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Prenatal stress and risk for psychopathology early or later in life: specific effects or induction of general susceptibility?

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3.1 Abstract

This review focuses on prenatal stress as a risk factor for psychopathology early or later in life. Evidence from animal studies is summarized and the relevance of prenatal stress models in animals for human studies is discussed. In the offspring of prenatally stressed animals, overactivity and impaired negative feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis are consistent findings, and may reflect a pathophysiological mechanism involved in the development of psychopathology. Reduced activity of the opioid, GABA/benzodiazepine, 5-HT and dopamine systems and increased activity of the sympathico-adrenal system been found as well. These alterations have been linked to a diverse spectrum of psychopathology. Therefore, the evidence supports the view that exposure to prenatal stress may result in a general susceptibility to psychopathology, rather than exerting a direct effect on a specific form of psychopathology. Recommendations for future research are provided.

3.2 Introduction

In ancient times, it was already a common belief that the emotional state of a mother may affect the child she is carrying (Ferreira, 1965). Prospective studies have substantiated this belief by reporting that maternal stress or anxiety in pregnancy is associated with an adverse obstetric outcome. This is reflected in increased risk for premature delivery, or low birth weight for gestational age (Pagel et al., 1990; Hedegaard et al., 1993; Copper et al., 1996; Lou et al., 1994). Recently, it was further found that prenatal stressors of human life were associated with a significantly smaller head circumference, when corrected for birth weight (Lou et al., 1994). Prenatal stress also significantly worsened the scores on the neonatal neurological examination. This indicates that prenatal stress is able to directly affect fetal brain development in humans. Along similar lines, work in internal medicine and epidemiology has adduced growing evidence that variations in the prenatal environment can influence the physiological responses of the offspring for life. For example, undernutrition in utero changes the body's structure, physiology and metabolism, and predicts the susceptibility to hypertension, coronary heart disease and stroke in adult life (Barker, 1995). The principle that the endocrinologic and metabolic environment afforded by the mother has lasting or lifelong significance has been called fetal programming (Lucas, 1998).

The aim of this paper is to review the importance of prenatal stress as a determinant of the susceptibility to human psychopathology later in life. Such a relationship has been alluded to in papers that described maternal stress in pregnancy as a potential risk factor for schizophrenia (Huttunen et al., 1994; van Os & Selten, 1998; Selten et al., 1999). Although these studies suggest a direct effect of prenatal stress on a specific form of psychopathology, schizophrenia, the question is if there is any evidence for this hypothesis. The present paper explores if rather than having a specific effect, prenatal stress may result in a general susceptibility to psychopathology. Several issues concerning the relationship between prenatal stress and the subsequent fetal and infant development are highlighted, such as: "Which behavioral domains or physiologic systems are particularly affected by prenatal stress? Which effects of prenatal stress are short-lived, and which effects are long-lasting? Does individual sensitivity to prenatal stress play a major role? What are the physiologic mechanisms that mediate the long-term effects of prenatal stress?"

Animal models of prenatal stress are of great value in answering these questions because they allow for a much greater experimental control and afford the opportunity to standardize the exposure to stress and to isolate stress from other lifestyle factors that are interwoven with stress in the human situation. Therefore, results of animal experiments on prenatal stress will be reviewed extensively first. Then we will examine to what extent animal findings are relevant to the human situation. Finally, we will draw implications for our understanding of how the susceptibility to psychopathology in humans may evolve and focus on the issue if this susceptibility is specific or nonspecific.

3.2.1 The prenatal stress paradigm in animal experimental studies

The common element of prenatal stress studies in animals is that pregnant females are subjected to an experimentally controlled stressful situation that leads to changes in the maternal physiology and presumably to alterations in the fetal environment. Subsequently, the influence of the altered fetal environment is examined by pregnancy outcome measures, such as litter size, birth weight, presence of malformations, and by testing the behavioral and physiologic responses of the offspring under standardized conditions. However, studies vary widely according to the methodology employed and the rigor of control for confounding influences. This complicates the comparability of results across studies and may explain discrepant findings.

First, pregnant animals have been exposed to a variety of stressors, including conditioned avoidance training (Thompson, 1957), suspension (Alonso et al., 1991), crowding (Dahlof et al., 1978), rehousing with unfamiliar confederates (Schneider & Coe, 1993), social isolation, repeated electric tail shocks (Takahashi et al., 1991), noise (Clarke et al., 1994), saline injections (Peters, 1982; Cratty et al., 1995), immobilization (Ward & Weisz, 1984) or restraint (Deminière et al., 1992). These stressors are not readily comparable with each other, because some comprise the infliction of pain, some are non-painful physical stressors, and for still other stressors, like crowding, the social element is rather prominent. As a consequence, each of these stressors may give rise to partly different physiologic stress responses in the pregnant animal. Furthermore, the removal of the dam from the home cage in order to inflict stress could be the crucial variable to cause effects in itself, as there were no behavioral differences between the offspring from mothers who were only handled and from those given conditioned avoidance training (Hutchings & Gibbon, 1970). Few studies have controlled for handling and other nonspecific factors when reporting about prenatal stress (Sapolsky, 1997).

Second, the timing, frequency, and duration of the stress application are major variables (Weinstock et al.,1988). Exposure to stress at different times during pregnancy could produce different responses in the offspring (Archer & Blackman, 1971). For instance, the effects have been compared of noise and light stress applied either daily throughout pregnancy, randomly three times weekly throughout pregnancy, or daily only in late pregnancy (Fride & Weinstock, 1984). Following randomly applied stress, pups exhibited an overall delay in motor development, whereas following late daily stress a somewhat accelerated motor development was observed. Thus, the same type of prenatal stress proved to either increase or delay the rate of maturation of early motor behavior of the offspring according to the timing of its application. Daily stress applied throughout pregnancy did not differ in its effects on development from the control condition, whereas exposure to stress in only the last week of pregnancy resulted in altered development (Fride & Weinstock, 1984). Stress exposure on a regular base, for example the presentation of noise in a consecutive series of days at fixed times, may lead to rapid adaptations and may differ in its effect on the physiology of the dam from stress delivered on an unpredictable basis (Fride & Weinstock, 1984). A related issue is the influence of the intensity of the stressor. Due to the mentioned methodological variation, the findings of various studies with regard to intensity and dose-response relationship of the stressor are ambiguous. It seems self-evident that the intensity of the mother's

physiological response rather than the stimulus intensity is the decisive factor, as suggested by Archer and Blackman (1971).

Third, not all designs have included the measurement of the changes in the pregnant animal's physiology brought about by stress exposure. This would be both a methodological control on the effectiveness of stress application and a strategy to learn about the stress sensitivity and stress reactivity of pregnant animals and about dose-response relationships of various types of stressors. In any case, each of the stressors described earlier, including handling, has been shown to activate the HPA axis and to elevate the plasma levels of glucocorticoids of the pregnant animal, when the animal is exposed for the first time (Hennessy & Levine, 1978). Prolonged activation of the HPA axis of the mother, as reflected by persistently elevated levels of glucocorticoids following exposure to chronic stress, was established for the application of restraint stress (Ward & Weisz, 1984) and repeated saline injections (Peters,1986). However, exposure of rats to noise on a regular daily basis led to habituation of the endocrinologic stress response, in contrast to unpredictable noise stress (Fride & Weinstock, 1984). Noise stress or repeated social stress presented to pregnant nonhuman primates also led to an activation of the HPA axis (Mendoza et al., 1979; Schneider et al., 1993). In a similar vein, it is important to document physiological changes in the fetus during and immediately following the stress application to the mother. The two noise schedules described above (Fride & Weinstock, 1984) resulted in different patterns of fetal rat plasma corticosterone. Regular daily stress was associated with a corticosterone peak occurring one day earlier than that in controls. By contrast, unpredictable noise stress produced lower and later fetal peak levels of corticosterone (Barbazanges et al., 1996; Ward & Weisz, 1984; Douglas, 1975).

Fourth, the species that is studied is of importance. Most prenatal stress work has been done in rodents, but a couple of interesting studies have been performed in rhesus monkeys. One should appreciate that there are clear differences between rodents, nonhuman primates and humans in the timing of birth relative to the degree of maturation of the brain and the body at birth (Dobbing & Sands, 1979). At birth, the rat's brain is only about 12 percent its adult weight. However, the rat's postnatal development is extremely rapid and it attains its adult weight within 40 days. Brain development in the rat at postnatal days 12-14 is comparable to that in human babies near term. In contrast, the rhesus monkey's brain growth is nearly complete at birth. The growth of the human brain has a slower speed than that of rat and monkey and is rather prolonged until childhood for most parts and even until young adulthood for some structures of the brain. As a consequence, early programming effects may be expected to occur foremost during the perinatal and early postnatal period in rats, primarily prenatally in rhesus monkeys and over a much more prolonged period encompassing both gestation and the first years of life in humans (Sikich & Todd, 1988). Nonhuman primate models of prenatal stress are rather suitable for extrapolations to the human situation because of long gestations that make it more easy to contrast stress exposure during different periods of gestation, single births, and slower postnatal growth that allows more refined evaluation of neuromotor development than in rapidly developing rodents (Schneider et al., 1999).

Fifth, a number of other methodological issues matter. It is necessary to control for maternal weight loss during pregnancy following stress exposure, particularly when immobilization or restraint stress is used, since weight loss by itself has been shown to adversely

affect fetal development (Guo et al. 1993; Ward & Wainwright, 1988). Some of the stress procedures could also directly and physically affect the fetus, independent of eventually mediating changes of the fetal environment (Hultman et al.,1997; Giberson & Weinberg, 1995). Last but not least, the results of prenatal stress studies may also depend on the choice of the control conditions employed. In some studies comparison was made between a stressed and a nonstressed group, whereas in others it was between two groups that have been stressed under different regimes (Archer & Blackman, 1971). Since it is likely that a prenatally stressed mother will present alterations of postnatal maternal behavior compared to nonstressed mothers, another methodological requirement is to differentiate prenatal effects on the offspring from postnatal effects. This is usually accomplished by using a cross-fostering design, in which the offspring of prenatally stressed mothers are raised by either stressed or nonstressed foster dams (e.g., Maccari et al., 1995). In addition, to not confound treatment with litter effects, it is essential to use the whole litter as the unit of analysis (as opposed to the split litter method), and to retain both female and male pups in the litter. It is known that dams differentially attend to female and male pups with respect to anogenital licking and this differential attention contributes to adverse sexually dimorphic behaviors (Moore, 1984). However, these requirements have often been violated, when researchers used split or single sex litters.

