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REVIEW

Inflammation in psychiatric disorders: what comes first?

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Neuropsychiatric disorders (i.e., mood disorders and schizophrenia) and inflammation are closely intertwined, and possibly powering each other in a bidirectional loop. Depression facilitates inflammatory reactions and inflammation promotes depression and other neuropsychiatric disorders. Patients with neuropsychiatric disorders exhibit all cardinal features of inflammation, including increased circulating levels of inflammatory inducers, activated sensors, and inflammatory mediators targeting all tissues. Inflammation may contribute to the pathophysiology and clinical progression of these disorders. Of note, proinflammatory cytokines modulate mood behavior and cognition by reducing brain monoamine levels, activating neuroendocrine responses, promoting excitotoxicity (increased glutamate levels), and impairing brain plasticity. What are the sources of this chronic inflammation? Increasing evidence indicates that changes in neuroendocrine regulation, metabolism, diet/microbiota, and negative health behaviors are important triggers of inflammation. Finally, recent data indicate that early-life stress is associated with overt inflammation prior to the development of neuropsychiatric disorders.

Keywords: inflammation; cytokines; mood disorders; HPA axis; cortisol; psychosocial stress

Introduction

Neuropsychiatric disorders (notably, mood disorders and schizophrenia) and inflammation are closely intertwined. Increasing evidence indicates that depression and inflammation are powering each other. In this bidirectional loop, depression facilitates inflammatory reactions and inflammation promotes depression and other disorders. Patients with mood disorders and schizophrenia exhibit all cardinal features of inflammation. A typical inflammatory response consists of four major components[1] (Fig. 1): (1) inflammatory inducers, known as pathogen- or damage-associated molecular patterns (PAMPs or DAMPs, respectively); (2) sensors detecting the inducers (i.e., receptors expressed by immune cells); (3) inflammatory mediators induced by the sensors (e.g., cytokines, chemokines, prostaglandins, and reactive oxygen species); and (4) target tissues that are affected by the inflammatory mediators. The chronic inflammation scenario observed in neuropsychiatric disorders is compatible with sterile inflammation, which is likely driven by DAMPs released after physical or psychological stressors.

This article will present an overview of the inflammatory phenomenon present in neuropsychiatric disorders, especially in mood disorders and schizophrenia. We will focus on preclinical and clinical evidence that sterile inflammation may contribute to the pathophysiology and clinical progression of these disorders. We will also discuss how inflammation is translated into mood changes as well as providing the reader with insights into potential sources triggering the inflammatory markers.

Inflammation in neuropsychiatric disorders: inducers, sensors, and mediators

Patients with mood disorders and schizophrenia present several markers of immune dysfunction and premature senescence at different levels (molecular,

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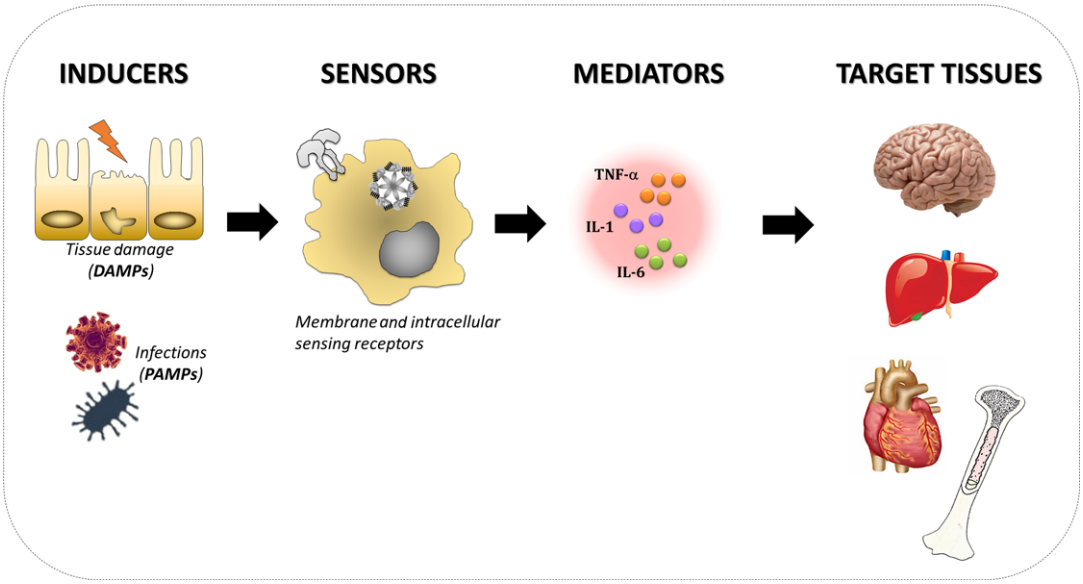

