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PRENATAL INFECTION, MATERNAL IMMUNE ACTIVATION, AND RISK FOR SCHIZOPHRENIA

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Abstract

A body of epidemiological literature has suggested an association between prenatal infection, subsequent maternal immune activation (MIA), and later risk of schizophrenia. These epidemiological studies have inspired preclinical research using rodent and primate models of prenatal infection and MIA. The findings from these preclinical studies indicate that severe infection and immune activation during pregnancy can negatively impact offspring brain development and impair adult behavior. This review aims to summarize the major epidemiological and preclinical findings addressing the connection between prenatal infection and immune activation and later risk of developing schizophrenia, as well as the more limited literature addressing the mechanisms by which this gestational insult might affect offspring neurodevelopment. Finally, directions for future research will be discussed.

Keywords

Prenatal infection; Maternal immune activation; Schizophrenia; Polyinosinic-polycytosinic acid (Poly IC); Cytokines; Neurodevelopment

Introduction

In recent decades it has become increasingly accepted that schizophrenia is a disorder of neurodevelopment [1]. Accordingly, many research studies relevant to schizophrenia have focused on understanding how genes or early environmental factors affect brain maturation. A body of epidemiological literature has suggested an association between prenatal infection, subsequent maternal immune activation (MIA), and later risk of schizophrenia [2,3]. These epidemiological studies inspired preclinical research using rodent and primate models of prenatal infection and MIA. The findings from these preclinical studies indicate that severe infection and immune activation during pregnancy can negatively impact offspring brain development and impair adult behavior [4,5]. This review aims to summarize the major epidemiological and preclinical findings addressing the connection between prenatal infection and immune activation and later risk of developing schizophrenia, as well as the more limited literature addressing the mechanisms by which this gestational insult

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might affect offspring neurodevelopment. Finally, directions for future research will be discussed.

Epidemiological studies

Early ecological studies identifying prenatal infection as a risk factor for schizophrenia used naturally occurring epidemics to query an association between *in utero* exposure to infection and later development of this psychiatric disorder (for review, see [2]). In Finnish, Danish and English populations, the occurrence of schizophrenia was higher among offspring *in utero* during influenza epidemics than among offspring *in utero* during comparable non-epidemic periods [6–9]. However, the effect sizes for these associations were small and the findings were not consistently replicated [10–13]. Significant heterogeneity in the results from these studies may have reflected the difficulty of accurately classifying exposure status. In particular, misclassification of exposure was likely to occur because all offspring who were *in utero* during an epidemic were classified as `exposed' to infection, when in reality only a modest percentage of those mothers actually contracted influenza [2]. This type of misclassification is likely to have biased the results towards the null.

To address some of the limitations of these ecological studies, subsequent epidemiological studies utilized population-based birth cohorts where data on infection status was available for each of the individual pregnancies. In some of these cohorts, infection verification came from analysis of medical records, while in others, infection status was determined serologically—either from archived maternal serum samples or from neonatal filter paper blood spots. The cumulative results of both of these types of studies have been reviewed extensively elsewhere [2], so this review will focus primarily on results from cohorts with archived biological specimens.

Most of the serological studies to date have come from 3 cohorts: 1) The Child Health and Development Studies (CHDS) cohort composed of all the births from 1959–1967 in Alameda County, California, 2) The Collaborative Perinatal Project (CPP) cohort comprised of multiple birth cohorts born between 1959 and 1967 based in different regions of the United States and 3) A Danish national birth cohort comprised of all pregnancies in that country since 1981. Maternal serum samples were archived during the CPP and CHDS pregnancies, while the Danish cohort used filter paper blood spots taken from the neonates to infer maternal exposure status.

In all of these studies, seropositivity for a particular infection was defined as having an IgG antibody titer against that pathogen greater than a given cut-off value. In one study, based on the CHDS birth cohort, influenza antibody levels above a threshold value were shown to correlate with acute infection as measured by seroconversion using a comparison of IgG levels across multiple blood draws [14], but this kind of validation was not performed in any of the other studies. Thus, seropositivity reflects a heightened immune response to a particular pathogen, but it does not necessarily indicate a recent time frame of exposure. As a result, studies that are based on serologic measures of infection, and not validated against infection during pregnancy, do not readily distinguish between the effects of acute versus chronic infection during pregnancy.

