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Research report

Immune involvement in schizophrenia and autism: Etiology, pathology and animal models

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ABSTRACT

There is increasing evidence of immune involvement in both schizophrenia and autism. Of particular interest are striking abnormalities in the expression of immune-related molecules such as cytokines in the brain and cerebral spinal fluid (CSF). It is proposed that this represents a permanent state of brain immune dysregulation, which begins during early development. One possibility is that maternal infection, a known risk factor for schizophrenia and autism, sets this immune activation in motion. Several animal models are being used to investigate this hypothesis. There is also recent evidence that, among schizophrenic subjects, those associated with maternal infection display a distinctive pathology, which suggests that diverse causes for this disorder may explain some of its heterogeneity. The human and animal results related to immune involvement suggest novel therapeutic avenues based on immune interventions.

1. Immune dysregulation in schizophrenia and autism

Both long standing as well as recent, novel findings point to immune dysregulation in schizophrenia and autism. There have been many reports of abnormalities in peripheral immune cells, as well as associations between variants of genes for cytokines, their receptors and HLA in these disorders. In addition, numerous epidemiological studies have associated schizophrenia and autism with autoimmunity and allergies [1–6]. The meaning of these associations is not yet clear, but they suggest that immune status is relevant for these mental disorders. Most important is the recent evidence of dysregulation of immune-related genes in the schizophrenic brain, and striking microglial and astrocyte activation as well as cytokine up-regulation in the autistic brain and CSF [7–13]. It is worth emphasizing that many different types of assays were used to come to this conclusion: histology, ELISA, PCR and microarray. Moreover, independent laboratories have verified the initial findings. The fact that this dysregulation is found in the adult brain indicates that this is a permanent state. Since this dysregulation is also found in children (in autism), the suggestion is that immune dysregulation in the brain begins early and is maintained by a positive feedback mechanism. Major research questions include, what initiates this subclinical, inflammatory-like state, how is it maintained, and does it influence behavior in the adult as well as modify connectivity during development?

2. Maternal infection is an immune-related risk factor associated with schizophrenia and autism

A leading candidate for initiating immune changes early in development is maternal infection. Following the important work of Mednick, over 25 studies have analyzed schizophrenia incidence following influenza epidemics, and the majority have found an increased incidence among exposed offspring. Although these early studies were critical in highlighting this risk factor, their retrospective design had drawbacks. Brown and colleagues [14] used a prospective approach to examine the medical records of over 12,000 pregnant women, and found that maternal respiratory infection increases the risk for schizophrenia in the offspring 2-fold. A more recent prospective study found an incidence rate ratio of 8 for maternal influenza infection [15]. Because of the high prevalence of influenza infection, Brown et al. estimate that 14–21% of schizophrenia cases would not have occurred if maternal infection had been prevented. This inference is further supported by an association between schizophrenia in the offspring and elevated cytokines or anti-influenza antibodies in archived maternal serum [16,17]. Imaging and cognitive testing has also been done on this cohort of patients, and a particular structural abnormality (enlarged cavum septum pellucidem) and a type of memory deficit are associated with the schizophrenic offspring of infected mothers rather than the schizophrenic offspring of mothers for which there was no evidence of infection [18]. This intriguing finding suggests that it may be possible to separate schizophrenia cases according to causes or risk factors, which could be relevant for future individualized therapies.

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The association of schizophrenia with maternal infection is not specific to influenza, however, as there is similar serological evidence linking maternal rubella, toxoplasma and genital/reproductive infections with schizophrenia [14,19]. Moreover, new findings have revealed an association between elevated risk for schizophrenia and maternal bacterial infection [20]. Maternal infection may also play a role in the pathogenesis of autism. Ciaranello and Ciaranello [21] concluded that, "the principal non-genetic cause of autism is prenatal viral infection". For instance, prenatal exposure to rubella or cytomegalovirus greatly increases the risk for autism [22,23]. What these various insults have in common is activation of the maternal immune response [19,24,25].

The relevance of this growing literature is, first, that the immune status of the mother and fetus is presumably important for their responses to maternal infection. This would help explain the association of autism and schizophrenia with autoimmune disease and allergy, particularly in the mother. Second, maternal infection could alter the immune status of the fetal brain. In addition, since the placenta serves as the source of hematopoietic stem cells for the fetus [26], maternal infection could also permanently alter the peripheral immune system of the fetus. It is worth noting that pathology in the placenta has recently been associated with autism [27].

