The intersection between psychopathology and inflammation: A review of the current evidence

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BACKGROUND

The field of psychoneuroimmunology studies the interaction between the brain and the immune system. During the past years, inflammation has been found to play a role in the origin of mood, anxiety, and psychotic disorders. Studies show that a myriad of pro-inflammatory cytokines are increased in a subgroup of psychiatric patients; however, not every subject with elevated inflammatory markers will develop a psychiatric illness. As some conditions appear to be resistant to our conventional pharmacological treatments, agents with anti-inflammatory properties are being studied in an effort to improve disease outcomes.

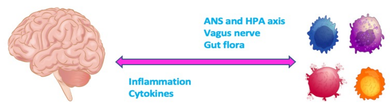
The current review aims to describe the role of inflammation in psychiatric disorders and the anti-inflammatory therapies that have been used to aid in their treatment.

METHODS

A literature search in PubMed and Cochrane Library was performed from 2010 to April 2020. Keywords included "inflammation", "psychiatric disorder", "depression", "schizophrenia" and "anti-inflammatory". Seven articles were included for this review.

INTRODUCTION

- The immune system and the brain are connected by the autonomic nervous system (ANS), which has three components: the sympathetic nervous system, the parasympathetic nervous system, and the enteric system.
- The sympathetic branch of the ANS can modulate the balance of lymphocyte T-helpers by stimulating β-adrenergic receptors.
- The parasympathetic branch of the ANS modulates several immune reactions through the vagus nerve.
- The gut microbiota can alter immune signals, and the enteric system, stimulated by the gut flora, produces neuronal impulses that travel directly to the brain via the vagus nerve.
- Another component that connects the brain with the immune system is the hypothalamic-pituitary-adrenal (HPA) axis. When the homeostasis of the HPA axis is altered due to inflammation, immune dysfunction and disturbances in the production of neurotransmitters will ensue.



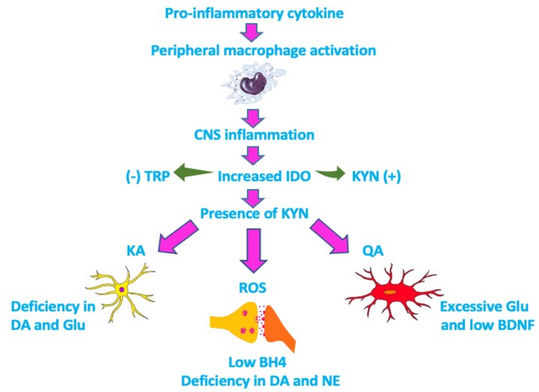
- Cytokines are considered the “hormones” of the immune system and can be either pro-inflammatory or anti-inflammatory. Among the pro-inflammatory types, we have interleukins (IL), tumor necrosis factors (TNF), transformation growth factors (TGF), and interferons (IFN).
- Peripheral cytokines can reach the brain via leaky areas in the blood-brain barrier (BBB), or by peripheral afferent nerve fibers. Cytokines can also be produced in the central nervous system (CNS) by astrocytes and microglia.

DISCUSSION

Figure 1:

- Pro-inflammatory cytokines activate macrophages, which cross the BBB and produce CNS inflammation. This reaction triggers the production of indoleamine 2,3 dioxygenase (IDO), which will decrease levels of tryptophan (TRP), hence reducing serotonin availability.
- The excess of IDO will give rise to kynurenine (KYN).
- KYN stimulates astrocytes to generate kynurenic acid (KA) that will block cholinergic receptors and decrease the release of dopamine (DA) and glutamate (Glu).
- KYN concomitantly stimulates microglia to produce quinolinic acid (QA), which will over-stimulate the NMDA receptor, causing excessive Glu, excitotoxicity, a decrease in brain-derived neurotrophic factor (BDNF), and neuronal cell death.
- KYN will also affect the presynaptic terminals of the basal ganglia and generate ROS. These molecules will reduce the availability of tetrahydrobiopterin (BH4), an essential cofactor in tyrosine metabolism, hence decreasing DA and norepinephrine (NE) production.
- Ultimately, inflammation appears to affect the metabolism of different neurotransmitters that are tightly related to the onset of depression, psychosis, negative symptoms, and cognitive dysfunction.

Figure 1



- As mentioned above, inflammation activates microglia. Eventually, abnormalities in the microglia network can result in excessive synaptic pruning, which has been linked with certain psychiatric conditions like schizophrenia, ADHD and ASD.
- Inflammation and hyperactive microglia can also affect brain regions associated to the onset of psychiatric diseases. These regions include the amygdala, hippocampus, insula, anterior cingulate cortex, dorsolateral prefrontal cortex and orbitofrontal cortex.

- The interaction between the immune system and psychiatric disorders has been investigated in multiple studies.
- Evidence points towards a bi-directional association between psychiatric illnesses and autoimmune conditions.
- Subjects diagnosed with a psychiatric disease or a family history of psychiatric conditions have higher rates of autoimmune disorders and vice versa.
- Schizophrenia, MDD, and bipolar illness have been associated with multiple sclerosis, Grave’s disease, psoriasis, SLE, rheumatoid arthritis, diabetes mellitus, IBD, idiopathic thrombocytopenic purpura, and polymyalgia rheumatica, among others.

