Anti-Inflammatory Therapy as a Promising Target in Neuropsychiatric Disorders

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Abstract

This chapter analyzes the therapeutic potential of current anti-inflammatory drugs in treating psychiatric diseases from a neuro-immunological perspective. Based on the bidirectional brain-immune system relationship, the rationale is that a dysregulated inflammation contributes to the pathogenesis of psychiatric and neurological disorders, while the immunology function is associated with psychological variables like stress, affective disorders, and psychosis. Under certain social, psychological, and environmental conditions and biological factors, a healthy inflammatory response and the associated "sickness behavior," which are aimed to resolve a physical injury and microbial threat, become harmful to the central nervous system. The features and mechanisms of the inflammatory response are described across the main mental illnesses with a special emphasis on the profile of cytokines and the function of the HPA axis. Next, it is reviewed the potential clinical utility of immunotherapy (cytokine agonists and antagonists), glucocorticoids, unconventional anti-inflammatory agents (statins, minocycline, statins, and polyunsaturated fatty acids (PUFAs)), the nonsteroidal anti-inflammatory drugs (NSAIDs), and particularly celecoxib, a selective cyclooxygenase-2 (Cox-2) inhibitor, as adjuvants of conventional psychiatric medications. The implementation of anti-inflammatory therapies holds great

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promise in psychiatry. Because the inflammatory background may account for the etiology and/or progression of psychiatric disorders only in a subset of patients, there is a need to elucidate the immune underpinnings of the mental illness progression, relapse, and remission. The identification of immune-related bio-signatures will ideally assist in the stratification of the psychiatric patient to predict the risk of mental disease, the prognosis, and the response to anti-inflammatory therapy.

Keywords

Anti-inflammatory agents · Cytokines · Glucocorticoids · Inflammation · Mental disorders · Psychoneuroimmunology

20.1 Introduction

Over 2000 years ago, Aristotle hypothesized a connection between physical health and mood. The concept reached its zenith with Descartes, who proposed the major advances in medicine, the Cartesian mind-body dualism. With the lighting up of psychoneuroimmunology in the 1980s of the past century, scientists began to explore one critical phenomenon of this dualistic paradigm, the interaction between psychological processes and the nervous and immune systems of the human body [1]. The immune system and the central nervous system maintain a relationship hitherto underestimated in many psychiatric illnesses. On one hand the immune system function is commonly associated with psychological variables like stress, distress, and affective disorders. Psychosocial stress together with cumulative genetic and epigenetic risk factors plays a role in the disturbances of the immune homeostasis [2]. On the other hand, a dysregulated inflammatory response of the immune system to harmful stimuli contributes to the pathogenesis of psychiatric and neurological disorders. This is the case of schizophrenia, autism spectrum disorders, bipolar disorders, depression, or even anorexia nervosa, whose neuropathological mechanisms may in some cases engage chronic inflammation [3–7]. Numerous epidemiological data have demonstrated the link that exists between a whole series of immune-inflammatory diseases and mental illnesses. For example, all the articles currently published on the microbiota and mental illnesses imply the same mechanism: inflammation increases the permeability of the digestive barrier and allows antigens to pass into the circulation which, normally, do not enter and will cause the appearance of autoantibodies and autoimmune diseases [8]. This is a phenomenon that is built up gradually, more or less quickly depending on the exposure. It is estimated that at least one third of patients with these severe conditions have elevated inflammatory markers. Some diseases heretofore considered to be exclusively psychiatric may also have a neurological and even immunological explanation. Understanding these psychiatric diseases from a neurological and immune perspective opens up new therapeutic possibilities [9].

Certain immunosuppressive treatments already known to treat multiple sclerosis or autoimmune encephalitis could find their place in the management of these mental conditions [10]. Trials currently being carried out with anti-inflammatory drugs associated with treatment, in particular in resistant depression [11], confirm our idea that this immuno-inflammatory pathway is extremely promising. This immunology approach is not only likely to move psychiatry towards neuropsychiatry but also to encourage healthcare professionals to look for signs of inflammation via certain additional examinations such as an MRI of the brain or assays in the blood and CSF of certain markers, such as C-reactive protein or CRP, and pro-inflammatory cytokines TNF-α or interleukin-6 (IL-6) [12, 13]. Many answers still remain to be found regarding the mechanisms of occurrence of these diseases and the effectiveness of anti-inflammatory treatments. To meet these challenges, the association of neurologists and psychiatrists in this new field, that is, immunoneuropsychiatry, seems promising for many patients. Recognition that inflammation may represent a common mechanism of disease extended to include neuropsychiatric disorders shakes up concepts in psychiatric illness.

An approach to exploring the connection between the immune system and mental condition is through medical illnesses associated with immune system dysfunction like HIV infection [14] and autoimmune disorders such as systemic lupus erythematosus (SLE) [15]. Immunomodulatory drugs have been known and have been used for many years to treat classic neurological autoimmune diseases such as multiple sclerosis and encephalitis. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are induced by autoimmune disorders, toxins, infections, and even psychosocial stress to trigger both peripheral and central immune reactions through the binding to pattern recognition receptors (PRRs). The major consequences of ligating PRRs are to initiate a cascade of responses that direct inflammation, a process characterized by the activation of immune and non-immune cells that protect the host by eliminating threats and promoting tissue repair and recovery [16].

A healthy inflammatory response engages an acute immune response temporally restricted to the period the threat is present. Depending on the degree and extent of inflammation, specific energy-saving behaviors can occur that conserve metabolic energy and allocate more nutrients to the activated immune system. Biobehavioral effects of the immune system activation or “sickness behaviors” include sadness, anhedonia, fatigue, reduced libido and food intake, altered sleep, and social-behavioral withdrawal [17], which are critical for survival during times of physical injury and microbial threat. However, under certain social, psychological, environmental, and biological factors, the inflammatory response either fails to eliminate the damage or does not resolve once the threat has passed. Then, the process enters in a state of chronic, low-grade inflammation which is distinct from that in the onset. While acute inflammation is initiated by PAMPs, chronic inflammation is typically triggered by DAMPs in the absence of an acute physical insult and microbial threat. Shifts in the inflammatory response from short- to long-lived can cause a breakdown of immune tolerance [18].