Studies from all three cohorts found an increased risk of psychosis or schizophrenia among offspring whose mothers were seropositive for a number of different pathogens during pregnancy. A nested case-control study drawn from the CHDS cohort demonstrated that serologically documented exposure to influenza during the first half of pregnancy was linked to a 3-fold increase in risk of developing schizophrenia; for exposure occurring in the first trimester, the increase in risk was 7-fold [14]. In the CHDS cohort, offspring of women with the highest level (upper decile) of IgG antibody to *Toxoplasma gondii* had a 2.6-fold

increase in risk of developing schizophrenia [15]. This association was replicated in a Danish cohort that used neonatal levels of *Toxoplasma* IgG measured on filter paper blood spots to infer prenatal maternal *Toxoplasma* IgG levels; subjects with IgG levels in the upper quartile were at a 1.78-fold increased risk of developing early-onset schizophrenia [16]. In the CPP Rhode Island cohort, a small case-control study demonstrated that offspring with affective or non-affective psychoses had mothers with significantly elevated levels of serum IgG antibody against HSV-2 at term [17]. This finding was subsequently replicated in a larger case-control study drawn from three different CPP sites (Boston, Philadelphia and Providence) where offspring of mothers with elevated levels of serum IgG antibody against HSV-2 at term were at a 1.6-fold increased risk of developing these disorders [18].

There were also some discordant findings among these three different birth cohorts. For example, the association between prenatal seropositivity for HSV-2 and increased risk of schizophrenia was not replicated in the CHDS cohort [19]. Additionally, the CPP analysis that showed elevated levels of HSV-2 antibody in the maternal serum of mothers of schizophrenia patients failed to detect an increase in IgG antibody to *Toxoplasma gondii* [17], as was seen in the CHDS and Danish birth cohort studies described above. Regarding HSV-2, the different studies may have yielded divergent findings because of differences in the populations assessed as well as the outcomes measured. HSV-2 was less prevalent in the CHDS cohort than in the CPP cohort, reducing the CHDS study's power to detect an association of HSV-2 exposure with later development of schizophrenia. Additionally, the outcome in the CPP studies was the development of either affective or non-affective psychosis, while in the CHDS study, the outcome was the development of schizophrenia or schizoaffective disorder. The broader inclusion criteria in the CPP studies may have increased their power to detect an association between HSV-2 exposure and offspring development of these disorders [2].

Findings from birth cohort studies without biological markers of infection were also mixed. A small cohort study reported that offspring of mothers with rubella exposure documented in the medical record and maternal sera had a marked increase in the risk of developing schizophrenia [20]. A study of Danish births between September 1, 1959 and December 31, 1961 in Copenhagen found that offspring of women with a documented history of bacterial infection during the first or second trimester of pregnancy were at an increased risk of developing schizophrenia (1^{st} trimester OR: 2.53; 2^{nd} trimester OR: 1.17) [21]. However, this same study failed to find an association between schizophrenia and prenatal exposure to viral infection as had been previously described [14,17,18]. Finally, two cohort studies of offspring *in utero* during the 1957 influenza epidemic in England and Ireland, whose mothers were documented to have been infected during the pregnancy, found no association with increased risk for developing schizophrenia [22,23]. These two studies were limited, however, by small sample sizes and retrospective self-reports of influenza during pregnancy.

Several recent studies also suggest that prenatal infection may alter aspects of brain function relevant to schizophrenia. In the Developmental Insult and Brain Anomalies and Schizophrenia Study (DIBS), based on the schizophrenia and control offspring of the CHDS birth cohort, Brown and collaborators showed that prenatal exposure to influenza or *Toxoplasma gondii* was associated with impairment in executive function in adult patients with schizophrenia [24]. In a second study from the DIBS, exposure to maternal genital-reproductive infections was related to verbal and neuromotor deficits in adult schizophrenia patients [25]. Moreover, maternal infection was associated in that cohort with increased size of the cavum septum pellucidum, a replicated neuromorphologic finding in schizophrenia that has embryologic origins [26].

Ongoing studies which capitalize on data from large national registries, such as the Finnish Prenatal Study of Schizophrenia (FiPS-S), will attempt to replicate and expand on these findings. The large sample size of these birth cohorts will provide the necessary power to address additional important questions, such as whether there is an interaction between infection and other genetic or environmental risk factors. Studies addressing 1) whether prenatal infection is associated with increased risk specifically for schizophrenia, as opposed to other psychiatric disorders, and 2) whether this happens in a particular sub-population that can be identified, are of critical importance.

