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Prenatal stress and glucocorticoid effects on the developing gender-related brain☆

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Abstract

Hormonal and neurotransmitter environment of nondifferentiated cells in the developing brain determines many of gender-specific behavioural and neuroendocrine functions. Early postnatal and long-term effects of maternal stress or prenatal glucocorticoid on sex-related peculiarities of the brain morphology, biogenic monoamine turnover, testosterone metabolism, hypothalamic noradrenaline (NA) and adrenocortical responses to an acute stress were studied in Wistar rat offsprings. Maternal stress (1 h immobilization daily for gestational days 15–21) prevented development of sexual dimorphism in neuronal cell nuclei volumes in suprachiazmatic nucleus (SCN) in 10 day old pups. That was associated with a disappearance of male–female differences in NA and 5-hydroxytryptamine turnover in the preoptic area (POA) and dopamine (DA) turnover in the mediobasal hypothalamus (MBH) by decreasing them in male pups. Hydrocortisone acetate (5 mg daily during the last week of pregnancy) produced changes in NA turnover in the POA of males and females which were quite similar to those after maternal stress. Changes in aromatase and 5α-reductase activities in the POA of male pups were quite opposite as affected by maternal stress or prenatal glucocorticoid. Sexual differences in 5α-reductase activity in the MBH appeared due to its increase in prenatally stressed male pups. In contrast to adult males, in adult females maternal stress did not restrict hypothalamic NA and blood plasma corticosterone response to acute stress (1 h immobilization). Our findings on morphology and functions of gender-related developing brain areas stand in correlation with modifying effects of maternal stress and prenatal glucocorticoid on behavior and neuroendocrine regulations.

1. Introduction

Organizing effects of gonadal and adrenocortical steroids on mammalian developing brain is a matter of fact that is generally recognized by neurobiologists. Despite the fact that brain development and its plasticity (neuronal growth, synaptogenesis, cellular communications) depend mainly on genetic program and intrinsic signals, many perinatal agents like stress, natural and synthetic glucocorticoids, neuropeptides, gonadal steroids are capable of modifying the brain morphology, chemistry and physiology. They exert the imprinting effects on steroid receptors, neurotransmitter synthesis, metabolism and receptors, expression of specific proteins, etc.

In 1972 I. Ward published a milestone work on feminizing effect of maternal stress on sexual behavior in adult male rat offspring [1]. Then G. Dörner reported about the disruption of brain sexual differentiation (BSD) in men as a result of maternal or the so-called prenatal stress (PS) [2]. Now new evidences demonstrating that early exposure of pregnant mammals to stress, hormone and neurotransmitter imbalance generates irreversible long-term alterations of behavior, neuroendocrine control of reproduction and stress-responsiveness of the hypothalamus–pituitary–adrenocortical (HPA) axis in the offspring have appeared [3–6]. These phenomena are suggested to occur due to stress-induced changes of catecholamine (CA) and sex steroids contents in dams and fetuses. Maternal stress lowers CA concentration and steroid aromatase activity (AA) in the brain and decreases blood plasma testosterone (T) and luteinizing hormone levels in fetuses and newborn male rats [7–11]. T or tyrosine, CA precursor, administration to pregnant rats prevents

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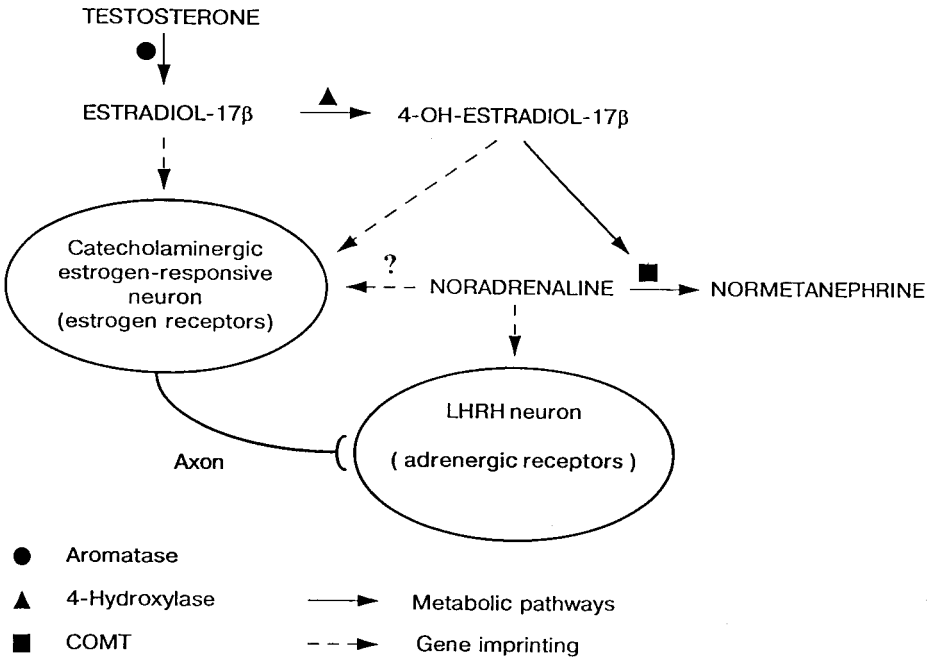

