Viral infection, inflammation and schizophrenia

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Abstract

Schizophrenia is a severe neurodevelopmental disorder with genetic and environmental etiologies. Prenatal viral/bacterial infections and inflammation play major roles in the genesis of schizophrenia. In this review, we describe a viral model of schizophrenia tested in mice whereby the offspring of mice prenatally infected with influenza at E7, E9, E16, and E18 show significant gene, protein, and brain structural abnormalities postnatally. Similarly, we describe data on rodents exposed to bacterial infection or injected with a synthetic viral mimic (PolyI:C) also demonstrating brain structural and behavioral abnormalities. Moreover, human serologic data has been indispensible in supporting the viral theory of schizophrenia. Individuals born seropositive for bacterial and viral agents are at a significantly elevated risk of developing schizophrenia. While the specific mechanisms of prenatal viral/bacterial infections and brain disorder are unclear, recent findings suggest that the maternal inflammatory response may be associated with fetal brain injury. Preventive and therapeutic treatment options are also proposed. This review presents data related to epidemiology, human serology, and experimental animal models which support the viral model of schizophrenia.

Keywords

Autism; Inflammation; Influenza; Schizophrenia; Viral infection

1. Introduction

The current review aims to highlight the impact of prenatal viral and bacterial infections and inflammation on the etiopathogenesis of schizophrenia. Genetic contributions to the genesis of schizophrenia have been widely studied, but the role of environmental influences is necessary to explain the approximately 40–55% discordance rate in monozygotic twins who do not share diagnoses of schizophrenia (reviewed in Brown, 2011).

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Significant epidemiologic data accumulated over the past 30 years has established the role of environmental factors in the acquisition of neuropsychiatric disorders (Fatemi, 2005a). For instance, influenza (H1N1) infection during the first trimester of pregnancy has been associated with schizophrenia (Brown et al., 2004). Increased levels of specific immunoglobulin G (IgG) to various infectious agents, such as *Toxoplasma gondii* (*T. gondii*), have been reported in maternal sera before birth (Brown et al., 2005) and in blood from infants at birth (Mortensen et al., 2007) and have been associated with schizophrenia or schizophrenia spectrum disorder in the offspring. Additional findings have also suggested that increased susceptibility to multiple pathogens in schizophrenic patients, rather than a specific agent, may play a role in the etiology of schizophrenia (Krause et al., 2010). Krause et al. (2010) examined the antibody titres of cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein–Barr virus, mycoplasma, Chlamydia, and toxoplasma in 31 schizophrenic patients and 30 healthy controls. Patients with schizophrenia were found to have a higher prevalence of antibodies in general, suggesting the possibility of an altered immune response in the central nervous systems of these individuals (Krause et al., 2010). These results are particularly salient due to immunosuppressive events that occur during pregnancy (Weinberg, 1984). Recently, Rowe et al. (2011) discovered that the expansion of Foxp3^{+} regulatory T cells (Tregs), a process that occurs naturally during pregnancy, is in fact an immunosuppressive event that increases prenatal susceptibility to infection. This upsurge in information regarding the association between prenatal infection and schizophrenia has initiated debate as to whether brain abnormalities result from direct infection of the fetal brain or from the maternal immune response (Aronsson et al., 2001, 2002; Fatemi et al., 2012; Gu et al., 2007; Hsiao and Patterson, 2011; Meyer, 2011, 2013–this issue; Shi et al., 2009).

2. Epidemiology

Schizophrenia is a severe psychiatric disorder affecting approximately 1% of the world's population (APA, 1994) with an incidence of 0.2 per 1000 per year (Easton and Chen, 2006). Schizophrenia has a higher incidence in males than females, with a male:female ratio of 1.4 (McGrath, 2005), with an early mean onset at age 20 in males, compared to age 25 in females (APA, 1994; Meltzer and Fatemi, 2000). Currently, a diagnosis of schizophrenia is based on behavioral criteria that requires the patient to experience two or more of the following symptoms for a significant duration over a 1 month period: positive symptoms (hallucinations and delusions), negative symptoms (avolition, apathy, asociality), and disorganization symptoms (grossly disorganized or catatonic behavior, disorganized speech, incoherence). However only one symptom is required if the individual experiences bizarre delusions, auditory hallucinations commentating on the patient's behavior or thoughts, or two or more voices conversing with one another (APA, 1994).

Various environmental risk factors for schizophrenia have been well documented, such as vitamin D deficiency (McGrath, 1999), being an immigrant of African descent in the United States or other industrialized countries (Dealberto, 2010; Selten et al., 2007), and birth in an urban environment (Marcelis et al., 1999). More striking, however, are the epidemiological findings associating birth season and risk of schizophrenia. An excess of approximately 5–15% of patients with schizophrenia are born during the winter months in the Northern

Hemisphere (Boyd et al., 1986; Bradbury and Miller, 1985; Davies et al., 2003; Gallagher et al., 2007; Machón et al., 1983; Pallast et al., 1994; Torrey et al., 1996). One report found an interesting association between seasonality of schizophrenic births and latitude band, with significant increases in the effect of seasonal birth with increasing latitude (Davies et al., 2003). While most studies in the Northern Hemisphere demonstrate concordant results (Boyd et al., 1986; Bradbury and Miller, 1985; Davies et al., 2003; Gallagher et al., 2007; Machón et al., 1983; Pallast et al., 1994; Torrey et al., 1996), studies examining the association between winter birth and schizophrenia in the Southern Hemisphere are less robust. Several reports of the southern hemisphere have found a positive association between birth during the winter months and an increased risk of schizophrenia (Morgan et al., 2001; Syme and Illingworth, 1978). Other reports have found associations between risk of schizophrenia and birth during peak rainfall season in Northeast Brazil (de Messias et al., 2001, 2006), late spring and summer births (Berk et al., 1996), as well as an increased risk of avolition and apathy in schizophrenic patients born during the autumn and winter months in Africa (Jordaan et al., 2006). While many of these studies outline the positive associations between season of birth in the Southern Hemisphere and risk of schizophrenia, other reports were unable to replicate these findings (d'Amato et al., 1996; Morgan et al., 2001).

3. Systemic inflammation, neuroinflammation, and neuroprogression

3.1. Schizophrenia and inflammatory markers

Schizophrenia is often accompanied by systemic inflammation and cell-mediated immune (CMI) activation as shown by increased levels of cytokines, interleukin 2 receptors (IL-2Rs), interleukin 1 receptor agonist (IL-1RA) (Lin et al., 1998; Maes et al., 2000; Miller et al., 2011; Zhang et al., 2004), acute phase reactants such as IL-1β, IL-6, and transforming growth factor (TGF)-β in plasma of subjects with schizophrenia (Meyer, 2011, 2013–this issue; Miller et al., 2011). Cytokines may be divided into various categories based on their role in inflammation and their derivation. Pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, are synthesized upon activation of the innate immune system and are responsible for febrile reactions, activation of phagocytes, vascular permeability, and release of inflammatory mediators, all of which are essential to the inflammatory response (Meyer, 2011, 2013–this issue). Many anti-inflammatory cytokines, such as IL-10 and TGF-β1, act to inhibit pro-inflammatory cytokine production, and these two factors in particular have been shown to exert an anti-hypoxic effect (Curfs et al., 1997; Levin and Godukhin, 2011).

Pro-inflammatory markers of immune system activation have been widely recognized in schizophrenia, with evidence that schizophrenic patients may possess a hyper-active pro-inflammatory system (Kim et al., 2009) as supported by increased levels of IL-6, IL-1β, and TNF-α in the sera of these individuals (Kim et al., 2009; Liu et al., 2010; O'Brien et al., 2008). Polymorphisms of the IL-1 gene complex have been associated with schizophrenia (Xu and He, 2010) and, specifically, ventricular enlargement (Papiol et al., 2005). High levels of pro-inflammatory cytokines such as IL-1β, IL-6, and IL-2 have also been observed in the CSF of patients with schizophrenia, further supporting this effect (Garver et al., 2003; McAllister et al., 1995; Soderlund et al., 2009).