Two observations from these epidemiological studies stimulated the hypothesis that it is the maternal immune response stimulated by infection, rather than the specific pathogen, that mediates the effect on offspring risk of this disorder. First, an association between maternal infection and later risk of psychopathology in offspring has been found for several different pathogens with different clinical characteristics [2]. Second, several studies found that elevated levels of cytokines during pregnancy were associated with increased risk of the offspring developing schizophrenia later in life. Specifically, the mothers of offspring who later went on to develop schizophrenia had significantly elevated levels of interleukin-8 (IL-8) in the second and early third trimester [27], and tumor necrosis factor alpha (TNFα) in the third trimester [28], relative to the mothers of offspring who did not develop schizophrenia. Moreover, maternal IL-8 levels were correlated with cerebrospinal fluid (CSF) ventricular volume, the most widely replicated neuromorphologic finding in schizophrenia [29]. The MIA theory provided the first suggestion of a mechanism, albeit a broad one, by which prenatal infection might be acting to affect the developing neonatal brain. The epidemiological evidence implicating prenatal infection, and subsequent MIA, as risk factors for schizophrenia inspired preclinical studies to test the causality of this association and investigate underlying neurobiological mechanisms in animal models.

Preclinical studies

The earliest animal model of prenatal infection was one in which pregnant mice were directly infected with influenza virus via intranasal infusion [30,31]. The adult offspring of influenza-injected mothers demonstrated several behavioral abnormalities thought to be analogous to behavioral impairments found in adult patients with schizophrenia [31]. Most prominently, these mice showed deficits in prepulse inhibition (PPI), a measure of sensory motor gating that is also impaired in patients with schizophrenia. These measures were normalized by acute administration of antipsychotics. Additionally, these mice showed profound increases in anxiety, manifested as less time spent in the center of an open field task [31].

Subsequently, investigators injected pregnant mice with the viral mimic, polyinosinic-polycytosinic acid (Poly IC), or the bacterial mimic, lipopolysaccharide (LPS), to test the effect of MIA in the absence of pathogen on adult offspring behavior. By binding to Toll-like receptors 3 and 4, respectively, Poly IC and LPS stimulate many aspects of the immune response initiated by normal infection, such as production of TNFα, interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) [32,33]. Intriguingly, adult offspring of immune-activated mothers displayed deficits in pre-pulse inhibition and increased anxiety, similar to the adult offspring of influenza-injected mothers (for review see [5]). Behavioral characterization of these Poly IC and LPS offspring has been extensive and abnormalities in cognitive and executive tasks, such as the Morris water maze, reversal learning and latent inhibition, have also been described [5]. Furthermore, adult offspring of mothers administered the cytokine, IL-6, also showed deficits in pre-pulse inhibition, latent inhibition and social behavior [34]. These behavioral findings provided support for the hypothesis that MIA is the critical factor

mediating the effect of prenatal infection on some of the behavioral abnormalities associated with risk for developing schizophrenia.

Neurobiological mechanisms of behavioral abnormalities

Both epidemiological and preclinical evidence suggest that prenatal infection, and subsequent MIA, can result in behavioral impairments in adult offspring. But what are the neurobiological substrates underlying these behavioral abnormalities? To address this question, substantial preclinical work in rodents has focused on characterizing adult brain abnormalities elicited by MIA. For a detailed analysis of this literature, the interested reader is directed to a recent review, which summarizes the behavioral, morphological, neurochemical and molecular changes seen in response to LPS, Poly IC and influenza administration [5].

