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Individual differences in the effects of prenatal stress exposure in rodents

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ABSTRACT

Exposure to prenatal stress alters the phenotype of the offspring in adulthood. When the prenatal and adult environments do not match, these alterations may induce pathology risk. There are, however, large individual differences in the effects of prenatal stress. While some individuals seem vulnerable, others appear to be relatively resistant to its effects. In this review we discuss potential mechanisms underlying these individual differences with a focus on animal models. Differences between rodent models selected for stress coping traits are discussed. In addition, the role of circulating factors, like glucocorticoids and cytokines, factors involved in brain development and influences of epigenetic and genetic factors in prenatal stress induced phenotype are covered.

1. Introduction

The acute stress response, characterized by activation of the sympathetic nervous system, the hypothalamus-pituitary-adrenal axis and the immune system, is a physiologically adaptive response that enables the organism to deal with environmental threats. However, when the stress exposure is chronic, prolonged activation of the stress response may become maladaptive and have adverse consequences for the individual. In addition to disorders directly linked to stress exposure, like post traumatic stress disorder, risk of the development of several other disorders such as affective disorders, type 2 diabetes and cardiovascular disease have been associated with stress (reviewed in (de Kloet et al., 2005)).

Chronic stress during adulthood may have adverse consequences, but the effects of stress exposure during gestation or early childhood may have more severe consequences as it may alter brain development and thereby have long-term consequences on adult phenotype. The idea that the early life environment may alter adult phenotype is described in the Developmental Origins of Health and Disease (DOHaD) hypothesis. This hypothesis states that adverse conditions during the early life period may result in persistent changes in physiology and metabolism that in turn alter risk for disease development in adulthood and was first proposed by David Barker (Barker, 1988). Therefore, this hypothesis was initially referred to as the "Barker Hypothesis". This hypothesis was based on the observation that low birth weight was associated with increased risk for coronary heart disease in adulthood (Barker and Osmond, 1986). Over the last decades more data supporting this hypothesis have become available from studies in both humans as well as in animal models.

2. Human evidence

Evidence that this hypothesis may hold true comes from epidemiological studies in individuals who were exposed to adverse environmental conditions, like natural disasters or war, showing increased risk for metabolic, immune and stress-related disorders later in life. For example, children born during or right after the Dutch Hunger Winter were found to be at increased risk for development of psychiatric and metabolic disorders (Brown et al., 1995; Franzek et al., 2008; Hoek et al., 1998). Similar observations were reported in offspring of women pregnant during Chinese famine in 1959–1961 as higher incidence of schizophrenia was reported in these offspring (St Clair et al., 2005). Interestingly, a study in Russia of individuals exposed to a famine during the same period as the Dutch Hunger Winter, found no adverse effects on metabolic disease susceptibility (Stanner et al., 1997). In contrast to the Netherlands where the famine was followed by a period of growth and abundance, the standard of living in Russia remained

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poor throughout adulthood, suggesting that disorders associated with the prenatal environment may occur when the prenatal and postnatal environment do not match. This concept of a mismatch between the early life and adult phenotype resulting in pathology development has been elegantly described by Nederhoff and Schmidt (Nederhof and Schmidt, 2012).

3. Individual differences – susceptibility and resilience

3.1. The animal model

The studies in humans investigating the effects of exposure to stressful events during pregnancy like war, however, are confounded by changes in food availability and variation in the severity of exposure within and between studies. Furthermore, data from a Swedish study indicated that the perceived level of stress may be an important factor was well. During the Chernobyl disaster, the perceived level of stress predicted the offsprings' risk of emotional and cognitive disorders better than the actual experience level of radiation (Kolominsky et al., 1999). In order to understand the underlying mechanism of prenatal stress exposure on the offspring's health, better controlled studies are necessary. Better control of environmental factors can be obtained by using animal models in a laboratory setting. The most common models of prenatal stress either use repeated restraint stress or chronic variable stressors. However, there are some studies that have specifically targeted social stress using a social defeat paradigm.

Exposure to prenatal stress (PNS) has been associated with higher risk of affective disorders in humans (Brown et al., 1995; Watson et al., 1999). Rodent models support this association, as decreased exploration in an elevated plus maze and increased reactivity to novelty was shown in PNS-exposed rats (Vallee et al., 1997), indicative of increased anxiety-like behavior. Additionally, in behavioral tests designed to assess depression-like phenotypes, prenatally-stressed rats display increased immobility, suggesting increased depression-like behavior (Morley-Fletcher et al., 2003, 2004). Furthermore, PNS rats showed decreased social interaction (Lee et al., 2007), however, there were no differences in sucrose intake in this study (Lee et al., 2007). These studies suggest that, at least in males, PNS exposure may predispose towards a depression- and anxiety-like phenotype. In addition to alterations in affective behaviors, PNS also has effects on cognitive functioning and neurodevelopmental disorders. Deficits in spontaneous spatial recognition and working memory performance have been reported (Vallee et al., 1999). Additionally, PNS offspring have been shown to have impaired prepulse-inhibition responses and increased locomotor activity after amphetamine administration, both of these phenotypes have been associated with development of a schizophrenia-like phenotype (Koenig et al., 2005).