Figure 1. Components of a typical inflammatory response. The inflammatory response consists of four major components: (1) inflammatory inducers, (2) sensors expressed on immune and nonimmune cells, (3) inflammatory mediators, and (4) the target tissues that are modulated by the inflammatory mediators. The long-term effects of inflammatory mediators on target tissues include neuroinflammation (brain), metabolic disease (liver/pancreas), cardiovascular disease (heart), and osteoporosis (bone). PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns.

cellular, and tissues) (Table 1). In particular, recent data indicate the presence of all components of a typical inflammatory response. First, psychosocial stress has been associated with increased levels of circulatory inflammatory inducers, notably DAMPs. Examples of DAMPs include extracellular ATP, circulating uric acid, heat shock proteins (HSPs), high mobility group box 1, and oxidized molecules. Preclinical studies have revealed that all of these DAMPs are induced by psychosocial stress and can activate both central (i.e., neuroinflammation) and peripheral inflammatory responses.[2] DAMPs are endogenous molecules derived from self, and are increased after cellular and oxidative stress, stressor exposure, and tissue damage.[2] These molecules function as DAMPs when they are in the extracellular milieu due to stress-induced release or necrotic cell death. In the absence of tissue damage, stress-induced DAMPs may induce systemic sterile inflammation (Fig. 2). Indeed, high levels of HSP72 observed after tail shock are blocked by α-adrenergic, but not β-adrenergic or glucocorticoid receptor (GR), antagonists.[3] There is some evidence of increased circulating DAMPs in neuropsychiatric disorders, and high serum uric acid and HSP70 levels have been reported in bipolar disorder (BD) and major depressive disorder (MDD).[4–6] More studies are necessary to confirm the involvement of DAMPs in triggering chronic low-grade inflammation in neuropsychiatric disorders. It is also largely unknown what their releasing signals, cellular sources, and targets are.

Patients with mood disorders have immune cells with more activated sensors to PAMPs or DAMPs. BD subjects have been shown to have an expansion of some Toll-like receptors (TLRs) in peripheral monocytes and lymphocytes, as well as increased TLR-mediated intracellular signaling.[7] Also, the intracellular innate sensor Nod-like receptor 3 (NLRP3) inflammasome and caspase-1 have been found to be increased in blood cells and associated with high serum levels of interleukin (IL)-1β and IL-18 in MDD patients.[8] Furthermore, increased NLRP3 levels were found in the frontal cortex of patients with BD, and associated with increased levels of the cytokines tumor necrosis factor (TNF)-α, IL-1β, IL-6, and IL-10.[9] Inflammasomes are intracellular protein complexes that form in response to pathogens and sterile stressors, including DAMPs. Furthermore, aging also involves

Table 1. Evidence of immune dysfunction and premature senescence in neuropsychiatric disorders

