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ORIGINAL PAPER

Gender Differences in the Effects of Prenatal Stress on Brain Development and Behaviour

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Abstract An increased incidence of anxiety, depression and attention deficits in children has been linked to psychological stress during pregnancy. Subjection of a pregnant rat to stress at a time when the foetal limbic and hypothalamic pituitary adrenal (HPA) axes develop results in anxiogenic and depressive behaviour and learning and attention deficits in the offspring, which depend on its gender, intensity and timing of the maternal stress and behaviour being tested. Maternal stress increases corticosterone levels in the foetal brain, decreases foetal testosterone and brain aromatase activity in males, and alters brain catecholamine activity to that in females. Learning deficits, reductions in hippocampal neurogenesis, LTP and dendritic spine density in the prefrontal cortex are more readily seen in prenatally-stressed males, while anxiety, depression and increased response of the HPA axis to stress are more prevalent in females. Genders may differ in the sensitivity of developing brain areas to stress hormones.

Keywords Prenatal stress · Male and female rats · Anxiety and depression · Spatial learning

Introduction

Emotional disturbance and distress during pregnancy resulting from natural or man-made disasters, chronic interpersonal tensions or adverse conditions in the home or workplace have been linked to an increased incidence of behavioural disorders in the children. These include impairment of intellectual activity and language development, autism, attention deficits, schizophrenia, anxiety disorder and depression [1–4]. Most of the studies in humans do not mention whether there were any differences in behaviour according to the gender of the offspring and several of them have only been conducted in males [5, 6]. While no difference was found in the occurrence of schizophrenia in men and women whose mothers were exposed to psychological stress during the first semester, there was a higher incidence of schizophrenic symptoms only in men when the mothers were exposed to stress in the second trimester [2]. The influence of the time of stress on the occurrence of schizophrenia in men may be due to their slower rate of cortical development than in women [7], thereby making the male brain susceptible to insult for a longer period. The incidence of major depression was also higher in young males than in females after their mothers had been exposed to a major earthquake during pregnancy [8].

A significant association was reported between maternal perceived stress and plasma levels of corticotropin releasing hormone (CRH), ACTH and cortisol during the 20–30th week of gestation [9]. High plasma levels of these hormones were associated with preterm births and low birth weight [10] which itself is a cause of cognitive neurological dysfunction [11, 12]. However, genetic factors, the continuation of maternal stress in the postnatal period and its effect on the quality of maternal care also contribute to the development and behaviour and cannot readily be separated from prenatal influences. Therefore the most reliable support for an effect of gestational stress on the development and behaviour of the offspring has come from experimental studies in rats, some of which have been replicated in nonhuman primates. In such studies it is

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possible to control the timing, intensity and duration of stress exposure and the nature of the behaviour tests in the offspring. Like in humans, prenatal stress has been found to increase fear of novelty [13, 14], decrease the propensity for social interaction in juveniles [15], induce behaviour consistent with depression [16, 17], as well as learning [18, 19] and attention deficits [20].

The majority of experiments on the effects of prenatal stress in rats have also only been conducted on the male offspring. The relatively few comparative studies that have been performed in rats of both sexes clearly indicate that some of the structural and functional alterations induced by prenatal stress differ according to gender and these may be dependent on the time during gestation that the stress occurred, its duration and severity. This review will focus on the similarities and differences in the influence of gestational stress in male and female rats on the regulation of the hypothalamic pituitary (HPA) axis, fear-related and depressive-like behaviour and learning in relation to the morphological, neurophysiological and neurochemical changes underlying them.