3. Animal models of maternal infection – influenza

Since maternal influenza infection is a well-established risk factor for schizophrenia, it was of interest to characterize its effects in an animal model. Respiratory infection with human influenza virus in pregnant mice at mid-gestation results in specific histological abnormalities in the hippocampus and cortex of the neonatal offspring [28,29] (Table 1). These include layer- and region-specific changes in the expression of the presynaptic marker SNAP-25, as well as in nNOS and reelin. Pyramidal cells are more densely packed, which is reminiscent of schizophrenia [30]. Young and adult offspring also display a spatially restricted deficit in Purkinje cells [31], a neuropathology that is commonly found in autism [32,33]. In addition, adult mice born to infected mothers display a striking abnormality in neuronal migration to layer 2/3 in the cortex (L. Shi, N. Malkova and P.H. Patterson, unpublished). This migration defect is very similar to that observed when DISC1 (disrupted in schizophrenia 1, a candidate gene for schizophrenia) is downregulated in the mouse fetus [34].

In addition, the offspring of influenza infected mothers display a series of behavioral abnormalities that are relevant to both schizophrenia and autism, including deficits in social interaction, prepulse inhibition (PPI), and open field and novel object exploration [35] (Table 1). Transcription is altered in the brains of these offspring, as is the level of serotonin in the cerebellum [36–38].

4. Animal models of maternal infection – peridontal bacteria

Bacterial infections have recently been associated with schizophrenia [20], and obstetrical complications caused by such infections increase the risk for schizophrenia (e.g., [15]). Intrauterine infections are prevalent among women who give birth prematurely, and very low birth weight is correlated with perinatal mortality and neonatal morbidity, including serious neurological disorders. Among the microorganisms isolated from the preterm placenta are gram-negative bacteria that are known to be involved in periodontal disease, *F. nucleatum* and *P. gingivalis*. Moreover, epidemiological evidence links periodontal disease with premature delivery [39]. In a pregnant mouse model, I.V. injection of *F. nucleatum* results in premature delivery and stillbirth [40], and the infection is confined to the uterus. In an alternative mouse model using *P. gingivalis*, systemic induction of maternal immune activation (MIA) leads to fetal growth restriction in every litter, but not in every fetus. Importantly, *P. gingivalis* DNA is found only in the placentas of affected fetuses, and those placentas show elevation of pro-inflammatory and reduction of anti-inflammatory cytokines [41]. These results link cytokines with fetal morbidity, and they highlight the importance of heterogeneity among placentas within the same uterus. Placental status is a key issue in interpreting genetic heritability in twin studies of schizophrenia [19].

5. Animal models of maternal immune activation – poly(I:C)

An alternative to infection is to induce a maternal anti-viral inflammatory response using the synthetic dsRNA, poly(I:C), in the absence of pathogen. Poly(I:C) acts through the toll-like receptor (TLR)3, and its injection in pregnant rats or mice is sufficient to cause all of the behavioral and histological abnormalities assayed for thus far in the offspring of maternal influenza infected mothers [31,35,42]. The poly(I:C) model of MIA has been widely adopted and many results have been reproduced, including deficits in PPI, social interaction, latent inhibition, working memory and novel object exploration, altered eyeblink conditioning, as well as increased amphetamine-induced locomotion and enhanced reversal learning (Table 1) [35,42–51]. Adult offspring also display increased levels of $GABA_A$ receptor $\alpha 2$ immunoreactivity [52] and dopamine hyperfunction [48], as seen in schizophrenia, as well as a delay in hippocampal myelination [53]. Importantly, post-pubertal emergence of the hallmark structural abnormality in schizophrenia, ventricular enlargement, is also observed in poly(I:C) MIA [54]. Other neuropathological and neurochemical deficits identified in the polyI:C model include reduced NMDA receptor expression in hippocampus and reduced numbers of reelin- and parvalbumin-positive cells in prefrontal cortex [55] and reduced dopamine D1 and D2 receptors in prefrontal cortex and enhanced tyrosine hydroxlyase in striatal structures [56]. These changes are all clearly relevant to schizophrenia.

