

## Neuroinflammation and Anti-inflammation Treatment in Psychiatric Disorders

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Neuroinflammation has been accepted as a common characteristic of several mental health conditions such as major depression, bipolar disorder (BD), posttraumatic stress disorder (PTSD) and schizophrenia (SCHZ). It is hypothesized that inflammatory processes trigger and/or further deteriorate mental dysfunction of the brain [1].

In a comprehensive overview of the cytokine profile at the onset of psychosis un-confounded by medication, Upthegrove, *et al.* [2] summarized significant elevations in levels of the pro-inflammatory cytokines of IL-1 $\beta$ , sIL-2r, IL-6, and TNF- $\alpha$  in the serum of patients with medication-naive first episode psychosis, adding to the evidence of a pro-inflammatory immune deregulation in schizophrenia. Many studies have also measured markers of neuroinflammation in postmortem brain samples from schizophrenia patients. Of them, some studies suggest an increase in microglial activity and other markers [3]. In addition, studies consistently demonstrated aberrant T-cell mediated immunity in schizophrenia [4,5]. T cell dependent molecular changes leading to altered immune function was also reported in first-onset schizophrenia patients [6].

The presence of inflammatory responses and the crucial role of cytokines in depression have also been a research interest, exemplified by the macrophage theory of depression that endeavors to explain and describe the underlying biological mechanisms of depression and suicide outcomes [7]. This hypothesis was first formulated on the basis of the observations of depressive symptoms precipitated by cytokine therapy in psychiatrically healthy, physically ill human patients [8,9]. Later on, studies reported that human populations suffering from chronic inflammatory conditions, such as type II diabetes, rheumatoid arthritis, and cardiovascular disease, showed increased incidences of depressive disorders [10]; while other studies with depressed human patients reported higher levels of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, in this clinical population compared to controls [11-13]. Meta-analyses summarized increases of inflammatory parameters in the blood of patients with MDD [14,15]. Moreover, studies have demonstrated that administration of cytokines or cytokine inducers affects the synthesis, reuptake and release of monoamine neurotransmitters such as 5-HT, NE, DA and excitatory amino acid glutamate [16].

In addition to schizophrenia and depression, increasing evidence suggests an essential role of neuroinflammation in the pathogenesis of BD. The analysis of blood and plasma from BD patients showed an increase of the pro-inflammatory cytokines nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-kB), IL-6, IL-1 $\beta$ , and TNF- $\alpha$  [12,17-19]. The up-regulated expression of pro-inflammatory cytokines is believed to decrease levels of serotonin and BDNF in BD patients [16,20,21].

There is growing evidence suggesting a role for inflammation in the emergence of autism spectrum condition (ASC). Complementary to this, a number of neuroimaging and neuropathological studies reported microglial activation in patients with ASC [22]. A number of blood biomarker studies reported significantly elevated levels of proinflammatory markers, such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and C-reactive protein (CRP) in patients with PTSD compared to healthy controls [23].

Relevant to the neuroinflammation in psychiatric disorders, brain inflammation may be used as a biomarker of disease status and regarded as therapeutic targets for these mental disorders. According to a meta-analysis, antipsychotic treatment significantly decreases IL-1 $\beta$ , IL-6 and TGF- $\beta$ , but increases sIL-2R and IL-12 levels in schizophrenia patients [24]. Another meta-analysis showed that antipsychotic treatment significantly increases plasma levels of sIL-2R but reduces the plasma levels of IL-1 $\beta$  and IFN- $\gamma$  [25]. In accordance with these meta-analyses, a recent human study found that higher levels of IL-6, IL-10 and TNF- $\alpha$  in first-episode psychosis patients were decreased significantly after risperidone treatment [26]. Similarly, aripiprazole significantly reduced plasma IL-1 $\beta$ , IL-6, TNF- $\alpha$ , sTNF-R1, IL-12, IL-23, IL-1Ra and IL-4 in schizophrenia patients [27]. On the other hand, anti-inflammatory drugs have been used as add-on to antipsychotic treatment in patients with schizophrenia [28].

There are many studies showing a direct effect of antidepressants on inflammatory cytokines. In patients with major depression, long-term treatment with selective serotonin reuptake inhibitors decreased TNF- $\alpha$ , CRP, and leukocyte levels similar to those found in controls [29,30]. Similarly, bupropion, mirtazapine, citalopram, paroxetine, or venlafaxine significantly decreased levels of proinflammatory cytokines in depressed patients [31]. The whole blood from healthy controls and treatment-resistant patients, after incubated with lipopolysaccharide and treated with antidepressants, showed markedly lower levels of proinflammatory cytokines compared with untreated blood [32,33].

On the other hand, anti-inflammatory agents exhibit antidepressant effects via modulating neurotransmitter systems, neuroplasticity markers and glucocorticoid receptor signaling. Furthermore, clinical trials and meta-analyses support a beneficial effect of anti-inflammatory add-on therapy in depression [34]. And in a double-blind, randomized, placebo-controlled study of aspirin and n-acetylcysteine as adjunctive treatments for BD, the co-administration of N-acetyl-cysteine and aspirin during a period of 16 weeks was associated with a reduction in depressive symptoms while the adverse effects of the co-administration were minimal [35]. Although these findings are preliminary, they may serve as a starting point for future studies assessing the efficacy, tolerability, and safety of anti-inflammatory and antioxidant agents in the treatment of BD. Relevantly, studies have observed that physical exercise show benefits as adjunctive and individual therapy in MDD patients [36,37] or be a strategy for the prevention of MDD [38]. Moreover, antidepressant efficacy of electroconvulsive therapy is associated with a reduction of the innate cellular immune activity in the cerebrospinal fluid in patients with depression [39].

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