3.2.2 Effects of prenatal stress on behavior of rodent offspring

Aspects of development that have been studied as a function of prenatal stress particularly include early physical and motor development, exploration in a novel environment, disturbance behavior under stressful conditions, learning abilities, and social and sexual behaviors. Many studies report lower birth weights of the pups following prenatal stress (Weinstock et al., 1988), though some studies found no effect on birth weight (e.g. Rojo et al., 1985) or even an increase in birth weight (Dahlof et al., 1978). Early motor development appears to be sensitive to maternal stress as well. The offspring of vehicle-injected damns showed decreased motor abilities, as reflected by the quality of the righting reflex and of climbing at the age of five days, when compared to the offspring of untreated damns (Grimm & Frieder, 1987). Similar findings of a delay in early motor development resulting from prenatal stress have been described by others (Fride & Weinstock, 1984; Barlow et al., 1978).

Most early studies found that prenatal stress affected the behavior of rodent offspring in a novel situation, with prenatally stressed offspring showing a decreased exploration and more defecation in an open field (Archer & Blackman, 1971). Later studies replicated the finding that in a novel environment, such as an open field or a plus-maze, prenatally stressed animals show less exploratory behavior and display signs of heightened emotionality or fear and anxiety, as is reflected by a decrease in locomotor activity and increased defecation (Weinstock et al.,1992; Wakshlak & Weinstock, 1990; Grimm & Frieder, 1987). Other studies, however, revealed a reverse trend, with shorter latencies to explore in the prenatally stressed rodents and more active behavior in a novel situation (Deminière et al., 1992), or found no influence of prenatal stress on these behavioral measures (Chapman & Stern, 1979; Moore & Power, 1986). Genetic factors might contribute to these differing results, since it was found

that prenatal stress caused different offspring activity levels depending on the characteristics of their breed (Thompson & Olian, 1961; Weir & DeFries, 1964). For instance, two inbred strains of mice, which showed either high or low activity levels, were used to study the influence of genetic factors on the offspring response to prenatal stress. The male offspring of a low-activity strain of prenatally stressed mothers were more active than control males, whereas prenatally stressed male offspring of a high activity strain were less active. Female offspring of both strains were less active (Stohr et al., 1998). Thus, both sex effects and genetic effects seem relevant to explain different results following the exposure to prenatal stress. Environmental variables also proved to be relevant, since exploratory activity in reaction to novelty was significantly less in a bright light but not in dim light conditions (Poltyrev et al., 1996). In fact, in the latter condition an increase in locomotor response to novelty was observed (Deminière et al., 1992).

Prenatal stress further affects the adaptation to postnatal stressful conditions. During the preweaning period, 14-day-old prenatally stressed rat pups emit fewer ultrasonic vocalizations than control pups when placed in social isolation (Takahashi et al., 1990). Reduced vocalization is an index of behavioral inhibition that generally occurs in response to threatening situations (Takahashi, 1994). Shock-induced freezing, when tested between postnatal days 70 and 90, was significantly longer in prenatally stressed rats than in control rats (Takahashi et al., 1992). This suggests that the early predisposition toward heightened behavioral defensiveness, which was experimentally induced in rats by prenatal stress, is present at young age and remains unchanged into early adulthood. In general, behavioral differences between prenatally stressed animals and controls are magnified in aversive conditions, such as forced swimming (Alonso et al., 1991), electric foot shocks, or air puffs (Fride et al., 1985, 1986).

Studies on learning abilities of the offspring of stressed damns have revealed impairments on a number of tasks. Early work has adduced evidence for impairments of discrimination learning (Archer & Blackman, 1971; Grimm & Frieder, 1987), reversal of a learning set on a T-maze and acquisition of an operant response (Smith, 1981) in the offspring of prenatally stressed rats. The results of two recent studies, however, are conflicting. Using crowding combined with one daily painful experiences as stressors in Wistar rats, learning acquisition in a water-maze at day 30 did not differ between the prenatal stress and control conditions (Hayashi et al., 1998). In the reversal task, however, prenatally stressed rats spent more time than control animals searching for the platform. After the application of restraint stress in Sprague Dawley rats in the last week of pregnancy, the cognitive performance of the adult offspring (age 120 days) was tested in the water-maze and using a two-trial memory test in a Y-maze with progressive inter trial intervals (Vallee et al., 1997). Though in this design the animals showed problems in coping with novelty, expressed as an increased escape behavior, spatial learning or memory performance proved not to be affected by prenatal stress. These findings suggest that learning impairments due to prenatal stress may be present at young rather than at older age in rats, although the difference in strain and also other design variance of the studies may explain the discrepancies.

The study of social behavior of the offspring of prenatally stressed dams has been a relatively disregarded topic. In an experiment by Takahashi et al. (1992), stress procedures began on day two of pregnancy and lasted throughout pregnancy (day 20) and consisted of an uncontrollable electric shock every other day for ten sessions. On postnatal days 25 and 26,

the social interactions of sibling pairs, consisting of an experimental and a control juvenile male rat, were observed. When the behavioral responses that are indicative of social play were measured by means of the latency to pounce on the opponent, prenatally stressed rats exhibited significantly longer latencies to initiate social play than control rats.

The effect of prenatal stress on altered sexual behavior in the offspring has received a lot of attention by researchers. Restraint stress in the third week of pregnancy was associated with a significant reduction in the testes weight and anogenital distance at birth (Dahlof et al., 1978). It has been shown that maternal stress in the third week of pregnancy, in both mice and rats, demasculinized and feminized the sexual behavior of male offspring (Holson et al., 1995). Prenatal stress was associated with disruptions in the normal course of sexual differentiation and subsequent alterations in reproductive behavior (Rhees & Fleming, 1981), such as impaired ejaculatory behavior and increased female lordotic behavior in male offspring of stressed pregnant rats (Ward, 1972; Ward & Reed, 1985). These behavioral alterations have collectively been named the 'prenatal stress syndrome' (Ward, 1984). The etiology of this syndrome could stem from the same hormonal mechanism underlying sexual behavior differentiation in both normal males and females (see below).

The effects of prenatal stress in rodent offspring behavior are summarized in Table 3.1.

Table 3.1
Prenatal stress effects in rodent offspring behavior

		References
Behavioral effects	Less activity, more defecation, more emotionality in novel situation	Thompson, 1957; Wakshlak & Weinstock, 1990; Fride & Weinstock, 1988; Fride et al., 1986; Grimm & Frieder, 1987; Takahashi et al., 1988, 1990, 1992; Weinstock et al., 1992
	More shock-induced defensive freezing	Takahashi et al., 1992
	Fewer ultrasonic vocalizations when placed in social isolation	Takahashi et al., 1990
	Changes in sexual dimorphic behaviors (play, maternal behaviors)	Ward, 1991
	Impaired sexual function	Holson et al., 1985; Rhees & Fleming, 1981; Ward & Reed, 1985; Ward, 1972
	Reduced propensity for social interaction	Takahashi et al., 1992
	Increased locomotor response to novelty	Deminière et al., 1992
Learning ability	Impairment of maze learning	Archer & Blackman, 1971; Grimm & Frieder, 1987
	Reversal of learning set	Smith et al., 1981; Hayashi et al., 1998
	No effect	Vallee et al., 1997
Motor development	Decreased quality of righting reflex and of climbing	Barlow et al., 1978; Fride & Weinstock, 1984; Grimm & Frieder, 1987

3.2.3 Prenatal stress and behavior of nonhuman primate offspring

Schneider and colleagues have looked at prenatal stress effects in nonhuman primate offspring. In an initial study, rhesus macaques were mildly stressed five times per week during pregnancy from day 90 to day 145 by loud noise. The neuromotor responses of the prenatally stressed infants were assessed at two weeks after birth, employing a modified procedure of the human neonatal assessment protocol used in the clinical setting, the Brazelton Neonatal Assessment Scale. The stressed infants had lower birth weights and compromised physical growth, and exhibited retarded motor development, shorter attention spans, and delays in the development of Piagetian object permanence, when compared to infants born to nonstressed mothers (Schneider, 1992b). When the prenatally stressed subjects were tested at six months of age in a novel environment, they showed significantly more disturbance behaviors and lower amounts of exploratory behaviors compared to controls (Schneider, 1992a). In addition, half of the prenatally stressed infants showed an abnormal response to novelty in the form of falling asleep, while none of the control infants displayed this behavior (Schneider, 1992a).

In a somewhat similar design, the effects of prenatal stress on the offspring of pigtail macaques were examined (Worlein & Sackett, 1995). The applied stressor was restraint in the period from 30 to 130 days of gestation. Infants of prenatally stressed mothers appeared to spend almost twice as much time as nonstressed infants exhibiting fearful behavior in a novel environment. Furthermore, during the first eight months postpartum the stressed infants appeared to be less socially adept, to initiate fewer social interactions and to withdraw from social interactions more often. The adverse influence on motor development as observed by Schneider et al. (1992a) in 6-months-old infants was not confirmed. An explanation for these discrepant findings may be that the prenatally stressed population of Schneider et al. 's study had lower birth weights compared to their nonstressed sample, whereas both the stressed and nonstressed groups of Worlein and Sackett's study (1995) had similar birth weights. Since birth weight in itself was positively correlated with motor maturation ($r=.58$, $p<0.01$; Schneider et al., 1992b), the influence on motor development may be due to lower birth weight rather than to a direct effect of prenatal stress. It is a common finding also in human infants that low-birth weight is associated with a higher incidence of developmental deficits (e.g. Dewey et al., 1999; Pharoah et al., 1994).

