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## Review

# The long-term behavioural consequences of prenatal stress

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### ABSTRACT

Maternal distress during pregnancy increases plasma levels of cortisol and corticotrophin releasing hormone in the mother and foetus. These may contribute to insulin resistance and behaviour disorders in their offspring that include attention and learning deficits, generalized anxiety and depression. The changes in behaviour, with or independent of alterations in the function of the hypothalamic pituitary adrenal (HPA) axis, can be induced by prenatal stress in laboratory rodents and non-human primates. The appearance of such changes depends on the timing of the maternal stress, its intensity and duration, gender of the offspring and is associated with structural changes in the hippocampus, frontal cortex, amygdala and nucleus accumbens. The dysregulation of the HPA axis and behaviour changes can be prevented by maternal adrenalectomy. However, only the increased anxiety and alterations in HPA axis are re-instated by maternal injection of corticosterone. *Conclusion:* Excess circulating maternal stress hormones alter the programming of foetal neurons, and together with genetic factors, the postnatal environment and quality of maternal attention, determine the behaviour of the offspring.

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## 1. Introduction

Most of our information about the long-term effects on the offspring of human mothers subjected to prolonged emotional disturbance and distress during pregnancy has, of necessity, been obtained from retrospective studies. Such distress can result from natural or man-made disasters like earthquakes, floods, freezing storms, war or terrorist acts, as well as from chronic interpersonal tensions or adverse conditions in the home or workplace. These studies have linked maternal gestational stress to evidence mild impairment of intellectual activity and language development in their children (Brouwers et al., 2001; Watson et al., 1999). Other behaviour disorders reported in the offspring include attention deficits, schizophrenia, anxiety and depression, and have been described fully in earlier reviews (Koenig et al., 2002; Kofman, 2002; Weinstock, 1997, 2001).

More recent prospective studies have examined the presence of self-reported maternal anxiety, rather than direct evidence of psychological stress at different periods of pregnancy, on behaviour in their infants and children. Such infants were more irritable and showed a higher incidence of sleeping and feeding problems than those of non-anxious mothers (de Weerth et al., 2003; Huizink et al., 2002). The children and adolescents of such mothers were more likely to show emotional problems, hyperactivity and attention deficits, resulting in lower school grades (Beversdorf et al., 2005; de Weerth et al., 2003; DiPietro et al., 2006; Glover et al., 2004; Gutteling et al., 2006; Huizink et al., 2002; Laplante et al., 2004; Linnert et al., 2003; Niederhofer and Reiter, 2004; Van den Bergh et al., 2005; Wurmser et al., 2006).

In general the design of the studies could not enable one to rule out a contribution made by a genetic component of anxiety or of an adverse postnatal environment to the infant behaviour. Such a differentiation between genetic and postnatal factors is more easily obtained from studies performed in experimental animals. These have the advantage of being able to control the timing, intensity and duration of stress exposure and evaluate the interaction of the mother with her offspring in a controlled environment. Many, but not all of them have demonstrated long-term effects of prenatal stress on offspring behaviour. The discrepancies probably result from the species and strain of animal used in the tests, the duration and intensity of the stress and when during pregnancy it occurred in relation to foetal development. In this context it should be remembered that in contrast to primates and guinea pigs, a considerable amount of neuroendocrine and neural development occurs in the rat and mouse brain after birth, making it more sensitive to environmental conditions and maternal attention (Matthews, 2002), which can contribute to the overall effect of prenatal stress on offspring behaviour. This review will discuss the more recent findings concerning these behavioural alterations in humans and experimental animals, together with what is known about the morphological, neurophysiological and neurochemical changes underlying them.

## 2. Increase in circulating hormones during gestational stress

Maternal stress could affect foetal development by exposure to stress hormones that are transported through the placenta. In addition, stress may suppress the developing immune system which could account for the higher incidence of respiratory and other infections in the infants (Stott, 1973). Stress hormones reaching the foetal brain from the maternal circulation include catecholamines, CRH and adrenal steroids. Maternal stress has also been shown to constrict the placental arteries thereby reducing foetal blood flow and the supply of essential nutrients and oxygen (Myers, 1975) which could also compromise its development and function.

CRH is released from the human placenta and can induce the release of glucocorticoids from the foetal adrenal by activating CRH type 1 receptor that is present from mid-gestation (Smith et al., 1998). For a more detailed account of hormones released during maternal stress see Weinstock (2005).

Glucocorticoids act predominantly via two intracellular receptors, glucocorticoid (GR) and mineralocorticoid (MR), with low and high affinity respectively, which function as ligand-activated transcription factors (De Kloet et al., 1998). GRs are activated as levels of glucocorticoids increase either by stress or during the appropriate period of the circadian rhythm (morning in humans, afternoon and evening in rodents). GRs are found everywhere in the brain including the frontal and cingulate cortex, hippocampus, basolateral and basomedial nuclei of the amygdala, accumbens and thalamus, but are most abundant in hypothalamic CRH neurons and pituitary where they serve as a means to regulate negative feedback of CRH release. MRs are found in highest concentrations in the hippocampus and may therefore be involved in the regulation of learning and memory (De Kloet et al., 1998).

### 2.1. Human subjects

In human pregnancy, plasma CRH levels increase several-fold during the last semester but the peptide remains inactive as long as it is attached to a binding protein (CRH-BP), thereby protecting the foetus from exposure to abnormal increases in maternal CRH (Perkins et al., 1995). The levels of the binding protein fall near term thereby increasing free circulating CRH which can release ACTH and  $\beta$ -endorphin from the maternal and foetal hypothalamic pituitary adrenal (HPA) axis (Chan et al., 1993; Martin et al., 1977). Plasma CRH, ACTH and  $\beta$ -endorphin are elevated in the early third trimester of gestation in women reporting high levels of perceived stress at unspecified times during pregnancy (Wadhwa et al., 1996; Weinstock, 2005). This suggests that the usual mechanisms for suppressing the HPA axis during gestation and preventing the abnormal increase in free CRH are overcome by prolonged periods of uncontrollable stress resulting in excess hormone levels. Circulating levels of cortisol also gradually increase during a normal pregnancy reaching 2–3 times higher concentrations in the last trimester than those in non-pregnant women (Mastorakos and Ilias, 2003). Cortisol levels also rise in foetal plasma but the

concentrations remain about 13-fold lower than in the mother (Gitau et al., 2001) because about 80% is metabolized by 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD)-2 to inactive cortisone in the placenta. It is possible that as in experimental animals prolonged stress may decrease the activity of 11 $\beta$ -HSD or levels of cortisol binding globulin (CBG) resulting in exposure of the foetus to excessive amounts of the steroid. However, there is no direct evidence from human studies to support such a suggestion. The effect of hormonal elevation on the foetuses of stressed mothers was shown in a number of studies that reported alterations in heart rate variability and movements (reviewed in Van den Bergh et al., 2005). Others related high circulating levels of CRH in stressed mothers to a deficit in the adaptation of the foetus to an acoustic stimulus (Sandman et al., 1999), implying a possible action on specific receptors in the foetal amygdala, hippocampal and limbic cortical areas.

## 2.2. Experimental animals

Unlike primates, other experimental animals do not have CRH in the placenta. Nevertheless maternal stress was found to increase levels of other circulating stress hormones both in the mother and foetuses of rodents and non-human primates. These include cortisol (Schneider et al., 2002) in monkeys, corticosterone (COR) (Takahashi et al., 1998; Ward and Weisz, 1984; Weinstock et al., 1988; Williams et al., 1999), ACTH and aldosterone (Williams et al., 1999) and catecholamines (Rohde et al., 1989) in rats. Repeated stress in pregnant rats during days 14–21 of gestation elevated maternal circulating COR for much longer than a single stress episode (Takahashi et al., 1998). Since chronic stress also reduced plasma levels of CBG (Takahashi et al., 1998), the foetal brain was probably exposed to free COR for longer periods of time. COR and other hormones could then have produced alterations in its structure and function depending on the hormone and the amount and time of elevation in relation to the appearance of particular neural and endocrine systems and of steroid and catecholamine receptors.

