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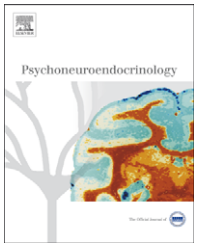

Effects of prenatal restraint stress on the hypothalamus–pituitary–adrenal axis and related behavioural and neurobiological alterations

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Summary
Chronic hyper-activation of the hypothalamus–pituitary axis is associated with the suppression of reproductive, growth, thyroid and immune functions that may lead to various pathological states. Although many individuals experiencing stressful events do not develop pathologies, stress seems to be a provoking factor in those individuals with particular vulnerability, determined by genetic factors or earlier experience. Exposure of the developing brain to severe and/or prolonged stress may result in hyper-activity of the stress system, defective glucocorticoids-negative feedback, altered cognition, novelty seeking, increased vulnerability to addictive behaviour, and mood-related disorders. Therefore, stress-related events that occur in the perinatal period can permanently change brain and behaviour of the developing individual. Prenatal restraint stress (PRS) in rats is a well-documented model of early stress known to induce long-lasting neurobiological and behavioural alterations including impaired feedback mechanisms of the HPA axis, disruption of circadian rhythms and altered neuroplasticity. Chronic treatments with antidepressants at adulthood have proven high predictive validity of the PRS rat as animal model of depression and, reinforce the idea of the usefulness of the PRS rat as an interesting animal model for the design and testing of new pharmacologic strategies in the treatment of stress-related disorders.

1. The hypothalamus–pituitary–adrenal (HPA) axis

The adaptation of an organism to environmental challenges involves mechanisms of response to stress activating central and peripheral circuitries: the HPA axis, the sympathetic

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system and the central limbic stress loop. Such response is under the control of stimulating and inhibiting inputs to the hypothalamic paraventricular nuclei (PVN), which control the secretion of corticotropin-releasing hormone (CRH), vasopressin (VP) into the pituitary portal circulation and other neuropeptides (De Kloet et al., 1998). CRH and VP secretion leads to pituitary release of adrenocorticotropin (ACTH) and adrenal glands activation, with release of glucocorticoids. Corticosteroids that bind preferentially to hippocampal mineralocorticoid receptors appear to be involved in maintaining basal activity of the HPA axis, while glucocorticoid receptors mediate the effects of corticoids aimed at restoring the homeostasis in the reactive mode. The activity of the HPA axis is involved in the regulation of important physiologic functions of individuals for life, as well as, growth and reproduction. The effects of chronic hyper-activation of the HPA axis associated with the suppression of reproductive, growth, thyroid and immune functions may lead to disease vulnerability, like central obesity (metabolic syndrome X), hyperthyroidism and diabetes mellitus (Pasquali et al., 2006). Recently, a link between other HPA axis/glucorticoids dysfunctions and increased susceptibility to depressive/anxiety disorders (Holsboer, 2001) as well as to drug abuse (Huizink et al., 2006; Prendergast and Little, 2007) has also been proposed although direct evidence is still lacking.

2. Early environmental influences on HPA axis development

Although many individuals experiencing stressful events do not develop pathologies, stress seems to be a provoking factor in those individuals with particular vulnerability, determined by genetic factors or earlier experience (McEwen and Sapolsky, 1995). The chronic hyper-activation of HPA axis can be determined by multiple factors including genetic and environmental factors. The perinatal life, infancy, childhood and adolescence are periods of increased plasticity for the stress system and are, therefore, particularly sensitive to stressors. Adverse stressors during these critical periods of life, may affect behaviours and physiologic functions, such as growth, metabolism, reproduction and the inflammatory/immune response (Seckl, 2001). These environmental triggers or stressors may not have a transient, but rather a permanent effect on the organism. Barker (1995) has emphasised how adult vulnerability to disease may be programmed during the foetal stage. Indeed, non-genetic factors that could act early in life to organise or imprint permanently physiological systems are known as perinatal '*programming*'. It can be speculated that prenatal plasticity of physiological systems allows environmental factors, acting on the mother and/or the foetus, to alter the set-point or 'hard-wire' the differentiated functions of an organ or tissue system to prepare the unborn animal optimally for the environmental conditions *ex utero*.

The intrauterine under-growth and low birth weight are considered as an index of prenatal stress in humans. 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. These intriguing findings have spawned the '*fetal origins*' *hypothesis* of adult disease. The brain is very sensitive to prenatal programming and glucocorticoids in particular have powerful brain-programming properties. In rats, substantial evidence suggests that prenatal stress programs the HPA axis as well as behaviour, and that plasticity of developing brain monoamine system underlies, in part, these changes. Because an important feature of the stress response is the secretion of high levels of glucocorticoids, these steroids have become an obvious candidate for the role of '*programming factor*' in the prenatal stress paradigm. A large number of animal studies have described the effects of prenatal exposure to the synthetic glucocorticoid dexamethasone, which relatively readily passes the placenta. Moreover, prenatal dexamethasone exposure has recently been implicated in the development of adult hyperglycaemia and hypertension as well as behavioural changes and HPA activation (Welberg et al., 2001).

3. The prenatal restraint stress model in the rat

Numerous animal models of early stress are currently being developed because early stress results in long-term disruptions of neuronal functions and the development of long-term behavioural disorders. During the last 15 years, we have studied the influences of a prenatal restraint stress (PRS) in a rat animal model. The prenatal stress procedure we have used consisted in restraining the pregnant rat in a transparent Plexiglas cylinder, 3 times/day for 45 min under bright light at the day 11 of pregnancy until delivery at 21–22 days (Maccari et al., 1995, 2003; Morley-Fletcher et al., 2003). The HPA axis functioning of the PRS offspring is long-term impaired with a prolonged corticosterone stress response (Maccari et al., 1995, 2003; Koehl et al., 1999) and reduced levels of both mineralocorticoid and glucocorticoid receptors in the hippocampus at the adolescent and adult stage (Henry et al., 1994; Maccari et al., 1995; Van Waes et al., 2006). The age-related HPA axis dysfunctions are enhanced by PRS. Indeed, the HPA axis period of hyporesponsiveness was abolished in new-born PRS rats (Henry et al., 1994) and circulating glucocorticoid levels of PRS middle-aged animals were similar to those found in old non-stressed animals (Vallée et al., 1999). Recently, we have showed pro-inflammatory consequences on the immune system of PRS adult animals (Vanbesien-Mailliot et al., 2007).

The impact of PRS is already detectable at the foetal stage, giving further support to prenatal stress programming in adult pathophysiology. In the placenta of PRS rats, the expression of glucose transporters type 1 (GLUT1) was decreased, whereas GLUT3 and GLUT4 were slightly increased. Moreover, placental expression and activity of the glucocorticoid barrier enzyme 11beta-hydroxysteroid dehydrogenase type 2 was strongly reduced. At E21, PRS foetuses exhibited reduced body weight and decreased weight of the adrenals, pancreas and testis. These alterations were associated in the offspring with reduced pancreatic beta-cells mass, plasma levels of glucose, growth hormone and ACTH, whereas corticosterone, insulin, IGF-1 and CBG levels were unaffected (Mairesse et al., 2007a).