20.2 Immune-Associated Pathophysiology of Mental Diseases

Inflammation aggresses the CNS and increases the risk for psychiatric disease [19]. Long considered to be protected by the immune system, the central nervous system (CNS), and in particular the brain, can also be the site of chronic inflammation. Cytokines are produced in CNS glial cells [20]. Astrocytes and microglia are key components of the innate immune system that can cause detrimental processes when activated while producing beneficial processes when quiescent. Cytokines increase neuronal excitotoxicity, reduce brain trophic factors and neurogenesis, and provoke oxidative stress directly by the release of reactive oxygen [3] and indirectly through the conversion of kynurenic acid, a product of the normal metabolism of amino acid L-tryptophan, to neurotoxic quinolinic acid (QA) and 3-hydroxykynurenine (3-HK) by activated microglia [21]. Although the entire region of brain parenchyma is excluded from the peripheral immune system, immune responses of the CNS are in close communication with the peripheral immune reactions [22, 23]. Circulating cytokines released by endothelial and immune cells in cerebral vasculature can diffuse passively or interact directly with BBB receptors stimulated by the central noradrenergic system to induce cyclooxygenase-2 (Cox-2) inflammatory signaling within the brain parenchyma. In addition, peripheral cytokines can also bind to receptors located on the liver, the spleen, or the nodose ganglion to relay cytokine signals to the brain via afferent sensory fibers of the vagus nerve to trigger neural firing or lead the synthesis of IL-6 by microglia [24, 25]. In the CNS, cytokines may also exert their effects by activating the hypothalamus-pituitary-adrenal (HPA) axis [26]. Given the abnormal profiles of pro-inflammatory and anti-inflammatory cytokines observed in some groups of psychiatric patients, an inappropriate CNS-immune communication may be the hallmark of neurodevelopmental, neurodegenerative, and neuro-immunomodulatory disorders.

How is immunity involved in the pathophysiology of mental diseases? Mental illnesses are due to the interaction between a genetic background and environmental factors. In the case of dysimmunity, the immunogenic background of the person does not allow him to defend himself sufficiently effectively against early environmental factors associated with the onset of mental pathologies, such as infections or severe stress, which are pro-inflammatory factors. This results in the appearance of an immuno-inflammatory cascade which varies according to the pathologies. Exposure to other environmental factors that are repeated throughout life, such as infections, stress, an unbalanced lifestyle (diet, physical activity, sleep, etc.), maintains this low-level inflammation, which will have consequences at the peripheral level, at the cerebral level, and on the digestive tract. Several lines of evidence suggest that dysfunction of innate immunity, including the microglia, the brain's resident immune cells derived from the monocyte lineage, may occur in a number of neuropsychiatric conditions [27]. Raised inflammatory processes (microglia activation and elevated cytokine levels) across diagnoses may disrupt neurobiological mechanisms regulating glutamate release and uptake, oxidative stress, and excitotoxicity [28]. Finally, cytokines activate the HPA axis to fuel inflammation and catecholaminergic neurotransmission [29].

20.2.1 Anxiety Disorders

Inflammation in the CNS primarily reflects physical and psychological stress. Early-life stress is more clearly associated with overt inflammation prior to the development of neuropsychiatric symptoms. For example, childhood trauma is associated with significantly elevated peripheral levels of C-reactive protein, IL-6, and TNF-α among other pro-inflammatory markers [30]. Stress can lead to increased cytokine levels and an induction of catecholamines via an activation of the HPA axis [29]. This in turn increases pro-inflammatory cytokines within and outside the CNS through a complex positive feedback loop [31]. Abnormalities in serotonergic function are involved in the pathogenesis of anxiety. The pro-inflammatory cytokines affect serotonin (5-HT) metabolism by reducing tryptophan levels. Cytokines appear to activate indoleamine-2-3-dioxygenase (IDO), an enzyme which metabolizes tryptophan, thereby reducing serotonin levels and creating neurotoxic serotoninergic metabolites 3-HK and QA, which next cause oxidative stress and permanent neuro-inflammatory damage [32]. Furthermore, inflammatory cytokines, such as IL-1β, may reduce extracellular 5-HT levels, via activation of 5-HT transporter mechanisms [33]. Disturbances in the microglial system increases TNF-α, oxygen radicals and oxidative stress [34], QA, and complement factors along with a decrease of neurotrophic factors of individuals genetically predisposed to hyper-anxiety [35].

Post-streptococcal autoimmune disorders are related to delayed neurological complications that persist throughout life in the function of the basal ganglia [5]. It would explain the enhanced pro-inflammatory innate immune response in the etiopathogenesis of obsessive compulsive disorders (OCD) [36]. The first evidence of the nexus between inflammation and OCD was found in the late 1980s, when the National Institute of Mental Health reported for the first time the association between streptococcal-induced Sydenham chorea and the abrupt, early-onset of obsessive-compulsive symptoms in pediatric patients. Although the syndrome was originally denominated pediatric autoimmune neuropsychiatric disorders associated with streptococcus or PANDAS [37], it has been reconsidered and evolved towards pediatric acute-onset neuropsychiatric syndrome (PANS) [38] and/or childhood acute neuropsychiatric syndrome (CANS) [39] all characterized by the presence of typical OCD symptoms and tics. In the case of adult OCD patients, it has been associated with a previous history of rheumatic fever following group A β-hemolytic streptococcal pharyngitis [40]. Other infectious agents like *Toxoplasma gondii* or Borna disease virus may also be of paramount importance to OCD. A complete picture of the changes in immune parameters in OCD is not possible owing to the scarce number of studies. Conversely to schizophrenia and BD, the circulation of the inflammatory cytokine IL-1β is decreased in patients with OCD [41]. Although this finding seems to indicate a non-inflammatory profile in OCD, this cytokine is likely to play a role in re-myelination, which is in agreement with the structural changes reported in OCD. The alterations of immune cells should be considered a state-dependent marker, perhaps related to stress associated with OCD. The

OCD-immune system relationship [42] hints for possible anti-inflammatory therapies in OCD [43].

