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Review Article

Microglial Abnormalities in the Pathophysiology of Schizophrenia

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Abstract

The etiology of schizophrenia remains unclear while, in many aspects, the neuropathology of schizophrenia has recently been reported to be closely associated with microglia dysfunction. Microglia, which are the major players of innate immunity in the CNS, respond rapidly to even minor pathological changes in the brain and contribute directly to neuroinflammation by producing various pro-inflammatory cytokines and free radicals. Recent human studies have revealed microglial activation in schizophrenia using postmortem brains or *in vivo* neuroimaging techniques. We and other researchers have recently shown the inhibitory effects of some antipsychotics on the release of inflammatory cytokines and free radicals from activated microglia, both of which have recently been known to cause the synaptic pathology, a decrease in neurogenesis, and white matter abnormalities often found in the brains of patients with schizophrenia. In addition, recent evidence strongly suggests a neurodevelopmental role of microglia in regulating synapse formation/function by their interaction with synapses and phagocytotic activity. It is not known whether microglia dysfunction and microglia-orchestrated neuroinflammation are the primary cause of schizophrenia but they are closely related to the progression and outcomes of schizophrenia. Understanding microglial pathology may shed new light on the therapeutic strategies for schizophrenia.

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INTRODUCTION

Research into neuropsychiatric disorders has been "neuronocentric". However, several categories of neuropsychiatric disorders show no common alterations of brain structure dictated by neuronal architecture, leaving neuropathologists and neuroanatomists clueless. Schizophrenia, for example, was famously named "the graveyard of neuropathologists" (Iritani, 2007). However, recent neurochemical and brain imaging studies have moved microglia into the center of attention. To evaluate microglia activity *in vivo*, a few radioligands have been developed. One radiotracer, [^{11}C]-(R)-PK11195 ([11C](R)-(1-[2-chrorophynyl]-N-methyl-N-[1-methylpropyl]-3 isoquinoline carboxamide) which is a specific ligand of peripheral benzodiazepine receptors, specifically binds to activated microglia and is widely used (Benavides et al., 1988, Pike et al., 1993). The availability of well-preserved post-mortem brain samples and several established microglial histological markers in recent years also allows neurochemical evaluations of microglia in diseased brains. Microglia are highly mobile, incessantly surveying the brain environment, and ready to react to even the slightest perturbation. At the experimental biology level, innovative molecular genetic and biophotonic approaches begin to enable investigators to visualize the dynamic microglial behavior in health and disease *in vivo*, and to introduce microglia-targeted deletions and ablations (Wake et al., 2009 & Li et al., 2012). Therefore, we are at the threshold of making fundamental discoveries regarding microglial contributions to neuropsychiatric disorders.

Here, we will review one of the prominent neuropsychiatric disorders, schizophrenia, to exemplify the pathological roles of microglia, either acting as primary instigators or responding to pre-natal, perinatal, or postnatal insults as well as environmental impacts specific to the diseases of interest. In the pathophysiology of schizophrenia, emphasis has been placed on the gene-environment interplay in the pathophysiology (van Os et al., 2010), as microglia serve as interphase between environmental alterations and regulated brain responses.

SCHIZOPHRENIA

Schizophrenia is a severe neuropsychiatric disorder affecting about 1% of the world population. The onset of full-blown schizophrenia is typically in late adolescence or early adulthood and includes distinct symptom classes which are commonly referred to as positive (hallucinations, delusions, and

psychomotor excitement), negative (avolition and amotivation), and cognitive symptoms. In addition to severely disrupting the life of the patient and their family, schizophrenia incurs a great cost to society in terms of lost productivity and treatment-related expenses. Current treatments are ineffective at addressing the full spectrum of symptoms. The etiology of schizophrenia still remains to be elusive while dopaminergic hyperfunction in the limbic system and dopaminergic hypofunction in the frontal cortex as well as glutamatergic hypofunction are known to play important roles in the pathophysiology of schizophrenia (Lieberman, 1999). We herein review the role of neuroinflammation in the pathophysiology of schizophrenia especially focused on microglia. And also, we suggest the therapeutic strategy of schizophrenia through the inhibition of microglial activation.

