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Full-Length Review

The potential influence of maternal stress hormones on development and mental health of the offspring

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Abstract

Recent studies in humans suggest that alterations in the activity of the neuroendocrine system mediate the effects of psychosocial stress on fetal development and birth outcome. Chronic maternal distress compromises the normal regulation of hormonal activity during pregnancy and elevates free circulating corticotrophin-releasing hormone (CRH), probably of placental origin, before the normal increase occurs at term. Excess CRH, and other hormones like cortisol and met-enkephalin that pass through the placenta, could precipitate preterm labor, reduce birth weight and slow growth rate in prenatally stressed infants. CRH and/or cortisol have also been associated with impaired fetal habituation to stimuli and temperamental difficulties in infants. These changes may result from actions of the hormones on their receptors in the fetal limbic system. In the rat, gestational stress and excess maternal and fetal plasma corticosterone cause downregulation of fetal glucocorticoid (GR) and mineralocorticoid (MR) receptors and impair the feedback regulation of the hypothalamic–pituitary adrenal (HPA) axis in infancy and adulthood. The impairment in HPA axis activity can be prevented by maternal adrenalectomy and mimicked by administration of glucocorticoids. Gestational stress also increases CRH activity in the amygdala and the incidence of anxiogenic and depressive-like behavior in rats and non-human primates, which can be ameliorated by CRH antagonists. Excess amounts of CRH and cortisol reaching the human fetal brain during periods of chronic maternal stress could alter personality and predispose to attention deficits and depressive illness through changes in neurotransmitter activity.

Keywords: Maternal stress; Placental CRH; Glucocorticoids; HPA axis; GR and MR; Hyperanxiety

1. Introduction

It is becoming increasingly clear that an interaction between genes and environment determines the functional development of an organism. Because of its rapid growth, the fetus is particularly vulnerable to insults and the attendant changes in its hormonal milieu. The rate of growth is in turn a predictor of developmental outcome. This has led to the suggestion that adverse life situations experienced by the pregnant mother and her reactions to them can induce alterations in the fetal environment and result in deleterious effects on the rate of development, mental and physical health of the child (Maccari et al., 2003; Wadhwa et al., 2001; Weinstock, 2001). The incidence of preterm birth (before 37th week) is increased together with lower birth weight (less than 2.5 kg) (Hedegaard et al., 1993, 1996; Rondo et al., 2003; Ruiz et al., 2002; Stein et al., 1987; Wadhwa et al., 1993). There is also a slower rate of development of walking, speech, toilet training, and attainment of other milestones (Meijer, 1986; Stott, 1973). In turn, low birth weight and preterm delivery have been associated with long-term developmental impairments and motor disabilities (Knoches and Doyle, 1993).

There have also been a number of reports linking maternal stress or antenatal anxiety to the appearance of emotional problems, hyperactivity, and attention deficits

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(Clements, 1992; Linnet et al., 2003; Minde et al., 1968; O'Connor et al., 2003) and Tourette's syndrome (Leckman et al., 1990) in children. In the adult, antenatal stress particularly during mid-gestation has been associated with a higher incidence of schizophrenia (Hultman et al., 1999; Imamura et al., 1999; Van Os and Selten, 1998), depression and drug abuse (Huttunen and Niskanen, 1978; Watson et al., 1999). In these retrospective studies, a causal role of prenatal stress was inferred from interviews with the mothers or answers to questionnaires filled in by them. It was not possible to relate the outcome in the offspring directly to maternal stress since most studies did not control for attendant confounding factors such as concomitant illness, smoking or drug intake (Lobel, 1994). Thus, any direct support for a detrimental effect of prenatal stress on offspring development and behavior has come from experiments in rodents and non-human primates, in which it is easier to control for genetic factors, timing of stress, parity, and the maternal pre- and postnatal environment (Maccari et al., 2003; Weinstock, 1997, 2001). These experimental data have provided a possible hormonal basis for the behavioral alterations induced by maternal stress and have led to the measurement of circulating hormones in pregnant women with high levels of perceived stress during the second and early third trimester. At the same time, more attention has been paid to confounding factors in experimental design and their role in the overall effect on offspring development (Hobel et al., 1999; Wadhwa et al., 1998).

Detailed descriptions of the neuroanatomical and behavioral changes induced by prenatal stress in humans and experimental animals have appeared in previous reviews (Weinstock, 1997, 2001). These have included the factors other than alterations in hormone levels in both the mother and fetus, like autonomic nervous system activity and its influence on placental blood flow that also contribute to changes in the offspring. Evidence in support of a role of glucocorticoids in the development of schizophrenia has been reviewed recently (Koenig et al., 2002). The purpose of the current review is to focus on the similarities and differences in the hormonal changes induced in humans and rodents by gestational stress. It will also discuss critically the evidence that maternal stress hormones influence the regulation of the hypothalamic–pituitary adrenal (HPA) axis and hormone production in the fetus and ultimately, the mental and physical development of the offspring.

