Intrauterine Factors as Determinants of Depressive Disorder

Marta Weinstock, PhD

Department of Pharmacology, The Hebrew University Hadassah Medical Center, Jerusalem, Israel

ABSTRACT

Although the etiology of major depressive disorder (MDD) is unknown, it is precipitated in susceptible individuals by adverse events. This review examines the role of intrauterine factors resulting from exposure to stress hormones in the increased vulnerability of the organism to MDD. Severe maternal stress or alcohol intake during the second and third trimesters causes excess release of corticotropin releasing hormone (CRH) and cortisol. These hormones reduce birth weight; impair the feedback regulation of the hypothalamic pituitary adrenal axis (HPA) axis and 5-HT1A and 5-HT2A signaling in key brain areas. Similar changes are seen in patients with MDD and in experimental animals after chronic inescapable stress, prenatal stress or alcohol, which also induce depressive-like behavior in rats, alterations in sleep and circadian rhythms reminiscent of those in humans with MDD. Clinical improvement of MDD by antidepressants is accompanied by normalization of the regulation of the HPA axis and of serotoninergic transmission.

INTRODUCTION

Major depressive disorder (MDD) remains one of the most frequently seen psychiatric illnesses that still presents a treatment challenge since many patients do not respond adequately to existing therapies (1). MDD is believed to result from a combination of genetic and environmental interactions. A depressive episode may be precipitated in vulnerable individuals by a major stressful life event or exposure to prolonged periods of distress (2). The ability to cope under conditions of adversity varies considerably among individuals. Failure to do so may lead to impaired regulation of the hypothalamic pituitary adrenal (HPA) axis, prolongation of cortisol release and concomitant changes in serotoninergic and noradrenergic mediated neurotransmission (3). The susceptibility to develop depressive illness in the face of adverse situations is greater in subjects with a family history of depression and in those who had been subjected to sexual or physical abuse during early childhood (4, 5). Depressive illness is also more likely to occur in subjects whose mothers suffered from depression during pregnancy (6) or were exposed to uncontrollable stress (7), infection (8) or alcohol (9).

The developing fetal brain is particularly sensitive to hormones, cytokines and noxious substances reaching it from the maternal circulation that may permanently alter its structure and function. Stress hormones include adrenaline, cortisol (corticosterone [COR] in rodents) and corticotrophin releasing hormone (CRH). This review will focus on the changes in brain morphology, regulation of the HPA axis and brain serotoninergic system associated with depressive-like behavior in the offspring resulting from maternal stress hormones, alcohol abuse and infection and that could lead to a greater vulnerability to develop depressive illness.

ASSOCIATION BETWEEN PRENATAL STRESS AND DEPRESSION IN HUMAN SUBJECTS

Although many retrospective studies have linked exposure to adverse events during pregnancy to a higher incidence of schizophrenia (reviewed in 10), there have been only a few reports linking intrauterine factors to depressive illness. One of these reported an incidence of 30% with

Address for Correspondence: ✉ Professor Marta Weinstock, Department of Pharmacology, School of Pharmacy, The Hebrew University Medical Center, Ein Kerem, Jerusalem 91120, Israel. martar@ekmd.huji.ac.il

severe depression in the adult offspring of women who were subjected to the severe "hunger winter" in Holland during World War II. The frequency of depression was greatest when stress exposure occurred during the second and third trimesters, and its prevalence was higher in men than in women (11). No differentiation was made between nutritional deficiency and the degree of stress in the etiology of the depression in this study. However, an incidence of severe depression of 13.3% was reported in the 18-year-old offspring of women pregnant during a severe earthquake (7.8 on the Richter scale) compared to 5.5% in those born a year later. More men than women were found with depression, particularly when the stress exposure occurred during the second trimester of pregnancy (7).