## 3. Maternal stress, birth weight and its relation to offspring pathology

### 3.1. Human subjects

Many studies that attempted to relate the influence of the prenatal environment to the health of the offspring have focused on a reduction in gestational age and birth weight. These can be altered by maternal stress hormones but also by levels of available nutrients and oxygen (Cosmi et al., 1990). Pre-term births have been associated with an accelerated increase in CRH levels in the maternal and umbilical cord blood (McLean et al., 1995). Wadhwa et al. (1996, 1998) found that the levels of circulating CRH in the 28–30th week showed a significant negative correlation to the length of gestation. Pre-term births were more likely to occur when plasma concentrations of CRH were about double than those in pregnancies that reached full term. Subsequent studies used low birth weight and gestational age as indirect indicators of maternal stress and found a higher incidence of emotional problems, anxiety, depressive symptoms and learning difficulties in these children than in those of normal birth weight (Rice et al., 2007).

Attempts to relate the timing of the gestational stress to emotional problems in the offspring revealed that these were more likely to appear if maternal stress occurred during late gestation (O'Connor et al., 2002, 2003), when the brain undergoes rapid growth and is particularly susceptible to reduction in oxygen and nutrients. On the other hand, deficits in cognitive functioning in toddlers and adolescents were related to maternal anxiety at 12–

22 weeks of pregnancy (Van den Bergh and Marcoen, 2004; Laplante et al., 2004), when the brain is susceptible to alterations in its programming because it undergoes a cascade of timed processes of neuron proliferation, migration and early differentiation.

Epidemiological evidence has also shown a negative relation between infant birth weight and insulin resistance and type 2 diabetes in adulthood (Barker, 2003; Eriksson et al., 2003; Jaquet et al., 2003). It was hypothesized that predisposition to diabetes results from foetal exposure to high levels of glucocorticoids and intra uterine growth restriction. Indirect support for this suggestion was found in the inverse relation between birth weight and fasting cortisol in men aged 65 (Phillips and Jones, 2006). Other studies have shown a higher incidence of syndrome X comprising diabetes, hypertension and hyperlipidemia in low birth weight infants (Barker et al., 1993). More detailed accounts of the role of maternal glucocorticoid excess in foetal growth retardation and physiological changes in the offspring can be found in (Barker, 2003; Seckl, 2004).

### 3.2. Experimental animals

The majority of studies on the effect of maternal stress in rats or mice did not report data on the length of gestation or birth weight. In contrast to humans, in most of the other studies in which such data were included, prenatal stress did not affect either the number of pups in the litter or their birth weights after a variety of stressors (Chung et al., 2005; Keshet and Weinstock, 1995; Poltyrev et al., 1996; Smith et al., 2004; Takahashi et al., 1998; Van den Hove et al., 2005; Ward et al., 2000). Very severe stress of immobilization and heat reduced birth weight but this may have been due a decrease in maternal food intake (Kinsley and Svare, 1986).

Recently, an attempt was made to see whether evidence of alterations in glucose or insulin homeostasis could be obtained in the male offspring of rats stressed by immobilization either during the first, second or third week of gestation. While the maternal stress markedly increased maternal COR levels, it had no effect on birth weight basal glucose or insulin levels or those after a glucose tolerance test in 120 day old offspring (D'Mello and Liu, 2006). By contrast, juvenile or adult male offspring of rats injected with dexamethasone during the last week of pregnancy showed reduced birth weight and severe hepatic insulin resistance (Buhl et al., 2007; Nyirenda et al., 1998). Unlike COR, dexamethasone is not metabolized by placental 11  $\beta$ HSD-2, therefore the foetuses in the latter study could have been exposed to much higher concentrations of the glucocorticoid than after maternal stress, resulting in effects on the liver as well as on the developing HPA axis.

## 4. Alterations in the reactivity of the HPA axis as a result of gestational stress

### 4.1. Development of the HPA axis

The development and maturation of the HPA axis relative to birth is species specific (Dobbing and Sands, 1979). In primates, ruminants and guinea pigs maximal brain growth and a large proportion of neuroendocrine development takes place before birth, but in rats, mice and rabbits much of this occurs during the early postnatal period. In the human, GR and MRs are present in the hippocampus at 24 weeks of gestation (Noorlander et al., 2006). In the rat, GR mRNA can be detected in the hippocampus, hypothalamus and pituitary from day 13 of gestation (Cintra et al., 1993) and increases rapidly after birth. On the other hand, MR mRNA appears in the hippocampus only on day 16 of gestation (Diaz et al., 1998). In the mouse, MR mRNA is first detected on day

**Table 1**

List of the various types of maternal and offspring stress used in rats and mice

Number	Stress
<b>Maternal</b>	
1	20 min restraint, once daily
2	30 min restraint, once daily
3	30 min restraint, 3 times daily
4	45 min restraint, once daily
5	45 min restraint, 3 times daily
6	60 min restraint, 3 times daily
7	90 min restraint, variable times
8	6 h restraint daily
9	120 min immobility (rat limbs were taped to a platform)
10	Footshocks, day 1–21, every other day for 100 min
11	20–30 min intermittent footshocks
12	Noise, 95 db and flashing lights for 4 h, thrice weekly on random basis
13	Intermittent noise 90 db for 15 min, once daily
14	Forced swimming for 15 min accompanied by the noise (77 dB) every minute, once daily
15	Variable stress: exposure to one two or three conditions daily consisting of restraint for 1 h: exposure to cold (4 °C) for 6 h; overnight food deprivation; 15 min swim at room temperature; light for 24 h and overcrowded housing condition during dark phase of cycle
16	Randomized stress: each day, dams were exposed to one of three types of stress: restraint stress (three 45 min sessions); foot shock stress (one 30 min session of two randomized foot shocks); injection stress (one 0.5 cc sc saline injection)
<b>Offspring</b>	
i	Maternal separation for 30 min
ii	30 or 120 min exposure to novelty
iii	20 min restraint
iv	30 min restraint
v	45 min mild footshock
vi	5 min in open field
vii	20 min active avoidance

15.5 of gestation but GR mRNA appears on postnatal day 5 (Noorlander et al., 2006). The paraventricular nucleus (PVN) develops in the rat between days 13 and 15 and is able to react to maternal COR on day 15 of gestation (Fujioka et al., 1999, 2003). In the guinea pig, GR and MR mRNAs are present in the PVN, cortex and hippocampus by gestational day 40 (term 70 days) (Kapoor et al., 2006). GRs increase dramatically between days 40 and 50 in the hippocampus and cortex, but MRs decrease (Matthews, 2002). These species differences should be taken into consideration when comparing the effects of the timing of gestational stress on the regulation of the HPA axis and on alterations in foetal neuroplasticity due to actions of stress hormones.