Another interpretation problem of both studies includes stress-related changes in the pregnant animal's food and water intake and weight gain. Restraint stress has been found to result in reductions in maternal food and water intake, and the concomitant decrease in maternal nutritional status might account for some effects of prenatal stress on offspring behavior. It has been demonstrated that the offspring of prenatally stressed mice and of pair-fed mice that were fed according to the intake of the stressed mice but did not receive stress themselves, did not differ from each other on a number of brain and behavior developmental factors, whereas both differed from the offspring of controls (Ward & Wainwright, 1988). In a similar vein, Schneider et al. (1992b) noted that the stressed females gained less weight during their pregnancy than nonstressed females. This weight difference could confound possible effects of maternal stress on the infant outcome.

In another study, Schneider and Coe (1993) tried to replicate and extend the earlier findings in three ways: squirrel monkeys were used as another primate species, repeated social stress was applied instead of noise stress, and chronic stress was contrasted with only mid gestational stress and a control condition. The social stress procedure involved changes in housing conditions after which the pregnant animals were exposed to unfamiliar confederates. There were no differences in birth weight between the infants from the three experimental conditions. Assessment of neuromotor functions at two weeks postpartum revealed that infants born following chronic stress were significantly behind in motor maturity and activity than the controls, with the scores of the mid gestation stressed infants falling in-between. Furthermore, infants from pregnancies under chronic stress maintained shorter attention spans, and had shorter durations of orienting episodes, a shorter post rotary nystagmus and less well developed balance control compared to controls. Thus, the adverse influence of prenatal stress on neuromotor development could be replicated, even in the absence of an overt effect on physical growth. When the infant monkeys were examined at the average age of 18.5 months using a separation stress design, prenatally stressed infant monkeys did not differ from controls on environmental exploration or on nonsocial behavior, such as locomotion. They turned out to be different, however, in their social repertoire in that they showed more mutual clinging both in baseline and stress conditions (Clarke & Schneider, 1993). Mutual clinging can be considered as abnormal behavior, since it is rarely observed in normally reared animals.

The aim of a next study was to clarify the period of greatest vulnerability to prenatal stress in rhesus monkeys by contrasting the effects of unpredictable noise stress in early gestation to that in mid-late gestation and to a nonstress condition (Schneider et al., 1999). Early gestation stress was associated with significantly lower birth weights than the mid-late gestation stress and the control condition. Further, infants born following either one of the stress conditions were clearly behind compared to the controls on measures of motor development and attention, but early gestation stress was associated with more pronounced and pervasive motor impairments than mid-late gestation stress (Schneider et al., 1999). Early rather than mid-late gestation stress was also associated with a significant decrease of activity levels. The conclusion is that susceptibility to prenatal stress in nonhuman primates peaks during early gestation and tapers off during mid-late gestation.

The effects of prenatal stress in nonhuman primate offspring are summarized in Table 3.2.

Table 3.2
Prenatal stress effects in nonhuman primate offspring behavior

		References
Behavioral effects	Shorter attention span	Schneider, 1992bSchneider & Coe, 1993
	In novelty: More disturbance behavior	Schneider, 1992a; Worlein & Sackett, 1995
	Less exploration	Schneider, 1992a
	Abnormal response: falling asleep	Schneider, 1992a
	Social behavior: Fewer social interactions and withdrawal from social interactions	Worlein & Sackett, 1995
	More mutual clinging in baseline and stress conditions	Clarke & Schneider, 1993
Development	Retarded motor development	Schneider, 1992b; Schneider et al., 1999; Schneider & Coe, 1993
	Delay in development of Piagetian object permance	Schneider, 1992b

3.2.4 Prenatal stress and offspring behavior: Summary of animal experimental results

Before proceeding, it is useful to summarize the effects of prenatal stress on behavior and learning abilities of offspring. Prenatal stress causes a delay in motor development in both rodents and nonhuman primates. In rodents, prenatal stress is further associated with decreased exploratory behavior, increased emotionality, and impaired adaptation to conditions of conflict or aversion. Exploratory behavior in response to stress or novelty does not seem to be affected in nonhuman primates, although the subjects show more fearful behavior in these contexts. Furthermore, sexual behavior in rats and social behavior in both rodents and nonhuman primates are altered after exposure to prenatal stress. Finally, learning deficits can be found in prenatally stressed rat offspring.

We confined ourselves to reviewing the reported effects of prenatal maternal stress on offspring behavior in rodents and nonhuman primates, two groups of placental mammals that have been studied most extensively. Therefore, the above mentioned summary statements seem acceptable. However, as no attempt was made to critically evaluate the relevant literature, the possibility exists that observed effects in some studies were the result of some variable other than gestational stress alone, due to methodological and procedural shortcomings.

It appeared from the presented evidence that the occurrence of some sort of behavioral effect is not limited to a particular type of maternal stressor and that the same stressor may produce different effects in different species and even in different strains of the same species. These generalized conclusions have important implications for our understanding of the origin of human psychopathology.

3.2.5 Mechanisms underlying alterations in offspring behavior and development

Numerous studies have attempted to uncover the mechanism by which prenatal maternal stress affects offspring. Early attempts involved the possible role of the sympathico-adrenergic system. Maternal administration of catecholamines (e.g., adrenalin), which to some extent mimic the effects of stress, has indeed been found to induce behavioral effects in the offspring, particularly on open-field behavior, comparable to those seen after some forms of prenatal stress. However, this kind of experiment has as yet not provided conclusive proof that it is the maternal catecholamine secretion resulting from stress that is responsible for the alterations in offspring behavior (Thompson & Quinty, 1964; Lederman et al., 1981).
In contrast, during the past two decades a large body of evidence has emerged relating stress-induced disturbances in the maternal HPA axis activity to impaired offspring development. Although the regulation of the stress system, including the HPA axis, under normal and stress conditions is well understood in adult animals and man (see for reviews Chrousos, 1998 and Vázquez, 1998), little is known about the route and mechanism(s) by which maternal stress affects intrauterine development. It will become clear in the next section that no single factor or hormone is to be implicated conclusively as the sole causative agent. After description of the general stress response of the HPA axis in adults, presumed mechanisms of transduction of maternal 'stress' to the fetus will be discussed. Then we will provide evidence that excess of hormones involved in HPA regulation may exert deleterious effects on the offspring's behavior and development. Finally, we will review the effects of prenatal stress on the offspring's brain, including HPA axis regulation and the possible roles of glucocorticoid receptors, opioid receptors, and brain neurotransmitters.

3.2.6 Regulation of the stress system under normal and stress conditions

The HPA axis is considered a peripheral limb of the stress system and consists of three components: the hypothalamus, specifically the paraventricular nucleus (PVN), the anterior pituitary and the adrenal cortex. Within these parts, corticotropin releasing hormone (CRH),

vasopressin (AVP), adrenocorticotropin hormone (ACTH) and ß-endorphin (ß-E) and glucocorticoid hormones (cortisol in humans and nonhuman primates; corticosterone in rodents) are secreted. CRH and AVP are produced in the PVN in response to different stressors. Their role consists of stimulation of receptor systems in the pituitary for ACTH production and secretion. ACTH is mainly produced in the anterior pituitary and stimulates glucocorticoid synthesis and secretion in the adrenal cortex. CRH further influences cells in the arcuate nucleus of the hypothalamus that contain pro-opiomelanocortin (POMC), a large precursor molecule from which ACTH and ß-E are processed. Opioid peptides, such as ACTH and ß-E, contribute to the feedback regulation of CRH release in response to stress, among others by a direct action on CRH terminals in the PVN. Another level of feedback regulation of the HPA axis consists of glucocorticoid receptors. Two types of glucocorticoid receptors have been described, type I and type II receptors. Type I receptors, which are mainly confined to the septohippocampal system, are essentially fully occupied at normal physiological concentrations of cortisol (about 10 ng/ml). Type II receptors are more diffusely distributed throughout the brain and are partially occupied at low circulating cortisol concentrations, but are essentially fully occupied at circulating cortisol concentrations typical of stressed individuals (50-60 ng/ml) (Uno et al.,1994; Weinstock, 1997). Glucocorticoids exert a negative feedback effect on both CRH and ACTH production and secretion at the levels of the hypothalamus and the pituitary, respectively. Glucocorticoids, which are the final effectors of the HPA axis, take part of a complex signaling system between the external environment, the brain and the periphery (McEwen et al., 1997).

The central components of the stress system include the PVN-CRH and the locus coeruleus/noradrenergic-sympathetic (LC/NE) systems. The stress system interacts with other brain systems, a.o. the mesocorticolimbic dopaminergic system, the amygdala, the hippocampus, and the arcuate nucleus POMC neuronal systems. All are activated during stress and, in turn, influence the activity of the stress system. The hippocampus exerts a mostly inhibitory influence on the PVN-CRH and LC/NE systems and the amygdala. The latter can directly stimulate the central components, as well as influence the activity of the dopaminergic system, probably in a lateralized fashion (Chrousos,1998).

Prenatal stressors, including handling, have been shown to activate the maternal HPA axis and to elevate the plasma levels of glucocorticoids in the pregnant animal. The final result is dysregulation of the HPA axis with chronically elevated levels of circulating glucocorticoids and altered feedback regulation. There are several possibilities to explain this: (1) down regulation of receptors in the hippocampus, the hypothalamus, the pituitary or adrenal glands; (2) decreased sensitivity of the receptors at any of these levels; (3) alteration in CRH levels, or altered levels or affinity of plasma binding proteins (Clarke, Wittwer, Abbott, & Schneider, 1994).