Fig. 1. Conceptual model of androgen-dependent brain differentiation. See text for description.

long-term disturbances of sexual behavior in adulthood induced by PS [12, 13].

Long-term effects of maternal stress on stress-induced HPA reactivity and sexual behavior in adult male rat offspring may be caused by endogenous hypercorticoidism [1, 4, 14]. In this connection neuroendocrine effects of prenatally administered glucocorticoid are of particular interest because of an increase of adrenocortical steroids in maternal blood and their ability to cross placental and blood–brain barriers. Nevertheless, mechanisms underlying perinatal stress and hormonal modification of neuroendocrine system are not well understood yet.

This paper reviews our recent results on prenatal stress or glucocorticoid effects on gender-related developing brain and HPA stress-responsiveness.

2. Lessons from previous studies

An early modification of neuronal reactivity to hormones and neurotransmitters seems to be a key point of genetic imprinting in the developing brain. There is a general consent that T-induced development of the masculine pattern of neuroendocrine regulation of pituitary gonadotropin secretion is associated with a decrease of the content of estrogen receptors in the brain and insufficient noradrenergic reactivity that cause a refracterness of the neural ovulation center to an estrogen.

In the previous studies we used males and neonatally androgenized female rats to estimate the role of hypothalamic CA and locally formed estrogenic metabolites of T as possible determinants of masculine, that is acyclic pattern of gonadotropin release. Steroid aromatase inhibitors, CA synthesis and adrenoreceptor blockers, the inhibitor of catechol-*O*-methyl-transferase, as well as a number of steroids with catecholestrogens included used for that aim.

In newborn female rats, T gave a rise to CA content in the hypothalamus on the 7th–10th days of postnatal life [15, 16]. That rise was prevented using steroid aromatase inhibitors or α-methyl-*p*-tyrosine, tyrosine hydroxylase blocker [17, 18]. At the same time, these inhibitors prevented T-induced anovulation.

On the other hand, one of the catecholestrogens tested, 4-hydroxy-estradiol-17*β*, which is considered to be a natural metabolite of T in the central nervous system, when applied to newborn females produced elevation of the CA content in the hypothalamus and caused anovulation like T did [16]. We suggested that the catecholestrogen is responsible for T-induced rise of hypothalamic CA due to the inhibiting effect of the catecholestrogen on catechol-*O*-methyl-transferase.

Selective increase of hypothalamic catecholamine level in newborn females using tropolone, pharmacological agent that inhibits catechol-*O*-methyl-transferase, did not induce anovulation [19]. Applied together with testosterone, it enhanced the ability of an androgen to defeminize the pattern of gonadotropin secretion.

From these experiments we came to a conclusion that an early androgen-induced organization of acyclic gonadotropin secretion requires: (i) a rise in hypothalamic CA levels, (ii) conversion of T into estrogens in the neural tissue and then into catecholestrogens, es-

pecially 4-hydroxyestradiol-17β, (iii) joint actions of estrogenic metabolites and CA on the developing brain. In accordance with the conceptual model, noradrenaline (NA) and locally formed estrogens are the determinants of the androgen-dependent neuronal differentiation during early ontogenesis [20] (Fig. 1).

We hypothesized that effects of maternal stress and prenatally administered glucocorticoid on neuroendocrine and behavioural functions in offspring could be mediated by an alteration of steroid metabolism and biogenic monoamines disorders in the developing brain.