#### 4.2. Human subjects

In a number of studies in human subjects, high levels of maternal anxiety have been used as an indirect indicator of the presence of chronic stress. In the 10-year old offspring of such mothers a significant correlation was found between the degree of maternal anxiety and waking levels of plasma cortisol (O'Connor et al., 2005). In another prospective study, self reported anxiety at 12–22 weeks of pregnancy was associated with a lower than normal cortisol output on awakening but higher than expected secretion in the evening in 15-year-old male and female offspring. In the girls only, the altered profile of diurnal cortisol was correlated with depressive symptoms. Maternal anxiety between 23 and 31 or 32 and 40 weeks of pregnancy had no effect on diurnal cortisol in the offspring (Van den Bergh et al., 2007). This appears to be the first study to relate prenatal anxiety during a defined period of pregnancy to alterations in the regulation of the HPA axis in the adolescent children. Since hippocampal mRNA of MR and GRs in human fetuses were only measured from the age of 24 weeks (Noorlander et al., 2006), we do not know whether the receptors are present before that date. However, the selective effect of maternal anxiety at 12–22 weeks of pregnancy on the regulation of the circadian rhythm of cortisol in the

offspring suggests that excess maternal stress hormones could well interfere with the normal development and activity of MRs. It also suggests that such hormones may cause less or no disruption in programming once the regulation of the circadian rhythm in the foetus is fully developed and accords with the finding in guinea pigs described in Section 4.2. The foregoing data imply that the alterations in the programming of the foetal HPA axis may arise at an earlier time during gestation than those responsible for the increase in emotional behaviour. The latter were associated with maternal stress or anxiety that occurred in the last trimester, as mentioned in Section 3.1.

The regulation of the feedback response to stress of the HPA axis is mediated via GRs, which also appears to be altered by prenatal stress. This was shown in teen-aged male twins of low birth weight in whom acute psychological stress caused a greater increase in salivary COR that remained elevated for a longer time than in those of normal birth weight (Wust et al., 2005). Previous reports had shown an association between low birth weight and raised levels of CRH due to maternal stress during the 26th week of gestation (Inder et al., 2001; Weinstock, 2005). The increase in response of the HPA axis to psychological stress in the boys correlated significantly with low birth weight but not with maternal age, parity or mode of delivery. More data are needed to show whether there is a clear relation between the presence of maternal stress at a defined period during pregnancy and an increase in and/or prolongation of the response of the HPA axis to a psychological stressor in their offspring.

#### 4.3. Rats and mice

While most studies in rats did not find differences in basal morning resting levels of plasma COR in adults as a result of prenatal stress (Weinstock, 2005), prenatally stressed (PS) rats of both sexes were shown to secrete higher amounts than controls of total and free COR at the end of the light period, while PS females

**Table 2**  
Effect of prenatal stress on the activation of the HPA axis to stress and steroid receptor binding

Species/strain	Reference	Maternal stress	Days in gestation	Offspring		Plasma COR in Males			Plasma COR in Females			
				Age	Stress	Peak (min)	Duration (min)	MR, GR	Peak (min)	Duration (min)	MR, GR	
<b>Rats</b>												
Wistar	Henry et al. (1994)	(5)	14–21	3 d	(i)	↑ (30)	NT	=	NT	NT	NT	
		(5)	14–21	21 d	(ii)	↑ (30)	NT	MR ↓GR ↓	NT	NT	NT	
		(5)	14–21	3 mo	(ii)	=	↑ (120)	MR ↓GR ↓	NT	NT	NT	
Sprague–Dawley	Maccari et al. (2003)	(5)	11–21	4–7 mo	(iv)	= (30)	↑ (120)	MR ↓	NT	NT	NT	
Sprague–Dawley	Vallee et al. (1997)	(5)	15–21	4 mo	(iv)	= (30)	↑ (120)	NT	NT	NT	NT	
Sprague–Dawley	Poltyrev et al. (2005)	(5)	14–21	3 Mo	(ii)	= (30)	↑ (120)	NT	= (30)	↑ (120)	NT	
CD	Richardson et al. (2006) <sup>a,b</sup>	(5)	14–21	Adult	(v) <sup>c</sup>	↓ (30)	= (120)	=GR <sup>d</sup> , ↑GR <sup>e</sup>	= (30)	↑ (120)	=GR <sup>d</sup> , =GR <sup>e</sup>	
		(16)	14–21	Adult	(v) <sup>c</sup>	= (30)	= (120)	=GR <sup>d</sup> , =GR <sup>e</sup>	= (30)	= (120)	=GR <sup>d</sup> , =GR <sup>e</sup>	
Fisher 344	Van den Hove et al. (2005)	(5)	14–21	6 mo	(iii)	↓ (30)	NT	NT	NT	NT	NT	
Sabra	Weinstock et al. (1992)	(12)	1–21	6 mo	(vi)	= (15)	= (90)	GR =	= (15)	↑ (120)	GR ↓	
Sprague–Dawley	Weinstock et al. (1998) <sup>b</sup>	(12)	1–21	4–4.5 mo	(v)	↑ (20)	= (90)	NT	NT	NT	NT	
Long–Evans	McCormick et al. (1995) <sup>b</sup>	(1)	15–19	5 mo	(iii)	=	=	GR ↓ <sup>f</sup>	↑ (20)	↑ (20)	GR ↓ <sup>f</sup>	
Sprague–Dawley	Fujioka et al. (2001)	(2)	15–17	3–4 mo	(vii)	= (30)	= (120)	NT	NT	NT	NT	
Wistar	Cannizzaro et al. (2006)	(9)	16	47 d	(v)	↓ (30)	NT	NT	NT	NT	NT	
Sprague–Dawley	Koenig et al. (2005)	(16)	7–13	56 d	(iv)	= (30)	= (150)	NT	NT	NT	NT	
Sprague–Dawley	Koenig et al. (2005)	(15)	14–21	56 d	(iv)	= (30)	↑ (150)	NT	NT	NT	NT	
<b>Mice</b>												
C57bl/6J	Ishiwata et al. (2005)	(5)	15–21	21d	(iv)	↑ (45)	NT	NT	NT	NT	NT	
ICR	Chung et al. (2005)	(8)	8.5–19.5	50–63 d	(iv)	= (30)	↑ (60)	GR ↓ <sup>g</sup> MR =	NT	NT	NT	

Maternal and offspring stress, as in Table 1.

<sup>a</sup> Females were all in diestrous.

<sup>b</sup> Measured by an indwelling catheter.

<sup>c</sup> Mild footshock 45 min.

<sup>d</sup> Immunoreactivity in dentate gyrus, hippocampus (not binding).

<sup>e</sup> Immunoreactivity in CA<sub>1/2</sub>, hippocampus.

<sup>f</sup> Amygdala.

<sup>g</sup> GR protein levels ↓ in hippocampus, hypothalamus and amygdala.

↑, Higher in PS than in control; ↓, lower in PS than in control; =, no difference between PS and controls; NT, not tested.

secreted more COR over the whole diurnal cycle (Koehl et al., 1999). The majority of studies on the effect of prenatal stress on the response of the HPA axis to subsequent stress in the offspring has been performed in rats that had been stressed by a variety of stressors during the last week of gestation (Table 1). These range from a single session of immobilization for 2 h on day 16 of gestation (Cannizzaro et al., 2006), to restraint for 20 or 30 min once (McCormick et al., 1995; Fujioka et al., 2001) or thrice daily for 45 min on days 11 or 14–21 (Maccari et al., 2003; Henry et al., 1994). Two studies stressed the mothers three times weekly throughout gestation (Weinstock et al., 1992, 1998) or starting during the second week (Koenig et al., 2005; Chung et al., 2005) using unpredictable noise or varied forms of stress.

In male rat and mouse offspring it was only possible to detect an increase in the peak concentration of plasma COR when the stress induced a sub maximal increase in controls (Henry et al., 1994; Ishiwata et al., 2005; Weinstock et al., 1998). Abnormal feedback regulation of the HPA axis was found in the males born to rats and mice that had been subjected to thrice daily restraint or chronic variable stress during the last week of gestation, and was associated with down-regulation of MR and GR receptors (Chung et al., 2005; Henry et al., 1994; Koenig et al., 2005; Maccari et al., 2003) (Table 2). To my knowledge, only one study compared the effect of maternal stress during the second and third week on the regulation of the HPA axis in adult male offspring. A difference from control rats was found only if maternal stress occurred during the third week of gestation when both MR and GR are present (Koenig et al., 2005). Offspring of rats stressed on days 15–17 of gestation did not differ from controls in their stress response (Fujioka et al., 2001), while those whose mothers were stressed

only on day 16, showed a smaller increase than controls in plasma COR (Cannizzaro et al., 2006). In three studies, maternal stress of shorter duration or intensity produced an increase in HPA axis activation only in their female offspring (McCormick et al., 1995; Richardson et al., 2006; Weinstock et al., 1992).