The poly(I:C) model is also being used for testing therapeutics. While it has been shown previously that acute antipsychotic drug administration can block some of the behavioral deficits in influenza infected and poly(I:C) MIA [35,43,48], Piontkewitz et al. [54] and Meyer et al. [57] tested such drugs in immature MIA offspring, before the onset of behavioral abnormalities and ventricular enlargement. Treatment for a week, many weeks before behavioral testing prevented the abnormalities and the ventricular enlargement. This encourages the idea that antipsychotic drug treatment of high-risk subjects is worthy of further investigation. While the classic action of these drugs is blocking the D2 dopamine receptor, it is also worth noting in the present context that many of them have also been shown to influence cytokine expression [58,59].

6. Animal models of maternal immune activation – LPS

To mimic bacterial infection, another method of MIA is used. Pregnant mice, rats, rabbits or ewes are injected (intrauterine, I.P. or I.V.) with lipopolysaccharide (LPS), which acts through TLR4. Some of the same behavioral abnormalities seen in the offspring of poly(I:C)-treated mothers have been observed in the offspring of LPS-treated mothers (Table 1) [24,60–62]. For instance, a severe schedule of LPS administered I.P. causes a PPI deficit in the offspring [63]. Moreover, single or double maternal injections of LPS can cause increased anxiety, deficits in social interaction and learning, and increased amphetamine-induced locomotion in the adult offspring.

Table 1
Behavior and histology outcomes following various types of MIA.

References	Species and treatment	Behavioral findings	Histological findings
[109]	4 mg/kg LPS I.P. E18, 19 rat P8 histology	N.R.	Increased GFAP, decreased MBP; altered microglial staining
[110]	10,000 EU/kg LPS I.P. E10.5 rat Adult histology	N.R.	Fewer TH+ neurons and increased microglial staining in substantia nigra
[63]	1 mg/kg LPS S.C. Alternate days throughout rat pregnancy Adult histology	PPI deficit corrected by antipsychotic drugs	Increased GFAP, MHCII staining of microglia; TH increase in NAC
[66]	2 mg/kg LPS S.C. Daily through rat pregnancy Adult histology	PPI deficit corrected by antipsychotic drugs	DA increased in NAC; DARPP-32 deficit in PFC; increased synaptophysin in PFC and hippocampus
[111]	20–80 μg/kg LPS S.C E15–19 rat (increasing dose schedule)	Increased entries into all arms of plus maze, slips in beam walking test.	N.R.
[44]	50 μg/kg LPS I.P. E18 and 19 rat	Increased amph-induced locomotion, acoustic startle response	N.R.
[112]	0.75–1.0 poly(I:C) I.P. E15 and 16 or E18 and 19	No deficit in PPI	N.R.
[112]	50 or 100 μg/kg LPS I.P. E15 and 16 or E18 and 19	PPI deficit	N.R.
[113]	1 mg/kg LPS I.P E18 rat E20 or P9–30 histology	N.R.	Less MBP, PLP and myelin staining at P9-30; more microglia at E20
[114,115]	0.12 mg/kg LPS I.P. E17 mouse Adult histology	Normal exploration and motor function, mostly normal learning/memory but specific deficits	Smaller, denser neurons in hippocampus; more pyknotic cells in cortex
[30,31,35]	Intranasal influenza E9 mouse Adult histology	PPI, open field, novel object, social interaction deficits	Large adult brain; pyramidal cell atrophy; Purkinje cell deficit
[31,42]	20 mg/kg poly(I:C) I.P. E12 mouse Adult and P11 histology	PPI, LI, open field, social interaction deficits	Purkinje cell deficit
[43,45]	4 mg/kg poly(I:C) I.V. E15 rat Adult histology	LI deficit, enhanced reversal learning, normal water maze, increased amph and MK-801 locomotion	Pyknotic cells in hippocampus; increased KCl-stimulated dopamine release in striatum
[47,52,55,56]	5 mg/kg poly(I:C) I.V. E9 mouse adult histology	PPI, LI, open field, working memory deficits; increased amph-induced locomotion	GABAA receptor increase, no increase in pyknotic cells in hippocampus; reduced reelin+ and parvalbumin+ cells in PFC; reduced D1 and D2 receptors in PFC; enhanced TH in striatum
[48]	5 mg/kg poly(I:C) I.P. Daily E12–17 mouse Adult histology	PPI, open field, working memory deficit, increased amph locomotion	Altered dopamine metabolism in striatum
[51]	4 mg/kg I.V. E15 rat	PPI deficit	N.R.
[116]	20 mg/kg poly(I:C) I.P. E12 mouse	Impaired extinction of conditioned eyeblink response	N.R.