Sex differences in size of brain structures and in behaviour of unstressed rats

Before examining the effect of prenatal stress on behaviour in male and female rats, one should take into account the role of sex hormones that exert a potent influence on brain development in the two genders. The action of these hormones on the nervous system can be detected during the last week of gestation that extends until about 10 days post partum [21, 22]. Development of normal male sexual dimorphic behaviour and sexual activity depends on the presence of appropriate levels of testosterone, brain oestrogen receptors and activity of aromatase in critical brain areas on days 18 and 19 of gestation [23]. Sexual differentiation by testosterone occurs through its conversion to estradiol by aromatase that is present in neural structures [24]. Sex hormones organize the neuronal circuitry involved in neuroendocrine functions and behaviour and are responsible for gender differences in the size of certain brain areas, synaptic connections, neurotransmitter concentrations and their activity [25]. For example, in males but not in females Krieg's areas 2 and 3 on the right side of the cerebral cortex are thicker than on the left side [26, 27]. Males have a larger sexual dimorphic nucleus in the preoptic area of the hypothalamus (SDN-POA) [28], which has been attributed to prevention of neuronal apoptosis by circulating testosterone after its conversion to estradiol [29]. On the other hand, the rostral anterior commissure, a fibre tract uniting the left and right hemispheres and several brain regions including the lateral amygdala nucleus, accumbens and endopiriform cortex, is larger in females than in males [30].

Such sex differences in brain development could explain some of the differences in behaviour both under normal and stressful conditions. For example sweet preference is greater in female than in male rats [31], while adult males take longer than females to enter an open field, in which they show less ambulation and rearing and higher defecation [25, 32]. Males also spend less time in the open arms of the elevated plus maze (EPM) [33, 34] and the locomotor activity of females in a novel environment is less disrupted by aversive stimuli than that of males [35]. The response to novelty and the development of learned helplessness of females in the forced swim test (FST) is dependent on the stage of the oestrous cycle. Proestrous females show less timidity in the EPM and immobility in the FST than males or females in dioesterus [36, 37].

In addition to the effect of sex steroids in organising behaviour, the lesser degree of timidity in unstressed females may result from a larger number of benzodiazepine binding sites in the prefrontal cortex [38] and hippocampus [39] than in male rats. The direction and extent of the effect of maternal stress on these behaviours may be differentially affected according to the degree of alteration induced by stress hormones and their interaction with testosterone and aromatase in the development of sexually dimorphic brain structures and release of neurotransmitters.

Effect of prenatal stress on hormone levels, aromatase activity and brain structures underlying sexually dimorphic behaviours

More than 30 years ago it was shown that immobilization of pregnant rats three times a day for 45 min under bright lights and elevated temperature on days 14–21 of gestation (prolonged restraint stress) altered the timing of the appearance of the normal testosterone peak from day 18 to day 17 [40], and impaired sexual activity at adulthood [41]. No differences were seen in testosterone or progesterone levels in prenatally stressed (PS) females from those in controls. Prenatal restraint stress increased foetal corticosterone (COR) in males and female foetuses and decreased testosterone and the activity of aromatase in the hypothalamus and amygdala in males but not in females on days 18 and 19 of gestation [42], thereby interfering with the normal development of these brain regions. Since aromatase activity was also reduced by prenatal exposure to hydrocortisone [43], it is possible that raised levels of maternal glucocorticoids mediated the effect on aromatase. The relative lack of testosterone and of aromatase activity in PS males resulted in an alteration in their cortical asymmetry [27], volume of the SDN-POA [44] and size of

the anterior commissure to resemble those of control females. While prenatal stress had no effect on these structures in females it reduced the size of the anterior commissure to that in control males.