Chronic psychological stress during pregnancy has been shown to decrease the length of gestation and birth weight (12, 13). Antenatal stress, as assessed from self-reported high levels of anxiety or depression, was associated with raised circulating levels of CRH and of cortisol in both the 18-20th and 28-30th weeks of gestation (6, 14). In contrast to the inhibition by cortisol of CRH release from the hypothalamus, stress levels of cortisol stimulate CRH release from the placenta (15). Plasma CRH and cortisol were inversely related to birth weight (reviewed in 13). Therefore, other studies have used low birth weight (LBW) as an indicator of maternal stress. LBW infants have a higher prevalence of emotional problems, anxiety and learning difficulties than those of normal birth weight (reviewed in 16, 17). However, an association between LBW and depression is found in some (18-20) but not other studies (21, 22). The reasons for these discrepancies are not clear but may depend on the age at which the subjects are assessed and whether or not other factors, like a family history of depression or childhood hardship, contribute to the outcome.

Low birth weight may be considered as an indicator of poor intrauterine conditions for growth and development that provoke physiological adjustments that have long term consequences for health and function (23). While such adjustments increase the chances of fetal survival, they could render the individual less able to cope with stressful conditions during later life. A significant association was found between LBW and hypertension (24, 25), and was recently tested in relation to the incidence of childhood depression (18). In the absence of other adverse conditions during childhood, such as violence between parents or physical abuse, the rate of depression in LBW teenage boys and girls did not differ from those of normal birth weight. However, exposure of LBW girls but not boys to one or two such hardships during childhood resulted in depressive symptoms around puberty in 20% and 60% respectively, compared to 4% and 20% of controls. It is possible that the greater prevalence of depression in girls than in boys in these studies, in contrast to those in adults described above, is due to the younger age at which the assessments were made since depression has an earlier onset in females (26). These data allow the inference that an adverse maternal milieu in girls can interact with hormonal changes associated with puberty and stress and predispose the individual to depressive and other mental health illness in later life. It should be emphasized that in none of these studies was any attempt made to analyze a possible contribution to the outcome of a family history of affective disorder.

ASSOCIATION BETWEEN PRENATAL INFECTION AND DEPRESSION IN HUMAN SUBJECTS

Epidemiological studies show that maternal exposure to infection increases the release of pro inflammatory cytokines, tumor necrosis factor alpha (TNFα) and interleukin-1beta (IL-1β) from macrophages into the circulation (27). Excess levels of these cytokines could induce premature birth (28), itself a possible risk factor for depression (see preceding section). Exposure of pregnant women to the A2/Singapore influenza epidemic resulted in a significantly higher incidence of major depression in their offspring than in those born six years earlier. Again, the prevalence of depression was greater in men than in women and when the mothers were exposed to the disease during the second trimester of pregnancy (8). Severe stress during pregnancy also increased circulating levels of IL-6 and TNFα (29) and reduced those of progesterone and IL-10 that are involved in the maintenance of pregnancy. It therefore appears that the effect of gestational stress on the developing fetus involves several interacting factors including alterations in cytokines and stress hormones.

ASSOCIATION BETWEEN MATERNAL ALCOHOL INTAKE AND DEPRESSION IN HUMAN SUBJECTS

Ethyl alcohol can have both direct and indirect effects on the developing fetus. It readily crosses the placenta and can affect the integrity of fetal neurones but can also influence maternal endocrine function resulting in excess release of stress hormones which can also adversely affect the developing fetal brain. Abnormalities in development

and behavior in children exposed prenatally to alcohol are well documented and some of them resemble those seen after prenatal stress. They include deficits in learning, memory and executive functioning, hyperactivity, impulsivity, aggression and delinquency and poor communication and social skills (30, 31). An incidence of depressive symptoms of 27% was also found in children exposed to high levels of prenatal alcohol (cited by 9). This may be an important predictor of depression in adulthood since about 44% of adult offspring of mothers drinking large amounts of alcohol during pregnancy were reported to be seriously depressed (32). The interpretation of the findings is complicated since alcohol intake is significantly associated with maternal depression (33). A study made to assess the contribution of maternal depression independently of alcohol intake found that each of these independently increased the likelihood of childhood depression (9). However, the highest incidence of depression occurred, particularly in girls, when maternal depression was accompanied by moderate to heavy alcohol intake (3-5 or more drinks per occasion). The weakness of this study is that it failed to include data on paternal drinking in spite of the fact that paternal alcoholism has been shown to be a major predictor of depression of early onset in the offspring (34). Moreover, women with alcoholic partners are twice as likely as those with non-alcoholic partners to abuse alcohol (35). Neither was consideration given to the probability that living with an alcoholic husband increases the likelihood of psychological stress in the mother with the attendant effects on the developing fetus and later on the child.

