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Review

Effects of prenatal infection on brain development and behavior: A review of findings from animal models

Patricia Boksa *

Department of Psychiatry, McGill University, Douglas Mental Health University Institute, 6875 LaSalle Blvd., Montreal, Verdun, Quebec, Canada H4H 1R3

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ABSTRACT

Epidemiological studies with human populations indicate associations between maternal infection during pregnancy and increased risk in offspring for central nervous system (CNS) disorders including schizophrenia, autism and cerebral palsy. Since 2000, a large number of studies have used rodent models of systemic prenatal infection or prenatal immune activation to characterize changes in brain function and behavior caused by the prenatal insult. This review provides a comprehensive summary of these findings, and examines consistencies and trends across studies in an effort to provide a perspective on our current state of understanding from this body of work. Results from these animal modeling studies clearly indicate that prenatal immune activation can cause both acute and lasting changes in behavior and CNS structure and function in offspring. Across laboratories, studies vary with respect to the type, dose and timing of immunogen administration during gestation, species used, postnatal age examined and specific outcome measure quantified. This makes comparison across studies and assessment of replicability difficult. With regard to mechanisms, evidence for roles for several acute mediators of effects of prenatal immune activation has emerged, including circulating interleukin-6, increased placental cytokines and oxidative stress in the fetal brain. However, information required to describe the complete mechanistic pathway responsible for acute effects of prenatal immune activation on fetal brain is lacking, and no studies have yet addressed the issue of how acute prenatal exposure to an immunogen is transduced into a long-term CNS change in the postnatal animal. Directions for further research are discussed.

1. Introduction

Epidemiological studies in humans have provided substantial evidence that prenatal infection is associated with an increased risk for the development of several psychiatric and neurologic disorders, most prominently schizophrenia, autism and cerebral palsy. While these associations provide rationale for suggesting that prenatal infection might contribute to the cause of these disorders, they do not prove causation. Animal modeling provides an opportune approach to ask if prenatal infection can actually cause transient or lasting changes in CNS function, and what the mechanisms for this might be. Since 2000, there has been a veritable explosion of studies from various laboratories that have used in vivo animal modeling, mainly in rodents, to characterize effects of systemic prenatal infection on brain development and behavior. The aim of this review is to provide a comprehensive overview of these findings from animal models of prenatal infection, in an effort to tease out consistencies, trends and deficiencies in the literature and to suggest possibilities for future directions.

In order to understand directions these animal modeling studies have taken, I will first provide a short introduction to the epidemiological literature associating prenatal infections with increased risk for CNS disorders in humans, although it is not the purpose of this paper to review this area in depth. An extensive literature has described that increased risk for schizophrenia is associated with a history of prenatal infection with a wide variety of different infectious agents (reviewed by Brown and Derkits, 2010). First reported by Mednick et al. (1988) in the mid-1980s, numerous groups (although not all) have replicated the finding that maternal influenza during pregnancy is associated with an increased incidence of schizophrenia (Barr et al., 1990; O'Callaghan et al., 1991; Sham et al., 1992; Adams et al., 1993; Mednick et al., 1994; Takei et al., 1996; Battle et al., 1999; Munk-Jorgensen and Ewald, 2001; Limosin et al., 2003; Brown et al., 2004; Ebert and Kotler, 2005; Byrne et al., 2007; Selten et al., 2009). Increased incidence of schizophrenia has also been associated with other viral infections (measles, rubella, varicella-zoster, polio, herpes simplex virus type 2), with bacterial infections (pneumonia and other respiratory infections, pyelonephritis, diverse bacterial infections) during pregnancy, with maternal infection with the toxoplasmosis parasite and with maternal genital/reproductive infections arising from various

* Fax: +1 514 762 3034.
E-mail address: patricia.boksa@mcgill.ca

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organisms (Torrey et al., 1988; O'Callaghan et al., 1994; Suvisaari et al., 1999; Brown et al., 2000, 2005; Brown and Susser, 2002; Babulas et al., 2006; Mortensen et al., 2007; Buka et al., 2008; Clarke et al., 2009; Sørensen et al., 2009). While most studies have relied on maternal recall and retrospective or prospective hospital records to assess maternal infections, recent studies assessing maternal infection via analysis of archived maternal serum have confirmed the association between prenatal viral infection and increased schizophrenia risk (Brown and Susser, 2002; Brown et al., 2004, 2005; Mortensen et al., 2007; Buka et al., 2008; Xiao et al., 2009). In more detailed recent studies examining symptom subsets in psychosis, Zammit et al. (2009) have reported a significant association between maternal infection during pregnancy and the presence of psychosis-like symptoms in adolescents at 12 years of age. Ellman et al. (2009) have reported that persons with schizophrenia and affective psychosis showed greater deficits in verbal IQ and other aspects of cognitive functioning prior to the onset of psychosis if they had been exposed prenatally to serologically confirmed influenza B. In a similar vein, Brown et al. (2009) documented that patients with schizophrenia who were exposed to serologically confirmed influenza or toxoplasmosis in utero showed greater deficits in cognitive tests of set-shifting ability, compared to patients not exposed to prenatal infection. As an additional aspect, Clarke et al. (2009) have recently reported that maternal pyelonephritis during pregnancy is associated with increased risk for schizophrenia only in persons with a positive family history of schizophrenia, suggesting a gene x environment interaction as the mechanism for increased schizophrenia risk.

With respect to timing of the infection, numerous studies have identified the 2nd trimester of pregnancy as the critical period for exposure to influenza and other viral infections, leading to increased schizophrenia (Torrey et al., 1988; O'Callaghan et al., 1994; Suvisaari et al., 1999; Brown et al., 2000; Ebert and Kotler, 2005). However, the most pronounced association of rubella infection with schizophrenia spectrum disorders was found with 1st trimester exposure (Brown and Susser, 2002). Moreover, a recent study confirming presence of influenza antibodies in archived maternal serum has described increased schizophrenia risk with exposure during the 1st third to half of pregnancy (Brown et al., 2004), while another recent study has associated increased schizophrenia with bacterial infection during the 1st trimester (Sørensen et al., 2009). Thus it appears that animal modeling of both viral and bacterial infection during the equivalent of the 1st and 2nd trimesters of human pregnancy may be relevant to the pathophysiology of schizophrenia.

Evidence implicating a role for prenatal infection in the etiology of autism is much less extensive. Two larger studies have reported increased incidence of autism following congenital rubella or maternal viral infection during pregnancy (Chess, 1977; Wilkerson et al., 2002), however, the trimester of increased vulnerability was not identified. Beyond this, several case reports have linked autism to prenatal exposure to various viruses, such as cytomegalovirus (Ciaranello and Ciaranello, 1995; Libbey et al., 2005). Increased risk for cerebral palsy has most often been associated with chorioamnionitis (i.e. intra-uterine infection), although there is some evidence that extra-uterine maternal infections during pregnancy may also play a role (Murphy et al., 1995; Clark et al., 2008). Meta-analysis has indicated a significant association between chorioamnionitis and cerebral palsy for both preterm and term infants (Wu and Colford, 2000; Wu, 2002).

2. Animal models of systemic prenatal infection

To date, animal modeling to assess effects of maternal infection during pregnancy on CNS function in offspring has been done almost exclusively using rats and mice. Both bacterial and viral infections during pregnancy have been modeled, using three main immunogenic approaches, namely, administration of lipopolysaccharide (LPS), influenza virus or polyinosinic:polycytidylic acid (poly IC) to the pregnant rodent. LPS or poly IC have been injected intraperitoneally, intravenously or subcutaneously, while influenza virus has been administered intranasally. I have confined this review to studies in which immunogens have been administered systemically to pregnant animals, and have omitted, for example, studies in which LPS is administered directly to fetal sheep or locally into the uterus or cervix in rodents. Direct administration of LPS to the fetus may differ substantially from systemic maternal LPS administration since LPS does not enter the fetal compartment when administered systemically to the pregnant rat dam (Goto et al., 1994; Ashdown et al., 2006). I have also not included studies in which immunogens or cytokines have been administered directly to neonatal animals.

The gestational age at which immunogen was administered varies across these studies on prenatal infection, ranging from daily administration of LPS or poly IC every day throughout pregnancy to a single administration on 1 day early or late in gestation. Average gestation length is about 22 days in the rat and 19 days in the mouse, and rat or mouse brain at birth is known to be less mature than the brain of the human neonate. Mapping the developmental stage of human perinatal brain onto that of the rodent is a complex issue and still an ongoing subject of research, since rates of a myriad of developmental events taking place at different rates may be compared across species. Rat brain at roughly postnatal day 7–13 has generally been taken to be equivalent to the developmental stage of human brain at term (Romijn et al., 1991; Avishai-Eliner et al., 2002). Thus the 1st and 2nd halves of rat gestation are usually assumed to approximate the 1st and 2nd trimesters of human pregnancy, although translating developmental dates between species using a linear scale is an oversimplification (Clancy et al., 2007).

Administration of LPS, a cell wall component from Gram negative bacteria, is a well-characterized and widely accepted model of bacterial infection. Systemic LPS administration leads to activation of the innate immune response consisting primarily of cytokine induction, inflammation, fever, complement cascade activation, hypothalamic–pituitary–adrenal axis activation and sickness behavior. Binding of LPS to toll-like receptor-4 (TLR-4) on macrophages and other immune cells triggers a signal transduction cascade leading to activation of transcription factors such as nuclear factor kappa B (NFκB) and subsequent transcription of genes coding for pro- and anti-inflammatory mediators such as cytokines, chemokines and proteins of the complement system (Aderem and Ulevitch, 2000). In response to LPS, synthesis and release of a family of pro-inflammatory cytokines, most prominently interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α) is elicited. IL-1 and TNF-α are produced locally and act on fibroblast and endothelial cells to induce their own synthesis as well as that of IL-6 and other cytokines (Luheshi, 1998). Circulating IL-6 then interacts with targets in the brain to induce cyclooxygenase-2 (COX-2)-mediated synthesis of prostaglandins (PG) in the hypothalamus. PGE_2 acting on thermosensitive neurons in the preoptic area of the anterior hypothalamus mediates a rise in core body temperature, i.e. fever (Roth et al., 2009).

Poly IC is a synthetic double-stranded RNA analog, used to mimic aspects of a viral infection. Poly IC has been shown to induce hyporesponsive acute phase reactions on subsequent challenge with influenza virus in rabbits, indicating that poly IC can substitute for the virus in eliciting fever and other acute phase responses (Kimura-Takeuchi et al., 1992). Viruses and double-stranded RNAs like poly IC bind to TLR-3 resulting in translocation of NFκB to the nucleus and induction of cytokines (including IL-1, IL-6 and TNF-α)

as well as type I interferons (Fortier et al., 2004b; Doughty et al., 2006; Koga et al., 2009).