Pregnant Wistar rats were exposed to strict immobilization for 1 h a day or treated with hydrocortisone acetate during the last week of pregnancy. Based on the previous experience, 10 day old pups and adult 3 month old offsprings of both genders were chosen for this research. It should be emphasized that rat brain is sensitive to organizing effects of steroid hormones during the first 10–12 postnatal days.

3. Early postnatal effects of maternal stress and prenatal glucocorticoid in the brain

3.1. Karyometric studies

The morphologic manifestation of PS impact on BSD is the changes of sexually dimorphic nucleus of the preoptic area (POA) [21].

Neuronal cell nuclei volumes were measured by light microscopy in frontal sections of the suprachiazmatic nucleus (SCN) stained with cresyl violet. Sexual dimorphism of SCN average nuclei volume was found in 10 day old pups being higher in males than in females. This difference disappeared due to the decrease of neuronal nuclei size by 20% in PS males.

The SCN is known to be involved in neuroendocrine control of the male sexual behavior in rodents while in females it is associated with circadian gonadotropin secretion and trigger mechanism of ovulation [3]. Thus SCN karyometric data obtained may reflect PS-induced behavioural alterations.

3.2. Biogenic monoamines

There are numerous reports on sexual differences in morphology and function of CA system of the brain [22, 23]. In the meantime, the mechanisms of the development of monoaminergic sexual dimorphism and its structural localization remain unclear.

We studied the effects of PS on catecholamine and indoleamine content and turnover in discrete brain regions of 10 day old male and female rat offspring. CA turnover rate was calculated from measuring NA and dopamine (DA) tissue concentrations before and then 60 and 120 min after injection of α-methyl-*p*-tyrosine, a potent catecholamine synthesis inhibitor. It is generally accepted that turnover rate during the first hour after enzyme blockade relates to utilization of the catecholamine functional pool.

In the previous study of hypothalamic CA content during early postnatal life we found a significantly higher NA level in males as compared with females on the 10th day after birth [16]. Further experiments were carried out in sex-related brain areas, i.e. POA and mediobasal hypothalamus (MBH), considering their different function in neuroendocrine control of reproduction in adult animals. It is well known that the POA is associated with male sexual behavior and female ovulation center while centers of gonadotropin negative feedback and of female sexual behavior are located in the MBH [24, 25].

On the 10th postnatal day normal males demonstrate lower levels of NA in the POA and DA concentration in the MBH in comparison with normal females [26]. Maternal stress prevents these gender-related differences. NA concentration in the POA of PS males was increased up to normal female level, while DA in the MBH of PS females rose up to the level observed in normal males. Simultaneuosly, maternal

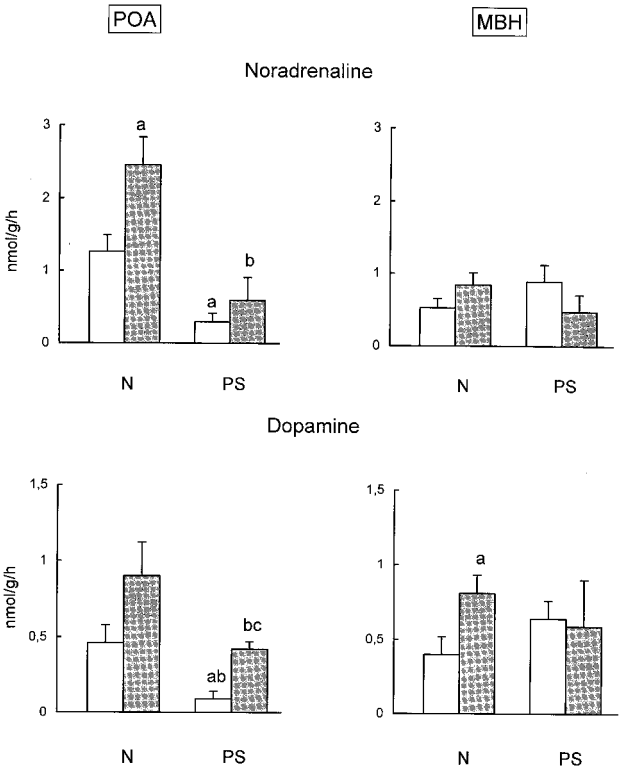

Fig. 2. Effect of maternal stress on catecholamine turnover rates in the preoptic area (POA) and mediobasal hypothalamus (MBH) of 10 day old female (light bars) and male (dark bars) rats. N, normal rats; PS, prenatally stressed rats. Data are mean $\pm$ SEM $^{a}p < 0.05$ vs normal females, $^{b}p < 0.05$ vs normal males, $^{c}p < 0.05$ vs prenatally stressed females.

