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Review

Maternal corticosterone effects on hypothalamus–pituitary–adrenal axis regulation and behavior of the offspring in rodents

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ABSTRACT

The behavioral and physiological traits of an individual are strongly influenced by early life events. One of the major systems implicated in the responses to environmental manipulations and stress is the hypothalamus–pituitary–adrenal (HPA) axis. Glucocorticoid hormones (cortisol in humans and corticosterone in rodents) represent the final step in the activation of the HPA system and play an important role in the effects induced by the perinatal environment. We demonstrated, in rats with some differences between males and females, that mothers whose drinking water was supplemented with moderate doses of corticosterone throughout the lactation period, give birth to offspring better able to meet the demands of the environment. The progeny of these mothers, as adults, show improved learning capabilities, reduced fearfulness in anxiogenic situations, lower metabotropic glutamate receptors and higher glucocorticoid receptors in the hippocampus with a persistent hyporeactivity of the HPA axis leading to a resistance to ischemic neuronal damage. Other studies performed in mice showed that low doses of corticosterone in the maternal drinking water, which, as in our rat model, may reflect a form of mild environmental stimulation, enhanced the offspring's ability to cope with different situations, while elevated doses, comparable to those elicited by strong stressors, caused developmental disruption. Significantly, adult rats and mice that had been nursed by mothers with a mild hypercorticosteronemia provide an example of how a moderate corticosterone increase mediates the salutary effects of some events occurring early in life. Both maternal and infantile plasma levels of the hormone may play a role in these effects, the first influencing maternal behavior, the second acting directly on the central nervous system of the developing rat.

Contents

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1. Introduction

The perinatal environment may affect the course of development, causing structural and functional changes in the central nervous system (CNS) which influence individual adult traits. Early life events activate several endogenous systems, both in mothers and in pups; these include the hypothalamus–pituitary–adrenal (HPA) axis, which ultimately leads to glucocorticoid secretion by the adrenals (cortisol in humans and corticosterone in rats), and represents a complex signalling structure between the external environment and the brain. Glucocorticoids bind to two cytoplasmic receptor subtypes: mineralcorticoid receptors (MR), which are mainly expressed in limbic regions and bind corticosterone with high affinity (KD of 0.5 nM), and glucocorticoid receptors (GR), which are ubiquitous and bind corticosterone with a 10-fold lower affinity (KD of 5 nM). HPA axis activity is regulated by a negative feedback loop that dampens the central drive of the axis via the actions of the secreted glucocorticoids. In the first few weeks of life, CNS vulnerability to glucocorticoid hormones is high. This is because the free active fraction of corticosterone is elevated as the CBG level is low and the half-life of corticosterone is prolonged to about three times that observed in adult rats (Leeper et al., 1988; Schroeder and Henning, 1989).

Perinatal exposure to glucocorticoids may 'programme' a range of tissue-specific pathophysiologies (Seckl, 2004). Key targets of glucocorticoid programming include metabolic tissues, such as liver, visceral adipose tissue, skeletal muscle and pancreas, and regions of the brain with important functions regarding cognition, mood and neuroendocrine control. The HPA axis, and its key limbic regulator, the hippocampus, are particularly sensitive to glucocorticoids and their perinatal programming actions.

In animal research it has been demonstrated that a number of different manipulations in early development can permanently modify the HPA axis function. Broadly, these can be split into prenatal and postnatal manipulations. Examples of prenatal manipulation are maternal stress (Maccari and Morley-Fletcher, 2007; Ward and Weisz, 1980, 1984; Weinstock, 2001; Welberg and Seckl, 2001), exposure to synthetic glucocorticoids (Liu et al., 2001; Matthews, 2000) and nutrient restriction (Lesage et al., 2002; Lingas and Matthews, 2001). Postnatal manipulations that modify HPA axis function in adult offspring include neonatal handling (Meaney et al., 2000), maternal deprivation (Macri et al., 2004; McCormick et al., 2002; Meaney, 2001), exposure to synthetic glucocorticoids (Bakker et al., 2001), infection (Nilsson et al., 2002), as well as the naturally occurring modification of maternal behavior (Meaney, 2001). In species such as rats or mice that give birth to immature young, part of the neuroendocrine development occurs in the postnatal age (Darlington et al., 1999), which suggests the importance of studies on hormonal manipulations during this stage of life.