Posttraumatic stress disorder or PTSD is a debilitating psychiatric disorder that follows trauma exposure. There is evidence that the immunological balance is skewed towards a pro-inflammatory state (IFN-γ, IL-6, TNF-α, and IL-17) in the plasma and increased levels of immune stimulatory Th1 and inflammatory Th17 cells in the blood following an initial trauma event [6]. Because of hyper-arousal state, people living with PTSD commonly manifest dysregulations of the systems that regulate the stress response, the HPA axis, and the sympatho-adrenomedullary system. The release of excess levels of stress hormones further contributes to low cortisol levels and chronic immune dysregulation in PTSD. This potentially causes the development of autoimmune disease, especially in younger individual. PTSD increase presents elevated risks for rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, and thyroiditis [44]. Interestingly, among the genetic variations associated with the risk for PTSD after trauma exposure, there are included genes encoding regulators of the immune function [45]. Enhanced cell-mediated immune function and pro-inflammatory cytokine level significantly increase the odds of developing clinically worse courses of PTSD. For instance, there is a direct correlation between PTSD severity and spontaneous overnight secretion of IL-6 and TNF-α by the leukocytes [46]. Because of the close association between PTSD and neuroendocrine and immune dysfunction, and given the increased risk for comorbid somatic autoimmune and inflammatory disorders in PTSD, the targeting of the neuroendocrine and immune dysfunction is likely to improve PTSD symptoms [47].

20.2.2 Mood-Related Disorders

Altered cytokine activity in the periphery and the brain of a subpopulation of depressed patients [48] brings support to the concept of depression-associated inflammation [49]. Patients with major depressive disorders (MDD) demonstrate that C-reactive protein and inflammatory cytokines are strongly correlated with CSF markers of neuro-inflammation, which suggests that peripheral inflammatory biomarkers may reflect similar findings in the CNS [50]. Psychosocial stress, a well-known precipitant of mood disorders, is capable of stimulating neuro-inflammatory pathways within the brain [3], while MDD occurs at a substantially higher rate in patients with inflammatory disorders in peripheral organs such as multiple sclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, and myocardial infarction. Individuals with autoimmune diseases who are given inflammation-based therapies (e.g., interferon, typhoid vaccination, or endotoxin) are at an increased risk of presenting with mood disorders [51]. When used for immunotherapy in cancer or hepatitis, large doses of pro-inflammatory IL-2 and/or IFN-α induce depressive symptoms that can be efficiently treated by antidepressants [52, 53]. The overactivation of the immune system over the course of life (e.g., aging-related and comorbid disease-related inflammatory processes) also increases

the vulnerability to anxiety and depression. In accordance with the phenotypic heterogeneity of MDD, a pattern of low-grade inflammation is present in at least one third of MDD cases, with being atypical depression a more pro-inflammatory condition [54]. Somatic or neuro-vegetative symptoms of depression (fatigue, sleep disturbances, poor appetite) are more associated with inflammation than emotional/cognitive symptoms (depressed mood, worthlessness, anhedonia, poor concentration). In this vein, depression probably represents a maladaptive version of "sickness behavior" (social withdrawal, reduced appetite, and low energy), which might occur in the presence of an exacerbation in intensity and/or duration of the innate immune response [55].

Small physiologic differences in the immune system can have a huge effect over time on depression if they are consistently skewed in one direction. It has been hypothesized that the activation of microglia from stress or preexisting pro-inflammatory state causes metabolic changes in the tryptophan-kynurenine pathway [56]. Tryptophan is the main precursor of 5-HT, whose deficiency leads to depression, whereas kynurenine is the precursor of the neuroprotective molecule kynurenic acid that antagonizes the NMDA receptor. However, pro-inflammatory cytokines activate the IDO enzyme, which metabolizes kynurenine into excitotoxic metabolites like 3-HK and QA [21]. Oxidative stress induced by the overweight of N-methyl-D-aspartate (NMDA) agonism leads to the loss of glial elements, altered glutamate release/reuptake, and decreased neurotrophic support that characterize depressive disorders. Cytokines cause tryptophan depletion by the stimulation of the IDO synthesis and the promotion of the neurotoxic pathway of the kynurenine pathway [32]. Another pivotal mechanism by which cytokines may induce depression is the activation of the HPA axis [57]. Pro-inflammatory cytokines like IL-1, IL-6, TNF-α, and IFN-γ can result in the synthesis of corticotrophin-releasing factor (CRF), which in turn stimulates adrenocorticotropic hormone (ACTH) release and the subsequent hyperactivity of the HPA axis [26]. Clinical studies have demonstrated hyperactivity of the HPA axis and increased levels of cortisol in patients with major depression, because of an impairment of glucocorticoid receptor (GR)-mediated negative feedback or glucocorticoid resistance [58]. Reduction of GR function is the main neuroendocrine abnormality in depression, and hypercortisolemia is seen as a compensatory mechanism in the presence of reduced brain sensitivity to glucocorticoids. Although corticosteroids are generally anti-inflammatory, at normal endogenous levels, adrenal steroids appear to function as immune regulators rather than simply immune suppressors [59]. A lack of the "positive" effects of cortisol on the brain, because of "glucocorticoid resistance," is likely to be involved in the pathogenesis of melancholic depression.

