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Maternal immune activation leads to behavioral and pharmacological changes in the adult offspring

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Abstract

Maternal exposure to viral infection has been associated with an increased risk of schizophrenia in the offspring, and it has been suggested that the maternal immune response may interfere with normal fetal brain development. Although studies in rodents have shown that perinatal viral infections can lead to neuropathological and behavioral abnormalities considered relevant to schizophrenia, it is not clear whether these consequences are due to the infection itself or to the maternal immune response to infection. We show that an induction of maternal immune stimulation without exposure to a virus by injecting pregnant dams with the synthetic cytokine releaser polyriboinosinic-polyribocytidilic acid (poly I:C) leads to abnormal behavioral and pharmacological responses in the adult offspring. As in schizophrenia, these offspring displayed excessive behavioral switching, manifested in the loss of latent inhibition and in rapid reversal learning. Consistent with the clinical pharmacology of schizophrenia, both deficits were alleviated by antipsychotic treatment. In addition, these offspring displayed increased sensitivity to the locomotor-stimulating effects of MK-801, pointing to developmental alterations of the dopaminergic and/or glutamatergic systems. Prenatal poly I:C administration did not produce learning deficits in classical fear conditioning, active avoidance, discrimination learning and water maze. These results show that the maternal immune response is sufficient to cause behavioral and pharmacological alterations relevant to schizophrenia in the adult offspring.

Keywords: Maternal immune activation; Poly I:C; Latent inhibition; Reversal learning; Schizophrenia; Neurodevelopment; Cytokines

1. Introduction

Recent years have witnessed a growing emphasis on the contribution of neurodevelopmental factors to the pathophysiology of schizophrenia (Beckmann, 1999; Bogerts, 1993; Weinberger, 1995). Among environmental factors that may detrimentally affect neurodevelopment, prenatal exposure to viral infection has been implicated by several large epidemiological studies indicating that such exposure increases the risk of schizophrenia in adulthood (Adams et al., 1993; Izumoto et al., 1999; O'Callaghan et al., 1994; Torrey et al., 1988; Watson et al., 1984). Although the mechanisms whereby viral insults during neuro-ontogenesis can cause latent pathology in the CNS remain unknown, it has been suggested that the maternal immune response, and in particular pro-inflammatory cytokines released by the maternal immune system, may interfere with normal fetal brain development (Gilmore and Jarskog, 1997; Kirch, 1993; Marx et al., 2001; Nawa et al., 2000; Pearce, 2000, 2001; Waltrip et al., 1984; Wright et al., 1993). The role of cytokines is underscored by

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findings that prenatal exposure to a variety of infections has been associated with an increased incidence of schizophrenia indicating that such an association may be mediated by a host response that is common to all infections (Gilmore and Jarskog, 1997; Marx et al., 2001; Nawa et al., 2000; Pearce, 2001).

Although studies in rodents have shown that perinatal viral infections can lead to neuropathological and behavioral abnormalities considered relevant to schizophrenia (Borrell et al., 2002; Engel et al., 2000; Fatemi et al., 1999; Pearce et al., 2000; Rothschild et al., 1999), it is not clear whether the consequences of prenatal infection are due to the infection itself or to the maternal immune response to infection. One approach to this question is to induce a maternal anti-viral-like response without exposure to a virus. This can be achieved by injecting pregnant dams with the synthetic double-stranded RNA, polyriboinosinic-polyribocytidilic acid (poly I:C). Systemic administration of poly I:C is commonly used to mimic viral exposure because it elicits immune responses analogous to those observed during viral infection, most notably by inducing the release of pro-inflammatory cytokines (Doukas et al., 1994; Katafuchi et al., 2003; Kimura et al., 1994; Pruett et al., 2003; Snell et al., 1997; Toth et al., 1990).

We have recently shown that the offspring of dams injected with poly I:C on gestational day (GD) 15, exhibited after puberty loss of latent inhibition (LI), the phenomenon whereby the behavioral control of stimuli is downgraded following their inconsequential preexposure (Zuckerman et al., 2001, 2003; Zuckerman and Weiner, 2003). Disrupted LI is a well-established model of schizophrenia as rats and humans treated with amphetamine as well as acute schizophrenia patients show deficits in LI (Gray et al., 1991; Moser et al., 2000; Weiner, 2000, 2003). Therefore, LI loss following prenatal poly I:C administration indicated that maternal immune response was sufficient to cause long term abnormalities potentially relevant to schizophrenia. This was supported by our findings that antipsychotic treatment restored LI in the adult poly I:C offspring, and that these rats exhibited excessive amphetamine-induced activity (Zuckerman et al., 2003), as well as by a recent report that prenatal poly I:C administration led to an additional schizophrenia-like deficit, loss of prepulse inhibition, in mice (Shi et al., 2003).

The present study sought to further validate the prenatal poly I:C model of induction as a model of schizophrenia, and in particular, the specificity of the cognitive deficits and response to drugs produced by this manipulation. For this end, we administered poly I:C on GD-15 or GD-17, a time during the proliferation and migration of limbic cortical neurons (Bayer, 1980; Bayer and Altman, 1991; Bayer et al., 1991), and tested the adult offspring in several behavioral tasks in addition to LI, namely, a position discrimination and reversal task, the Morris water maze task, and locomotor activity following the administration of the NMDA receptor antagonist MK-801. In addition, we assessed LI in two different procedures, namely, a conditioned emotional response (CER) procedure and a two-way active avoidance procedure, in order to evaluate the effects of prenatal poly I:C treatment on classical fear conditioning and operant aversive conditioning, respectively (in the nonpreexposed groups). Finally, we tested whether behavioral deficits induced by immune activation during pregnancy would be reversed by the atypical antipsychotic drug (APD) clozapine. Since administration on both GDs produced the same effects on LI (Experiment 1) and reversal (Experiment 2), in the following experiments poly I:C was administered only on GD-15.

2. Materials and methods

2.1. Subjects

Male Wistar rats, 3 months old and weighing 350–400 g, bred in our laboratory, were housed four to a cage under reversed cycle lighting (lights on: 19:00–07:00) with ad lib food and water, except for one week prior to and during the LI in CER experiments (see below). All experimental protocols were carried out according to the guidelines of the Institutional Animal Care and Use Committee of Tel Aviv University.

2.2. Prenatal treatment

Wistar rats (Harlan Laboratories, Jerusalem) were mated at about an age of 3 months and the first day after copulation was defined as day 1 of pregnancy. Pregnant rats were anesthetized with Halothane (SIGMA, Israel), and received either a single i.v. injection of poly I:C (4.0 mg/kg, SIGMA, Israel) dissolved in saline, or an equivalent volume of saline. Poly I:C caused weight loss for approximately one day, without affecting gestational period or litter size. At birth litters were culled to 8, composed of 4 males and 4 females when possible. On day 21 the pups were weaned and housed 4 to a cage by sex and litter, and maintained undisturbed until the age of 3 months when behavioral testing was conducted. The offspring were derived from two different breeding batches. In the first batch, poly I:C was administered on GD-15 or GD-17, and the adult offspring were tested in LI in the conditioned emotional response procedure and in discrimination reversal. Since poly I:C administration on both GDs exerted the same behavioral effects, in the second batch