Compared to live pathogens like influenza virus, use of poly IC or LPS mimics the immune activation accompanying a viral or bacterial infection while conferring control over time course and dose of immunogen exposure. This may allow more precise identification of windows of vulnerability. On the other hand, use of poly IC or LPS clearly does not mimic the entire time course of a propagating viral or bacterial infection. Another issue related to the use of LPS is that each batch and lot of LPS typically contains differing pyrogenic and cytokinogenic activity since LPS is extracted and purified from bacteria (Ray et al., 1991). For example, it has been shown that equal doses of different serotypes of LPS prepared from *Escherichia coli* may differ with respect to the time course of cytokine induction and the propensity to produce a hypothermic rather than hyperthermic response (Akarsu and Mamuk, 2007). Thus doses of LPS may not be directly comparable across laboratories on a mg/kg basis; expressing LPS dosage in terms of international activity units would be preferable, but such practice is not yet routine in the literature. Moreover, higher doses of LPS, intravenous route of administration, higher ambient temperature and use of animals naïve to LPS appear to increase the probability of hypothermic rather than hyperthermic responses to LPS (Feldberg and Saxena, 1975; Derijk et al., 1994; Romanovsky and Székely, 1998; Fofie and Fewell, 2003). It is unclear if differing batches of poly IC may also differ in immunogenic activity on a weight basis. Another issue to keep in mind with respect to LPS dosing is that LPS (but not poly IC) exhibits tolerance such that successive daily dosing results in attenuated fever and cytokine responses (Wilkinson and Kasting, 1990; Soszynski et al., 1991; Chen et al., 2005). The interested reader is directed to an excellent recent review by Meyer et al. (2009) discussing methodological issues related to the design of experiments with rodent models of prenatal immune activation, and the advantages and disadvantages of various models.

One key question with respect to how maternal infection can affect fetal brain development is the issue of which component of the acute inflammatory response might be a required mediator. Is alteration in a specific maternal cytokine, glucocorticoids, prostaglandins, fever, etc. necessary to produce effects on fetal brain? Administration of LPS or poly IC to the rodent during pregnancy can clearly increase maternal levels of serum cytokines, including IL-1β, IL-6 and TNF-α, and produce fever (see e.g. Fortier et al., 2004a; Gayle et al., 2004; Ashdown et al., 2006, 2007; Meyer et al., 2006a). However, it has been well documented that, during late pregnancy near term, the fever response to LPS and other immunogens becomes attenuated due to reduced PGE_2 induction of COX-2, in several mammalian species including rats and guinea pigs (reviewed by Mouihate et al., 2008). The complete mechanism responsible for this reduced fever response at term is unknown but may involve increased induction of anti-inflammatory cytokines like IL-1 receptor antagonist (IL-1ra) and elevated brain nitric oxide (Ashdown et al., 2007; Begg et al., 2007; Mouihate et al., 2008; Spencer et al., 2008). It is interesting to speculate that the association of human disorders like schizophrenia with prenatal infection during the first two trimesters but not the last trimester of pregnancy may be due, in part to this altered neuroimmune responsiveness during late pregnancy.

In addition to inflammatory responses in the maternal compartment, changes in cytokines or other mediators in the placenta have also been of interest as possible mediators of prenatal infection-induced changes in brain function (Table 1). Inflammation-induced compromise of the placenta may have detrimental consequences on fetal brain development, because increased levels of inflammatory cytokines, such as TNF-α, in placenta have been implicated in placental dysfunction and trophoblast apoptosis (Kakinuma et al., 1997; Haider and Knöfler, 2009).

Of course, assessing acute neurochemical changes in fetal brain are of importance in understanding mechanisms mediating longer term CNS changes in offspring following maternal infection. Measurement of fetal brain cytokines has been of particular interest in the hours following prenatal infection (Table 1). In addition to their role in the inflammatory response, cytokines also have important effects on CNS development, including effects on neuronal survival, differentiation and apoptosis, expression of transmitters and neurotrophins and excitotoxicity in developing brain (Balasingam et al., 1994; Chao and Hu, 1994; von Coelln et al., 1995; Ling et al., 1998; Qui et al., 1998; Marx et al., 2001; Deverman and Patterson, 2009).

A major aim of recent studies on effects of prenatal infection has been to characterize the effects of the infection on CNS function in the offspring at various stages of postnatal development and into adulthood. Outcomes related to CNS function that have been studied in offspring can roughly be categorized as behavioral, morphological, neurochemical (related to specific neurotransmitter systems) or molecular alterations. Tables 2–5 are an attempt to tabulate a comprehensive summary of postnatal changes in offspring in each of these categories, that have been reported in various studies of systemic prenatal infection in rodents. In order to give some sense of the reproducibility of findings, each entry represents findings emanating from one laboratory or group, although multiple references from that laboratory may be cited. The summary is biased in that only positive findings are tabulated, due to space constraints; inclusion of reported negative findings could provide additional information with respect to reproducibility of findings. Only outcomes measures that were quantitated and statistically analyzed are included in Tables 1–5; findings substantiated, for example, only by sample photographs, were not included. I have not noted the sex of the offspring studied, since most studies examined either mixed groups of male and female offspring or only male offspring, and sex specificity of effects were not systematically examined. However, where examined, some studies have observed sex dependent changes in CNS outcome due to prenatal infection, indicating that sex of offspring may be a relevant factor contributing to outcome variability (e.g. Samuelsson et al., 2006; Lanté et al., 2007; Meyer et al., 2008e; Wang et al., 2010). A more systematic examination of sex dependence of effects of prenatal infection is certainly warranted given the sex differences in the incidence of human CNS disorders associated with increased prenatal infection (Aleman et al., 2003; McGrath et al., 2004; Zahn-Waxler et al., 2008).

3. Acute effects of prenatal immune activation on fetal brain

Table 1 shows a summary of changes in fetal brain measured acutely (usually within 24 h) following administration of LPS or poly IC to pregnant rats or mice. Findings for placenta, amniotic fluid and other fetal tissues, that were reported in these studies, are also listed. The most often studied parameter has been cytokine expression in the fetal brain. Increased mRNA for IL-1β and also TNF-α or IL-6, in fetal brain has been reported by three groups following maternal LPS at E18 in the rat or mouse (Cai et al., 2000; Paintlia et al., 2004; Liverman et al., 2006). However, a third group using lower doses of LPS in the E18 rat reported no change in fetal brain mRNA for IL-1β, TNF-α, IL-6 or IL-10 (Gayle et al., 2004). Changes in protein levels of these cytokines in fetal brain have not been prominent or consistently reported. Urakubo et al. (2001) reported that maternal LPS in the E16 rat decreased fetal brain TNF-α, while Ashdown et al. (2006) using a lower dose of LPS, that still, however, produced fever in the E18 rat (Ashdown

Table 1
Acute changes in the fetal compartment after prenatal immune activation.

Fetal changes	Immunogen, dose, route	Time of administration	Species	References
↓ TNF-α in brain; ↑ IL-6, TNF-α in placenta; ↑ TNF-α in amniotic fluid (2 h)	LPS, 2.5 mg/kg, ip	E16	Rat	Urakubo et al. (2001)
↑ IL-1β, IL-6, TNF-α in placenta; ↑ IL-6 in amniotic fluid (2 h, 8 h)	LPS, 500 μg/kg, ip	E16	Rat	Urakubo et al. (2001)
↑ IL-1β, IL-6, TNF-α, IL-1ra in placenta	LPS, 200 μg/kg, ip	Twice daily from E17 to birth	Rat	Girard et al. (2010)
↑ mRNA for IL-1β (1–48 h), TNF-α (1–24 h), iNOS (24–48 h) in brain; ↑ apoptosis in subventricular zone, ↓ OPCs and ↑ microglial activation in brain (48 h); ↑ oxidative stress, ↓ reduced glutathione, ↓ peroxisomal function in brain (24 h, 48 h), ↑ phospholipid metabolism and lipid peroxidation in placenta	LPS, 700 μg/kg or 1 mg/kg, ip	E18	Rat	Paintlia et al. (2004, 2008)
↑ mRNA for CRH in brain (6,12 h); ↑ mRNA for IL-1β, IL-6, TNF-α in placenta (1–24 h); ↑ IL-1β, IL-6, TNF-α in amniotic fluid (1–12 h)	LPS, 100 μg/kg, ip	E18	Rat	Gayle et al. (2004)
↑ IL-1β, IL-6, TNF-α in placenta (2–8 h); ↑ IL-1β in fetal plasma (4 h)	LPS, 50 μg/kg, ip	E18	Rat	Ashdown et al. (2006)
↑ protein carbonylation (1–4 h), ↓ reduced/oxidized glutathione (16 h), ↓ α-tocopherol (4 h) in hippocampus	LPS, 500 μg/kg, ip	E19	Rat	Lanté et al. (2007, 2008)
↑ necrotic neurons in mesencephalon (E18)	LPS, 5 or 2.5 μg/ pregnant mouse	E10 or E10 and E12	Mouse	Haesaert and Ornoy (1986)
↑ IL-6 (3 h), ↑ BDNF (9 h) in brain	LPS, 120 μg/kg, ip	E17	Mouse	Golan et al. (2005)
↑ TNF-α in brain, liver and amniotic fluid (1.5 h)	LPS, 500 μg/kg, ip	E17	Mouse	Ning et al. (2008)
↑ mRNA for IL-1β, IL-6, MCP-1, necdin, VEGF, YB-1 in brain (1–12 h); ↓ mRNA for groucho, semaphorin 5b in brain (6 h)	LPS, 50 μg, ip	E18	Mouse	Liverman et al. (2006)
↑ mRNA for TNF-α and IFN-γ in brain (E16.5)	Campylobacter rectus, sc chamber	E7.5	Mouse	Offenbacher et al. (2005)
↓ TNF-α in whole brain (24 h); ↓ TNF-α in liver/spleen; ↑ TNF-α, ↓ BDNF, NGF in placenta	Poly IC, 10 or 20 mg/kg, ip	E16	Rat	Gilmore et al. (2005)
↓ IL-1β, ↑ IL-6, ↓ IL-10 in brain (3 h); ↑ IL-1β, IL-6, TNF-α in brain (5 or 6 h)	Poly IC, 2 or 5 mg/ kg, iv	E9	Mouse	Meyer et al. (2006a, 2008b)
↑ IL-1β, IL-6, TNF-α, IFN-γ in placenta (2 h, 4 h)	Poly IC, 4.5 mg/ kg, ip	E16.5	Mouse	Koga et al. (2009)
↑ IL-1β, IL-10 in brain (3 h); ↑ IL-6 in brain (6 h)	Poly IC, 5 mg/kg, iv	E17	Mouse	Meyer et al. (2006a)
↑ mRNA for IL-1α, ↓ mRNA for IL-1 receptor II in brain (E18)	Cytomegalovirus, ip	E4	Immunodeficient mouse	Woolf et al. (2007)