3.2.7 Mechanisms of transduction of stress from mother to fetus

The mechanisms presumably involved in transducing stress from the pregnant mother to the fetus are only partly understood. We consider three possibilities which may act in concert: (1) transplacental transport of maternal stress hormones to the fetus; (2) maternal stress-

induced release of placental hormones that in turn enter the fetal circulation; and (3) maternal stress-induced effects on the blood flow to the placenta.

3.2.7.1 Transplacental transport of maternal stress hormones

Abnormal offspring development may be due to in utero exposure to high levels of maternal glucocorticoids. The main argument is that maternal stress is associated with increased secretion of glucocorticoids and that corticosterone, the main glucocorticoid in rodents, easily crosses the placental and blood-brain barriers (Arishima et al., 1977; Zarrow, 1970). Direct evidence for this mechanism is provided in a study in which offspring of prenatally stressed mothers were compared to offspring of prenatally stressed mothers with blocked corticosterone secretion, the latter achieved by removing the adrenal gland and corticosterone substitution (Barbazanges et al., 1996). The offspring of the intact animals showed prolonged stress-induced secretion of corticosterone and a decrease in hippocampal type I corticosteroid receptors, whereas these responses were abolished in the offspring of the mothers with blocked corticosterone secretion. When the adrenalectomized mothers with corticosterone substitution were in addition given an injection of corticosterone to mimic stress levels of glucocorticoids, the usual effects of prenatal stress could be reinstated (Barbazanges et al., 1996). However, adrenalectomy not only affects circulating levels of glucocorticoids, but also influences the levels of other hormones, including ACTH, ß-E, and catecholamines. Alterations of these hormones may play a role as well in producing long-term changes in behavior and neuroregulation in the offspring, in addition to an excess of glucocorticoids.

In contrast to the situation in rodents, where corticosterone easily crosses the placenta, human and nonhuman primate fetuses are relatively protected from the 2-10 times higher maternal levels of cortisol by the placental enzyme 11ß-hydroxysteroid dehydrogenase (11ß-HSD). This enzyme, which exists in at least two isoforms, converts cortisol into the bio-inactive cortisone. Synthetic glucocorticoids (betamethasone, dexamethasone) escape from placental inactivation and readily enter the fetal circulation. In a study in dually perfused freshly isolated intact human placentas a considerable variation between individual placentas was observed in 11ß-HSD activity with a minimum of around 50% and up to 80-90% conversion of cortisol to cortisone (Benediktsson, 1997). Placental 11ß-HSD activity was further positively correlated with birth weight (Stewart, 1995). However, in a study that measured plasma cortisol levels in paired maternal and fetal venous samples at 13-35 weeks' gestation, fetal concentrations of cortisol were found to be linearly related ($r = .63$) to maternal cortisol levels (Gitau et al., 1998). Thus, in spite of the importance of variation in the placental 11ß-HSD barrier to maternal cortisol, maternal cortisol did account for about 40% of the variance in fetal concentrations. Further, a contribution of 10-20% from the mother could still double fetal concentrations, given that fetal concentrations are much lower.

3.2.7.2 Production of stress hormones by the placenta

Maternal 'stress' may also be transduced to the fetus by increased production of CRH and related stress hormones by placental cells under the influence of maternal stress. This mechanism has been found only in primates. During pregnancy the placenta becomes an important transient endocrine unit that is the source of ACTH, CRH and many other hormones (Petraglia et al., 1996). Placental CRH is identical to that present in the hypothalamus and shows the same immunoactivity and bioactivity, but is not subjected to the negative feedback regulation within the HPA axis (Majzoub & Karalis, 1999; Challis et al., 1995). Placental CRH is secreted into both the maternal and fetal circulations and participates, on either side of the placenta, in positive feedback loops. Paradoxically, glucocorticoids stimulate placental CRH, which, in turn, activates the maternal HPA axis, as evidenced by steeply increasing levels of cortisol and ACTH in maternal blood near the end of pregnancy (maternal positive feedback loop). Similarly, placental CRH, entering the fetal circulation via the umbilical vein, stimulates the fetal HPA axis, resulting in increased levels of fetal ACTH and cortisol. The latter enters the placental circulation through the umbilical artery and stimulates further placental CRH secretion, thereby completing the fetal positive feedback loop (Majzoub & Karalis, 1999). A possible physiologic implication of placentally derived CRH is to contribute to fetal maturation, including the early maturation and regulation of the fetal HPA axis. CRH has also been implicated in the control of fetal-placental blood flow and the timing of delivery (McLean & Smith, 1999).

Noradrenaline, acetylcholine, oxytocin and AVP are also known to increase the release of placental CRH (Petraglia et al., 1996). Enhanced activity of maternal stress systems, i.e., an increase in circulating glucocorticoids and noradrenaline, could easily lead to further stimulation of placental CRH and the positive feedback loops. Abnormalities of the placental CRH system, therefore, might be involved in the pathogenesis of preterm delivery and fetal growth retardation (McLean & Smith, 1999), and in the altered regulation of the HPA axis in offspring of prenatally stressed animals.

3.2.7.3 Changes in uteroplacental bloodflow

Maternal stress may reduce uteroplacental blood flow, since cortisol and catecholamines in particular are known to affect vessel tone. Stress-induced activation of the sympathetic nervous system in the pregnant mother could thus reduce the blood flow through the placenta, the more so as placental tissue contains a high density of adrenergic receptors. Indeed, it has been shown that high anxious women have a significant reduction of uterine blood flow in the third trimester of pregnancy as determined by means of Doppler ultrasound, when compared to low anxious women (Teixeira et al., 1999). Moreover, maternal stress is associated with increased uterine activity. The regularly occurring uterine contractions, especially when they are long-lasting, may repeatedly hamper the transplacental transport of oxygen and nutrients to the fetus and thus impair fetal development (Mulder & Visser, 1987). In turn, reduced supply of oxygen and nutrients to the fetus constitutes a significant source of stress for the fetus and may lead to increased release of placental CRH, thereby contributing to the above mentioned positive feedback loops (Challis, 1989).

3.2.8 Effects of excess maternal HPA axis hormones on offspring development

3.2.8.1 Behavioral effects

Prolonged elevated levels of glucocorticoids due to repeated stressors or maternal administration of natural or synthetic glucocorticoids have been shown to affect behavioral development of offspring. Indirect evidence for the excess of glucocorticoid hypothesis may be found by comparing the effects in the offspring of administering HPA axis hormones (CRH, ACTH and glucocorticoids) to pregnant dams with those following prenatal stress. An interpretation problem involved in using this approach is that maternal injection of vehicle alone is quite stressful in rats and able to produce a rise of circulating glucocorticoids and behavioral changes in adult offspring (Grimm & Frieder, 1987).

Activation of the entire HPA axis by administering CRH to pregnant rat females led to increased vocalizations in a novel environment and a shorter anogenital distance in male offspring (Williams et al., 1995). These findings closely resemble abnormalities observed following a combination of heat, light and restraint stressors in the third week of pregnancy (Williams et al., 1998).

The administration of ACTH during pregnancy in rodents has been found to exert inconsistent effects on offspring behavior, with some studies reporting alterations of sexual behavior (Harvey & Chevins, 1984; Rhees & Fleming, 1981) and others failing to observe any changes (Holson et al., 1995; de Cantanzaro et al., 1986). Endocrine activation of pregnant rhesus monkeys by means of a 2-week period of ACTH administration resulted in similar early impairments in motor coordination, attention and temperament as found after prenatal exposure to intermittent noise stress (Schneider et al., 1992). Since ACTH has not been found to cross itself the placental barrier (Dupouy, 1980; Milkovic, 1961), other hormones of the HPA axis (e.g., cortisol and ß-E) likely mediate the ACTH effect.

To determine the possible influence of maternal corticosterone, pregnant rats were subjected to a low dose in the last week of pregnancy (Diaz et al., 1995). The locomotor activity in the prepubertal offspring was increased in the prenatally treated animals as compared to controls. In another study by Diaz et al. (1997), corticosterone administration to pregnant rats resulted in sex-specific alterations in behavior in the offspring at adult age. Males exhibited more exploratory activity than females, and females showed more spontaneous locomotion with no change in exploratory behavior. Corticosterone administration to mice also resulted in abnormal motor behavior, including hyperactivity, impaired avoidance reaction, and decreased motor coordination (Benesova & Pavlik, 1989). Feminized sexual behavior has been observed in male offspring of rats treated with daily dexamethasone injections during the last week of pregnancy (Holson et al., 1995). Mice offspring exposed to a single dose of betamethasone or dexamethasone on gestational day 14 showed specific alterations in anxiety, memory, and socialization when compared to control animals, but no changes in sensory, motor, motivation, and learning performance (Rayburn et al., 1997). Rat pups exposed to either betamethasone or dexamethasone when in utero showed impaired walking in the first week of life, characterized by an abnormal postural tremor and deviant postural control. Complex motor reactions to vestibular stimulation (negative geotaxis and free-fall righting) were markedly retarded. These results, which were previously found in postnatally treated

pups, indicate that synthetic corticosteroids interfere with the development of cerebellar functions involved in complex motor patterns (Gramsbergen & Mulder, 1998). Rhesus monkeys prenatally treated with dexamethasone exhibited no motor or behavioral deficits at young age (Uno et al., 1994).

Activation of the maternal HPA axis under the influence of prenatal stress leads also to increased levels of ß-E that is able to cross the placenta and enters the fetal circulation. There is evidence from rodents that the impairment of early motor development, the feminization of male sexual behavior, and the signs of increased emotionality in the open field following prenatal stress are mediated, in part, by an excess of ß-endorphin. First, similar changes in the offspring can be induced by opioid administration to pregnant animals (Zagon et al., 1970; Ward & Weisz, 1984; Vathy et al., 1985; Ward et al., 1986). Second, treatment of stressed pregnant rats with naltrexone, a long-acting blocker of the mu-opioid receptors, prevents the delay in early motor development, the reduction in anogenital distance in males, and the emergence of increased anxiety in the plus-maze (Keshet & Weinstock, 1995).