The role of anti-inflammatory and immunosuppressive markers in schizophrenia has also been examined. Reduced IL-4 levels have been found in schizophrenic patients during acute episodes (O'Brien et al., 2008). Interestingly, IL-4 has also been shown to induce apoptosis of microglia (Soria et al., 2011). Reductions in anti-inflammatory cytokines may indicate an inability to limit the inflammatory response in these patients. However, increases in levels of anti-inflammatory cytokines have also been found in the sera of patients with schizophrenia, notably soluble IL-1RA (sIL-1RA), IL-2R, TNF-α, IL-10, and TGF-β (reviewed in Meyer, 2011). While anti-inflammatory activity is necessary for preventing the potentially deleterious effects of over-active pro-inflammatory markers, excessive anti-inflammation may induce various physiological abnormalities and reduce an individual's resistance to infectious agents (Meyer, 2011).

3.2. Neuroinflammation, oxidative stress, and schizophrenia

While peripheral immune activation recruits inflammatory mediators near the site of insult, this type of activation is capable of activating immune markers in the brain, such as microglia and cytokines (Patterson, 2011). Neuroinflammation as a response to bacterial and viral infections is often described as the accumulation of mobile innate and/or adaptive immune cells present in tissue that have circulated through the bloodstream (Graeber et al., 2011). These mobile cells, which may be macrophages (e.g. microglia) or neutrophils (e.g. granulocytes) possess powerful tissue-destructive effects (Rock et al., 2010).

Oxidative stress is also thought to play a role in schizophrenia (Wood et al., 2009), although the results are somewhat mixed. Several reports have shown reductions in antioxidant enzymes in schizophrenia (Dadeech et al., 2008; Raffa et al., 2009; Singh et al., 2008) while other reports have documented no change (Srivastava et al., 2001), or increased antioxidant presence in individuals with schizophrenia (Dakhale et al., 2004; Kuloglu et al., 2002; Kunz et al., 2008).

3.3. Neuroprogression in schizophrenia: structural and genetic involvement

Neuroprogression, such as neurodegenesis, apoptosis, and reduced neurogenesis/neuroprotection may be caused by oxidative stress and neuroinflammation (Andreasen et al., 2011; Berk et al., 2011; Madje, 2010; Maes et al., 2011; Niizuma et al., 2009; Sayre et al., 2008). Various neuroanatomical abnormalities in schizophrenia are indicative of tissue loss, such as ventricular enlargement and reduced hippocampal, parahippocampal gyrus, and potentially temporal lobe volume (reviewed in Csernansy, 2007). Other studies of neuroprogression in schizophrenia show evidence for apoptotic pathway involvement (Chen et al., 2009; Jarskog et al., 2004), neurodegeneration (Andreasen et al., 2011; Archer, 2010; Ashe et al., 2001) and neurotoxicity (Lahti and Reid, 2011). A few neuroprogressive genes involved in schizophrenia are outlined in Table 1. Infection via bacterial and viral agents has been shown to be relevant to the neuroprogressive pathway. Bacterial infection with Campylobacter rectus (C. rectus) has been shown to increase levels of interferon (INF)-γ (Offenbacher et al., 2005), a mediator of neuronal oxidative stress and apoptosis (Vartanian et al., 1995). Viral agents, such as Human herpesvirus 6 (HHV-6) have also been demonstrated to induce the apoptotic pathway in primary human fetal astrocytes (Gu et al., 2011). Because of the complexities involved in in vivo measurements of apoptosis and

oxidative stress in relation to prenatal infection, translational models in rodents are necessary in order to gain insight into the effects of prenatal viral infection and possible therapeutic interventions on the developing brain (Meyer et al., 2009). Rodents reach adulthood quickly and have a much shorter gestational period than humans. In addition, prenatal infection with bacterial lipopolysaccharide (LPS) has been helpful for comparing the effects of bacterial and viral agents on the developing brain. While prenatal exposure to polyriboinosinic polyribocytidilic acid (PolyI:C) may mimic the viral model, it is not identical and does not affect the same genes as the influenza virus. However, this model has generated much support for other markers of immune activation that have been shown to affect fetal brain development.

4. Animal models of viral infection

Rodent models of prenatal viral infection are important for further substantiating the viral theory of schizophrenia. Cotter et al. (1995) was the first to examine brain pathology in the offspring of pregnant mice infected with the H2N2 influenza virus during the second trimester. The offspring, which were sacrificed on postnatal day 21 (P21) did not validate the hypothesized pyramidal cell disarray (Cotter et al., 1995). Studies by Fatemi et al. (1998, 1999, 2000, 2002a,b, 2005, 2008a,b,c, 2009a,b, 2012) further investigated this topic, and discovered that prenatal viral infection with human influenza (H1N1) at various embryonic time points resulted in various brain, behavioral, and genetic abnormalities in offspring, based on time of insult. These results will be summarized and described in the next subsections (see Sections 4.1–5.2).

4.1. Gene expression and human influenza viral infection

The expression of a number of important brain genes were altered in offspring infected at embryonic days 7, 9, 16, and 18 (E7, E9, E16, E18). At E7, prenatal infection was shown to induce changes in gene expression in frontal cortex and hippocampus of the exposed progeny. Many of these genes are associated with hypoxia, inflammation, and schizophrenia (Fatemi et al., 2012). Compared to other time points, these gene expression changes were minor, with significant upregulation of 21 genes and downregulation of 57 genes in the frontal cortex and hippocampus (Fatemi et al., 2012). At E9, significant upregulation of 214 genes and downregulation of 175 genes was observed in the cerebellum and neocortex of Balb/c mice (Fatemi et al., 2005; Fatemi et al., 2008b, 2008c). Many of these genes are known to regulate cell structure and function, such as cytosolic chaperone system, HSC70, Bicaudal D, aquaporin4, carbonic anhydrase 3, glycine receptor, norepinephrine transporter, and myelin basic protein (Fatemi et al., 2005). At E16, prenatal H1N1 infection was associated with a significant number of gene alterations, many of which are related to myelination in the cerebellum and hippocampus and known to be implicated in schizophrenia (Fatemi et al., 2009a,b). In total, 1463 genes were found to be upregulated and 797 genes downregulated in the cerebellum, frontal cortex, and hippocampus of the exposed offspring (Fatemi et al., 2009a,b). Examples for some of the altered genes include myelin associated glycoprotein (Mag), proteolipid protein 1 (Plp1), myelin and lymphocyte-associated protein (Mal), myelin basic protein (Mbp), myelin-associated oligodendrocytic basic protein (Mobp), myelin oligodendrocyte glycoprotein (Mog), cell adhesion molecule,

neuronal 1 (Ncam1), and regulator of G protein signaling 4 (RGS4) (Fatemi et al., 2009a,b). By E18, microarray data showed 533 upregulated and 209 downregulated genes in the frontal cortex, hippocampus, and cerebellum of virally exposed offspring, many of which have been implicated in schizophrenia (Fatemi et al., 2008a). These include Sema3a, Trfr2, and Vldlr (Fatemi et al., 2008a). At this time point, several genes involved in influenza-mediated RNA processing were also upregulated in frontal cortex, hippocampus, and cerebellum and were present at P0, including non-structural protein 1(NS1) influenza binding protein and aryl hydrocarbon receptor nuclear translocator (Fatemi et al., 2008a).