At the age of 10 days, unstressed females were found to have higher levels and a lower turnover of noradrenaline (NA) than males in the SDN-POA and lower levels of dopamine (DA) in the mediobasal nucleus of the hypothalamus (MBH). Prenatal stress increased NA and decreased DA levels in males to those in females in the SDN-POA and MBH respectively [45]. The alterations in aromatase and catecholamine activity by prenatal stress may also explain the feminine pattern of juvenile play [46], open field behaviour [47] and saccharin preference [48] in male offspring of mothers subjected to the same form of severe stress. The development of the feminine pattern of saccharin preference in PS males was prevented by the administration of a β-adrenergic antagonist propranolol to the pregnant rats during their exposure to stress [48]. This suggests that excess activation of foetal β receptors by higher levels of catecholamines induced by maternal stress contributed to the feminization of the developing male brain. Increased catecholamine activity during development could inhibit the activity of aromatase in the medial amygdaloid nucleus [49] and the nuclear uptake of oestradiol after its conversion from testosterone [50]. Shorter periods of maternal restraint that allow movement, were shown to heighten sexual activity of the male offspring at maturity and did not affect behaviour in a novel environment [51]. Thus, the differential effect of various maternal stressors on male sexual behaviour may depend on the identity and relative amounts of hormones released in the mother in relation to foetal brain development [52]. It is likely that in addition to glucocorticoids and catecholamines, excess opioid activity is involved in the reduction in male sexual function since this can be prevented by maternal administration of an opioid antagonist, naltrexone [53, 54]. It remains to be determined whether the milder forms of maternal stress influence the timing of the appearance of the normal testosterone peak in PS males, and what influence if any they have on the development of the SDN-POA, right-left differences in cortical thickness and brain neurotransmitters.

Changes in the maternal and foetal HPA axis in response to stress

Several studies have provided evidence that maternal stress during the last week of pregnancy in rats (14–21 days) causes an elevation of circulating COR in the foetus [40, 55, 56]. Maternal stress also increases foetal circulating catecholamines [57]. The increase in COR results from a combination of a reduction in maternal COR-binding globulin and impairment in the regulation of her HPA axis, indicated by the slower return to normal of plasma COR with succeeding days of stress [55].

During foetal and early postnatal life the brain undergoes rapid growth that is characterized by a high turnover of neuronal connections. This makes the foetal brain especially vulnerable to hormones that may reach it in excess amounts from the maternal circulation as a result of stress. Peptides, like CRH and β endorphin, and COR may impede the formation of correct neural connections and reduce plasticity in the developing foetal brain. Stress induced levels of COR activate glucocorticoid receptors (GR) which are present in the rat hippocampus, hypothalamus, pituitary, cingulate cortex and amygdala from day 13 of gestation [58]. The ability of the foetal HPA axis to respond to maternal stress was shown by the observation of increased expression of CRH mRNA in the foetal paraventricular nucleus (PVN) on day 15 of gestation [59]. Furthermore, the degree of response as measured by cFos in the PVN of the foetuses paralleled that in the mothers and was related to the extent of the elevation of plasma COR [60].

There appears to be only one study that examined the response of male and female foetuses separately to maternal stress. While ACTH increased in maternal plasma to a similar extent in response to forced immobilization on each of days 19–22 of gestation, levels of the peptide were higher in male foetuses than in controls on days 18–21, but in females, only on days 20 and 21. There was no gender difference in the reduction in the levels of ACTH or catecholamines in the hypothalamus in response to maternal stress measured on day 20 [61, 62].

Alterations in the reactivity of the HPA axis in prenatally-stressed rats

Experimental evidence showing that chronic stress applied when the foetal HPA axis develops results in its dysregulation is summarized in previous reviews [63, 64]. There are relatively few studies in which the response to stress was compared in PS male and female offspring. Basal plasma levels of ACTH or COR were reported to be higher than in controls in PS males and females aged 14, 60, or 365 days [55] but in two other studies only in adult females aged 6 and 12 months respectively [65, 66]. These differences in the effect of prenatal stress on basal COR levels may result from the time of day that the blood was taken as prenatal stress was shown to cause a phase shift in the circadian rhythm of COR release in rats. Moreover, PS rats of both sexes were found to secrete higher amounts than

controls of total and free COR at the end of the light period, while PS females secrete more COR over the whole diurnal cycle [67].