Under "Fetal changes", the time point at which fetuses were sacrificed after administration of prenatal immunogen is shown in parentheses.
Abbreviations: BDNF, brain-derived neurotrophic factor; CRH, corticotrophin releasing hormone; E, embryonic day; IFN, interferon; iNOS, inducible nitric oxide synthase; IL, interleukin; IL-1ra, interleukin receptor antagonist; in, intranasal; ip, intraperitoneal; iv, intravenous; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; NGF, nerve growth factor; OPC, oligodendrocyte progenitor cell; P, postnatal day; poly IC, polyinosinic: polycytidylic acid; sc, subcutaneous; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; YB, Y-box-binding protein.

et al., 2006), found no changes in fetal brain levels of TNF-α, IL-1β or IL-6. In contrast, in the E17 mouse, maternal LPS has been reported to increase fetal brain TNF-α, as well as IL-6 (Golan et al., 2005; Ning et al., 2008). Only one group (Meyer et al., 2006a) has examined effects of maternal poly IC on fetal brain cytokines; these effects were complex, dependent on the gestational day at which poly IC was administered and the time after poly IC administration at which fetal brains were assayed. Poly IC treatment in the E9 mouse decreased fetal brain IL-1β at 3 h post-treatment then increased it at 6 h, while poly IC in the E17 mouse increased IL-1β at 3 h. Poly IC given at E9 decreased fetal brain IL-10 but given at E17 increased fetal brain IL-10. Fetal brain IL-6 was increased by poly IC given at either E9 or E17, while TNF-α was increased only after poly IC at E9. Overall the current data on fetal brain cytokine changes do not yet provide compelling evidence to suggest if and how changes in fetal brain cytokines might affect fetal brain development after maternal infection. However, it should be noted that all studies to date have assessed cytokines in whole fetal brain, while changes in cytokine expression may be region specific. Moreover, cytokine protein levels in fetal brain are low compared to other tissues, likely adding to variability in their measurement in brain. The possibility that changes in cytokine processing or signaling in fetal brain occur after maternal infection, in the absence of significant changes in cytokine levels, has not yet been explored.

Two groups have reported changes in multiple markers indicative of oxidative stress in the fetal brain in the first hours to days following LPS treatment of the pregnant rat at E18 or E19 (Paintlia et al., 2004, 2008; Lanté et al., 2007, 2008). Finally, a few changes in various neuromodulators in fetal brain have been reported, each in single studies from one group. Increased message for inducible nitric oxide synthase (Paintlia et al., 2004) and corticotrophin releasing hormone (Gayle et al., 2004) and increased brain-derived neurotrophic factor protein (Golan et al., 2005) have been reported in fetal brain after LPS administration to the E18 or E17 rat.

Relatively consistent findings have been reported with respect to acute cytokine changes in the placenta in response to maternal infection. In studies by five different groups, placental levels of TNF-α are reported to be increased following either LPS or poly IC treatment in the E16–E18 rat or mouse (Urakubo et al., 2001; Gilmore et al., 2005; Ashdown et al., 2006; Koga et al., 2009; Girard et al., 2010). IL-1β and IL-6 were also increased in placenta following LPS treatment of the pregnant rat at E16–E18 or poly IC treatment of the E16 mouse (Urakubo et al., 2001; Ashdown et al., 2006; Koga et al., 2009; Girard et al., 2010). Given evidence for a role for elevated levels of placental cytokines like TNF-α in placental dysfunction (Haider and Knöfler, 2009), these findings are consistent with the idea that increased levels of placental cytokines consequent to maternal infection could contribute to altered placental

Table 2
Behavioral changes in offspring after prenatal immune activation.

Postnatal changes	Immunogen, dose, route	Time of administration	Species	References
↓ PPI (P70, P100, P300)	LPS, 1 mg/kg, sc	Alternate days for whole pregnancy	Rat	Borrell et al. (2002)
↓ PPI (P35, P70, P170, P180, P400)	LPS, 2 mg/kg, sc	Daily for whole pregnancy	Rat	Romero et al. (2007, 2010)
↑ ethanol intake and preference, ↓ rearing (P100–P130)	LPS, 1 mg/kg, sc	Alternate days for whole pregnancy	Rat	Liu et al. (2004)
↑ locomotor activity (P90), ↓ locomotor activity (P480)	LPS, 1 mg/kg, ip	E10.5–E11	Rat	Ling et al. (2009)
↓ PPI (P70)	LPS, 100 μg/kg, ip	E15 and E16	Rat	Fortier et al. (2007)
↓ latency to fall off rotarod (P30, P35, P40)	LPS, 200 μg/kg, ip	Twice daily from E17 to birth	Rat	Girard et al. (2009, 2010)
↑ latency to initiate sexual behavior and ↓ intromission by males (P91)	LPS, 0.2 or 2.0 μg/pregnant rat, iv	E18	Rat	Wijkstra et al. (1991)
↓ PPI, ↑ AMPH-induced locomotion (P70)	LPS, 50 μg/kg, ip	E18 and E19	Rat	Fortier et al. (2004a, 2007)
↓ spatial learning in water maze (P28)	LPS, 500 μg/kg, ip	E19	Rat	Lanté et al. (2007, 2008)
↓ learning and retention in radial arm maze, altered open field and burrowing/hoarding behavior, impaired beam walking (P70, P200, P400, P600)	LPS, 8 μg/kg, ip	Daily from E8 to E15	Mouse	Wang et al. (2010)
↑ exploration of familiar vs. novel object (P85)	LPS, 300 μg/kg, sc	E9	Mouse	Coyle et al. (2009)
↑ audiogenic seizures (P28)	LPS, 2.5 μg/pregnant mouse	E10 and E12	Mouse	Haesaert and Ornoy (1986)
↓ associative learning in cued version of water maze; ↑ novel object recognition; ↑ anxiety; ↓ passive avoidance (P240); ↑ exploration in open field (P240, P600)	LPS, 120 μg/kg, ip	E17	Mouse	Golan et al. (2005, 2006a,b)
↓ PPI, ↓ exploration in open field and novel object test, ↓ social behavior (P28–P56)	Influenza, in	E9.5	Mouse	Shi et al. (2003)
↓ PPI (P56)	Poly IC, 4 mg/kg, iv	E15	Rat	Wolff and Bilkey (2008)
↓ LI, ↑ reversal learning of left–right discrimination, ↑ AMPH- and MK801-induced locomotion (P90)	Poly IC, 4 mg/kg, iv	E15 or E17	Rat	Zuckerman et al. (2003) and Zuckerman and Weiner (2003, 2005)
↓ PPI and ↑ startle reactivity, ↓ LI, ↓ exploration in open field, ↑ AMPH- and/or MK801-induced locomotion (P35, P90–P120)	Poly IC, 2 or 5 mg/kg, iv	E9	Mouse	Meyer et al. (2006a,b, 2008b,c,d,e)
↓ PPI (P42–P56)	Poly IC, 20 mg/kg, ip	E9.5	Mouse	Shi et al. (2003)
↓ PPI (P63)	Poly IC, 60 mg/kg, ip	E9.5	Mouse	Makinodan et al. (2008)
↓ PPI, ↓ thigmotaxis, ↓novel object recognition; ↑ MAP-induced locomotion (P63–P70)	Poly IC, 5 mg/kg, ip	E12–E17	Mouse	Ozawa et al. (2006)
↓ PPI, ↓ LI, ↓ exploration in open field, ↓ social interaction (adult, age unspecified)	Poly IC, 20 mg/kg, ip	E12.5	Mouse	Smith et al. (2007)
↓ reversal learning of left–right discrimination; ↓ working memory in water maze; ↑ AMPH- and MK801-induced locomotion (P98–P112)	Poly IC, 5 mg/kg, iv	E17	Mouse	Meyer et al. (2006a, 2008c)
↓ spatial learning in Morris water maze (P140)	IL-6, 9 μg/kg, ip	E8, E10 and E12 or E16, E18 and E20	Rat	Samuelsson et al. (2006)
↓ PPI, ↓ LI (adult, age unspecified)	IL-6, 5 μg, ip	E12.5	Mouse	Smith et al. (2007)

Under "Postnatal changes", the age at which offspring were behaviorally tested is shown in parentheses.
Abbreviations: AMPH, amphetamine; MAP, methamphetamine; PPI, prepulse inhibition of acoustic startle; LI, latent inhibition; see legend to Table 1 for additional abbreviations.

function with downstream effects on fetal neurodevelopment. In support of this idea, studies designed to assess effects of maternal LPS treatment on fetal growth retardation in mice have shown that LPS (75 μg/kg, ip) on E15–E17 induces lipid peroxidation and glutathione depletion in the placenta and produces intra-uterine fetal growth restriction as assessed by decreased fetal weight, decreased crown-rump and tail lengths, and retarded skeletal ossification (Chen et al., 2006; Xu et al., 2006; Zhang et al., 2007). Moreover, the deficits in fetal weight and skeletal ossification were reported to be reversed by pentoxifylline, a compound which reduces production of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 (Xu et al., 2006).

4. Behavioral changes in offspring after prenatal immune activation

The most frequently observed behavioral alteration in rodent offspring as a result of prenatal immune activation is a deficit in prepulse inhibition (PPI) of acoustic startle (see Table 2). In the rat, deficits in PPI in adult offspring have been reported following prenatal administration of either LPS or poly IC (Borrell et al., 2002; Fortier et al., 2004a, 2007; Romero et al., 2007, 2010; Wolff and Bilkey, 2008). In the mouse, PPI deficits following prenatal poly IC exposure during mid gestation (E9–E12.5) have been reported by four separate laboratories (Shi et al., 2003; Ozawa et al., 2006; Smith et al., 2007; Makinodan et al., 2008; Meyer et al., 2008b,c,d). Interestingly one of these groups reported that PPI deficits are present following poly IC at E9 but not at E17, supporting the idea that mid gestation may be a period of increased sensitivity to poly IC, with respect to alterations in PPI (Meyer et al., 2008c). PPI deficits in the mouse have also been reported following prenatal administration of influenza virus or of interleukin-6 (Shi et al., 2003; Smith et al., 2007). Thus PPI deficits appear to be a fairly consistent finding across rodent species and types of prenatal immunogens. However, the relative frequency with which PPI deficits are reported compared to other behaviors may owe something to

Table 3
Morphological changes in the brains of offspring after prenatal immune activation.