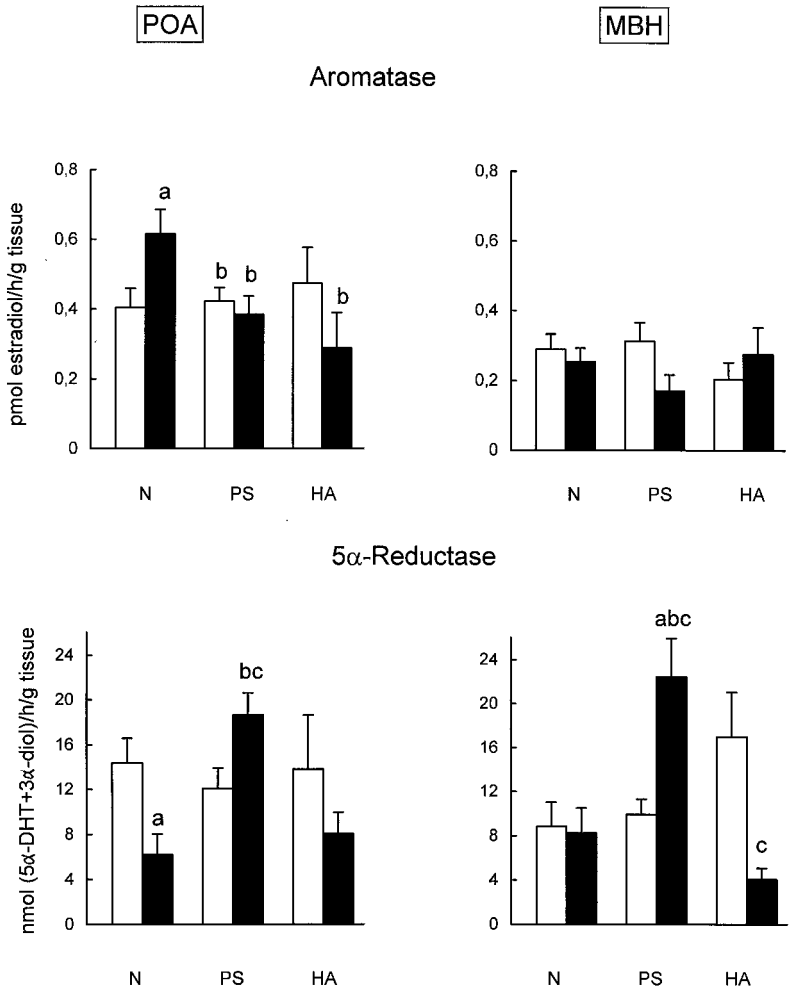

Fig. 3. Effects of maternal stress or prenatal glucocorticoid on testosterone metabolism in the preoptic area (POA) and mediobasal hypothalamus (MBH) of 10 day old female (light bars) and male (dark bars) rats. N, normal rats; PS, prenatally stressed rats; HA, rats prenatally exposed to hydrocortisone acetate. Data are mean ± SEM $^{a}p < 0.05$ vs normal females, $^{b}p < 0.05$ vs normal males, $^{c}p < 0.05$ vs prenatally stressed or exposed to hydrocortisone acetate females, respectively.

stress did not prevent developmental male–female differences in NA content in the MBH.

In intact animals, NA turnover rate in the male POA was higher than that of female's [27] (Fig. 2). It became considerably less in both PS males and females. Sex-related differences were absent in those pups because of deeper slowing down of NA turnover in males. There were no statistically significant differences of NA turnover in the MBH either in intact or in PS animals.

Interestingly, hydrocortisone acetate, when injected daily in a dose of 5 mg during the last week of pregnancy, produced changes in NA turnover in the POA of males and females which were quite similar to those after maternal stress. Therefore, stress-induced elevation of glucocorticoids in maternal and presumably in fetal blood circulation seems to be responsible for modification of NA turnover rate in the developing brain.

