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Multiple pathways in prevention of immune-mediated brain disorders: implications for the prevention of autism

S. Hossein Fatemi

Departments of Psychiatry Neuroscience and Pharmacology, University of Minnesota Medical School, Minneapolis, MN

Autism represents a neurodevelopmental disorder that is highly genetic, with monozygotic concordance rates of approximately 91% (Bailey et al., 1995). Clearly, however, environmental factors which contribute to the genesis of autism play major roles in its etiopathology (Realmuto and Azeem, 2008). It is hypothesized that by far the most important environmental risks for autism, and also schizophrenia, consist of intrauterine infections (Patterson, 2007). A major consensus arrived at and based on several decades of robust epidemiologic reports and more recent animal experimental and human serologic work has established that maternal infection is responsible for immune dysregulation which leads to high susceptibility to development of autism and schizophrenia (Fatemi et al., 2005a; Brown et al., 2006; Patterson, 2009).

Autism is characterized by the presence of social and language deficits, and repetitive behavior (APA 1994). Pathologic findings of the brain show abnormalities including macrocephaly (Courchesne et al., 2003) and minicolumnar pathology (Casanova et al., 2002), which point to a neurodevelopmental origin. Molecular and neuropathologic abnormalities in autism (Palmen et al., 2004) include decreased levels of Reelin and Bcl-2 and increased levels of P53, causing cortical dysgenesis (Fatemi et al., 2005b; Fatemi and Halt, 2001); GABAergic derangements such as decreased glutamic acid decarboxylase 65/67 levels (Fatemi et al., 2002; Blatt, 2005) and GABA_A & B receptor abnormalities (Fatemi et al., 2009a,b; Oblak et al., 2009), and cholinergic alterations (Perry et al., 2001). Several of these abnormalities have also been associated with virally mediated animal models for autism (Meyer et al., 2009) and immune activation (Laurence and Fatemi, 2005; Vargas et al., 2005).

In a series of studies and over a decade, Fatemi and collaborators showed that maternal infection of mice with a H1N1 strain of human influenza virus at various gestational periods results in the development of brain structural (Fatemi et al., 1999, 2008), genetic (Fatemi et al. 2005, 2008), behavioral (Shi et al., 2003), and neurochemical (Fatemi et al., 2008) abnormalities in the offspring which resemble several anomalies observed in cases of autism and schizophrenia. Similar experiments using PolyI:C have replicated the validity of above experiments and extended the tenet that maternal immune activation can also lead to brain structural and behavioral abnormalities in offspring of exposed rodents (Meyer et al., 2009). Indeed, other animal models of immune activation using bacterial lipopolysaccharide (LPS) and periodontal bacteria have pointed to major roles of proinflammatory cytokines such as interleukin 6 (IL-6) in causation of most pathologies in fetal brain (Patterson, 2009).

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The question then arises that if proinflammatory cytokines, either directly or indirectly, lead to such havoc in pregnancies, can we take steps to prevent or diminish the deleterious effects on developing brains in fetuses? As discussed later in this issue, these authors, (Parker-Athill et al, 2009) show elegantly how use of flavonoids can act as prophylaxis to prevent IL-6-induced behavioral deficits in offspring of C57BL/6 mice exposed to IL-6 at embryonic date 12.5 (E12.5). The investigators show that luteolin, a citrus derived flavonoid, and its analogue diosmin, inhibit neuronal Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) phosphorylation both *in vivo* and *in vitro* following IL-6 challenge and significantly diminish behavioral deficits in social interaction in this rodent model of maternal immune activation (MIA). Members of the JAK-STAT family of signaling pathway molecules (Cattaneo et al., 1999; Schindler et al., 2007) are cytoplasmic proteins which upon activation by cytokines mediate a number of cellular processes including cell death, cell proliferation, and cell differentiation (Stephanou and Latchman, 2005). JAK2 receptors are stimulated by IL-3 and IFN- γ cytokines. STAT3 activity, in turn, is regulated by tyrosine kinase JAK2 (Saltzman et al., 1998). However, STAT3 is known to transduce IL-6, IL-10, GCSF, leptin, IL-21, and IL-27 signals. Additionally, STAT3 is involved in anti-apoptotic gene actions (Schindler et al., 2007). Recent evidence has suggested that disruption of the JAK2/STAT3 pathway by amyloid- β may lead to memory impairment in subjects with Alzheimer's disease (Chiba et al., 2009). Additionally, several reports implicate involvement of JAK-STAT signaling in actions of LPS and influenza-mediated immune activation (Zhang et al., 2006; Sriram et al., 2004).

The current study (Parker-Athill et al, 2009), replicates the use of anti IL-6 antibody which also blocked the effects of MIA on the behavior of the offspring as recently shown by Patterson and colleagues (Smith et al., 2007). Importantly, Parker-Athill et al. in this issue, identify a potential treatment to counteract the negative effects of influenza infection on the fetus, possibly preventing the development of neurodevelopmental disorders, including autism. Interestingly, Pang et al (2006) showed that anti IL-6 antibody can also diminish LPS-induced ventricular dilatation, astrocytic activation, and reduce behavioral abnormality. Clearly, more mechanistic studies are needed to explain the role of numerous brain genes which become activated during viral infection of the matter in fetal brain (Fatemi et al., 2008). Recent unpublished preliminary experiments performed in the author's laboratory have shown the protective effects of oseltamivir in reducing the effects of viral infection in C57BL/6 E16 mice, whereby induction of virally-induced hippocampal gene transcription was reduced significantly at birth (Fatemi, Folsom & Reutiman, unpublished observations). This effect was clearly due to neurominidase inhibitory effect of oseltamivir on maternal immune system benefiting the fetal brain from direct viral effects.

Studies such as those performed by Parker-Athill and colleagues are needed to identify additional pathways for intervention in prevention of immune-mediated brain disorders like schizophrenia and autism. Indeed, the available literature points to the usefulness of agents such as flavonoids (Nagai et al., 1995; Wang et al., 2006; Liu et al., 2008), macrolides (Kido et al, 2007; Miyamoto et al., 2008), pentoxifylline (Kaplan et al., 1995), thiazolidinediones (Boris et al., 2007), and even antiviral drugs or vaccines.

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