Postnatal changes	Immunogen, dose, route	Time of administration	Species	References
↑ activated microglia in SN basally (P120, P210, P420, P510) and in response to postnatal intranigral LPS (P210–P294)	LPS, 1 mg/kg, ip	E10.5	Rat	Ling et al. (2006, 2009)
↓ neurogenesis in hippocampal dentate gyrus (E18, P14)	LPS, 50 or 100 μg/kg, ip	E15 and E16 or E18 and E19	Rat	Cui et al. (2009)
↓ dendritic arborization in mPFC and hippocampal CA1 (P10, P35, P60); ↓ dendritic length in mPFC (P10, P35) and CA1 (P60); ↓ spine density in mPFC (P60)	LPS, 100 μg/kg, ip	E15 and E16	Rat	Baharnoori et al. (2009)
↑ cerebral cortical lesions (i.e. shrunken neuronal cell bodies and nuclei) (P3, P8); ↑ proliferating and total microglia in forebrain white matter (P9)	LPS, 200 μg/kg, ip	Twice daily from E17 to birth	Rat	Larouche et al. (2005) and Girard et al. (2010)
↓ OPCs and immature oligodendrocytes in corpus callosum and lateral ventricles with ↓ mRNA for MBP and PLP in brain; ↓ MBP immunostaining in corpus callosum and cingulum (P9, P16, P23, P30)	LPS, 700 μg/kg or 1 mg/kg, ip	E18	Rat	Paintlia et al. (2004, 2008)
↑ apoptosis and ↓ MBP immunostaining in periventricular white matter (P7)	LPS, 500 μg/kg, ip	E18 and E19	Rat	Kumral et al. (2007) and Yesilirmak et al. (2007)
↑ apoptosis in striatum, PWM and germinative ventricular zone (P1, P7); ↓ MBP immunostaining in external and internal capsule (P7); ↑ ibotenate-induced cortical lesions and PWM cysts (P9); ↑ ibotenate-induced microglial activation and astrogliosis in various regions (P9)	LPS, 300 or 400 μg/kg, ip	E19 and E20	Rat	Rousset et al. (2006, 2008)
↑ microglial density in hippocampus (P0)	LPS, 120 μg/kg, ip	E15	Mouse	Roumier et al. (2008)
↓ hippocampal CA1 width (P7), ↑ hippocampal CA1 width and ↓ dentate length (P14); ↑ dentate width (P240); ↑ cell density in hippocampal CA1 (P240)	LPS, 120 μg/kg, ip	E17	Mouse	Golan et al. (2005)
↑ cell death in corpus callosum, PWM and cortex (E52)	LPS, 300 or 500 μg/kg, ip	E45	Guinea Pig	Harnett et al. (2007)
↑ pyramidal cell density in hippocampus (P0, P98); ↓ thickness of cerebral cortex, ↓ total area of brain hemisphere (P0), ↑ brain weight and size, ↓ VBR (P98)	Influenza, in	E9	Mouse	Fatemi et al. (1999, 2002a)
↓ cerebellar Purkinje cells (P11, P270–P420); ↑ thickness of cerebellar external granule cell layer and delayed granule cell migration (P17)	Influenza, in	E9.5	Mouse	Shi et al. (2009)
↓ ventricular area (P0), ↓ total brain area and cerebellar area (P14), ↓ hippocampal area (P35) by post-mortem MRI; altered white matter anisotropy by DTI (P0, P14, P56)	Influenza, in	E16	Mouse	Fatemi et al. (2009a,b)
↓ brain volume by MRI (P35); ↓ anisotropy in corpus callosum by DTI (P35)	Influenza, in	E18	Mouse	Fatemi et al. (2008a)
↓ neurogenesis in hippocampus by doublecortin immunostaining (P24)	Poly IC, 5 mg/kg, iv	E9 or E17	Mouse	Meyer et al. (2006a)
↑ lateral and 4th ventricle volumes by MRI (P84)	Poly IC, 5 mg/kg, iv	E9 or E17	Mouse	Li et al. (2009)
↓ axonal size and ↓ myelin thickness in hippocampal CA1; ↓ MBP immunostaining in hippocampal CA1 and CA3 (P14)	Poly IC, 60 mg/kg, ip	E9.5	Mouse	Makinodan et al. (2008)
↓ cerebellar Purkinje cells (P120)	Poly IC, 20 mg/kg, ip	E12.5	Mouse	Shi et al. (2009)
↓ neurons and ↑ astrocytes in hippocampus (P168)	IL-6, 9 μg/kg, ip	E8, E10 and E12 or E16, E18 and E20	Rat	Samuelsson et al. (2006)

Under "Postnatal changes", the age at which measures were taken in offspring is shown in parentheses.
Abbreviations: DTI, diffusion tensor imaging; MBP, myelin basic protein; mPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; OPC, oligodendrocyte progenitor cell, PLP, proteolipid protein, PWM, periventricular white matter; SN, substantia nigra; VBR, ventricular brain ratio; see legend to Table 1 for additional abbreviations.

the fact that PPI is a relatively quick, easy and well-automated behavior to monitor. A complex and fairly well described neural circuitry mediates PPI (Swerdlow et al., 2001), thus alterations in any component of this network by prenatal exposure to immunogens may be responsible for deficits.

With regards to other behavioral alterations following prenatal LPS exposure, decreased spatial learning in the Morris water maze has been reported following prenatal LPS at E19 in the rat (Lanté et al., 2007, 2008). In contrast, no changes in spatial learning or retention in the water maze were found in mice exposed to prenatal LPS at E17, although a deficit in associative learning in the cued version of the maze was reported (Golan et al., 2005). Deficits in learning and retention in the radial arm maze have, however, been reported following LPS administration to mice daily from E8 to E15 (Wang et al., 2010). The Novel Object Recognition Test (NORT) is a memory task in which control animals recall previous exposure to an object and typically spend more time investigating a novel vs. a familiar object when presented with both; animals that spend equal time exploring novel and familiar objects (i.e. decreased novel object recognition) are characterized as having a memory deficit. In two studies with mice exposed prenatally to LPS, somewhat unexpected findings have been reported in the NORT. Golan et al. (2005) found that mice showed increased novel object recognition following LPS at E17, while Coyle et al. (2009) found increased exploration of the familiar object in mice following LPS at E9 compared to controls. Thus LPS-exposed mice had no problem recalling the familiar object and discerning it from the novel one, but did show preference for either the novel or the familiar object depending on whether LPS was administered at E17 or E9, respectively. There have been single reports of additional behavioral alterations following prenatal LPS, that have not been followed up as yet by other laboratories; these include increased ethanol preference (Liu et al., 2004) and decreased sexual behavior (Wijkstra et al., 1991) in rats and increased vulnerability to audiogenic seizures in mice (Haesaert and Ornoy, 1986).

With regards to behavioral changes following prenatal poly IC, one group using a rat model and two groups using mouse models have reported deficits in latent inhibition (Zuckerman et al., 2003; Zuckerman and Weiner, 2003, 2005; Meyer et al., 2006b, 2008b,d; Smith et al., 2007) and increases in MK801- and amphetamine- or methamphetamine-induced locomotion (Zuckerman et al., 2003; Zuckerman and Weiner, 2005; Meyer et al., 2008b,c,d,e; Ozawa et al., 2006) due to prenatal poly IC exposure; these changes are thought to reflect pathophysiological changes similar to those occurring in humans with schizophrenia. Memory deficits including a decrease in working memory in the water maze and decreased novel object recognition have been reported by two laboratories following prenatal poly IC administration in the

Table 4
Changes in neurotransmitter systems and CNS electrophysiology in offspring after prenatal immune activation.

Fetal or postnatal changes in offspring	Immunogen, dose, route	Time of administration	Species	References
↑ TH immunoreactivity in NAc and bed nucleus of stria terminalis (P100, P300)	LPS, 1 mg/kg, sc	Alternate days for whole pregnancy	Rat	Borrell et al. (2002)
↓ DA in NAc (P39), ↑ DA in NAc (P170, P180, P400), ↑ DOPAC in striatum (P180)	LPS, 2 mg/kg, sc	Daily for whole pregnancy	Rat	Romero et al. (2007, 2010)
↓ THir cells in SN/VTA and ↓ DA innervation of striatum in organotypic cultures	LPS, 100 μg/kg, ip	E10, E14 or E18	Rat	Snyder-Keller and Stark (2008)
↓ THir cells in SN (P21, P120, P210, P420, P510) and VTA (P21); enhanced DA neuron loss in SN after postnatal rotenone, 6-OHDA or intranigral LPS; ↓ DA and ↑ HVA/DA in striatum (P120, P510) and numerous other brain regions (P120)	LPS, 1 mg/kg, ip	E10.5	Rat	Ling et al. (2002, 2004a,b, 2006, 2009) and Wang et al. (2009)
↓ DA in NAc (P83)	LPS, 20–80 μg/kg increasing daily, sc	E15–E19	Rat	Bakos et al., 2004
↑ KCl-induced DA release from striatal slices (P100)	Poly IC, 4 mg/kg, iv	E15	Rat	Zuckerman et al. (2003)
↑ THir cells (E13, E17) and ↑ DATir cells (E17) in mesencephalon; ↑ TH immunoreactivity in striatum and NAc (P120); ↑ DA, ↑ DOPAC in PFC and globus pallidus (P84); altered mRNA for genes involved in DA development, Shh, Fgf8, Nurr1, Pitx3 (E11, E17); ↓ D1 receptor immunoreactivity in medial PFC (P180)	Poly IC, 5 mg/kg, iv	E9	Mouse	Meyer et al. (2008a,c,e) and Winter et al. (2008a)
↑ DOPAC, ↑ HVA and ↓ D2 receptor binding in striatum (P63–P70)	Poly IC, 5 mg/kg, ip	E12–E17	Mouse	Ozawa et al. (2006)
↓ TPHir cells in dorsal raphe, ↓ 5-HT and ↑ 5-HIAA/5-HT in various brain regions (P120)	LPS, 1 mg/kg, ip	E10.5	Rat	Wang et al. (2009)
↓ 5-HT, ↓ 5-HIAA in cerebellum (P14); ↓ 5-HT, ↓ taurine in cerebellum (P35)	Influenza, in	E16 or E18	Mouse	Fatemi et al. (2008a) and Winter et al. (2008b)
↓ 5-HT, ↓ 5-HIAA in NAc, globus pallidus, hippocampus; ↓ taurine in hippocampus (P84)	Poly IC, 5 mg/kg, iv	E9	Mouse	Winter et al. (2008a)
↑ Glu-induced hydroxyl radical release (mGlu I mediated) in striatum (P14)	LPS, 300 μg/kg, ip	E19	Rat	Cambonie et al. (2004)
↑ ratio of AMPAR/NMDAR currents in hippocampus (P28)	LPS, 500 μg/kg, ip	E19	Rat	Lanté et al. (2007)
↑ ratio of AMPAR/NMDAR currents in hippocampus (P28)	LPS, 120 μg/kg, ip	E15	Mouse	Roumier et al. (2008)
↓ immunoreactivity for Glu-R1 subunit of AMPA receptor in NAc (P120)	Poly IC, 5 mg/kg, iv	E9	Mouse	Meyer et al. (2008e)
↓ NR1 receptor subunit immunoreactivity in dorsal hippocampus (P180)	Poly IC, 5 mg/kg, iv	E17	Mouse	Meyer et al. (2008c)
↑ mRNA for NR1 and $GABA_{A\alpha5}$ receptor subunits in hippocampus (P28, P168)	IL-6, 9 μg/kg, ip	E16, E18 and E20	Rat	Samuelsson et al. (2006)
↑ $GABA_{A\alpha2}$ receptor subunit immunoreactivity in ventral dentate and basolateral amygdala (P180)	Poly IC, 5 mg/kg, iv	E9	Mouse	Nyffeler et al. (2006)
↑ hippocampal CA1 synaptic transmission and ↑ CA1 pyramidal cell excitability; ↓ presynaptic excitability in CA1 (P20–P25)	LPS, 100 μg/kg, ip	E15 and E16	Rat	Lowe et al. (2008)
↓ LTP in hippocampus (P28)	LPS, 500 μg/kg, ip	E19	Rat	Lanté et al. (2007, 2008)