NEUROINFLAMMATION AND SCHIZOPHRENIA

Jurius Wagner-Jauregg, who was awarded the Nobel Prize in Medicine in 1927, proposed the treatment of mental diseases by inducing fever. His well-known "pyrotherapy" might be the beginning of the study on the immunological concepts of schizophrenia. Many recent neuroimaging studies using magnetic resonance imaging (MRI) have shown progressive brain atrophy in schizophrenia and these results suggest that even schizophrenia has an aspect of neurodegenerative disorder (Davis et al., 2003, Kumra et al., 2005, Salisbury et al., 2007, Hulshoff Pol and Kahn, 2008). Recent genome-wide studies in schizophrenia have shown the association of schizophrenia with markers in the MHC (major histocompatibility complex) region and suggest immune system involvement in schizophrenia (Stefansson et al., 2009, Jia et al., 2010). An accumulating body of evidences point to the significance of neuroinflammation in schizophrenia, characterized by an increased serum concentration of several pro-inflammatory cytokines (Drzyzga et al., 2006, Potvin et al., 2008, Meyer, 2011, Miller et al., 2011). Increased serum and cerebrospinal fluid (CSF) levels of S100B, a suitable marker for the destruction of CNS tissue in the context of different disease including neurodegenerative disorder, were reported in schizophrenia patients with negative symptoms or chronic duration (Schmitt et al., 2005). Increased serum concentrations of interleukin (IL)-2, IL-6 and IL-8 have been observed in schizophrenic patients (Lin et al., 1998, Zhang et al., 2004). Moreover, a recent report has shown the elevated IL-1β levels in the cerebrospinal fluids of the patients with drug-naïve schizophrenia (Soderlund et al., 2009). A recent meta-analysis has demonstrated that the cytokine abnormalities an acute exacerbation of schizophrenia is independent of antipsychotic medication (Miller et al., 2011). Peripheral inflammatory responses in schizophrenia have also been linked to the changes in the numbers of circulating monocytes and T-cells (Drexhage et al., 2010). It has recently been reported that blood lymphocyte abnormalities in drug -naïve first episode psychosis suggest an effect may be independent of antispychtoic medications (Miller et al., 2013). Epidemiologic studies demonstrate significant environmental impact of maternal viral infection and obstetric complications on the risk of schizophrenia. Elevated inflammatory process is known to play an important role under these circumstances. Infection during the perinatal period of life acts as a vulnerability factor for late-life alterations in cytokine production, and marked changes in cognitive and affective behaviors throughout the remainder of lifespan. A series of infection during pregnancy have been associated with risk of schizophrenia in offspring, including influenza, rubella, herpes simplex virus-type2, and toxoplasma gondii. Evidence from recent animal studies suggests that most viral infection do not appear to cross the placenta; therefore, the teratogenic influence might be more related to maternal, fetal, and/or placental response to infection. Two nested case-controlled studies have demonstrated an association between elevated serum levels of maternal tumor necrosis factor α (TNF-α) or interleukin-8 (IL-8) with increased risk for schizophrenia in the offspring (Nawa and Takei, 2006, Ashdown et al., 2006, Deverman and Patterson, 2009, Ellman and Susser, 2009, Brown and Derkits, 2010). A DNA microarray study has shown the increased expression of genes related to immune and chaperone function in the prefrontal cortex (BA46) in schizophrenia (Arion et al., 2007). Another study using prefrontal cortex of schizophrenia has shown that molecular basis for schizophrenia changes from early to chronic stages, providing evidence for a changing nature of schizophrenia with disease progression. Short-term illness was particularly associated with disruption in gene transcription, metal-binding, RNA expression and vesicle-mediated transport. In contrast, while long-term illness was associated with inflammation, stimulus-response and immune functions (Narayan et al., 2008). The latest two studies using postmortem human tissues have also demonstrated increased inflammatory markers identified in BA46 of the patients with schizophrenia (Fillman et al., 2013, Dean et al., 2013). Dean et al. have demonstrated that levels of TNF receptor 1 mRNA are increased in BA46 (82%) in patients with schizophrenia (Dean et al., 2013).

