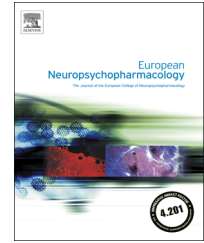




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Prenatal stress and subsequent exposure to chronic mild stress in rats; interdependent effects on emotional behavior and the serotonergic system



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Abstract

Exposure to prenatal stress (PS) can predispose individuals to the development of psychopathology later in life. We examined the effects of unpredictable chronic mild stress (CMS) exposure during adolescence on a background of PS in male and female Sprague-Dawley rats. PS induced more anxiety-like behavior in the elevated zero maze in both sexes, an effect that was normalized by subsequent exposure to CMS. Moreover, PS was associated with increased depression-like behavior in the forced swim test in males only. Conversely, sucrose intake was increased in PS males, whilst being decreased in females when consecutively exposed to PS and CMS. Hypothalamo-pituitary-adrenal (HPA) axis reactivity was affected in males only, with higher stress-induced plasma corticosterone levels after PS. Markedly, CMS normalized the effects of PS on elevated zero maze behavior as well as basal and stress-induced plasma corticosterone secretion. At the neurochemical level, both PS and CMS induced various sex-specific alterations in serotonin (5-HT) and tryptophan hydroxylase 2 (TPH2) immunoreactivity in the dorsal raphe nucleus, hippocampus and prefrontal cortex with, in line with the behavioral observations, more profound effects in male offspring. In conclusion, these findings show that prenatal maternal stress in Sprague-Dawley rats induces various anxiety- and depression-related behavioral and neuroendocrine changes, as well as alterations in central 5-HT and TPH2 function, predominantly

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in male offspring. Moreover, CMS exposure partially normalized the effects of previous PS experience, suggesting that the outcome of developmental stress exposure largely depends on the environmental conditions later in life and vice versa.

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1. Introduction

Prenatal maternal stress has been related to various psychiatric conditions like anxiety disorders and depression later in life (Huizink et al., 2004). In rats, prenatal stress (PS) has been associated with e.g. disturbances in the hypothalamo-pituitary-adrenal (HPA) axis (see review by Weinstock, 2005) and increased anxiety- and depression-like behavior (Dickerson et al., 2005; Estanislau and Morato, 2005; Griffin et al., 2003; Secoli and Teixeira, 1998; Vallee et al., 1997). In addition, anxiety- and depression-like effects of PS could be counteracted by treating PS offspring with various kinds of antidepressants that are known to impact upon the serotonin (5-hydroxytryptamine, 5-HT) system (Alonso et al., 1999; Morley-Fletcher et al., 2003; Morley-Fletcher et al., 2004; Poltyrev et al., 2005), which suggests a central role for 5-HT in mediating the effects of PS exposure. In support of this notion, PS has been associated with alterations in the 5-HT system (see review by Huizink et al., 2004; Van den Hove et al., 2006). Before acting as a neurotransmitter in the matured central nervous system (CNS), 5-HT, which is produced by the enzyme tryptophan hydroxylase 2 (TPH2) in neurons located in the raphe nuclei, is involved in the development of the CNS, regulating the growth and maturation of the 5-HT neurotransmitter system during fetal development (Whitaker-Azmitia, 2001). Moreover, the 5-HT system and the HPA axis are known to be closely interrelated and corticosteroid-5-HT interactions may in fact be critically involved in the development and course of stress-related disorders (Porter et al., 2004). Taken together, it is tempting to speculate that environmental perturbations during fetal development can adversely affect the development of the 5-HT system, and thus contribute to an altered stress-responsivity and the etiology of emotional disorders like depression in later life. Along similar lines, chronic mild stress (CMS) in later life has also been associated with alterations in the 5-HT system (Grippo et al., 2005; Lanfumey et al., 1999). Given the close interrelation between the 5-HT system and the HPA axis (Sierksma et al., 2010), also chronic postnatal stress might eventually contribute to the development of affective disorders such as depression. The exact mechanisms underlying the behavioral effects of distinct stressful episodes during various stages of life, as well as their interaction, in particular in view of the 5-HT system, remain to be elucidated though.

Accordingly, the aim of the present study was twofold. First, to examine whether or not exposure to PS would affect the behavioral and neuroendocrine effects of subsequent exposure to chronic mild stress (CMS) in later life. Second, to examine whether possible differences in behavior were reflected in changes in innervation patterns of 5-HT pathways, i.e. cell body areas and projection areas, in terms of levels of 5-HT and the rate-limiting enzyme in the neuronal synthesis of 5-HT, i.e. TPH2. Based on the "cumulative stress" concept (Nederhof and Schmidt, 2012),

we hypothesized that PS offspring would be more vulnerable to the effects of CMS, resulting in more anxiety- and depression-like behavior and altered HPA axis (re)activity in subjects exposed to both PS and CMS.

2. Experimental procedures

2.1. Animals and procedures

The animal studies were all approved by the Animal Ethics Board of Maastricht University, The Netherlands. Acclimatized pregnant Sprague-Dawley rats (Charles River, The Netherlands) were used. Animals were housed individually within a temperature-controlled environment (21 ± 1 °C) with a 12 h light/12 h dark cycle (lights on from 7.00 to 19.00 h) and had access to standard rat chow and water ad libitum. Pregnancy was determined by observation of vaginal plugs (embryonic day 0 - E0). Restraint stress was performed daily during the last week of pregnancy (E14-E21). Pregnant female rats ($n=12$) were individually restrained three times a day (at approximately 9.00, 13.00, and 17.00 h) for 45 min in transparent plastic cylinders whilst being exposed to bright light (Michelsen et al., 2007; Ward and Weisz, 1984). Control (C) pregnant females ($n=9$) were left undisturbed in their home cages. Within an hour after the last pup of a litter had been born, pups were individually labeled by means of toe cut, and sex (based on anogenital distance) and individual body weights were determined. Only litters of ten or more pups were included in this study. Litters were culled to ten pups if necessary. At postnatal day 21 (P21), pups were weaned and housed together (two male or two female rats/cage; $n=12-14$ rats per experimental condition per sex) for further examination. Rats were kept at a reversed day-night cycle from this point onwards (lights on from 17.00 to 5.00 h). At P77 half of all animals were subjected to unpredictable chronic variable mild stress (CMS) for 3 weeks. Stressors (housing in mice cage, cage tilt [angle of 45°], housing in an empty cage [no sawdust], wet bedding in cage [200 ml cold water added per cage], flashing light [stroboscope; low intensity, 2.5 Hz] during the dark phase) were applied in a random order. Per day two stressors were used, each lasting for 3 hours. Body weights of the offspring were measured at P0 (birth), P21 (weaning), P77, P84, P91, P98 and P112. Anxiety- and depression-like behavior was analyzed from P100 onwards. Behavioral tests were performed from least invasive to most invasive to reduce the likelihood of altered behavior due to a prior test (order see next subsection). At P120, the animals were anesthetized with pentobarbital (60 mg/kg, i.p.) and perfused transcardially with a tyrode solution followed by 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). Brains were taken out and post-fixed with the same fixative overnight, after which they were subsequently immersed in 10%, 20% and 30% sucrose in 0.1 M phosphate

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