

# Neuroinflammation in Schizophrenia Focused on the Pharmacological and Therapeutic Evidence

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## ABSTRACT

**Background:** Schizophrenia is a heterogeneous mental disorder with a variety of symptoms. Although, there are no pathognomonic abnormalities in brains of schizophrenia patients, recent years have witnessed research progresses in revealing pathologic changes in cellular and molecular levels. **Objective:** This article reviewed recent human studies showing neuroimmune alterations in schizophrenia patients and offered explanations for roles of neuroinflammation in the pathogenesis of schizophrenia by citing some of experimental data from non-human studies. The focus of this review was put on pharmacological and therapeutic evidence pointing to a recommendation of anti-inflammatory treatment for patients with schizophrenia. Particularly, it provided compelling evidence supporting an anti-inflammatory effect of antipsychotics by reviewing a relatively large body of studies in the categories of *in vitro*, animals and humans. **Conclusion:** Then, it reviewed recent clinical trials with minocycline, a second-generation tetracycline, or the selective COX-2 inhibitor celecoxib. Most of these clinical trials provided promising results of superior beneficial treatment effects as the consequence of co-administration of standard antipsychotic drugs and anti-inflammatory compounds, compared with antipsychotic drugs alone.

**Key words:** Schizophrenia, neuroinflammation, antipsychotics, minocycline, celecoxib

Pharmacologia 6 (8): 438-453, 2015

## INTRODUCTION

Schizophrenia is a heterogeneous mental disorder with a variety of symptoms that can be categorized into positive symptoms, negative symptoms and cognitive impairments. The heterogeneity of this disease is also exemplified by the involvement of many players in the etiopathogenesis of it, including a number of genes being reported to be abnormal in their structure and functions in the patients<sup>1</sup> and environmental factors, such as social stress, drug abuse and infections, which may induce or exacerbate the manifestations of schizophrenia<sup>2</sup>. Although, the clinical manifestations of schizophrenic patients have been well-documented, it is still an open question as to what happened in brains of the patients. Indeed, there are no pathognomonic abnormalities in brains of schizophrenia patients. Nevertheless, recent years have witnessed research progresses in revealing pathologic changes in cellular and molecular levels in schizophrenia patients. The most notable pathological evidence found in patients points to the existence of neuroinflammation in schizophrenia.

This article reviewed recent human studies presenting neuro inflammation data in schizophrenia patients and focused on pharmacological and therapeutic evidence. It also offered explanations for roles of neuroinflammation in the pathogenesis of schizophrenia by citing some of experimental data from non-human studies.

## ASSOCIATION BETWEEN INFECTIONS AND SCHIZOPHRENIA

A significant association between prenatal maternal infection and increased risk of schizophrenia in the offspring has been demonstrated in a variety of epidemiological studies. It has been repeatedly described that off-springs, whose mother were infected during pregnancy, in particular in the second trimester, developed schizophrenia later<sup>3-5</sup>. Increased risk for developing psychoses later on was also detected after infection of the Central Nervous System (CNS) in early childhood<sup>4,6-9</sup>. In a recently published 30 year population-based study, having an autoimmune disease or a prior hospitalization for serious infection increased the risk of developing schizophrenia by 29 and 60%, respectively<sup>10</sup>. The infectious agents implicated in the

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association between infections and schizophrenia include; influenza<sup>4,11</sup>, rubella<sup>12</sup>, measles<sup>13</sup>, polio<sup>14</sup> and herpes simplex viruses<sup>15</sup>, as well as bacterial pathogens causing sinusitis, tonsillitis and pneumonia<sup>16</sup>, genital and/or reproductive infections<sup>17</sup> and the protozoan parasite *Toxoplasma gondii*<sup>18,19</sup>. It seems that the link between infections and enhanced schizophrenia risk is not pathogen-specific. It is likely that common immunological factors interact with other schizophrenia risk factors, such as genetic predisposition, thus increase the risk of developing schizophrenia. In support of this hypothesis, a DNA microarray study has shown the increased expression of genes related to immune and chaperone function in the prefrontal cortex in schizophrenia<sup>20</sup>. Another two genome-wide studies have shown the association of schizophrenia with markers in the MHC (major histocompatibility complex) region<sup>21,22</sup>. This region spans more than 200 genes, many of which encode key regulators of immune system function, such as the Human Leukocyte Antigen (HLA) genes, TNF superfamily genes and complement cascade genes<sup>23</sup>.