Taken together, the data from studies in rats and mice indicate that alterations are only seen in programming of the HPA axis of the offspring if the maternal stress is of sufficient intensity, and is administered at least once daily between days 14 and 21 of gestation or beginning before that date. The HPA axis in female rats appears to be more sensitive than that of males to the disrupting effects of gestational stress on its regulation. There may also be a genetic component that can determine the sensitivity of the developing HPA axis to stress, as indicated by the difference in response of rats from the CD and Fischer strains from those of other strains to the same maternal stress regime (Table 2).

#### 4.4. Other species

In guinea pigs the influence of maternal stress on the offspring HPA axis was also found to be highly dependent on the stage of gestation that it occurred. When stress consisting of high frequency strobe light was applied for 2 h 3 times daily on gestational days 50–52, but not on days 60–62, the adult offspring exhibited higher basal adrenocortical activity as measured from COR levels obtained with a chronic indwelling catheter (Kapoor et al., 2006). This is consistent with an effect of maternal stress on the developing HPA axis at a time when MR and GR appear but not when the axis is already fully developed.

In the juvenile offspring of rhesus monkeys, stressed daily in mid gestation from day 90 to 145 of gestation (Clarke et al., 1994), or early gestation (day 45–90) (Schneider et al., 2002), both basal plasma levels of ACTH and cortisol and the increase in response to stress was higher than in controls. It is not known when GR and MR appear in this species.

#### 4.5. Putative mechanisms of altered regulation of HPA axis by prenatal stress

PS rats have a higher number of Fos-IR neurons in the hippocampus and locus coeruleus (Viltart et al., 2006) and greater noradrenaline turnover in this brain area (Huttunen, 1971; Takahashi et al., 1992) which could cause the reduction in MR and GR binding in the hippocampus (Maccari et al., 1992). After exposure to a relatively mild stress, Fos expression increased in the locus coeruleus and hippocampus in control but not in PS rats which had already shown maximal activity under basal conditions. This suggests that increased neuronal activity in the locus coeruleus may contribute to the deficit in the feedback mechanism controlling the HPA axis in PS rats.

The prefrontal cortex (PFC) is known to play an important role in the regulation of emotion and in the integration of affective states by modulating the activity of the neuroendocrine system (Sullivan, 2004). A greater release of dopamine in the PFC may alter the behavioural and physiological response to stress (Spencer et al., 2004). In the rat, the right PFC is normally dominant in the activation of stress-related systems, while the left plays a role in countering this activation through inter-hemispheric inhibition. The finding that there is a reduction in inter-hemispheric coupling in PS rats (Fride and Weinstock, 1987) and a higher dopamine release in the right PFC (Fride and Weinstock, 1988) could also contribute to their greater HPA activation in response to stress.

## 5. Prenatal stress, HPA axis dysregulation and depressive disorder

### 5.1. Human subjects

Psychological stress or perceived threat activates neuronal circuits in the cortex and limbic system to induce an appropriate response. Disruption of forebrain limbic circuits that could occur through alterations in their programming during development has been proposed to explain affective and anxiety disorders (Ehler et al., 2001). Such disorders are often associated with hyperactivity of the HPA axis. Their recovery either spontaneously or after treatment with antidepressants is accompanied by reversal of the abnormality in the control of the HPA axis (Holsboer, 2000; Nikisch et al., 2005).

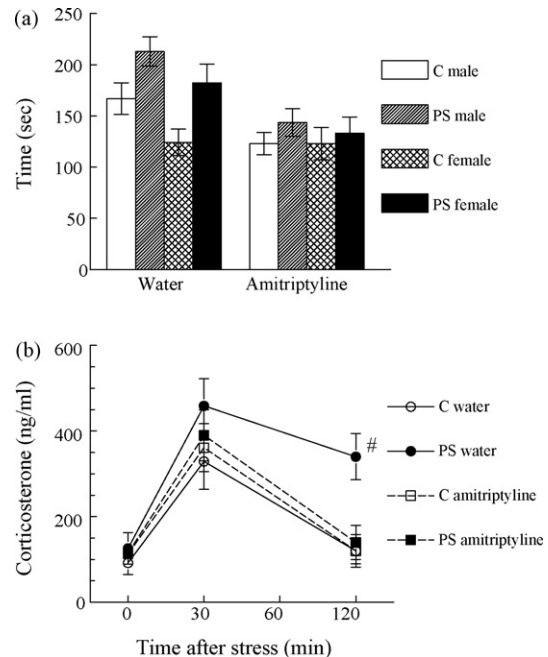
A higher incidence of major depression than in aged matched controls was reported in young men and women whose mothers had been exposed to a major earthquake, thereby providing a further link between prenatal stress and affective disorder (Watson et al., 1999). However, no significant difference was detected in this study in the incidence of depression in relation to the trimester of pregnancy in which the stress occurred. Although the activity of the HPA axis was not assessed in these individuals, a body of circumstantial evidence supports the suggestion that its regulation is impaired in humans with major depression. Total 24 h concentrations of free cortisol are significantly higher in those with depression than in normal subjects (Deuschle et al., 1998; Wong et al., 2000) and the increase in response to stress is greater and prolonged (Burke et al., 2005). A significant proportion of depressed subjects show a decrease in dexamethasone suppression of plasma cortisol indicating down-regulation of their GR receptors (Holsboer-Trachsler et al., 1991). It is possible that

depression and dysregulation of the HPA axis could occur independently of each other if the time of stress exposure coincided only with the development of the limbic system, 7th to 11th week, or of the HPA axes, 5th and 7th week respectively (Bayer et al., 1993), or together, if the duration of the stress is long enough to affect both systems. Such a separation between an effect of maternal stress on the offspring HPA axis and on behaviour was suggested in previous sections of this review.

### 5.2. Depressive-like behaviour in rats and mice

The core symptoms of clinical depression involve changes in mood which cannot be assessed in animals. However, behavioural parameters clearly related to human depression, such as loss of active coping, social withdrawal, and inability to feel pleasure (anhedonia) can be measured under appropriate conditions. Loss of coping or immobility is seen in the development of learned helplessness and can be induced by inescapable stress in the forced swim test (Porsolt et al., 1978). Prenatal stress in rats and mice increases the duration of immobility in this test, and this is more evident in females than in males (Alonso et al., 1991, 2000; Frye and Wawrzycki, 2003). Furthermore, PS females are more likely than males to show anhedonia, indicated by a decrease in saccharin preference (Keshet and Weinstock, 1995).

Induction of depressive-like behaviour by prenatal stress was associated with an alteration in the reactivity of the HPA axis in two studies in which the mothers were stressed daily during the last week of gestation (Morley-Fletcher et al., 2003; Poltyrev et al., 2005). Like depressed patients, PS rats showed a phase shift in circadian rhythm of cortisol secretion and sleep function (Maccari et al., 2003) and increased amounts of paradoxical sleep that are positively correlated to their plasma COR levels (Dugovic et al.,



**Fig. 1.** Effect of chronic treatment with amitriptyline on depressive-like behaviour, and the response of the HPA axis to stress PS rats. (a) Selective reduction by amitriptyline in PS rats of duration of immobility in forced swim test. Amitriptyline was given orally at a dose of 4.5 mg/kg/day for 3 weeks from the age of 6 weeks. Rats were tested at the age of 9 weeks. ANOVA for gender ( $F_{1,85} = 5.02$ ,  $P < 0.05$ ); Maternal treatment (stress or control) ( $F_{1,85} = 6.4$ ,  $P < 0.025$ ); Offspring treatment amitriptyline or water ( $F_{1,85} = 12.7$ ,  $P < 0.001$ ); Maternal  $\times$  Offspring treatment interaction ( $F_{1,85} = 4.46$ ,  $P < 0.05$ ). No Gender  $\times$  Maternal treatment interaction  $P = 0.1$ . (b) Prevention by amitriptyline of prolonged release of COR in response to novelty stress in PS female rats. These rats were litter mates of those used in the forced swim test. #Significantly different from all other groups  $P < 0.05$ .