Other studies measured the response of the HPA axis to different stressors in PS offspring. When prolonged restraint was used to stress the mothers, the release of COR in male and female offspring in response to environmental stress was greater and of a longer duration than that in controls [68–71]. This was associated with a decrease in the number of hippocampal mineralocorticoid (MR) and GR receptors indicating impairment in the feedback regulation of the HPA axis [63, 66]. However, once daily maternal restraint [72], unpredictable noise [66] or saline injections [73] only altered the response to subsequent stress in the female offspring. These findings suggest that the developing HPA axis in the female foetus may be more sensitive than that in males to circulating stress hormones and respond to the lower concentrations present after a milder form of stress [60]. This is supported by the finding that administration of dexamethasone, a synthetic glucocorticoid to pregnant guinea pigs elevated basal and stimulated levels of COR in the female but not in the male offspring [74]. Direct evidence for a role of excess maternal COR in mediating the effect of prenatal stress on the control of the HPA axis was demonstrated by maternal adrenalectomy (ADX) performed prior to the week of gestational stress with replacement of basal COR levels. This treatment completely prevented the prolongation of the response to stress and down-regulation of MR receptors in the male offspring [75]. Administration of COR to the ADX rats to mimic the increase induced by stress restored the changes in the HPA axis. The effect of maternal ADX was not determined on the response of the HPA axis in female offspring.

An early study from our group determined whether the HPA axis of adult (6 month old) PS and control rats differed in its adaptation to repeated exposure to the same stressful environment. It was found that while control male rats no longer showed an increase in plasma COR by the fourth exposure to a brightly lit open field, PS males continued to release higher amounts of COR up to eighth exposure [13]. These data were essentially replicated in a more recent study in which the response of the HPA axis to restraint was determined in males and females aged almost 3 months and a similar lack of adaptation was shown in PS males [76]. However neither control nor PS females showed any reduction in the amount of COR released or in the duration of the response of the HPA axis on repeated exposure to the same stress. This may have been due to the fact that both PS and control females were repeatedly subjected to vaginal smears during the experiment, itself a stressful procedure, to determine the stage of the oestrus cycle.

Depressive-like behaviour induced by prenatal stress

Regulation of the HPA axis is also impaired in humans with major depression. This is indicated by higher 24 h secretion of cortisol [77, 78] and a greater increase in response to stress than in control subjects [79]. Depressed subjects may show a decrease in dexamethasone suppression of plasma cortisol, indicating down-regulation of their GR receptors [80]. 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 ability to feel pleasure (anhedonia) can be measured under appropriate conditions. Loss of coping or immobility occurs in response to inescapable stress in the FST [81], and is prevented by different classes of antidepressant drugs [82]. Prenatal stress in rats was reported to increase the duration of immobility in this test to a greater extent in females than in males [16, 36], probably because control males displayed a longer duration of immobility than females. Chronic treatment of the PS offspring with antidepressants prevented the development of immobility in the FST without affecting that of controls [83, 84].

In contrast to the finding in males in which an increase in sweet preference was induced by prenatal stress [48], females showed a decreased preference possibly indicating depressive-like behaviour [53]. This suggestion is supported by the finding that saccharin preference was reduced in adult males by chronic mild stress and restored by treatment with antidepressants [85]. Saccharin preference in adult male rats was also restored by intra-accumbens injection of DA agonists [86] suggesting that it could be due to a reduction in DA release in that nucleus. The DA pathway projecting from the ventral tegmental area to the nucleus accumbens is thought to play a major role in mediating the rewarding effects of different stimuli [87]. On the other hand, it has been hypothesized that depression is related to a reduction in DA transmission in the nucleus accumbens [88]. The finding that DA release was reduced in the nucleus accumbens of PS females but not in males [89] supports the suggestion that females show a greater propensity to develop depressive-like behaviour.

Anxiety and impaired coping in adversity induced by prenatal stress

Prenatal stress can induce a chronic anxiety state which may be considered to be the result of inappropriate activation of defensive responses arising from an erroneous assessment of danger [25]. This can be seen in the poor coping behaviour of the children under adversity [5], and occurs in autistic children who also secrete more cortisol in

response to psychological stress than normal children [90]. Such an anxiety state is indicated in rats by increased fear and freezing behaviour or attempted flight, and occurs when they are exposed to well-lit, unfamiliar open spaces like the open field or the EPM.