## SCHIZOPHRENIA PATIENTS SHOW NEUROIMMUNE ALTERATIONS

**Microglia activation:** In the CNS, microglia and astrocytes are the major immune-competent cells regulating both the induction and limitation of inflammatory processes<sup>24-26</sup>. Post-mortem studies have reported microglia activation and increased microglia cellular density at least in subpopulations of individuals with schizophrenia<sup>27-29</sup>. Similarly, HLA-DR positive microglia increased in hippocampus of paranoid schizophrenia patients versus residual schizophrenia and controls<sup>30</sup>.

The density of MHC-II positive cells morphologically resembling microglia also significantly increased in schizophrenia patients in a recent study<sup>31</sup>. By means of PET and using [<sup>11</sup>C]-(R)-PK11195, a peripheral benzodiazepine receptor ligand that can be used for the imaging of activated microglia cells and thus neuroinflammation, microglia activation was seen in the grey matter of patients with schizophrenia within the first 5 years after the onset of disease<sup>32</sup>. In another study, a significantly higher binding potential of [<sup>11</sup>C]-(R)-PK11195, indicative of neuroinflammation, was found in the hippocampus of schizophrenic patients compared to healthy volunteers<sup>33</sup>. However, in a more recent study, which took advantage of a novel second-generation TSPO (the translocator protein

18 kDa expressed by activated microglia) radio-ligand N-acetyl-N-(2-[<sup>18</sup>F]fluoroethoxybenzyl)-2-phenoxy-5-pyridinamine ([<sup>18</sup>F]-FEPPA) to evaluate whether there is increased neuroinflammation in patients with schizophrenia, no significant difference in neuroinflammation indexed as [<sup>18</sup>F]-FEPPA V<sub>T</sub> was observed between the patients and controls in either gray or white matter regions<sup>34</sup>. The authors suggested that neuroinflammatory processes might take place early in disease progression or had been affected by antipsychotic treatment.

**Astroglial histopathology:** Initial morphological studies on astrocytes in schizophrenia have reported signs of gliosis indicated by increased density of astrocytes in various cortical areas, the hippocampus and the periaqueductal grey matter<sup>35-39</sup>. However, no evidence for schizophrenia-related astrogliosis was found in later studies that applied other techniques to localize and quantify astrocytes<sup>40-46</sup>. Instead, some of recent studies reported astrocyte loss in various cortical and subcortical areas of brains of schizophrenia patients<sup>42,45</sup>. These inconsistent findings are thought to be related to the following issues: (1) Major Depressive Disorder (MDD) comorbidity, which is more often associated with glia loss, (2) Age variation, because older patients showed many more GFAP-positive cells<sup>41,47,48</sup>, (3) Regional<sup>49</sup> and cortical layer variability<sup>42</sup>, (4) Treatment with antipsychotics and (5) Disease state, exemplified by a study in which patients with schizophrenia were divided into demented and non-demented subtypes, those with dementia demonstrated significantly greater numbers of GFAP-positive astrocytes than those without dementia<sup>50</sup>. In line with this finding, a recent study reported S100B-immunopositive glia elevation in paranoid, but not residual schizophrenia<sup>51</sup>. If go further, we may suggest that astroglial histopathology exists in part or a subgroup of schizophrenia patients. This suggestion coincides with the report in a recent study with clear evidence of astrogliosis in a subset of people with schizophrenia<sup>52</sup>.