2. Organization of the stress response in the adult organism

Stress is defined as a state that threatens or is perceived by the individual to threaten his physiological equilibrium. Such a state results in activation of appropriate central nervous and peripheral systems to prepare the individual for the appropriate responses. In general, the stress response is designed to be of a limited duration and the resulting changes in hormone and neurotransmitter activity are rapidly restored to pre-stress levels within minutes or a few hours. However, when stress is of a chronic nature and the individual fails to adapt to it, prolonged activation of the HPA and sympathetic nervous systems may occur which could induce disorders similar to those that are seen after prenatal glucocorticoid administration. Examples of such disorders are hyperanxiety, depression, diabetes, alcoholism, smoking, and drug abuse (Charmandari et al., 2003; Seckl, 2001), together with alterations in immune competence (Coe et al., 2002). The central components of the system are located in the hypothalamus and brainstem. Corticotrophin-releasing hormone (CRH), the principal regulator of the pituitary adrenal axis, is found in paraventricular nuclei (PVN) of the hypothalamus from which it is released into the portal circulation together with arginine vasopressin (AVP) in response to perceived stress. CRH acts on the anterior pituitary to release adrenocorticotropic hormone (ACTH) and β-endorphin. ACTH and CRH activate the adrenal gland to increase circulating cortisol (corticosterone, CORT in rodents) and catecholamines (Chrousos and Gold, 1992). In this way, behavior, vascular and immune responses in the organism are modulated. The release of CRH and ACTH is controlled via cytosolic glucocorticoid (GR) and mineralocorticoid (MR) receptors, through which cortisol exerts an inhibitory effect. In its neurotransmitter role, CRH activates noradrenergic, serotoninergic, and glutamatergic systems to influence attention, mood, and motor performance (Cole and Robbins, 1992; Makino et al., 2002).

3. Hormonal regulation during gestation (human and experimental animals)

During gestation in primates and rodents, several changes occur in the regulation of the neuroendocrine system designed to protect the developing fetus and ensure successful delivery. These include mechanisms for suppressing the response to stress of the HPA axis, which have so far only been demonstrated in rodents (Neumann, 2003), and plasma binding proteins that prevent the activity of circulating CRH and of glucocorticoids. In humans and some species of apes the placenta releases CRH and other neuropeptides which, through their interaction with those of the HPA axis, modulate the response of the pregnant woman to stress. Noradrenaline (NA), angiotensin II, vasopressin, oxytocin (OXT), PGE_2 and PGF_2 (Florio et al., 2002) release CRH from both the placenta and the hypothalamus. Interleukin 1 (Il1) releases CRH from placental tissue, probably via activation of cyclo-oxygenase and the arachidonic acid–prostaglandin cascade, since its

effect is prevented by non-steroidal anti inflammatory agents (Petraglia et al., 1987, 1996).

The placental content of CRH gradually increases from the seventh to eighth week of gestation in humans (Chan et al., 1993; Goland et al., 1988). Although plasma CRH levels also increase several-fold, the biological activity of the peptide is curtailed by a binding protein (CRH-BP) that is present in plasma and amniotic fluid of humans and apes but not in other species (Bowman et al., 2001). The levels of CRH-BP fall towards the end of pregnancy thereby releasing free CRH and increasing its activity (Perkins et al., 1995). CRH can be detected in the fetal hypothalamus from the 12th week of gestation (Mastorakos and Illias, 2003), but unlike that in the mother, the fetal blood level of CRH does not increase significantly during gestation (Gitau et al., 2004). Circulating ACTH remains relatively unchanged as long as CRH is bound to CRH-BP. Near term, plasma levels of ACTH and β-endorphin increase in humans and other species (Chan et al., 1993; Martin et al., 1977). This could be due to an action of CRH on the placenta, the pituitary, or both and are associated with the initiation of parturition.

In contrast to ACTH and β-endorphin, cortisol levels gradually increase during pregnancy, particularly during the last trimester, reaching 2–3 times the levels found in non-pregnant women (Mastorakos and Illias, 2003). This is partly due to a direct action of CRH on the adrenal cortex. In contrast to its inhibitory action in the brain, cortisol stimulates the release of CRH from the placenta, thereby establishing a positive placental–adrenal feedback loop (Robinson et al., 1988). Fetal plasma levels also increase in parallel to those in the mother but remain about 13-fold lower (Gitau et al., 2001). Although cortisol crosses the placenta from the maternal blood, about 80% is metabolized to cortisone en route. Nevertheless, a rise of 10–20% in maternal plasma cortisol could still cause significant increases in the fetus. At 28 weeks of gestation a high correlation was found between maternal plasma levels of ACTH and β-endorphin but only a small association between ACTH and cortisol (Wadhwa et al., 1996). The former was indicative of the release of ACTH and β-endorphin from a common precursor molecule, pro-opiomelanocortin (POMC), and the latter reflected the normal negative feedback control exerted by cortisol on ACTH release from the pituitary.

Placental CRH is secreted into the fetal circulation and may release hormones from the fetal adrenal, as the CRH type 1 receptor is present in human fetal adrenal tissue from mid-gestation (Smith et al., 1998). However, fetal plasma β-endorphin levels remain essentially unchanged during normal gestation, and unlike those of cortisol, do not appear to correlate with β-endorphin in the maternal blood until labor begins, when both maternal and fetal levels reach their peak (Zivny et al., 1986). The mechanism by which raised CRH initiates labor involves the release of prostaglandins and oxytocin from the placenta. Both of these substances can cause uterine contraction. PGE_2 can also stimulate CRH release from the placenta, thereby initiating a positive feedback control for uterine contraction (Florio et al., 2002).