3.2.8.2 Morphological effects

It has repeatedly been reported that corticosteroid treatment during neuro-ontogeny leads to abnormalities in brain development, characterized by a.o. decreased proliferation of neural and glial elements, retarded myelination, and increased cell death (see for review Matthews, 2000). The hippocampus is a brain structure that appears to be particularly vulnerable to insult during early development (Levitt et al., 1996; Meaney et al., 1989; Henry et al., 1994; O'Donnell et al., 1994). The hippocampal pyramidal neurons contain a high concentration of glucocorticoid receptors that are highly sensitive to either hypercortisolemia caused by severe stress or to exposure to exogenous glucocorticoids (Uno et al., 1994). Treatment of pregnant rhesus monkeys with dexamethasone, that binds preferentially to type II receptors, led already in low physiologic dosages and in a dose-dependent way to neurotoxic effects on hippocampal neurons (Uno et al., 1990, 1994). Severity and extent of the neurotoxicity of dexamethasone further appeared to depend on the age of the individual. Administration of dexamethasone in the early fetal stage was found to induce severe cerebral deformities, whereas administration in the late fetal stage affects the hippocampal pyramidal neurons that provide the glucocorticoid receptors (Uno et al., 1994).

The effects of excessive amounts of HPA axis hormones during pregnancy have not only been examined with regard to the behavioral and morphological development of offspring, but also in terms of their influence on the HPA axis and neurochemistry of offspring.

3.2.9 Altered activity of the HPA axis in prenatally stressed offspring

There is abundant evidence of an overactive and dysregulated HPA axis in the offspring of prenatally stressed animals. First, a number of studies have measured higher levels of circulating glucocorticoids under baseline conditions in adult rodents that were exposed to stress when in utero (Fride et al., 1986; Weinstock et al., 1992; Ader & Plaut, 1968; McCormick,

1995; Weinstock, 1998). Second, prenatally stressed rats exhibit faster (Fride et al., 1986), stronger (Fride et al., 1986; Takahashi et al., 1988; Takahashi, 1992; Peters, 1982; McCormick, 1995; Weinstock, 1995), and/or more prolonged (Henry et al., 1994; Vallee et al., 1996; Weinstock, 1995) endocrine responses than control animals in reaction to novelty stress, tail shocks or open field observation. For example, Fride et al. (1986) reported that unpredictable noise and light stress, administered weekly in rat pregnancy, changed the corticosterone release of the offspring in adulthood in response to repeated exposure to a novel environment. The release of corticosterone was significantly higher in prenatally stressed rats in response to stress than in controls. More specifically, there was a faster onset of the corticosterone response to a novel environment and delayed habituation upon repeated exposure in prenatally stressed offspring.

Female rodent offspring appear to be more sensitive to the effects of prenatal stress on the HPA axis than male offspring (McCormick, 1995; Weinstock et al., 1992). This is in line with the observation that normal baseline levels of glucocorticoids have been measured exclusively in prenatally stressed males (Henry et al., 1994; Maccari et al., 1995; Takahashi, 1992). In contrast, following maternal ACTH administration in the last week of pregnancy, both male and female adult offspring had elevated basal levels of corticosterone, but lower corticosterone responses than control rats after exposure to stress (Fameli et al., 1994). This suggests that the basal level of adrenal function is programmed at a higher set-point than normal. The continuous hyperactivity of the HPA axis could have led to its exhaustion, since the applied stress challenge did not induce an appropriate endocrine response.

The age at which the activity of the HPA axis is examined in the offspring should also be considered. Basal levels and the stress response of corticosterone were determined in 3-, 21-, and 90-day-old male rats after restraint stress in the third week of pregnancy (Henry et al., 1994). Basal levels of glucocorticoids did not differ between the control and the prenatally stressed groups at all ages. In 3- and 21-days-old prenatally stressed animals, a higher corticosterone secretion in response to novelty was found as compared to controls. At 90 days of age, the experimental animals showed a prolonged response and diminished recovery of circulating glucocorticoids after stress as compared to controls (Henry et al., 1994). These animals also had higher glucose levels, which is consistent with overactivity of the HPA axis (Vallee et al., 1996). Another study showed the presence of an overactive HPA axis in young prenatally stressed rats, while the secretion of HPA hormones did not differ between prenatally stressed and nonstressed groups at adult age (Takahashi, 1992).

In rhesus monkeys the picture is less clear. In prenatally stressed subjects, the ACTH response rather than the cortisol response to a stressor proved to be increased, and the disparity between the ACTH and cortisol levels was greatest in the most stressful condition (Clarke et al., 1994; Clarke & Schneider, 1993; Schneider, 1998). Baseline levels of cortisol and ACTH were normal in 8-months-old monkeys following prenatal noise stress, but were elevated in 18-months-old animals following social stress during pregnancy (Clarke et al., 1994; Schneider, 1998). These data demonstrate that previously stressed and nonstressed monkeys differ in some aspect of feedback regulation within the HPA axis, but both the response type and age effect appear to be different from those seen in rodents.

In several of the above cited studies, an association was found between overactivity and altered feedback regulation of the HPA axis and the earlier described behavioral changes in prenatally stressed animals (Fride et al., 1986; Takahashi, 1992). The altered physiology and

morphology of the HPA axis in prenatally stressed offspring is summarized in Table 3.3.

Table 3.3

Altered physiology/morphology of the HPA axis in prenatally stressed offspring

Rodents	**References**
Higher levels of glucocorticoids (CORT) in baseline	Fride et al., 1986; Weinstock et al., 1992; Weinstock, et al., 1998; Ader & Plaut, 1968; McCormick, 1995
Faster & stronger CORT response to novelty, shock, open field	Fride et al., 1986; Takahashi et al., 1988; Takahashi, 1992; Peters, 1982; McCormick, 1995; Weinstock, 1995
Prolonged CORT response to stress	Henry et al., 1994; Vallee et al., 1996; Weinstock, 1995
Reduction in hippocampal corticosteroid receptors	Barbazanges et al., 1996; Maccari et al., 1995; Henry et al., 1994; Weinstock et al., 1992
Decreased synaptic density in hippocampus	Hayashi et al., 1998
Higher levels of CRH in the amygdala	Cratty et al., 1995; Makino et al, 1994
Nonhuman primates	**References**
Baseline levels of cortisol and ACTHElevated (18 months postpartum)	Clarke et al., 1994
Baseline levels of cortisol and ACTH normal (8 months postpartum)	Schneider, 1998
Increased ACTH response to stressor	Clarke et al., 1994; Clarke & Schneider, 1993; Schneider, 1998

3.2.10 Mechanisms underlying altered HPA axis regulation in prenatally stressed offspring

The generally held hypothesis is that (1) prenatal stress leads to enhanced release of maternal stress hormones, (2) maternal and/or placental stress hormones enter the fetal circulation and, in turn, (3) affect fetal hippocampal ontogeny by down-regulating glucocorticoid receptors, altering receptor sensitivity, and/or exerting neurotoxic effects on hippocampal cells, finally resulting in altered HPA axis regulation (McEwen, 1991; Sapolsky, 1987; Sapolsky et al., 1990). Though not all of these mechanisms which may underlie alterations in feedback regulation of the HPA axis after prenatal stress have been thoroughly investigated as yet, there are at least two clues: a decrease in hippocampal corticosteroid receptors, and higher levels of CRH in the amygdala in offspring exposed to in utero stress.

Clear-cut changes in the hippocampal corticoid receptors have been observed in the offspring of prenatally stressed rodents, with a 70% reduction of type I receptors and a 30% reduction of type II receptors (Barbazanges et al., 1996; Maccari et al., 1995; Henry et al., 1994; Weinstock et al., 1992). Since very young (3-days-old) pups have higher levels of corticosterone but still an almost equal density of hippocampal glucocorticoid receptors, it is likely that the lower amount of receptors at older age is due to exposure to higher levels of steroid hormones, and not vice versa (Henry et al., 1994).

The offspring of rhesus monkeys that had been treated with dexamethasone during pregnancy had at nine months of age higher baseline and post-stress levels of cortisol than vehicle-treated controls. Furthermore, MRI scans of the brain at 20 months of age showed an approximately 30% reduction in size and segmental volumes of the hippocampus following prenatal exposure to dexamethasone. These results therefore indicate that the hippocampus mediates the negative feedback of cortisol release and is especially vulnerable to elevations of glucocorticoids during early development.

Another neural structure that may contribute to increased responsiveness of the HPA axis following prenatal stress is the amygdala. The content of CRH appeared to be substantially increased in the amygdala of prenatally stressed rats compared to levels in control animals (Cratty et al., 1995). Because glucocorticoids have been shown to influence the regulation of the expression of neuropeptide genes (Harlan, 1988), elevated levels of stress hormones induced by prenatal stress may result in increasing CRH mRNA expression in the amygdala (Makino et al., 1994). In turn, increased levels of CRH in the amygdala have been found to be associated with increased emotionality and anxiety-like behaviors and seem to facilitate stress-induced behavior and autonomic activation (Brown & Gray, 1988; Takahashi, 1998).

Thus, prenatal stress significantly augments the responsivity and decreases the feedback regulation of the HPA axis of offspring. During fetal brain development both glucocorticoid receptor immunoreactivity and mRNA levels are present in multiple areas of the brain, including regions containing the monoaminergic neurotransmitter systems (Cintra et al., 1993). The appearance of glucocorticoid receptors in these areas of the fetal brain suggests a possible role of glucocorticoids in normal brain development. Therefore, prenatal stress may result in alterations of other biochemical systems in the brain, such as the opioid and neurotransmitters systems. These alterations could underlie some of the behavioral and physiological effects observed after prenatal stress and may further affect later stress responses. This will be discussed in the following sections.

