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Strain-dependent effects of prenatal maternal immune activation on anxiety- and depression-like behaviors in offspring

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ABSTRACT

There is converging evidence that prenatal maternal infection can increase the risk of occurrence of neuropsychiatric disorders like schizophrenia, autism, anxiety and depression in later life. Experimental studies have shown conflicting effects of prenatal maternal immune activation on anxiety-like behavior and hypothalamic–pituitary–adrenal (HPA) axis development in offspring. We investigated the effects of maternal immune activation during pregnancy on anxiety- and depression-like behaviors in pregnant mice and their offspring to determine whether these effects are dependent on strain. NMRI and C57BL/6 pregnant mice were treated with either saline or lipopolysaccharide on gestational day 17 and then interleukin (IL)-6 and corticosterone (COR) levels; anxiety or depression in the pregnant mice and their offspring were evaluated. The results indicate that maternal inflammation increased the levels of COR and anxiety-like behavior in NMRI pregnant mice, but not in C57BL/6 dams. Our data also demonstrate that maternal inflammation elevated the levels of anxiety-and depression-like behaviors in NMRI offspring on the elevated plus-maze, elevated zero-maze, tail suspension test and forced swimming test respectively, but not in the open field and light–dark box. In addition, we did not find any significant change in anxiety- and depression-like behaviors of adult C57BL/6 offspring. Our findings suggest that prenatal maternal immune activation can alter the HPA axis activity, anxiety- and depression-like behaviors in a strain- and task-dependent manner in offspring and further comprehensive studies are needed to prove the causal relationship between the findings found here and to validate their relevance to neuropsychiatric disorders in humans.

1. Introduction

There is increasing evidence that transient challenges such as maternal infection and stress during pregnancy can increase the risk of occurrence of neuropsychiatric disorders like schizophrenia, autism, anxiety and depression in later life (Alonso et al., 1991; Brown and Derkits, 2010; Enayati et al., 2012; Kinney et al., 2008; Matrisciano et al., 2013; Patterson, 2011; Vallée et al., 1997). There are likely common genetic pathways between these psychiatric disorders (Braga et al., 2005; Buckley et al., 2009; Emsley et al., 1999; Huppert et al., 2001; Mazefsky et al., 2010; Simonoff et al., 2008; White et al., 2009). However, the underlying mechanisms that can result in such persistent brain and behavioral abnormalities are largely unknown. Although human studies have been informative regarding the outcomes of prenatal infection and stress on psychiatric diseases in children, studies of the underlying neurobiological mechanisms of these phenomena have relied primarily on experimental animal models. Lipopolysaccharide (LPS, a component of gram negative bacteria) and Polyinosinic:Polycytidylic acid (Poly I:C, a synthetic double stranded RNA) administration are well-known to mimic bacterial and viral infections in pregnant mice (Harvey and Boksa, 2012). Obviously, LPS can induce the production of interleukin (IL)-6, tumor necrosis

Abbreviations: LPS, lipopolysaccharide; Poly I:C, polyinosinic–polycytidylic acid; IL, interleukin; TNF-α, tumor necrosis factor-alpha; COR, corticosterone; HPA, hypothalamic-pituitary-adrenal; EPM, elevated plus maze; FST, forced swimming test; OF, open field; LDB, light–dark box; GD, gestational day; PND, postnatal day; IZT, inner zone time; IZE, inner zone entries; OAT, open arm time; OAE, open arm entries; LMA, locomotor activity; LD, latency of entry into the dark compartment; LL, latency of entry into the light compartment; LCT, light compartment time; LCE, light compartment entries; OQT, time spent in the open quadrant; LOPE, latency to first entry into the open quadrant; OQE, the number of entries into the open area; HD, the number of head dips in open region; SAP, the number of stretch attend postures; TST, tail suspension test; ANOVA, analysis of variance; S.E.M, standard error of the mean; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartic acid; 11β-HSD2, 11β-hydroxysteroid dehydrogenases 2; MR, mineralocorticoid receptor; GR, glucocorticoid receptor.

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factor-alpha (TNF-α), IL-1β and stress hormone (corticosterone: COR) in pregnant mice (Enayati et al., 2012).

A wide spectrum of studies have indicated that stress, anxiety and depression during pregnancy increase the levels of COR in humans and animals (Glover et al., 2010; Harris and Seckl, 2011; Van den Bergh et al., 2005). It is important to note that the elevation of the levels of COR after immune challenge and stress during gestation can be a common pathway between maternal immune activation and stress models. The ability of IL-6 and COR to cross the placenta and blood–brain barrier was demonstrated (Brummelte et al., 2010; Dahlgren et al., 2006; Threlkeld et al., 2010). Indeed, IL-6 and COR differently are thought to mediate the relationships between maternal infection and stress and neurodevelopmental damages in offspring. In other words, two possible hypotheses are that either damage or change in particular brain regions may be due to the direct effects of IL-6 or COR on the fetal brain in these two models of prenatal insults. In support of this idea, it was found that IL-6 plays an important role in survival, death, proliferation and differentiation of neurons, synaptic activity, inflammation and apoptosis (Spooren et al., 2011). Moreover, glucocorticoids are crucial agents for normal brain development (Harris and Seckl, 2011), survival (Sloviter et al., 1993) and differentiation of neurons (Rua et al., 1994); and both structural and functional developments of synapses (Antonow-Schlorke et al., 2003; Huang et al., 2001). Actually, any fluctuations and especially excess in the levels of these agents can have profound effects on the normal development of the brain; inhibit fetal growth and alter the pathway of tissue maturation. Based on this evidence, we believe that the presence of these elements together may impose multiple risk factors for the normal development of fetal brain during pregnancy. So far, few studies have been conducted to evaluate the side effects of maternal LPS treatment during gestation on anxiety and hypothalamic–pituitary–adrenal (HPA) axis activity in pregnant mothers, thus our knowledge about an ideal animal model of prenatal maternal infection is limited.