Under "Fetal or postnatal changes in offspring", the age at which measures were taken is shown in parentheses.
Abbreviations: AMPAR, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor; DA, dopamine; DATir, dopamine transporter immunoreactive; DOPAC, 3,4-dihydroxyphenylacetic acid; Fgf8, fibroblast growth factor 8; GABA, γ-aminobutyric acid; Glu-R1, glutamate receptor subunit 1; 5-HIAA, 5-hydroxy-3-indole acetic acid; 5-HT, serotonin; HVA, homovanillic acid; LTP, long-term potentiation; NAc, nucleus accumbens; NMDAR, *N*-methyl-D-aspartate receptor; NR1, NMDA receptor subunit 1; 6-OHDA, 6-hydroxydopamine; PFC, prefrontal cortex; Shh, sonic hedgehog; SN, substantia nigra; THir, tyrosine hydroxylase-immunoreactive; TPHir, tryptophan hydroxylase-immunoreactive; VTA, ventral tegmental area; see legend to Table 1 for additional abbreviations.

mouse (Ozawa et al., 2006; Meyer et al., 2008c). In mice or rats both exposed to poly IC on E17, opposite results have been reported for reversal learning of left–right discrimination; mice show decreased reversal learning characterized by the authors as perseveration (Meyer et al., 2006a), while rats show enhanced reversal learning characterized by the authors as excessive behavioral switching (Zuckerman and Weiner, 2003). Deficits in social interaction have also been reported in mice following prenatal poly IC (Smith et al., 2007).

In summary, consistently decreased PPI and latent inhibition and increased drug-induced locomotion are observed in rat and/or mouse offspring following prenatal immune activation. Deficits in learning and memory are also fairly often reported, although the precise conditions under which these deficits are detected vary from study to study.

5. Morphological changes in brains of offspring after prenatal immune activation

Table 3 shows morphological changes measured several days to months after birth in the brains of offspring that had been exposed to prenatal immune activation. In response to prenatal LPS exposure, increases in cerebral cortical lesions characterized by shrunken neuronal cell bodies and nuclei (Larouche et al., 2005), increased ibotenate-induced cortical lesions (Rousset et al., 2008) and increased striatal apoptosis (Rousset et al., 2006) have been observed at early postnatal ages (P3–P9) in the rat. As a component of the reaction to inflammation or tissue injury, increases in hippocampal microglial density (Roumier et al., 2008), proliferating and total microglia in forebrain white matter (Girard et al., 2010) and ibotenate-induced microglial activation in various brain regions (Rousset et al., 2008) have been found at early postnatal ages (P0, P9) after prenatal LPS administration to mice or rats. Increases in numbers of activated microglia have been observed as late as age 4–17 months in the substantia nigra of rats administered relatively high doses of LPS prenatally (Ling et al., 2006, 2009). Decreases in hippocampal neurogenesis (Cui et al., 2009) and decreases in dendritic length, arborization and spine density in the hippocampus and medial prefrontal cortex (Baharnoori et al., 2009) have also been described at various postnatal ages following prenatal LPS in the rat. Three separate groups of investigators have reported similar types of white matter abnormalities following prenatal LPS administration during late

Table 5
Molecular changes in brains of offspring after prenatal immune activation.

Postnatal changes	Immunogen, dose, route	Time of administration	Species	References
↓ synaptophysin in FC (P21, P400), ↑ synaptophysin in FC, hippocampus (P170, P180), ↓ DARPP-32 in FC (P180), ↓ GSK-3β (P400)	LPS, 2 mg/kg, sc	Daily for whole pregnancy	Rat	Romero et al. (2007, 2010)
↑ GR in hippocampus after euglycemic hyperinsulinemia (P84)	LPS, 790 μg/kg, ip	E8, E10 and E12	Rat	Nilsson et al. (2001)
↓ GR and MR in hippocampus, ↑ GR in anterior pituitary (P90)	LPS, 30 μg/kg, ip	E10	Rat	Reul et al. (1994)
↑ TNF-α in striatum (P21, P120, P210, P510) and SN (P210); ↓ reduced/oxidized GSH (P120, P210, P510), ↓ enzyme activity for GSH synthesis, ↑ GSH redox recycling enzyme activities, ↑ lipid peroxidation (P120, P510) and protein oxidation (P480) in various brain regions	LPS, 1 mg/kg, ip	E10.5	Rat	Ling et al. (2002, 2004a,b, 2006), Zhu et al. (2007)
↓ TNF-α in FC (P7)	LPS, 100 μg/kg, ip	E14, E15 and E16	Rat	Gilmore et al. (2005)
↑ GFAP in various brain regions (P8)	LPS, 500 μg/kg, ip	E18	Rat	Cai et al. (2000)
↓ peroxisome markers (i.e. ↓ DHAP-AT, PMP70, PPAR-α mRNA and protein), ↑ GFAP immunostaining in corpus callosum and/or cingulum (P9, P16, P23, P30)	LPS, 700 μg/kg, ip	E18	Rat	Paintlia et al., 2008
↑ IL-1β, IL-6, TNF-α in whole brain (P7)	LPS, 500 μg/kg, ip	E18 and E19	Rat	Kumral et al. (2007) and Yesilirmak et al. (2007)
↑ mRNA for IL-1β (P1), ↓ mRNA for TNF-α (P7) in whole brain	LPS, 300 μg/kg, ip	E19 and E20	Rat	Rousset et al. (2006)
↓ BDNF in cortex, hippocampus (P21); ↑ BDNF in thalamus (P270); ↓ NGF in hippocampus (P21); ↑ NGF in thalamus (P7, P270)	LPS, 120 μg/kg, ip	E17	Mouse	Golan et al. (2005)
↓ reelin-ir cells in hippocampus, cortex (P0); altered SNAP-25 immunoreactivity in hippocampus (P0); microarray/PCR: 7 genes altered in whole brain (P0); ↑ GFAP immunostaining in cortex (P14) and hippocampus (P35); altered nucleolin, microcephalin, connexin 43 and aquaporin 4 protein in various regions (P35, P56)	Influenza, in	E9	Mouse	Fatemi et al. (1998, 1999, 2002b, 2005, 2008b)
↑ mRNA for neuroleukin, FGF5, ring finger protein 1B, Akv MuLV in whole brain (P90 and/or P280); ↑ neuroleukin in whole brain (P90)	Influenza, in	E14	Mouse	Asp et al. (2005)
Microarray/PCR: 13 genes altered (P0), 4 genes altered (P14), 3 genes altered (P56) in hippocampus; ↓ MBP, ↓ MAG, ↑ splice variant of PLP1 in cerebellum (P14, P35, P56)	Influenza, in	E16	Mouse	Fatemi et al. (2009a,b)
↑ Foxp2 in cerebellum (P0, P35); microarray/PCR: 12 genes altered (P0), 2 genes (P56) altered in various brain regions	Influenza, in	E18	Mouse	Fatemi et al. (2008a)
↓ reelin-ir cells in hippocampus (P24) and in mPFC (P180); ↓ parvalbumin-ir cells in mPFC (P180)	Poly IC, 5 mg/kg, iv	E9	Mouse	Meyer et al. (2006a, 2008c)
↓ MBP, ↓mRNA for MBP, ↓ pAkt in hippocampus (P14)	Poly IC, 60 mg/kg, ip	E9.5	Mouse	Makinodan et al. (2008)
↓ reelin-ir cells in mPFC (P180); ↓ parvalbumin-ir cells in mPFC and ventral hippocampus (P180)	Poly IC, 5 mg/kg, iv	E17	Mouse	Meyer et al. (2008c)
↑ procaspase-3, active caspase-3; ↑ mRNA for GFAP, IL-6 and caspase-3 in hippocampus (P28, P168)	IL-6, 9 μg/kg, ip	E16, E18 and E20	Rat	Samuelsson et al. (2006)

Under "Postnatal changes", the age at which measures were taken in offspring is shown in parentheses.
Abbreviations: BDNF, brain-derived neurotrophic factor; DHAP-AT, dihydroxyacetone-phosphate acyltransferase; FC, frontal cortex; FGF, fibroblast growth factor; GFAP, glial fibrillary acidic protein; GR, glucocorticoid receptor; GSK, glycogen synthase kinase; GSH, reduced glutathione; IL, interleukin; MAG, myelin associated glycoprotein; ir, immunoreactive; MBP, myelin basic protein; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; MuLV, murine leukemia virus; NGF, nerve growth factor; nNOS, neuronal nitric oxide synthase; PCR, polymerase chain reaction; SN, substantia nigra; PLP1, proteolipid protein 1; PMP70, 70 kDa peroxisomal membrane protein; PPAR, peroxisome proliferator activated receptor; TNF, tumor necrosis factor; see legend to Table 1 for additional abbreviations.

gestation (E18–E20) in the rat. These include increased cell death and decreased myelin basic protein immunostaining in white matter regions at various postnatal ages and decreased numbers of immature oligodendrocytes and oligodendrocyte precursors, indicative of white matter injury (Paintlia et al., 2004, 2008; Kumral et al., 2007; Yesilirmak et al., 2007; Rousset et al., 2006). Increased cell death has also been reported in white matter regions of fetal guinea pig brain 1 week following prenatal LPS exposure (Harnett et al., 2007).

Fatemi and colleagues have published several studies examining changes in brain morphology in mice following prenatal exposure to the influenza virus. A complex series of changes were observed following influenza exposure on E9; these included a decreased area of the hemispheres and decreased thickness of the cerebral cortex at P0 followed by a contrasting increase in brain weight and area and decrease in ventricular brain ratio indicative of increased brain size at adulthood (3 months of age) (Fatemi et al., 1999, 2002a). More recently the same group has examined brain morphology using post-mortem magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) in mice exposed to prenatal influenza at E16 or E18. With influenza exposure at E16, MRI showed a decrease in ventricular area at P0 and in cerebellar area at P14 in one study, and a decrease in total brain area at P14 and in hippocampal area at P35 in a second study (Fatemi et al., 2009a, 2009b). DTI results showed a decrease in fractional anisotropy in the right but not the left internal capsule at P0 but increases in fractional anisotropy in the corpus callosum at P14 and in the right but not the left middle cerebellar peduncle at P56 (Fatemi et al., 2009a). In contrast, with influenza exposure at E18 rather than E16, Fatemi et al. (2008a) have reported decreased brain volume at P35 by MRI and decreased fractional anisotropy in the corpus callosum at P35 by DTI. These results would suggest that morphological changes are highly dependent on the time of influenza infection and the postnatal age of the offspring. Clearly, these multifaceted results require replication; comparison of effects of prenatal influenza at various times in gestation in a single experiment would be informative. Only one other group has reported on morphological changes in brain following prenatal influenza exposure. With influenza exposure to mice on E9.5 and focussing on the cerebellum, Shi et al. (2009) found a decrease in Purkinje cell number specifically in cerebellar lobule VII both at P11 and at 9 months of age, together with an increased thickness of the cerebellar external granule cell layer and delayed granule cell migration at P17.

