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Effects of immune activation during early or late gestation on schizophrenia-related behaviour in adult rat offspring

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ABSTRACT

Maternal exposure to infectious agents during gestation has been identified as a significant risk factor for schizophrenia. Using a mouse model, past work has demonstrated that the gestational timing of the immune-activating event can impact the behavioural phenotype and expression of dopaminergic and glutamatergic neurotransmission markers in the offspring. In order to determine the inter-species generality of this effect to rats, another commonly used model species, the current study investigated the impact of a viral mimetic Poly (I:C) at either an early (gestational day 10) or late (gestational day 19) time-point on schizophrenia-related behaviour and neurotransmitter receptor expression in rat offspring. Exposure to Poly (I:C) in late, but not early, gestation resulted in transient impairments in working memory. In addition, male rats exposed to maternal immune activation (MIA) in either early or late gestation exhibited sensorimotor gating deficits. Conversely, neither early nor late MIA exposure altered locomotor responses to MK-801 or amphetamine. In addition, increased dopamine 1 receptor mRNA levels were found in the nucleus accumbens of male rats exposed to early gestational MIA. The findings from this study diverge somewhat from previous findings in mice with MIA exposure, which were often found to exhibit a more comprehensive spectrum of schizophrenia-like phenotypes in both males and females, indicating potential differences in the neurodevelopmental vulnerability to MIA exposure in the rat with regards to schizophrenia related changes.

1. Introduction

It is widely accepted that risk for schizophrenia has a neurodevelopmental origin in which adverse events experienced during critical perinatal periods of brain development, as well as genetic predispositions, produce lasting but often behaviourally dormant neurodevelopmental changes, which manifest later in life (Lewis and Lieberman, 2000; Lewis and Moghaddam, 2006; Lyon et al., 2012; Owen et al., 2005; Wilson and Terry, 2010). Maternal immune activation (MIA) as a result of infection during the critical prenatal period considerably increases the risk of developing schizophrenia. Epidemiological studies have revealed that maternal exposure to a range of bacterial (Babulas et al., 2006; Sorensen et al., 2009) and viral agents (Brown et al., 2001; Buka et al., 2001; Suvisaari et al., 1999; Torrey et al., 1988) during pregnancy significantly increases the risk of schizophrenia developing in the offspring. In addition, an association between maternal infection and increased risk of schizophrenia in offspring has been identified using serological evidence in which infection (and cytokine up-regulation) during pregnancy was confirmed in blood samples from mothers of those who later developed the disorder (Brown et al., 2004a,b, 2005; Buka et al., 2001). Studies using animals have provided additional support for the link between MIA and adult behavioural and neurobiological changes related to

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schizophrenia. Rats and mice exposed prenatally to various immune activating agents such as the influenza virus (Fatemi et al., 1999, 2008; Shi et al., 2003), the viral mimetic Polyriboinosinic-polyribocytidilic acid (Poly (I:C)) (Howland et al., 2012; Ozawa et al., 2006; Wolff and Bilkey, 2010; Wolff et al., 2011; Zuckerman and Weiner, 2005), the bacterial endotoxin lipopolysaccharide (LPS) (Fortier et al., 2004; Lante et al., 2008, 2007; Romero et al., 2010) and pro-inflammatory cytokines (Samuelsson et al., 2006) develop behavioural and neurological 'schizophrenia-like' phenotypes.

The timing of prenatal exposure to an immune activating agent such as Poly (I:C) has been identified as an important factor which can influence the behavioural and neurochemical phenotype displayed by adult mouse offspring (Boksa, 2010; Meyer and Feldon, 2012). Specifically, differences between exposure in early/middle (gestational day; GD9) and late gestation (GD17) have been identified in a mouse model of MIA, approximately translating to the mid-first and early- second trimester in humans, respectively (Workman et al., 2013, http://www.translatingtime.net). The majority of evidence from retrospective epidemiological studies implicates the second trimester as a particularly sensitive period with regard to the association between maternal infection and schizophrenia risk (for review, (Brown and Derkits, 2010). However, a birth cohort study found that influenza infection (determined by presence of antibody in maternal serum samples) during the first trimester was associated with a 7-fold increase in schizophrenia risk, which fell to 3-fold when the entire first half of pregnancy was considered (Brown et al., 2004a). Poly (I:C) exposure at GD9 in mice was associated with dopamine-related behavioural and neurobiological alterations including deficits in prepulse inhibition (PPI) and latent inhibition, reduced expression of dopamine D1 and D2 receptors (D1R, D2R) in the prefrontal cortex and D2R in the striatum, as well as increased striatal tyrosine hydroxylase (TH) (Li et al., 2009; Meyer et al., 2008a,b,c). In contrast, the offspring of dams administered with Poly (I:C) during late (GD17), but not early, gestation displayed phenotypes more consistent with negative/cognitive symptoms of schizophrenia and N-methyl-D-aspartate (NMDA)-receptor alterations including impaired reversal learning, working memory deficits, increased locomotor sensitivity to the NMDA receptor antagonist dizocilpine (MK-801) and reduced hippocampal expression of the obligate NMDA receptor subunit, NR1 in the hippocampus (Meyer et al., 2006, 2008c). Taken together, these findings show that early gestational MIA may be more informative as a model for investigating the rodent equivalents of the positive, dopamine-related symptoms of schizophrenia in humans, including how they could potentially be treated. Accordingly, late gestational exposure in rodent models could be used to do the same for negative/cognitive symptoms (Meyer and Feldon, 2012).