In this context, previous studies have clearly shown that maternal exposure to stress during pregnancy increases anxiety- and depression-like behaviors in offspring (Alonso et al., 1991; Brunton, 2013; Davis and Sandman, 2012; Estanislau and Morato, 2005; Fride and Weinstock, 1988; Glover, 2013; Laloux et al., 2012; Marrocco et al., 2012; Miyagawa et al., 2011; Murmu et al., 2006; Rayen et al., 2011; Sun et al., 2013; Vallée et al., 1997). Furthermore, several animal studies have indicated conflicting effects of prenatal maternal immune activation on anxiety and depression-like behaviors in offspring. For instance, we have previously reported that prenatal exposure to LPS in late gestation can increase the levels of anxiety and depression with increasing the stress-induced COR level in male NMRI offspring on elevated plus maze (EPM) and forced swimming test (FST) (Enayati et al., 2012). Interestingly, Shi et al., demonstrated that maternal exposure to the human influenza virus in mid-gestation resulted in increased anxiety levels in adult C57BL/6 and BALB/c mice offspring on the open field (OF) (Shi et al., 2003). Similarly, two recent studies have demonstrated that prenatal exposure to LPS in mid-pregnancy elevated the levels of anxiety (Lin et al., 2012) and depression (Lin and Wang, 2013) with increasing the stress-induced COR level in adult Sprague–Dawley rats' offspring on EPM, OF and FST. In addition, Hava and her colleagues have shown that maternal immune activation with LPS in late gestation led to a slight increase in anxiety of adult C57BL/6 mice offspring on EPM (Hava et al., 2006). It has also been reported that maternal Poly I:C treatment during late pregnancy can induce anxiety-like behavior in Sprague–Dawley rats' offspring on EPM (Yee et al., 2011). Consistent with this finding, another study indicated that maternal treatment with LPS in late gestation augmented anxiety on EPM, while decreased the levels of anxiety on OF in Swiss mice offspring in males (Chlodzinska et al., 2011). Contrary to these findings, we have already reported that prenatal LPS exposure in mid pregnancy resulted in reduced levels of anxiety in adult C57BL/6 mice offspring on EPM without any change in the COR level after LPS injection (Asiaei et al., 2011). Meanwhile, Chen et al., demonstrated a slight decline in the levels of anxiety in light–dark box (LDB) for males following maternal exposure to LPS during late pregnancy in CD-1 mice offspring (Chen et al., 2011). In parallel to these findings, a recent study indicated that maternal exposure to LPS in mid-gestation decreased the levels of anxiety on EPM, while did not affect depression-like behavior and COR levels in NMRI mice offspring on FST (Solati et al., 2012). On the other hand, other research groups did not find any significant difference in anxiety levels of adult mice and rats' offspring following maternal immune activation. In more details, in the study conducted by Bakos et al., no signs of anxiety and change in COR level following maternal treatment with LPS in late gestation were observed in Wistar rats' offspring on EPM (Bakos et al., 2004). Moreover, Schwendener et al., reported that the level of anxiety-like behavior as assessed in the EPM and OF tests were not affected by the maternal Poly I:C treatment in late gestation in adult C57BL/6 mice offspring (Schwendener et al., 2009). Interestingly, recently, this group led by Urs Meyer again reported that maternal immune activation with Poly I:C in mid pregnancy did not affect anxiety in adult C57BL/6 mice offspring on EPM (Giovanoli et al., 2013). On the whole, it seems reasonable to speculate that these contrasting findings can be likely due to differences in study design; the type, dose and timing of immunogen administration during gestation; animal species and strains; the type of behavioral testing; postnatal age, sex, and the number of offspring in each experimental group.

It is well documented that the HPA system is highly susceptible or sensitive to programming during fetal development (Zhang et al., 2005). Compelling evidence originated from human and animal studies indicates that programming of HPA axis function by early life events like maternal immune activation and stress is associated with neuroendocrine disorders and different neurobehavioral dysfunctions such as schizophrenia, depression, anxiety and impaired stress response in offspring (Brown and Derkits, 2010; Catalani et al., 2011; Enayati et al., 2012; Glover et al., 2010; Harris and Seckl, 2011; Howerton and Bale, 2012; Maccari and Morley-Fletcher, 2007; Patterson, 2011). In addition, it was found that the phenotype of HPA axis function following early manipulation depends on different parameters including the timing of the insult, the nature of the stressor, the gender of the fetus, the animal species and strains (Kundakovic et al., 2013; Matthews, 2002; Mueller and Bale, 2008; Stöhr et al., 1998). Besides these factors, the interaction between genetic and environmental risk factors has been recognized for investigating the normal patterns of behavior and the underlying mechanisms of brain vulnerability which may be a risk factor for the development of behavioral abnormalities in humans. The rodent models of prenatal maternal infection and stress are frequently used in research laboratories to investigate the possible mechanisms of brain vulnerability in offspring in later life. In this frame, previous studies have demonstrated the strain-dependent effects of prenatal maternal immune activation and stress on autism-, stress- or depression-like behaviors as well as genes expression in the brain of offspring (Neeley et al., 2011; Schwartzer et al., 2013; Stöhr et al., 1998). In addition, nowadays, "strain differences" in anxiety and depression-related behaviors among various mouse strains have been well demonstrated (Crowley et al., 2005; Kundakovic et al., 2013; Millstein and Holmes, 2007; Mineur et al., 2006; Stöhr et al., 1998). As noted above, in previous studies outbred and inbred strains of mice and rats have been used for investigating the effects

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