Chronic (low-grade) dysregulated immune activation (e.g., Guillain-Barré syndrome, autoimmune hepatitis, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and autoimmune thyroiditis) in patients suffering from bipolar disorder (BD) is present at higher rates than in normal population, suggesting a significant cross-talk between autoimmune processes and BD [60]. Indeed, patients with BD exhibit increased rates of obesity and metabolic syndrome, conditions associated with low-grade inflammation. Immune-BD

interaction may be bidirectional. BD increases the risk of the development of comorbidities, such as cardiovascular and metabolic diseases. Increased and decreased levels of IL-1β and IL-6 respectively in the cerebrospinal fluid of a subset of BD patients during mania and depression are suggestive of the CNS-focused immune mechanisms [61]. BD patients present a hypo-responsive glucocorticoid receptor (GR) in peripheral tissues, which could be at least partly responsible for a deficient cortisol-mediated negative feedback loop of the HPA axis and basal hypercortisolemia. Pro-inflammatory cytokines contribute to a chronic HPA activation and inflammatory responses in BD [62].

Finally, immune deficiencies are secondary processes to malnutrition observed in the development and progression of another mood-related disorder, anorexia nervosa [63]. During the course of anorexia, there are metabolic changes; hormonal imbalances, particularly with regard to secretion of cortisol; and altered production of various neurotransmitters, which result in a dysfunctional immune system [64]. Malnutrition causes a significant reduction in the percentage of T-cells and unchanged or slightly elevated B-cell numbers which provokes a high instability in the immune system of anorexia patients [65]. Consequently, the severity of anorexia nervosa correlates with higher levels of peripheral inflammatory markers [66]. Plasma levels of the pro-inflammatory cytokines TNF-α and IL-1β in plasma significantly increase in patients with anorexia nervosa, while the levels of prostaglandins PGE_2 (pro-inflammatory) and 15d-PGJ_2, (anti-inflammatory) and their PPARγ receptor implicated in their modulation diminish [7]. Cytokines directly interact with hunger centers, especially IL-1 and TNF-α, which additionally affects peripheral signals to satiety centers, leading to temporary gastric emptying inhibition. Of especial interest are the adverse effects of increased TNF production on anorexia, since this cytokine has an exacerbating central effect of food intake suppression and/or increased tissue catabolism [67]. Despite the immune deficiencies and changes in immunological parameters, an unexplained, remaining paradox is that many people suffering from anorexia appear very healthy and do not suffer from viral infections excluding cases of advanced malnutrition.

20.2.3 Schizophrenia

Schizophrenia is a neurodevelopmental disease driven by risk genes, and the immune system is positioned as a common link between the seemingly diverse genetic and environmental risk factors for schizophrenia [68]. Appearance of psychotic symptoms represents a relatively late manifestation triggered by environmental stress factors and disturbances of the immune system. Accordingly, the contribution of the immune dysregulation to the pathogenesis of schizophrenia may occur even before the onset of full-blown psychosis [69]. Schizophrenic patients with a history of prenatal exposure to influenza infection (second trimester) and rubella infection (first trimester) show impaired neurocognitive performance and structural abnormalities (e.g., synaptic pruning) in the brain [70]. The critical mediators of neuro-inflammation IL-6, which is highly expressed in fetal brains

following maternal immune activation [71], and IL-1β alter the neuronal development of the dopaminergic and serotonergic systems [72], thus causing functional deficits in the brain. These alterations may even prime the innate CNS immunocompetent cells so that they would later on exaggerate inflammatory responses. This would explain why physical and mental stress, HIV and influenza infections, and autoimmune disorders such as systemic lupus erythematosus (SLE) are associated with psychotic symptoms in more vulnerable individuals. Pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α are increased in the peripheral blood of patients with schizophrenia during acute psychotic exacerbations and related to a greater severity of both cognitive deficits and negative symptoms [73]. TNF-α and IL-6 cross the blood-brain barrier (BBB) and modulate several molecular/cellular processes, including, but not limited to, monoamine metabolism. It suggests that immunological alterations may even affect their clinical status after the onset of the illness.

There is an intertwined interaction of pro-inflammatory cytokines with the dopaminergic and glutamatergic neurotransmitter systems in areas affected by schizophrenia like the prefrontal cortex and hippocampus [74]. Conversely to depression, type-1 immune responses (e.g., IL-2 release) is blunted in schizophrenia, which may lead to an unbalance in IDO and in the tryptophan-kynurenine metabolism associated with an imbalance in the glutamatergic neurotransmission and NMDA antagonism in schizophrenia [75]. In addition, low concentrations of IL-2 may also alter dopamine-mediated neurotransmission. Neuroleptic medications used for psychosis also influence immune factors, often normalizing or reversing the direction of the abnormalities described in premedicated patients. Neuroleptic administration is associated with type-1 activation, including decreased IL-6 and soluble IL-6 receptors (sIL-6R), normalization of IFN-γ production, and increased sIL-2R. Nevertheless, recent studies suggest that the cytokine profile changes with the clinical status of the patients, with a high level of pro-inflammatory cytokines like IL-1β, IL-6, and transforming growth factor-beta (TGF-β) during the acute phase of diseases, which is absent in the remission phase [76].

20.2.4 Autism Disorders

In the case of autism, pro-inflammatory factors, infections, or autoimmune diseases are most likely involved during pregnancy, leading to genetically predisposed fetuses to develop this condition before the age of three [77]. The first evidence of the familial link of polyendocrine autoimmune disorder with autism was reported 50 years ago. Since then, some large population-based studies support the theory that autoimmune responses and immune dysfunction at or around the time of pregnancy may be related to a later diagnosis of autism in the offspring [78]. For instance, increased rates of rheumatoid arthritis, celiac disease, psoriasis, and type 1 diabetes, as well as immune-mediated disorders such as asthma and allergies, are found in mothers of children with autism. In addition, animal models known as immune activation in the mother, in which inflammation is induced through infections during