1999). We found that chronic treatment of prepubertal PS rats but not controls with the antidepressant, amitriptyline prevented both the depressive like behaviour in the forced swim test and HPA axis dysregulation in adulthood (Fig. 1), as shown in human subjects with depression. In another study, the depressive-like behaviour of PS males was associated with a decrease in MR and GR binding capacities in the hippocampus and an increase 5HT1A mRNA in the frontal cortex. Chronic treatment of adult PS rats with imipramine for 3 weeks abolished the depressive-like behaviour and restored glucocorticoid binding and 5HT1A mRNA to control levels (Morley-Fletcher et al., 2004).

These data show that like in humans, the depressive-like behaviour appears to be associated with down-regulation of GRs and dysregulation of the HPA axis and these can be restored to normal by treatment with antidepressants. While the data demonstrate a possible role of prenatal stress in the aetiology of depressive behaviour, genetic factors are also important. Thus, in contrast to the findings in Sprague–Dawley and Wistar rats, thrice daily maternal restraint stress did not induce anxiety or depressive-like behaviour in rats of the Lewis or Fisher strains (Stohr et al., 1998; Van den Hove et al., 2005). Moreover, other studies have used these inbred strains to demonstrate a complete dissociation between the reactivity of the HPA axis to stress and the behaviour (Solberg et al., 2003; Stohr et al., 2000).

## 6. Prenatal stress, anxiety and impaired coping in adversity

Maternal stress has been associated with poor coping behaviour under adversity (Meijer, 1985) that is also seen in autistic children who also secrete more cortisol in response to psychological stress than normal children (Corbett et al., 2006). Prenatal stress may induce a chronic anxiety state in adult humans (Ward, 1991), although data from prospective studies are lacking. Another study found a significant relation between maternal anxiety during 12–22 weeks, but not at 32–40 weeks of gestation and self-reported anxiety in their 8–9-year-old children (Van den Bergh and Marcoen, 2004). By contrast, others (O'Connor et al., 2002, 2003; Davis et al., 2007) found that stress during late gestation was a better predictor of fearful temperament and anxiety in the infants and children. The difference in the effect of the timing of maternal

stress from that in the study by Van den Bergh and Marcoen (2004) was found even though it was assessed in a similar manner by questionnaires that measured state and trait anxiety (O'Connor et al., 2002), or also by increases in salivary cortisol (Davis et al., 2007). More studies are needed using larger numbers of pregnant women and their children to clarify the effect of timing of the stress, as well as postnatal care on the behavioural outcome.

### 6.1. Rats and mice

An anxiety state has been modelled in experimental animals in tests involving fear-like reactions, which can be elicited in unfamiliar open spaces like the “open field” or in the elevated plus maze (EPM) and are accompanied by COR release. The EPM has two open and two closed arms presenting the rat with a conflict between the desire to explore a novel situation and its fear of height and open spaces (Handley and Mithani, 1984). Several studies showed that the male and female offspring of rats stressed either throughout gestation (Estanislau and Morato, 2005; Fride and Weinstock, 1988), or by restraint 3 times daily from days 17 to 21 (Murmur et al., 2006; Vallee et al., 1997) spent less time than controls in the open arms of the EPM (Table 3) indicating higher levels of anxiety. PS rats were also more anxious than controls in a novel environment like a brightly lit open field (Dickerson et al., 2005; Poltyrev et al., 1996; Ward et al., 2000) or in the cage emergence test (Van den Hove et al., 2005). However, no difference in the behaviour of PS and control males were found in the EPM test when mothers were restrained only once daily for 45 min (Zagron and Weinstock, 2006), or when the test was carried out in bright light, thereby greatly reducing the time spent by controls in the open arms (“floor effect”). Moreover, a single exposure to severe stress only on day 16 of gestation resulted in lower levels of anxiety in two tests than in control offspring (Cannizzaro et al., 2006) (Table 3). These apparently opposing effects of maternal stress could be explained by the direction of gene transcription (repression or enhancement) following the interaction of adrenal steroids with their receptors, and/or with various nuclear factors such as cAMP-response element binding protein (CREB) (De Kloet et al., 1998).

It was possible to obtain significant anxiogenic behaviour in PS rats by maternal stress procedures that did not produce any

**Table 3**  
Effect of prenatal stress on anxiogenic behaviour

Species/strain	Reference	Maternal stress	Days in gestation	Offspring age	Anxiety levels	
					Male	Female
<b>Rats</b>						
Sprague–Dawley	Vallee et al. (1997)	(5)	15–21	4 mo	↑	NT
Sabra	Fride and Weinstock (1988)	(12)	1–21	4 mo	↑	↑
Sprague–Dawley	Poltyrev et al. (2005) <sup>a</sup>	(5)	14–21	2 mo	=	=
Wistar	Zagron and Weinstock (2006)	(4)	14–21	35 d	=	↑
Wistar	Cannizzaro et al. (2006)	(9)	16	38 d	↓	NT
CD	Richardson et al. (2006)	(5)	14–21	Adult	=	↑
		(16)	14–21	Adult	=	=
Fisher 344	Van den Hove et al. (2005) <sup>b</sup>	(5)	14–21	6 mo	↑	NT
Sprague–Dawley	Murmur et al. (2006)	(15)	17–21		↑	↑
Wistar	Estanislau and Morato (2005)	(10)	17–20	60 d	↑	NT
Wistar	Rimondini et al. (2003)	(6)	14–21	4 mo	=	NT
<b>Mice</b>						
ddY	Nishio et al. (2006)	(13)	10–18	35 d	=	=
Swiss	Pallares et al. (2007)	(5)	15–21	3 mo	=	↓
ICR	Chung et al. (2005)	(8)	8.5–19.5	50–63 d	=	NT

Maternal stress, as in Table 1.

Unless otherwise stated anxiogenic behaviour indicated by time spent in open arms of elevated plus maze.

<sup>a</sup> Measured under bright light.

<sup>b</sup> Latency in cage emergence test.

↑, increase; ↓, decrease; =, no change; NT, not tested.

evidence of an alteration in the response of the HPA axis to stress (Fride and Weinstock, 1988; Richardson et al., 2006; Van den Hove et al., 2005). Anxiogenic behaviour was also seen in the male offspring of mice lacking the enzyme 11  $\beta$ -HSD-2, but they did not show any difference from controls in the response of their HPA axis to stress (Holmes et al., 2006). On the other hand, prenatal stress on days 8.5–19.5 (Chung et al., 2005), 10–18 (Nishio et al., 2006) or 15–21 (Pallares et al., 2007) of pregnancy in mice did not induce any significant anxiogenic behaviour in the male or female offspring, but it altered the regulation of the HPA axis in association with down regulation of GR receptors in several brain regions (Chung et al., 2005; Ishiwata et al., 2005).

The offspring of rhesus monkeys, stressed during day 90–145 (term 165 days) of gestation also showed signs of anxiety in a novel situation indicated by irritability, clinging to companions, less exploration and social interaction than in controls (Clarke et al., 1994; Schneider, 1992a). Like rats (see below) these young monkeys also show poorer cognitive performance (Schneider, 1992b).