Patients with schizophrenia have a reduced lifespan of > 20 years, with cardiovascular disorders being the main cause of death while diabetes mellitus is a particularly strong risk factor for cardiovascular mortality, being a risk equivalent of myocardial infarction. There has been an exponential increase in the schizophrenia literature discussing the high prevalence of type2 diabetes mellitus and pre-diabetic states such as the metabolic syndrome while diabetes mellitus is well-known to be a pro-inflammatory state. These results are very important because insulin resistance can be observed even in antipsychotic-naïve patients with schizophrenia and second generation antipsychotics, especially olanzapine and clozapine, have been associated with the metabolic syndrome and the development of type2 diabetes mellitus (Meyer and Stahl, 2009, Nielsen et al., 2010, Devaraj et al., 2010, Steiner et al., 2014). Beumer et al have recently demonstrated the increased levels of serum cytokines, chemokines and adipokines in patients with schizophrenia is associated with disease and metabolic syndrome (Beumer et al., 2012). C-reactive protein (CRP) is a pentameric protein which is generated largely in the liver and secreted in the blood. CRP in the blood provides a reliable marker of chronic inflammation. It has recently been reported that high sensitivity CRP (hs CRP) is elevated in schizophrenia while cardiovascular risk factors during second generation antipsychotic (a newer antipsychotic with fewer side effects than first generation antipsychotic such as haloperidol) treatment are associated with increased hs CRP (Dieset et al., 2012, Dickerson et al., 2013).

SCHIZOPHRENIA AND MICROGLIAL ACTIVATION

Bilbo et al have shown the hypothesis that long-term changes in brain glial cell function underlie this vulnerability. They hypothesize that a subsets of microglia are permanently maintained in an activated or primed state into adulthood as a consequence of perinatal infection and that a subsequent immune challenge in adulthood can cause exaggerated levels of cytokines from primed microglia (Bilbo and Schwarz, 2009, Bland et al., 2010). Interestingly, some recent animal studies have shown that even psychological stress, which may be relevant to the pathology of schizophrenia, can induce microglial activation in vivo (Frank et al., 2007, Schiavone et al., 2009, Tynan et al., 2010, Wohleb et al., 2011, Hinwood et al., 2012). A recent study using an analog of viral double-strand RNA (polynsinic-polycytidylic acid sodium salt [poly I:C] has shown that maternal infection during embryogenesis contributes to microglial activation in the offspring (Juckel et al., 2011). Other known risk factors for schizophrenia such as malnutrition and stress involve upregulation of inflammatory cytokines in maternal serum (Deverman and Patterson, 2009). It has recently reported that there is increased prevalence of *Chlamydophila* DNA in post-mortem brain frontal cortex from patients with schizophrenia. (Fellerhoff and Wank, 2011) Many infections have been shown to induce symptoms of mental illness, but these symptoms generally disappear after recovery from the acute illness. However, some symptoms may not disappear if acute infection becomes chronic. Microbes, which have the ability to permanently reside in the body, could permanently disturb brain functions. The primary targets of *Chlamydophila* infection in the blood are monocytes while the primary targets of *Chlamydophila* infection in the brain are probably microglia, which arise from monocyte populations. Persistent *Chlamydophila*- infected microglia or neuronal cells may impair neuronal circuits and thus be mechanism for causing illness in the patients with schizophrenia (Fellerhoff and Wank, 2011). Prolonged microglial hyperactivity may lead to neuronal apoptosis and brain damage which are commonly seen in neurodegenerative disorder such as Parkinson disease (PD) and Alzheimer's disease (AD) through the overproduction of inflammatory cytokines and free radicals (Block and Hong, 2005). A neurodegenerative and neurodevelopmental process is indicated in the course of schizophrenia (Lieberman, 1999, Perez-Neri et al., 2006) and may be associated with the microglial activation. Hypoglutamatergic states and impaired *N*-metyl-D-aspartate (NMDA) signaling underlie the pathophysiology of schizophrenia. NMDA antagonists such as phencyclidine (PCP), ketamine, and MK-801 offer an appropriate animal model of schizophrenia. All three NMDA antagonists are known to induce microglial activation in rodent brains (Nakki et al., 1995, Nakki et al., 1996). Interestingly, microglial activation or increased microglial cellular density has also been suggested by postmortem studies, at least in subpopulations of individuals with schizophrenia (Bayer et al., 1999, Radewicz et al., 2000, Steiner et al., 2006, Schnieder and Dwork, 2011). Highly elevated microglial cell numbers has been demonstrated in the anterior cingulate cortex and mediodorsal thalamus of patients with schizophrenia who had committed suicide during acute psychosis (Steiner et al., 2006). By using the technique of [11C] (R)-PK11195 used to systematically study microglial activation in vivo, researchers recently have reported increased microglial activation in the grey matters or hippocampus of patients with schizophrenia, while it is unclear whether or not the effects of this microglial activation is neuroprotective or detrimental (van Berckel et al., 2008, Doorduin et al., 2009). These positron emission computed tomography (PET) studies have demonstrated that activated microglia are present in schizophrenia patients within the first 5 years of disease onset (van Berckel et al., 2008) or in a psychotic state (Doorduin et al., 2009), respectively. Another recent PET study in chronic schizophrenia has shown that there are no significant differences between microglial activation of the cortical regions of normal controls and the patients with schizophrenia while microglial activation is positively correlated with positive symptoms scores as well as the duration of illness (Takano et al., 2010). A recent PET study has shown microglial activation in young patients with autism spectrum disorders (Suzuki et al., 2013). These results are very interesting because there are many similarities between schizophrenia and autism spectrum disorders (Lugnegard et al., 2013).