Morphological changes due to prenatal poly IC exposure have only been investigated in the mouse, although some findings parallel results with prenatal LPS in the rat. For example, mice administered poly IC on E9 or E17 are reported to exhibit decreased hippocampal neurogenesis (Meyer et al., 2006a) as well as decreased myelin thickness and myelin basic protein immunostaining in the hippocampus (Makinodan et al., 2008). In contrast to the decreased ventricular size found by Fatemi et al. (2002a) in adult (P98) mice infected with influenza on E9, recent in vivo MRI studies by Li et al. (2009) reported increased lateral ventricular volume in adult (P84) mice administered poly IC on E9, as well as increased 4th ventricular volume with poly IC on E17, suggesting possible differential effects of influenza and poly IC. However, similar to influenza, prenatal poly IC was reported by Shi et al. (2009) to produce a decrease in cerebellar Purkinje cell number in lobule VII.

In summary, the most replicated morphological finding appears to be cell death in white matter and decreased myelin basic protein immunostaining following prenatal LPS in rats, as well prenatal poly IC in mice. It has been suggested that such changes might model aspects of cerebral white matter injury in cerebral palsy. Several studies indicate that microglial activation, decreased hippocampal neurogenesis and dendritic alterations occur in response to prenatal immune activation. Lobule VII of the cerebellum may be a localized target for developmental abnormalities following prenatal immune activation. Recently emerging MRI and DTI studies await replication to confirm early findings.

6. Changes in neurotransmitter systems and CNS electrophysiology in offspring after prenatal immune activation

At the neurochemical level, neurotransmitter systems that have been examined following prenatal immune activation include dopamine (DA), serotonin (5-HT) and the amino acids, glutamate and GABA (Table 4). Ling, Carvey and colleagues have published a large series of studies in which they have repeatedly shown that prenatal exposure of rats to a relatively high dose of LPS on E10.5 results in decreased tyrosine hydroxylase (TH) immunoreactive neurons in dopaminergic cell body regions at various postnatal ages (Ling et al., 2002, 2004a,b, 2006, 2009). They also showed that prenatal LPS enhances the effects of a variety of postnatally administered toxins to promote loss of nigral DA neurons (Ling et al., 2004a,b, 2006). In support of these findings, Snyder-Keller and Stark (2008) showed that dopaminergic cell cultures prepared from fetal rats exposed prenatally to LPS on E10, E14 or E18 showed an accelerated loss of DA neurons with time in culture. With regards to DA levels and innervation, most studies using models of prenatal LPS in the rat report decreased DA levels or innervation in nucleus accumbens or striatum (Bakos et al., 2004; Ling et al., 2002, 2004a, 2009; Romero et al., 2010; Snyder-Keller and Stark, 2008), although increased DA levels and TH immunoreactivity in nucleus accumbens have also been observed under some conditions (Romero et al., 2007, 2010; Borrell et al., 2002). Three groups using models of prenatal poly IC administration report findings suggestive of increased dopaminergic activity in various brain regions of poly IC-treated offspring. Zuckerman et al. (2003) report increased KCl-induced DA release from striatal slices prepared from rat offspring exposed prenatally to poly IC on E15. Meyer et al. report a variety of alterations related to the dopaminergic system in offspring following poly IC administration to the E9 pregnant mouse. These include increased TH- and DA transporter (DAT)-immunoreactive cells in the mesencephalon of offspring as fetuses as well as increased TH immunoreactivity in DA-innervated regions (striatum, nucleus accumbens) at adulthood (P120), increased levels of DA in the prefrontal cortex and globus pallidus and decreased D1 receptor immunoreactivity in the medial prefrontal cortex at adulthood (Meyer et al., 2008a,c,e; Winter et al., 2008a). Ozawa et al. (2006) found increased DA turnover (measured as increased DOPAC and HVA levels) as well as decreased D2 receptor binding in striatum at adulthood following poly IC administration from E12 to E17 in the mouse. Overall, the disparate results on DA systems to date might suggest that DA function may be decreased in models of prenatal LPS but increased in models of prenatal poly IC. However, differences between experiments may also be due to a variety of other variables including the dose of immunogen used and timing of its administration during gestation, postnatal age of the offspring and brain region examined, the specific dopaminergic parameter measured, etc.

Three studies have examined serotoninergic parameters in three different models of prenatal immune activation, however, all generally found decreases in serotonin measures in various brain regions of offspring. Wang et al. (2009) found decreased numbers of tryptophan hydroxylase-immunoreactive neurons in the dorsal raphe and decreased 5-HT levels in various brain regions following prenatal LPS in the rat. Similarly, in the mouse, decreases in 5-HT levels were observed in the cerebellum following prenatal influenza infection (Fatemi et al., 2008a; Winter et al., 2008b) and in various brain regions following prenatal poly IC (Winter et al., 2008a).

With regards to glutamatergic function, it is notable that two independent groups reported very similar findings of an increased ratio of AMPA receptor/NMDA receptor currents in the hippocampus of offspring following prenatal LPS administration in the rat on E19 (Lanté et al., 2007) or mouse on E15 (Roumier et al., 2008). Consistent with this, decreased hippocampal NR1 receptor subunit immunoreactivity has also been found following prenatal poly IC exposure in mice on E17 (Meyer et al., 2008c). Also consistent with an observed increased ratio of AMPAR/NMDAR currents, Lanté et al. (2007, 2008) found reduced long-term potentiation (LTP) in the hippocampus of P28 offspring using their model of prenatal LPS on E19 in rats. In contrast, Lowe et al. (2008) reported no change in LTP in P20–P25 offspring following LPS on E15 and E16 in the rat. However, Lowe et al. did find appreciable alteration of hippocampal electrophysiology in their model, including increased synaptic transmission and pyramidal cell excitability accompanied by decreased presynaptic excitability in the hippocampal CA1 region. Overall these electrophysiological findings converge to suggest that one of the consequences of prenatal immune activation may be an alteration in hippocampal synaptic transmission and glutamatergic function.

7. Molecular changes in brains of offspring after prenatal immune activation

Table 5 lists additional long-term molecular changes observed in brains of offspring at various postnatal ages following prenatal immune activation. With prenatal administration of relatively high doses of LPS (>500 μg/kg) in rats (Table 5), at least two independent laboratories have observed increased levels of various markers of oxidative stress (Ling et al., 2004b, 2006; Zhu et al., 2007; Paintlia et al., 2008), increased cytokine levels (Ling et al., 2002, 2004a,b; Kumral et al., 2007; Yesilirmak et al., 2007) and increased glial fibrillary acidic protein (Cai et al., 2000; Paintlia et al., 2008) in various brain regions, suggesting that ongoing deleterious mechanisms continue to be induced in brains of offspring well after the initial prenatal insult. Increased hippocampal and cortical GFAP immunostaining has also been observed in the model of influenza administration to the mouse at E9 (Fatemi et al., 2002b). Consistent with the findings of decreased myelin basic protein immunostaining described in Section 4, two additional laboratories have de-

scribed decreased levels of myelin basic protein and other myelin-related components following influenza in the E16 mouse (Fatemi et al., 2009a) or poly IC in the E9 mouse (Makinodan et al., 2008). Other long-term molecular changes such as changes in synaptophysin (Romero et al., 2007, 2010), growth factors (Golan et al., 2005), neuroleukin (Asp et al., 2005), and reelin and parvalbumin (Meyer et al., 2006a, 2008c) following prenatal immune activation have each been reported by a single laboratory.

8. Mechanisms responsible for brain changes due to prenatal immune activation

8.1. Timing

Prenatal immune activation at a specific time during pregnancy will impact on the particular developmental events occurring in fetal brain at that time. Thus delineating specific time windows in gestation during which prenatal immune activation alters specific CNS systems is an important first step to understand mechanisms mediating these effects. An optimum approach to investigate this issue is for immune activation at different gestational periods to be examined by a single laboratory in the same study. To date, this type of approach is rare with the notable exception of a series of studies by Meyer and colleagues (Meyer et al., 2006a, 2008c; Li et al., 2009), and a few other laboratories (Zuckerman and Weiner, 2005; Fortier et al., 2007; Cui et al., 2009).

Other important issues related to timing are whether CNS changes induced by prenatal immune activation in offspring are acute or more long-term, and if long-term, when in postnatal life they emerge and how long they last. These issues have been examined in some studies examining the same CNS parameter in the brains of offspring at various postnatal ages following prenatal immune activation (e.g. Ling et al., 2009; Romero et al., 2010; Baharnoori et al., 2009; Wang et al., 2010; Fatemi et al., 2009a,b). Other studies with more targeted hypotheses related to schizophrenia have shown that CNS behavioral changes due to prenatal poly IC emerge postpubertally but not prepubertally (Meyer et al., 2006b; Zuckerman et al., 2003; Zuckerman and Weiner, 2003), similar to the emergence of the major symptoms of schizophrenia.

8.2. Placental transport

To determine the mechanisms by which prenatal infection affects brain development, it is important to know if infectious agents, immunogens and cytokines in the maternal circulation are able to cross the placenta to reach the fetal compartment, thus raising the possibility of direct effects on the fetus. Following intranasal infection of pregnant mice with influenza A/WSN/33 strain on E14, Aronsson et al. (2002) detected influenza viral RNA by RT-PCR in fetal brain and lungs taken 3 days later. Moreover viral RNA could be detected in the brains of some prenatally exposed offspring as late as P90. In contrast, Shi et al. (2005) detected no viral RNA by RT-PCR in brains of fetuses taken 2–7 days after intranasal infection of pregnant mice with influenza strain A/NWS/33 on E9. Following injection of radiolabelled LPS to pregnant rats on E18, Ashdown et al. (2006) found negligible levels of the radiolabel in the fetus, including fetal brain and liver several hours after injection. Consistent with this, Goto et al. (1994) reported finding no endotoxin-like activity in fetal plasma after exposure of pregnant rats to LPS on E19, and it has been shown that LPS does not cross human chorioamniotic membranes in vitro (Romero et al., 1987). With regard to cytokines, Dahlgren et al. (2006) found evidence for transplacental transport of IL-6 by showing the presence of radiolabelled IL-6 in fetuses 30 min after administration of ^{125}I-IL-6 to pregnant rat dams on E11–E13 or E17–E19. Interestingly fetal levels of ^{125}I-IL-6 were higher with IL-6 administration at the earlier stage of gestation, compared to the later stage, raising the possibility that variability in transplacental transport of cytokines throughout gestation could play a role in determining specific time windows of vulnerability to prenatal immune activation. Consistent with these findings in rats, Zaretsky et al. (2004) found evidence for appreciable transplacental transfer of IL-6, but not IL-1α or TNF-α, using an in vitro preparation of human placenta at term. Reisenberger et al. (1996) reported negligible transfer of IL-8 across perfused human placenta in vitro.

