Anti-Inflammatory Properties of Antipsychotics *Via* Microglia Modulations: Are Antipsychotics a 'Fire Extinguisher' in the Brain of Schizophrenia?

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Abstract: Schizophrenia is one of the most severe psychiatric diseases noted for its chronic and often debilitating processes; affecting approximately 1% of the world's population, while its etiology and therapeutic strategies still remain elusive. In the 1950s, the discovery of antipsychotic effects of haloperidol and chlorpromazine shifted the paradigm of schizophrenia. These drugs proved to be antagonists of dopamine D2 receptor (D2R), thus dopamine system dysfunction came to be hypothesized in the pathophysiology of schizophrenia, and D2R antagonism against dopamine neurons has been considered as the primary therapeutic target for schizophrenia. In addition, abnormalities of glutamatergic neurons have been indicated in the pathophysiology of schizophrenia. On the other hand, recent neuroimaging studies have shown that not only dementia but also schizophrenic patients have a significant volume reduction of some specific regions in the brain, which indicates that schizophrenia may involve some neurodegenerative process. Microglia, major sources of various inflammatory cytokines and free radicals such as superoxide and nitric oxide (NO) in the CNS, play a crucial role in a variety of neurodegenerative diseases such as dementia. Recent postmortem and positron emission computed tomography (PET) studies have indicated that activated microglia may be present in schizophrenic patients. Recent *in vitro* studies have suggested the anti-inflammatory effects of antipsychotics on microglial activation. In this article, we review the anti-inflammatory effects of antipsychotics on microglia, and propose a novel therapeutic hypothesis of schizophrenia from the perspective of microglial modulation.

Keywords: Antipsychotics, schizophrenia, microglia, inflammation, cytokines, free radicals, oxidative stress, dopamine D2 receptors.

INTRODUCTION

Schizophrenia is one of the most severe psychiatric diseases noted for its chronic and often debilitating processes; affecting approximately 1% of the world's population, while its etiology and therapeutic strategies still remain elusive [1].

Microglia, major sources of various inflammatory cytokines and free radicals such as superoxide and nitric oxide (NO) in the CNS, play a crucial role in a variety of neurodegenerative diseases such as dementia and neuropathic pain [2-9]. Neuroimaging studies have shown that not only dementia but also schizophrenia patients have a significant volume reduction, which indicates that schizophrenia may involve some neurodegenerative process [10-12]. In addition, recent postmortem brain studies using class II human leucocyte antigen (HLA)-DR have revealed microglial activation in the brains of schizophrenic patients [13, 14]. Positron emission computed tomography (PET) studies with specific ligand of the peripheral benzodiazepine-binding sites (PBBS), have indicated that activated microglia may be present in schizophrenic patients [15-17]. On the other hand, COX-2 inhibitor and minocycline, both of which have proved to inhibit microglial activation, are suggested to have antipsychotic effects [18-20]. We recently investigated the anti-inflammatory effects of antipsychotics on microglial activation *in vitro* [21-24].

In this article, we review the anti-inflammatory effects of antipsychotics on microglia, and propose a novel therapeutic hypothesis of schizophrenia from the perspective of microglial modulation.

HISTORY OF THERAPEUTIC STRATEGIES FOR SCHIZOPHRENIA: FROM WATER THERAPY TO D2R ANTAGONISTS

The pathophysiology of schizophrenia has been investigated from ancient times, and its therapeutic strategies

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have shifted through history. In ancient times, traditional remedies such as hypothermia (cold narcosis) and water therapy, as if extinguishing 'fire' in the brain, had been conducted, however these remedies are now even regarded to be nonsensical. In late 19th century, Kraepelin categorized a psychotic syndrome, which is now regarded to be schizophrenia, as one of the brain diseases, and he named it 'dementia praecox [early dementia]' to distinguish it from other forms of dementia such as Alzheimer's disease which typically occur late in life [25]. From that time, with the discovery of brain volume reduction in the brain of dementia patients, many researchers focused on the neuropathologies of schizophrenia, while significant pathological discoveries did not eventuate, leading to the remark that "schizophrenia is the graveyard of neuropathologists" [26].