### 6.2. Putative mechanisms of anxiogenic behaviour

The changes in the brain of the offspring that mediate either the increased or decreased anxiety in intimidating situations are not fully understood. PS rats showing anxiogenic behaviour have fewer benzodiazepine (BDZ) receptors in the hippocampus and central nucleus of the amygdala (ceA) (Barros et al., 2006; Fride et al., 1985). The amygdala, which plays a role in the control of emotional and autonomic responses to stress, contains CRH nerve terminals, cell bodies and receptors. The adult male offspring of rats stressed by daily saline injections from day 14 to 21 of gestation had higher concentrations than controls of CRH in the amygdala, and greater amounts of the peptide were released from amygdala minces in response to depolarization (Cratty et al., 1995). Intra-cerebroventricular injection of a CRH receptor antagonist abolished the increased fear and sensitivity to the environment of such PS offspring (Ward et al., 2000). On the other hand, such anxiogenic behaviour was induced in normal rats by injection of CRH into the basolateral nucleus of the amygdala (bLA) (Merali et al., 2004). Moreover, transgenic mice with a disruption of GR in the cortex and hippocampus that have increased CRH<sub>1</sub> receptor expression in the CA1 region of the hippocampus and dentate gyrus show increased anxiety and depressive-like behaviour (Boyle et al., 2006). This indicates that the anxiogenic behaviour induced by prenatal stress could result from the consequences of a reduction in GRs in the cortex and limbic systems and greater activity of CRH on CRH<sub>1</sub> receptors in specific brain regions.

In summary, the data in the preceding sections suggest that maternal stress during a critical phase of foetal brain development may increase the likelihood of anxiety and depressive disorders in rats and monkeys. However, their appearance depends on the timing and intensity of the maternal stress, gender, conditions of the test and its effect on controls animals and genetic factors. There do not appear to be any data from prospective studies in humans or non-human primates indicating such a gender difference in association with prenatal stress, although the incidence of a chronic anxiety state and depression is higher in women than in men (Wauterickx and Bracke, 2005), particularly if associated with prior stressful events (Sherrill et al., 1997). In mice, a similar maternal stress regimen administered over the same period of gestation as that in rats failed to induce increased anxiety even though it altered regulation of the HPA axis and induced learning deficits. This disparity may be related to a difference in the time of development of crucial limbic pathways in the two species in relation to the stress.

## 7. Learning and memory deficits induced by prenatal stress

### 7.1. Human subjects

Evidence of impairment of intellectual activity and language ability has been found in children and young adults whose mothers that experienced stress during gestation or who reported periods of state anxiety. One such study was made in 2-year-old children of mothers that were exposed to different degrees of stress as a result of a freezing ice storm in Quebec, Canada in 1998. It was found that the mothers' objective stress exposure (but not subjective assessment of the stress) significantly accounted for poorer general intellectual and language outcomes, as measured by means of the Mental Scale of the Bayley Scale of Infant Development (Laplante et al., 2004). A significant relation between the degree of maternal stress and intellectual outcome in the children was only found if the mothers experienced the stress during the first or second trimester. The study was restricted to toddlers that were born at full term thereby enabling the authors to differentiate their findings from previous studies performed on pre-term infants. Another study was also able to relate a reduction the children's school marks at the age of six to self assessed stress in the mothers during early pregnancy (Niederhofer and Reiter, 2004).

A decrement in mental ability in toddlers aged 14–19 months was found in another study in which maternal state stress during late gestation resulted in increased fearfulness (Bergman et al., 2007). However, there was no correlation between these two outcomes. Unfortunately, no information was given as to whether the children with altered mental ability were from mothers stressed at an earlier period of pregnancy than those with increased fearfulness. Further studies are needed to establish whether maternal stress can induce changes in cognitive function in the offspring independently of increased emotional reactivity and if it occurs at an earlier time during pregnancy.

### 7.2. Rats and mice

Maternal stress administered in the form of restraint once or thrice daily for at least 6 days from day 8, 13, 14 or 15 of gestation or as 20–30 min or daily foot shocks, slowed the acquisition of spatial learning in rats and mice in some (Ishiwata et al., 2005; Lemaire et al., 2000; Son et al., 2006; Yang et al., 2006), but not in other studies (Vallee et al., 1997) (Table 4). Learning deficits in mice were associated with a reduction in spine density of pyramidal neurone dendrites in the hippocampal CA3 region (Ishiwata et al., 2005). Since these were conducted only in males it is not known whether the same maternal stress also affects learning and memory in female offspring.

By contrast, like its effects on anxiogenic behaviour and regulation of the HPA axis, maternal stress given from day 17 (Meunier et al., 2004) or only on 3 days (Fujioka et al., 2001) or 1 day (Cannizzaro et al., 2006), either did not cause a memory deficit, or resulted in a faster rate of learning (Cannizzaro et al., 2006). Once daily restraint from day 14 to 20 of gestation impaired learning in male but not in female offspring (Zagron and Weinstock, 2006) suggesting that the developing male brain may be more sensitive to the effects of maternal stress hormones.

It appears from the foregoing that learning and memory deficits can be induced in mice and rats by gestational stress and can be detected in males under conditions in which there are no changes in the regulation of the HPA axis or anxiogenic behaviour. Like the other alterations induced by prenatal stress in behaviour those in learning and their direction appears to be dependent on the intensity, duration and timing of the maternal stress, but also on the method by which learning is assessed (Yaka et al., 2007).



**Table 4**  
Effect of prenatal stress on spatial learning and memory

Species/strain	Reference	Maternal stress	Days in gestation	Offspring age	Learning and memory	
					Males	Females
<b>Rats</b>						
Sprague–Dawley	Vallee et al. (1997) <sup>a</sup>	(5)	15–21	4 mo	=	NT
Sprague–Dawley	Lemaire et al. (2000) <sup>a</sup>	(5)	15–21	4 mo	↓	NT
Sprague–Dawley	Meunier et al. (2004) <sup>a</sup>	(7)	17–20	27–30 d	=	=
Wistar	Yang et al. (2006) <sup>a</sup>	(11)	13–19	35–40 d	↓	NT
Wistar S/T	Nishio et al. (2001) <sup>a</sup>	(14)	10–18	42–47 d	=	NT
Wistar	Zagron and Weinstock (2006) <sup>a</sup>	(4)	14–20	3 mo	↓	=
Wistar	Yaka et al. (2007) <sup>a</sup>	(15)	17–21	23–28 d	↓	NT
Sprague–Dawley	Fujioka et al. (2001) <sup>b</sup>	(3)	15–17	3–4 mo	↑	NT
Wistar	Cannizzaro et al. (2006) <sup>a</sup>	(9)	16	38–42 d	↑	NT
<b>Mice</b>						
C57bl/6J	Ishiwata et al. (2005) <sup>a</sup>	(5)	15–21	21 d	↓	NT
ICR	Son et al. (2006) <sup>b</sup>	(8)	8.5–19	49 d	↓	NT

Maternal stress, as in Table 1.

<sup>a</sup> Morris water maze test.<sup>b</sup> Radial arm maze.

↑, improved; ↓, impaired; =, not impaired; NT, not tested.

