligible adrenal responsiveness results from insufficient stimulation by ACTH because the ACTH response is stimulus- and age-dependent during this period (Suchecki et al., 1993a, 1995; Walker et al., 1991). If this were indeed the case, exogenous administration of ACTH should sensitize the adrenal gland, rendering it responsive to a mild stressor. We tested this hypothesis by administering ACTH to non-deprived neonates (NDEP + ACTH) and comparing CORT levels between NDEP and deprived (DEP) pups (see legend of Fig. 1 for details on experimental procedures and results).

The results demonstrated that the adrenal gland responded to its trophic factor and to the stress of injection, given the augmented adrenal grand. Importantly, this effect did not translate into increased basal or stress-induced CORT levels, as seen in DEP pups. Thus, some aspect(s) of the mother–infant relationship functions as a shield for the adrenal glands. Overall, these findings suggest that the low CORT levels found in NDEP pups are not due to insufficient stimulation of the adrenal glands by low levels of ACTH.

Because the SHRP is such a sensitive period for CNS development, disruptions of the mother–infant relationship during this