4. Hormonal response to stress in pregnant humans and their fetuses

4.1. Hormonal responses to acute stress in pregnant mother and fetus

Relatively few studies in human subjects have measured changes in both maternal and fetal hormone levels in response to acute stress. The invasive stress of piercing the fetal abdomen was found to increase levels of cortisol, β-endorphin and NA in the fetal but not in the maternal blood (Giannakoulopoulos et al., 1994; Gitau et al., 2001). Circulating β-endorphin was also increased in the fetus by anoxia (Ruth et al., 1986). This showed that the hormonal changes in the fetus probably do not result from a placental release of CRH into the maternal and fetal blood, but from a response to the stress mounted by the fetal pituitary independent of that in the mother. While this indicates that the fetal HPA can already respond from mid-gestation to stress directed to the fetus itself, experimental data are lacking that the fetal HPA axis can also react to increased concentrations of hormones reaching it from the maternal blood.

4.2. Relationship between high preterm hormone levels and birth weight

In pregnancies terminated by preterm labor, CRH levels were found to be significantly increased in the maternal and umbilical cord blood compared to those in gestational-matched control subjects. A significant association has been reported between preterm delivery and an accelerated rate of increase in plasma CRH during the course of pregnancy (McLean et al., 1995). Plasma CRH levels of more than 90 pM at 26 weeks of gestation had a predictive value for preterm delivery of more than 45% (Inder et al., 2001). In addition to increasing circulating hormones of the HPA axis, maternal stress could impair fetal growth through excess sympatho-adrenal activation resulting in a decrease in uteroplacental perfusion (Cosmi et al., 1990; Myers, 1975).

Wadhwa et al. (1996, 1998) conducted a series of studies to determine whether preterm births and low birth weight were correlated to the degree of perceived maternal stress during gestation. They found that the levels of circulating CRH in the 28–30th week showed a significant negative correlation to the length of gestation. Preterm births were more likely to occur when plasma concentrations of CRH were about double

those in pregnancies that reached full term. The elevated CRH could have resulted from prolonged psychosocial stress, since plasma levels of ACTH and β-endorphin were also higher than normal in the early third trimester of gestation (Wadhwa et al., 1996). The finding of excess levels of peptides also suggests that the usual suppression of HPA axis during gestation can be overcome by prolonged periods of uncontrollable or inescapable stress, resulting in excess maternal hormonal activity. Further support for a role of gestational stress in the etiology of preterm birth comes from the observations that maternal social support, particularly from husbands or partners reduced maternal hormonal levels (Oakley et al., 1990) and the likelihood of this negative outcome in women at risk (Feldman et al., 2000).

4.3. Effect of maternal stress hormones on fetal development

Although a considerable amount of data relates preterm births to maternal stress and elevated CRH, there is much less information regarding an effect of CRH and other stress peptides on neuronal function and integrity in the human fetal brain and their consequences for behavior. High plasma CRH early in the third trimester in association with greater perceived maternal stress was able to suppress the normal habituation of the fetal response to an acoustic stimulus (Sandman et al., 1999). This could have occurred as a result of a direct action of CRH on specific receptors in the fetal amygdala, hippocampus, and limbic cortical areas at a critical stage of development, when they are especially sensitive to the peptide. Alternatively the effect could have been produced by excess cortisol released in the fetus in response to CRH, a view supported by reports of an attenuated startle response in fetuses aged 24–34 weeks after the administration of the synthetic glucocorticoid, betamethasone to the mother (Rotmensch et al., 1999). However, betamethasone could be acting directly on fetal GR or indirectly by stimulating the release of CRH from the placenta. It is only possible to determine the identity of the mediator of these effects in the fetus more precisely by studies in experimental animals.

In addition to CRH and cortisol, adequate levels of β-endorphin appear to be necessary for development of normal motor co-ordination and function. A significant inverse correlation was found between the concentration of β-endorphin in the umbilical cord during labor and the degree of impairment in sensory motor tasks and motor co-ordination in neonates and infants aged 6 and 36 months (Rothenberg et al., 1996). It is not known whether changes in the level of other hormones could have contributed to the effect since they were not determined in this study, neither are there data showing whether β-endorphin was also lower during delivery in the blood of preterm infants that had high circulating CRH during the 28–30th weeks of gestation. Nevertheless, the findings of Rothenberg and his colleagues support data in rats and mice which showed that β-endorphin plays an important role in motor development (Khan and Smith, 1995; Smith and Hughes, 1994).

In view of the difficulty in relating maternal stress to alterations in behavior of human offspring, most of our information has of necessity been obtained from studies in experimental animals. While the experimental studies have led to a greater awareness among clinicians of the possible relevance of maternal stress to changes in the mental health, several important species differences in hormonal regulation in response to stress make it unwise to extrapolate too readily from data in rodents to those in humans. These differences will be referred to in the following sections. Furthermore, unlike guinea pigs, ruminants, and primates, a considerable amount of neuroendocrine and neural development takes place in the postnatal period in rats and they are therefore more sensitive to influences of maternal attention, and postnatal environmental conditions (Matthews, 2002).