In the 1950s, the discovery of antipsychotic effects of haloperidol and chlorpromazine shifted the paradigm of schizophrenia. These drugs proved to be antagonists of dopamine D2 receptor (D2R), thus dopamine system dysfunction came to be hypothesized in the pathophysiology of schizophrenia, and D2R antagonism against dopamine neurons has been considered as the primary therapeutic target for schizophrenia [27, 28]. In addition, abnormalities of glutamatergic neurons have been indicated in the pathophysiology of schizophrenia [29, 30].

As shown in the introduction, recent neuroimaging studies have shown that not only dementia but also schizophrenic patients have a significant volume reduction of some specific regions in the brain, which indicates that schizophrenia may involve some neurodegenerative process [10-12], and recent postmortem and PET studies have indicated that activated microglia exist in schizophrenic patients [13-17]. These findings seem to revive the Kraepelin's hypothesis of schizophrenia as a neurodegenerative disorder in modern psychiatric world [31].

NEUROPROTECTIVE EFFECTS OF ATYPICAL ANTIPSYCHOTICS

Classical antipsychotics such as haloperidol and chlorpromazine had been mainly used for the treatment of schizophrenia since the 1960s, while atypical antipsychotics are becoming standard drugs due to their less severe side-effects and greater effectiveness on the negative symptoms of schizophrenia [32, 33]. Atypical antipsychotics (also called as 'second-generation antipsychotics) are characterized by having various functions in comparison with traditional antipsychotics which were only focused on dopamine affinities [27]. Some recent reports have suggested the possibility of specific atypical 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 [11, 12].

The underlying mechanisms of these effects have yet to be determined. We hypothesize that these protective effects may result in microglial modulation by atypical antipsychotics, and herein introduce novel knowledge regarding effects of antipsychotics on microglia as follows.

ANTIPSYCHOTICS MODULATE MICROGLIAL INFLAMMATORY ACTIVATION *IN VITRO*

To the best of our knowledge, there have been a few reports that studied the effects of antipsychotics on microglial activation *in vitro*. Regarding classic typical antipsychotics, Kowalski *et al*. demonstrated that flupentixol and trifluperidol reduced the secretion of tumor necrosis factor (TNF)-α and NO by the lipopolysaccharide (LPS)-activated microglia from rat primary cultures [34], in addition flupentixol, trifluperidol, chlorpromazine and loxapine have been reported to reduce interleukin (IL)-1β and IL-2 release by the LPS-activated microglia [35, 36]. Until recently, the pharmacological action of atypical antipsychotics on microglial cells has not been well understood. Hou *et al*. demonstrated that olanzapine inhibited NO secretion from the LPS-activated microglia (murine N9 cells), while haloperidol and clozapine did not [37]. We demonstrated that risperidone, one of the major atypical antipsychotics, significantly inhibited the productions of NO and pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α from the interferon (IFN)-γ-activated microglia (murine 6-3 cells) in comparison to haloperidol, a typical antipsychotic drug [21]. Next, we demonstrated the similar inhibitory effects on IFN-γ-induced microglial activation by other atypical antipsychotics such as perospirone and quetiapine. Perospirone, quetiapine and ziprasidone significantly inhibited the NO release, and quetiapine and perospirone significantly inhibited the TNF-α release, while ziprasidone significantly increased the TNF-α release [22]. Zheng *et al.* reported that spiperone, a typical antipsychotic drug, also inhibited the production of NO and pro-inflammatory cytokines such as IL-1β and TNF-α from LPS-activated microglia (murine BV-2 cells and mouse primary cultures), besides spiperone proved to be neuroprotective as the drug reduced microglia-mediated neuroblastoma cell death in the microglia/neuron co-culture [38].

All of above-mentioned antipsychotics have D2R antagonism, while aripiprazole is a novel unique atypical antipsychotic drug, which is a high-affinity D2R partial agonist [39, 40]. In spite of its different pharmacological profile, aripiprazole is effective against the positive and negative symptoms of patients with schizophrenia like other antipsychotics with fewer side effects [33, 41]. We demonstrated that aripiprazole significantly inhibited the generation of NO and TNF-α from IFN-γ-activated microglia (murine 6-3 cells and rat primary cultures), while quinpirole, a D2R full agonist, did not. Our study demonstrated that not only antipsychotics which have D2R antagonism but also aripiprazole with a D2R partial agonism has anti-inflammatory effects *via* the inhibition of microglial activation [23].