SCHIZOPHRENIA AND NEUROGENESIS

The relationship between depression and neurogenesis has been described in general (Warner-Schmidt and Duman, 2006) while one recent human postmortem brain study using Ki-67 immunoreactivity indicated that the phenomenon of neurogenesis is much more related to the pathophysiology of schizophrenia than that of depression (Reif et al., 2006). Repeated administration of PCP as well as MK-801 has recently been reported to inhibit hippocampal neurogenesis in vivo (Juan et al., 2006, Maeda et al., 2007). Mice harboring compound disruption in the neuronal PAS domain protein 3 (NPAS3) and related NPAS1 genes manifest behavioral and neuroanatomical abnormalities reminiscent of schizophrenia (Pickard et al., 2006). Basal neural precursor cell proliferation in the dentate gyrus of NPAS3 gene deficiency mice has been found to be reduced significantly, which indicated the impaired neurogenesis involved in schizophrenia (Pieper et al., 2005). Disrupted-In- Schizophrenia 1 (DISC1) is a well-known schizophrenia susceptibility gene. A recent study has shown that DISC1 regulates integration of newly generated neurons in the adult brain (Duan et al., 2007). The above results indicate the close relationship between schizophrenia and neurogenesis. With regard to neurogenesis, atypical antipsychotics not typical antipsychotics induced neurogenesis in adult brain of rodents (Maeda et al., 2007, Wakade et al., 2002, Kodama et al., 2004). On the other hand, CNS inflammation is detrimental for adult hippocampal neurogenesis (Monje et al., 2003, Ekdahl et al., 2003). The negative effects of inflammation on differentiation and survival of the neuronal cells are due, in vitro, to microglia-derived TNF-α and NO (Monje et al., 2003, Cacci et al., 2005). Pro-inflammatory cytokines such as Il-1β and TNF-α have been reported to inhibit neurogenesis in vivo (Iosif et al., 2006, Kaneko et al., 2006). In addition, in vivo, neurogenesis can be restored by anti-inflammatory drugs such as minocycline and indomethacin that inhibit microglial activation (Monje et al., 2003, Ekdahl et al., 2003).

