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Editorial

Immuno-inflammatory, oxidative and nitrosative stress, and neuroprogressive pathways in the etiology, course and treatment of schizophrenia

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In recent decades, a significant role for altered immuno-inflammatory, oxidative and nitrosative stress (IO&NS) pathways in schizophrenia has been recognized (Smith and Maes, 1995; Wood et al., 2009). Importantly, such processes have provided crucial clues to the etiology, course and management of this devastating disorder. This is the focus of this special edition.

Epidemiological findings supporting a role for prenatal viral, bacterial and protozoan infections in the etiology of schizophrenia have provided a seminal contribution to the neurodevelopmental hypothesis of schizophrenia (Brown and Derkits, 2010). The early developmental etiology of schizophrenia to a lesser extent has been focused on decreased vitamin D in early development, including via vitamin D modulation of the immune response to infection (McGrath et al., 2003). Interactions between these factors is suggested by the fact that vitamin D has a documented role in immune modulation, especially during placental development and in early childhood (Battersby et al., 2012; Liu et al., 2011). The maximal risk period for maternal infection association with offspring schizophrenia is shown to be early pregnancy (Brown et al., 2004; Khandaker et al., 2012). Interestingly many schizophrenia susceptibility genes are regulated by hypoxia, suggesting close interactions among IO&NS genes and obstetric complications leading to enhanced risk of schizophrenia (Nicodemus et al., 2008; Schmidt-Kastner et al., 2006). Other conditions of pregnancy, including hypoxia associated preeclampsia (Kendell et al., 1996), also increase the risk of the offspring being classed as having schizophrenia, emphasizing the profound impact of prenatal events.

The evidence for the role of prenatal infection, both epidemiological and experimental, is excellently reviewed by Urs Meyer (2013–this issue) who has published extensively in this area. Many of the developmental effects of infection are driven not only by O&NS and proinflammatory cytokine increases in the placenta and fetus, but also by associated hypoferremia and zinc deficiency (Ganz and Nemeth, 2009; Prasad, 2009). Such changes render the offspring prone to subsequent second hits over the course of post-natal development, contributing to both the emergence and progression of disease manifestations. This is an important area of experimental research given that the elimination of the effects of maternal infection is estimated to decrease the incidence of schizophrenia by as much as 46% (Brown and Derkits, 2010).

The paper by Kneeland and Fatemi (2013–this issue) in this issue focuses specifically on the role of maternal viral infections in the etiology of schizophrenia. This review highlights the findings of animal studies on the effects of viral infection at embryonic days 7, 9, 16 and 18 on the expression of gene as well as protein and brain structural alterations in the offspring. The data discussed in this review, clearly indicate that viral effect depends on multiple factors including time of gestation, viral types and subtypes, viral load, involvement of placenta and susceptibility of various brain areas affected. Additionally, effects of various viral strains are not always similar to the effects of poly: I.C. in different experimental protocols (Kneeland and Fatemi, 2013–this issue). Interestingly emerging data suggests that viral infection at embryonic day 17 increases Alzheimer's associated changes subsequently (Krstic et al., 2012; Meyer et al., 2006), indicating a role for maternal infection in the etiology of Alzheimer's, and perhaps overlapping schizophrenia and Alzheimer's within an early developmental context. The paper in this issue by Anderson and Maes (2013–this issue) also highlights the overlap in susceptibility genes and protein changes that occur in schizophrenia and Alzheimer's, suggesting that Kraepelin's concept of dementia praecox (literally “early dementia”) may have been prescient. It will be interesting to determine as to whether maternal infection at different stages of pregnancy is differentially associated with the neurodegeneration, apoptosis and reduced neurogenesis, which is the essence of neuroprogressive processes in schizophrenia (Berk et al., 2010).

A further indicant of the role of immune changes in early development as well as at later time points, is the data implicating variation or altered expression of the major histocompatibility complex (MHC) in the etiology and progression of schizophrenia. Recent genome wide association studies have established MHC region variants as a major risk factor for the development of a range of autoimmune disorders, as well as schizophrenia (Fernando et al., 2008), implying that the MHC region may be relevant to conceptualizations of schizophrenia as an inflammatory and/or autoimmune disorder. The immunological, genetic and expression studies on the role for MHC variants in schizophrenia is reviewed in this issue by Debnath and colleagues, leading to suggestions for future research (Debnath et al., 2013–this issue).