Molecular	↑ expression and polymorphisms of immune-related genes (IL-1β, TNF-α, and CRP) ↑ activation of intracellular pathways (MAPK and NF-κB) ↑ activated sensors (TLRs and inflammasome) ↓ telomere length
Cellular	↑ monocytes ↑ activated T and B cells ↑ senescent T cells ($CD8^+$ $CD28^-$) ↓ regulatory T cells ($CD4^+$ $CD25^+$ $FOXP3^+$)
Peripheral blood	↑ proinflammatory cytokines ↑ endothelial cell activation markers ↑ adipokines ↑ acute phase proteins (e.g., CRP) ↑ oxidative stress markers ↑ autoantibodies ↑ antibodies to CMV
Central nervous system	↑ proinflammatory cytokines in cerebrospinal fluid ↑ proinflammatory cytokines in frontal cortex and anterior cingulate area ↑ microglia activation (neuroinflammation)
Clinical	↑ prevalence of autoimmune diseases ↑ prevalence of diseases with a proinflammatory status (cardiovascular diseases, diabetes mellitus, and obesity)

↑,increased; ↓, decreased. CMV, cytomegalovirus; CRP, C-reactive protein; IL-1β, interleukin 1β; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor α.

systemic low-grade inflammation ("inflammaging"), which is associated with increased age-related morbidities and mortality.[10] Of note, mice deficient in NLRP3 have reduced systemic inflammation, improved cognitive function and neuroinflammation, better glycemic control, attenuated bone loss, and reduced functional decline during aging.[11] Therefore, in addition to their key role in triggering peripheral inflammatory responses, sensors of the innate immune system are involved with neuroinflammation and pathological aging.

Patients with neuropsychiatric disorders have increased levels of inflammatory mediators. Indeed, patients with BD, MDD, and schizophrenia have been shown to have high levels of plasma proinflammatory cytokines and their receptors, increased levels of acute-phase reactants (e.g., C-reactive protein, CRP), chemokines, and soluble adhesion molecules in peripheral blood and cerebrospinal fluid (CSF).[12–16] Increased counts of innate immune cells, such as monocytes and neutrophils, activated T cells, and enhanced intracellular signaling, were associated with cell activation and proliferation.[17,18] To identify the cellular sources of this chronic low-grade inflammation, some studies have demonstrated that lymphocytes of BD subjects stimulated *in vitro* produced higher levels of proinflammatory (T_H1/T_H17) cytokines than healthy controls.[17] Increased inflammation has been associated with the progression or clinical severity of mood disorders. Indeed, higher CRP and IL-6 predicted the development of depressive symptoms in MDD.[19] Similarly, some data suggest that serum cytokine concentrations, including IL-6, are associated with disease severity, duration, and antipsychotic therapy in schizophrenia.[20,21] Remission of MDD was associated with a normalization of inflammatory markers.[22] Furthermore, it should be noted that both the number and the severity of comorbid inflammatory conditions influence inflammation and the risk of depression.[23] The association between proinflammatory markers and illness severity in BD is not as clear, as high plasma levels of proinflammatory cytokines and soluble receptors have been described during mania,[24] depressive episodes,[25–27] and even when mood is stabilized by medication (i.e., euthymia[17]).

