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In utero programming alters adult response to chronic mild stress: Part 3 of a longitudinal study

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ABSTRACT

Exposure to stress before birth may lay the foundation for the development of sensitivities or protection from psychiatric disorders while later stress exposure may trigger either their expression or suppression. This report, part three of a longitudinal study conducted in our laboratory, aimed to examine the interaction between early and adult stress and their effects on measures of anxiety and depression. In parts one and two, we reported the effects of gestational stress (GS) in Long Evans rat dams and their juvenile and young adult offspring. In this third and final installment, we evaluated the effects of GS and chronic mild stress (CMS) in the adult female offspring at 6 month and 12 month time-points. The two by two design included a combination of GS and CMS and the appropriate control groups. Using Hierarchical Linear Modeling, main effects of GS on corticosterone level at the 12 month time-point was found while main effects of CMS were seen in body weight, sucrose preference, and corticosterone, and significant interactions between group at the 6 and 12 month time-points. The GS group had the lowest sucrose preference during CMS at 6 months supporting a cumulative effect of early and later life stress. The GS/CMS group showed lower corticosterone at 12 months than the GS/noCMS group indicating a possible mismatch between prenatal programming and later life stress. These results highlight the importance of early life factors in exerting potentially protective effects in models involving later life stress.

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1. Introduction

Environmental factors can alter brain development and are important in the establishment of vulnerabilities to or protection from developing psychopathology (Marco et al., 2011). Much attention is now being devoted to the role of environmental influences in the context of stress-related psychiatric disorders, such as depression, highlighting the importance of the interaction between genes and environment in the expression of pathophysiology. Perinatal life is marked by increased plasticity, particularly in the stress system; it may therefore represent a period of heightened sensitivity to stress mediated by exposure to abnormal maternal hormones and/or maternal care behavior and resulting in permanent epigenetic change (Darnaudery and Maccari, 2008).

The most robust and well-established findings in psychiatric epidemiological research are that being both female and exposed to stress significantly increase one's risk of depression (Fuchs

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and Flugge, 2011; Kessler, 2003). The stress-depression link in females is observed across the lifespan (Paykel, 2003; Hammen, 2005; Liu and Alloy, 2010) with exposure to daily stressors, more so than acute stressors, being a strong predictor of the development of depression (Fuchs and Flugge, 2011; McGonagle and Kessler, 1990). The role of stress in the expression of psychopathology is hypothesized to vary depending on the timing of exposure; before maturation, normal neural trajectories may be altered resulting in depressogenic sensitivities, while after maturity, the neurochemical milieu may be transiently altered leading to an increased likelihood of its expression (for review see Morley-Fletcher et al., 2013). This stress-related vulnerability to depression may be related to epigenetic factors associated with changes in the hypothalamic pituitary adrenal (HPA) axis (Tsankova et al., 2007). For example, multiple studies have shown that maternal care and other parental effects can create epigenetic modifications of the HPA axis through changes in hippocampal glucocorticoid receptor gene expression in the adult offspring (Weaver et al., 2001). In turn, gestational stress (GS) may also induce epigenetic modification in offspring making them either more resilient or vulnerable to the effects of later life stress. Typically, the likelihood of developing psychopathology is thought to correlate with multiple episodes of adversity accumulated throughout the lifespan (Lupien et al., 2009). This is known as the cumulative or "double-hit" hypothesis.

However, an interesting alternative is the mismatch hypothesis which suggests that the likelihood of developing psychopathology increases only if there is a mismatch between early life programming and the adult environment (Nederhof and Schmidt, 2012). In essence, early life stress may confer resilience to the offspring and attenuate the negative effects of later life stress. However, if these later life challenges never occur, the early programming for an adverse adult environment becomes maladaptive creating a mismatch and can lead to developing psychopathology. Finally it may be that both cumulative and mismatch hypotheses are at play in the occurrence of depression.