A permanent and disruptive effect of glucocorticoids on the HPA system during neonatal life has been extensively demonstrated in a number of experiments in which the hormones were directly administered to the pups by injection, pellet implantation or gavage, and the behavioral and neuroendocrine outcomes were observed in adulthood (Bakker et al., 2000; Benesova and Pavlik, 1989; de Kloet et al., 1988; Felszeghy et al., 2000; Meyer, 1985). Neonatal treatment of rats with glucocorticoids transiently alters the expression of arginine–vasopressin in hypothalamic corticotropin-releasing hormone (CRH) neurons in weeks 2 and 3 of life (Bakker et al., 1997); in addition, it delays the developmental onset of HPA axis responsiveness to stressful stimuli, and reduces HPA reactivity to stress at 20–25 days of age (Erskine et al., 1979; Kamphuis et al., 2002; Ulrich et al., 1976). After treatment with hydrocortisone on day 2 of life, a delay is observed in the appearance of circadian rhythm in the HPA activity, as well as in the HPA response to stressful stimuli (Krieger, 1972, 1974). Adult basal levels of corticosterone are lower in rats implanted with pellets of corticosterone (25 mg/100 g body wt) at postnatal days 3, 6, 12, or 18 (Turner and Taylor, 1976). Long-lasting reduction of GR immunoreactivity is present in the hippocampal field CA1 after neonatal treatment with corticosterone in the first week of life (Zoli et al., 1990) and a decrease in the number of MR is observed in the hypophysis, hypothalamus and hippocampus after administration of hydrocortisone in the first five postnatal days (Garina et al., 1986). Moreover, neonatal dexamethasone treatment decreases GR in the brain of the adult rat (Felszeghy et al., 1996). Several variables of learning and memory functions are also impaired in adulthood after glucocorticoid injection or pellet implantation in pups: performance in passive (Nyakas and Endroczi, 1972) and active avoidance learning tests score lower (Olton et al., 1975) and spatial memory in the Morris water maze test is also impaired (Vicedomini et al., 1986). Daily administration of corticosterone by gavage from day 2 to day 16 of life induces a delay in the development of swimming skills (Pavlovska-Teglia et al., 1995). Rats treated in infancy with glucocorticoids show a deviation from normal exploration strategies in a radial maze, and long term changes in behavioral functioning are important in that they enable the organism to adjust to environmental changes (Golub, 1982). Glucocorticoids have been shown to delay the manifestation of spontaneous alternating behavior, which is assumed to be under the control of the hippocampus, and general motor activity, as well as novelty-induced psychomotility, is increased in the adult rat after subcutaneous corticosterone administration during the first days of life (Nyakas, 1983).

All of the above mentioned deleterious effects of glucocorticoids in infancy explain why a physiological mechanism exists in order to protect the neonate from high plasma levels of these hormones: by the end of the first week of life and continuing into the second one, young rats display a "stress hyporesponsive period" (SHRP), reacting only weakly to a variety of stressful stimuli that persistently elicit a dramatic increase in the HPA function in animals of other ages (Sapolsky and Meaney, 1986; Schoenfeld et al., 1980; Walker et al., 1991). This mechanism smoothes deleterious fluctuations in glucocorticoids, limiting their adverse effects, and hence, defends neonates against adverse programming of the HPA system.

On the other hand, a mother–offspring pituitary–adrenal interrelationship is at play during postnatal life in the rat, and corticosterone present in milk passes into the suckling (Angelucci et al., 1983); in a recent paper Brummelte et al. (2010) showed that daily injections of 40 mg/kg of corticosterone post partum (days 2–21) given to the dam results in elevated levels of corticosterone in the offspring in an age-and tissue-dependent manner. Thus, even if the corticosterone produced by the infant is low, the hormone of maternal provenance, which may be increased by environmental events, reaches the pups and is able to influence the maturation of the HPA axis of the developing rat.

In this review, the focus is placed on the effects of maternal corticosterone during lactation on HPA/behavioral programming of the progeny, as well as on the potential mechanisms that underlie these processes in rodents. Maternal increase of corticosterone may be induced by environmental events or by administering the hormone to the mothers. We have mainly considered the studies in which corticosterone is administered to the mothers in a non invasive way, because any kind of administration by injection, pellets, etc. implies separation from the pups and stress linked to the procedure. It is important to consider that maternal hypercorticosteronemia itself may alter parental care, which may mediate the outcomes of maternal hormonal increase (Caldji et al., 2000). Thus, when hormonal manipulations take place during neonatal life, studies must include a parallel observation of maternal–infant interactions as well as of maternal behavior.