**Cytokine alterations:** Cytokines are key regulators of inflammation. They are classified into pro-inflammatory and anti-inflammatory ones. Pro-inflammatory cytokines include; IL-1 $\beta$ , IL-2, IL-6, TNF- $\alpha$  and IFN- $\gamma$ . They are secreted primarily by microglia, Th1 lymphocytes and M1 phenotype monocytes/

macrophages. Anti-inflammatory cytokines include; IL-4, IL-5 and IL-10. They are primarily secreted by astroglia, Th2 lymphocytes and M2 phenotype monocytes/ macrophages<sup>53,54</sup>. Pro-inflammatory cytokines promote harmful inflammation, whereas anti-inflammatory cytokines limit harmful inflammation by converting the pro-inflammatory M1-phenotype into the beneficial anti-inflammatory M2-phenotype and promoting the neuroprotective microglial phenotype<sup>55,56</sup>.

There is increasing evidence for aberrant cytokine levels in both patients with schizophrenia and their first-degree relatives, although results have not always been consistent between individual studies. Of the early studies, one example showed that IL-2 serum levels were significantly lower and IL-1 $\beta$  and TNF- $\alpha$  were significantly higher in schizophrenic patients compared with healthy controls<sup>57</sup>. Another one reported that serum levels of soluble IL-2 receptor (sIL-2R), IL-6 and IL-1 receptor antagonist (IL-1RA) in schizophrenia patients were elevated and maintained at high levels throughout the treatment period of 8 weeks<sup>58</sup>. In a meta-analysis, which analyzed data from 62 studies involving a total sample size of 2298 schizophrenia patients and 1858 healthy volunteers, schizophrenia patients had higher levels of IL-1RA, sIL-2R and IL-6, but no significant effect sizes were obtained for the other cytokines<sup>59</sup>. In a subsequent review, IL-1 $\beta$ , IL-6 and TGF- $\beta$  were increased in both acutely relapsed inpatients and first-episode psychosis and the changes were normalized by antipsychotic treatment. These cytokines therefore were referred to as state markers. In contrast, IL-2, IFN- $\gamma$ , TNF- $\alpha$  and sIL-2R appeared to be trait markers, as levels of them remained high in acute exacerbations following antipsychotic treatment<sup>60</sup>. In a recent study, Song *et al.*<sup>61</sup> reported high levels of IL-1 $\beta$ , IL6 and TNF- $\alpha$  in drug naïve-first episode schizophrenia patients, when compared with healthy controls matched for age, gender, smoking status and body mass index. In a more recent study, which carried out standardized multiplex immunoassay analyses of 9 cytokines in serum from 180 antipsychotic-naïve first-episode schizophrenia patients and 350 matched controls across 5 clinical cohorts, the levels of IL-1RA, IL-10 and IL-15 were increased significantly in patients across the cohorts, whereas the levels of IL-1RA and IL-10 were decreased in 32 patients, who had been followed up and treated for 6 weeks with atypical antipsychotics. Interestingly, the changes in IL-10 were significantly correlated with the improvements in negative, general

and total symptom scores, suggesting that this cytokine can be used as a potential treatment response biomarker in schizophrenia<sup>62</sup>.

## THEORETICAL ROLES OF NEUROINFLAMMATION IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

It is no doubt that neuroinflammation is an important player in the pathophysiology of at least one subtype of schizophrenia. However, it remains to be an ongoing challenge to elucidate how neuroinflammation plays its roles in the pathogenesis of schizophrenia. Here, we introduced some of existing theories explaining the roles of neuroinflammation and relating it to distinct symptom classes of schizophrenia.

**Neuroninflammation and CNS glutamate dysfunction:** As reviewed above, both astrocytes and microglia are abnormal in schizophrenia. The interaction between these two glial cell types has been hypothesized to increase the production of quinolinic acid by microglia and kynurenic acid (KYNA) by astrocytes<sup>63</sup>. Elevated KYNA can inhibit NR1 subunit of the NMDA Receptor (NMDAR) and  $\alpha 7$  nicotinic acetylcholine receptor ( $\alpha 7$ nAChR)<sup>64, 65</sup> thereby leading to decreased NMDAR function and reduced  $\alpha 7$ nAChR-mediated glutamate release. In support of this theory, KYNA has been found to be elevated in the CSF of drug-naïve first episode schizophrenia patients<sup>66</sup>, as well as in chronically ill patients<sup>67</sup>. Therefore, KYNA provides a direct link between neuroinflammation and hypoglutamatergic neurotransmission in schizophrenia. Via the inflammation-mediated modulation of the central kynurenine pathway and the subsequent impairments in NMDA receptor-mediated signaling, the enhanced pro-inflammatory activity has been related to cognitive, behavioral and psychiatric impairments<sup>65,68-72</sup>.