In summary, severe maternal stress in humans caused by uncontrollable factors such as prolonged famine, a major earthquake or maternal infection can increase the incidence of depression in adult offspring. The highest incidence is associated with stress occurring in the second trimester of pregnancy when circulating levels of cortical and CRH are elevated and appears to be more prevalent in males. On the other hand, LBW, prenatal maternal anxiety, depression and/or excessive alcohol intake are more likely to induce depressive symptoms in adolescent girls than in boys if this is accompanied by additional hardship during childhood.

MATERNAL STRESS HORMONES AND PROGRAMMING OF THE FETAL BRAIN

Acute stress, whether environmental or psychological, activates the HPA axis and sympathetic nervous system and causes a transient increase in plasma glucocorticoids and catecholamines. The response of the HPA axis to chronic stress depends on whether the organism has developed coping strategies and adapts to the stress. In pregnant women who do not adapt to the adverse circumstances and report high levels of stress, circulating CRH, ACTH and β-endorphin and cortisol are elevated in the second and third trimester of gestation (6, 13, 36). The fetus is normally protected from excess levels of glucocorticoids by placental hydroxysteroid dehydrogenase (11β-HSD) that converts cortisol to inactive cortisone, and by COR binding globulin (CBG) which sequesters any cortisol released into the circulation. However, in rats both prenatal stress (37) and chronic maternal malnutrition (38) reduce the activity of 11β-HSD, while prenatal stress also decreases the levels of CBG in maternal plasma (39), thereby potentially increasing the levels of circulating free COR. The blood levels of glucocorticoids are also controlled by negative feedback on the HPA axis via glucocorticoid receptors (GR) in the pituitary, hippocampus, hypothalamic CRH neurons and prefrontal cortex (PFC) (40). In the hippocampus, these GR and mineralocorticoid receptors (MR) become desensitized by chronic stress (40). Together, a decrease in MR and GR signaling, a fall in placental 11β-HSD activity and in circulating CBG levels increase the exposure of the fetal brain to glucocorticoids. If these reach the fetal brain in sufficient concentrations at a critical time during development they could alter its structure and function thereby sensitizing it to the effects of subsequent stress exposure.

EFFECT OF PRENATAL STRESS, ALCOHOL OR INFECTION ON THE REGULATION OF THE OFFSPRING HPA AXIS

Although an association has been found between maternal stress, impaired feedback regulation of the HPA axis and MDD in adult humans (41, 42) it is not known whether this results from altered intrauterine, genetic or postnatal factors, or a combination of them. Some depressed subjects, but not others, show a deficit in dexamethasone-CRH suppression indicating a decrease in GR activation (43). More direct support for a role of intrauterine factors in the alteration of the HPA axis and in the etiology of MDD have come from studies in experimental animals (for detailed reviews see 17, 44). Chronic exposure of the fetal rat brain to COR in the course of prenatal stress does not usually alter resting morning (low) levels of the steroid in

the adult offspring, but may increase the total output over 24 hrs (13) and reduce hippocampal MR and GR (44, 45). However, on exposure to stress, plasma COR increases more in prenatally-stressed (PS) rats (44, 46, 47) and monkeys (48, 49) than in controls. The duration of COR elevation is also longer in PS rats (17), indicating impaired regulation of the HPA axis.