3.2.11 Prenatal stress and the brain opioid system

It has been noted for some time that endogenous opiates released during stress early in fetal development may mediate stress effects attributed to gonadal steroids. For example, the feminizing effects of prenatal stress on sexual behavior in male offspring can be blocked if naltrexone, an opiate antagonist, is administered to the mother prior to the stressor (Ward et al., 1986). Also, exogenous opiates administered to a pregnant female have been shown to suppress plasma levels of testosterone in the fetus (Singh et al., 1980) and to result in long-term changes in sexual behavior (Ward et al., 1983). In addition to effects on gonadal steroids, opiates have trophic roles during neural development by altering the elaboration of processes, the formation of synapses and the normal rate of cell attrition (Insel et al., 1990).

Prenatal stress has been found to be associated with a diminished activity of the opioid system and with fewer brain opioid receptors in the offspring compared to controls (Insel et al., 1990). In the latter study, female rats were exposed to heat and restraint stress from gestational day 15 through day 22, with a second group of pregnant females left undisturbed. The offspring from stressed females showed a decreased binding of a selective mu opiate receptor ligand in homogenates of the striatum on postnatal day 42. The decrease was largely due to a reduced number of receptors and not to changes in affinity. In vitro analysis revealed decreases in ligand binding in various areas of the brain, such as the caudate-putamen, nucleus accumbens, lateral amygdala and the endopiriform nucleus. On the behavioral level, this was reflected by a reduction of opioid-mediated behaviors, such as morphine and stress-induced analgesia or forced swimming (Kinsley et al., 1986; Alonso et al., 1991). Higher circulating levels of glucocorticoids following prenatal stress seem to be responsible for the reduction of opioid receptors, as well as for the reduction of GABA/benzodiazepine (BZD) receptors in the hippocampus (Fride et al., 1985). In turn, both opioid and GABA/BZD receptor activities contribute to the inhibitory control of CRH release, as administration of naloxone, an opioid blocker, leads to an increased release of glucocorticoids in both normal and prenatally stressed rats, though the increase is much larger in the stressed animals (Poltyrev & Weinstock, 1997). Further, the increased activation of the HPA axis following opioid blockade can be prevented by stimulation of the GABA/BZD receptors (Torpy et al., 1993). As a consequence, the reduced activity of both opioid and GABA/BZD systems following prenatal stress augments the increased activity of the HPA axis.

3.2.12 Prenatal stress and brain neurotransmitter systems

3.2.12.1 The serotonergic system

There is a close relationship between the regulation of the HPA axis and the serotonin (5-HT) system (Mitchell et al., 1990). Further, 5-HT is believed to play a role in early brain development through facilitating synapse formation and maintenance (Hayashi, 1998). Therefore, the 5-HT system could hold the key to the problem of identifying where stress effects on the fetal brain take place. Earlier work already showed that prenatal stress is able to change 5-HT turnover in the fetal brain (Peters, 1990). After daily saline injections combined

with crowding during the third week of pregnancy in rats as a stress procedure, the levels of free tryptophan in plasma and therefore the amount of tryptophan available to the fetal brain were significantly elevated compared to control animals. Since tryptophan is a precursor to 5-HT, the amounts of 5-HT and 5-HIAA, a 5-HT metabolite, were increased in the fetal brain. These changes were maintained after birth until postnatal day 10, and were found to be associated with a reduced number of 5-HT receptors in the brain of adult rats (Peters, 1986; 1988). A reduction of 5-HT binding sites in the hippocampus in particular is consistent with suppression of the negative feedback by corticosteroids on type I and II glucocorticoid receptors in this area. Decreased levels of 5-HT and increased levels of 5-HIAA were measured on day 35 in the brains of offspring of prenatally stressed rats (Hayashi, 1998) and in experimental males following ACTH injections during pregnancy (Fameli et al., 1994). This reflects a substantially increased metabolic rate of 5-HT. Moreover, the synaptic density in the hippocampus of stressed offspring was decreased by about 30%. Thus, a stress-induced increase in fetal brain 5-HT synthesis and diminished synaptic density in the hippocampus seem to be mechanisms through which prenatal maternal stress may lead to increased activation of the HPA axis and affects postnatal development and behavior (Peters, 1990).

3.2.12.2 The noradrenergic system

The majority of noradrenergic cell bodies in the brain originate in the locus coeruleus, located in the dorsolateral pons, and project widely to various cortical areas. The noradrenaline-coeruleus system is the central component of the sympathico-adrenal stress system and is involved in attentional processes and in stress responses. Prenatal stress has been reported to elevate the basal concentration of noradrenaline (NE) in the hypothalamus (Peters, 1982) and to diminish it in the medial preoptic area and the median eminence (Moyer, 1978), whereas no alterations were measured in NE levels in cortical, brain stem, and cerebellar regions under basal conditions (Peters, 1982). More important, the concentration of noradrenaline in the cerebral cortex and the locus coeruleus was significantly reduced in prenatally stressed adult rats when measured immediately following a shock stress rather than under basal conditions (Takahashi et al., 1992). Combined with the finding of elevated concentrations of NE metabolites in these brain areas, this suggests that prenatal stress produces an overactive noradrenergic system with increased central NE turnover. Plasma levels of NE and its metabolites did not differ between prenatally stressed and control animals under baseline conditions (Weinstock et al., 1998). Foot shock stress, however, produced a significantly greater activation of the sympathetic nervous system in the prenatally stressed than in the control animals. Furthermore, the activities of the HPA axis and the sympathico-adrenal system were correlated in the control group under both basal and stress conditions, but there was no correlation between plasma corticosterone and indices of sympathetic activity in the prenatally stressed group, indicating a differential activation of the two systems in these animals (Weinstock et al., 1998).

3.2.12.3 The dopaminergic system

Several effects on the offspring of prenatal stress, such as delayed early motor development (Barlow et al., 1978), a stronger locomotor response to novelty (Deminière et al., 1992), and increased fearfulness to stressful situations (Fride & Weinstock, 1988), have been attributed to changes in the dopaminergic system. After prenatal stress in rats, elevated rates of dopamine turnover were observed in the right prefrontal cortex and reduced dopamine activity in the right nucleus accumbens and left corpus striatum (the mesolimbic and nigrostriatal dopamine pathways) (Fride & Weinstock, 1988). Also, a reduction in the degree of hemispheric asymmetry for dopamine and 5-HT turnover rates was seen in the experimental animals (Alonso et al., 1994). In the locus coeruleus reduced levels of dopamine were found following prenatal stress, concomitantly with increased levels of DOPAC (Takahashi et al., 1992). All these changes in the dopamine turnover are similar to those measured following conditioned fear in adult animals and are commonly associated with increased suppression of behavior in the forced swimming test (Alonso et al., 1994). These data suggest that maternal stress during gestation alters the cerebral lateralization of dopaminergic activity and increases the risk for depression and anxiety in the offspring.

Alterations of dopamine receptor systems of offspring following prenatal stress have been documented as well (Henry et al., 1995). The density of the D2 receptor increased markedly in the nucleus accumbens, while that of the D3 receptor decreased considerably in the core and the shell of the nucleus accumbens. In addition, the offspring were also more rapidly sensitized to amphetamine (Henry et al., 1995).

It is surmised that these changes in dopamine receptor densities develop when the animals are adults, with a potential role for impaired control of corticosterone secretion in the offspring (Henry et al., 1995). To determine the possible influence of maternal corticosterone on the nigrostriatal and mesolimbic dopamine pathways, pregnant rats were subjected to a low dose of corticosterone in the last week of pregnancy (Diaz et al., 1995). The locomotor activity in the prepubertal offspring was increased in the prenatally treated animals as compared to controls, and this was found to be associated with an increased dopamine metabolism in the ventral striatum. Furthermore, maternal corticosterone treatment resulted in a disappearance of the asymmetry of dorsal striatal dopamine metabolism in males only. These effects may be mediated by direct activation of corticosteroid receptors in the brain.

3.2.12.4 The cholinergic system

Interest in possible changes of the cholinergic systems after prenatal stress has been stimulated by the modulatory influence of cholinergic neurotransmission on the activity of the HPA axis (Sitichocke & Marotta, 1978) and the regulation of hippocampal glucocorticoid receptors (Yau et al., 1992; Alema et al., 1995). Furthermore, stress increases the release of acetylcholine in the hippocampus (Mark, 1996) and cholinergic tone may be involved in emotional affect (Janowsky, 1994). The female and male adult offspring of pregnant rats that were exposed to restraint stress and bright light exhibited no differences in basal release of acetylcholine, when compared to control animals (Day et al., 1998). Mild stress, however, was found to increase hippocampal acetylcholine release to a greater extent in prenatally

stressed rats than in controls. Furthermore, administration of CRH produced greater release of acetylcholine in prenatally stressed rats than in controls (Day et al., 1998). These findings underscore that prenatal stress has long-term effects on the development of forebrain cholinergic systems and that these changes in cholinergic systems could mediate the increased responsivity of the HPA axis.

The effects of prenatal stress on the aforementioned neurotransmitter systems are summarized in Table 3.4.

Table 3.4
Effects of prenatal stress on neurotransmitter systems

Rodents		References
Serotonergic system	Increased 5-HT in fetal brain	Peters, 1986; 1988
	Increased metabolic rate of 5-HT	Hayashi et al., 1998; Fameli et al., 1994; Peters, 1990
Noradrenergic system	Elevated basal concentrations of noradrenaline (NE) in hypothalamus	Peters, 1982
	Diminished NE levels in medial preoptic area & median eminence	Moyer, 1978
	Reduced NE in cerebral cortex & locus coeruleus after stress	Takahashi et al., 1992
Dopaminergic system	Elevated rates of dopamine turnover in right prefrontal cortex	Fride & Weinstock, 1988
	Reduced dopamine acitivity in right nucleus accumbens & left corpus striatum	Fride & Weinstock, 1988
	Reduced levels of dopamine & increased levels of DOPAC	Takahashi et al., 1992
	Increased density of D2 and decreased density of D3 receptors in nucleus accumbens	Henry et al., 1995
Cholinergic system	Increased hippocampal acetylcholine release	Day et al., 1998

In summary, the mechanisms involved in prenatal stress effects on the fetus are shown in Figure 3.1.