SCHIZOPHRENIA AND APOPTOSIS

Structural brain abnormalities have been extensively and consistently described in schizophrenic patients. Longitudinal

studies using high-resolution MRI to examine brain structure have found that MRI volume changes were progressive over time and related to the course of illness and treatment outcome in schizophrenic patients (Davis et al., 2003, Kumra et al., 2005, Salisbury et al., 2007). A recent review has shown that continuous progressive brain tissue decreases and lateral ventricle volume increases in chronically ill patients with schizophrenia, up to at least 20 years after the first symptoms (Hulshoff Pol and Kahn, 2008). In fact, multiple lines of evidence combine to implicate the increased susceptibility for apoptotic death in the pathophysiology of schizophrenia. Reduced neuronal and glial cell numbers (mainly in astrocyte), decreased neuropil (especially of the synapse elements), lack of gliosis, and in vivo neuroimaging evidence of progressive gray matter loss early in the disorder, as mentioned above, make apoptosis as a plausible mechanism to explain the neurodegenerative course of schizophrenia. The activation of apoptotic process can lead to rapid neuronal death. However, emerging data also indicate that sub-lethal apoptotic activity can lead to a limited form of apoptosis in terminal neuritis and individual synapses to cause elimination without cell death (Glantz et al., 2006, Jarskog et al., 2005). Inappropriate activation of apoptosis occurs not only in the neurons, but also in the oligodendrocytes and synapses (Glantz et al., 2006). Proinflammatory cytokines such as TNF-α has been well characterized as a mediator of oxidative stress, and they induce the apoptosis in the human cortical neuron as well as oligodendrocytes (Medina et al., 2002, Buntinx et al., 2004). In addition, NO has been reported to directly induce neuronal apoptosis, but also to be involved in cytokine-mediated neuronal apoptosis (Palluy and Rigaud, 1996, Hu et al., 1997). The interaction between NO and superoxide anion (O^{2-}), which can be generated from activated microglia, forms peroxynitrite ($ONOO^{-}$). Peroxynitrite is highly toxic and triggers apoptotic cell death. Moreover, high levels of NO and TNF-α may also affect synaptogenesis, synaptic plasticity and connectivity, and the composition of synaptic membranes (Sunico et al., 2005, Stellwagen and Malenka, 2006). The alteration in the synaptic organization of the brain is one of the key features of schizophrenia (Roberts et al., 2005). Several postmortem studies have examined dendritic spine density changes in brain regions showing the greatest indice of gray matter loss in schizophrenia and these results support the view that spine density changes directly contribute to gray matter loss in the disease. Reduced spine density with gray matter loss is reported in dorsolateral prefrontal cortex (DLPFC), superior temporal gyrus, and hippocampus. These results reveal a strong association between brain region-specific loss of gray matter, reduced spine density and functional hypoactivity in schizophrenia (Penzes et al., 2011).

SCHIZOPHRENIA AND WHITE MATTER DISORDERS

Neuroimaging studies have shown that first-episode schizophrenia patients had a significant volume reduction in white matter with abnormal brain connectivity (Price et al., 2006, Schlosser et al., 2007, Lee et al., 2013, Wang et al., 2013). The reduced density and compromised morphology of the oligodendroglia cells as well as signs of deviant myelination have been evident in schizophrenia (Uranova et al., 2004, Bernstein et al., 2009, Uranova et al., 2007). Combined with the evidence of dysregulation of the myelination-related genes, a disruption of the oligodendrocyte function in schizophrenia is strongly implicated (McCullumsmith et al., 2007). Microglial activation in the CNS has been implicated in the pathogenesis of white matter disorders and it has recently been reported that microglial cytotoxicity of oligodendrocyte is mediated through free radical-related molecules such as NO and peroxynitrite generated by activated microglia (Li et al., 2005, Merrill et al., 1993) and inflammatory cytokines such as TNF-α and IFN-γ (Buntinx et al., 2004). In addition, TNF-α has been shown to compromise the growth of oligodendrocytes and the expression of mRNA for myelin basic protein (MBP) in cultures (Cammer and Zhang, 1999). Furthermore, it inhibited the survival and proliferation of the oligodendrocyte progenitors and their subsequent differentiation into mature myelinating phenotypes (Feldhaus et al., 2004). These results are intriguing because Mittelbronn et al. have demonstrated that local distribution of microglia in the normal adult human brain differs by up to one order of magnitude and that there are significantly more microglia in white matter than in gray matter (Mittelbronn et al., 2001).

