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Neuroscience and Biobehavioral Reviews 27 (2003) 119–127

NEUROSCIENCE AND
BIOBEHAVIORAL
REVIEWS

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Prenatal stress and long-term consequences: implications of glucocorticoid hormones

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Accepted 29 January 2003

Abstract

We have shown that prenatal restraint stress (PNRS) induces higher levels of anxiety, greater vulnerability to drugs, a phase advance in the circadian rhythm of locomotor activity and an increase in the paradoxical sleep in adult rats. These behavioral effects result from permanent modifications to the functioning of the brain, particularly in the feedback mechanisms of the hypothalamic-pituitary–adrenal (HPA) axis: the secretion of corticosterone is prolonged after stress and the number of the central glucocorticoid receptors is reduced. These abnormalities are associated with modifications in the synthesis and/or release of certain neurotransmitters. Dysfunction of the HPA axis is due, in part, to stress-induced maternal increase of glucocorticoids, which influences fetal brain development. Some biological abnormalities in depression can be related to those found in PNRS rats reinforcing the idea of the usefulness of PNRS rats as an appropriate animal model to study new pharmacological approaches.

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Keywords: Prenatal restraint stress; Corticosterone; Maternal behavior; Circadian rhythms; Antidepressants

1. Perinatal events in humans

There is increasing evidence that variations in prenatal environment can influence the responses of the new-born. Barker [1] has emphasized how adult vulnerability to cardiovascular disease may be programmed during the fetal period. Indeed, non-genetic factors that could act early in life to organize or imprint permanently physiological systems are known as *perinatal programming* [2,3]. It can be speculated that prenatal plasticity of physiological systems allows environmental factors, acting on the mother and/or the fetus, to alter the differentiate functions of an organ or tissue system to prepare the unborn animal optimally for the environmental conditions *ex utero*. However, in extreme conditions like stress and/or under-nutrition, offspring of stressed mothers during pregnancy displayed short and long-term physiological and behavioral abnormalities such as reduced birth weight, increased infant

morbidity, locomotion and cognition retardation, increased anxiety or sleep disturbances [4–6].

The fetus is sensitive to maternal environment and it has been shown that anxious pregnant women, who present an altered blood flow in the uterine arteries [7], can influence the development of the fetus she carries [1,8,9]. Similar results are also observed later, indeed there is an evidence showing that adverse environmental experiences early in life predispose individuals to the development of affective and anxiety disorders in adulthood [10].

Glucocorticoids may underlie the association between low birth weight and adult stress-related cardiovascular, metabolic and neuroendocrine disorders such as hypertension, type 2 diabetes, ischaemic heart disease and affective disorders [11]. These intriguing findings have spawned the *fetal origins hypothesis* of adult disease [1]. The brain is very sensitive to prenatal programming and glucocorticoids in particular have powerful brain-programming properties [11]. One of the most intensively systems studied is the hypothalamic-pituitary–adrenal (HPA) axis. Substantial evidence suggests that prenatal stress programs the HPA

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axis, and that plasticity of developing brain monoamine systems underlies, in part, these changes. Because an important feature of the stress response is the secretion of high levels of glucocorticoids, this steroid has become an obvious candidate for the role of *programming factor* in the prenatal stress paradigm. Thus, in human cohorts, it has been shown associations between low birth weight and adult hyperactivity of the HPA axis [12–14].