Table 1 (*Continued*)

References	Species and treatment	Behavioral findings	Histological findings
[49]	20 mg/kg poly(I:C) I.P. E12 mouse	normal LTP at Schaffer collateral synapses; reduced frequency and increased amplitude of mEPSCs with increased sensitivity to DA	N.R.

Different rows represent different research groups. Amph, amphetamine; DA, dopamine; GABA, g-aminobutyric acid; GFAP, glial fibrillary acidic protein; I.P, intraperitoneal; I.V., intravenous; MBP, myelin basic protein; NAC, nucleus accumbens; N.R., not reported; PFC, prefrontal cortex; PLP, proteolipid protein; PPI, prepulse inhibition; LI, latent inhibition; LPS, lipopolysaccharide; S.C., subcutaneous; TH, tyrosine hydroxylase.

Also in common with the poly(I:C) findings are observations of brain inflammation, as defined by astrogliosis (enhanced glial fibrillary acidic protein (GFAP) staining) and altered microglial immunostaining [24,61] and PET imaging [64] in young animals. A GFAP increase was also reported for neonatal offspring of influenza infected mothers [65]. Permanent activation of astrocytes and microglia were observed in the adult offspring using a severe maternal LPS protocol [63]. This evidence of inflammatory changes in the brains of offspring of LPS-treated mothers is consistent with the striking findings of immune dysregulation in human autism and schizophrenia. The severe maternal LPS protocol is also able to achieve a permanent inflammatory state in the periphery, with elevated IL-6 in sera of adult offspring [66].

Not covered in the present review is work on direct injection of LPS into the fetus, which was reviewed by Wang et al. [67]. Alternative protocols involving injecting LPS, viruses or cytokines during the early postnatal period have also been well reviewed by others [67–69]. A much broader discussion of a variety of different types of animal models of various features of autism was recently published [70].

7. Maternal immune activation elevates cytokines in the fetal environment

In addition to the alterations in placental cytokines by periodontal infection, there is a significant literature on the cytokines induced in the fetal environment by LPS-induced MIA. It is clear that several cytokines are elevated in the placenta (IL-1β, IL-6, TNFα) and amniotic fluid (IL-6, TNFα) [24,61]. The more difficult and interesting issue is whether cytokines are altered in fetal brain, and significant increases in IL-1β, IL-6, TNFα and IFNγ in fetal brain were found when LPS was delivered into the uterine horn (Table 2) [71].

Similar studies are underway for poly(I:C)-induced MIA, and several of the same cytokines appear to be increased in the fetus (Table 2) [24,61,62,72]. At 6 h post-injection, IL-1β, IL-6, IL-10 and TNFα are all significantly increased in fetal brain, as are several IL-6 response genes ([47]; E. Hsiao and P.H. Patterson, unpublished). Cytokine expression in the neonatal brain is also altered by MIA [73]. The induction of pro-inflammatory cytokines and their downstream signaling pathways in the developing brain is of particular interest in the context of the possibility of initiating a positive feedback system of an inflammatory-like state. Indeed, the IL-6-mediated induction of IL-6 mRNA in the fetal brain is an example of such mechanism.

8. The pro/anti-inflammatory cytokine balance mediates MIA effects on the fetus

MIA induces cytokines, but what are their effects on the fetus? Two approaches have been taken towards answering this question: injecting or up-regulating cytokines during pregnancy in the absence of MIA, or blocking endogenous cytokines or preventing their induction during MIA. Investigation of the role of TNFα in LPS-induced fetal loss and growth restriction showed that injection of anti-TNF(antibodies or an inhibitor of TNFα synthesis (pentoxifylline) can reduce these effects of LPS. Conversely, injection of TNFα alone can induce fetal loss [74,75], which is exacerbated significantly in IL-18 knockout mice, but not in IL-1α/β knockout mice [76]. Conversely, IL-10 can protect against white matter damage caused by maternal *E. coli* infection [77].