**Neuroinflammation and neurogenesis:** Neurogenesis is a complex process of generating new neurons from neural stem or progenitor cells. Newly-generated neurons in adulthood have a role in synaptic plasticity and cognitive functioning and are involved in psychiatric diseases, such as depression and schizophrenia<sup>73,74</sup>. Abnormal neurogenesis has been consistently reported in schizophrenia postmortem studies<sup>75,76</sup>. Although, the mechanisms underlying the abnormal neurogenesis in schizophrenia remain unknown, neuroinflammation is thought to be an

important contributor. Various pro-inflammatory cytokines have individual effects on neurogenesis. For example, IL-1 $\beta$  induces focal and sustained hippocampal inflammation, resulting in severe depletion of developing neuroblast and distorting the fate of neural stem cells in the subventricular zone<sup>77</sup>. This cytokine was also found to suppress cell proliferation in the dentate gyrus<sup>78</sup>. Another example is IL-6, a most important cytokine involved in microglial activity and inflammatory response. A recent study of a sample of patients with first onset psychosis reported that increased IL-6 expression and higher salivary cortisol levels predicted smaller hippocampal volumes and that a history of childhood maltreatment was related to current inflammatory markers<sup>79</sup>. It is suggested that IL-6 inhibits adult neurogenesis by stimulating the Hypothalamic-Pituitary-Adrenal (HPA) axis<sup>80</sup> and by acting on the IL-6 receptor or a common signal transducer, glycoprotein 130 (gp130), in the dentate gyrus<sup>81</sup>.

**Neuroinflammation and apoptosis:** Multiple lines of evidence converge to implicate increased susceptibility to apoptotic death in the pathophysiology of schizophrenia<sup>82</sup>. Theoretically, inappropriate activation of apoptosis may occur in both neurons and oligodendrocytes (OLs). In neurons, sub-lethal apoptotic activity can lead to a limited form of apoptosis in terminal neurites and individual synapses to cause elimination without cell death<sup>83,84</sup>. However, a same factor may be lethal to OLs that provide supports and protection to neurons. This point of view coincides with the recent findings of reduced density and compromised morphology of OLs as well as signs of deviant myelination in schizophrenia patients<sup>85-87</sup>. In the disruption of OL function and cell death, microglial and pro-inflammatory cytokines play important roles. In support of this, TNF- $\alpha$  has been shown to compromise the growth of OLs and the expression of mRNA for Myelin Basic Protein (MBP) in cultures<sup>88</sup>. In addition, this cytokine inhibited the survival and proliferation of OL progenitors and their subsequent differentiation into mature myelinating phenotypes<sup>89</sup>.

In addition to its effects on pro-inflammatory cytokine secretion, infection and subsequent induction of inflammatory responses are strongly associated with oxidative stress, an imbalance between the production and elimination of Reactive Oxygen Species (ROS). Upon activation, innate immune cells secrete ROS and

Reactive Nitrogen Species (RNS, such as nitric oxide)<sup>90</sup>. Increased ROS, in turn, enhance microglial activation and increase the production of pro-inflammatory cytokines, via stimulating NF- $\kappa$ B<sup>91</sup>. By this pathological positive feedback loop, oxidative stress is exacerbated and perpetuated with the results of lipid peroxidation, damages to membrane phospholipids and their membrane-bound monoamine neurotransmitter receptors and depletion of endogenous antioxidants<sup>54</sup>.