TREATMENT OF SCHIZOPHRENIA THROUGH THE CONTROL OF NEUROINFLAMMATION

Although here we describe two apparently disparate groups of disorders, they do share some clinical characteristics such as social cognition (King and Lord, 2011, Sugranyes et al., 2011, Lugnegard et al., 2013). Epidemiology studies reveal that maternal infections and obstetric complications impose high risk for both schizophrenia and autism. A recent complex network and computational analysis revealed that genetic variations associated with schizophrenia can occur in the same molecular pathways and functional domains (Cristino et al., 2013). From the above discussion, it is clear that abnormal microglial activation or intrinsic microglial abnormalities are also a shared feature of schizophrenia. Taming microglia-associated neuroinflammation as a therapeutic approach has been extensively studied in schizophrenia

ANTI-INFLAMMATORY STRATEGY FOR SCHIZOPHRENIA

Second generation antipsychotics such as olanzapine and risperidone are becoming standard drugs for the treatment of schizophrenia due to their less adverse effects and more effectiveness for the negative symptoms of schizophrenia (Lieberman et al., 2005). Some recent reports have suggested the possibility of specific second generation antipsychotics having pharmacological properties that could produce neurotrophic, neurogenetic, or neuroprotective effects. Namely, specific atypical antipsychotics such as olanzapine and risperidone have been reported to decrease the reduction of MRI volume during the clinical course of schizophrenia (Lieberman et al., 2005, Chakos et al., 2005, Massana et al., 2005, Girgis et al., 2006) while a recent report has shown a brain tissue loss due to the long-time antipsychotic treatment (Ho et al., 2011). There have some reports that studied the effect of antipsychotics on neuroinflammation in vitro or in vivo. Kowalski et al. demonstrated that flupentixol and trifluperidol reduced the secretion of TNF-α and NO by the activated microglia (Kowalski et al., 2003), and flupentixol, trifluperidol, chlorpromazine and loxapine have been reported