5. Hormonal response to stress in pregnant animals and their fetuses

The placenta of humans and some species of apes are unique in their ability to synthesize CRH which could mediate some of the effects of maternal stress on fetal growth and neuronal development. That may be the reason significant reductions in the length of gestation and birth weight in rats were only seen in relatively few studies, and those were usually associated with reduced maternal food intake (Weinstock, 1997, 2001). Severe maternal stress was even reported to increase gestation length while decreasing birth weight of the pups in one study (Rhees and Fleming, 1981). Changes in plasma hormone levels during normal gestation may also be different in humans and rodents, as both CORT and prolactin do not differ during 14–21 days of gestation from those in non-pregnant female rats in contrast to their increase in humans (Neumann et al., 1998; Williams et al., 1999). Circulating ACTH and β-endorphin were reported to be significantly lower on days 17–21 in rats in one study (Williams et al., 1999), but not in the other (Neumann et al., 1998).

In an attempt to mimic in rats the raised circulating levels of CRH seen in stressed pregnant women, the peptide was injected subcutaneously in the mothers on days 14–21 of gestation (Williams et al., 1995). This treatment resulted in a reduction in birth weight and a replication of some of the effects of prenatal stress, including a reduction in anogenital distance, which results from interference by stress hormones in the activity of brain aromatase (Murase, 1994).

5.1. Influence of alterations in maternal circulating hormones on the fetal HPA axis

It has been known since the 1960s that the rat fetal HPA axis can respond to changes in the level of maternal stress hormones and release ACTH and CORT from around day 17 of gestation (Boudouresque et al., 1988). Maternal adrenalectomy was shown to decrease CORT in the fetal circulation, resulting in disinhibition of the HPA axis in the fetus. The resulting increase in the levels of ACTH induced fetal adrenal hypertrophy and greater steroid production (Joffe, 1978). Conversely, administration of ACTH to the mother increased her circulating steroids that suppressed CRH release and ACTH output from the fetal pituitary, resulting in atrophy of the fetal adrenals. Similarly, depending on the dose, administration of corticosteroids to the pregnant rat suppressed both maternal and fetal ACTH output.

GR receptor mRNA can be detected in several areas in the rat brain from day 13, but MR mRNA only appears in the hippocampus on day 16. The amounts of these receptors increase considerably at the time of parturition (Cintra et al., 1993). Thus, changes in maternal steroid levels occurring after day 13 could influence neuronal activity and the function of the HPA axis in the offspring by interacting with GR receptors.

5.2. Response of maternal and fetal HPA axis to acute stress

During the last week of gestation, the rise in plasma concentrations of CORT and ACTH in response to acute stress is smaller in pregnant than in virgin females. However, it is not known if similar systems operate to attenuate the response of the HPA axis to stress in human pregnancy. Attenuation of the response of the HPA axis to stress during pregnancy in the rat may result from a lower number of CRH binding sites in the pituitary (Neumann et al., 1998) and/or a reduction in the normal excitatory effect of endogenous opioids on ACTH secretion (Wigger et al., 1999).

Relatively few studies have measured changes in plasma hormone levels in response to acute or chronic stress in both rat mothers and their fetuses (Erisman et al., 1990; Ohkawa et al., 1991a; Takahashi et al., 1998; Weinstock et al., 1988). While CORT, (Zarrow et al., 1970) and β-endorphin (Sandman and Kastin, 1981) can cross the placental barrier and influence the developing fetal brain, ACTH acts indirectly by increasing circulating maternal adrenal hormones. ACTH and CORT can be detected in the plasma of fetuses in unstressed pregnancies from day 16 of gestation in rats when the fetal HPA axis is active (Boudouresque et al., 1988). Prior to that, as in an experiment performed on day 10 of gestation, plasma ACTH only increased in the maternal blood, while CORT levels rose in both the maternal and fetal circulation (Erisman et al., 1990). Presumably, the latter resulted from the passage of CORT from the maternal circulation. However, when the pregnant rats were stressed on day 20 of gestation, there was an increase in plasma ACTH and CORT in both the mothers and fetuses (Ohkawa et al., 1991a). Thus, the effect of maternal stress on fetal hormone levels depends on the time of its application during gestation in relation to that at which the fetal HPA axis develops, and whether or not the mother adapts to it after repeated exposure (Ohkawa et al., 1991a; Takahashi et al., 1998; Weinstock et al., 1988; Williams et al., 1999). Maternal stress on day 20 also reduced CRH and β-endorphin levels in the hypothalamus and β-endorphin and ACTH in the pituitary, together with NA and dopamine levels in the fetal hypothalamus (Ohkawa et al., 1991b). Additional evidence that the fetal brain can respond to maternal stress was provided by the finding that the expression of CRH mRNA was increased in the fetal PVN in response to maternal restraint on day 15 of gestation (Fujioka et al., 1999).