pregnancy, trigger the appearance of autism-mimicking behaviors in offspring. Accordingly, global immune dysfunction in mothers during pregnancy, rather than specific diseases, may be associated with increased risk for autism disorder. This risk nexus is not limited to the mothers, since a higher rate of the autoimmune condition type 1 diabetes is reported in fathers, which suggests underlying heritable immunogenetic factors [79]. Nonetheless, observations of autoimmunity are not limited to families of the children with autism disorder, but also to the presence of immune dysfunction in some children with autism disorder. Increased levels of pro-inflammatory cytokines such as IL-6 and TNF-α in brain specimens and CSF, as well as in the periphery in autism disorder individuals, point that to an ongoing neuroinflammatory process in autism disorder [80]. The presence of antibodies directed against adult brain or CNS tissue, but not fetal brain tissue, has been repeatedly reported in children with autism disorder [77]. Findings so far published suggest a complex pattern of immune activation that varies among different subgroups of individuals with autism disorder. Unfortunately, the extent of immune abnormalities in the broader autism disorder phenotype is not yet well understood, neither are known the mechanisms by which immune dysfunction contributes to the etiology of autism disorder.

20.3 Anti-Inflammatory and Immune-Based Therapies for Treatment-Resistant Mental Illness

Psychiatric disorders present a tremendously large heterogeneity that accounts for the lack of responsiveness and high rates of treatment resistance to conventional neuroleptic, antidepressant, and anxiolytic drugs. Although the monoaminergic hypothesis has been dominant in our understanding of the pharmacological effects of psychotropic medications, additional mechanisms might also play a role. Neurotransmitters involved in the neurobiology of mental health and disease like dopamine, serotonin, and glutamate have been found altered in low-level neuroinflammation. Therefore, dysfunction of the immune system and brain-immune interactions may be some of the sources of the neurotransmitter deficits historically ascribed to the major mental disorders [81]. In recent years, there has been a paradigm shift to place abnormal cytokine profiles at the center of psychiatric symptoms. Pro-inflammatory cytokine levels like TNF-α and IL-6 are related to the level of mental distress in some psychiatric inpatients suggesting that low-grade inflammation is probably a cause of resistance to conventional pharmacological treatments [54, 82]. In this vein, some recent studies have shown promising results with anti-inflammatory therapies like steroids, plasmapheresis, intravenous immunoglobulin, cyclophosphamide, or monoclonal antibodies acting on B cells, particularly in the treatment of certain children with autism, who suffer from inflammation, or adults with schizophrenia, for whom immunosuppressive therapy or a bone marrow transplant has significantly reduced psychiatric symptoms [83]. Some studies have even made it possible to highlight the anti-inflammatory role, hitherto unknown, of successful antidepressant treatment like selective serotonin reuptake

inhibitors widely used today [84]. The antidepressant bupropion interferes with the production of cytokines, while antipsychotic drugs like clozapine, risperidone, and haloperidol influence the balance between anti-inflammatory and pro-inflammatory cytokines upon stimulation of the immune system. In the light of this, drugs with demonstrated anti-inflammatory effects may well show improvement of mental conditions when used as add-on treatments to conventional psychiatric medications [85–91]. Increasing evidence demonstrates that anti-inflammatory agents are likely to modify the relationship between cytokines and mental distress (Table 20.1). Nonetheless, no superiority has been found in anti-inflammatory monotherapy, raising the question of the mechanism behind the effect.

20.3.1 Cytokine Antagonists and Agonists

Given their specificity, immunotherapy against cytokines offers an unparalleled opportunity to directly test the hypothesis of whether immune dysfunctions play a causal role in psychopathology. The use in schizophrenia of monoclonal antibodies like natalizumab, siltuximab¸ canakinumab, and tocilizumab targeting specific immune molecules is an illustrative example [92]. The same holds true for the treatment of depression. Anti-TNF therapy, which is being considered as an option in improving postoperative cognitive dysfunction, has shown clinical efficacy on cognition and depressive symptoms [93]. However, the complex signaling pathways of TNF-α and its receptors and the duality of its function in being both neuroprotective and neurodegenerative preclude long-term benefits of anti-TNF-α therapies [94]. The pro-inflammatory cytokine IFN-γ plays a pivotal role in modulating immune and inflammatory responses. The effect of IFN-γ-1b on stimulating the type-1 immune response showed preliminary, but encouraging, results in reducing clinical symptoms of schizophrenia [95]. Immunotherapy may also have possible psychiatric adverse effects: there is evidence that the treatment of hepatitis C with IFN-α precipitates depressive episodes [96]. Before considering immunotherapy as an adjunctive to conventional psychotropic medications, there is the need to improve our understanding of cytokine actions in the CNS and how peripheral inflammation reflects or perpetuates psychiatric symptoms.

20.3.2 Glucocorticoids

Glucocorticoids produced by the zona fasciculata of the adrenal cortex are a class of steroid hormones that are part of the feedback mechanisms of the immune system. Glucocorticoids are often exploited for their immune-suppressor properties [97], since they inhibit prostaglandins (PGs) and leukotrienes, the two main products of inflammation. Glucocorticoids act at the level of phospholipase A_2 (PLA_2), the enzyme that supplies the arachidonic acid (AA) substrate to both cyclooxygenase/PGE isomerase (COX-1 and COX-2 isoenzymes), to synthetize prostaglandin H_2 (PGH_2), and to the lipoxygenases that catalyze the dioxygenation of AA in a class of

Table 20.1 Evidence for anti-inflammatory therapies in neuropsychiatric disorders