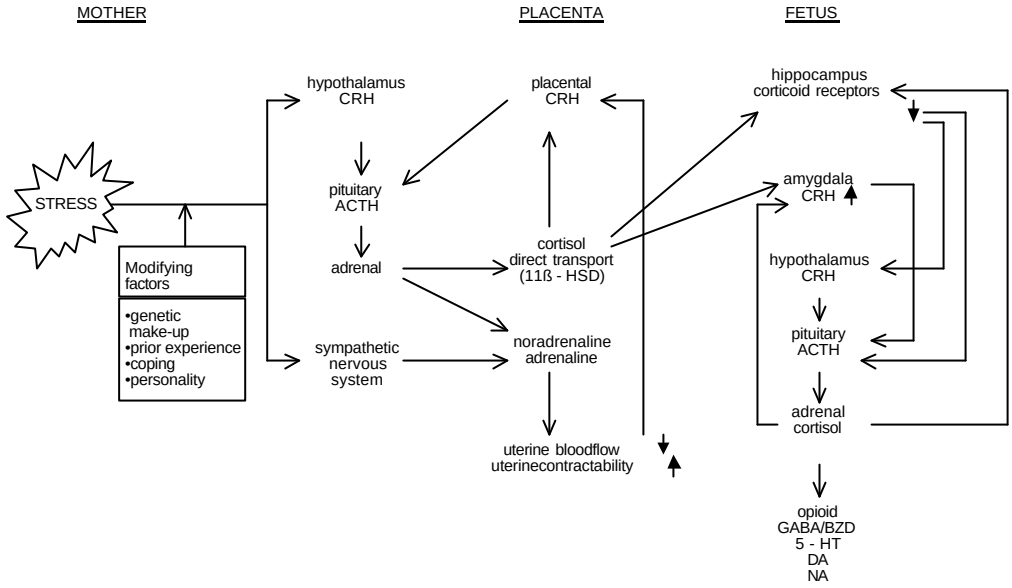

Figure 3.1. Mechanisms involved in the prenatal stress effects on the fetus including several positive feedback loops.

3.2.13 Effects of prenatal stress: modification by postnatal influences

A specific experiential variable can have opposing effects depending on an individual's maturational stage at exposure. For instance, prenatal handling inhibits postnatal exploration, whereas postnatal handling facilitates later exploration (Denenberg & Zarrow, 1971). In fact, a body of evidence exists to show that postnatal handling attenuates fearfulness in novel environments (Levine et al., 1967) and is able to reverse the increase in emotional reactivity induced by prenatal stress (Wakshlak & Weinstock, 1990). Memory performance in a water maze and a two-trial memory test, however, was not affected by prenatal stress nor postnatal handling (Vallee et al., 1997).

On a neuroendocrinologic level, early in postnatal life handled young adult rats were found not to differ from nonhandled rats in basal corticosterone levels at any time point over the diurnal cycle (Meaney et al., 1992). However, the responsivity of the HPA axis of handled rats was significantly attenuated compared to that of nonhandled animals, as was reflected by a decreased secretion of corticosterone and ACTH to a variety of stressors compared to nonhandled rats (Meaney et al., 1993; Vallee et al., 1997). Corticosterone levels of handled

rats also showed a faster return to basal levels following the termination of stress than do corticosterone levels of nonhandled animals (Meaney et al., 1989). In accordance with the altered feedback regulation of the HPA axis and the decreased number of hippocampal corticoid receptors following prenatal stress (see above), postnatal handling was associated with improved feedback regulation and increased density of glucocorticoid receptors in the hippocampus and frontal cortex (Meaney et al., 1989). A recent study showed that these effects of postnatal handling on the development of the HPA axis were mediated by effects on the mother-pup interaction (Sapolsky, 1997). Handling almost doubled the frequency of licking and grooming, and these maternal behaviors were associated with reduced plasma ACTH and corticosterone responses to restraint stress in adult offspring. Apparently, the effects of prenatal stress on the development of HPA responses to stress can be compensated by early postnatal environmental factors. In addition, on a behavioral level, well-groomed pups showed more open-field exploration. Thus, behavior itself can be influenced by the mother-pup interaction shortly after birth (Sapolsky, 1997).

Another method to examine the reverse effects of the postnatal environment on deleterious effects of prenatal stress is by using a cross-fostering design. In such a design, a group of prenatally stressed pups was placed with an adoption mother shortly after birth and compared to prenatally stressed pups raised by their biological mother (Maccari et al., 1995). Adoption increased maternal behavior, since foster mothers spent more time licking and picking up pups than did the biological mothers. The adopted pups showed an attenuated responsiveness of the HPA axis to stress compared to pups who were raised by their biological mother. Adoption led also to an increase in type I glucocorticoid receptors in the hippocampus (Maccari et al., 1995). This long-term effect of adoption in the early postnatal period needs to be examined more thoroughly in order to elucidate the exact mechanisms behind it.

Postnatal factors not only are able to compensate for prenatal negative effects, but can also be harmful. Maternal separation during the neonatal period results in higher basal corticosterone levels and greater corticosterone responses to stress (Thomas et al., 1968), which last until adulthood (Plotsky & Meaney, 1993). This effect could be explained by a significant reduction in glucocorticoid receptor density in the hypothalamus, hippocampus, and frontal cortex, resulting in a decreased negative feedback sensitivity of the HPA axis. In addition, hypothalamic hypersecretion of CRF was observed after maternal deprivation which in turn could predispose to the development of depression in adulthood (Gold et al., 1988; Coplan et al., 1997).

3.2.14 Relevance of animal prenatal stress models for the human

Although corticosteroids are essential for normal brain development, exposure to excessive amounts of these hormones can have long-lasting effects on neuroendocrine function and behavior. Several animal studies have shown evidence of permanent programming of the brain, including the hippocampus and HPA axis, and other organ systems, such as the endocrine pancreas (insulin) and the cardiovascular system (Matthews 2000). These studies have deepened our insight into the possible mechanisms underlying at least some physical problems in later life (high blood pressure, diabetes). So, with no hesitation, one may say

that animal models of prenatal stress are of significant importance for human development. However, when generalizing the results of prenatal stress models in animals to humans there are some caveats, especially as regards to the pathogenesis of human mental health problems.

We already discussed the differences in the timing of brain maturation between rodents, nonhuman primates, and humans. It is important to scale developmental processes in animals to those in man, and particularly to take into account differences in the stage of brain development at the time of birth.

Species differences also apply to transducing maternal 'stress' to the fetus. In contrast to most other mammals, the human and non-human primate fetus are relatively protected from increased maternal cortisol levels due to placental 11ß-HSD activity, although cortisol may cross the placenta to some extent in these species, especially in stressful conditions. On the other hand, only in primates, two positive feedback loops involving placental CRH are present in the maternal-placental-fetal unit, by which mechanism maternal stress signals reach the developing fetus.

The third comment relates to the experimental character of stress in animal models. Common across these studies is a circumscribed and well-defined form of stress that is externally inflicted upon the animal. Similarly, stress encountered during human pregnancy may be entirely due to external circumstances and be independent of the actions of the individual, like in case of earth quakes, sudden floods, war, or sudden death of significant others. By contrast, many other forms of human stress that are linked to the occurrence of life events or daily hassles, are, at least partially, attributable to the person and may be interwoven with personality and lifestyle factors. This implies the importance to differentiate between personality factors and exogenous life stress in human studies on prenatal stress. The human situation is more complicated with regard to stress responses, since social support and coping style may have mediating or moderating effects on the stress response and may reflect aspects of cognitive control over a stressful situation (Huizink et al., 2000). Furthermore, pregnancy-related anxieties have appeared to be unique elements of stress in human pregnancy and may give rise to altered behavior and development in infants as well (Huizink et al., 2000).

Experimental studies in pregnant animals have, in general, not focused on stress research in a naturalistic social setting. The important roles of the social environment as a main source of stress and of individual differences in stress responsivity and adaptation have been largely neglected. Most of the applied stressors in the earlier mentioned experiments (noise, restraint, electric foot-shock etc.) have little heuristic value as they bear little or no relation to the environmental challenges an animal may meet in its everyday life, although crowding might be an exception. To better mimic the etiology of human stress pathology, one may think of study designs that take into account housing condition (animals living in colonies, in small groups, in pairs, or individually), the social structure (hierarchy, pair bonding) and stability of a group of animals, and the way and ease of food acquisition (food ad libitum vs active foraging under unpredictable circumstances). Thus far, only a few studies of ethological and ecological relevance have been performed in relation to perinatal stress and offspring development. Of particular interest are the studies by Sachser in guinea pigs (Sachser & Kaiser, 1997) and by Nemeroff and colleagues in monkeys (see Coplan et al., 1998), which emphasized the impact of social support and daily hassles, respectively.

Finally, two different coping strategies have been found in adult rats (Koolhaas et al., 1998, 1999) and pigs (Schouten & Wiegant, 1997). Individuals are predisposed to either an active or passive coping style determined by their genetic constitution and early life experiences. Actively coping animals appear to differ from those using a passive coping style as regards to behavior, physiology, endocrinology, and immunology. However, we are unaware of any study of gestational stress that has incorporated maternal coping style and individual differences in response to stress.