Similar alterations in the regulation of the HPA axis are seen in the offspring of rodents or humans exposed prenatally to alcohol (50, 51) or infection (52, 53). Maternal adrenalectomy prevents the changes in the offspring HPA axis induced by stress (54) or alcohol intake (55). Injection of COR to mimic the plasma levels induced by stress reinstates the changes in the offspring HPA axis, thereby confirming its role as a mediator of the altered programming. In general, the HPA axis in the female offspring of rats exposed to stress, alcohol or cytokines is more sensitive than that of males (45, 53, 56). There do not appear to be any reports of studies on the effects of prenatal infection on the regulation of the HPA axis in humans.

DEPRESSIVE-LIKE BEHAVIOR INDUCED IN RATS BY PRENATAL STRESS

While depression cannot be diagnosed and assessed in experimental animals, one can discern some of its distinctive features and the appropriate physiological changes in PS rats. These include a phase shift in circadian rhythms of plasma cortisol and body temperature (57) and a disturbance in the normal sleep pattern (58). These phenomena can be reproduced in rats by maternal stress (59, 60). Moreover, the changes in rapid-eye movement and slow wave sleep in PS rats were found to be correlated with the magnitude of the increase in plasma COR in response to restraint stress (59). Prenatal stress in some rat strains (61-64) but not others (65) induces a form of learned helplessness in the forced swim test more readily than in controls. This behavior is accompanied by an increased response of the HPA axis to stress like in depressed human subjects. It therefore appears that intrauterine and genetic factors play a role in rats in the ultimate effects of brain programming by maternal stress.

DEPRESSIVE-LIKE BEHAVIOR INDUCED IN RATS BY ALCOHOL OR MATERNAL INFECTION

Daily administration of alcohol to pregnant rats also induces depressive-like behavior (66) and enhances the response of the HPA axis to stress particularly in the female offspring (67-69). On the other hand, there do not appear to be any studies on the behavior of rats subjected in utero to infection. Injection of lipopolysaccharide into pregnant mice on day 17 of gestation to mimic bacterial infection results in anxiety and reduces social interaction in the offspring (70) like that seen in PS mice (71), but its effect on depressive-like behavior has not been investigated.

DEPRESSION, HPA AXIS REGULATION AND THE BRAIN SEROTONIN SYSTEM

The brain serotonin (5-HT) system has been strongly implicated in anxiety and depression (72), and drugs that prolong the action of 5-HT by inhibiting its inactivation by monoamine oxidase or its neuronal uptake are effective antidepressants (73). Although there are many types of 5-HT receptors particular attention has been focused on the 5-HT_{1A} and 5-$HT_{2A/C}$ subtypes in relation to affective disorders (72). In humans, 5-HT_{1A} receptors (5-HT_{1A}R) are expressed presynaptically in 5-HT cell bodies in the raphé nuclei. They are also found postsynaptically on pyramidal cells in the hippocampus, hypothalamus and frontal cortex (74) where their activation inhibits glutamate-mediated depolarization (75). Hippocampal 5-HT_{1A}R are believed to maintain adaptive behaviors in the face of aversive stimuli, and a decrease in their activation can lead to learned helplessness in rats and depression in humans. 5-HT is also involved in the regulation of the HPA axis. Stimulation of 5-HT_{2A}R on CRH neurons in the hypothalamus (76), and of 5-HT_{1A}R and 5-HT_{2A}R in the anterior pituitary (77) increases the release of ACTH.

A. CHRONIC STRESS IN RATS AND 5-HT RECEPTORS

Adrenal steroids and chronic stress inhibit the expression of postsynaptic 5-HT_{1A}R in the hippocampus and other brain regions of rats (78, 79). Adrenal steroids produce their effect on 5-HT_{1A}R mainly via MR but GR also play a role (80) Chronic treatment of repeatedly-stressed adult rats with different types of antidepressants prevents the down regulation of postsynaptic hippocampal 5-HT_{1A}R and restores MR and GR density to pre-stress levels (78, 81). In contrast to their effect on 5-HT_{1A}R, glucocorticoids and chronic stress in rats increase the expression of 5-HT_{2A}R in the FC and hippocampus (81-83).