Mental disorder	Immune-associated pathophysiology	Anti-inflammatory drug [Ref.no.]
Anxiety	Catecholamine depletion and excessive oxidative stress due to elevated cytokines via HPA axis	NAC [109, 111] Aspirin [161] Diclofenac [162] Naproxen [162] Ketoprofen [162]
OCD	Autoimmune syndrome largely caused by β-hemolytic streptococcal infections	NAC [109] Celecoxib [154]
PTSD	Autoimmune dysregulation caused by excessive levels of stress hormones	Glucocorticoids [106, 107]
MDD	Low-grade chronic inflammation caused by aging-related and comorbid disease-related inflammatory processes	Anti-TNF-α [93] Minocycline [115] Omega-3 FA [125, 126] Probiotics [128] Celecoxib [150–153] NSAIDs [161, 162]
BD	Autoimmune diseases and low-grade chronic inflammation	Minocycline [116] Celecoxib [116, 155]
Anorexia nervosa	Dysfunctional immune system caused by malnutrition	Unknown
Schizophrenia and psychosis	Immune dysregulation caused by perinatal influenza and HIV infections and autoimmune disorders	Cytokine monoclonal Ab [92] NAC [110, 158] Statins [122] Omega-3 FA [124] Celecoxib [138, 151, 159] Minocycline [158] Aspirin [158, 160]
Autism-related disorders	Infections and autoimmune disease during pregnancy	Celecoxib [157]

Ab antibody, *BD* bipolar disorder, *FA* fatty acids, *MDD* major depressive disorder, *NAC* N-acetylcysteine, *NSAIDs* nonsteroidal anti-inflammatory drugs, *OCD* obsessive compulsive disorder, *PTSD* posttraumatic stress disorder

lipids called leukotrienes characterized by containing a cis, cis-1,4-pentadiene. In addition, glucocorticoids also inhibit both COX isoenzymes, an effect being much like that of NSAIDs (see next section). Finally, glucocorticoids suppress COX expression, which reinforces their anti-inflammatory effects.

How endogenous or exogenous glucocorticoids, through their immune and inflammatory inhibiting or promoting properties, would alter brain function and

behavior is unknown and requires investigation. At normal endogenous levels, adrenal steroids appear to function as immune modulators [98]. They shift cytokine production to favor the type-2 immune response while inhibiting type-1 response. Chronic or acute stress and Cushing's disease can produce an excess of endogenous corticosteroids, thus increasing susceptibility to mood changes, cognitive deficits, and even psychosis [99]. Likewise, acute corticosteroid treatment with prednisone and dexamethasone adversely impacts memory, executive functions, and mood [100]. Exacerbated glucocorticoid levels cause neuronal damage and lasting alterations to the plasticity and structural integrity of the hippocampus and prefrontal cortex, and this mechanism may plausibly contribute to impaired memory and cognition in critical illness survivors [101] and in children and adolescents with inflammatory bowel disease [100]. Among the behavioral outcomes of high glucocorticoids, mood and anhedonia appeared to be the most consistently and strongly affected [102]. Chronic stress primes neuro-inflammatory responses in a glucocorticoid-dependent manner [103]. Therefore, the glucocorticoid state of the patient preceding illness may be important for the eventual outcome. According to the glucocorticoid resistance hypothesis of depression [104], increased levels of cortisol may be the consequence of an impairment of glucocorticoid receptor (GR)-mediated negative feedback on the HPA axis. Rather than using immunosuppressive corticoid-based treatment, the therapy of depression and mood-related disorders may well benefit from manipulating GR function with both agonists and antagonists. Conversely, glucocorticoid-based therapy can possibly protect against the development of PTSD given the association with low cortisol levels. Glucocorticoid treatment at the time of acute stress may prevent changes in hippocampal and amygdala architecture and associated changes in affective behavior [105]. The exogenous treatment with glucocorticoids has shown promise for the prevention of PTSD after a traumatic experience [106]. High doses of glucocorticoids administered with appropriate timing may block fear memory formation or retrieval, although moderate doses would also be expected to enhance fear memory, depending on their timing [107].

20.3.3 Unconventional Anti-Inflammatory Agents

N-Acetylcysteine (NAC) is a synthetic derivative of the endogenous amino acid L-cysteine and a precursor of glutathione with well-known anti-inflammatory and antioxidant properties [108]. Several studies have demonstrated that NAC regulates impaired glutamate and dopamine neurotransmission. There is preliminary, but encouraging, evidence of the therapeutic potential of NAC in disorders such as anxiety and attention deficit hyperactivity disorder [109]. Some evidence exists to support the use of NAC as an adjunct treatment to reduce the total and negative symptoms of schizophrenia [110]. In addition, NAC also appears to be effective in reducing craving in substance use disorders, especially cocaine and cannabis [111].

Minocycline is a tetracycline antibiotic with potential as an adjunctive treatment in psychiatry [112] due to its anti-inflammatory and anti-apoptotic/neuroprotective

properties and inhibition of cytochrome P450 enzymes that metabolize antipsychotics such as clozapine [113]. Minocycline has been checked in open-label or small randomized controlled trials in psychiatry showing divergent outcomes, with positive results in some studies counterbalanced by a number of cases with no significant improvements [114]. Anecdotal evidence supports minocycline's efficacy for augmentation of antidepressants in treatment-resistant depression patients with low-grade peripheral inflammation [115]. Minocycline may potentially be useful as an adjunctive for BD [116]. There is no evidence that minocycline or celecoxib monotherapy was superior to placebo for the treatment of BD. Minocycline reduces fear processing and improves implicit learning in healthy volunteers [117] and may still hold promise like a candidate treatment for depression owing to its neuroprotective role.

Statins are cholesterol-lowering agents that act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase. Several studies have suggested that statins may have anti-inflammatory properties, with lowering pro-inflammatory markers such as IL-1β, IL-6, TNF-α, and C-reactive protein levels [118]. Simvastatin also could alleviate cognitive function, since it modulates muscarinic M_1 and M_4 receptors, central dopamine D_1 and D_2 receptors, and the serotonin transporter [119]. Whereas conflicting evidence exists about the relationship between statins and mood amelioration [120, 121], a meta-analysis of statin adjunctive therapy for schizophrenia showed that statins improved the Positive and Negative Syndrome Scale (PANSS) [122].