to reduce IL-1β and IL-2 release by the activated microglia (Kowalski et al., 2004, Labuzek et al., 2005). Until recently, the pharmacological action of second generation antipsychotics on microglial cells has not been well understood. Hou et al. demonstrated that olanzapine inhibited NO release from the activated microglia, while haloperidol and clozapine did not (Hou et al., 2006). We recently demonstrated that risperidone significantly inhibited the IFN-γ-activated microglia-derived production of NO and pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α in comparison to haloperidol a typical first generation antipsychotics (Kato et al., 2007). There have been some reports that suggested the relationship between schizophrenia and IFN-γ, a major immunoactivator in the CNS. The most important immunological studies in schizophrenia have shown a shift fromTh1-like cellular to Th2-like humoral immune reactivity to be the most characteristic common immune findings and these studies have suggested a blunted IFN-γ signal in schizophrenia (Schwarz et al., 2001). However, Rothermundt et al. have argued that the reduced IFN-γ production in vitro may reflect an increased production in vivo, as it is found in several autoimmune disorders (Rothermundt et al., 2001). Furthermore, the serum levels of IL-2 and IFN-γ, and the production of these cytokines from the peripheral blood mononuclear cells (PBMC) stimulated by phytohemagglutinin (PHA) have been reported to be significantly higher in schizophrenic patients than in controls (Cazzullo et al., 2001). A recent systematic quantitative review on the inflammatory cytokine alterations in schizophrenia did not necessarily support the Th2 shift hypothesis of schizophrenia while the levels of IL-6, the Th2 related cytokine, were increased after eliminating medication effects (Potvin et al., 2008). We furthermore demonstrated the same inhibitory effects on IFN-γ-induced microglial activation by other atypical antipsychotics such as perospirone and quetiapine (Bian et al., 2008). Spiperone, a typical antipsychotic, also inbibited the production of NO and pro-inflammatory cytokines such as IL-1β and TNF-α from activated microglia while spiperone was neuroprotective, as the drug reduced microglia-mediated neuroblastoma cell death in the microglia/neuron co-culture (Zheng et al., 2008). Sugino et al. have demonstrated that clozapine, olanzapine, and risperidone, but not haloperidol suppress production of pro-inflammatory cytokines such as TNF-α and IL-6 and up-regulate anti-inflammatory cytokines such as IL-10 in LPS -treated mice. They have also demonstrated that clozapine alone suppress poly I:C-induced inflammation (Sugino et al., 2009). Risperidone have also recently been reported to normalize increased inflammatory parameters and restores anti-inflammatory pathways in a model of neuroinflammation (MacDowell et al., 2013). Aripiprazole is a novel second generation antipsychotic, which is a high-affinity dopamine D2 receptor partial agonist. We also demonstraretd that aripiprazole significantly inhibited the generation of nitric oxide (NO) and TNF-α from IFN-γ-activated microglia while quinpirole, dopamine D2 full agonist did not in vitro. Our results demonstrated that not only antipsychotics which have dopamine D2 receptor antagonism but also aripiprazole, a dopamine D2 receptor partial agonist, have anti-inflammatory effects via the inhibition of microglial activation (Kato et al., 2008). Social isolation has been reported to cause behavioral and pathological alterations in rats due to the oxidative stress by superoxide derived from the nicotinamide dinucleotide phosphate (NADPH) oxidase (NOX) system in activated microglia (Schiavone et al., 2009). We have recently demonstrated that aripiprazole inhibits superoxide generation through the NOX system in phorbol-myristate-acetate (PMA)-stimulated microglia in vitro (Kato et al., 2007). These results are very intriguing because the loss of fast-spiking, parvalbumin (PV)-positive interneurons found in the prefrontal cortex of ketamine mice model of schizophrenia is reported to be mediated by the oxidative stress through the Nox system. Repetitive adult exposure to the NMDAR antagonist ketamine has been reported to increase the levels of IL-6 in brain which, through the activation of NOX2 system, lead to the loss of the GABAergic phenotype of PV-interneurons and to the decreased inhibitory activity in prefrontal cortex (Behrens et al., 2007, Behrens and Sejnowski, 2009, Powell et al., 2012). Microglia are known to have some neurotransmitter receptors including dopamine D2 receptors (Pocock and Kettenmann, 2007). However, since second generation drugs such as olanzapine have positive effects on neuronal cell growth and survival by unique signaling pathways (Lu and Dwyer, 2005), the pharmacological basis for their neuroprotective effect appears not to be only directly related to the conventional neurotransmitter receptors. All of these studies suggest that some antipsychotics may therefore have a potentially useful therapeutic effect on patients with schizophrenia by reducing the microglial inflammatory reactions, which may cause the apoptotic process, and the white matter abnormalities in the brains of patients with schizophrenia. It is consistent with the evidence showing their influences on slowing the progressive reduction in cortical gray matter in schizophrenia (Lieberman et al., 2005). However, some recent reports have shown some antipsychotics to increase the production of pro-inflammatory cytokines (Kluge et al., 2009, Himmerich et al., 2011). Some recent reports have demonstrated the possible antipsychotic effect of minocycline which is a potent inhibitor of microglial activation. In these studies, adjunctive therapy of minocycline to antipsychotics were reported to be beneficial for the treatment of schizophrenia (Miyaoka et al., 2007, Miyaoka et al., 2008, Levkovitz et al., 2010, Kelly et al., 2011). A recent study by Chaudhry et al has demonstrated that adjunctive therapy of minocycline to antipsychotics predominatly improved negative symptoms, which are usually treatment –resistant to antipsychotics (Chaudhry et al., 2012).