Hippocampal long-term potentiation (LTP) and long-term depression (LTD) have been measured in PS rats in an attempt to provide a physiological basis to learning deficits. LTP and LTD are activity-dependent synaptic processes that modify the strength of hippocampal glutamatergic synapses, and are believed to be critical for spatial learning and memory (Bliss and Collingridge, 1993). Such processes are the means by which the hippocampus is able to regulate the storage of information, and require activation of glutamate-gated *N*-methyl-D-aspartate (NMDA) receptors (Malenka and Nicoll, 1999). Varied forms of daily stress, thrice daily restraint or repeated foot shocks in rat or mice suppressed LTP in their male offspring (Fujioka et al., 2006; Son et al., 2006; Yaka et al., 2007; Yang et al., 2006). The suppression of LTP was associated with a reduction in the expression of the NR2B subunit of the glutamate type NMDA receptor and the GluR1 subunit of the AMPA receptor, both of which are important modulators of LTP (Yaka et al., 2007). By contrast, maternal restraint stress of only 30 min duration increased both the rate of learning and LTP (Fujioka et al., 2001, 2006), thereby confirming that the direction of the effect of gestational stress on physiological processes associated with learning and memory also depend on the intensity and duration of the stress as mentioned in preceding sections. The data support the findings in human subjects that learning deficits are more likely to be seen when there is clear evidence of prolonged maternal distress, while there may even be signs of improved learning in children of mothers exposed to mild forms of gestational stress (DiPietro et al., 2006).

### 8. Programming of the foetal HPA axis by maternal glucocorticoids

Since there are no neural connections between the pregnant mother and her foetus, the effect of maternal stress on the foetus must be mediated by stress hormones and/or alterations in placental blood flow and transient hypoxia that is induced by adrenaline (Cosmi et al., 1990). Indeed, reductions in uterine blood flow were found during the 28–32nd week of pregnancy in women with high levels of anxiety, indicating that their foetuses could have been exposed to periods of hypoxia (Van den Bergh et al., 2005).

Glucocorticoids readily reach the foetal brain and are therefore likely, but not the only candidates. CRH may also reach the foetus through the placental circulation (Weinstock, 2005). As mentioned

in preceding sections, stress induced levels of glucocorticoids activate GR which are present in the hippocampus, hypothalamus, pituitary, cingulate cortex and amygdala during development.

The role of excess COR in mediating the impairment in feedback regulation of the HPA axis in the offspring was demonstrated by means of maternal adrenalectomy (ADX) and maintenance of basal levels of COR (Barbazanges et al., 1996). This treatment completely prevented both the prolonged response of the HPA axis to stress and the down-regulation of MR and GR in the adult male offspring. These were re-instated by daily injection of COR to mimic the effects of stress. A similar effect of excess maternal COR on HPA axis regulation was found in the male and female offspring of ADX mothers implanted with COR pellets that increased the circulating level of the hormone by 50% compared to that in intact controls (Wilcoxon and Redei, 2007). Like PS offspring, females but not males, born to ADX mothers with implanted COR pellets showed more immobility than controls in the forced swim test.

As shown in Section 6.1, milder forms of gestational stress or those of shorter duration at a later time during foetal development that do not influence the offspring HPA axis, can still induce fear of novelty and learning deficits in rats (Fride and Weinstock, 1988; Richardson et al., 2006; Van den Hove et al., 2005). This suggests that either they are mediated by different maternal hormones or that the relevant brain areas show differing sensitivity to such hormones according to their stage of development. Maternal adrenal hormones play a role in the production of anxiety and learning deficits in PS rats since they could be completely prevented by maternal ADX and maintenance of plasma COR at resting levels (Zagron and Weinstock, 2006). However, while the increased anxiety was re-instated by maternal COR injections, the learning deficits were not (Salomon and Weinstock, 2007). The finding is in accordance with that of Wilcoxon and Redei (2007), in which elevation of COR by a sustained release pellet in ADX rats increased anxiety in the male and female offspring but did not induce learning deficits. Moreover, administration of COR 25 mg/kg or dexamethasone 1 mg/kg to rats on days 18–19 of gestation also increased anxiety in the EPM test and depressive-like behaviour in the forced swim test in offspring of both sexes but did not induce learning deficits (Oliveira et al., 2006). These data show that elevation of circulating maternal COR can lead to an alteration in the development of the foetal HPA axis and other brain areas like the amygdala and hippocampus (Matthews, 2000) resulting in increased fear of novelty and depressive-like

behaviour. Adrenal hormones other than COR, or ischemia resulting from adrenaline-induced constriction of placental blood vessels could mediate the development of learning deficits.

## 9. Changes in brain morphology induced by prenatal stress

During foetal life the brain undergoes rapid growth that is characterized by a high turnover of neuronal connections that predicts the behavioural outcome. This rapid growth rate makes the foetal brain especially vulnerable to hormones that reach it in excess amounts as a result of maternal stress. Such hormones and/or hypoxia may impede the formation of correct neural connections and reduce plasticity and neurotransmitter activity, which can induce subtle changes in cognitive function and behaviour. In spite of the large number of studies on the effect of prenatal stress on motor development and behaviour, there have been relatively few that determined its effect on brain morphology.

### 9.1. Amygdala

The amygdala is involved in mood regulation and in the mediation of fear and anxiety (Davis, 1992) and is bi-directionally related to the frontal cortex (McDonald, 1998) and hippocampus (Pitkanen et al., 2000). The bIA is activated by emotionally arousing experiences and its neurons are generated during days 14 and 17 of gestation in the rat (Bayer et al., 1993) and are responsive to CRH and COR. Excess maternal COR and CRH reaching the bIA during this period of gestation may permanently alter its reactivity to the environment. Thus, higher levels of CRH and of its receptors were found in amygdala extracts from PS rats and larger amounts were released on stimulation (Cratty et al., 1995; Ward et al., 2000). Prenatal stress also caused expansion of the lateral nucleus, an area in which learned fear is encoded (Salm et al., 2004), and increased the number of neurons expressing neuronal nitric oxide synthase immunoreactivity in the bIA (Miller et al., 1999). In PS males, the central nucleus (ceA) of the amygdala, but not the bIA also has fewer BDZ binding sites, a finding consistent with their greater anxiogenic behaviour in the EPM (Barros et al., 2006). Although the significance of these findings is not clear at the present time, they

indicate that the amygdala may be a target for excess stress hormone activity during foetal development resulting in permanent alterations in neuronal activity.

### 9.2. Frontal cortex

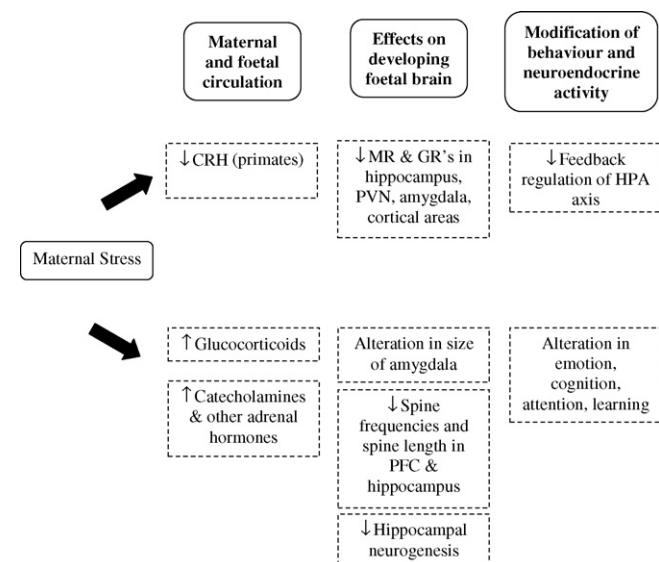
The anterior cingulate and orbitofrontal cortex are known to be implicated in attention processes, working memory and in the regulation of emotional behaviour (Dalley et al., 2004). Varied prenatal stress on days 17–21 of gestation resulted in a significant reduction in spine frequencies on layer II/III pyramidal neurons of the anterior cingulate and orbitofrontal cortex in both male and female offspring aged 23 days. PS males but not females also showed a pronounced decrease in the length and complexity of pyramidal apical dendrites in both cortical regions (Murmur et al., 2006). Other studies have shown that prenatal stress alters subtypes of dopamine and glutamate receptors in different forebrain regions of male rats (Berger et al., 2002) and can thereby permanently change the development and formation of corticostriatal and corticolimbic pathways. These data accord with the finding cited in a following section that prenatal stress decreases a number of genes that are associated with vesicle trafficking and NR1 and NR2A subunits of the NMDA receptor/postsynaptic complex and NMDA receptor in cortical brain areas (Kinnunen et al., 2003).