In a study conducted only in the male offspring of mothers subjected to prolonged restraint or chronic variable stress [91, 92] it was found that they spent less time than controls in the open arms of the EPM. Since this behaviour can be induced in control rats by injection of anxiogenic agents and prevented by anxiolytics, like diazepam [93], it is taken as a sign of anxiety. Others found that gestational stress of unpredictable noise induced anxiogenic behaviour in rats of both genders [33], or only in females [69]. The differences among the findings in these studies may be due to the nature and intensity of the maternal stress, strain of rat, the conditions under which the test is performed (in a well lit or relatively dark room), age of rat when tested, stage of the oestrous cycle and whether the rat had previously been exposed to other stressors. Thus when performing the experiment in low light we found that increased fear in the EPM could already be detected in PS female rats aged 4–5 weeks in the Wistar strain after subjection of the mother to a variable stress paradigm [94] or once daily restraint [95] during the last week of gestation. Others using electric foot shocks administered on alternate days throughout pregnancy in the same rat strain were only able to detect greater anxiogenic behaviour than in controls at the age of 60 days [96].

In order to test the hypothesis that females may be more sensitive than males to maternal stress hormones, as indicated by the studies on the regulation of the HPA axis, we compared the effects of maternal stress of long and short duration on offspring behaviour in the EPM in the same rat strain. We found that adult control females spent more time than males in the open arms of the EPM and that prolonged maternal restraint from day 14–21 of gestation decreased the time spent in the open arms in both sexes. The same stress applied only once daily for 45 min had no effect in males but reduced the time in open arms in females [95] to that seen in control males. The role of excess secretion of maternal adrenal hormones in mediating the increased fear of novelty in PS rats was confirmed by the finding that maternal ADX on day 12 of gestation with maintenance levels of COR completely prevented the difference in behaviour of PS rats and controls in the EPM [95].

Anatomical basis of increased fear of novelty induced by prenatal stress

The basolateral amygdala is activated by emotionally-arousing experiences and its neurons are generated during days 14 and 17 of gestation in the rat [97] and are responsive to CRH and COR reaching it from the maternal circulation. Prenatal stress has been shown to influence the structure and activity of the amygdala but all the studies described below were only performed on males. The lateral nucleus of the amygdala was larger [98] in adult PS than in control male rats and had more neurons expressing neuronal nitric oxide synthase immunoreactivity [99]. In a later study, differences in the volume and number of neurons and glia in the basolateral, central and lateral nuclei of the amygdala were detected in PS males from the age of 7 days and were most extensive at 25 days [100]. The amygdala of PS males also has larger amounts of CRH and its receptors than in control rats [101, 102]. These findings suggest that the enlarged amygdala may be activated by increased amounts of stress hormones during foetal development thereby sensitizing its response to environmental stimuli in adulthood. It is not known whether prenatal stress also increases the size of these amygdaloid nuclei in the female offspring.

Taken together, the data in the preceding sections suggest that maternal stress and excess adrenal hormone release during a critical phase of foetal brain development may increase the likelihood of anxiety and depressive disorders. These disorders are more readily detected in females possibly because they show less fear and depressive–like behaviour in the non-stressed state.

Learning and memory deficits induced by prenatal stress

The majority of the studies on the effect of prenatal stress on learning ability have been performed in male rats. Prolonged maternal restraint stress three times daily or 20–30 min of daily foot shocks were reported to slow the acquisition of spatial learning in the Morris water maze. This was associated with a reduction in hippocampal neurogenesis and suppression of long-term potentiation (LTP) [18, 19]. On the other hand, shorter periods of restraint or other forms of maternal stress either did not impair acquisition of spatial learning in males or females [65, 103], or only affected that in males [35, 95]. Like its effect on sexual behaviour, mild gestational stress was even shown to improve learning in male rats [104, 105]. The effect of this mild stress on aromatase activity and foetal testosterone is not known. Furthermore, as females were not tested in these experiments we do not know whether their learning would also have been improved under these conditions. However, dexamethasone administration during gestation slowed maze learning in male guinea pigs while improving it in females [106]. Moreover the deficits in spatial learning in males induced by prenatal stress were

prevented by maternal adrenalectomy, indicating that they resulted from the action of adrenal hormones on developing neurons [95]. These could include either COR and/or catecholamines. Support for a role of catecholamines in mediating the learning impairment in PS males was provided by McGivern et al. [48]. They showed that together with feminized saccharin preference induced by maternal restraint stress, spatial learning deficits could be prevented by administration of propranolol to the pregnant rat during her exposure to stress.