5.3. Changes in hormone levels in response to chronic maternal stress during gestation in the rat

In contrast to an elevation of plasma CORT of 1–2 h duration in response to a single stress (Ohkawa et al., 1991a; Williams et al., 1999), chronic exposure from day 2 of gestation resulted in maternal and fetal CORT levels that were elevated by more than 30% on day 20, 48 h after the last stressor (Takahashi et al., 1998). This was partly due to the reduction by maternal stress of plasma CORT binding globulin (CBG). The escalating response of the maternal HPA axis to repeated stress in this study probably also resulted from a downregulation of brain GR, which has been shown to occur in non-pregnant rats (Makino et al., 2002), with a consequent reduction in the negative feedback by CORT on CRH and ACTH release. In response to acute stress in pregnant rats, as in humans, fetal plasma CORT levels increased to a much lesser extent than those in the mothers (Ohkawa et al., 1991a), because the enzyme 11β-hydroxysteroid dehydrogenase (11βHSD) catalyzes the conversion of active CORT to inert 11-dehydrocortisone. However, after repeated stress during gestation, maternal and fetal plasma CORT levels were similarly increased and highly correlated 2 days before parturition (Takahashi et al., 1998). Although it was not measured, it is possible that stress may also have reduced the activity of 11βHSD in addition to that of CBG. This suggestion is supported by studies in rats that found a positive correlation between birth weight and activity of placental 11βHSD (Benediktsson et al., 1997). These data suggest that the fetal brain is probably exposed to excessive concentrations of glucocorticoid for much longer periods during chronic maternal stress than after a single episode. The

finding could explain why in human subjects the most significant correlation with infant morbidity and later psychopathology was prolonged psychosocial stress rather a single stressful episode, however unpleasant (O'Connor et al., 2003; Stott, 1973; Wadhwa et al., 2001).

In an attempt to distinguish between responses of male or female fetuses to maternal stress in rats, Ohkawa et al. (1991a,b) found that ACTH increased in maternal plasma to a similar extent in response to forced immobilization on each of days 19–22 of gestation. However, in their male fetuses, levels of the peptide were higher than in controls on days 18–21, while in females, only on days 20 and 21. There was no gender difference in the fall in hypothalamic peptide or catecholamine levels in response to maternal stress measured only on day 20.

6. Effect of prenatal stress or excess steroid exposure on programming of fetal HPA axis

The pioneering work of Thompson (1957) showed that maternal psychological stress in rats could affect the behavior of the offspring and prompted several authors to relate these changes to increases in circulating maternal stress hormones. This was accomplished by manipulating the output from the adrenal gland of the stressed rat by adrenalectomy (Smith et al., 1975) and hormone replacement, or by the administration of stress hormones during gestation and comparing their effects with those that had been reported after gestational stress. In the hormone administration studies, control mothers were injected with saline, a procedure that itself caused significant effects on the behavior and response to stress in the offspring (Drago et al., 1999; Peters, 1982). Since a control, non-injected group was not included in these studies, it is difficult to know how much of the changes were due to the specific hormone injected or to a combination of stress and hormone or an interaction between them. Also if a single hormone, like CORT or dexamethasone was administered, its effects on the offspring may differ from those of maternal stress in which other hormones like β-endorphin that also crosses the placenta could participate.

6.1. Effect of prenatal stress on the regulation of the HPA axis in the offspring

A considerable number of experiments have been performed in rats in an attempt to determine whether prenatal stress (PS) causes permanent alterations in the regulation of the HPA axis. Most of them were confined to male offspring but the results of the experiments are inconsistent, for which there may be several reasons. There were differences in the nature and timing of the stress in relation to the time that the fetal HPA becomes active and in the age of the offspring at which its activity was tested. In some studies, measurements referred only to basal CORT and ACTH levels and in others, to their changes in response of the HPA axis to stress. The discrepancies could also have arisen from the time of day the measurements were made relative to the light cycle under which the rats were maintained. These times were not mentioned in most of the studies. Circadian periodicity of the HPA axis only becomes established in the rat between 21 and 25 days of age (Krieger, 1972). Thereafter CORT levels are highest at the end of the light period. Since PS rats show an earlier peak in the circadian rhythm (Koehl et al., 1999), basal CORT levels would be higher than in controls if measured at this time in rats aged more than 25 days. Table 1 summarizes data on basal and stress-induced activation of the HPA axis in control and prenatally stressed rats aged from 3 to 365 days, taken from experiments in which various forms of maternal stress of differing severity were applied at different times during gestation.

