EDITORIAL

Anti-Neuroinflammatory Effects of Psychopharmaceuticals: Further than Monoamine Modulators

In recent years the conception that neuroinflammation plays a pivotal role in the pathogenesis of a number of neurodegenerative diseases has been extended to even archetypal endogenous psychoses, namely mood disorder and schizophrenia. The neuroinflammation associated with these neuropsychiatric diseases is revealed by increased levels of inflammatory mediators, including cytokines, in the peripheral blood and by abnormal glial activation in the diseased CNS. Accumulating evidence indicates that psychopharmaceuticals such as the antidepressants, antipsychotics and cannabinoids have potency to attenuate neuroinflammation. Accordingly, the efficacy of these psychotropics may be partially attributable to suppression of neuroinflammation. In fact, agents that possess anti-inflammatory properties such as the cyclooxygenase-2 inhibitor celecoxib [1] and omega-3 fatty acids [2] have been reported to have beneficial effects in mood disorder and schizophrenia. This mini-hot topic issue has collected 4 expert mini-reviews on this theme.

Both *in vivo* and *in vitro* studies have shown that antidepressants possess anti-neuroinflammatory properties, inhibiting inflammatory mediator expression and the pathological activation of glial cells. The first review gives a brief description of the term neuroinflammation and provides an overview of those studies. It also proposes possible mechanisms of the anti-neuroinflammatory efficacy.

Antipsychotics, especially novel atypical antipsychotics, have been also documented to exert anti-neuroinflammatory effects on activated glial cells. The second article by Kato *et al*. presents data on the effects of various types of antipsychotics on glial activation and speculates that the anti-neuroinflammatory mechanisms of the drugs involve effects on intracellular Ca^{2+} kinetics.

The precise mechanisms by which certain psychopharmaceuticals exert anti-inflammatory effects still remain to be elucidated. However, recent studies have indicated that several non-conventional antidepressants [3] and antipsychotics [4] inhibit microglial activation through suppression of elevated concentrations of intracellular Ca^{2+}. Accordingly, modulating cellular Ca^{2+} signaling might be a common mechanism underlying the anti-neuroinflammatory effects of antidepressants and antipsychotics.

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin in the brain [5]. A number of animal studies have shown that both antidepressants [6, 7] and atypical antipsychotics [8, 9] induce BDNF expression in the hippocampus after chronic treatment. Furthermore, a postmortem study has shown that BDNF immunoreactivity in the hippocampus from subjects treated with antidepressants is increased compared to that in the hippocampus from antidepressant-untreated subjects [10]. Another postmortem study has revealed that the mRNA expressions of BDNF and its receptor trkB tyrosine kinase are decreased in the hippocampus of individuals with mood disorders and schizophrenia, suggesting that decreased brain levels of BDNF is involved in the etiologies of these endogenous psychoses [11]. Interestingly, recent studies have established that BDNF itself has anti-neuroinflammatory effects. In the brain of mice with experimental autoimmune encephalomyelitis, BDNF gene delivery decreased the mRNA expression of the inflammatory cytokines, tumor necrosis factor (TNF)-α and interferon-γ, as well as of the inflammatory adhesion molecules, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, whereas it increased that of the anti-inflammatory cytokines, interleukin (IL)-10 and IL-11 [12]. In the rat ischemic brain induced by cerebral artery occlusion, intranasal BDNF administration downregulated TNF-α, while it upregulated IL-10 at both protein and mRNA levels [13]. In the present special issue, Mizoguchi *et al*. discuss the possible role of BDNF in the pathophysiology of neuropsychiatric disorders by focusing on its effect on intracellular Ca^{2+} signaling in microglial cells. They also give details of the mechanism by which BDNF induces sustained elevation of on intracellular Ca^{2+} in rodent microglia.

The plant *Cannabis sativa*, commonly known as marijuana, has been used for medicinal purposes due to its manifold bioactivity such as sedative, analgesic and appetite-stimulating properties. In fact, it was one of the most commonly prescribed medicines in the U.S. pharmacopoeia until its criminalization in the late 1930s [14]. Cannabinoids, which include phytocannabinoids and synthetic compounds mimicking phytocannabinoid actions, have been demonstrated to exert anti-inflammatory effects through the activation of cannabinoid receptor type 2. In addition, cannabinoids have been reported to possess anti-oxidant properties aside from the interaction with cannabinoid receptors. Therefore, cannabinoids appear to have a therapeutic potential against such neurodegenerative disease as Parkinson's disease (PD). However, cannabinoids could also contribute to neurotoxicity since they may impair the activity of mitochondrial enzyme and increase oxidative stress. In this special issue, Little *et al*. discusses the pros and cons of the cannabinoid influence on the PD pathogenesis associated with neuroinflammation.

Although some psychopharmaceuticals could be useful for treatment or prevention against the various CNS pathologies associated with inflammation, further studies are clearly warranted to consolidate the evidence of their anti-neuroinflammatory properties and mechanisms. The editor would like to thank the authors for their great contribution to this special issue and the anonymous reviewers for their insightful comments. Sincere acknowledgements are also extended to Dr. Edith G. McGeer for her kind support and Ms. Sabiha Aftab for publication management.

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