The differential sensitivity of male and female rodents to the effect of prenatal stress on spatial learning could also be related to sex differences in the structure of the hippocampus and in the induction of LTP [23, 107]. In the female, apical dendrites in the hippocampal CA3 region are longer and have more branch points than in males and the hippocampal neurons are differentially affected by glucocorticoid treatment [108]. In spite of this observation, another study found that prolonged maternal restraint selectively reduced the number of hippocampal neurons in one month old female rats, the largest effect occurring in the dentate gyrus [109]. A single exposure to restraint on day 18 of gestation also reduced the number of granule cells in the dentate gyrus selectively in adult female rats [110]. Since glucocorticoids administered to adult rats also reduced neurogenesis in this area, the authors attributed the neuron loss to the higher release of COR in PS females than in males and to the presence of MR and GR in this area. In spite of reduced neurogenesis in the dentate gyrus of PS females they do not develop memory deficits as readily as males. This could be explained by the influence of estradiol which is only reduced in females by the most severe forms of gestational stress [111]. Oestogens can increase dendritic spines, LTP and glutamate NMDA receptor binding in the hippocampus [4] and promote cholinergic transmission in the hippocampus and basal forebrain [112], which may overcome any decrease in neurogenesis.

In PS males neurogenesis was reduced at the age of three months when deficits in spatial learning were seen after thrice daily maternal restraint during the last week of gestation [18]. This maternal stress had been shown to decrease testosterone levels and aromatase activity [40, 42] in male foetuses. Since testosterone may also promote neurogenesis in the dentate gyrus [113], it is possible that a lack of this hormone, together with a reduced nuclear uptake of estradiol [50] may contribute to the memory deficits in males. From the data available to date it appears that females are more resistant than males to the disruptive effect of maternal stress on spatial learning. This may be due to a combination of a gender difference in hippocampal and cortical structure, a lack of testosterone in males during development and the role of estrogens in maintaining spine density and cholinergic transmission in females.

The anterior cingulate and orbitofrontal cortices are known to be implicated in attention processes, working memory and in the regulation of emotional behaviour [114]. 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 [115]. It is possible that these structural changes contribute to the memory and attention deficits or to the other behavioural alterations induced by prenatal stress.

Differential effect of prenatal stress on brain neurotransmitters

There have been very few reports on the effect of prenatal stress on brain neurotransmitters in rats of both sexes. One study found a significant gender difference in the concentration of NA and 5HT in the prefrontal cortex (PFC) and of DA in the CA3 region of the hippocampus [32]. Prolonged maternal restraint did not abolish this gender difference in the offspring even though it altered the behaviour of the females to resemble that of males in the open field and radial arm maze [32], in contrast to the observation of Reznikov and Nosenko [45] in the SDN-POA and MBH nuclei. However, prenatal stress had a differential effect on these neurotransmitters in the PFC. It increased DA turnover in females and decreased 5HT turnover of males. The same form of maternal stress reduced $5HT_{1A}$ receptor binding in the ventral hippocampus on males to a greater extent than in females but had no effect on $5HT_{2A}$ binding in either the ventral or dorsal hippocampus [116].

Prenatal stress in males also produced a permanent increase in D_2 dopamine and NMDA glutamate receptors in the medial and dorsal prefrontal cortices, and in the CA1 region of the hippocampus in males [117, 118]. It is not known whether similar or different changes in these or other receptors occur in PS females. Further comparative studies are needed to relate the changes in brain morphology and in the activity of neurotransmitters in discrete brain areas to the disparate effect of prenatal stress in males and females.

