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Neuroendocrine disorders in adult rats treated prenatally with hydrocortisone acetate

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Abstract

We investigated the effects of hydrocortisone acetate administered to pregnant rats over the last gestational week on some neuroendocrine characteristics in adult female and male offspring.

Prenatal glucocorticoid eliminated sex dimorphism of the neurons nuclei volumes in the medial preoptic area and the suprachiasmatic nuclei. There was no elevation of blood plasma corticosterone level after noradrenaline infusion into the third brain ventricle in experimental males; meanwhile, in females adrenocortical response was augmented. Male offspring exhibited a decrease of plasma corticosterone response to an acute stress (1 h restraint) that was not accompanied by post-stress changes neither in the hypothalamic noradrenaline content nor hippocampal glutamate decarboxylase activity. On the contrary, moderate augmentation of adrenocortical stress reactivity and inhibitory effect of GABAergic system were found in females.

It was concluded that exposure to prenatal glucocorticoid is able to alter development of the neuroendocrine systems related to reproduction and stress responses both in males and females and resulted in modification of its sex-dimorphic features in adult life.

Keywords: Prenatal glucocorticoid; Sexual differences; Acute stress; Hypothalamus; Neuroendocrine system; Neurotransmitters; Rat

Introduction

A high-level of the hypothalamic–pituitary–adrenocortical (HPA) activity is a feature of pregnancy in human and most other mammals. Presumably, elevated cortisol levels depend, at least partly, on the increased output of estrogens, which stimulate synthesis of corticosteroid-binding globulin (CBG) in the liver. The rise in blood cortisol level can be mimicked by estrogen injection to non-pregnant women. It is generally recognized that high concentrations of CBG in maternal blood and placental 11β-hydroxysteroid dehydrogenase, which converts cortisol into a less potent glucocorticoid, cortisone, protect the fetus from an excess of glucocorticoid hormones in maternal blood circulation (Edwards

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et al., 1996). Nevertheless, under some conditions those protective mechanisms are being insufficient, that can lead to an increase of cortisol level in fetal blood and disorders of hormone-conditioned imprinting of the developing brain (Seckl, 2004).

There are species-specific peculiarities of the brain development during fetal life. Glucocorticoid exposure of pregnants in late gestation can affect the fetal brain and neuroendocrine development in sex- and species-specific manner. It was demonstrated, that morphological pattern of the limbic system of the fetal rat at term is developmentally equivalent to that of the human fetus at the 80th day of gestation (Darlington et al., 1999). While extrapolating between species, the corticosteroid receptor sensitivity could be taken into consideration (Claman, 1972). Current evidence indicates that prenatal glucocorticoid exposure can programme brain and neuroendocrine function in both corticosteroid-sensitive (rabbits, mice and rats) and corticosteroid-resistant (primates, sheep and guinea pigs) animals (Matthews, 2000, 2001).

It has been shown that stress stimulates HPA axis in pregnant rats and thus modulates neuroendocrine regulations of stress in adult offspring including alterations in hypothalamic corticotrophin-releasing hormone (CRH) and CRH mRNA contents (Plotsky and Meaney, 1993), density of glucocorticoid receptor distribution in the brain tissues (McCormick et al., 1995; Weinstock, 1997), and the brain catecholaminergic system (Takahashi et al., 1992). In our studies, modifying effects of prenatal stress on adrenocortical activity stress responses and HPA noradrenergic reactivity, biogenic monoamines contents and turnover, androgen metabolism, and neurons morphology in the discrete brain regions related to neuroendocrine control of reproduction and stress responses have been demonstrated (Reznikov et al., 1999, 2000, 2004b).

Follow-up observations of long-term neuroendocrine effects of prenatal exposure to exogenous glucocorticoids are helpful in understanding the possible role of maternal adrenal corticosteroids as hormonal mediators of stress-induced changes in HPA and reproduction systems. Animal studies of behavioral, neuroendocrine and metabolic consequences of prenatal treatment with exogenous glucocorticoids are of great importance, because glucocorticoid drugs are widely prescribed by medical practitioners at risk of preterm labor with the aim of preventing respiratory insufficiency in the newborns (NIH Consensus Development Conference, 1995; Ford et al., 1997). Prenatal administration of exogenous glucocorticoids can significantly alter adrenocortical responses to stress and noradrenergic regulation of HPA axis in male rats (Naumenko et al., 1990), brain monoamine metabolism (Muneoka et al., 1997), hypothalamic expression of CRH mRNA (Burlet et al., 2005) and brain glucocorticoid receptors (Levitt et al., 1996; Banjanin et al., 2004; Owen et al., 2005; Kapoor et al., 2006) in rats and guinea pigs.

Early postnatal effects of maternal exposure to hydrocortisone acetate and dexamethasone during the last gestational week on sexual differentiation of testosterone metabolism and biogenic monoamine contents and turnover in the discrete brain regions in 10-day-old male and female rat offspring have been demonstrated in our previous study (Reznikov et al., 2004a). Here, we report the results of investigation of long-term neuroendocrine effects of prenatal hydrocortisone acetate treatment of adult rats with special reference to their sexual differentiation. That should be reasonable for discovering possible adverse effects of prenatal glucocorticoids on developing brain.

Materials and methods

Animals

Experiments were performed according to the protocols approved by the Animal Care Commission at the Institute, in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes of Strasbourg.

Time-mated pregnant Wistar rats ($n = 10$) were subcutaneously injected with hydrocortisone acetate suspension (Gedeon Richter, Hungary) in a dose of 50 mg/kg body mass daily from the 15th until 21st gestational day. According to Naumenko et al. (1990), this dose modifies adrenal cortex responses to an acute stress and noradrenaline infusion into the brain ventricles in adult male rat offspring. Control mothers ($n = 8$) were injected with saline. Litter size averaged six pups. A total of 18 litters with 42 females and 54 male rats were allocated into groups. The culling of newborns was performed to exclude weak ones. The descendants aged 6 (weight range 180–200 g) or 8 (weight range 220–250 g) months were taken for the study. Based on microscopy of the vaginal smears, female rats were taken into experiments in diestrus to prevent any effects associated with the reproductive cycle. The difference in the descendant body mass values did not exceed 15%.

Morphometry

Six-month-old rats (both control and exposed to hydrocortisone acetate groups consisted of five animals) were euthanized by quick decapitation under light diethyl ether anesthesia. Brain regions containing the whole pre-optic area together with hypothalamus were isolated by dissection and fixed in Bouin's solution. After fixation, the brain preparations were embedded in