4.2. Protein expression and human influenza viral infection

Protein measurements throughout various embryonic dates yielded interesting results. Neuronal nitric oxide synthase (nNOS) is an enzyme that produces nitric oxide (NO), a potentially harmful molecule implicated in fetal brain injury under hypoxia–ischemia conditions (Rao et al., 2011). In the offspring of mice infected with H1N1 on E9, nNOS was shown to increase 147% at postnatal day 35 (P35), with an eventual 29% decrease at postnatal day 56 (P56) in rostral brain areas. Interestingly, nNOS levels decreased in middle brain areas by 27% at P56 (Fatemi et al., 1998; Fatemi et al., 2000). Reelin, an extracellular secretory protein responsible for proper lamination of neurons (Quattrocchi et al., 2002), was significantly reduced in the brains of neonatal offspring of E9 virally exposed mice reflecting abnormal neuronal migration and decreased synaptic plasticity (Fatemi et al., 1999). Significant elevations in numbers of glial fibrillary acidic protein (GFAP)-positive cells were also observed in the brains of exposed offspring reflecting astrogliosis and reactive injury (Fatemi et al., 2002a). Measurement of SNAP-25 (a presynaptic brain marker) immunoreactivity varied along the septo temporal axis of hippocampus with significant overall increases in septodorsal and mid septotemporal regions and overall decreases in temporal ventral areas of the hippocampus of E9 infected offspring (Fatemi et al., 1998). SNAP-25 has roles in axonal growth and neurotransmitter release (Grabs et al., 1996; Osen-Sand et al., 1993; Oyler et al., 1989), and also been associated with death of virally infected cells (Bregano et al., 2011). At E16, protein expression of Mbp 14 kDa isoform was significantly downregulated at P14 and Mbp 18.5 and 17.2 kDa isoforms were significantly downregulated at P56 in the cerebella of exposed offspring (Fatemi et al., 2009a). Mag protein expression was also significantly downregulated at P14 and P35 in the cerebella of exposed offspring (Fatemi et al., 2009a).

4.3. Brain structural abnormalities and human influenza viral infection

At E7, increased white matter maturation as seen by increased fractional anisotropy was observed in the right middle cerebellar penduncle at P35 (Fatemi et al., 2012). At E9, reduced area measurements in the cerebral cortex and unilateral brain hemispheres were also observed in infected neonates when compared to controls (Fatemi et al., 1999). Reduced hippocampal area (18.1%) was also observed, yet did not reach statistical significance (Fatemi et al., 1999). The offspring of mice exposed on E9 and sacrificed at P0 showed significantly increased pyramidal cell density and non-significantly decreased nonpyramidal cell density (Fatemi et al., 2002b). By postnatal week 14, the exposed mice exhibited significant increases in both pyramidal and nonpyramidal cell densities (Fatemi et al., 2002b). Additionally, the effects of E9 prenatal infection were long lasting, as seen by

overall increases in brain volume and decreases in ventricular area at 14 weeks (Fatemi et al., 2002b). While it is widely known that subjects with schizophrenia tend to show increased, rather than decreased, ventricular area (Chua and McKenna, 1995), slight reductions in overall brain volume have also been observed in these patients (Wright et al., 2000). At E16, exposed mice also exhibited significantly reduced cerebellar and total brain volume at P14, reduced hippocampal volume at P35, and reduced ventricular area volume at P0 (Fatemi et al., 2009a, b). Fractional anisotropy also revealed delayed maturation of white matter in the right internal capsule at P0 and accelerated maturation in the corpus callosum at P14 and right middle cerebellar penduncle at P56 (Fatemi et al., 2009a). Significant brain atrophy in E18 exposed offspring at P35 (4.3% reduction) was also observed (Fatemi et al., 2008a). Prenatal viral infection of other animal species such as the rhesus monkey, has also elicited structural abnormalities (Short et al., 2010). The offspring of rhesus monkeys infected with H3N2 1 month before term were found to have reduced gray area in much of the cortex and reduced white matter in the parietal cortex, at 1 year of age (Short et al., 2010).

4.4. Behavioral abnormalities and human influenza viral infection

Several behavioral abnormalities have also been observed in the offspring of virally exposed mice. Abnormal behavior, including decreased prepulse inhibition of the acoustic startle response (PPI) was demonstrated in offspring of E9 exposed mice (Shi et al., 2003). Other studies have replicated similar deficits of PPI in virally exposed offspring (Ibi et al., 2009; Wolff and Bilkey, 2008). These behavioral abnormalities could be reversed by chlorpromazine or clozapine (Shi et al., 2003). Neonatal Tap1$^{-/-}$ mice, which express lower levels of major histocompatibility complex 1, infected with the influenza A/WSN/33 virus showed reduced PPI, however infected wildtype (WT) mice did not differ from uninfected mice in adulthood (Asp et al., 2010). Other reports of mice exposed to H1N1 on E9.5 of pregnancy demonstrate increased head twitch response, a behavior typically induced by 5-HT2A agonists (Moreno et al., 2011). As these mice have been shown to express significantly elevated 5-HT2A receptor expression in the frontal cortex (Moreno et al., 2011), this supports previous findings of reduced serotonin in the cerebella of exposed offspring at P14 and P35 (Fatemi et al., 2008a; Winter et al., 2008). Additionally, Moreno et al. (2011) also reported reductions in the metabotropic glutamate receptor 2 in the frontal cortex of the exposed offspring.

4.5. Neurotransmitter abnormalities and human influenza viral infection

Abnormalities at the level of neurotransmitters have also been observed in the offspring of virally exposed mice. At E16, significant reductions in cerebellar levels of serotonin were revealed at P14, with no significant changes in dopamine expression (Winter et al., 2008). At E18, significant reductions in levels of taurine and serotonin were observed in the cerebella of virally exposed offspring, as compared to controls (Fatemi et al., 2008a). Taurine was significantly decreased at P35, serotonin was significantly decreased at P14 and P35, and 5-hydroxyindoleacetic acid was significantly decreased at P14 (Fatemi et al., 2008a). The reduction in serotonin levels during E16 and E18 is meaningful considering its role in brain development and its recent discovery in placenta (Bonnin and Levitt, 2011; Bonnin et al., 2011).

5. The role of the placenta in human influenza viral infection

The placenta plays an important role in the development and growth of the fetus (Pardi and Cetin, 2006). In mice, the placenta may be divided into three regions: the labyrinthine zone, the junctional zone, and a layer of trophoblast giant cells. The labyrinthine zone is comprised of a complex network of fetal capillaries and maternal blood spaces (MBS). The junctional zone primarily consists of spongiotrophoblast cells and glycogen cells, separating the labyrinthine zone from the maternal tissue. A layer of giant trophoblast cells lies between the junctional zone and maternal decidua. These giant trophoblast cells produce hormones and cytokines and may affect maternal physiology such that the fetal allograft is accommodated (Fig. 1). As such, abnormalities in placental gene expression and morphology can have profound effects on the developing fetus. For instance, placental insufficiency has been associated with low birth weight and an increased risk for fetal cardiovascular complications (Henriksen and Clausen, 2002). Recent reports have documented the placenta as a source of serotonin (5-HT) in the murine neonatal forebrain during early gestation (E10–E15). During later gestational periods (E16-birth), the hindbrain begins synthesizing 5-HT using maternal tryptophan in dorsal raphe neurons, which extend to the forebrain (Bonnin and Levitt, 2011; Bonnin et al., 2011). These results are particularly interesting in light of the aforementioned observed reductions of 5-HT in virally exposed mice at E16 and E18 (Fatemi et al., 2008a; Winter et al., 2008).

5.1. Structural abnormalities of the placenta and human influenza viral infection

Dams were infected with influenza A/NWS/33 (H1N1) on E7 and their placentae were harvested on E16 (Fatemi et al., 2012). Infected placental tissues exhibited cytoarchitectual disorganization (especially in the placental labyrinth), an increased presence of immune cells (Fig. 2), and the presence of various sized thrombi (Fatemi et al., 2012). Presence of thrombi clearly shows that occlusion of vessels by thrombi could induce hypoxia via reduction in blood flow and oxygen delivery to the fetal brain. Similar reports have shown a reduction in the thickness of the labyrinthine zone upon infection with *C. rectus* in mouse, which may result in impaired gas exchange and flow of nutrients and waste between mother and fetus (Offenbacher et al., 2005). As discussed earlier, *C. rectus* infection has also been associated with an increase in INF-γ levels (Offenbacher et al., 2005), which is known to mediate neuronal stress and neuronal apoptosis (Vartanian et al., 1995).