8.3. Cytokines and prostaglandins

Prime candidates for acute mediators of effects of maternal infection on fetal neurodevelopment are components of the inflammatory response, i.e. cytokines, prostaglandins, corticosteroids and fever. Although many studies have measured levels of inflammatory cytokines in fetal and maternal tissue following prenatal immune activation, only a few have attempted to manipulate components of the inflammatory response in order to determine their role in altering fetal neurodevelopment. Patterson and colleagues have provided several lines of evidence suggesting a key role for IL-6 in mediating behavioral changes caused by prenatal poly IC in mice (Smith et al., 2007). They showed that co-administration of an IL-6 antibody to pregnant mice prevented deficits in PPI, latent inhibition, exploratory behavior and social interaction in offspring caused by prenatal poly IC on E12. In addition, prenatal poly IC failed to produce deficits in PPI, exploratory behavior and social interaction in IL-6 knockout mice, while prenatal administration of IL-6 itself produced deficits in PPI and latent inhibition in offspring. Consistent with these findings, Samuelsson et al. (2006) have also shown that IL-6 administration to rats either early (E8, E10 and E12) or late (E16, E18 and E20) in gestation can produce deficits in spatial learning and alterations in the hippocampus of offspring, including neuronal loss, astrogliosis, and increased levels of $GABA_{A\alpha5}$ receptor subunit, NR1subunit and GFAP mRNA and caspase-3 protein.

Girard et al. (2010) have recently investigated the role of IL-1 in mediating effects of prenatal LPS on placental and neurodevelopmental deficits in rats. Systemic administration of the IL-1 receptor antagonist, IL-1ra, to the pregnant dam at the time of exposure to LPS was shown to prevent LPS-induced increases in microglial activation in forebrain white matter and motor deficits in postnatal offspring. The IL-ra treatment also prevented increases in placental cytokine levels and deficits in placental perfusion and clearance rates caused by prenatal LPS in the pregnant dam. These findings indicate that IL-1 is a required mediator in the sequence of events by which prenatal LPS produces neural deficits in offspring.

Meyer et al. (2008b) have examined effects of prenatal poly IC in mice overexpressing the anti-inflammatory cytokine, IL-10, compared to controls. They found that deficits in exploratory behavior, PPI and latent inhibition produced by prenatal poly IC in control mice were prevented in the IL-10 overexpressing animals, suggesting that the anti-inflammatory cytokine played a protective role under these conditions. However, IL-10 overexpression alone, in the absence of prenatal poly IC treatment also produced deficits in exploratory behavior and latent inhibition, leading the authors to suggest that a critical balance of pro- and anti-inflammatory cytokines is required for optimal neurodevelopment. Finally Cui et al. (2009) examined the role of prostaglandin (PG) production and fever in mediating effects of prenatal LPS. These investigators found that administering the COX inhibitor, ibuprofen, at a dose sufficient to suppress fever and hence also PG production, before prenatal LPS did not block decreases in neurogenesis found in P14 rats due to prenatal LPS. Thus these effects of prenatal LPS on neurogenesis did not appear to be

mediated by PGs or by the increased body temperature consequent to LPS administration.

8.4. Oxidative stress

Several groups have queried whether the mechanism by which prenatal LPS affects offspring neurodevelopment involves oxidative stress to the CNS. In support of this, increases in markers indicative of oxidative stress together with decreases in reduced glutathione levels have been observed both in the brains of rat fetuses at early times (several hours) following maternal LPS injection (Paintlia et al., 2004, 2008; Lanté et al., 2007, 2008), as well as in the brains of rat offspring at a range of postnatal ages (P9–P510) following prenatal LPS exposure (Ling et al., 2004b, 2006; Zhu et al., 2007; Paintlia et al., 2008). Two independent groups have reported that signs of oxidative stress in fetal brain could be prevented by treatment of the dam, either before or after prenatal LPS administration, with *N*-acetylcysteine, which is an anti-oxidant and inhibitor of NFκB and a drug permitted for use in pregnant women (Paintlia et al., 2008; Lanté et al., 2008). Moreover treatment of pregnant rat dams with *N*-acetylcysteine 4 h after prenatal LPS was also able to prevent deficits in hippocampal LTP and spatial learning observed in offspring at 28 days of age following prenatal LPS exposure (Lanté et al., 2008). Co-administration of another agent, activated protein C, at the time of prenatal LPS exposure has been shown to shown reverse prenatal LPS-induced increases in white matter apoptosis and myelination deficits in P7 rat offspring (Yesilirmak et al., 2007); activated protein C is an anti-coagulant factor with anti-oxidant, anti-inflammatory and anti-apoptotic activities. Since *N*-acetylcysteine and activated protein C are agents with multiple actions, their ability to reverse effects of prenatal LPS may be due to their anti-oxidant properties but could also be due to additional mechanisms.

8.5. Zinc

Coyle et al. (2009) have recently shown that supplementation of the maternal diet with increased levels of zinc (Zn) during pregnancy can prevent prenatal LPS-induced anomalies in novel object recognition in adult mouse offspring. Infection-induced increases in cytokine levels cause induction of acute phase proteins in liver including the zinc-binding protein, metallothionen (MT), while MT induction in pregnant rodents has been well-characterized to cause a fall in circulating maternal and fetal Zn levels. In support of this, studies have shown that LPS treatment of wild-type mice, but not MT-knockout mice, results in induction of MT and a fall in plasma Zn levels (Carey et al., 2003). IL-6 mediated induction of zinc transporters may also play a role in the hypozincaemia associated with LPS exposure (Liuzzi et al., 2005). Maternal dietary Zn supplementation was able to normalize Zn levels and prevent birth defects in offspring in the prenatal LPS model (Carey et al., 2003; Chua et al., 2006). Thus Coyle et al. propose that Zn supplementation prevents behavioral effects of prenatal LPS by restoring Zn to normal levels necessary for appropriate CNS development.

8.6. Anti-psychotic drugs

Several researchers interested in prenatal immune activation as a risk factor for schizophrenia have examined whether anti-psychotic drugs administered to adult offspring are able to reverse behavioral deficits caused by prenatal LPS or poly IC. The anti-psychotics were administered either acutely to adult offspring at the time of behavioral testing, or for several weeks to mimic the time course required for anti-psychotic efficacy in humans. Acute single injections of haloperidol, chlorpromazine or clozapine just prior to behavioral testing were shown to reverse PPI deficits in mice prenatally exposed to influenza (Shi et al., 2003) and to reverse changes in PPI (Borrell et al., 2002; Romero et al., 2007), latent inhibition and reversal learning (Zuckerman et al., 2003; Zuckerman and Weiner, 2005) due to prenatal LPS or poly IC in rats. Ozawa et al. (2006) showed that a 2 week treatment with clozapine, but not haloperidol, prior to testing reversed a deficit in novel object recognition in mice exposed prenatally to poly IC. In another paradigm, Meyer et al. (2008d) exposed mice prenatally to poly IC and then treated them with a typical anti-psychotic (haloperidol), an atypical anti-psychotic (clozapine), or a specific serotonin re-uptake inhibitor (SSRI) anti-depressant (fluoxetine) for 4 weeks during periadolescence (P35–P65) followed by behavioral testing at adulthood (P90–P120). Behavioral changes cased by prenatal poly IC were reversed by some of these drug treatments: PPI deficits were reversed by clozapine and fluoxetine, latent inhibition deficits were reversed by haloperidol and clozapine, increases in AMPH-induced locomotion were reversed by haloperidol and fluoxetine while increased MK801-induced locomotion was reversed only by haloperidol. The mechanism by which anti-psychotic drugs reverse effects of prenatal immune activation are not yet clear. This may be related to any of the multiple actions of anti-psychotic drugs including the ability to block dopamine D2 receptors, provide neuroprotection or enhance demethylation of gene promoters (Kapur and Mamo, 2003; Lieberman et al., 2008; Guidotti et al., 2009).

8.7. Maternal care

It is possible that some effects of prenatal immune activation on offspring might be due to abnormal maternal care by their dam who was exposed to the immunogen. In some studies, investigators cross-foster prenatally treated and control pups with control dams who were not exposed to a prenatal immunogen, to control for differential maternal care. However, the majority of studies do not employ cross-fostering. Meyer et al. (2006b) investigated this issue and reported similar latent inhibition deficits in prenatal poly IC-treated pups who were cross-fostered to poly IC-treated dams or to control dams. This suggests either that maternal care by poly IC-treated dams and control dams is similar or that differential maternal care does not influence deficits in poly IC-treated pups, at least in the case of latent inhibition. Meyer et al. did, however, also find that control pups cross-fostered to poly-IC-treated dams showed deficits in latent inhibition, indicating that altered maternal care may be sufficient to induce abnormalities in pups.

9. Discussion

Among the many reported findings on CNS changes due prenatal immune activation in rodents, several stand out because they have been independently described by more than one group. Acutely or at early ages after prenatal exposure to immunogens, changes indicative of oxidative stress and microglial activation have been found in brains of offspring. Increased levels of placental cytokines are consistently reported, suggesting that placental dysfunction could play a role in transducing acute effects of prenatal immune activation to the fetus. With regards to long-term changes in offspring during postnatal life, at a behavioral level, decreases in PPI and latent inhibition and increases in drug-induced locomotion are prominent. Increased cell death in white matter together with signs of hypomyelination, and increased GFAP in various brain regions have been found by several groups. Decreases in serotonin and alterations in a wide variety of dopaminergic markers have been often reported, although the precise nature of the dopaminergic changes appear to vary depending on specific experimental conditions. The hippocampus appears to be affected, with changes

including increases in AMPAR/NMDAR currents, altered synaptic transmission and decreased neurogenesis being reported by more than one group.