GS, in the form of physical restraint, and chronic mild stress (CMS) are rodent models of stress-induced depression. Both of these models have been extensively evaluated, particularly in male rodents (GS reviewed in Weinstock, 2008; CMS reviewed in Willner, 2005). It has been shown by our laboratory that GS significantly decreases weight gain in the dam and her female offspring (Baker et al., 2008). This is in line with other studies showing that maternal weight (Barlow et al., 1978; Darnaudery et al., 2004) and offspring weight (Hashemi et al., 2013; Williams et al., 1998) decrease after GS.

In males, GS appears to produce phenotypes resembling schizophrenia, including disrupted social behavior and stress axis dysregulation (Koenig et al., 2005; Lee et al., 2007; Green et al., 2011). The outcomes of GS can also vary depending on GS type (i.e. acute versus chronic). For instance, chronic, but not acute, GS leads to hyperactivity in male rat offspring (Weller et al., 1988). The study of GS and CMS can allow for the examination of the cumulative and mismatch models of stress.

Less is known about how female animals respond to GS. It appears to exert sexually dimorphic effects on behavior in that males tend to display greater deficits in learning and memory whereas females show greater effects in emotionality (reviewed in Weinstock, 2001). More recent studies further support the idea that female rats are not as affected by GS in cognitive tasks such as fear conditioning and object recognition tasks (Markham et al., 2010) but appear more sensitive to alterations in the regulation of the HPA axis (Weinstock et al., 1992; McCormick et al., 1995; Szuran et al., 2000; Richardson et al., 2006) and show greater depressive-like behavior (Alonso et al., 1991; Poltyrev et al., 2005) after GS. However, this profile is not consistent between strains as female Sprague–Dawley rats show less depressive-like behavior than males after GS in the forced swim test (Van den Hove et al., 2013). In contrast, in mouse models, GS has been shown to only affect learning and memory in female offspring (Abdul Aziz et al., 2012) although this appears to be strain-specific (Sierksma et al., 2013).

When female rats are administered the stressors associated with the CMS procedure, they appear to be more vulnerable to its effects as indexed by decreased sucrose intake and/or sucrose preference (a measure of anhedonia) and open field activity (measure of exploration), increased corticosterone levels, and decreased serotonergic activity in the hippocampus and hypothalamus (Baker et al., 2006; Bielajew et al., 2002; Dalla et al., 2005; Konkle et al., 2003, 2010). Further, CMS exposure is known to decrease weight gain in both male and female rodents (for review see Willner, 1997, 2005).

Van den Hove et al. (2014) reported that GS increased depressive-like behavior in the forced swim test only in males, and that being exposed to both GS and CMS increased sucrose preference in males while decreasing it in females (Van den Hove et al., 2014). Anxiety-like behavior was significantly increased after GS in both sexes but appeared to normalize with subsequent exposure to CMS (Van den Hove et al., 2014). To summarize, in Sprague–Dawley rats the mismatch hypothesis seems to have the best fit in considering anxiety-like responses in both sexes. In contrast, the cumulative stress of GS and CMS increases anhedonia in females but not males of this strain. Therefore the cumulative or mismatched response to stress in rats may not only be sexually dimorphic but also differ between outcome measures.

These are interesting hypotheses to consider in the context of the interaction between GS and CMS and may, to some extent, explain the sexual dimorphism seen in behavioral and cognitive patterns. However, the Van den Hove (2014) study is, to our knowledge, the only one to look at GS and CMS in both sexes. While ideal, this is not feasible for many laboratories due to time, space, and financial constraints that frequently prohibit such designs. The resulting compromise is that most researchers use male animal models exclusively due to the relative stability of their circulating hormones. In contrast, the use of female animal models requires consideration of their estrous cycle and changes in hormone milieu due to their effects on brain and behavior (for review see Mileva et al., 2013). Studies in female animals are vital, especially in the context of anxiety and stress as results may be informative to human studies that demonstrate a greater vulnerability for women who are at a much higher risk of developing anxiety or depression than men (Kessler, 2003).

The current study represents the third installment in a series of experiments that have documented the consequences of

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