5.2. Genetic abnormalities of the placenta and human influenza viral infection

Significant upregulation of 77 genes and downregulation of 93 genes were observed in the placentae of pregnant dams infected at E7 (Fatemi et al., 2012). Approximately 20% of placental genes significantly affected by viral infection play a role in apoptosis, 11% in hypoxia, 11% in inflammation, 10% in the immune response, and 9.4% in psychiatric disorders (Fatemi et al., 2012). Important downregulated genes in the placentae of these animals include: glutamate receptor, ionotropic, AMPA1 (alpha 1) (Gria1), catenin (cadherin associated protein) delta 1 (Ctnn1), forkhead box O3 (foxO3), and dysferlin (Dysf) (Fatemi et al., 2012). Important upregulated genes in E7 infected placental tissues include: phosphodiesterase 10A (Pde10a), fyn proto-oncogene (Fyn), programmed cell death 2 (Pdcd2), and quaking (Qk) (Fatemi et al., 2012). Importantly, evidence for presence of the

viral genes, matrix protein 1/matrix protein 2 (M1/M2), neuraminidase (NA), and nonstructural protein 1 (NS1), was not observed in the placentae of infected pregnant dams (Fatemi et al., 2012).

6. Use of PolyI:C to mimic viral infection

Similar, but not identical, neuropathological abnormalities have also been observed upon prenatal exposure with a viral mimic, PolyI:C, at critical stages of pregnancy. PolyI:C, a synthetic form of double-stranded RNA, has been demonstrated to elicit the immune response upon administration (Fortier et al., 2004; Shi et al., 2003). Activation of the maternal immune system in mice through PolyI:C administration has been demonstrated to impair fetal brain development, potentially through the pro-inflammatory cytokine, IL-6 (Smith et al., 2007). Recently, PolyI:C exposed maternal placenta was shown to express both increases in IL-6 mRNA and protein in the exposed placentae (Hsiao and Patterson, 2011). Other pro-inflammatory cytokines, such as IL-1β, TNF-α, and anti-inflammatory cytokine IL-10 induced by PolyI:C exposure have also been associated with deleterious effects on brain pathology (Meyer et al., 2005, 2006a, 2008, 2011).

6.1. PolyI:C and behavioral abnormalities

Animals treated with PolyI:C also exhibit several behavioral phenotypes similar to those seen in schizophrenia (Perry et al., 1999). The offspring of mice exposed to PolyI:C on E9 express deficits in PPI, exploratory behavior, and social interaction (Shi et al., 2003). Bitanihirwe et al. (2010) observed behavioral changes in the offspring of pregnant mice injected with PolyI:C during late gestation. These mice demonstrated social, learning, locomotor deficits, anhedonia and stereotyped behavior (Bitanihirwe et al., 2010). Another group observed sex-specific differences among the offspring of pregnant rats subjected to PolyI:C exposure, with male offspring exhibiting altered executive functioning (Zhang et al., 2012). In addition, disrupted latent inhibition (Piontkewitz et al., 2011; Zuckerman and Weiner, 2005), and rapid reversal learning (Zuckerman and Weiner, 2005) have also been observed in PolyI:C exposed animals. Disrupted latent inhibition and rapid reversal learning are both indicative of rapid behavioral switching in response to stimulus/reinforcement paradigms (Zuckerman and Weiner, 2005). Switching, also described as the tendency towards changing a learned response, has been documented in positive symptoms of schizophrenia (Yogev et al., 2003).

6.2. Time-dependent effects of PolyI:C exposure

Time-dependent effects due to prenatal PolyI:C administration and brain/behavior pathology has been observed in the exposed offspring (Fortier et al., 2007; Meyer et al., 2006a). As the maternal immune system is prone to fluctuations throughout the duration of pregnancy (Sargent, 1993), timing of prenatal infection may elicit variable deleterious consequences and may require different approaches to treatment. Prenatal PolyI:C exposure at E9 has been shown to reduce spatial exploration and impair latent inhibition, while exposure at E17 induces perseverative behavior (Meyer et al., 2006a,b).

6.3. Brain morphology and PolyI:C exposure

Brain structural abnormalities in PolyI:C exposed offspring have also been noted. Abnormal proliferation of cortical progenitor cells and impaired expression of Pak6, a regulator of gene transcription, have been found in the cerebral cortex in the offspring of mice exposed to PolyI:C injection (Soumiya et al., 2011). Additionally, altered development of the cerebellum (Shi et al., 2009), has been observed. Other groups have demonstrated concordant neuroanatomical abnormalities, such as ventriculomegaly, between offspring of rodents exposed to PolyI:C during pregnancy and patients with schizophrenia (Li et al., 2009; Piontkewitz et al., 2011). Prenatal PolyI:C exposure has also been shown to reduce the number of Reelin and Parvalbumin positive cells in the medial prefrontal cortex following exposure on E9 and E17 (Meyer et al., 2008) and in the hippocampal formation and dentate gyrus following exposure on E9 (Meyer et al., 2006a).

6.4. Neurotransmitters and PolyI:C exposure

Neurochemical abnormalities have also been reported in the offspring of animals prenatally exposed to PolyI:C injection. Increased dopamine and its major metabolites have been found in the lateral globus pallidus and prefrontal cortex of exposed offspring (Winter et al., 2009). Additionally, prenatal exposure reduced expression of serotonin and its metabolite in the hippocampus, nucleus accumbens, and lateral globus pallidus (Winter et al., 2009). While some studies have observed increased glutamate in prenatally PolyI:C exposed animals (Ibi et al., 2009), others have found glutamate to be unaffected (Winter et al., 2009).

7. Animal models infected with LPS

Other animal studies have examined the effect of prenatal administration of LPS on offspring. Investigations into the behavioral deficits and neuroanatomical abnormalities associated with prenatal LPS administration are important for determining the extent to which bacterial pathogens can alter brain development. Several studies have suggested that the offspring of animals exposed to LPS during pregnancy exhibit impaired motor activity (Kirsten et al., 2010) as well as learning and memory deficits (Hao et al., 2010). Monkeys prenatally exposed to LPS also exhibit PPI deficits, and behavioral disturbances (Willette et al., 2011).

Prenatal LPS infection has also been demonstrated to adversely affect brain development. In rhesus monkeys, LPS exposure during pregnancy at 6 weeks prior to term has been associated with increased production of white matter in offspring at 1 year of age (Willette et al., 2011). Cui et al. (2009) observed that LPS administration in pregnant rats during E15 and 16 elicited reduced dentate gyrus cell proliferation in P14 offspring while later gestational LPS administration, during E18 and 19, was associated with reduced dentate gyrus cell survival (Cui et al., 2009). Interestingly, offspring of animals exposed to LPS later in pregnancy, during E18 and 19, did not exhibit altered cell proliferation or survival in adulthood, at P60 (Cui et al., 2009). The authors of this study also observed that administration of ibuprofen was unable to block any decreases in cell survival at P14, suggesting that induction of maternal cytokines or corticosterone by LPS is likely responsible for mediating this effect (Cui et al., 2009). Rat models of prenatal bacterial

infection have also led to structural and biochemical brain abnormalities in the offspring of exposed rats. Recently, Wallace et al. (2010) injected pregnant rats with *Escherichia coli* (*E. coli*) on E17. While prenatal infection with *E. coli* did not affect birth weight, the authors did observe "surface righting and negative geotaxis" in the offspring (Wallace et al., 2010). Interestingly, infected offspring exhibited reduced Purkinje cell counts, density, and volume, and decreased calbindin, a calcium-binding protein expressed by Purkinje cells in the cerebellum and known for its involvement in motor coordination (Barski et al., 2003).