Microglia are known to have various receptors of neurotransmitters including D2R [23, 42]. However, since atypical antipsychotics have positive effects on neuronal cell growth and survival by unique signaling pathways [43], the pharmacological basis for their neuroprotective effect appears not to be only directly related to the conventional neurotransmitter receptors. We observed that the pretreatment with aripiprazole [23] and other atypical

Table 1. Effects of Antipsychotics on Microglial Activation *In Vitro*

Antipsychotics	Typical/Atypical (class)	Microglia	Species	Activator	Proinflammatory Cytokines	Free Radicals	References
Flupentixol	Typical (thioxanthenes)	Primary Culture	Rat	LPS	IL-1β & IL-2, TNF-α: Inhibited	NO: inhibited	Kowalski *et al*. (2003 & 2004)
Trifluperidol	Typical (butyrophenones)			LPS	IL-1β & IL-2, TNF-α: Inhibited	NO: inhibited	
Chlorpromazine	Typical (phenothiazines)	Primary Culture	Rat	LPS	IL-1β & IL-2: Inhibited	-	Labuzek *et al*. (2005)
Loxapine	Typical (dibenzoxazepines)			LPS	IL-1β & IL-2: Inhibited	-	
Haloperidol	Typical (butyrophenones)	Cell Line (N9)	Mouse	LPS	-	NO:not inhibited	Hou *et al*. (2006)
Clozapine	Atypical*			LPS	-	NO:not inhibited	
Olanzapine	Atypical			LPS	-	NO:inhibited	
Haloperidol	Typical (butyrophenones)	Cell Line (6-3)	Mouse	IFN-γ	IL-1β, IL-6 & TNF-α: Inhibited	NO:slightly inhibited	Kato *et al*. (2007)
Risperidone	Atypical			IFN-γ	IL-1β, IL-6 & TNF-α: Inhibited	NO:inhibited	
Quetiapine	Atypical	Cell Line (6-3)	Mouse	IFN-γ	TNF-α: Inhibited	NO:inhibited	Bian *et al*. (2008)
Perospirone	Atypical			IFN-γ	TNF-α: Inhibited	NO:inhibited	
Ziprasidone	Atypical			IFN-γ	TNF-α: Activated	NO:inhibited	
Aripiprazole	Atypical (D2R partial Agonist)	Cell Line (6-3)	Mouse	IFN-γ	TNF-α: Inhibited	NO:inhibited	Kato *et al*. (2008)
		Primary Culture	Rat	LPS	-	NO:inhibited	
Aripiprazole	Atypical (D2R partial Agonist)	Cell Line (6-3)	Mouse	PMA	-	superoxide: inhibited	Kato *et al*. (in press)
		Primary Culture	Rat	PMA	-	superoxide: inhibited	
Spiperone	Typical (butyrophenones)	Cell Line (BV-2)	Mouse	LPS	IL-1β, TNF-α: Inhibited (mRNA)	NO:inhibited	Zheng *et al*. (2008)
		Primary Culture	Mouse	ATP	-	NO:inhibited	

*Clozapine is the first atypical antipsychotic drug which was initially developed in 1971.
LPS, lipopolysacharide; IFN-γ, interfelon-γ; PMA, Phorbol 12-myristate- 13-acetate; ATP, adenyl triphosphate; IL, interleukin; TNF, tumor necrosing factor; NO, nitric oxide.