### 9.3. Hippocampus

Maternal stress of unpredictable noise during mid-gestation reduced hippocampal neurogenesis in juvenile non-human primates (Coe et al., 2003). Almost all the other reports about structural changes induced by prenatal stress in rats have come from experiments conducted in males. Daily maternal restraint during the last week of gestation resulted in a significant decrease in cell proliferation in the dentate gyrus in males from the age of 3 months (Fujioka et al., 2006; Lemaire et al., 2000). Aging caused a decline in cell proliferation in control rats, but this was significantly greater in PS rats. The reduction in cell proliferation could have resulted from increased glucocorticoid activity on cells in the dentate gyrus and may explain the deficit in learning and memory seen in these rats (Lemaire et al., 2000). In male mice, prolonged maternal stress reduced the density of dendritic spines and of synapses on CA3 pyramidal cells in the stratum radiatum of the hippocampus by 19–22% at the age of 9 weeks (Ishiwata et al., 2005). A decrease in cell proliferation was also found in most areas of the hippocampus in 10-day old male rats (Kawamura et al., 2006). By contrast, a milder form of prenatal stress was reported to increase neurogenesis in the dentate gyrus and the total length of neuronal processes in the CA1 region of the hippocampus. This can explain their faster acquisition of spatial learning (Fujioka et al., 2006). The alterations by maternal stress hormones in programming and structure of the foetal brain and their influence on behaviour are shown in Fig. 2.

### 9.4. Changes in cortical and hippocampal gene expression as a result of prenatal stress

Repeated variable prenatal stress from day 14–22 in rats induced a number of changes in mRNA in the frontal cortex of 56-day old male offspring. These included subunits of the NMDA receptor, NR1 and grina which were down-regulated whereas NR2A was up-regulated. A number of genes associated with synaptic vesicle exocytosis and neurotransmitter release were also down regulated by prenatal stress and include SNAP-25, VAMP-2 and complexin II (Kinnunen et al., 2003). A significant down regulation of hippocampal genes was also reported in 23-day-old



**Fig. 2.** Routes by which maternal stress hormones may induce changes in the foetal brain in the programming of offspring behaviour. The developing foetal brain is sensitive to the actions of excess amounts of glucocorticoids and other hormones. These may alter the structure and function of the limbic system and HPA axis resulting permanent changes in behaviour and neuroendocrine regulation in the offspring. ↑ = increase; ↓ = decrease.

female offspring of rats stressed from day 17 to 21 of gestation (Bogoch et al., 2007). This included presynaptic voltage-gated  $\text{Ca}^{2+}$  type P/Q and several  $\text{K}^+$  channels that regulate the electrical properties of the neuron and suggests a potential decrease in excitability and electrical properties of the newly formed synapses. Prenatal stress also reduced the expression of genes that participate in trafficking of synaptic vesicles and neurotransmitter release like synapsin, neurexin, synaptophysin, synaptotagmin, rab3A, and complexin, but not those that make up the postsynaptic density. In spite of the different maternal stress procedure and its timing, gender, strain of rat and brain area studied in these two reports, a consistent effect of prenatal stress was seen on the machinery responsible for controlling neurotransmitter release. Further studies on the changes induced in mRNA and proteins in different brain areas, both in the resting state and in response to stress and a learning task should provide more information about a link between behavioural alterations and changes in physiological and neurochemical processes induced by prenatal stress.

### 10. Contribution of deficient maternal care to behavioral alterations induced by gestational stress in rodents

Since the brain of rats and mice continues to develop during the first 2–3 weeks after birth it is sensitive to alterations in maternal attention. Normal lactating female rats show individual differences in the amount of attention they give to their pups, particularly licking, which affects the development of neural circuits that regulate their endocrine and behavioural responses to stress (Caldji et al., 1998; Meaney, 2001). Insufficient maternal licking and feeding by stressed mothers could contribute to the changes in behaviour in their offspring. Although assessments of behaviour towards their pups have been made in stressed and control mothers the data have been conflicting. It was found that stressed mothers either spent the same (Melniczek and Ward, 1994) or more time nursing their pups than controls (Muir et al., 1985), or that this depended strongly on the strain of the rat and not on the presence of stress (Poltyrev et al., 2005). However, none of these studies evaluated the behaviour of the offspring, so we do not know how such differences in maternal attention contributed to it. In another study it was found that reduction in nursing time in stressed mothers was associated with depressive-like behaviour both in the mothers and their offspring, together with an increased response of the offspring HPA axis to stress (Smith et al., 2004).

In an attempt to differentiate the contribution between a prenatal and postnatal rearing effect on the regulation of the HPA axis and behaviour a cross-fostering procedure was adopted. Such a procedure can only give reliable information if the quality and quantity of attention is the same to PS and controls pups. This clearly has not been found in several studies. Thus it was shown that rat PS male pups received less maternal licking both from their own mothers and from control foster mothers (Moore and Power, 1986; Power and Moore, 1986), while mouse foster pups, whether from control or stressed mothers, elicited less attention than those from their biological mothers (Meek et al., 2001). By contrast, one study reported that PS male rats received more attention from control foster mothers than from stressed ones and this prevented the dysregulation of the HPA axis (Maccari et al., 1995). The reasons for these disparate findings on maternal behaviour are not clear but may depend on the strain of rat or mouse, the duration and severity of the stress and the method by which the pup-directed behaviour was assessed.

In spite of these differences it was found that the anxiogenic behaviour and lower number BDZ binding sites in the hippocampus and ceA of PS rats could be restored to those of controls by the fostering them onto unstressed dams. However, control rats became more anxious when reared by a stressed dam in spite of the

fact that this resulted in an increase in the number of BDZ receptors (Barros et al., 2006), throwing doubt about the relation between these receptors and behaviour. The adoption of PS pups by control mothers also prevented the increase in dopamine  $\text{D}_2$  and NMDA receptors in the PFC and CA1 region of the hippocampus, but fostering control pups onto other control mothers changed receptor density in the opposite direction (Barros et al., 2004). In contrast to these findings in rats, the fostering procedure did not affect the learning impairment or the decrease in LTP in PS offspring of mice (Yang et al., 2006). Since maternal behaviour was not assessed in any of these studies we do not know if this could have explained the changes in behaviour.

The findings described above suggest that early postnatal factors such as maternal attention, and licking behaviour and/or by raised COR levels reaching the suckling in the milk (Muir & Pfister, 1989) could possibly influence the behaviour of the adult PS offspring. They also show that it is important to assess maternal and pup behaviour in the same study even if fostering is employed in order to differentiate a role of pre and postnatal factors in the mediation of the changes in the offspring.

### 11. Conclusions

The data described in this review provide evidence that maternal stress at critical periods of development may alter the programming of the foetal brain, thereby increasing susceptibility to psychopathology. Stress hormones like glucocorticoids and CRH could interact with their receptors in the foetal brain and influence neuronal differentiation and function at different stages of development. In this way they may cause learning and attention deficits, anxiety and depressive-like behaviour, depending on when the stress occurs. Increased hormonal activity in the foetal brain also appears to be responsible for altering circadian rhythms and the feedback regulation of the HPA axis. While small amounts of these hormones may have a beneficial effect on neuronal development and function, excess amounts may cause a decrease in ion channel regulation and synaptic activity resulting in impaired learning and memory. The alterations produced by maternal stress in the offspring clearly depend on the stage of development of particular neuronal systems and the presence of GR and MRs at the time of stress. Genetic factors, stress continuing postnatally and inadequate maternal attention also play a role in shaping development and behaviour.

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