It should be pointed out that mitochondrial is a major contributor to the oxidative stress and neuroinflammation in schizophrenia. Supporting evidence for this point includes; (1) Mitochondria are crucial in regulating redox homeostasis, (2) Postmortem studies have revealed abnormalities in mitochondria of schizophrenia patients<sup>92,93</sup>, (3) Pro-inflammatory cytokines, such as TNF- $\alpha$ , can impair mitochondrial oxidative metabolism<sup>94</sup>, leading to increased ROS production<sup>95,96</sup>, (4) Mitochondrial impairment induced by a short-term exposure to cuprizone, a copper chelator, produced oxidative stress<sup>97</sup> and induced neuroinflammation in C57BL/6 mice<sup>98</sup>. In the meanwhile, these mice showed behavioral changes relevant to some symptoms seen in schizophrenia<sup>97,98</sup> and (5) Ketamine was shown to induce mitochondrial dysfunction, while produced behavioral changes<sup>99</sup>. Moreover, social isolation rearing inhibited oxidative metabolism and induced oxidative stress in rats<sup>100,101</sup>, while it produced several behavioral outcomes similar to those observed in humans with early life stress<sup>100-102</sup>. Taken together, these previous studies suggest a connection between mitochondrial dysfunction and neuroinflammation in schizophrenia.

## ANTI-INFLAMMATORY EFFECTS OF ANTIPSYCHOTICS

Given the association between inflammation and schizophrenia, antipsychotics would be expected to have an anti-inflammatory effect. Indeed, a large body of evidence supports an anti-inflammatory effect of antipsychotics. In the following we will summarize the results from some of such studies in the categories of *in vitro*, animals and humans.

**In vitro studies:** In 1999, Moots *et al.* published a case report, in which treatment of a patient with acute mania by haloperidol was associated with marked improvement in activity of rheumatoid arthritis<sup>103</sup>. To explain this *in vivo* anti-inflammatory effect of haloperidol, the

authors examined the effects of this (typical) antipsychotic on inflammatory cytokine release *in vitro*. Haloperidol did inhibit lipopolysaccharide (LPS) stimulated production of both IL-1 $\beta$  and TNF- $\alpha$  in cultured peripheral blood cells in a dose dependent manner. This pioneer study inspired a number of investigators to examine possible anti-inflammatory effects of antipsychotics. Kowalski *et al.*<sup>104</sup> reported the reduction of TNF- $\alpha$  and NO from LPS-activated microglia in primary cultures treated with flupentixol and trifluoperidol. These two typical antipsychotic drugs, plus chlorpromazine and loxapine (another two antipsychotics) also reduced IL-1 $\beta$  and IL-2 release by the LPS-activated microglia as shown in later studies<sup>105,106</sup>. In addition, spiperone, another typical antipsychotic, inhibited the production of NO, IL-1 $\beta$  and TNF- $\alpha$ , from the LPS-activated microglia<sup>107</sup>. Similar to typical antipsychotics, the atypical antipsychotic olanzapine inhibited NO secretion from the LPS-activated microglia<sup>108</sup>. Risperidone, another atypical antipsychotic, inhibited the productions of NO, IL-1 $\beta$ , IL-6 and TNF- $\alpha$  from the IFN- $\gamma$  activated microglia<sup>109</sup>. Similar anti-inflammatory effects were also shown by perospirone and quetiapine, another two atypical antipsychotics<sup>110</sup>. In a recent study, both haloperidol and risperidone inhibited the secretion of S100B following IL-6 stimulation in C6 glioma cells<sup>111</sup>.

That both typical and atypical antipsychotics share similar anti-inflammatory effects suggest the existence of a pharmacological base that is unlikely related to the binding affinity of these drugs to dopamine D2 receptors. Of the putative mechanisms, microglial intracellular calcium (Ca<sup>2+</sup>) signaling was proposed to be involved in the anti-inflammatory effects of atypical antipsychotics<sup>112</sup>. This proposition was based on an *in vitro* study in which pretreatment with the aripiprazole antipsychotic attenuated the mobilization of intracellular Ca<sup>2+</sup> induced by IFN- $\gamma$  and LPS in murine microglia<sup>113</sup>. Intracellular Ca<sup>2+</sup> is one of the endogenous activators of Protein Kinase C (PKC), which has been reported to be an important initiator of the MAPK signaling pathway in microglia. The activation of PKC affects MAPK cascade proteins including ERK 1/2 and p38 MAPK<sup>114</sup>. The latter plays a major role in the activation of murine microglia by LPS, while ERK1/2 involves in the microglia activation by IFN- $\gamma$ <sup>115,116</sup>. Another mechanism was exemplified in a study with clozapine, which exerted neuroprotective effect via the attenuation of microglia activation through inhibition of NADPH oxidase-generated ROS production<sup>117</sup>.