antipsychotics (these data: not published) attenuated the mobilization of intracellular Ca^{2+} induced by IFN-γ and LPS in murine microglia. Intracellular Ca^{2+} is one of the endogenous activators of protein kinase C (PKC). Phorbol 12-myristate- 13-acetate (PMA), an activator of PKC, induces the activation of microglia [44]. In microglia, PKC has been reported to be an important initiator of the MAPK signaling pathway in the CNS. The activation of PKC affects MAPK cascade proteins including ERK 1/2 and p38 MAPK [45]. p38 MAPK plays a major role in the LPS-activated murine BV2 microglia while ERK 1/2 plays a major role in the IFN-γ activated BV2 microglia [46, 47]. Based on these reports, we can speculate that aripiprazole may inhibit IFN-γ-induced microglial activation through the suppression of IFN-γ-induced elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) in microglia. The effect of aripiprazole on Ca^{2+} regulation shown in Kato *et al*. (2008) is interesting because Ca^{2+} signaling dysfunction is proposed for the central unifying molecular pathology in schizophrenia [48]. However, aripiprazole may modulate the expression of other factors that act upstream of calcium to dampen IFN-γ-induced signaling. On the other hand, these intracellular activations translocate NF-κB from cytosol to nucleus in microglia, and which is well known to produce inflammatory cytokines and NO *via* nucleus response [44]. For example, spiperone was reported to inhibit LPS-induced microglial activation by inhibiting NF-κB activation and p38 MAPK phosphorylation [38]. Based on the above-mentioned data, we summarized and schematized possible mechanisms of anti-inflammatory actions of antipsychotics in Fig. (**1**).

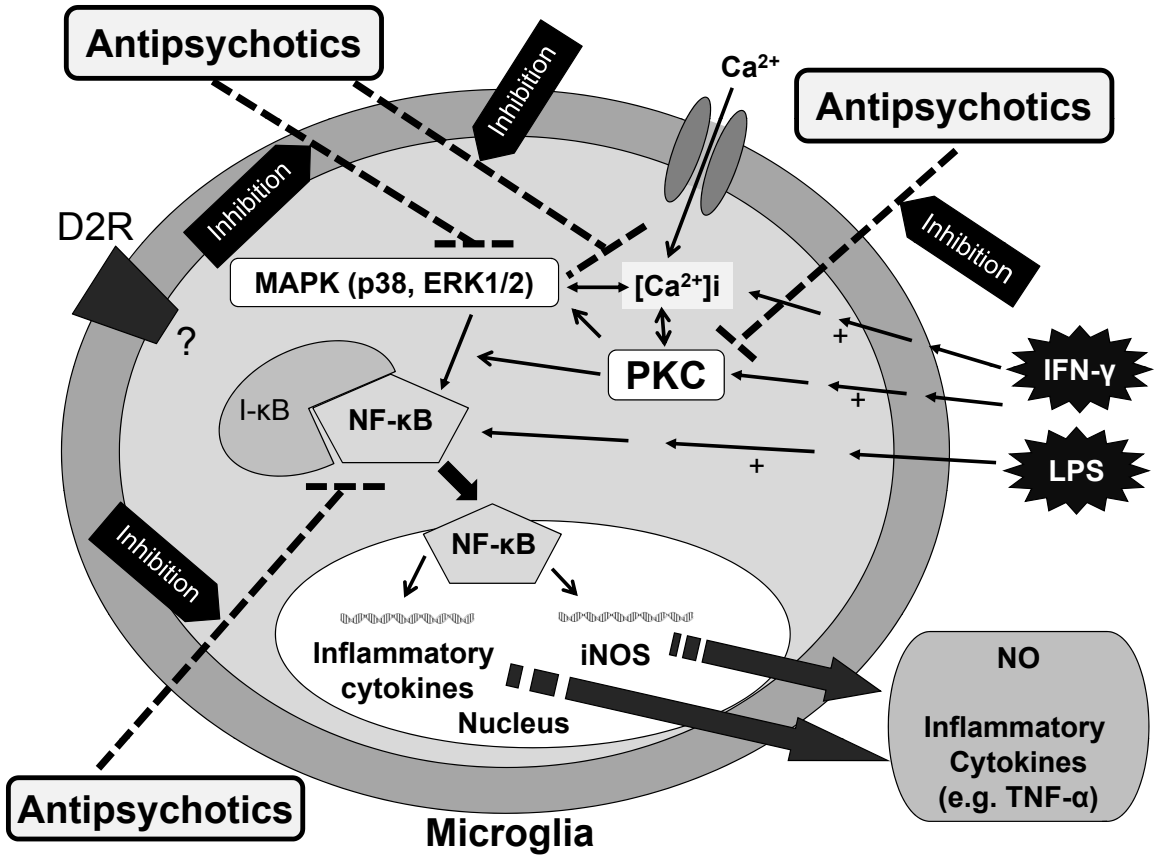

Fig. (1). Scheme for possible mechanisms of antipsychotics on anti-inflammatory action in microglia.