While the observation of differential early/late phenotypes has been demonstrated in the C57 strain of mouse (Meyer, 2014), it is thus far unknown if such findings translate to other species of rodent, such as the rat. Many studies in rats have used Poly (I:C) to show that prenatal exposure to MIA produces a range of schizophrenia-like phenotypes such as increased sensitivity to amphetamine (AMPH) and MK-801 (Vorhees et al., 2012, 2015; Zuckerman and Weiner, 2005), reduced PPI (Howland et al., 2012; Wolff and Bilkey, 2008, 2010), disrupted latent inhibition (Zuckerman and Weiner, 2003, 2005), and impaired cognition (Howland et al., 2012; Wolff et al., 2011). However, these studies have only demonstrated the effects of MIA during mid-gestation (GD14-17), and to our knowledge, no study in a species other than the mouse has replicated the divergent effects of MIA in early versus late gestation on schizophrenia-like behaviour. Extension of these effects to rats will provide evidence of inter-species generality of the early versus late gestation effects, increasing the likelihood of these results also being relevant to human neurodevelopment. Additionally, it will facilitate further investigations that are more readily performed in rats (such as proposed biomarkers for schizophrenia that are measured using EEG) (Dickerson et al., 2010; Harms, 2015; Harms et al., 2014; Light and Swerdlow, 2015).

In the current study, we investigated the effect of MIA at GD10 and 19 in the rat, which are approximately equivalent to GD9 and 17 in the mouse, respectively (Workman et al., 2013). We examined a range of behaviours that were altered in both early and late MIA-exposed mice (locomotor sensitivity to AMPH), and those that were selectively altered by early (PPI) or late (working memory, locomotor sensitivity to MK-801) gestational MIA. For all behavioural assessments, we used both male and female offspring and had sufficient power to detect Sex × Maternal Treatment effects. It was predicted that if there were sex differences in the sensitivity to behavioural perturbation by MIA, effects would be most pronounced in males. Males tend to develop schizophrenia at a higher incidence than females (McGrath et al., 2004), and have been demonstrated to have more prominent negative symptoms (Andreasen et al., 1990; Chang et al., 2011; Fenton and McGlashan, 1991; Kay et al., 1986; Morgan et al., 2008; Ring et al., 1991; Schultz et al., 1997). With regard to cognitive deficits, however, there is mixed evidence for sex differences, with some cognitive deficits more pronounced in males and some deficits more pronounced in females, potentially depending on the neural network involved (for review, (Mendrek and Mancini-Marie, 2015) In addition, there is evidence that estrogen may serve a somewhat 'protective' role with respect to schizophrenia (Kulkarni et al., 2012). To follow up MIA-associated changes in dopamine-related behaviour found in male rats only, we examined the impact of MIA exposure on midbrain and striatal mRNA expression of TH, the D1 and D2 receptors, and the dopamine transporter, DAT.

2. Methods

2.1. Animals and prenatal treatment

Male and female Wistar rats (n = 16 and 94 respectively) were obtained from the University of Newcastle's Central Animal House at 8 weeks of age. Animals were acclimated for two weeks before daily monitoring of oestrous cycle using an impedance probe began. On the day of proestrus females were mated with male rats overnight. The following morning, the presence of sperm via vaginal smear was used to identify day of conception, with the day of detection being identified as GD0. Pregnant dams were then randomly allocated to a treatment group (GD10 Control n = 24, GD10 MIA n = 26, GD19 Control n = 20, GD19 MIA n = 24). Control and MIA allocations within each GD were paired and time-matched (e.g. if one pregnant rat was allocated to the GD19 MIA group the next one would be allocated to the GD19 Control group), ensuring that the resulting offspring from Control and MIA dams were of similar ages. On the appropriate gestational day (10 or 19) dams were anaesthetised with isoflurane (induction 5%, maintenance 2.5–3%) and administered with either 4.0 mg/kg of Poly (I:C) (MIA group; Sigma-Aldrich, St. Louis, MO) or 0.1 M phosphate-buffered saline (Control group) via injection to the lateral tail vein at 1 mL/kg body weight. Following injection, a subset of dams were weighed once daily for 2 days, except if birth occurred during this time. All experiments were performed under strict adherence to the National Health and Medical Research Council Australian Code of Practice for the care and use of animals for scientific purposes and were approved by the University of Newcastle's Animal Care and Ethics Committee (Approval numbers A-2009-108 and A-2013-319).