Similar to the wide variety of brain abnormalities reported in the schizophrenia literature, MIA in rodents is associated with a panoply of changes in the brains of the adult offspring. Morphologically, both prenatal LPS and Poly IC have been linked to decreased white matter [35,36], decreased hippocampal neurogenesis [32,37] and increased microglial activation in the brain [38]. Neurochemically, there is evidence that several major neurotransmitter systems are affected. Alterations in dopaminergic systems have been widely reported but are not consistent with regard to whether they report loss of dopaminergic neurons and dopaminergic innervation to the nucleus accumbens, striatum and prefrontal cortex [39–43] or an increase in dopaminergic neuron number and dopamine release [44,45]. Alterations in glutamatergic systems have also been reported including an increased ratio of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) to N-Methyl-D-aspartate (NMDA) receptor currents in the hippocampus [46,47], decreased expression of the NMDA receptor subunit, NR1 [43], and deficient induction of hippocampal long-term potentiation (LTP) [46,48]. Several studies have found evidence that prenatal LPS or Poly IC results in decreased serotonin in various regions of the brain [49–52]. Finally, alterations in γ-aminobutyrate (GABAergic) systems have also been reported. These include increased $GABA_{A\alpha 2}$ receptors in the ventral dentate and basolateral amygdala and a reduction in parvalbumin and reelin-expressing GABAergic interneurons in the medial prefrontal cortex and hippocampus [43,53,54]. It is worth noting that most of the evidence of changes in these neurotransmitter systems comes from studies using static measures, such as quantification of immunohistochemically-detected markers. Consequently, it is difficult to predict the functional consequences of these observations. The functional studies that have been conducted thus far are generally consistent with increased dopamine release in the striatum [44,55], decreased NMDA-mediated glutamatergic transmission [46,47] and decreased GABAergic transmission in the hippocampus [53] - results consistent with some of the functional abnormalities believed to be occurring in schizophrenia.

The fact that a substantial number of the brain changes observed in adult MIA offspring parallel abnormalities found in adult patients with schizophrenia indicates that this animal model may be a useful tool to ultimately test a causal link between MIA and neurobiological correlates of schizophrenia. One approach that aids in establishing causality is to demonstrate that behavioral alterations in MIA offspring are rescued following correction of the brain abnormalities. Animal models may also support causality by identifying plausible developmental mechanisms by which prenatal exposure to infection early in life leads to long-lasting changes in brain development observed in schizophrenia. These approaches serve as a useful complement to the epidemiologic studies with regard to drawing such causal inferences.

Developmental origins of neurobiological abnormalities

Intriguingly, many immune signaling proteins also play a role in central nervous system development and plasticity (for review see, [56,57]). During development, cytokines such as leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), members of the epidermal growth factor (EGF) family, neuregulin 1 (NRG1) and transforming growth factor β (TGFβ) have been shown to affect neurogenesis and neuronal differentiation [56]. Furthermore, the chemokine, CXCL12 (also called SDF-1), has been shown to be critical for cell migration as well as axon guidance and path-finding [58–60]. Regarding plasticity, the inflammatory cytokine, TNFα, has been found to be important for modulating glutamatergic synaptic strength and also for homeostatic synaptic scaling in response to changes in network activity [61,62]. The complement protein, C1q, has been shown to be critical for efficient synaptic pruning, along with other immune signaling molecules, such as those of the major histocompatibility complex 1 (MHC-1) [63,64]. These are just a few examples of immune signaling molecules that play crucial roles in normal neuronal development and plasticity.

Prenatal infection may result in abnormal levels of these immune signaling molecules within the fetus (either via direct transfer from the maternal sera or by induction of the fetal immune system), which in turn result in improper signaling within the developing brain. Several lines of evidence support this hypothesis. First, as previously mentioned, elevated levels of maternal cytokines during human pregnancy are associated with increased risk of the offspring developing schizophrenia [27,28]. Second, preclinical studies have indicated that MIA results in greatly increased levels of cytokines in the maternal serum and the placenta [32,65]. Finally, in one study, injection of the cytokine, IL-6, is sufficient to recapitulate several of the behavioral abnormalities associated with prenatal administration of Poly IC [34]. In that same study, blocking maternal IL-6 production prevented the development of certain behavioral abnormalities in the MIA offspring. While these results provide compelling evidence that maternal cytokine induction is critical for mediating the effects of prenatal MIA on the developing fetal brain, it remains unresolved if, when or where there is a corresponding increase in cytokines in the fetal brain. Several studies have shown an increase in cytokine messenger ribonucleic acid (mRNA) in the fetal brain within twenty-four hours following prenatal LPS or Poly IC, but at the protein level results are more equivocal (for review see [5]). As baseline cytokine levels are extremely low in the brain, and all studies to date have examined whole brain rather than a particular region of interest, it may not be possible to detect meaningful regional increases in cytokine levels with the resolution afforded by the methodology that has been employed. However, it is of great importance to determine whether immune signaling proteins are induced in the developing fetal brain following MIA, and if they are, their specific time frame of elevation. In particular, it is necessary to address whether prenatal infection acutely and transiently increases immune signaling proteins in certain regions of the fetal brain, or if there is a more prolonged effect, perhaps transduced by secondary effects on fetal immune system function.