Antipsychotic anti-inflammatory action in microglia seems to be beyond actions *via* dopamine D2 receptors (D2R).

IFN-γ and/or LPS evokes inflammatory transactivations by upregulation of MAPK, PKC pathway and elevation of $[Ca^{2+}]_i$ in microglia. These activations translocate NF-κB from cytosol to nucleus, and which produce inflammatory cytokines and NO *via* nucleus response.

Antipsychotics seem to have potential inhibitory effects of microglial activation by modulating the intracellular cascades such as MAPK, PKC pathway, calcium signaling and NF-κB cascade.

EFFECTS OF ANTIPSYCHOTICS WITH ANTI-OXIDATIVE ACTION

Altered antioxidant status has recently been implicated in schizophrenia with increasing amount of clinical evidence measuring biochemical components for detoxification of reactive oxygen species (ROS) such as Glutathione (GSH) and superoxide dismutase (SOD) [49-51]. N-Acetyl cysteine (NAC), a glutathione precursor, has been reported to be effective for augmentation therapy of chronic schizophrenia and to improve impaired mismatch negativity in schizophrenic patients [52, 53]. Recently, the serum levels of SOD in chronic patients with schizophrenia are associated with psychopathology and response to antipsychotics [54]. These findings suggest that regulation of oxidative stress may be related to the pathophysiology and therapeutic mechanism of schizophrenia.

Antioxidants have recently been regarded to have protective effects in neurodegeneration, and microglial activation *via* NADPH oxidase has a key role in this process [55]. Interestingly, we have recently investigated the novel role of aripiprazole as an anti-oxidative drug by modulating microglia-induced superoxide *in vitro* [24]. Aripiprazole inhibited the superoxide generation from PMA-stimulated murine 6-3 microglia and rat primary microglia. Aripiprazole proved to inhibit the superoxide generation through the cascade of PKC activation, intracellular Ca^{2+} regulation and NADPH oxidase activation *via* cytosolic $p47^{phox}$ translocation to the plasma/phagosomal membranes.

EFFECTS OF ANTIPSYCHOTICS ON GLIAL ACTIVATION *IN VIVO*

Several animal studies have also indicated that atypical antipsychotics, but not typical antipsychotics, possess potency to attenuate glial activation, also referred to as gliosis, in the pathological brain. Zhang *et al*. (2008) have determined the effect of the atypical antipsychotic quetiapine on gliosis in the mouse brain [56]. Cuprizone is a copper chelator and is known as a demyelination inducer. Peroral administration of cuprizone caused demyelination in the cerebral cortex and both microgliosis shown by increased immunoreactivity of CD11b and astrogliosis shown by increased immunoreactivity of glial fibrillary acidic protein (GFAP) in the corpus callosum. Peroral administration of quetiapine significantly prevented such microgliosis and astrogliosis as well as demyelination. Arif *et al*. (2007) have shown a difference in effects on gliosis between typical and atypical antipsychotic drugs [57]. Intraperitoneal injection of

MK-801, an N-methyl-D-aspartate (NMDA) receptor antagonist, induced microgliosis, as indicated by the number of CD11b-positive cells, and astrogliosis, as indicated by the number of GFAP-positive cells and protein amount of GFAP, in the posterior cingulate and retrosplenial cortex of rats. Intraperitoneal pretreatment with the atypical antipsychotic clozapine significantly attenuated both the microgliosis and astrogliosis. In contrast, the typical antipsychotic haloperidol was devoid of such suppressive effects.

In line with these observations, intramuscular pretreatment with haloperidol had no influence on microglial activation, which was shown by the number of OX42-positive cells, in the retrosplenial cortex of rats intraperitoneally injected with ketamine, an NMDA receptor antagonist [58]. Likewise, haloperidol pretreatment failed to block microgliosis induced by the NMDA antagonist phencyclidine in the posterior cingulate and retrosplenial cortex of rats [58].