3.2.15 Human studies

Much interest has been paid to the possible effects of gestational stress in humans on the duration of pregnancy, birth weight, and related measures of obstetric outcome (Pagel et al., 1990; Hedegaard et al., 1993; Copper et al., 1996; Lou et al., 1994). These studies did not only include the effect of psychological stress during pregnancy, but also the effect of physical stress such as chronic exposure to loud noise in the vicinity of an international airport (Schell, 1981) or fatigue associated with occupational working conditions during pregnancy (Landbergis & Hatch, 1996; Mamelle & Munoz, 1987). Relatively few studies, however, have looked at the influence of prenatal stress on postnatal development in humans, and most of these are limited by the use of retrospective designs, small sample sizes, and/or non-standardized measurements. For example, infants of emotionally disturbed or high anxious pregnant women have been described as restless, irritable, overactive, poor sleepers, and less alert and responsive compared to infants of undisturbed or low anxious women (Ferreira, 1960; Turner, 1956; Ottinger & Simmons, 1964; Farber et al., 1981). Infants of high anxious women further had lower scores on the mental scale of the Bayley Scales of Infant Development than infants of low anxious women (Davids, 1963). In a birth-cohort study of about 1300 children, marital discord and interpersonal tensions during pregnancy produced elevated rates of both physical disease and behavioral problems at later age (Stott & Latchford, 1976). Furthermore, the prenatal history of severely emotionally disturbed children that were seen in partial hospitalization or in-patient programs revealed exposure above chance level to stressors like unplanned and/or rejected pregnancies, marital discord, and affective problems in the mother (Ward, 1991). Of course, all these reports focused on the influence of maternal personality variables on the postnatal development of the child rather than on the influence of prenatal stress per se. Other retrospective studies reported that specific forms of stress during pregnancy, such as the threat of and exposure to the six-day Arab-Israeli war (Meijer, 1985) and severe familial and marital discord (Stott, 1973), were associated with delays in early motor development and increased amounts of behavioral problems as excessive clinging, crying, hyperactivity, low frustration threshold and antisocial behavior at age 2-10 years.

Some studies have focused on the relation between prenatal stress and the risk for later severe psychopathology. Severe psychological stress in the pre- and perinatal period was retrospectively linked to a relatively high incidence of attention-deficit hyperactivity disorder (Clements, 1992). In a follow-up study to age 15 of the children born to mothers who faced the death of their spouse during pregnancy, a relatively high incidence of psychiatric disorders was found, when compared to infants that lost their father in the first year of life (Hut-

tunen, 1994). The disorders included schizophrenic episodes, depressive and neurotic symptoms, alcoholism and antisocial behavior. Children born from unwanted pregnancies have also been reported to have increased risk to develop schizophrenia (Myhrman, 1996). In a case-control design and using data from psychiatric case registers, prenatal stress exposure in the first trimester of pregnancy caused by the German invasion during the second World War in the Netherlands was associated with a small but significantly elevated risk for schizophrenia (van Os & Selten, 1998). In a similar design, a slight nonsignificant increase was found in the incidence of non-affective psychosis following prenatal exposure to stress induced by the Dutch flood disaster of 1953 (Selten et al., 1999).

Few studies have employed a prospective set-up. In a sample of 337 pregnant women, maternal anxiety, assessed prospectively during pregnancy by means of a self-report anxiety scale, proved to be significantly related to a difficult temperament of the baby at four months after birth (Vaughn et al., 1987). Since temperamental ratings were also obtained from the mothers, the association between pregnancy anxiety and later temperament may well be due to report bias, i.e., personality factors of the mother. Plasma levels of maternal cortisol, ACTH and ß-endorphin obtained during the third trimester of pregnancy, during the early stages of labor, at day one after birth, and from umbilical blood failed to show consistent relations with either maternal anxiety or temperamental variables of the infant (Vaughn et al., 1987). In another study among 70 nulliparous women, self-report measures of state and trait anxiety obtained during pregnancy showed significant positive correlations with fetal motor activity and fetal sleep state organization, assessed by means of ultrasound recordings in the third trimester or pregnancy (Van den Bergh, 1990). In addition, prenatally assessed maternal anxiety was correlated with temperamental problems in the infants at seven months of age. Path analysis suggested that maternal anxiety had indirect (by modifying fetal behavior) rather than direct effects on infant behavior. However, no differences were found between infants from high and low anxious mothers during neurological examination and standardized observations of feeding behavior, nor on the Bayley Scales of Infant Development between 1 and 28 weeks after birth. All in all, these studies also suggested the influence of maternal personality rather than that of prenatal stress on fetal and infant behavior.

3.2.16 Prenatally induced physiological changes and implications for human psychopathology

As reviewed above animal experimental work on prenatal stress has shown that the HPA axis in the offspring is overactive and has an impaired feedback regulation. Abnormalities of brain transmitter systems have been documented as well. In this section we will consider the potential implications of these physiologic changes for our understanding of the risk for human psychopathology later in life.

The neuroendocrinologic profile of the offspring of prenatally stressed animals is very similar to that found in humans with major depressive disorders. In about 50% of depressed patients, there is an increased secretion of cortisol throughout the 24 hours and loss of circadian rhythm. In addition, like in chronically stressed animals, there is an impaired negative feedback control of the HPA axis and hypertrophy of the adrenal gland (Checkley, 1996). Evi-

dence for an increased central drive to the HPA axis in depressed patients is that the brains of depressed suicides were shown to have a substantial increase in the number of CRH expressing cells in the paraventricular nucleus of the hypothalamus and an increase in the co-expression of CRH and arginine-vasopressin in the same region (Scott & Dinan, 1998). Thus, prenatal exposure to stress in humans may lead to an altered set-point of the HPA axis and increase susceptibility to later depressive disorders.

Though far less extensively documented than in depression, children with an inhibited temperament are characterized by a higher baseline tone of the HPA axis and the sympathico-adrenergic system (Kagan et al., 1988). These children show high levels of anxiety and behavioral inhibition in unfamiliar environments and when exposed to novelty and uncertainty (Kagan et al., 1987), and they are at increased risk to develop later anxiety disorders (Kagan et al., 1988). Another consequence of prenatally induced hyperactivation of the HPA axis may be later deficits in memory and cognition through neurotoxic effects on hippocampal neurons (O'Brien, 1997). Studies in rats and primates have revealed that hippocampal neurons and glucocorticoid receptors are lost during ageing (Djordjevic-Markovic et al., 1999; Ball, 1977). In parallel, during ageing the negative feedback regulation of the HPA axis is weakened and dexamethasone resistance increased. Cell loss in the hippocampus by early exposure to an excess of glucocorticoids thus could lead to further activation of the HPA axis and greater susceptibility to develop impairments in memory and learning at old age (Sapolsky, 1997).

A second neurochemical change following prenatal stress that may be of relevance for later psychopathology is a low central activity of the 5-HT system. The 5-HT system plays an important role in regulating early developmental processes, including differentiation, cell migration, and synaptogenesis. Hence, early disruption of the 5-HT system may have widespread effects on various brain functions. An abnormally low activity of central 5-HT has been implicated in an array of psychopathological conditions, varying from autism, impulsive aggression, depression, eating disorders, and chronic pain syndromes (Halperin et al., 1997; O'Dwyer et al., 1996; Petty et al., 1996; Lopez-Ibor, 1992; Haze, 1991; Hendler, 1982).

Thus, rather than exhibiting a direct effect on a specific psychopathology, prenatal stress hampers several physiological systems that are involved in a wide spectrum of psychopathology.

3.3 Conclusion

The main arguments of this review have been summarized in Figure 3.1. A voluminous literature in rats and nonhuman primates contains consistent evidence that exposure to a variety of stressors during pregnancy is associated with delays in neuromotor development, increased emotionality, decreased exploratory behavior, and impaired adaptation to conditions of conflict. In addition, altered sexual behavior and learning deficits have been described. Physiological changes include overactivity and impaired negative feedback regulation of the HPA axis. Furthermore, reduced activity of the opioid, GABA/benzodiazepine, 5-HT, and dopamine systems and increased activity of the sympathico-adrenal system have been found. Likely mechanisms to explain the transfer of stress from the mother to the fetus are the direct transport of glucocorticoids and ß-endorphin across the placenta, increased

placental production of ACTH and CRH under the influence of maternal stress, and changes in the uteroplacental blood flow.

In contrast, our knowledge about the short-term and long-term effects of maternal stress during pregnancy on the developing fetus and the child in man is rather scanty. Though the human fetus seems to be relatively protected from a massive direct transport of cortisol across the placenta through the 11ß-HSD enzyme, elevations of maternal cortisol levels seem to be able to affect a significant amount of variation in fetal cortisol levels. Genetic polymorphisms of 11ß-HSD and the quality of the placenta may further add to explain individual variation in the permeability of the placenta to maternal stress hormones.

Animal studies indicate that it is quite plausible that prenatal stress leads to increased predispositions for later psychopathology, including depression, anxiety disorders, and memory and cognitive deficits. Evidence for a specific effect of prenatal stress on schizophrenia and other mental disorders is rather weak and has been generally overstated. All studies have used a retrospective design which makes it very hard to control for many other factors involved in the development of psychopathology. Moreover, pathophysiological mechanisms were not studied. The findings summarized in this review suggest that prenatal stress may exert its effects on various physiological systems, which are more generally involved in the development of psychopathology. Thus, the effects of prenatal stress appear to be nonspecific by early programming of, for instance, the HPA axis reactivity. This calls not only for further prospective human studies, but also for reconsidering health system routines around prenatal care and thinking about new strategies to reduce stress in pregnancy.

Recommendations for such future studies include research on the stress reactivity and endocrinology of pregnant women in order to elucidate potential pathophysiological mechanisms that may mediate the effect of prenatal stress on the developing fetus. Genetic studies may shed more light on the genetic contribution on individual sensitivity of infants for exposure to prenatal stress. Future animal studies could try to link preclinical topics with clinical issues by designing prenatal stress studies in line with the stressors that may be encountered in human pregnancy. Thus, a lifestyle stressor approach, with daily hassles or social stress as predictors of offspring development and behavior, may provide more relevant and comparable results for human studies. In addition, coping behavior of pregnant animals confronted with stress also offers an interesting approach for future studies, since in human studies coping is regarded as a potential mediator of the stress response.

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