As far as DA turnover is concerned, its rate was higher in the MBH of normal male pups. This sexual dimorphism disappeared as a result of PS, however it was found in the POA of PS pups where DA turnover rates decreased both in males and females.

Similarly to NA turnover, gender-specific difference of 5-hydroxytryptamine metabolism in the POA of the pups, that has been evaluated by of 5-hydroxyindoleacetic acid/5-hydroxytryptamine ratio, was prevented by maternal stress. At the same time PS promoted male–female differences in 5-hydroxytryptamine and 5-hydroxyindoleacetic acid contents in the MBH with greater values in males.

These results stand in correspondence with developmental alterations of behavior and reproductive neuroendocrine functions in rats induced by maternal stress. Probably, PS-induced early postnatal alterations of NA-content and turnover in the POA result in demasculinization and feminization of sexual behavior in males [1]. PS-induced changes in DA-ergic system in

the female MBH might be a possible cause for some abnormalities of female sexual behavior and other reproductive processes [28]. Data on NA content in the MBH are of particular interest in connection with long-term effects of PS in female rats. In this study, NA content and turnover in the MBH of PS females remained normal, which is in line with the absence of disorders of the estrous cycle [3]. Different pattern of changes in brain biogenic monoamines content and turnover in PS rat males and females apparently reflects sex-specific hormonal sensitivity of immature monoaminergic system during pre- and early postnatal life. Perinatal glucocorticoids have been found to determine tyrosine hydroxylase activity in the developing brain tissues [29]. Hence, an increase in fetal plasma corticosteroids during maternal stress [14] should contribute to changes of CA synthesis in the developing brain. On the other hand, these changes might be caused by a decrease in blood T levels in PS fetal and newborn males [11, 14], which in turn leads to a decrease in hypothalamic AA that has been found in 10 day old males [30, 31]. This suggestion comes from our observations on the relationship between CA and steroid aromatase in the developing hypothalamus [32].

3.3. Testosterone metabolism

Sexual dimorphism in AA was found both in the whole hypothalamus [31] and the POA, but not in the MBH of 10 day old intact rats with the enzyme activity being significantly higher in males [32] (Fig. 3). Unlike AA, 5α-reductase activity (RA) in the POA was 2-fold greater in females than in males.

PS attenuated sexual dimorphism in the POA AA due to its 1.6-fold decrease in males. Similarly, low AA was observed in the POA of 10 day old male offspring whose mothers were injected with 5 mg hydrocortisone acetate on the 16th and 18th days of pregnancy. No stress-induced differences in AA were found in the MBH. PS caused an increase of RA in the POA of male pups, but not in females. In the MBH, PS induced the appearance of male–female

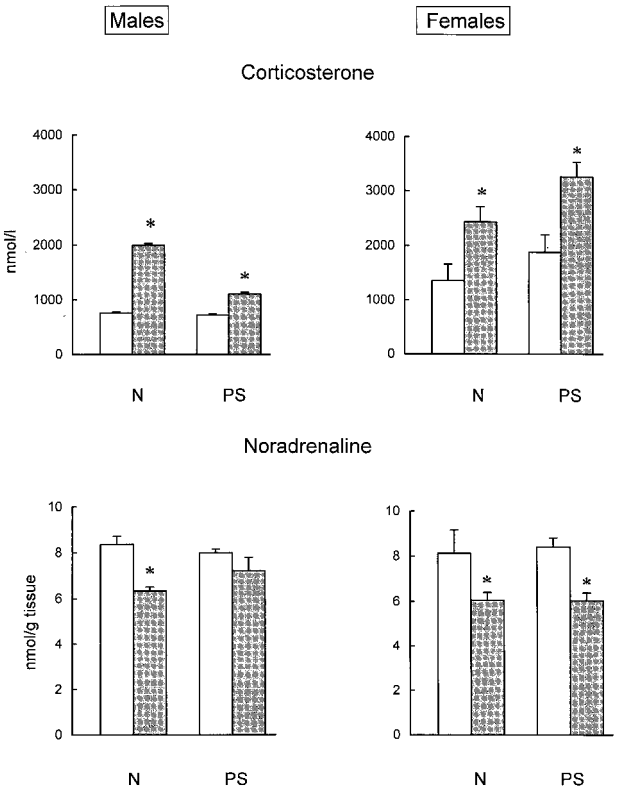

Fig. 4. Blood plasma corticosterone and hypothalamic noradrenaline responses to 1 h restriction in normal (N) and prenatally stressed (PS) adult rat offsprings. Light bars, resting levels; dark bars, after 1 h immobilization. *$p < 0.05$ compared to resting level.

difference in RA which was absent in intact pups. In contrast to AA, the brain RA was not affected by prenatal hydrocortisone acetate in the males.