DO ANTIPSYCHOTICS MODULATE ASTROCYTIC ACTIVATION?

The above-mentioned *in vivo* studies have suggested that antipsychotics also modulate astrocytic activation. We herein introduce recent reports regarding the effects of antipsychotics on astrocytic activation and functions *in vitro*.

Risperidone has been shown to upregulate intracellular production of both GSH and glutamine and glutamate uptake by rat astrocytic C6 cells, while haloperidol has no effect on those astrocytic functions except that the drug increases intracellular ROS production at relatively high concentrations (10 μM) [59]. Risperidone is also reported to increase the NO secretion from non-stimulated C6 cells [60], whereas spiperone is shown to decrease the NO secretion from murine primary astrocytes stimulated with LPS alone or LPS plus IFN-γ [38]. In contrast to risperidone, clozapine has been demonstrated to inhibit glutamate uptake accompanied with reduction in glutamate transporter-1 expression in rat primary astrocyte cultures [61].

Effects of antipsychotics on astrocytic production of S100B, an astrocyte-specific neurotrophic factor, are also controversial. Steiner *et al.* (2010) showed that both haloperidol and clozapine decreased C6 cell generation of S100B [62]. On the other hand, Quincozes-Santos *et al*. (2008) demonstrated that risperidone increased S100B secretion from C6 cells [63].

Taken together, above-mentioned studies show inconsistent effects of antipsychotics on astrocytic activity *in vitro*. These discrepancies may stem from a difference in drug concentrations used as pointed out by Steiner *et al.* [62]. For example, they tested 0.1-1 μg/ml of haloperidol and 1-10 μg/ml of clozapine on C6 cells. These concentrations appear to correspond to the therapeutic ranges of the drugs. Quincozes-Santos *et al.* employed risperidone at the range of 4105-16420 μg/ml [63], which is not toxic to C6 cells but seems to be beyond the therapeutic range. Further studies are needed to clarify whether antipsychotics inhibit astrocytic activation or not.

MICROGLIA HYPOTHESIS OF SCHIZOPHRENIA; IMPLICATION OF ANTIPSYCHOTICS AS A FIRE EXTINGUISHER FOR SCHIZOPHRENIA

Here again, focusing on microglia, we have been proposing a microglia hypothesis of schizophrenia (Fig. **2**). Recent findings have suggested that resting microglia are monitoring micro-environmental changes including synapses in the brain [64, 65]. Animal studies have reported that stressors, including physical pain and isolation, may induce microglial activation [66-68]. Another animal study indicated that microglial activation causes anxiety, which in turn can be decreased by minocycline treatment [69]. Therefore, these reports imply that various physical and psychological stresses such as traumas may have induced microglial activation in the course of developing schizophrenia.

Neuronal developments during early life stages have been suggested to develop schizophrenia [70-72]. Gene-environmental interactions such as infections, especially viral infections, during pre- and post- natal states and/or developing periods have long been indicated to have positive link to schizophrenia onset in adolescent periods [73-76]. Microglia is one of the key players in brain damages induced by virus infections in the CNS [5]. IFN-γ is released by infiltrating T cells as well as from activated microglia in the CNS [77]. The serum levels of IL-2 and IFN-γ, and the production of these cytokines from peripheral blood mononuclear cells (PBMC) stimulated by phytohemagglutinin (PHA) has been reported to be significantly higher in patients with schizophrenia than in controls [78, 79]. Therefore, microglia may be activated by immunological/inflammatory activators such as IFN-γ during episodes of life course stress (e.g. infections and physical/psychological traumas) during pre- and post- natal states, developmental states and other life events.

Recent schizophrenia hypothesis has been highlighting the following three brain pathological factors. Firstly, the increased susceptibility to apoptotic death has indicated in the pathophysiology of schizophrenia [80]. Secondly, a recent postmortem brain study has indicated a close relationship between schizophrenia and neurogenesis [81]. Thirdly, structural imaging studies, as well as gene expression studies and evidence for the dysfunction of myelin and oligodendrocyte, have suggested the presence of abnormalities of white matter in schizophrenia [82-84]. Regarding microglia, various evidences have indicated the positive relationship between microglial activation and the following brain damages such as the apoptotic process, the inhibition of neurogenesis and the white matter abnormalities. Increasing evidences support that microglia-derived inflammatory cytokines and free radicals can lead to apoptosis, neuronal death [3, 5, 85], the inhibition of neurogenesis [86-89] and the cytotoxicity of oligodendrocyte [90-92]. Therefore, microglial activation may cause the apoptotic process, the inhibition of neurogenesis, and the white matter abnormalities in the developing brains of children and adolescents and/or the brain of patients with onset/relapse stages of schizophrenia.