Following this early developmental etiology, the connection to the subsequent changes in immuno-inflammatory responses in schizophrenia is the theme of the paper by Altamura et al. (2013–this issue). Recent understanding of high-risk children showing neurodevelopmental abnormalities links to the long recognized changes in character and behavior observed by Kraepelin in children who subsequently go on to develop schizophrenia. These early developmental changes involve genetic, epigenetic and environmental risk factors and their interactions. Some have suggested that the second hit

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occurs around adolescence, being associated with excessive synaptic pruning and subsequent decreases in synaptic plasticity (Fatemi and Folsom, 2009). A range of behavioral, somatic, cognitive and social abnormalities is evident before and around adolescence. Changes in immune and glia driven inflammation due to elevation of cytokines are thought to play a crucial determining role in mediating these manifestations of altered neurodevelopment. The varying strength and interactions of such early developmental changes seems likely to contribute to the heterogeneity evident in schizophrenia and, ultimately, to drive a classification based on biological underpinnings (Bechter, 2013–this issue).

The article by Miller et al. (2013–this issue) emphasizes how human prenatal infection and immuno-inflammatory responses exert long-lasting brain and immune system changes and subsequently drive the susceptibility to adult manifestations of schizophrenia. Surprisingly few experimental studies are published on the association of maternal cytokine changes with a later diagnosis of schizophrenia, and those that are published are confounded by other factors such as preeclampsia and maternal obesity, which are known to modulate immuno-inflammatory responses. Of wider obstetric complications, gestational diabetes confers the highest risk of developing schizophrenia in the offspring, being also associated with definite psychotic symptoms at 12 years of age (Cannon et al., 2002; Zammit et al., 2009). It is unknown as to the significance of increased inflammation in mediating this and as to what is the role of increased leptin and leptin resistance in both these obstetric disorders. Leptin is a known modulator of the immune system and is dramatically increased in the placenta in preeclampsia (Chigusa et al., 2012). Dysregulated leptin is known to increase risk for de-novo depression (Pasco et al., 2008).

The study by Miller et al. (2013–this issue) highlights data suggesting that the association of maternal infection, inflammation or obstetric complications results in changes in cognition and brain morphology, in comparison to a schizophrenia sample without such complications. These are mainly preliminary findings but suggest a causal strand between early inflammation and specific aspects of symptom presentation. These authors review tantalizing data suggesting gene-environment and gene–gene interactions that will interact with and modulate the inflammatory responses, contributing to explaining the numerous but small individual gene susceptibility associations with schizophrenia. It is also likely that such genetic, epigenetic and environmental interactions will modulate the nature of the "second hit".

One probable candidate for a later "second hit" comes in the form of mild encephalitis, which is reviewed in this issue (Bechter, 2013–this issue). The core feature of which is low-level neuro-inflammation that may be initiated by stress, infections, autoimmunity, toxicity, Vitamin D deficiency or trauma around the time of disease onset. Bechter (2013–this issue) suggests a significant role for the extracellular space in the central nervous system as well as the cerebral spinal fluid in mediating wider changes in distributed brain dysfunction as well as driving peripheral alterations. Mild encephalitis is suggested to constitute a schizophrenia subgroup explaining about 40% of cases. The mild encephalitis hypothesis is also relevant to the initiation and course of wider affective psychoses as well as in regard to questions on the role of limbic autoantibody-associated encephalitis.

The overlapping of different diagnostic categories is perhaps of particular relevance in schizophrenia, where very high levels of comorbid depression are also evident from the first episode (Cotton et al., 2012). In one study, previously undiagnosed comorbid depression levels were 61% (Gozdzik-Zelazny et al., 2011). In DSM-IV such comorbidity leads to a schizoaffective classification, which is a diagnosis of low validity and reliability (Heckers, 2012). In this issue Anderson et al. (2013–this issue) review the underlying biological pathways linking depression and schizophrenia, suggesting that schizophrenia is primed for the expression of depression as a result of interlinked changes in immuno-inflammatory, O&NS and the tryptophan catabolite (TRYCAT) pathways (Anderson et al., 2013–this issue). Such processes also contribute to increased levels of autoimmunity in both disorders.