Early environmental influences

Since the brain in the rat continues to develop after birth it is possible to alter behaviour of PS offspring by early environmental manipulations like handling [94, 119] or

environmental enrichment [83]. The developing rat is also very sensitive to maternal attention, licking, nursing and other pup-directed activities. It was shown that gestational stress induced depressive-like behaviour in the mothers after parturition and this was associated with a reduction in the time spent in arched-back nursing. Both male and female offspring in this study showed an increased response of the HPA axis to stress and greater immobility in the forced swim test [70]. Others employed the method of fostering the PS pups onto control mothers to evaluate a possible effect of maternal attention on offspring behaviour. This procedure can only help to differentiate the role of prenatal and postnatal factors in their aetiology if the fostering procedure per se has no effect on offspring behaviour. However, this is not so. For example, it was shown that fostering PS pups onto control mothers prevented the increase in D_2 and NMDA receptors in the prefrontal cortex and CA1 region of the hippocampus. However, fostering control pups onto other control mothers changed receptor density in the opposite direction [117]. In another study, fostering PS pups onto control mothers had no effect on the learning impairment or suppression of LTP seen in PS males [19].

Several studies have examined the effect on maternal attention of fostering pups from stress to control mothers and *vice versa* but the results are also conflicting. One of these revealed that normal male pups received more maternal licking than females but those born to mothers stressed during pregnancy received less licking both from their own mothers and from control foster mothers [120, 121]. However, other studies either found no difference in the amount of licking of their pups by stressed and control mothers [122], or that this depended strongly on the strain of the rat and not on the presence of stress [123]. It was also found that foster pups, whether from control or stressed mothers, elicited less attention than did pups from their biological mothers [124]. In contrast to these data, others found that fostering either PS or control pups onto stressed or unstressed mothers increased maternal attention and prevented the change in the HPA axis induced by gestational stress [125]. Neither of the other studies reported the effect of these procedures on the changes induced in the offspring by prenatal stress. Moreover, as maternal behaviour was not investigated in the above mentioned fostering studies that examined offspring behaviour or neurotransmitter receptors, it is not known in what way this may or may not have contributed to the outcome. Fostering PS rats onto control mothers may also have produced its effect through provision of milk that does not contain high levels of COR like that of stressed mothers [126].

Since none of these experiments examined the effect of fostering on the behaviour of the female offspring we do not know to what extent maternal behaviour contributed to the changes induced by prenatal stress in their behaviour receptors densities, and regulation of the HPA axis.

Conclusions

A considerable body of evidence from studies in rodents provides support for the suggestion that maternal stress during critical periods of foetal brain development can induce long-lasting changes in the regulation of the HPA axis, including its feedback regulation via MR and GR receptors and the circadian rhythm of COR release. These effects are more readily detected in females and continue well into middle age. On the other hand, the HPA axis of PS males appears to take significantly longer than in controls to adapt to repeated exposure to the same stressor. The effect of repeated stress on the response of the HPA axis in females needs to be further explored. Depending on the timing and severity of the maternal stress, conditions under which the offspring are tested and their age, prenatal stress also causes alterations in behaviour. Fear of intimidating novel situations and development of learned helplessness may be more easily detected in adult PS females because controls are less fearful of novelty than adult males. On the other hand, deficits in spatial learning occur more readily in males even after relatively mild maternal stress.

Evidence is presented that the changes in the HPA axis and behaviour induced by prenatal stress result from a combination of the effects of maternal stress hormones like glucocorticoids, catecholamines and opioid peptides on the development of the sexual dimorphic brain. More intense and prolonged forms of maternal stress prevent the normal appearance of testosterone in males, reduce the activity of aromatase that converts it to estradiol and interfere with its genomic effects. Together, these hormonal perturbations feminize the structure of the male brain, by reducing the size of the SDN-POA and cortical thickness, interfere with neurogenesis and affect the normal activity of neurotransmitters in key brain regions. These studies could form the basis of an investigation of possible alterations that could occur during the development of the human foetus exposed to such stress hormones.

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