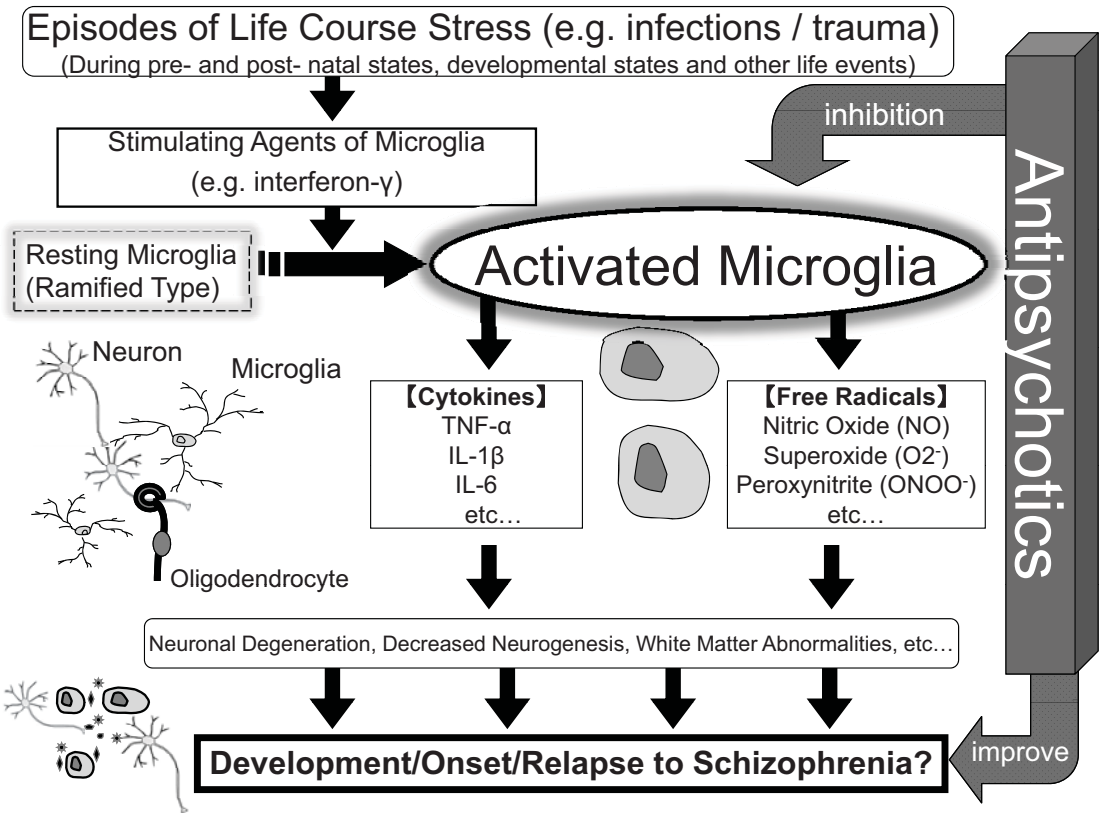

Fig. (2). Microglia hypothesis of schizophrenia

Microglia are activated by immunological/inflammatory activators such as interferon-γ during episodes of life course stress (e.g. infections and physical/psychological traumas) in pre- and post- natal states, developmental states and other life events. Activated microglia release proinflammatory cytokines and free radicals. These mediators are known to cause neuronal degeneration, decreased neurogenesis and white matter abnormalities. These neuron/oligodendrocyte-microglia interactions may thus be one of the important factors in the pathophysiology of schizophrenia.