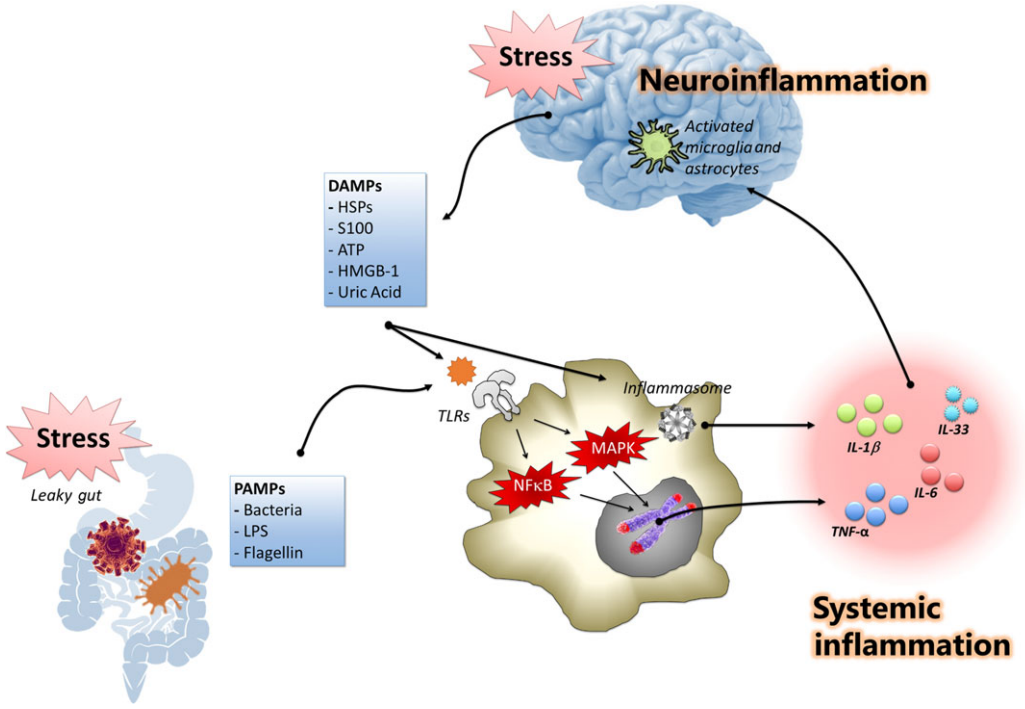

Figure 2. Psychosocial stress may drive both systemic and neuroinflammation. Chronic stress has been associated with neuroinflammation (i.e., activated microglia and astrocytes) and increased levels of circulatory damage-associated molecular patterns (DAMPs). Stress and neuropsychiatric disorders are associated with altered gut microbiota as well as their translocation from the gut into the blood ("leaky gut"), providing increased signals of pathogen-associated molecular patterns (PAMPs). Both DAMPs and PAMPs can signal through Toll-like receptors (TLRs) and the inflammasome in immune cells to increase the production of proinflammatory cytokines. Cytokines may then gain access into the brain where they activate microglia and astrocytes (neuroinflammation) and modulate key brain areas involved with depression and cognition.

Furthermore, polymorphisms in inflammatory genes, including genes expressing IL-1β, TNF-α, and CRP, have been associated with MDD, particularly with the treatment response.[28] Of note, inflammation was linked with antidepressant treatment nonresponsiveness. For instance, it has been shown that 45% of patients with nonresponse to antidepressants had a CRP of >3 mg/L, which is an accepted cutoff point for elevated inflammation.[29] Interestingly, antidepressants (notably, selective serotonin reuptake inhibitors) have significant anti-inflammatory effects, decreasing the production of TNF-α, IL-1, interferon (IFN)-γ, and increasing anti-inflammatory cytokines, for example, IL-10.[30,31] Conversely, anti-inflammatory drugs or monoclonal antibodies targeting cytokines have proven clinical efficacy for treating MDD or BD. A meta-analysis demonstrated that nonsteroidal anti-inflammatory drugs, notably the selective COX-2 inhibitor celecoxib, reduced depressive symptoms compared with placebo; MDD patients with higher inflammatory markers benefited most.[32] Clinical studies have indicated that a subgroup of MDD patients with elevated CRP levels had improved mood symptoms following anti-TNF treatment (infliximab).[29] A double-blind, randomized, placebo-controlled study with BD patients using celecoxib revealed that celecoxib was associated with a faster decrease in depression scores compared with placebo.[33]