2. An animal model characterization

In order to better understand mechanisms involved in the long-term effects of such early experiences and considering the obvious difficulties inherent to human research in this particular field, different kind of prenatal stress animal models have been developed. Pregnant rats have been subjected to various types of stressors: conditioned avoidance training [15], tail suspension [16], crowding [17], repeated electric shocks [18], noise [19] or saline injections [20]. During the last years we have studied the influences of prenatal restraint stress (PNRS) in a rat animal model according to a revised model of Ward and Weisz [21]. The prenatal stress procedure we have used consisted in restraining the mothers. Adult virgin Sprague-Dawley female rats (Iffa Credo, France) were group-housed (10 per cage size 60 × 80 cm²) for at least 10 days after arrival, to eliminate stress resulting from shipping and to coordinate their estrous cycle. Animals were then individually housed in the presence of a sexually experienced male Sprague-Dawley rat. Pregnant females were then randomly assigned to prenatal stress or control groups, and individually housed in plastic breeding cages. For all experiments, animals were allowed ad libitum access to food and water, and maintained on a regular light–dark cycle (lights-on 07:00–19:00 h) with constant temperature (23 °C) and humidity (60%). Prenatal stress was started between the days 11–15 of pregnancy until delivery at 21 days according to a revised model of Ward and Weisz: pregnant females were individually placed in plastic transparent cylinders (7 cm diameter, 19 cm long) and exposed to bright light for 45 min. Animals were daily submitted to three stress sessions starting at 09:00, 12:00 and 17:00 h, whereas control pregnant females were left undisturbed in their home cages. Male and female offspring were weaned 21 days after birth, and only offspring from litters containing 10–14 pups with similar numbers of males and females were used in the experiments. A maximum of two male pups were taken from each litter to remove any ‘litter effects’ [22,23].

2.1. Behavioral long-term consequences

It is clear from animal studies that the behavior of the adult offspring can be altered by PNRS. In rats, PNRS can exert profound influences on offspring’s development, inducing abnormalities which extend from early [24–26]

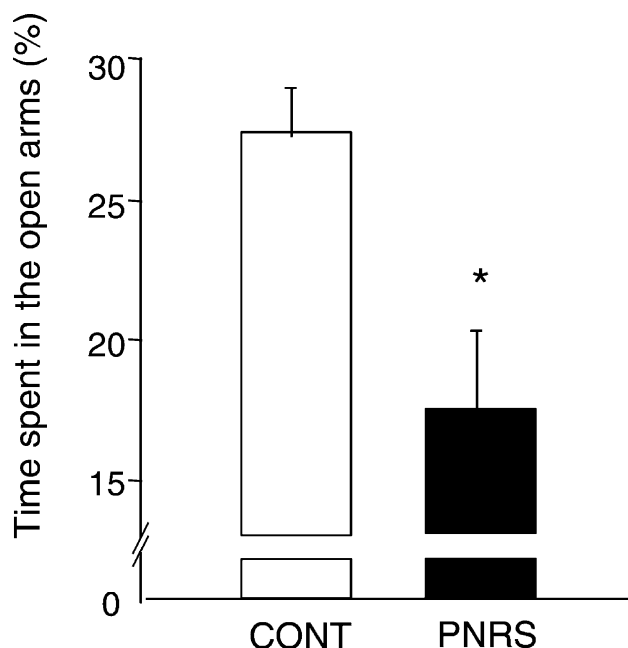


Fig. 1. The anxiety in the elevated plus maze. The time spent in the open arms was significantly shorter in males PNRS rats compared to control rats ($p < 0.05$). Error bars show SEM.

to later life [27]. Adult PNRS rats (4–7 months) exhibit increased ‘anxiety’ (Fig. 1) [28,29], drug addiction [30] ‘emotionality’ [15,31,32] or depressive-like behaviors [16, 33–35]. We also reported in PNRS rats enhanced age-related (16–22 months) recognition memory impairment in the Y-maze compared to controls, and altered working memory in the radial-maze [27]. Furthermore, our data provide evidence of a long-term effect of a prenatal stressful procedure on the circadian system. We have shown significant phase advances in the circadian rhythms of locomotor activity relative to the entraining light–dark cycle in both male and female stressed rats [36]. When subjected to an abrupt shift in the light–dark cycle, male and female PNRS rats resynchronized their activity rhythm to the new light–dark cycle slower than control rats [37,38]. Those results raise the possibility that the circadian clock in the hypothalamic suprachiasmatic nuclei (SCN) [39,40] of those animals has been altered by prenatal stressful events. The altered phase-relationship between the circadian clock and lights-off could be due to a change in the underlying period of the circadian clock during entrained conditions. In order to test this hypothesis, we analyzed the free-running period of locomotor activity in temporal isolation in constant darkness. The free-running period was significantly shorter in PNRS rats compared to control rats.

2.2. Neurobiological long-term consequences

The HPA axis has been shown to be affected by PNRS (Fig. 2), showing increased responsiveness to a novel stimulus [41,42]. Levels of both glucocorticoid type I and type II receptors were reduced in

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