Atypical antipsychotics have recently been suggested to have novel pharmacological properties that could produce neurotrophic, neurogenetic, or neuroprotective effects, while the underlying mechanisms of these effects have yet to be determined. Microglial modulation may be a key factor of these mechanisms. Antipsychotics may have therapeutic effects on patients with schizophrenia by reducing microglial inflammatory/oxidative reactions and following neuron/oligodendrocyte reactions, which puts forward a novel therapeutic hypothesis beyond dopamine/neuron doctrine in the field of schizophrenia research.

Atypical antipsychotics have recently been suggested to have novel pharmacological properties that could produce neurotrophic, neurogenetic, or neuroprotective effects, while the underlying mechanisms of these effects have yet to be determined. Microglial modulation may be a key factor of these mechanisms. We have lately reported that the formation of neuritic beading (from PC12 cells), induced by PMA-stimulated microglia, was attenuated by pretreatment of aripiprazole by the co-culture experiment [24]. Besides, one recent animal study indicates that aripiprazole prevents apoptosis in the brain of methamphetamine-treatment rodents [93]. These reports indicate that aripiprazole may be a neuroprotective agent *via* inhibiting microglial activation. Regarding neurogenesis, olanzapine and risperidone, both of which have anti-inflammatory effects on microglial activation *in vitro* [21, 37], have been reported to stimulate neurogenesis from *in vivo* studies [94-96]. In addition, one recent imaging report suggests that risperidone may be specifically impacting later-myelinating intracortical circuitry in patients with schizophrenia [97]. Therefore, antipsychotics, especially atypical antipsychotics not only with D2R antagonism but also with D2 partial agonism, may thus have therapeutic effects on patients with schizophrenia by reducing microglial inflammatory/oxidative reactions and following neuron/oligodendrocyte reactions, which puts forward a novel therapeutic hypothesis beyond dopamine/neuron doctrine in the field of schizophrenia research.

IMPLICATION OF ANTIPSYCHOTICS FOR OTHER PSYCHIATRIC DISEASES

Antipsychotics have been applied not only for schizophrenia but also for many other psychiatric diseases such as depression, bipolar and dementia, while the underlying mechanisms have not yet been well understood. It has recently been suggested that inflammation and pro-inflammatory cytokines play important roles in the pathophysiology of depression [98, 99]. Aripiprazole has proved to have therapeutic effects in depression, anxiety and other psychiatric disorders [100, 101]. In an animal study,

aripiprazole has proved to have protective effects on depression-induced oxidative stress in rat brains [102]. These reports suggest that the potential anti-inflammatory/oxidative effects of antipsychotics may be one of the therapeutic properties for depression and other psychiatric diseases.

CONCLUSION

We showed recent evidences of *in vitro* studies about the inhibitory effects of antipsychotics, especially novel atypical antipsychotics not only with D2R antagonism but also with D2 partial agonism, on the release of inflammatory cytokines and free radicals from activated microglia. Further investigations are needed to clarify whether these antipsychotics have any inhibitory effects on microglia activation itself from resting state. In addition, we should interpret these *in vitro* evidences carefully because microglia may have a variety of different functions according to the location of different regions in the brain and different species such as human, rat and mice.

Based on the above-mentioned evidences, we showed a novel therapeutic hypothesis of schizophrenia from the perspective of microglial modulation. D2R antagonism has long been considered as the primary therapeutic action for schizophrenia. Our presenting data suggest that antipsychotics may have psychotropic effects by reducing the microglial inflammatory/oxidative reactions and following neuronal reactions, which puts forward a novel therapeutic hypothesis in schizophrenia research. Further research is needed to clarify this hypothesis by *in vitro* and *in vivo* animal studies, and clinical trials are also necessary to develop this novel therapeutic strategy for schizophrenia.

ABBREVIATIONS

D2R	=	dopamine D2 receptor
GSH	=	glutathione
IFN-γ	=	interferon-γ
IL	=	interleukin
$[Ca^{2+}]i$	=	intracellular Ca^{2+} concentration
LPS	=	lipopolysaccharide
NO	=	nitric oxide
PMA	=	phorbol 12-myristate- 13-acetate
PKC	=	protein kinase C
ROS	=	reactive oxygen species
SOD	=	superoxide dismutase
TNF-α	=	tumor necrosis factor-α

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