Gene-environment interactions

Clearly, the prevalence of infection during pregnancy is much higher than that of schizophrenia. Thus, it is a pressing question whether there is a particular sub-group of people at higher risk of developing the disorder following exposure to prenatal infection. For example, prenatal infection may be most deleterious among people who already bear a genetic predisposition towards developing the disease. This is supported by results from the only epidemiological study to date that has tested the interaction between prenatal exposure and genetic risk in a human cohort. Clarke and collaborators found a synergistic interaction between prenatal exposure to pyelonephritis and family history of psychosis on the

development of schizophrenia [66]. This finding awaits replication from a study of a birth cohort large enough to have the necessary statistical power. Additionally, several recent preclinical studies have attempted to address this gene-environment question in rodents by modeling prenatal infection on a background of a genetic risk for schizophrenia.

In one study, mice with and without a mutation in the *DISC1* gene - one of the genes that has been well-replicated as associated with risk for developing schizophrenia - were exposed to prenatal Poly IC [67]. The authors found that prenatal Poly IC interacted with mutant *DISC1* genotype to produce increased anxiety and helplessness and decreased social behavior in the offspring. Additionally they found interactive gene-environment effects on hippocampal dendritic arborization as well as cytokine levels in the fetal brain. In another study, prenatal Poly IC exposure was coupled with genetic deficiency in *NURR1* - a gene that is crucial for normal dopaminergic development [68]. Intriguingly, the authors found additive effects of Poly IC and Nurr1 deficiency on spontaneous locomotor behaviors and prepulse inhibition, as well as interactive effects on latent inhibition and attentional impairments. Furthermore, they showed that there were both independent and synergistic effects of each of these manipulations on aspects of the dopaminergic system in both the striatum and prefrontal cortex, potentially underlying some of the behavioral abnormalities in these mice. This `multi-hit' mechanism, whereby several factors that target some of the same vulnerable neural substrates can act together to enhance neurobiological and behavioral abnormalities, could potentially explain why prenatal infection increases risk for schizophrenia in some people but not others.

Finally, in a meta-analysis of seventeen schizophrenia genome-wide association studies (GWAS), it is notable that associations between polymorphisms in the major histocompatibility complex (MHC) and schizophrenia retained statistical significance following correction for multiple comparisons. This represented one of the few genetic associations that persisted in this analysis [69]. The MHC locus encodes several genes that are involved in the innate and adaptive immune systems, and as noted above, MHC-1 is known to be important for synaptic pruning during neural development [64]. Additionally, in candidate gene studies, polymorphisms in several other immune signaling proteins including interleukins-2, 3, 4, 6 and 10 as well as nuclear factor κ-light-chain-enhancer of activated B cells (NFκB), have been associated with increased risk of developing schizophrenia [70–74]. These studies suggest that an immune-related basis to schizophrenia might be genetically, as well as environmentally, encoded. Moreover, people with specific polymorphisms or mutations in immune system-related genes might be more susceptible to the deleterious consequences of environmentally-induced maternal immune activation.

Conclusions and future research

Cumulatively, evidence from epidemiological and preclinical studies to date suggests that prenatal infection, and subsequent MIA, can affect offspring neurodevelopment in a way that may predispose toward later development of psychopathology. The heterogeneity in the results from epidemiological studies likely reflects both methodological limitations and the natural variability in the intensity, as well as the effects of, the exposure. Ideally, in our view, exposure to infection should be documented both serologically and in the medical history in each individual pregnancy, with all resulting offspring then followed forward until the age of onset. If these types of records could be obtained from large birth cohorts, it would be possible to begin to attempt to parse out sources of meaningful variability in these studies including differences in the type and intensity of the infection, as well as the interactions of the exposure with other risk and resilience factors. Preclinical studies, which offer the advantage of tight control of exposure and background variables, have provided evidence that intense, abnormal activation of the immune system during the prenatal and/or

early postnatal period can affect neurodevelopment. These findings dovetail with the elegant body of work demonstrating crucial roles for immune signaling proteins in normal brain development. These preclinical studies may then be able to suggest important variables that may modify the effects of abnormal immune exposure, which should be examined in epidemiological studies of humans. Most importantly, we believe that these preclinical studies should be used to examine mechanisms by which prenatal infection and MIA affect offspring neurodevelopment, in order to identify potential molecular targets for prevention and treatment of schizophrenia.

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