Fortier et al. (2007) examined the effect of timing and type of prenatal infection on PPI. In this study, pregnant rats were exposed to either LPS, PolyI:C, or turpentine, which is known to induce inflammation, at E10–11, E15–16, and E18–19 (Fortier et al., 2007). While PolyI:C had no effect on PPI, PPI deficits were observed with prenatal LPS exposure during E15–E16 and E18–E19 and with turpentine injection at E15–E16. Acute LPS exposure however, had no significant effect on PPI (Fortier et al., 2007).

8. Infection via protozoa and other inflammatory agents

Infectious agents other than viral and bacterial organisms can induce inflammation during pregnancy and cause placental changes in pregnant animals and brain abnormalities in the exposed offspring. *T. gondii* infection in pregnant mice has been associated with increased expression of multiple chemokines, which were shown to be dependent upon IFN-γ expression (Wen et al., 2010).

Other non-organismal agents have been demonstrated to elicit the inflammatory response. Mercury has recently been shown to induce inflammatory markers such as vascular endothelial growth factor (VEGF) and IL-6 to be released by human mast cells (Kempuraj et al., 2010). In light of these findings, Kempuraj et al. (2010) have suggested that mercury may have the potential to disrupt the blood brain barrier, thereby inducing brain inflammation. In pregnant women, even low-level mercury exposure has recently been associated with reduced cerebellar size in newborns (Cace et al., 2011).While there was no significant difference in the width, the length of the cerebellum was significantly smaller in offspring of mothers whose hair mercury levels were greater than 1 μg/g (Cace et al., 2011).

Intramuscular injection of turpentine is known to induce inflammation through induction of tissue damage (Sheikh et al., 2006), promoting local release of immune factors such as TNF-α, IL-1β, and IL-6 (Aguilar-Valles et al., 2007; Luheshi et al., 1997; Tron et al., 2005; Turnbull et al., 2003). Rats prenatally exposed to turpentine at E15 exhibited reduced PPI, increased latency to reach a platform in the Morris-water maze, prolonged fear conditioning response, and enhanced locomotion in response to amphetamine exposure (Aguilar-Valles and Luheshi, 2011). Enhanced mesolimbic dopaminergic activity was also observed in these animals, and was found to be attenuated after neutralization of IL-6 levels (Aguilar-Valles et al., in press).

Inflammation-induced hypoferremia, a common physiological response to all infections whereby cytokine activation reduces serum levels of non-heme iron, has also been shown to elicit long-lasting behavioral and dopamine changes in the offspring (Aguilar-Valles et al.,

2010). Thus, it becomes clear that many factors can activate inflammatory pathways and cause brain abnormalities (a description of such pathways is beyond the scope of this paper).

9. Mechanisms of viral/bacterial effects

There may be specific mechanisms differentiating the harmful effects of infectious pathogens. Foreign pathogens are known to activate the adaptive immune system, and may do so through toll-like receptors (TLRs). There are approximately 10 known members of the mammalian TLR family, each of which responds to different ligands produced by bacteria and viruses, as well as other pathogens (Akira and Hemmi, 2003). For instance, a well known ligand for mammalian TLR4 is the LPS component of Gram-negative bacteria (Poltorak et al., 1998; Qureshi et al., 1999). Recently, Watanabe et al. (2011) showed that PolyI:C causes activation of the TLR3 receptor via a cytoplasmic lipid raft protein, known as Raftlin, leading to production of interferon and inflammatory cytokines. TLR5 is found to be induced in human cells infected with H1N1 or H5N1, while TLR3 is induced in cells infected with H3N2 (Song et al., 2011). Other agents have been detected as TLR ligands, including Gram-positive bacterial peptidoglycans, double-stranded DNA (dsDNA), as well as single- and double-stranded RNA (ssRNA and dsRNA) (Ross, 2005). Interestingly, LPS treatment has been shown to increase TLR-2 expression in syncytiotrophoblast cells of the placenta (Ma et al., 2007). This finding is of particular interest as activation of TLRs cause induction of brain and behavioral abnormalities. TLR2 activation has been shown to have a deleterious effect on the developing mouse brain, as seen by reductions in white matter in the forebrain and cerebellar molecular layer and cerebral gray matter (Du et al., 2011). Tlr3 deficient mice exposed to PolyI:C injection show a lack of neural stem/ progenitor cell impairments, as compared to wildtype mice exposed to the same treatment (De Miranda et al., 2010).

9.1. Direct infection of the fetus

Several reports have postulated that the deleterious effects of prenatal viral, bacterial, or parasitic infections are due to direct infection of the fetal brain and placenta. Influenza A/WSN/33 has been detected in the central nervous system of immunodeficient mice at 17 months, post-inoculation, and with limited damage to tissues (Aronsson et al., 2001). The influenza A virus has also been discovered in fetal brain tissue 3 days after prenatal infection, and persisted for up to 90 days postnatally (Aronsson et al., 2002). By the same token, E7 H1N1 virally infected mice showed evidence of placental thrombosis, cytoarchitectural injury, and immune cell recruitment following H1N1 infection (Fatemi et al., 2012), suggesting virally induced injury to the placentae of exposed pregnant dams. However, investigation of H1N1 viral genes did not show evidence of viral RNA in placentae or brains of exposed offspring, pointing to maternal cytokine involvement in this pathogenic process.

Evidence for bacterial infection in the placenta has also been well documented. Han et al. (2004) found that the bacteria, *Fusobacterium nucleatum* (*F. nucleatum*), had colonized and proliferated within the mouse uterus after prenatal infection in as few as 6 h post-infection. The authors found that the infection originated in and was restricted to the deciduas basalis 24 h post-infection (Han et al., 2004). Between 48 and 72 h after infection, *F. nucleatum*

spread to the amniotic fluid and fetus, which the authors attribute to be the likely cause of stillbirth in these animals (Han et al., 2004). Upon prenatal infection, bacterial agents such as *C. rectus* and *Porphyromonas gingivalis* (*P. gingivalis*) have been found in the placenta and thought to induce hypermethylation of promoter genes such as insulin-like growth factor 2 (Igf2) which is involved in placental growth (Bobetsis et al., 2007; Constancia et al., 2002). Another report examining the effect of prenatal *Coxiella burnetti* (*C. burnetti*) in goats suggests that the choriallantoic membrane trophoblast cells are the first target cells of the placenta for bacterial infection (Sanchez et al., 2006). Here, abortion was associated with proliferation of *C. burnetti* within the fetal trophoblast cells (Sanchez et al., 2006). Reductions in blood levels of the parasite *Trypanosoma cruzi* has also been associated with improved pregnancy outcome (Solana et al., 2009), providing further support for this mechanism.

9.2. Inflammatory/cytokine response

The prevailing view is that brain abnormalities occur as a result of the maternal immune response and that viral and bacterial infections may be one factor that plays a role in inflammation through activation of the adaptive and innate immune systems (Meyer, 2011, 2013–this issue). Prenatal influenza infection has been associated with secretion of IL-6 and TNF-α proteins in cultured human fetal membrane chorion cells (Uchide et al., 2006). These results are particularly important in light of recent investigations that have demonstrated an association between IL-6 exposure and fetal brain injury (Elovitz et al., 2011; Hsiao and Patterson, 2011; Smith et al., 2007).

Many reports have shown that induction of the maternal immune response in the absence of an infectious agent is sufficient to induce impaired brain development in offspring (Meyer et al., 2005, 2006b; Shi et al., 2003; Zuckerman et al., 2003). Thus ultimately, infection with a virus, synthetic viral mimic, and bacterial endotoxin all induce maternal, and perhaps fetal, cytokine production. Recently, Ellman et al. (2010) measured archived maternal serum levels of IL-8 from the mothers of 17 patients diagnosed with schizophrenia and found that prenatal IL-8 exposure during the second and third trimesters of pregnancy were associated with increased ventricular volumes. Additionally, maternal IL-8 exposure was associated with reduced volume of the right caudate, bilateral putamen, and right superior temporal gyrus (Ellman et al., 2010).