Aside from the more severe symptoms of fetal loss and growth restriction, investigation of cytokine mediation of MIA effects on neuropathology and behavior in the offspring has focused on IL-6. Samuelsson et al. [78] injected IL-6 I.P. in pregnant rats for 3 days, which resulted in profound effects on the offspring. One remarkable finding was that IL-6 mRNA levels remain elevated in the hippocampus of the offspring at 4 and 24 weeks of age. This is reminiscent of the ongoing state of immune dysregulation in adult autistic and schizophrenic brains. Further evidence of this parallel is the astrogliosis and elevated GFAP levels in the adult hippocampus of the IL-6-exposed offspring and in autistic brains. One hippocampal-dependent behavior was monitored in that study, spatial memory in the water maze, and the IL-6-exposed offspring display increased escape latency and time spent near the pool wall. Thus, prolonged exposure to elevated IL-6 during fetal development causes a deficit

Table 2
Maternal immune activation increases cytokine levels in the fetal brain.

Reference	Treatment	Findings
[109]*	4 mg/kg LPS I.P. E18 rat	TNFα, IL-1β increased
[117]	2.5 mg/kg LPS I.P. E16 rat	TNFα increased
[113]*	1 mg/kg LPS I.P. E18 rat	TNFα, IL-1β, iNOS increased
[118]	0.05 mg/kg LPS I.P. E18 rat	No change in TNFα, IL-1β, IL-6
[73]	20 mg/kg poly(I:C) I.P. E16 rat	No change in TNFα
[114]	0.12 mg/kg LPS I.P. E17 mouse	IL-6 increased
[47]	5 mg/kg poly(I:C) I.V. E9 mouse	IL-1β, IL-6 increased
[47]	5 mg/kg poly(I:C) I.V. E17 mouse	IL-1β, IL-6, IL-10 increased
[119]*	50 μg LPS I.P. E18 mouse	IL-1β, IL-6, MCP-1, VEGF increased
[91]	2 mg/kg poly(I:C) I.V. E9 mouse	TNFα, IL-1β, IL-6, IL-10 increased

Assays were for cytokine protein, except where noted (*: mRNA assayed). While some authors report no changes in cytokine levels, the majority of studies show significant increases. The studies that report no changes use less severe methods of immune activation (lower dose of LPS or I.P. administration of poly(I:C)) which may not produce detectable changes. (Reprinted with permission from [62]).

in working memory, as is also seen in LPS- and poly(I:C)-induced MIA.

Although over-expression studies can be misleading regarding endogenous ligand function, blocking endogenous IL-6 action in MIA supports the key role of this cytokine [42]. Co-injection of a neutralizing anti-IL-6 antibody with maternal poly(I:C) blocks the effects of MIA on the behavior of the offspring (Fig. 1). Moreover, maternal injection of poly(I:C) in an IL-6 knockout mouse results in offspring with normal behavior. In addition to preventing the development of abnormal behaviors, the anti-IL-6 antibody also blocks the changes in brain transcription induced by maternal poly(I:C). As mentioned above, maternal injection of poly(I:C) induces expression of IL-6 mRNA in both fetal brain and placenta, and this is also dependent on the IL-6 induced by maternal poly(I:C) (E. Hsiao and P.H. Patterson, unpublished). This suggests a possible positive feedback mechanism for chronic inflammation.

IL-6 is also important in the neonatal brain response to intracerebral injection of LPS. The antibody attenuates ventricle dilation as well as astrocyte and microglial activation, and it improves behavioral outcome [79].

9. Sites and mechanisms of cytokine action – therapeutic implications

The evidence of elevated cytokines in the fetal brain following MIA raises the obvious possibility that cytokines act directly on developing neurons and glia. It is known, for instance, that transgenic, early over-expression of IL-6 in astrocytes causes major neuropathology and decreases seizure threshold [120], and seizures are a common symptom in autism. IL-6 and related cytokines strongly influence many features of brain development and neural repair [80].