Another significant commonality between schizophrenia and the mood disorders is the increased level of microglia activation (Beumer et al., 2012; Fillman et al., in press). Monji and colleagues have carried out extensive research in promoting the relevance of microglia activation in mediating some of the central inflammatory responses in schizophrenia, which they review in this issue (Monji et al., 2013–this issue). Microglia, the specialized resident macrophages in the CNS, respond rapidly to alterations in the brain environment, having both beneficial and detrimental effects. Microglia are also a significant target for IFNγ-induced indoleamine 2,3-dioxygenase (IDO) and the neuronal activity modulating effects of the TRYCATs, including quinolinic acid. Chronic unpredictable mild stress in rodents mediates its depressive effects via increased quinolinic acid in the amygdala and striatum (Laugeray et al., 2010, 2011), suggesting a role for microglia activation in stress-induced exacerbations. Activated microglia are also a significant source of pro-inflammatory cytokines, NO and pro-oxidants. As such microglia activation is a powerful mediator of the central changes associated with wider systemic immuno-inflammation, and is a significant treatment intervention target, with ketamine, a microglial inhibitor, for example showing promise in depression (Shibakawa et al., 2005).

Different bodies of data on the nature of schizophrenia, including prenatal infection, IO&NS pathways, hypo-N-methyl D-aspartate receptor function, dysregulated gamma-amino-butyric-acid-ergic activity, glutamate dysregulation, cognitive dysfunction, microRNA changes, metabotropic glutamate receptor regulation, neuroprogression as well as overlaps with depression and stress induced exacerbations are synthesized in the paper by Anderson and Maes (2013–this issue). Prenatal infection, in modulating subsequent immuno-inflammatory cascades, drives alterations in the O&NS and TRYCAT pathways, which have a more direct impact on neuronal activity and patterning.

The article by Müller and colleagues looks at the role of anti-inflammatory processes in shaping treatment in schizophrenia (Müller et al., 2013–this issue). Although antipsychotics have classically been modeled as mediating their efficacy via changes in dopaminergic activity, there is a growing appreciation that changes in dopamine and glutamate transmission in the CNS is immunologically driven. Redressing the imbalance in the immunological response, including in CNS glia cells, is crucial to the efficacy of treatment approaches in schizophrenia. These authors suggest clinical efficacy of anti-inflammatory therapy in the early course of the disorder.

A wider frame of reference for understanding the potentially neuroprotective effects of medications and other adjunctive treatments is the theme of the paper by Dodd et al. (2013–this issue). The wider therapeutic applications in the treatment of schizophrenia, including when coupled to comorbid depression, may be found in the use of medications and nutritional agents that modulate IO&NS and neuroprogressive processes. A number of factors are highlighted as possible candidates to enhance aspects of treatment, including melatonin, erythropoietin, N-acetylcysteine, statins as well as aspirin and its metabolites. Other candidates are drugs that have negative immunoregulatory properties, e.g. drugs that attenuate pro-inflammatory cytokines, e.g. interleukin-1, and/or increase interleukin-10, soluble interleukin-2 receptor, leukemia inhibitory factor receptor (LIF-R) and CC16 or Clara cell protein, an endogenous anti-inflammatory agent that is decreased in schizophrenia (Dodd et al., 2013–this issue). Another nutritional factor with both preventative and treatment implications are the polyunsaturated fatty acids (PUFAs) and their metabolites including lipoxins, resolvins, protectins, maresins and nitrolipids. ω3 PUFAs and their metabolites decrease levels of pro-inflammatory cytokines and developmentally are essential for neuronal and brain development. This work is reviewed here by Dr. Das, who suggests that synthetic analogs of ω3 PUFA metabolites may be of significant efficacy in management of schizophrenia (Das, 2013–this issue).