10. Correlation between human serology and animal models

Previous ecological exposure studies examining the 1957 A2 influenza epidemic found that individuals born 5 months after the peak exposure period were 88% more likely to develop schizophrenia (Mednick et al., 1988; O'Callaghan et al., 1991). However, these studies were based on associations between reported dates of peak infection and schizophrenic births. While these studies were highly valuable in reporting indirect associations, recent serologic work more reliably and directly associates the presence of maternal and fetal IgG antibodies specific to infectious pathogens and development of schizophrenia in offspring.

10.1. Prenatal and neonatal serology

Early serologic reports of maternal rubella infection demonstrated an increased risk of developing non-affective psychosis (Brown et al., 2000) and schizophrenia (Brown et al., 2001). Brown et al. (2004) observed that infection with influenza during the first trimester of pregnancy leads to a seven-fold increased risk of schizophrenia in the offspring. Other investigations have found that multiple bacterial, parasitic, and viral agents can exert similar effects. Various bacterial infections during the first trimester have been shown to increase susceptibility to developing schizophrenia by 2.53-fold in the offspring (Sorensen et al., 2009). Other reports investigating the intracellular protozoan *T. gondii* have replicated these results, associating maternal infection with a three-fold increased risk of developing schizophrenia in the offspring (Brown et al., 2005). A more recent report has shown a strong association between seropositivity in maternal sera and presence of maternal *T. gondii* antibodies in newborn children (Pedersen et al., 2011). Because newborn children will only begin producing *T. gondii* antibodies around 3 months of age (Wilson and McAuley, 1999), this demonstrates the interesting possibility of maternal *T. gondii* antibodies crossing the placenta and interacting with the fetus. To further investigate whether prenatal infection is associated with brain abnormalities, a recent study investigated the prenatal brain using magnetic resonance imaging in eight fetuses exposed to *T. gondii* (Malinger et al., 2011, in press). Two of these fetuses were diagnosed with congenital toxoplasmosis during the second trimester, while the remaining six were diagnosed during the third trimester of pregnancy (Malinger et al., 2011, in press). Interestingly, seven of these fetuses exhibited multiple echo-dense nodular foci in the parenchyma, periventricular zone, or caudothalamic zone (Malinger et al., 2011, in press), while one fetus exhibited severe brain damage due to ventriculomegaly (Malinger et al., 2011, in press), and brain disorganization resulting from infection.

10.2. Postnatal human serology

Postnatally, subjects with schizophrenia infected with HSV-1 have been shown to have decreased posterior cingulate gyrus gray matter and a decreased performance on the Wisconsin Card Sorting Test compared to subjects with schizophrenia who were HSV-1 negative (Prasad et al., 2011). Several other postnatal reports have found associations between the presence of antibodies reactive against infectious agents and risk of schizophrenia. In adult life, individuals with a high *T. gondii* IgG level are shown to be 1.73 times more likely to develop schizophrenia or associated spectrum disorders than those with lower IgG levels (Pedersen et al., 2011). Dickerson et al. (2006) found that individuals with deficit schizophrenia were more likely to have been infected with CMV compared to those with non-deficit schizophrenia. Exposure to HSV-1 and CMV in schizophrenic subjects is also linked with impaired cognitive function (Shirts et al., 2008; Yolken et al., 2011), and elevations of HSV-2 in children have been associated with later development of schizophrenia (Buka et al., 2001).

11. Preventive measures and therapeutic interventions

Since prenatal infections play such an important role in increasing the incidence of schizophrenia, it would be of special interest to consider preventive measures to mitigate the

teratogenic effects of intrauterine infections. A primary prophylactic treatment is important for affecting change in the mother, prior to pregnancy, in order to prevent infection. For instance, use of influenza vaccines before a planned pregnancy could be a potentially beneficial means for preventing the teratogenic effects of viral infection (Cono et al., 2006). The current mandate by the CDC to vaccinate pregnant mothers does not take into account the potential activation of maternal cytokine production. During pregnancy there is a concern that influenza vaccination may incite the generation of antibodies against influenza-related epitopes, inducing the maternal inflammatory response (Nahmias et al., 2006; Patterson, 2007). Additionally, use of oseltamivir to treat viral infection during pregnancy may not be fully safe as its administration in pregnant mice may affect fetal brain gene expression during postnatal development (vide infra) (Fatemi et al., unpublished observations). A recent study by Kanduc (2010) examines the peptide sequence homology of the influenza A H5N1 virus with human proteins. Indeed, many proteins that exhibit sequence homologies with H5N1 are involved in brain cell proliferation, development, and differentiation. Kanduc (2010) observed overlapping gene sequence homologies between the H5N1 virus and genes known to be abnormally regulated in schizophrenia. Interestingly, Kanduc (2010) demonstrated that both Neurexin 1 alpha and 1 beta, Reelin, and disrupted in schizophrenia 1 protein, contain sequence homologies with H5N1; these proteins are also known to be implicated in the etiology of schizophrenia (Fatemi et al., 2005; Fatemi, 2005b; Voineskos et al., 2011). This peptide-virus overlap may have a profound effect on the immune system's ability to identify foreign antigens as self antigens. High sequence homology between human proteins and infectious agents may also induce cross reactivity, eliciting an autoimmune response.

11.1. Prenatal treatment with oseltamivir

We have performed a pilot study to test the teratogenicity of oseltamivir by infecting or sham-infecting pregnant mice with H1N1 at E16 and concurrently treating them with either oseltamivir (20 mg/kg/day, oral gavage (o.g.) N = 20) or saline (200 μL, o.g.; N = 20). Pilot data demonstrate that oseltamivir had no major effects on pregnancy (all dams delivered pups), litter size/survival, weight of dams, body weights of pups at birth (P0; birth) and brain weights at birth (Table 2) (Unpublished observations, Fatemi et al.).

Gene expression results in hippocampus at P0 showed that in the offspring of infected mice with no oseltamivir, there were 95 downregulated genes and 145 upregulated genes with a fold change of at least 2.0 and p<0.05 when compared with sham-infected controls with no oseltamivir. These results are similar to what we have obtained previously for E16 infection at P0 (117 downregulated and 115 upregulated with a fold change of 2.0 and p<0.05). Significantly, there were no gene expression changes meeting our criteria (fold change of 2.0 and p<0.05) when comparing oseltamivir-treated infected versus oseltamivir-treated controls (Unpublished observations, Fatemi et al.). Therefore, treatment with oseltamivir dramatically reduced virally induced changes in gene expression. Moreover, when comparing control animals treated with oseltamivir and control animals with no drug treatment, only six genes were upregulated and zero downregulated by oseltamivir, while infected animals treated with oseltamivir versus infected animals without drug showed upregulation of 12 genes and downregulation of 22 genes at P0 (Unpublished observations,

Fatemi et al.). Interestingly, 10 of the 12 upregulated genes were downregulated in the infected animals that did not receive oseltamivir. Similarly, 18 of the 22 genes downregulated in infected animals additionally treated with oseltamivir were upregulated in infected animals that did not receive oseltamivir (Unpublished observations, Fatemi et al.). These results suggest that oseltamivir treatment alone can affect the direction of change in expression of some hippocampal genes. These results are significant because they are expected to provide interventions that may be used to prevent the "winter birth effect" in humans and thus, decrease the chances of individuals developing schizophrenia. Moreover, oseltamivir acts as a neuraminidase inhibitor, preventing viral replication, without any obvious effects on cytokine production. Its prevention of gene expression changes in the brains of virally exposed offspring suggest that maternal cytokine activation may not be totally responsible for gene expression changes seen in this model. Despite these early positive results, the effects of oseltamivir on gene regulation in other postnatal stages of brain development are unknown and require further investigation.