In addition to altering fetal brain development, it is likely that the permanent elevation of cytokines in the brain seen in the schizophrenic and autistic brain and CSF directly affects ongoing postnatal behavior. For instance, exogenous as well as endogenous IL-6 and IL-1 regulate neuronal excitability, long-term potentiation and learning [80]. IL-6 and related cytokines also regulate the stress response, feeding, sleep and depressive behaviors in the adult brain. Moreover, injection of certain cytokines can induce psychiatric symptoms in adult humans [80–83]. Such acute effects

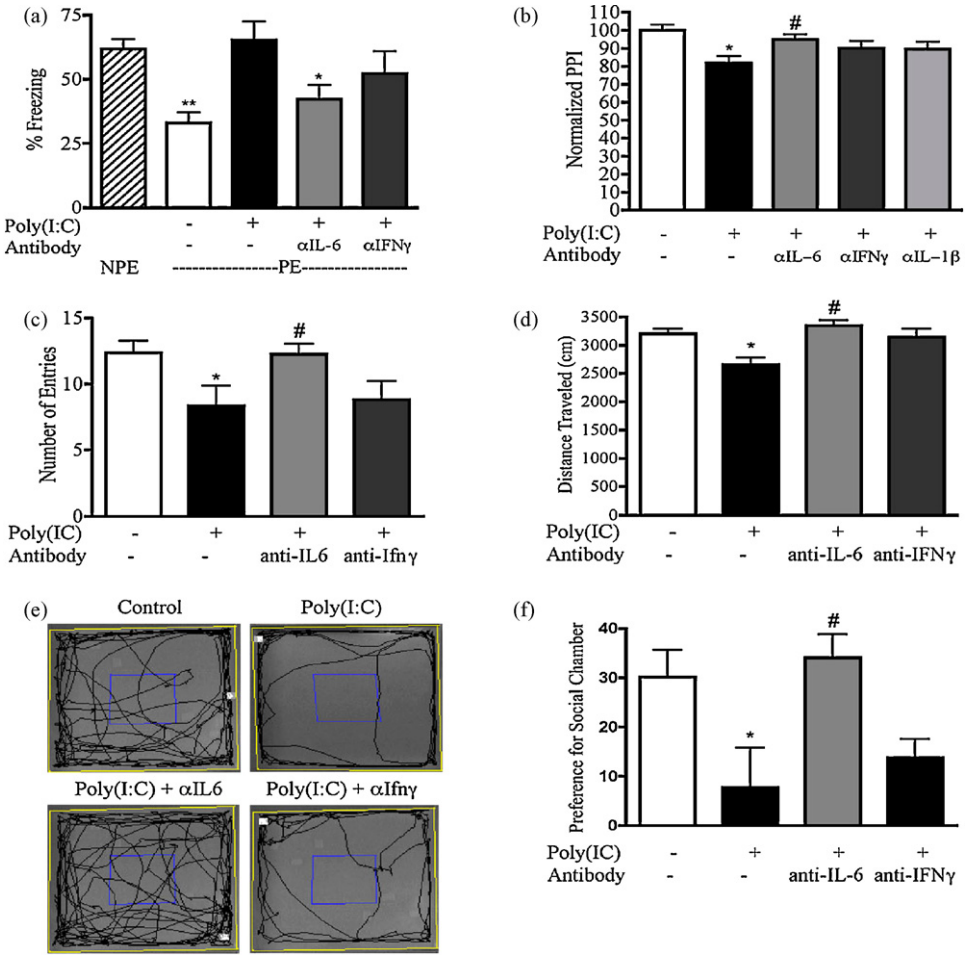

Fig. 1. Abnormal behavior in MIA offspring is prevented by maternal treatment with anti-IL-6 antibody. (a) Offspring of mice treated with poly(I:C) lack LI. Co-injection of anti-IL-6 with poly(I:C) restores significant LI, while co-injection of anti-IFNγ does not. [$F_{4,132} = 7.566$, $p < 0.0001$] $^{**}p < 0.001$ vs. NPE; $^{*}p < 0.01$ vs. NPE. (b) Compared to controls, the offspring of mice treated with poly(I:C) show a PPI deficit at a prepulse level of 85 Db. Co-injection with anti-IL-6 prevents this deficit. The PPI of offspring of mice co-injected with poly(I:C) and anti-IFNγ or anti-IL-1β are not significantly different from control or poly(I:C). [$F_{4,270} = 4.195$, $p < 0.005$] $^{*}p < 0.001$ vs. control; $^{\#}p < 0.05$ vs. poly(I:C). In the open field test, offspring of mice treated with poly(I:C) make fewer entries than controls into the center (c) and travel less total distance (d). Offspring of mice co-injected with anti-IL-6 enter the center as often as control mice [$F_{3,123} = 3.703$, $p < 0.05$] $^{*}p < 0.05$ vs. control, $^{\#}p < 0.05$ vs. poly(I:C), and move a similar total distance [$F_{3,123}$=6.666, p < 0.0005]; $^{*}p < 0.01$ vs. control; $^{\#}p < 0.001$ vs. poly(I:C). Offspring of mice co-injected with poly(I:C) and anti-IFNγ are not significantly different from controls or poly(I:C). (e) Tracks recorded during the open field session demonstrate increased thigmotaxis in offspring of poly(I:C)-treated mice compared to offspring of mice co-injected with an IL-6 antibody. (f) In the social interaction test, control mice show a strong preference for the social chamber, defined as (percent time in social chamber) – (percent time in opposite chamber), while the offspring of poly(I:C)-treated mice show no such preference. Again, the deficit is corrected by maternal administration of IL-6 antibody. [$F_{3,50} = 4.244$; $p < 0.01$]; $^{*}p < 0.05$ vs. control; $^{\#}p < 0.05$ vs. poly(I:C). (Reprinted with permission from [42]).

of elevated cytokines could perhaps explain a series of puzzling case studies that report the sudden onset of autistic symptoms in children and adults following encephalitis or infection with herpes simplex, varicella or cytomegalovirus [84]. CNS infections of this type are known to rapidly induce pro-inflammatory cytokine expression. In contrast, infections in autistic children are associated with acute amelioration of behavioral symptoms, which is also consistent with ongoing regulation of behavior by cytokines [85]. There are also reports that malarial infection can ameliorate psychosis [86,87].