B. 5-HT RECEPTORS IN HUMANS WITH MDD

Like chronically stressed rats, subjects with MDD showed a significant decrease in 5-HT_{1A}R binding in

the frontal, temporal and limbic cortices, the hippocampus-amygdala region and in raphé nuclei, as measured by neuroimaging with PET using [*carbonyl*-^{11}C] WAY-100635 (84). However, unlike the finding in chronically-stressed rats, this was not reversed by treatment with antidepressants (85, 86). An increase in 5-HT$_{2A}$R was found in the pre-FC of young suicide victims presumed to have suffered from MDD (87).

C. PRENATAL STRESS AND 5-HT RECEPTORS

So far it appears that only two studies have examined the effect of prenatal stress on 5-HT receptor immunoreactivity or expression in rats. As in humans with depression, a decrease was found in PS males in 5-HT$_{1A}$R binding in the ventral hippocampus, an area in the rat primarily linked to emotional processing (88). Surprisingly, others reported an increase in mRNA of 5-HT$_{1A}$Rs in the prefrontal cortex (PFC) (63), and a reduction in hippocampal MR and GRs together with depressive-like behavior. Although GRs are present in the PFC it is not clear why their down-regulation should be accompanied by an increase in 5-HT$_{1A}$R in this region. Chronic treatment with different classes of antidepressants prevented the development of learned helplessness in PS rats, restored GR receptors and normalized the regulation of the HPA axis (17, 64).

D. EFFECT OF PRENATAL ALCOHOL ADMINISTRATION IN RATS ON 5-HT RECEPTORS

Prenatal alcohol exposure in rats has been shown to cause depressive-like behavior in the offspring (66), but 5-HTRs were not measured in this study. Others found that the increased activity of the HPA axis in rats exposed prenatally to alcohol was associated with an alteration in the balance between 5-HT$_{1A}$R and 5-HT$_{2A}$R at different levels of the HPA axis in females but not in males (89). Thus, female rats exposed prenatally to alcohol showed a blunted release of ACTH in response to a 5-HT$_{1A}$ agonist, consistent with a reduction in this receptor signaling, together with an enhanced response to a 5-HT$_{2A}$ agonist. Prenatal alcohol exposure also increased the 5-HT transporter in cortical layers 5 and 6, hippocampal CA layers 2 and 3, lateral nucleus of the amygdala and in the dorsal raphé nucleus, thereby possibly reducing synaptic levels of 5-HT (90). There do not seem to be any reports on the effects of antidepressant treatment on depressive-like behavior, HPA axis regulation or 5-HT receptors in rats exposed prenatally to alcohol. The disparate findings in the effects of prenatal stress or alcohol on 5-HT receptors in rats that have evidence of dysregulation of the HPA axis may be due to the methods of assessment of 5-HT receptor activity, the different brain regions examined and the time of examination in relation to the measures of depressive behavior and HPA axis reactivity.

CHANGES IN BRAIN STRUCTURE IN HUMAN SUBJECTS WITH DEPRESSION

Post mortem studies in patients with MDD indicate a reduction in neuronal size in the orbito-frontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC) (91). Magnetic resonance imaging also detected a decrease in blood flow in the DLPFC that may produce psychomotor retardation and apathy (69). An increase in blood flow and cerebral glucose metabolism (CMG) was found in the ventromedial and lateral OFC which may explain the enhanced sensitivity to pain, anxiety and depressive thoughts in such patients (92). Successful treatment with antidepressants normalized CGM in the ventromedial and lateral OFC of MDD subjects (92). The amygdala is bidirectionally connected to the PFC and hippocampus and plays a crucial role in the regulation of mood and affect (93, 94). CGM is increased in the left amygdala of untreated subjects with MDD. In those showing a persistent positive treatment response to antidepressants there is also a reduction in the level of CGM towards the level in control subjects (84).