Both CORT and ACTH levels were reported to be higher in PS in rats aged 14 days in one study (Takahashi et al., 1988) but not in another by the same research group (Takahashi et al., 1990). Resting plasma ACTH was higher in PS males at 14 days of age (Takahashi et al., 1988) and in only one other study in 5-month-old rats (McCormick et al., 1995). In response to stress of varying severity, peak CORT levels were only higher in PS than in control males between 3 and 23 days of age. In two out of five studies in older PS males, the only difference from controls was the slower rate of decline in CORT levels. This was associated with a decrease in hippocampal MR and GR (Barbazanges et al., 1996; Henry et al., 1994), testifying to an impairment in the feedback regulation of the HPA axis. In experiments that did not show an effect of prenatal stress on peak CORT levels, the stress to which the rats were subjected resulted in a maximal rise even in controls, thereby precluding the possibility of detecting a greater increase in PS rats (Henry et al., 1994; Szuran et al., 2000; Takahashi et al., 1992). When a milder stress, exposure to the open field, was used to assess the response of the HPA axis in 7-week-old male offspring after once daily administration of dexamethasone (0.05 mg/kg) to the mother, a greater increase was demonstrated in plasma CORT than in controls (Muneoka et al., 1997).

Three out of four studies which compared HPA axis activity in PS male and female offspring found significant differences from controls in PS females but not in males. Basal plasma levels of ACTH or CORT were higher in PS females in which plasma samples were taken on days 14, 60, or 365 days of age (Takahashi et al., 1988; Szuran et al., 2000; Weinstock et al., 1992). The augmented HPA activity in response to stress in the offspring was seen irrespective of the time during gestation or type of stress to which the mother had been subjected (Table 1). The rate of recovery of the HPA axis

Table 1
Effect of different schedules of maternal stress on basal hormone levels and their changes in response to stress in offspring at different ages

Maternal stress	Timing of stress	Offspring parameters when tested		Basal measurement		Response to stress		Reference
		Age (days)	Sex	CORT	ACTH	CORT	ACTH	
3 × daily restraint	Days 14–21	3, 21, 90	M	C = PS, on all days	NT	PS > C at 30 min, 3 and 21 days; PS > C only at 2 h, 90 days	NT	Henry et al. (1994)
Inescapable tail shocks	Every 3 days after mating	14	M and F	PS > C, M and F	PS > C, M and F	PS > C	PS > C	Takahashi et al. (1988)
	From day 1 on alternate days	14	M		PS = C	NT	PS > C	Takahashi et al. (1990)
Saline injections	Day 17 and 19	20	M	PS = C	NT	PS > C F only	NT	Bakker et al. (1998)
	Daily from day 1	23	M	PS = C	NT	PS > C	NT	Peters (1982)
Unpredictable noise	From day 1, 3 times weekly	60–65	M and F	PS > C, F only	NT	PS > C, F only	NT	Weinstock et al. (1992)
Inescapable tail shocks	From day 1, on alternate days	70–90	M	PS = C	PS = C	PS = C	PS = C	Takahashi et al. (1992)
Once daily restraint	From days 13–17	120	M	PS > C	NT	NT	NT	Smythe et al. (1996)
	From days 15–19	150	M and F	PS = C	PS > C M only	PS > C F only	PS > C in F; M, only at later times	McCormick et al. (1995)
	From days 15–19	365	M and F	PS > C, F only	NT	PS = C	NT	Szuran et al. (2000)

PS, prenatally stressed; C, controls. M, males; F, females. NT, not tested.

from stress was slower in PS than in control females, who also had fewer hippocampal glucocorticoid binding sites, indicating impaired feedback regulation (Szuran et al., 2000; Weinstock et al., 1992). The shift in the circadian rhythm of CORT secretion (Koehl et al., 1999) suggests that prenatal stress altered the control exerted by the suprachiasmatic nucleus on the circadian periodicity. Similar shifts in circadian rhythm have been reported in human subjects with depressive disorder (Goodwin et al., 1982).

These data show that it is possible to detect an effect of prenatal stress on the HPA axis of the offspring from the neonatal period throughout the lifespan. It appears to be sufficient to stress the mothers or administer a glucocorticoid on days 15–19 of gestation to cause a long-lasting dysregulation of the response to stress of the HPA axis in the offspring. This coincides with the time at which the fetal HPA axis is able to react to maternal stress. In addition to increasing the response of the HPA axis to acute stress and slowing the rate of its recovery in the offspring, gestational stress impairs their ability to adapt to repeated exposure to the same stressful environment (Fride et al., 1986).

Two different strategies were employed to show that excess maternal CORT secreted in response to stress is responsible for inducing the dysregulation of the offspring HPA axis. In the first, placental 11βHSD was inhibited by daily injection of carbenoxelone from the beginning of gestation, to prevent the inactivation of CORT, thereby allowing higher concentrations to reach the fetus. While this treatment resulted in an increase in basal morning plasma CORT levels in newborn pups and in male offspring aged 6 months, it did not alter the response of the HPA axis to 20 min restraint stress (Welberg et al., 2000). Neither did carbenoxelone produce any significant reduction in GR or MR in the offspring hippocampus. These data on the HPA axis are at variance with those seen in PS male rats in which differences from controls were detected in response to stress but not under resting conditions (Henry et al., 1994; Barbazanges et al., 1996; Dugovic et al., 1999) and in which both MR and GR were reduced at 2 and 6 months of age (Henry et al., 1994; Barbazanges et al., 1996; Maccari et al., 2003). It is possible that the authors failed to detect a significant effect of maternal carbenoxelone treatment on the offspring because their control mothers had received saline injections, which have been shown to alter activity of the HPA axis in the offspring (Peters, 1982; Drago et al., 1999).