A key point about the hypothesis of cytokines directly inducing or influencing behavior is that it raises the possibility of developing treatments based on anti-cytokine or anti-inflammatory agents. In fact, a preliminary study in 25 autistic children of the anti-inflammatory thiazolidinedione, pioglitazone, revealed a significant decrease in irritability, lethargy, stereotypy and hyperactivity, with greater effects on the younger patients [121]. Anti-inflammatory drug trials have also been proposed for schizophrenia [6,88], although the initial results have been mixed [122]. It is provocative that antipsychotic drugs are known to influence cytokine expression [58,59], and can even induce fever [89], which is cytokine-mediated.

In contrast to postnatal interventions, potential treatments during pregnancy to block the developmental effects of maternal infection on the fetus present a far more difficult clinical challenge. For instance, blocking IL-6 function during maternal influenza infection results in more severe infection and miscarriage (this is why the poly(I:C) model was used in the IL-6 perturbation study rather than viral infection). Thus, there may be adverse effects in lowering the inflammatory response too much during pregnancy. On the other hand, administration of the anti-inflammatory cytokine IL-10 to pregnant rodents given a uterine bacterial infection or LPS prevents fetal loss and white matter damage [77,90]. Moreover, genetically-enforced expression of IL-10 in macrophages attenuates the effects of MIA by poly(I:C) as measured by assays of PPI, latent inhibition and open field anxiety in adult offspring [91]. An attractive feature of this potential therapeutic is that endogenous IL-10 is essential for resistance to LPS-induced preterm labor and fetal loss. Thus, administration of this cytokine enhances the natural protective mechanism by attenuating the production of pro-inflammatory cytokines [90]. Subcutaneous administration of IL-10 was non-toxic in long-term studies in mice and monkeys, although testing was not done during pregnancy [92]. A cautionary observation is, however, that enhanced levels of IL-10 in the absence of MIA in pregnant mice leads to behavioral abnormalities in the adult offspring [91].

In addition to the fetus, IL-6 and other cytokines generated by MIA may act on the placenta. As mentioned above, MIA can induce cytokine expression in the placenta, and poly(I:C) can stimulate interferon production by human trophoblasts in culture [93,94]. Moreover, poly(I:C) MIA activates the IL-6 signaling pathway in the placenta (E. Hsiao and P.H. Patterson, unpublished). This could alter the transfer of cells, nutrients, oxygen, growth factors and maternal antibodies, all of which can strongly affect fetal development.