11.2. Early antipsychotic treatment

Another therapeutic/preventive step is the use of low dose antipsychotics in children susceptible to developing schizophrenia. For example, once prodromal signs of schizophrenia have already occurred, treatment with a low-dose antipsychotic may be helpful. Clozapine treatment has been shown to improve memory deficits in the offspring of mice infected with PolyI:C on day 17 of pregnancy without affecting adult hippocampal neurogenesis (Meyer et al., 2010). Low-dose treatment with other antipsychotics has shown normalization of extracellular glutamate levels (Roenker et al., 2011), which are significantly increased upon prenatal infection with PolyI:C (Roenker et al., 2011). Additionally, PolyI:C exposed rats treated with risperidone and clozapine during adolescence did not develop the brain structural abnormalities found in untreated PolyI:C exposed rats (Piontkewitz et al., 2009, 2010, 2011, 2012). PolyI:C exposed rats treated with clozapine and/or risperidone on post-natal days 34–47 did not the exhibit the same ventricular enlargement and hippocampal reduction as compared to the PolyI:C saline treated rats (Piontkewitz et al., 2009, 2010, 2011, 2012). While use of certain antipsychotics as an early treatment option may be helpful, there is debate over the ethics of such early treatment. Several recent reports have highlighted the controversy over administration of antipsychotics in children, which include risk of weight gain and metabolic effects (Maayan and Correll, 2011; Pringsheim et al., 2011), induction of diabetes mellitus (Andrade et al., 2011), and neurologic side effects (Pringsheim et al., 2011).

11.3. Antipsychotic action and the immune system

Recently, the immune system has been put forth as a potential target for the action of certain antipsychotics (Drzyzga et al., 2006). Various cytokines have been associated as state and trait markers of schizophrenia (Miller et al., 2011). During acute exacerbations, IL-1β, IL-6, and TGF-β were shown to be increased in patients with schizophrenia, yet normalized upon treatment with antipsychotics, thus acting as state markers of disease (Miller et al., 2011). In contrast, other cytokines and their receptors, e.g. IL-12, IFN-γ , TNF-α, and soluble IL-2 receptor (sIL-2R) acted as trait markers of schizophrenia because they remained elevated both in acute exacerbations and after antipsychotic treatment (Miller et al., 2011).

Individuals with treatment resistant forms of schizophrenia have been shown to express higher IL-1RA, IL-6 and sIL-2R levels, as compared to controls (Maes et al., 2000; Miller et al., 2011). While Maes et al. (2000) and Zhang et al. (2004) were unable to observe reductions in IL-6 levels after prolonged treatment with clozapine, risperidone, or haloperidol, other reports suggest that use of neuroleptics and atypical antipsychotics may reduce serum levels of IL-6R and increase IL-2R (Maes et al., 1994; Muller et al., 1997). Increased IL-17 levels have been shown to be associated with chlorpromazine, clozapine, D-clozapine, haloperidol, and quetiapine treatment, at nearly all concentrations, in healthy female volunteers without history of psychiatric disorder (Himmerich et al., 2011). While clozapine, which has the potential to induce fever during the first stages of administration, has been associated with increased sIL-2r levels (Pollmacher et al., 1996), haloperidol and risperidol have been demonstrated to reduce plasma IL-2 (Kim et al., 2000; Zhang et al., 2004). This is particularly relevant, as significant elevations in sIL-2R alpha and IL-1RA have been observed in the sera of schizophrenic patients, as compared to controls (Suvisaari et al., 2011). Furthermore, anti-inflammatory therapy has gained support for the treatment of negative and cognitive symptoms of schizophrenia (reviewed in Meyer, 2011).

11.4. Alternative treatments

Other potential avenues for treatment include anti-inflammatory medications such as cyclooxygenase-2 (COX-2) inhibitors (Akhondzadeh et al., 2007; Muller, 2010; Muller et al., 2002) and acetylsalicylic acid (aspirin) (Laan et al., 2010). COX-2 is an important and selective mediator of inflammation in the periphery as well as the brain. Ablation of COX-2 expressing neurons in the forebrain has been demonstrated to elicit neuroprotective effects and reduce inflammation after seizure (Serrano et al., 2011). COX-2 inhibitors, such as celecoxib, added as an adjunctive therapy to antipsychotic treatment, have been demonstrated to greatly improve the total score on the Positive and Negative Syndrome Scale (PANSS) in patients with schizophrenia after 5 weeks (Muller et al., 2002) or 8 weeks (Akhondzadeh et al., 2007) of treatment. While celecoxib has been associated with cardiovascular complications (Solomon et al., 2005, 2006), other more cardioprotective and non-selective COX inhibitors, such as aspirin, may also exert potentially beneficial effects (Hayden et al., 2002). Aspirin is a nonsteroidal anti-inflammatory drug shown to non-selectively inhibit both COX-1 and COX-2 enzymes (Laan et al., 2010). Furthermore, when co-administered with antipsychotic treatment, aspirin has been shown to reduce symptoms of schizophrenia over a period of 3 months, as measured by PANSS, and was shown to be more effective in patients with high anti-inflammatory cytokine levels (Laan et al., 2010). While the authors of this study agree that the reduction in PANSS scores after celecoxib treatment is more profound than after treatment with aspirin, more investigation into the long-term effects of aspirin is needed.

Antibiotics, such as minocycline, have been reported to reduce psychotic symptoms in patients with schizophrenia (Miyaoka et al., 2007). Minocycline has also been shown to positively affect cognitive function and negative symptoms (Levkovitz et al., 2010). Minocycline has been postulated to have an anti-inflammatory effect (Chu et al., 2007) and can interfere with activation of microglia (Hashimoto, 2008). Medicinal plants containing bioactive compounds such as polyphenols, flavonoids, saponins, glucosides, and alkaloids

have also been shown to disturb viral propagation (reviewed in Wang et al., 2006). More specifically, flavonoids have been demonstrated to exert an anti-influenza effect (Parker-Athill et al., 2009; Fatemi, 2009; Liu et al., 2008; Nagai et al., 1995).

12. Conclusions

There is now considerable experimental and clinical evidence to show the significant risks of prenatal infection/inflammation as triggers for development of schizophrenia. Future studies to prevent and/or mitigate these insults, are needed to reduce the risks of developing certain types of psychotic disorders.

Acknowledgments

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Abbreviations

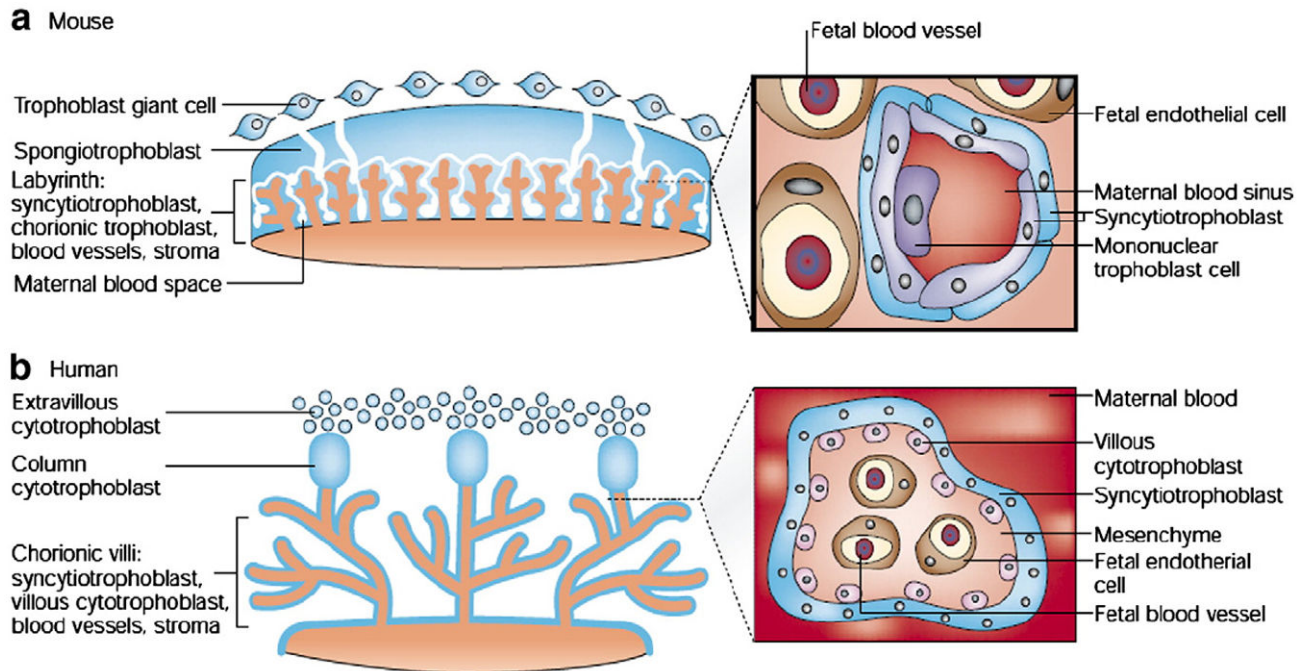|	
IgG	immunoglobulin
PolyI:C	polyriboinosinic polyribocytidilic acid
IL	interleukin
sIL-R	soluble IL-receptor
TNF	tumor necrosis factor
TGF	transforming growth factor
LPS	lipopolysaccharide
TLR	toll-like receptor
CMV	cytomegalovirus
HSV	herpes simplex virus