In the second strategy, steroid release was prevented in stressed rats by maternal adrenalectomy on day 13 of pregnancy. Normal levels of CORT were provided through implantation of a sustained release pellet. This treatment prevented both the delay in the decline in CORT levels in response to stress and the decrease in MR and GR in the adult male offspring (Barbazanges et al., 1996). Injection of

CORT to the adrenalectomized, stressed mothers in amounts that simulated those reached in response to stress in intact rats reproduced the dysregulation of the HPA axis. While these data provide additional support for the role of excess maternal CORT in the alteration of the activity of the HPA axis in the offspring, they do not entirely preclude the contribution of other hormones in mediating these changes.

7. Evidence linking alterations in behavior induced by prenatal stress to excess maternal hormone release during gestation

7.1. Alterations in activity of CRH in developing brain as a result of maternal or early life stress (human)

A number of anecdotal reports have linked an increased incidence of anxiety and depressive disorders in young adults to high levels of stress experienced by their mothers during pregnancy (Watson et al., 1999). These alterations in behavior could have resulted from increased activity of CRH in the neocortex and central nucleus of the amygdala, two areas that are involved in emotional processing (Owens and Nemeroff, 1991), and/or as a result of impaired regulation of the HPA axis induced by excess cortisol and the resulting alterations in neurotransmitter activity. Evidence in support of HPA axis dysregulation can be found in a significant proportion of patients with generalized anxiety disorders and anxiety-related depression who have abnormal dexamethasone suppression of plasma cortisol, (Holsboer-Trachsler et al., 1991). Depressed subjects have higher concentrations of CRH in the cerebrospinal fluid (Nemeroff et al., 1984), a greater number of neurons expressing CRH, and higher concentrations of CRH mRNA in the PVN at post mortem (Raadsheer et al., 1994, 1995). CRH concentrations are also greater in the cerebrospinal fluid testifying to increased CRH activity in depression. Although early life stress of sexual abuse has been shown to impair the regulation of the HPA axis and predispose to depression (Heim et al., 2000), it is not known whether similar changes can also occur as a result of stress during embryonic development.

7.2. Alterations in activity of CRH in developing brain as a result of maternal or early life stress (experimental animal)

Prenatal stress in rats has been shown to enhance the expression of CRH mRNA in the PVN on day 18 of gestation (Fujioka et al., 1999). Moreover, in the neonatal rat, stress is able to activate interneurons in the hippocampus that release CRH and activate specific receptors eliciting the expression of *Fos* in the amygdala and in CA1 and CA3 pyramidal cells in the hippocampus (Yan et al., 1998). These receptors are also present during fetal life, but decline in the mature animal suggesting they may play a role in the programming of fetal neuronal organization (Avishai-Eliner et al., 2002).

The earliest reports on the effects of prenatal stress on behavior in rodents described increased emotionality in novel and intimidating situations (Archer and Blackman, 1971). Later studies that have been extensively reviewed (Weinstock, 1997, 2001) show that in rats and monkeys, maternal stress induces anxiogenic and depressive-like behavior, characterized by behavioral suppression, learned helplessness and anhedonia. Several independent studies in rats using different methods of maternal stress have reported increased anxiety and behavioral suppression in PS rats in novel intimidating situations like the open field (Fride et al., 1986; Thompson, 1957), elevated plus maze (Fride and Weinstock, 1988; Poltyrev et al., 1996; Vallée et al., 1997; Zimmerberg and Blaskey, 1998) and in the defensive withdrawal test (Ward et al., 2000). Depressive-like behavior and learned helplessness in PS rats has also been replicated in a number of other studies (Alonso et al., 1991; Frye and Wawrzycki, 2003; Morley-Fletcher et al., 2003; Secoli and Teixeira, 1998; Weinstock, 2002). The hyperanxiety of PS was associated with increased plasma CORT levels (Vallée et al., 1997), a reduction in the number of [^{3}H]flunitrazepam, BDZ1 hippocampal binding sites (Fride et al., 1985) and an increase in the levels of CRH in the amygdala (Cratty et al., 1995).

Prenatal stress also results in expansion of the lateral amygdaloid nucleus (Salm et al., 2004). Similar enlargement in the volume of the amygdala has been detected by structural MRI studies in humans with anxiety disorders (Harrison, 2002), but it is not known if this also results from gestational or early life stress. The anxiogenic behavior of PS rats can be selectively reduced by CRH antagonists (Ward et al., 2000) and mimicked by injection of CRH into the amygdala of control rats (Davis, 1992). Clinical data have shown that non-peptide CRH antagonists also have anxiolytic and antidepressant activity (Zobel et al., 2000). These findings provide evidence of a possible association between alterations in hormonal activity as a result of gestational stress in rats and hyperanxiety in the offspring.