A third hypothesis for IL-6 action involves the adjustments made by the maternal immune system during pregnancy to prevent rejection of the fetus. Normal pregnancy can be viewed as a state of controlled inflammation [95]. Uterine natural killer (uNK) cells, important for maintaining pregnancy, may be the primary regulators of inflammation at the feto-maternal interface [96]. Injection of high doses of poly(I:C) causes loss of pregnancy in rats, and pre-treatment with an anti-uNK antibody prevents this loss, implicating uNK cells in miscarriage [97]. Thus, IL-6 could act on maternal immune cells, making them less tolerant of the fetus. While this may increase the possibility of fetal loss or low birth weight, it is not known if this mechanism could also alter fetal brain development and lead to the abnormal behaviors that have been described. IL-6 could also enhance production of maternal antibodies, which could cross-react with the fetal brain, as has been proposed for autism [98,123]. Future research can therefore productively focus on the effects of IL-6 on both the fetus and the placenta.

10. Other schizophrenia risk factors

Along with maternal infection, several other risk factors have been established, which appear at first glance to have little in common with each other or maternal infection. Among these are birth in winter–spring months, birth or development in an urban setting, prenatal nutritional deficiency, and maternal stress [99–102]. These diverse environmental factors can, however, be linked to the immune hypotheses in various ways. For instance, birth in winter–spring months and development in an urban setting are compatible with increased risk for maternal infection. Moreover, nutritional deficiency and stress are both known to elevate inflammatory cytokines [103–105]. Thus, it is possible to speculate that these diverse risk factors could share cytokine imbalance as a common mechanism contributing to schizophrenia susceptibility in the fetus.

11. Perspectives

There are a rapidly increasing number of studies showing immune dysregulation in the young and adult autistic and schizophrenia brain. The evidence is based on microarray, ELISA, histological and PCR techniques, and involves CSF as well as post-mortem material. Moreover, a variety of these findings have been replicated in independent laboratories. One gap in this story to date is that the evidence for activated astrocytes and microglia in the schizophrenic brain is much less striking than is the case for autism [106,107]. However, microglia can be triggered into a permanently primed or sensitized state by early infection or stress [108] and yet do not display the classic signs of neuropathology. More sophisticated analysis of the immune status of glia in schizophrenia is called for using techniques such as laser capture microdissection. Nonetheless, the permanent state of immune dysregulation is becoming established as a key part of the pathology of these disorders. Important questions for the future include, how does this altered immune state become established, how is it maintained, does it influence behavior in an acute, ongoing manner, and can it be manipulated for therapeutic benefit? Since maternal immune activation is a well-established risk factor for schizophrenia and it clearly alters the immune status of the fetal brain, it seems a logical possibility that this early dysregulation sets in motion events that lead to the permanent alteration in immune status. At the moment, however, there is insufficient evidence for an altered immune status in the adult brain of the animal models of maternal immune activation. The only published case of activated microglia and astrocytes in the adult offspring of immune-activated mothers is that of Borrell et al. [63], who employed a severe protocol of maternal LPS injections. Moreover, there are as yet no reports of altered cytokines in adult brains of immune-activated mothers. Clearly, more extensive investigation into the lasting effects of maternal immune activation is warranted.

Another deficiency in the available data is that relatively few epidemiological studies have reported on the possible involvement of maternal infection with autism. It is also clear that by no means all offspring of infected women develop autism or schizophrenia. Factors influencing this outcome would include the severity of the MIA, as the resulting effects on the fetus are dependent on the dose of the influenza virus or poly(I:C) ([35]; L. Shi, unpublished data),

as well as the genotype of the mother and fetus. Since genetic background plays a significant role in schizophrenia and particularly in autism, it is possible that some aspects of the genotype could influence the response to infection by the mother as well as the susceptibility to the effects of MIA on the part of the fetus. It is also clear that both disorders are quite heterogeneous in symptomatology, suggesting the possibility of multiple causes. This is also supported by the new finding that the neuropathology and cognitive deficits in schizophrenics born to infected mothers are different from schizophrenics born to uninfected mothers [18].

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