**Animal studies:** Driven by the anti-inflammatory effects of antipsychotics shown in *in vitro* and human studies (see the following subsection in details), a few recent animal studies have examined effects of some antipsychotics on neuroinflammation in various animal models of schizophrenia. In an early study, Paterson *et al.*<sup>118</sup> examined the levels of cytokine mRNAs in rat brain after acute and chronic administration of phencyclidine (PCP), in the presence and absence of antipsychotic drugs. Both antipsychotic drugs and PCP were shown to significantly reduce the levels of TNF in the prefrontal cortex compared to vehicle-treated animals, whilst other cytokines remained unchanged. In LPS-treated mouse, a more relevant animal model mimicking the neuroinflammation in schizophrenic brains, the anti-inflammatory effect of antipsychotics, including; clozapine, olanzapine, risperidone and haloperidol, on serum cytokine levels was measured. Atypical antipsychotics suppressed TNF- $\alpha$  and IL-6 and up-regulated IL-10<sup>119</sup>. Similarly, chronic administration of chlorpromazine or clozapine modulated the enhanced levels of IL-1 $\beta$ , IL-2 and TNF- $\alpha$  in the offspring of LPS-treated female rats. The drugs also ameliorated the deficit in prepulse inhibition (PPI) in the prenatally LPS-treated rats<sup>120</sup>. In a recent study, a relatively lower dose of LPS (0.5 mg kg<sup>-1</sup> i.p.) was administered to young adult rats to mimic the mild neuroinflammation, as seen in brains of schizophrenia patients. In the LPS-treated rats, risperidone normalized the increased inflammatory parameters and restored anti-inflammatory pathways<sup>121</sup>. In another animal model of progressive inflammatory and oxidative alterations induced by a neonatal immune challenge, Wistar rats at postnatal (PN) day 5-7 were administered the viral mimetic polyriboinosinic-polyribocytidilic acid (polyI:C). Clozapine was found to reverse microglial activation and inducible nitric oxide synthase increase, while it improved the accompanied deficits in PPI and working memory in adult (PN 74) rats<sup>122</sup>.

Of the antipsychotic drugs, quetiapine deserves to be highlighted for its anti-inflammatory effect and immunomodulatory capacity as shown in animal studies. In the Myelin Oligodendrocytes Glycoprotein (MOG) induced Experimental Autoimmune Encephalomyelitis (EAE) mouse model of Multiple Sclerosis (MS), quetiapine was shown to dramatically attenuate the severity of EAE symptoms, diminish demyelination and the infiltration of CD4<sup>+</sup>/CD8<sup>+</sup> T cells, as well as activation of local microglia in the spinal cord. Additionally, this drug attenuated MOG<sub>35-55</sub>-specific



immune response and inhibited effector T-cell proliferation in EAE mice<sup>123</sup>. These results suggest that quetiapine prevents mice from MOG-induced demyelination by its immuno-modulatory action.

In line with this suggestion, we found that quetiapine ameliorated the neuro inflammatory events indicated by astrogliosis, microglia activation and increased proinflammatory cytokines in brain of mouse fed with cuprizone-containing diet for 7 days, which induced oligodendrocyte decrease but not demyelination (unpublished data). The cuprizone-induced demyelination in mouse has been also used as an animal model of MS. In addition, quetiapine was shown to stimulate proliferation and maturation of oligodendrocytes<sup>124</sup>, increase antioxidant defenses and scavenge free radicals<sup>125</sup>. For all these capacities, clinical trials are justified to determine the safety, tolerability and efficacy of quetiapine in MS<sup>126</sup>.