Fig. 1.

a) Structure of the mouse placenta. The inset details the fetal–maternal interface in the labyrinth. b) Structure of the human placenta. The inset image shows a cross-section through the chorionic villus; trophoblast-derived structures (blue) and mesoderm-derived tissues (orange). The inset images illustrate the number and type of cell layers between the maternal and fetal blood. doi:10.1038/35080570.

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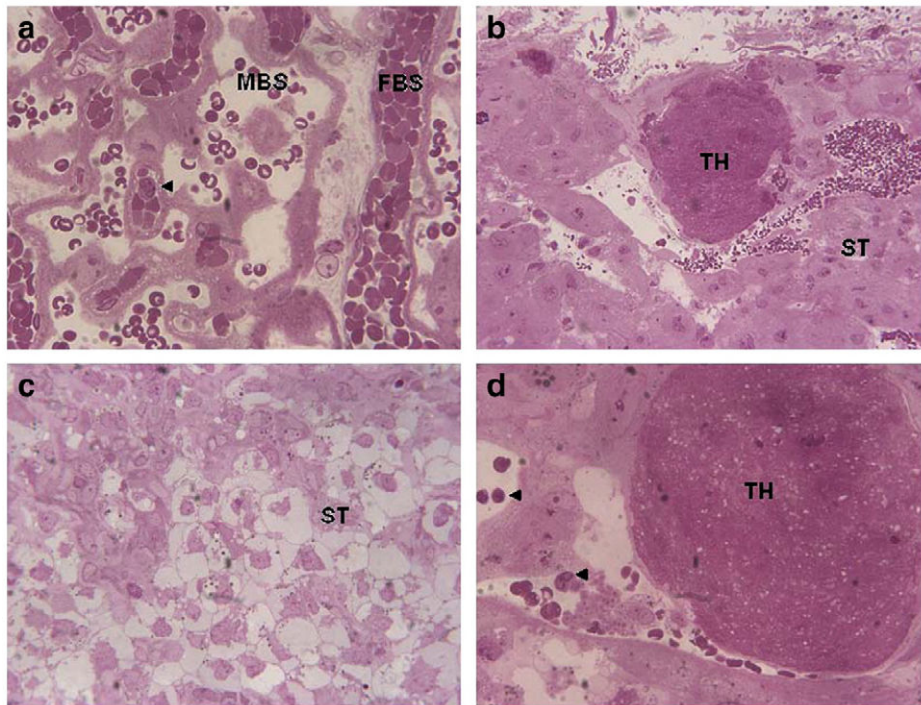
Fig. 2.
Placental abnormalities following prenatal viral infection. a. labyrinth zone of placenta (60×) from sham-infected dam showing fetal blood space (FBS) and maternal blood space. Arrow points to an inflammatory cell. b. Junctional zone of placenta (20×) from infected dam showing presence of thrombosis (TH). ST, spongiotrophoblast cells. c. Junctional zone of placenta (40×) from infected dam showing disorganization of ST cells. d. Junctional zone of placenta (60×) from infected dam showing presence of TH and inflammatory cells (arrows). Reprinted from Neuropharmacology, Fatemi, S.H., Folsom, T.D., Rooney, R.J., Mori, S., Kornfield, T.E., Reutiman, T.J., Kneeland, R.E., Liesch, S.B., Hua, K., Hsu, J., Patel, D.H., The viral theory of schizophrenia revisited: Abnormal placental gene expression and structural changes with lack of evidence for H1N1 viral presence in placentae of infected mice or brains of exposed offspring, 2012, with permission from Elsevier.

Table 1

Involvement of certain genes in schizophrenia, neuroprogression, and the viral model.

Gene name	Involvement in schizophrenia	Involvement in neuroprogression	Involvement in viral model
Fyn proto-oncogene (Fyn)	↑ mRNA and protein in PFC (Ohnuma et al., 2003); SNPs correlat ed with performance on the Wisconsin Card Sorting Test (Rybakowski et al., 2007)	Apoptosis (Chen et al., 2011; Saminathan et al., 2011), hypoxia (Garcia-Roman et al., 2010), inflammation (Smyth etal., 2011)	↑ in E7 virally infected placental tissue (Fatemi et al., 2012)
Quaking (Qk)	↓ mRNA in cortex and hippocampus (Haroutunian et al., 2006); ↓ mRNA in white matter (McCullumsmith et al., 2007)	Apoptosis in oligodendrocytes (Pilotte etal., 2001)	↑ in E7 virally infected placental tissue (Fatemi et al., 2012)
Regulator of G-protein signaling 4 (RGS4)	Associated with depression in schizophrenia (Rethelyi et al., 2010); Polymorphisms (Lane etal., 2008)	Hypoxia (Schmidt-Kastner et al., 2006)	↓ in E16 infected hippocampus at P0 and P14 (Fatemi et al., 2009b)
Semaphorin-3A (Sema3a)	↑ in cerebellum (Eastwood et al., 2003)	Apoptosis (Guttmann-Raviv etal., 2007)	↑ in E18 infected hippocampus at P0 (Fatemi et al., 2008a)
Transferrin receptor 2 (Trfr2)	↓ mRNA in white matter (McCullumsmith et al., 2007); Polymorphisms in Transferrin gene (Qu etal., 2008)	Protection against apoptosis (Lesnikov et al., 2008)	↑ in E18 infected cerebellum at P0 (Fatemi et al., 2008a)

Table 2

Effect of oseltamivir on litter size, weight of dams, weight of pups, and brain weight at birth following E16 infection with H1N1.

	−E16C	−E16V	+ E16C	+ E16V
Wt. of dams at sacrifice (g)	27.42 ± 0.98	25.85 ± 1.21	26.0 ± 1.15	26.0 ± 1.82
Litter size	7.21 ± 1.49	6.28 ± 1.49	6.85 ± 1.95	5.85 ± 2.11
Wt. of pups P0 (g)	1.40 ± 0.07 (n = 11)	1.45 ± 0.13 (n = 11)	1.36 ± 0.12 (n = 11)	1.44 ± 0.14 (n = 7)
Brain wt. at P0 (g)	0.086 ± 0.009 (n = 11)	0.11 ± 0.27[*] (n = 11)	0.085 ± 0.009 (n = 11)	0.081 ± 0.011 (n = 7)

(−) in absence of oseltamivir; (+) in presence of oseltamivir (dose = 20 mg/kg/day), oral gavage (o.g.); C = control, V = virally exposed;

[*] = p<0.05.