7.3. Role of CORT in the etiology of anxiogenic and depressive behavior of PS rats

To my knowledge there do not appear to be any studies that determined whether maternal adrenalectomy with replacement of normal CORT levels could prevent the behavioral changes induced by maternal stress in the offspring. When maternal CORT levels were increased by inhibition of placental 11βHSD with carbenoxelone, the increased expression of CRH mRNA in the PVN was replicated but the behavioral changes in PS rats

were not seen (Welberg et al., 2000). Specifically, maternal carbenoxelone treatment did not result in increased timidity in the open field, hyperanxiety in the elevated plus maze, nor depressive-like behavior in the forced swim test. As mentioned in the previous section, this could have been because the control mothers received daily injections of saline, which has been shown to induce hyperanxiety (Drago et al., 1999) and changes in brain neurotransmitter activity in the offspring (Peters, 1982, 1990).

Some but not all of the alterations in behavior and brain neurotransmitter activity induced by prenatal stress could be mimicked by antenatal injection of glucocorticoids, like dexamethasone that is not metabolized by placental 11βHSD. Failure to obtain such changes may be because: (a) the time that the glucocorticoid was injected during gestation did not coincide with the period that the mother was subjected to stress; (b) measurements were made on the offspring at different ages after the two types of maternal treatment; or (c) other hormones are implicated in their etiology. For example, gestational stress, applied daily throughout pregnancy increased cortical NA levels at 9 and 16, but not at 23, days of age (Peters, 1982), whereas antenatal injection of dexamethasone on days 17, 18, and 19 decreased cortical NA at both 3 and 14 weeks of age (Muneoka et al., 1997). Similarly, cortical 5HT levels in PS rats aged 2–10 days were higher than in controls (Peters, 1990), but neither prenatal stress (Fride and Weinstock, 1987) nor maternal injection of dexamethasone (Muneoka et al., 1997) produced any differences in 5HT levels or turnover in older rats. These data indicate that excess CORT in association with maternal stress appears to alter neurotransmitter activity in the fetus particularly during the period of greatest brain development. The changes in the activity of CRH and other neurotransmitters support the observations of increased anxiety and behavioral depression and suggest that maternal stress hormones may be responsible for programming the relevant neuronal systems.

In addition to hyperanxiety, PS rats show a significant alteration in their analgesic response to morphine (Kinsley et al., 1988), a decrease in brain μ-opioid receptors (Sanchez et al., 1996) and in the opioid component of their exploratory behavior in novel situations (Poltyrev and Weinstock, 1997). The loss of opioid activity in adulthood may have resulted from excess opioid stimulation in the fetus. This could also contribute to the production of enhanced fear and anxiety in PS rats through a lack of adequate opioid inhibition of the anxiogenic effect of CRH in the amygdala (Cratty et al., 1995). These observations prompted us to determine whether blockade of μ-opioid receptors by continuous administration of a low dose of naltrexone delivered to the mother via minipump to obviate the stress of repeated injection could prevent the developmental and behavioral sequelae of prenatal stress. We found that PS rats in the maternal naltrexone-treated group no longer showed hyperanxiety in the plus maze test. Naltrexone treatment also prevented the reduction in anogenital distance in the male neonates that results from an effect of maternal stress on fetal testosterone (Ward and Weisz, 1984), the reduced gain in weight in both sexes (Keshet and Weinstock, 1995). Similar effects on the fetal genital system were produced by opioid administration to the pregnant rat (Zagon and McLaughlin, 1983), confirming a role of excess opioid activity in their genesis. Furthermore, met-enkephalin has been shown to cross the placenta (Zagon et al., 2001) and interfere with growth in the offspring (McLaughlin et al., 2002). The data provide indirect support for the involvement of endogenous opioids in the mediation of some of the developmental and behavioral changes induced by gestational stress.

8. Conclusions

During pregnancy in rats the response of the HPA axis to acute stress is of a smaller magnitude than in non-pregnant animals, probably because of an increased feedback through higher circulating cortisol. Even if there is no increased inhibitory activity on the HPA axis in human pregnancy, glucocorticoids arising in the maternal blood are largely prevented from reaching the fetus through inactivation by placental 11βHSD or by binding to CBG. However, as a result of chronic maternal stress, the feedback regulation of the maternal HPA axis becomes impaired leading to higher circulating levels of cortisol, which in turn, stimulates the release of CRH from the placenta. Raised plasma CRH during 28–30 weeks of gestation predicts the risk for spontaneous preterm births and low birth weight. Excess hormonal activity during gestation may also be responsible for alterations in brain development. This is seen in failure of the fetus to habituate to acoustic stimuli and in the higher incidence of motor disabilities and temperamental difficulties in infants.

In rats, chronic gestational stress increases maternal and fetal plasma CORT, thereby leading to a reduction in GR and MR in the fetal hippocampus and limbic system. This alters the regulation of the HPA axis that can be detected from the age of 3 days to 1 year, testifying to its permanence. Increased activity of CORT and CRH in the developing brain may also alter its synaptic development and neurotransmitter activity resulting in alterations in behavior in adulthood. The hyperanxiety and depressive-like behavior of PS rats can be prevented by CRH receptor antagonists and could result from increased activity of CRH and NA in the amygdala. Such antagonists also have anxiolytic and antidepressant activity in human subjects. If similar alterations occur in the programming of the human fetal brain by

CRH and other stress hormones, they could provide an explanation for the increased incidence of depression and drug addiction that has been reported in association with chronic maternal stress.

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