**Human studies:** Although, the aforementioned *in vitro* and animal studies strongly suggest the existence of anti-inflammatory effects of antipsychotics, human studies on the effect of antipsychotic treatment on inflammation and more specifically on cytokine levels have so far given mixed results. For example, in an early study by Maes *et al.*<sup>127</sup>, higher plasma IL-6 in schizophrenic patients was lowered after treatment with neuroleptics; whereas the same group reported no effect of chronic treatment with clozapine on this cytokine<sup>128</sup>. However, a recent meta-analysis<sup>60</sup> reported that antipsychotic treatment significantly decreases IL-1 $\beta$ , IL-6 and TGF- $\beta$ , but increase sIL-2R and IL-12 levels in schizophrenia patients. A more recent meta-analysis showed that antipsychotic treatment significantly increases plasma levels of sIL-2R and reduces the plasma levels of IL-1 $\beta$  and IFN- $\gamma$ <sup>129</sup>. Coinciding with the conclusions of these meta-analyses, a most recent human study found that first-episode psychosis patients had significantly higher levels of IL-6, IL-10 and TNF- $\alpha$  than healthy controls. After risperidone treatment, these three cytokines and additionally IL-4 decreased significantly<sup>130</sup>. Similarly, aripiprazole, another atypical antipsychotic drug, significantly reduced plasma IL-1 $\beta$ , IL-6, TNF- $\alpha$ , sTNF-R1, IL-12, IL-23, IL-1Ra and IL-4. Interestingly, the high clinical efficacy of this drug was linked to a 2.7% weight loss<sup>131</sup>. This effect on body weight may help account for inconsistent effects of antipsychotics on pro-inflammatory cytokine levels. For example, effects

of clozapine and olanzapine on cytokine levels are closely linked to weight gain<sup>132</sup>. This response of cytokines to the body weight side effect of antipsychotic drugs was elegantly demonstrated in a recent study in which levels of IL-1 $\beta$  and IL-6 decreased in the first weeks of risperidone treatment, but increased back to baseline levels by the end of 6 months treatment, which happened alongside a steady weight gain<sup>133</sup>.

## ANTI-INFLAMMATORY TREATMENT STRATEGIES IN SCHIZOPHRENIA

In view of the apparent involvement of inflammation in schizophrenia, the use of compounds with anti-inflammatory properties has attracted increasing attention in the pharmacotherapy of this mental disorder. Indeed, recent clinical trials have provided promising results of superior beneficial treatment effects as the consequence of co-administration of standard antipsychotic drugs and anti-inflammatory compounds, compared with antipsychotic drugs alone. The results of some recent trials with these compounds are summarized as follows by focusing on two of them.

**Minocycline:** Minocycline is a second-generation tetracycline that exerts anti-inflammatory and antimicrobial effects. It has excellent brain tissue penetration, is well tolerated and is almost completely absorbed when taken orally. This drug has been shown to have a distinct neuroprotective profile<sup>134</sup>. It countered the disruptive effects of NMDA antagonist on visuospatial memory and sensorimotor gating<sup>135</sup>, attenuated behavioral changes and the increase of dopamine in the frontal cortex and striatum after administration of MK801<sup>136</sup> and improved cognitive disturbances induced by phencyclidine, another NMDA receptor antagonist<sup>137</sup>. Furthermore, minocycline attenuated microglial activation in mouse brains produced by methamphetamine and 3, 4-methylenedioxymethamphetamine<sup>138,139</sup>. These preliminary findings in animal studies sparked interest in minocycline's potential for the aid of patients with schizophrenia.

Of the early human studies, Miyaoka *et al.*<sup>140</sup> first reported the antipsychotic effects of minocycline in two patients with schizophrenia, followed by a 4 week open-label study with 22 schizophrenia patients. Treatment with minocycline (adjunct to antipsychotic medication) caused no adverse events, but produced a