Polyunsaturated fatty acids like omega-3 present antioxidation, anti-inflammation, and neuroprotection. In humans, dietary deficiencies of omega-3 fatty acids, in particular eicosapentaenoic and docosahexaenoic acids, have been linked to increased risk of developing MDD, BD, schizophrenia, dementia, attention deficit hyperactivity disorder, and autism [123]. Diet omega-3 fatty acids are essential because of their anti-inflammatory, antioxidative, and neuroprotective effects on neuronal membrane fluidity. Randomized clinical trials have found a significant benefit of omega-3 adjunctive schizophrenia therapy in the total, positive, and negative PANSS scores of patients or in their cognitive function [124]. For the remaining psychiatric disturbances, the data are too scarce to draw any conclusion regarding the benefits of diet supplementation with omega-3 fatty acids. Omega-3 fatty acid replacement therapy has only been shown to have a mild effect for the treatment of mood disorders and ADHD [125, 126].

Probiotics have traditionally been used to reestablish the physiological functions of the gastrointestinal tract. Given the extensive bidirectional communication between the gastrointestinal tract and the CNS, the gut-brain axis [127], probiotics are capable of changing the behavior and decreasing the levels of systemic inflammatory markers in animal models. A meta-analysis of randomized controlled trials has suggested that probiotics may be associated with a significant reduction in depression [128].

20.4 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): The Targeting of Cox-2

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used as antipyretic, anti-inflammatory, and analgesic agents. NSAIDs work by inhibiting the activity of cyclooxygenase Cox-1 or Cox-2 isoenzymes [129]. There are two types of NSAIDs available: nonselective and Cox-2-selective inhibitors (celecoxib, etoricoxib). Non-selective NSAIDs are typically divided into groups based on their chemical structure: acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen), acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam), anthranilic acids (meclofenamate, mefenamic acid), and naphthylalanine (nabumetone). Cyclooxygenases (Cox) are a group of heme-containing enzymes that catalyze a rate-limiting conversion of AA to largely bioactive prostaglandins (PGs) involved in inflammation, through the addition of molecular oxygen [130]. The Cox-1 isoform is a housekeeping enzyme constitutively expressed in all tissues. Although the mitogen-inducible Cox-2 is activated to cause inflammation, this isoform is also constitutively expressed in certain tissues as in the kidney and in the brain. In the human brain, Cox-1 is preferentially expressed in microglia, where Cox-2 is in glutamatergic neurons in the cerebral cortex, hippocampus, and amygdala [131]. Prostaglandin PGE_2 may be the predominant metabolite of the enzymatic activity of Cox-2 in the brain where it may function as neuromodulators of the inflammation as well as may be involved in important physiology functions in synaptic plasticity and long-term potentiation [132]. Immunological disturbances may lead to an increased PGE_2 production and probably also in an increased Cox-2 expression that would also contribute to neuropathology by enhancing glutamate excitotoxicity [133], promoting neuronal cell death, and metabolizing the endogenous cannabinoid 2-arachidonoyl-glycerol into PGE_{2G} through the oxidation of its AA moiety. Some studies suggest upregulation of Cox-2 expression in inflammatory and neurodegenerative diseases [134] as well as schizophrenia [135] and bipolar disorder [136].

NSAIDs penetrate the brain [137], and the use of NSAIDs as adjunctive treatments in neuropsychiatric disorders—including schizophrenia, bipolar disorder, and major depressive disorder—is currently under investigation [138–141]. NSAID treatment benefits on the brain in depression are thought to be due to their ability to block Cox-1 during pro-inflammatory microglial activation and neuronal Cox-2, which may affect glutamatergic and monoaminergic neurotransmission [133]. Cox-2 expression is upregulated in inflammatory schizophrenia and bipolar disorder. Accordingly, the selective Cox-2 inhibitor celecoxib has so far been the most studied NSAIDs in psychiatry [142, 143] because of the inhibition of microglial activation and glutamate release, the enhancement of serotonergic and noradrenergic output in the prefrontal cortex, and the modulation of glucocorticoid receptors (off-target mechanism of action). When reviewed the literature to determine whether selective Cox-2 and nonselective Cox inhibitor NSAIDs as adjuncts or monotherapy affect depressive symptoms [144–146], the search gives mix results regarding efficacy. Possible confounding factors [147] include age range (young versus elderly

subjects), sex, presence of antidepressant use, medical comorbidities (diabetes, metabolic syndrome), method of depression measure (somatic symptoms are more sensitive than subjective feelings to the influence of NSAIDs), severity of depressive symptoms, clinical phase of the illness (most of the studies rest on trials in acute depression), duration and study design (randomized controlled trials, cohort studies, and an open label), and pharmacological strategies (add-on treatments versus monotherapy). Despite the negligible therapeutic effects of NSAIDs reported by one meta-analysis in MDD [148], celecoxib reaches the CNS in humans in concentrations sufficient to inhibit Cox-2 [149] and thus improve the therapeutic management of depression [150–153], BD [117], and schizophrenia [138]. In effect, celecoxib works as an adjunctive treatment to fluvoxamine in moderate to severe OCD [154], to escitalopram in treatment-resistant BD [155], and to reboxetine and vortioxetine in MDD [156]. The combination of risperidone and celecoxib is superior to risperidone alone in treating irritability, social withdrawal, and stereotypy of children with autism [157]. In schizophrenia, celecoxib has shown efficacy in augmentation of amisulpride treatment in the early disease stages and first psychosis episode [158] as well as an effective adjuvant agent to risperidone in the management of patients with chronic schizophrenia [159]. It should be noticed that the use celecoxib in the treatment of schizophrenia reduces the symptoms only when administered in combination with the anti-schizophrenic drugs (i.e., risperidone, olanzapine, amisulpride). In the fact of BD, celecoxib monotherapy is not superior to placebo either. Strikingly, aspirin, which is a nonselective Cox inhibitor with preferential selectivity for the Cox-1 isoenzyme, significantly reduced the positive and negative symptoms of schizophrenia regardless it is administered either alone or as adjunctive therapy [160]. In a large register-based cohort study in Sweden, aspirin and other NSAIDs have demonstrated their effectivity in decreasing the risk of depression, anxiety, and stress-related disorders during the first year following cancer diagnosis [161]. A population-scale retrospective analysis has demonstrated the anxiolytic effects of ketoprofen, diclofenac, and naproxen in patients with pain [162].