Several imaging studies, but not others (reviewed in 91, 95) found a significant reduction in left and right hippocampal volume in patients with MDD compared with controls (96, 97). The degree of hippocampal reduction appears to be directly proportional to the number and the duration of untreated depressive episodes suggesting they may be the result rather than the cause of the depression (98). In patients treated with antidepressants (no details of which are given) the hippocampal volume loss no longer increased with time, suggesting that the drugs may have had some beneficial effect. One can really only determine whether antidepressants can restore hippocampal structure if measurements are made before and after treatment in the same subjects. Nevertheless, other data suggest that a reduction in hippocampal function and volume is more likely to occur in subjects with a significant history of prepubertal physical or sexual abuse than in those with no abuse (99, 100). It is not known whether hippocampal volume is also reduced in human subjects in whom

depression is associated with prenatal stress or infection. However, hippocampal volume was smaller in PS Rhesus monkeys that showed an abnormal dexamethasone suppression test, indicating alterations in the control of the HPA axis (101). It is also not clear from studies in humans with MDD whether antidepressant therapy alters the structural and functional changes in different brain regions associated with this condition. However, chronic treatment with paroxetine of young subjects with obsessive compulsive disorder significantly reduced the enlarged volume of the left amygdala that is also observed in MDD. The extent of the reduction in amygdala volume was correlated with the total dose of paroxetine (102).

CHANGES IN BRAIN STRUCTURE IN HUMAN SUBJECTS EXPOSED PRENATALLY TO ALCOHOL

Structural abnormalities in the cerebellum, basal ganglia and corpus callosum have been reported in humans exposed prenatally to high levels of alcohol (103). Brain imaging and analytic techniques in such subjects have indicated specific alterations including displacements in the corpus callosum, increased gray matter density in the perisylvian regions, altered gray matter asymmetry, and disproportionate reductions in the frontal lobes (31). Apart from the greater changes in the PFC there was no clear resemblance between the structural changes induced by prenatal alcohol and those in subjects with MDD. The lack of such a similarity could be due to a direct toxic effect of alcohol on the developing brain which may mask smaller changes associated with deficits in the regulation of the HPA axis.

STRUCTURAL CHANGES IN THE BRAIN OF ANIMALS SUBJECTED TO PRENATAL STRESS

The anterior cingulate (AC) and OFC are known to be implicated in the regulation of emotional behavior (104). Prenatal stress on days 17-21 of gestation produced a significant reduction in frequencies of dendritic spines on layer II/III pyramidal neurons of the AC and OFC in both males and females aged 23 days. PS males, but not females, also showed a decrease in the length and complexity of pyramidal apical dendrites in both cortical regions (105). This agrees with the finding in depressed patients of a decrease in size of the OFC (91) which may also have been partly due to a loss of dendritic spines and spine length. In one study in which only males were examined PS rats showed a 32% decrease in the density of synapses in the CA3 region of the hippocampus (106). Another study found that young female but not male PS rats showed a significant reduction in the total number of hippocampal neurons (107). However, no assessments were made of their behavior or of the reaction of the HPA axis to stress. In PS male mice which showed an increase in the HPA axis response to stress, a 19-22% reduction was found in the density of synapses and number of dendritic spines in hippocampal CA3 pyramidal cells. These changes were reversed by administration of the antidepressant fluoxetine from the age of 1-3 weeks (108).

CONCLUSIONS

Data from retrospective and prospective studies on the etiology of depression in humans support a role of stress hormones, cytokines and alcohol in the intrauterine environment. Stress hormones like cortisol that reach the fetal brain during a critical time of development alter its programming and sensitize the organism to the effects of stress in childhood and early adulthood. Such sensitization is manifested by alterations in the feedback regulation of the HPA axis to stress via MR and GR, and in the actions of 5-HT via presynaptic and postynaptic 5-HT_{1A}R and postsynaptic 5-HT_{2A}R, all of which can increase the likelihood to develop depression. Successful treatment by antidepressants is associated with restoration of the regulation of the HPA axis and possibly also of 5-HT activity.

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