clinical improvement on PANSS (positive and negative syndrome scale), which was maintained at a follow-up evaluation 4 weeks after the end of minocycline treatment<sup>141</sup>. Similarly, a double blind, randomized placebo-controlled study by Levkovitz *et al.*<sup>142</sup> demonstrated that the add-on treatment of minocycline has a beneficial effect on negative symptoms, cognitive functions and general outcomes in early phase patients with schizophrenia. In a recent randomized double-blind placebo-controlled clinical trial, minocycline benefitted negative symptoms in early schizophrenia<sup>143</sup>. Despite of the above positive reports, a recent update of efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia concluded that minocycline showed no significant effect on symptom severity<sup>144</sup>. This meta-analysis, however, only included four randomized control led trials (RCTs), but excluded all case reports including the recent ones, which showed that minocycline augmentation of antipsychotic treatment significantly reduced PANSS positive subscale scores<sup>145</sup>, improved delusion and positive symptoms<sup>146</sup> and successfully treated persistent negative symptoms in schizophrenia<sup>147</sup>. In a more recent case report, Qurashi *et al.*<sup>148</sup> described two cases in a UK mental health service where minocycline was found to be useful and well-tolerated as an augmentation agent with clozapine in the improvement of previously resistant positive and negative symptoms. Furthermore, a later meta-analysis including two of RCTs<sup>149,150</sup> published after the first meta-analysis, concluded that minocycline was superior to placebo for decreasing PANSS total scores, PANSS negative subscale scores and PANSS general subscale scores<sup>151</sup>. In line with the above conclusion, two more recent RCTs produced results supporting the effectiveness of minocycline, as an adjuvant treatment with antipsychotic drugs for treating negative symptoms of patients with schizophrenia<sup>152,153</sup>. In addition to significantly reducing positive and negative symptoms, when compared with placebo, add-on of minocycline ameliorated the gray matter volume decrease in the mid-posterior cingulate cortex and in the precentral gyrus shown in the patients in the placebo group, suggesting that minocycline may protect against gray matter loss and modulate fronto-temporal areas involved in the pathophysiology of schizophrenia<sup>153</sup>.

#### **Non-steroidal anti-inflammatory drugs (NSAIDs):**

The drugs in this class include the mixed COX-1/2

inhibitor acetylsalicylic acid (aspirin) and the selective COX-2 inhibitor celecoxib. Here we only reviewed the recent clinical trials with celecoxib as an add-on to antipsychotic drugs in treating schizophrenia.

In the first clinical trial conducted in patients with acute exacerbation of schizophrenic psychosis, celecoxib given in conjunction with risperidone was shown to be superior to the antipsychotic alone in improving PANSS scores<sup>154</sup>. The same authors also reported beneficial effects of celecoxib add-on therapy on cognitive symptoms in schizophrenia patients<sup>155</sup>. But the subsequent studies by other groups reported inconsistent results. In a study by Akhondzadeh *et al.*<sup>156</sup>, the combination of risperidone and celecoxib showed a significant superiority over risperidone alone in the treatment of positive symptoms, general psychopathology symptoms as well as PANSS total scores. But, in a study by Rapaport *et al.*<sup>157</sup>, celecoxib augmentation of continuously ill outpatient subjects with schizophrenia did not improve clinical symptoms or measures of disability. The authors suggested that previous reports of the benefit of celecoxib augmentation for subjects with an acute psychotic exacerbation cannot be extended to continuously symptomatic outpatients with schizophrenia. Indeed, the results of a recent RCT showed a superior therapeutic effect in the celecoxib group compared to placebo in the treatment of early stage schizophrenia<sup>53</sup>. Different reasons may be responsible for this phenomenon, such as the duration of disease and the anti-inflammatory therapy, antipsychotic treatment with neuroleptics, or therapeutic problems associated with chronic inflammation<sup>53</sup>. Although, further studies are needed before a definite conclusion can be accepted, a recent meta-analysis concluded that celecoxib augmentation could be a potentially useful strategy to reduce symptom severity in schizophrenia<sup>158</sup>.

#### **CONCLUSION**

Schizophrenia is a complex and heterogeneous brain disorder. Of the environmental factors, neuroinflammation may induce or exacerbate the manifestations of the schizophrenia at least in a subtype of patients. Some antipsychotic drugs show immunomodulatory effects although inconsistent results exist. Anti-inflammatory treatment strategies have produced promising results in clinical trials with schizophrenia patients. More encouraging results of anti-inflammatory treatment on schizophrenia are expected, as more efforts are being made to search new

approaches of add-on of anti-inflammatory compounds to antipsychotic drugs for the treatment of this severe mental disorder.

## ACKNOWLEDGMENT

The author thanks Ms. Yuan Shao for her assistance in organizing the reference list of this manuscript.

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