Despite these promising preliminary results, the efficacy and safety of chronic NSAID exposure have been called into question in the treatment of both symptoms of depression [163], particularly in the elderly [164], and of psychotic disorders [148, 165]. The conflicting evidence may be due to the methodological heterogeneity of the clinical trials and the selection bias (inadequate assessment of the inflammatory and clinical status of patients). Another neglected aspect is that Cox selectivity of NSAIDs matters. Although neuro-inflammation is originally triggered by the induction of glial Cox-2 expression, the activity of Cox-1 also yields a prooxidant/pro-inflammatory action. Neuronal Cox-2 plays a homeostatic role in synaptic transmission and plasticity [133]. Deviations in inflammatory levels in both directions may actually impair neural plasticity. Studies show that both inflammation and neural plasticity act as key players in the vulnerability and recovery from psychiatric disorders with an impact on anxiety and memory [166]. Accordingly, a failure in the Cox-2/Cox-1 ratio might cause behavioral disturbances that otherwise would be commonly ascribed to neuro-inflammation [167].

Blanket blockade of Cox-2 may not be advisable because Cox-2 expression might in fact have pro-resolution properties [168]. In addition, selective Cox-2 inhibitors may alter the metabolism of the endocannabinoid system of the brain [169]. Given the significance of different Cox isoforms and their unknown role of their relative levels in the CNS, careful attention must be given to selection and evaluation of specific NSAIDs. Aspirin whose activity on Cox-1 prevails over Cox-2 alleviates psychiatric symptoms on its own (Hu et al., 2020). An interesting alternative to Cox inhibition would be the pharmacological intervention of the AA cascade. Some genetic evidence supports the notion that disturbances of the PLA_2-Cox-2 axis underlie abnormalities of monoaminergic neurotransmission in schizophrenia [170], BD [171, 172], and MDD [173]. In addition, preclinical experiments have also confirmed that mood stabilizers like lithium chloride target the upstream release of AA substrate for Cox enzymes [174].

20.5 Final Remarks

Although we now know by decades of research that there is a robust and complex link between inflammation and mental illness, one must be cautious about the apparent simplicity of the idea that anti-inflammatory agents could improve psychiatric symptoms. Meta-analyses do not undermine the potential clinical utility of anti-inflammatory agents, but they suggest that clinical trials carry a variety of caveats that need careful consideration. What the reviewed cohort studies and follow-up studies have actually demonstrated is that the inflammation-mental health link lacks diagnostic specificity and varies considerably among individuals and with each clinical phase of illness. Given the multifactorial etiology, preexisting inflammatory conditions may then account for at least a subset of psychiatric patients. Moreover, the biology of inflammation and related immune alteration may depend on the stage of the illness as it does the clinical symptomatology. For example, in schizophrenia and BD, a marked inflammation appears during episodes of acute decompensation so that chronic, low-grade inflammation seems to precede the initial illness episode [69]. Most of the studies in the field have not considered the inflammatory status before starting the anti-inflammatory clinical trials. Finally, while the onset of mental disorders appears well explained by its inflammatory background, the immune underpinnings of their progression, relapse, and remission remain to be elucidated. In some cases, anti-inflammatory treatments used outside the acute clinical phase may be detrimental because of the ambivalence nature of the inflammatory response.

There are some interesting future prospects to undertake the difficulties found in implementing anti-inflammatory therapies in psychiatry. Firstly, a number of publications indicate the importance of stratifying patients on the basis of their degree of phase-specific neuro-immune dysfunction and surrogate biological signatures of inflammation [12, 175–177] aided by neuroimaging to launch therapeutic trials. The identification of immune-related bio-signatures will ideally assist in predicting risk of disease, prognosis, and response to therapy. A broad immune-phenotyping is likely to be essential to identify the subpopulations of psychiatric

patients who are likely to respond to anti-inflammatory therapy either alone or when combined with conventional psychiatric drugs. In the second place, there are important gaps in our knowledge about the immune-associated pathophysiology. For example, the majority of studies investigating the role of inflammation in psychiatry conditions assessed peripheral levels (i.e., plasma or serum) of cytokines, while only a few studies evaluated CSF cytokine levels [178, 179], which may reflect better CNS levels and, therefore, any ongoing neuro-inflammatory process. Surprisingly, microglia activation shows no significant association with specific diagnostic categories of mental conditions [180], which means that it is not present in all psychiatric patients. It should then be explored how peripheral and neural immune mechanisms interact in these cases, particularly at the level of the blood-brain barrier as well the dynamics of the innate and adaptive immune responses. Finally, in the advent of precision medicine in psychiatry, it is important to understand the pharmacological off-target effects of the anti-inflammatory agents described in this chapter. The enhanced neuroprotection plus a reduction in inflammation may be an extended avenue for future interventions at least in depression. The complex opposing functions of TNF-α (neuroprotective and neurodegenerative) advice against the long-term benefits of anti-TNF-α therapies [181]. The lack of knowledge on immune-physiology and neurobiology of Cox enzymes limits the therapeutic potential of selective Cox-2 inhibitors, since Cox-1 is also pro-inflammatory.

In summary, anti-inflammatory pharmacotherapy may need to be used according to the phase of illness and be tailored based on the immune profile of the patient. Future studies with larger arrays of cytokine profiles may provide more sensitive and specific modes of diagnostics in determining etiology of psychiatric conditions and provide guidance in individual therapies. A better understanding of the pharmacological mechanism of current anti-inflammatory agents will help discover new therapeutic targets and drugs. This multimodal approach will ultimately foster the understanding of the biological basis of mental disorders and their interaction with the immune system. Despite the drawbacks highlighted by some meta-analyses, the preliminary results are very promising.

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