Depressive disorders:

- ”Sickness behavior”: the appearance of anhedonia and fatigue after an infectious process.
- Patients with hepatitis C treated with IFN-α: onset of depressed mood, psychomotor retardation, sleep and appetite disturbances, and SI.
- Subjects with depression have elevated QA in serum and CSF.
- Different studies, including meta-analyses, found that elevation of C-reactive protein (CRP), TNF-α, IL-6, and soluble IL-2 (sIL-2) are correlated to the appearance of depressive symptoms in a subset of patients.

Bipolar disorders:

- Chronic low-grade inflammation seems to be related to depression, mania, and cognitive deficits seen in bipolar patients.
- Post-mortem studies detected elevated IL-1β and decreased TGF-β in the cortex of bipolar people compared to controls.
- Studies found that IL-4, IL-6, TNF-α, soluble receptor of TNF-α type 1 (STNFR1) and IL-1 receptor antagonist (IL-1Ra) are elevated during a manic phase.
- STNFR1 was elevated during the euthymic, depressed, and manic phases.

Anxiety and trauma-related disorders:

- Chronic stress suppresses glucocorticoids’ ability to overcome inflammatory processes. At the same time, pro-inflammatory cytokines may perpetuate symptoms like avoidance and hypervigilance.
- Parental separation in early childhood and exposure to traumatic events (including combat exposure) have been linked to elevated inflammatory markers.
- PTSD is associated with increased IL-2, IL-6, IL-1β, CRP, TNF-α, and IFN-γ, and decreased IL-4, IL-8, and IL-10.
- GAD correlates with elevated IL-2, CRP, and TNF-α.
- Panic disorder is associated to increased IL-6, IL-1β, IL-2, and TNF-α.

Schizophrenia and other psychotic disorders:

- Evidence suggests that people with schizophrenia have inflammatory anomalies in CSF, serum, and the CNS.
- Increased levels of IL-6 during childhood have been correlated with adult-onset psychosis.
- Individuals at clinical high risk for psychosis who have altered inflammatory markers during their prodromal phase may develop full-blown psychosis in the future.
- A meta-analysis showed that, compared to healthy controls, antipsychotic-naïve patients with a first psychotic break had elevated IL-1β, IL-1Ra, soluble IL-2 receptor (sIL-2R), IL-6, IL-8, IL-10, IL-12, TGF-β, and TNF-α.
- Other studies suggest cytokine alterations may vary with clinical status, and treatment-resistant schizophrenia has been associated with IL-1β and IL-6.

Noteworthy, not every patient with baseline elevated inflammatory markers will develop a psychiatric disorder. Many elements are required for the genesis of psychopathology. Several risk factors like obesity, sleep problems, history of trauma, CV diseases, DM, and cancer can make a person prone to inflammation-related psychopathology. Likewise, complement system anomalies, exposure to in-utero viral and parasitic infections, alterations in the gut microbiota, and genetic/epigenetic changes are associated with a higher risk of developing an inflammatory psychiatric illness.

Table 1 summarizes the most studied agents with anti-inflammatory properties used as monotherapy or adjuvant therapy for the treatment of common psychiatric disorders. The results have been mixed so far, and their use should be considered on a case-by-case basis.

DISCUSSION (CONTINUED)

Table 1

Agent	Anti-inflammatory mechanism	Psychiatric illnesses
NSAIDs	Reduction of prostaglandin synthesis by selective and non-selective COX inhibition	Depressive disorders, bipolar disorder (manic phase), and schizophrenia
Monoclonal antibodies	Inhibition of pro-inflammatory cytokines	Depressive disorders, bipolar disorder (depressed phase), and schizophrenia
Statins	Reduction of NF-κB activity, inhibition of nitric oxide, and modulation of NMDA receptor activity	Depressive disorders
Minocycline	Suppression of microglial activation, decrease in chemokine expression and T cell migration in the CNS, and regulation of p38 MAP kinase pathway	Depressive disorders, bipolar disorder (depressed phase), and schizophrenia
Polyunsaturated fatty acids	Inhibition of protein C kinase and NF-κB pathways, regulation of prostaglandins and leukotrienes, and increase in BDNF	Depressive disorders and bipolar disorder (depressed phase)
N-acetylcysteine	Decrease of ROS and inhibition of NF-κB activity	Depressive disorders, bipolar disorder (manic and depressed phase), and schizophrenia
Thiazolidinediones (the “glitazones”)	Attenuation of oxidative damage, prevention of c aspase-3 activation, and increase in BDNF	Depressive disorders and bipolar disorder (depressed phase)
Estrogen	Reduction of nitric oxide and TNF-α	Schizophrenia
Coenzyme Q-10	Suppression of NF-κB signaling and attenuation of LPS-induced chemokine release	Bipolar disorder (depressed phase)

CONCLUSIONS

Inflammation plays a role in the inception of common psychiatric illnesses. The interplay between cytokines and neurotransmitters with environmental, genetic, and epigenetic factors contributes to the pathogenesis of inflammatory psychiatric disorders. Given the necessary presence of these factors for disease onset, not every subject with elevated pro-inflammatory markers will develop psychiatric symptoms. Psychiatric disorders tend to be resistant to usual treatments. Therefore, therapeutic agents with anti-inflammatory properties are being studied as a novel treatment option for these conditions, and they could be considered in refractory cases or in subjects who have elevated inflammatory markers at baseline. Nonetheless, the evidence is inconclusive yet, and more research is needed.

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