There is a large body of literature on the effects of PNS on stress responsivity and hypothalamus-pituitary-adrenal (HPA)-axis functioning. Exposure to prenatal stress has been shown to alter corticosterone levels throughout the circadian cycle; in adult male rats increased corticosterone levels have been found at the end of the light phase, a time period where typically the highest corticosterone levels are observed (Koehl et al., 1999). Consistent with heightened corticosterone levels, hypertrophy of the adrenals has been reported (Lemaire et al., 2000). Furthermore, several studies showed increased glucocorticoid levels and associated decreased negative feedback of the HPA-axis after acute stress (Koehl et al., 1999; Henry et al., 1994; Barbazanges et al., 1996; Maccari et al., 1995). At the level of the brain, alterations in the glucocorticoid system have been shown; the binding capacity of both the mineralocorticoid receptor and the glucocorticoid receptor were decreased in PNS offspring (Koehl et al., 1999; Maccari et al., 1995).

In addition to effects on stress-related traits, prenatal stress has also been reported to affect the metabolic phenotype of the offspring. Lesage and colleagues showed that chronic restraint stress during the last week of pregnancy induced hyperphagia and impaired glucose tolerance in adult male offspring (Lesage et al., 2004). Similar to the human studies, PNS offspring had lower birth weights than control, which may have contributed to their metabolic phenotype later in life. Metabolic syndrome-predisposing effects of PNS in rats were confirmed in a study that used a variable stress paradigm during the last week of pregnancy and in this study differences in birth weight were not found. Tamashiro and colleagues showed that offspring of prenatally stressed dams were also impaired in an oral glucose tolerance test. However, these differences were only apparent in PNS rats that were weaned onto a high fat diet (Tamashiro et al., 2009). Stress exposure earlier during pregnancy seems to have some contrasting effects, offspring of mice exposed to stress during the first week of pregnancy were shown to gain less weight on a high fat diet, whereas they were hyperphagic on a standard chow diet (Pankevich et al., 2009). This suggests that the timing of the stress is an important variable in the metabolic risk associated with prenatal stress exposure.

3.2. Individual variation in the phenotype

Although a clear effect of PNS on the phenotype is shown in most experiments, large variation is observed among individuals within a study, suggesting that there might be vulnerable and resistant individuals within PNS populations. These individual differences have become apparent in rodent models selectively bred for specific traits. The Lewis and Fischer 344 rats are rodents with heightened (Fischer 344) or attenuated (Lewis) HPA-axis reactivity, and have been shown to differ in a wide range of HPA-axis-related behavioral and physiological traits (Sternberg et al., 1992). Stohr and colleagues showed that PNS had differential effects in the Lewis and Fischer 344 rats. In Lewis rats, PNS improved acquisition of active avoidance, decreased immobility in the forced swim test, and reduced novelty-induced locomotion, whereas in Fischer 344 rats PNS had no effect in the active avoidance or forced swim test, and increased novelty-induced locomotion (Stohr et al., 1998). Studies in rats selectively bred for High and Low anxiety traits suggest that PNS has opposite effects in anxious versus non-anxious rats. Rats bred for high anxiety traits became less anxious after PNS, whereas rats bred for low anxiety traits became more anxious (Bosch et al., 2006). In a similar fashion, rats selectively bred for low novelty seeking behavior were reported to show less anxiety than their controls, whereas those rats selectively bred for high novelty seeking behavior were not affected by PNS (Clinton et al., 2008). Taken together these studies suggest that PNS may have opposite effects dependent on the genetic background of the individual.

In addition to the differences in anxiety traits or HPA-axis responsivity, the way a stressor is perceived may play an important role in effects of PNS. The stress-coping style of an individual determines the behavioral and physiological response of an organism to stress. Two clear stress-coping phenotypes can be distinguished, the proactive and passive stress-coping styles. Behaviorally, proactive stress-copers are characterized by active responses to stressors; they will attempt to modulate the environment to reduce the stress (Koolhaas et al., 1999). This proactive stress response is illustrated in rodents during a defensive burying test. In this test proactively coping rats will bury an electrified prod that is placed in their cage with saw dust in order to avoid a shock. In contrast, passive stress-copers respond to stress in a more inhibited manner. In the defensive burying test, passive rodents