On the other hand, microglia can secrete neurotrophic factors other than proinflammatory cytokines including BDNF and free radicals. BDNF is well known to have a key role in the brain developmental problems associated with schizophrenia (Weickert et al., 2003). In addition, some in vitro data indicate an impairment of intracellular Ca^{2+} signaling in patients with schizophrenia (Bojarski et al., 2010). Recently, we have shown that BDNF induces sustained elevation of intracellular Ca^{2+} in rodent microglia, which might be important for the pathopsysiology and/or the treatment of schizophrenia (Mizoguchi et al., 2009). A recent study has shown that α7 nicotinic acetylcholine receptor agonist (α7nAChR) can modify microglial activation toward a neuroprotective role by suppressing the inflammatory state and strengthening the protective function (Suzuki et al., 2006). These results are very interesting because some α7nAChR agonists are known to improve the cognitive dysfunction of schizophrenia (Lieberman et al., 2008). Omega-3 fatty acids, which can inhibit microglial activation, have recently been reported to reduce

the rate of progression to first-episode psychotic disorders (Lu et al., 2010, Amminger et al., 2010). Based upon the above results, the appropriate control of microglial activation may thus be a promising target for the prevention and treatment of schizophrenia.

Immunomodulatory drugs such as cyclooxygenase-2 (COX-2) inhibitors have recently been reported to show beneficial effects on schizophrenic symptoms. Another recent randomized, double-blind, placebo-controlled trial has shown that adjuvant acetylsalicylic acid (aspirin) therapy reduces symptoms of schizophrenia spectrum disorders (Akhondzadeh et al., 2007, Muller et al., 2005, Muller et al., 2010, Laan et al., 2010). A recent meta-analysis on the use of non-steroidal anti-inflammatory agents (NSAIDs) in schizophrenia have demonstrated that NSAID augmentation could be a potentially useful strategy for the treatment of positive and negative symptoms of schizophrenia and that aspirin may have the additional benefit reducing cardiac and cancer mortality in schizophrenia (Sommer et al., 2012&2014). Successful treatment of psychosis with infliximab, a monoclonal antibody against TNF-α has also been reported in a patients with Crohn's disease (Reimer et al., 2009). Immunosuppressive or immunomodulatory drugs may thus be beneficial at least for the treatment of acute schizophrenia (Knight et al., 2007). Controlling anti-inflammatory signaling is also important for the treatment of schizophrenia (Meyer, 2011). Reactive oxygen species derived from activated microglia are also relevant to the pathophysiology of schizophrenia. Anti-oxidants such as N-Acetyl-Cysteine (NAC) may thus be useful for the treatment of schizophrenia. Some randomized, double-blind studies shown the effectiveness as the augmentation therapy of schizophrenia of NAC (Sansone and Sansone, 2011).

CONCLUSIONS

In many aspects, the neuropathology of schizophrenia is closely associated with neuroinflammation, especially microglial activation. As described above, their respective anti-neuroinflammation therapies are also strikingly similar. Our understanding about the connection between microglial abnormalities and neuropsychiatric disorders is at its infant stage, but we foresee the tremendous potential of therapeutic approaches targeting microglia. This anticipation is based on two considerations. First, microglia quickly respond to various stimuli with an amazingly dynamic behavioral repertoire, therefore are highly transmutable by therapeutic interventions. Second, our view of the brain being "immune privileged" is fundamentally changed in recent years, with the realization that the systemic immune system has the ability to modulate multiple brain functions (Lynch and Mills, 2012), in part through interactions between peripheral immune cells such as dendritic cells and mast cells with their CNS counterparts, such as microglia. Therefore, approaches to modify the neuroinflammatory environment that is conducive to neuropsychiatric disorders can be launched peripherally. Peripheral immune cells are relatively straightforward to isolate and manipulate *ex vivo*, and are able to enter the CNS via endogenous mechanisms (Derecki et al., 2013), providing a foundation for novel cell-based therapies or "vaccines". To achieve this goal, a fundamental question that needs to be investigated in depth is how peripheral immune modulation affects brain function. In our view, schizophrenia provides excellent opportunities for gaining such understanding of the complex interactions between CNS and systemic immune system, a gateway to a true "mind-body" problem (Feigenson et al., 2014).

THE BULLET POINTS

*An accumulating body of evidences point to the significance of neuroinflammation in schizophrenia.

*The neuropathology of schizophrenia is closely associated with microglial abnormalities in many aspects.

*Some typical or atypical antipsychotics have been reported to inhibit the release of inflammatory cytokines and free radicals from activated microglia.

*The treatment through the control of microglial abnormalities may shed new light on the therapeutic strategy of schizophrenia.

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