Additionally to abnormal NA turnover in the POA in PS animals, a disruption of androgen metabolism seems to be responsible for the deviation of sexual differentiation of that brain region, which is traditionally associated with neuroendocrine control of male sexual behavior. A high level of RA in the POA and MBH of PS males could contribute to programming altered reproductive functions.

Earlier G. Dörner's and I. Ward's research groups found a lowering effect of maternal stress on pre- and

Table 1
Long-term effects of maternal stress in rat offsprings

Males	Females
Feminization of sexual behavior	Decrease of fertility and fecundity
Aggravation of aggressive behavior	Aggravation of aggressive behavior
Morphological changes in sexually dimorphic brain area	Delay of sexual maturation
Suppression of pituitary response to LHRH	Changes of estrous cycle
Decrease of hypothalamic catecholamine response to acute stress	Moderate increase of adrenocortical response to acute stress
Decrease of adrenocortical response to acute stress	
Noradrenergic hypersensitivity of the HPA	
Decrease of glucocorticoid receptor density in the hippocampus	

early postnatal levels of blood plasma T in male rats [10, 11]. As T upregulates steroid AA in the fetal and neonatal brain [33], an androgen deficiency possibly causes low steroid AA in the developing brain of PS males.

4. Long-term neuroendocrine effects of maternal stress

4.1. Karyometric studies

Karyometric pattern of sexual differences persisted in normal adult rats, but effect of PS on male SCN neuronal nuclei volumes was even more pronounced making them on average 40% less as compared to undisturbed animals.

4.2. Testosterone metabolism

In normal 3 month old offspring sexual dimorphism of brain AA was not observed. In the POA of intact adults there was a significant male–female difference in RA with higher values in females than in males.

No changes in AA resulting from PS were found either in the POA or in the MBH. On the other hand, the formation of 5α-reduced T metabolites in the MBH decreased in males. The MBH is known to be involved in the negative feedback control over pituitary gonadotropin secretion in males. In this connection, it should be mentioned that PS induces alterations in neuroendocrine regulation of pituitary LH release [34].

4.3. HPA axis

Male offspring of dams exposed to stress during the last week of pregnancy show altered HPA responses to stress [35, 36]. In our previous studies PS-induced diminution of blood plasma corticosterone response to 1 h restraint stress in adult rat males was observed. While acute stress caused the lowering of hypothalamic NA concentration in intact males, such a response was not seen in PS ones [37]. There was no regular NA response in PS male rats, which perhaps resulted from the enhancement of stress-limiting brain mechanisms and impairment of brain CA system.

Following that study we investigated adrenocortical and hypothalamic CA responses to acute stress in PS adult female offspring because the effects may be gender-related [38, 39]. In accordance with these observations, both normal and PS females responded to strict immobilization with NA depletion in the hypothalamus, exactly like males did (Fig. 4). Magnitudes of stress-induced plasma corticosterone responses in intact and PS females were similar [40].

The data obtained indicate appearance of sexual differences in HPA responses to an acute stress in adult PS rats because of its suppression in males and its maintenance in females.

5. Conclusions

Long-term neuroendocrine effects of maternal stress on the rat offspring with a special reference to sexual dimorphism are summarized in Table 1. One can see that the developing brain of female fetuses is less sensitive to maternal stress exposure, however, a few alterations in adulthood are described like enhancement of aggressive behavior or estrous cycle disorders. Many of these alterations are predetermined by changes in biogenic monoamines and androgen metabolism in the developing brain. Neurotransmitters seem to be a meeting point in PS- or glucocorticoid-induced deviations of the imprinting of neuroendocrine control of behavior, reproduction and HPA stress-reactivity.

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