An impediment to drawing general conclusions on CNS changes in rodent models of prenatal immune activation is the wide variety of different models and parameters used by various labs. Studies vary with respect to the type, dose and timing of immunogen administration during gestation, the species used, the postnatal age examined and the specific outcome measure that is quantified. This results in few findings being confirmed through replication by independent laboratories. It is difficult to draw conclusions across studies on issues such as windows of vulnerability during gestation or differential effects of different immunogens, although in a few cases a single lab has specifically addressed these questions experimentally. Thus, issues that remain unresolved include defining specific windows of vulnerability to prenatal infection during gestation in rodents, determining what events during those periods of vulnerability make particular CNS systems susceptible to alteration by prenatal infection, and having a clear understanding of how periods of vulnerability in rodent systems map onto human neurodevelopment. It is also likely that prenatal exposures to different immunogens (e.g. viral vs. bacterial) may have differing effects on fetal neurodevelopment or that there may be differential dose effects, since qualitatively different mechanisms may be activated by these variations. For example, the high doses of LPS or poly IC used in some studies may lead to severe hypothermia and symptoms of sepsis including hypotension, endothelial damage, intravascular coagulation and hypoperfusion of tissues such as placenta (Fofie and Fewell, 2003; Opal, 2007). Such mechanisms may not come into play with more moderate doses of immunogen. Studies comparing effects of differing doses and types of immunogens within a single experiment may contribute to resolve these issues. Careful recording of the time course of fever during natural influenza infection in humans has revealed that the fever course may be either mono- or bi-phasic with the frequency of bi-phasic fever differing between types of influenza virus (Suzuki et al., 2007; Suzuki and Ichihara, 2008). Prenatal infection of experimental animals with native virus or bacteria, reproducing the time course of a natural infection, may have different neurodevelopmental consequences compared with single or multiple injections of immunogens; thus this is another area where direct experimental comparison would prove useful. With regard to outcome measures that are assessed in offspring after prenatal immune activation, the focus is often on those measures most relevant to the disease of interest to the researcher. Researchers interested in schizophrenia tend to examine PPI, latent inhibition, DA, hippocampus and frontal cortex; cerebral palsy researchers concentrate on white matter and myelination; those interested in autism include an examination of the cerebellum, while Parkinson's disease researchers focus on DA. This tendency may hinder conclusions about the specificity of effects of prenatal immune activation on particular CNS systems.

Despite these caveats, over the last decade we have gained considerable information from rodent models concerning how prenatal infection affects CNS function. To provide an overview, Fig. 1 summarizes a potential sequence of events implicated in causing acute changes in fetal neurodevelopment and/or long-term changes in brain function and behavior following prenatal exposure to the immunogen, LPS. Prenatal immune activation may activate a variety of acute responses which have been shown, in independent studies, to be capable of affecting fetal and/or postnatal brain function. These include increases in circulating cytokines (e.g. IL-6) in the maternal circulation, fever, maternal undernutrition, increased maternal glucocorticoid secretion, maternal hypoxincaemia, placental insufficiency, oxidative stress and direct exposure of fetal neurons to cytokines. Studies examining the relative importance of each of these (and other) factors in mediating the CNS changes following prenatal immune activation are only beginning to emerge. To date it has been shown that blocking effects of either IL-1 or IL-6 in the maternal circulation, replenishing maternal Zn deficiency or inhibiting oxidative stress are able to prevent some CNS deficits caused by prenatal LPS or poly IC (Smith et al., 2007; Paintlia et al., 2008; Lanté et al., 2008; Coyle et al., 2009; Girard et al., 2010). It is likely that additive or interactive effects of various of these acute responses activated by the immunogen contribute to the spectrum of CNS abnormalities observed. The relative role for different mediating factors in producing specific aspects of these CNS changes needs to be further clarified (e.g. might glucocorticoid hypersecretion be important in mediating changes in brain DA metabolism while oxidative stress contributes more to white matter injury). Such information will provide for a deeper and more detailed understanding of acute mechanisms responsible for specific CNS changes following prenatal immune activation.

While some of the acute mechanisms likely responsible for effects of prenatal immune activation have been identified in recent studies, a clear gap in knowledge exists on the question of how an acute exposure to an immunogen in the prenatal period is eventually transduced into a long-term CNS change in the postnatal offspring. Several different mechanisms for consolidating expression of these long-term alterations in brain function can be hypothesized. (1) For instance, prenatal infection might alter expression of early developmental signals (e.g. specific proteins, trophic factors or neurotransmitters) at a critical period when neuronal pathways are being elaborated, resulting in long-term alterations in neurocircuitry. In this context, recent work using in utero gene transfer techniques has shown that transient prenatal knockdown of DISC-1, a gene that plays a role in neuronal development and is associated with schizophrenia, is sufficient to produce deficits in dopaminergic function and behavior in the resulting mouse offspring at adulthood (Niwa et al., 2010). It is possible that prenatal infection at a critical time in gestation might cause transient dysregulated expression of key genes like DISC-1 or other neurodevelopmental signals. (2) Alternatively, or in addition, prenatal infection could cause epigenetic modifications (e.g. DNA methylation or histone modification) of CNS genes, leading to permanent changes in gene expression and long-term changes in structure or function of specific neuronal pathways. The idea that early environmental insult might cause lasting effects on neural function by altering epigenetic programming is supported, for example, by studies showing that variations in early maternal care can permanently alter the methylation status of the glucocorticoid receptor gene promoter, resulting in long-term changes in stress reactivity (Weaver et al., 2004; Zhang and Meaney, 2010). (3) A third possibility is that prenatal infection may cause permanent dysregulation of peripheral systems which can influence brain function. For example, rat offspring that had been exposed to prenatal LPS have been reported to have increased levels of plasma IL-6 at adulthood (Borrell et al., 2002; Romero et al., 2007). Such long-term increases in cytokine levels are of potential significance to CNS function, since systemic increases in circulating IL-6 in adult rodents have been shown to alter brain DA turnover and sensitize AMPH-induced locomotor activity, indicating modulation of brain DA systems by circulating IL-6 (Zalcman et al., 1994, 1999; Song et al., 1999).

In conclusion, we are at the point in the evolution of the field where many labs have now clearly demonstrated that prenatal immune activation can actually cause changes in CNS function in off-

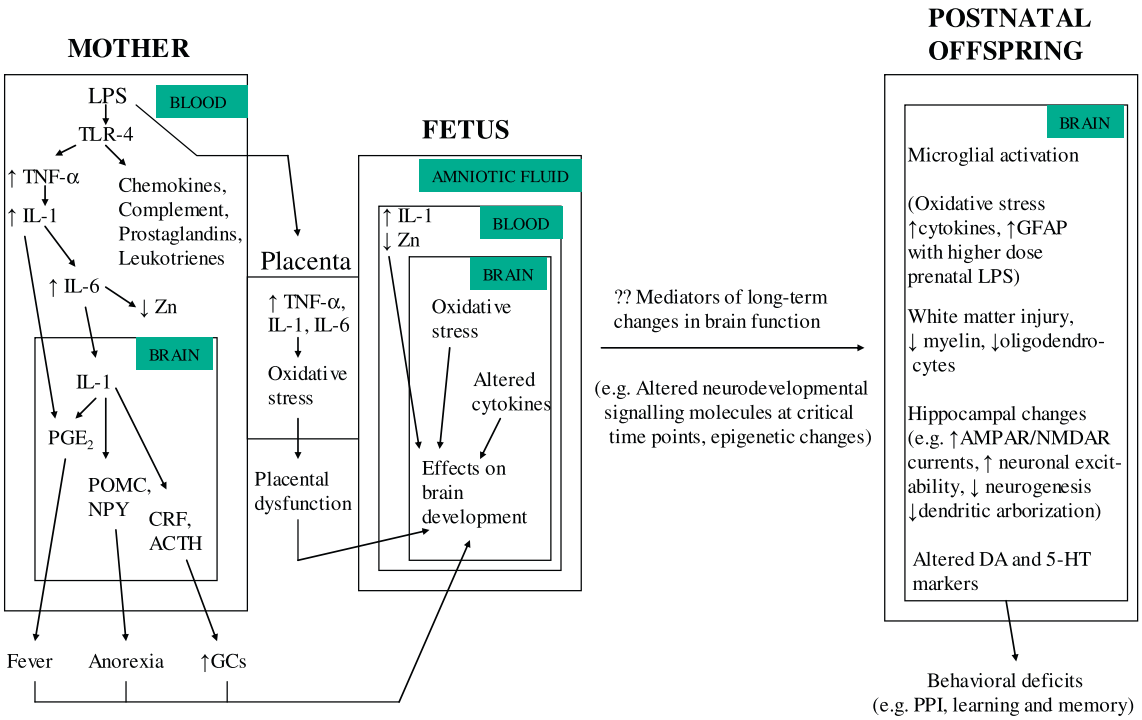

Fig. 1. Potential mechanisms mediating effects of prenatal infection on brain function. The diagram illustrates mechanisms implicated in mediating acute and long-term effects of systemic administration of bacterial endotoxin (lipopolysaccharide, LPS) to the pregnant mother on brain function in offspring. Binding of LPS to TLR-4 induces pro- (TNF-α, IL-1, IL-6) and anti-inflammatory cytokines, chemokines, prostaglandins, leukotrienes and the complement cascade in the maternal circulation. Circulating IL-6 interacts with targets in brain to induce cyclo-oxygenase-2-mediated synthesis of hypothalamic PGE_2 leading to fever, together with neuropeptide-mediated anorexia and increased glucocorticoid secretion. Increased cytokine production also leads to decreased plasma Zn levels in maternal and fetal blood, via induction of metallothionen in liver. LPS increases placental cytokines and oxidative stress, factors known to contribute to placental dysfunction. At the level of the fetal brain, LPS exposure has been shown to cause acute oxidative stress and may alter cytokine function. Several of the above mentioned factors have been shown to affect fetal brain development and/or long-term brain function in resulting offspring and thus likely contribute to prenatal LPS-induced changes in brain function; these factors include increased maternal plasma IL-6 or glucocorticoid levels, fever, maternal undernutrition, placental dysfunction, maternal/fetal hypozincaemia, oxidative stress and direct exposure of fetal neurons to increased cytokine levels. One notable gap in knowledge is our poor understanding of mechanisms by which acute responses induced by prenatal infection eventually mediate long-term changes in brain function and behavior. Some of the more prominent long-term changes observed in the brains of postnatal offspring as a result of prenatal LPS exposure include microglial activation, increased oxidative stress, increased cytokine and GFAP levels, white matter injury and hypomyelination, structural and electrophysiological changes in hippocampus and altered monoamine transmitter metabolism. If and how these or other specific changes in CNS structure and function lead to prenatal LPS-induced behavioral deficits is not yet clear. *Abbreviations:* AMPAR, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor; CRF, corticotrophin releasing factor; DA, dopamine; GCs, glucocorticoids; GFAP, glial fibrillary acidic protein; 5-HT, serotonin; IL, interleukin; LPS, lipopolysaccharide; NMDAR, *N*-methyl-D-aspartate receptor; NPY, neuropeptide Y; PGE, prostaglandin E; POMC, pro-opiomelanocortin; PPI, prepulse inhibition of startle responses; TLR, toll-like receptor; TNF, tumor necrosis factor; Zn, zinc.

spring, using rodent models. This suggests that the association between prenatal infection and CNS disorders in humans may, in fact, reflect a causal relationship. At this point, more in depth characterization of CNS changes due to prenatal immune activation in animal models is needed. Experiments examining the mechanisms responsible for these CNS changes are of high priority. It is important to define not only the acute mediators of effects of prenatal immune activation, but also developmental mediators responsible for maintaining long-term CNS changes. Extending studies to species other than rat and mouse, such as guinea pig that has a more mature CNS during gestation may increase relevance of findings to humans, while key studies in primates would be valuable. Since neurodevelopmental disorders like schizophrenia and autism, are of multifactorial etiology with a strong genetic component, the interaction of prenatal infection with genetic background (especially schizophrenia candidate genes) is an area ripe for study.

Conflict of interest statement

The author declares that there are no conflicts of interest.

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