Risk factors associated with inflammation in mood disorders

Individuals with chronic stress or mood disorders develop negative health behaviors (e.g., a sedentary lifestyle, poor diet, obesity, poor sleep, and smoking) that can lead to uncontrolled inflammation and depression.[34] For instance, subjects with MDD have a 58% higher risk of becoming obese.[35] Depression promotes obesity,

which in turn promotes depression. Indeed, 55% of obese individuals develop MDD during lifetime.[35] Obesity may increase the risk for depression by promoting inflammation. Indeed, obesity has been defined as a state of chronic inflammation due to elevated plasma IL-6, TNF-α, and CRP levels.[36] Also, adipocytes may produce and secrete IL-6 and TNF-α, and up to 30% of circulating IL-6 may be derived from adipose tissue.[36] A sedentary lifestyle and lack of physical activity can contribute to, or be a risk factor for, many clinical conditions (e.g., cardiovascular disease, diabetes, cancer, osteoporosis) and depression. Physically active subjects have lower inflammation than sedentary ones.[37] Increasing evidence supports the notion of exercise in preventing and treating depression.[38] In addition, lack of sleep and sleep impairment has been associated with increased production of proinflammatory cytokines and related cellular inflammatory signaling.[39] Disturbed sleep has been associated with many comorbidities associated with inflammation. Finally, smoking has been clearly associated with increased inflammatory responses.[40]

A poor diet may lead to important changes in microbiota composition, which in turn have been implicated with chronic low-grade inflammation and depression. The composition of microbiota is influenced by genetic and environmental factors (e.g., stress). Increasing evidence indicates that gut bacteria may have an important role in immune responses, including inflammation.[41] Recent studies have reported important microbiota changes in depression. Of note, MDD patients have been shown to have increased circulating antibodies (IgA and IgM) to Gram negative enterobacteria, as compared with normal volunteers, indicating enhanced bacterial translocation from the gut to the blood.[42] These changes are in part mediated by stress-induced enhancement of intestinal permeability.[43] Lipopolysaccharide (LPS) is part of the bacterial wall of Gram negative bacteria and may induce inflammation through binding to TLR4 and activation of nuclear factor (NF)-κB and its regulated proinflammatory cytokine genes. The application of *Bifidobacterium infantis* (a probiotic) to rats separated maternally was found to reduce depressive behavior in the forced swim test, to lower IL-6 levels in the plasma, and to regulate norepinephrine (NE) levels in the brain.[44] These data suggest that the composition of intestinal microbiota and its translocation from the gut into the blood ("leaky gut") during stress may lead to inflammation and depression-like behavior.

Persistent activation of the stress system leads to inflammation

Neuropsychiatric disorders (notably, mood disorders) can be understood as chronic stress disorders, as they present long-lasting dysfunctional physiological responses of the stress system. Schizophrenia can be conceptualized as either a neurodevelopmental disorder or a chronic stress disorder (because of its chronic clinical course). Exposure to environmental and psychosocial stress is associated with robust activation of the stress system, with elicited brain changes and peripheral neuroendocrine responses aimed to restore homeostasis. The neuroendocrine responses are characterized by increased plasma levels of NE, glucocorticoids (GCs), and epinephrine. If these adaptive responses are inadequate, excessive, or prolonged, they may impair the functioning of metabolism, growth, circulation, reproduction, and inflammatory reactions.[45]

Glucocorticoids regulate both the hypothalamic–pituitary–adrenal (HPA) axis and the immune system through binding to GRs. Once activated, GRs may translocate to the nucleus and upregulate expression of anti-inflammatory genes (e.g., IL-10) and repress inflammatory signaling pathways, including the inhibition of the transcription factor NF-κB, a major transcription factor for genes coding proinflammatory cytokines (Fig. 3). These mechanisms are the basis for the pharmacologic use of GCs as powerful anti-inflammatory drugs. In addition to the anti-inflammatory actions, GCs may also have pleiotropic effects on immune cells, including immunosuppressive, regulatory, and immune-enhancing effects.[46] These contrasting effects are due to tissue-related differences, including differential expression of GRs, GC signal transduction events, and metabolizing enzymes that limit the final hormonal concentrations. Low GC concentrations are immune enhancing, whereas very high ones are known to be immunosuppressive. For example, in macrophages activated by LPS and IFN-γ, high doses of corticosterone inhibit the transcription of inflammatory genes, whereas low doses of corticosterone enhance inflammatory gene expression.[47]

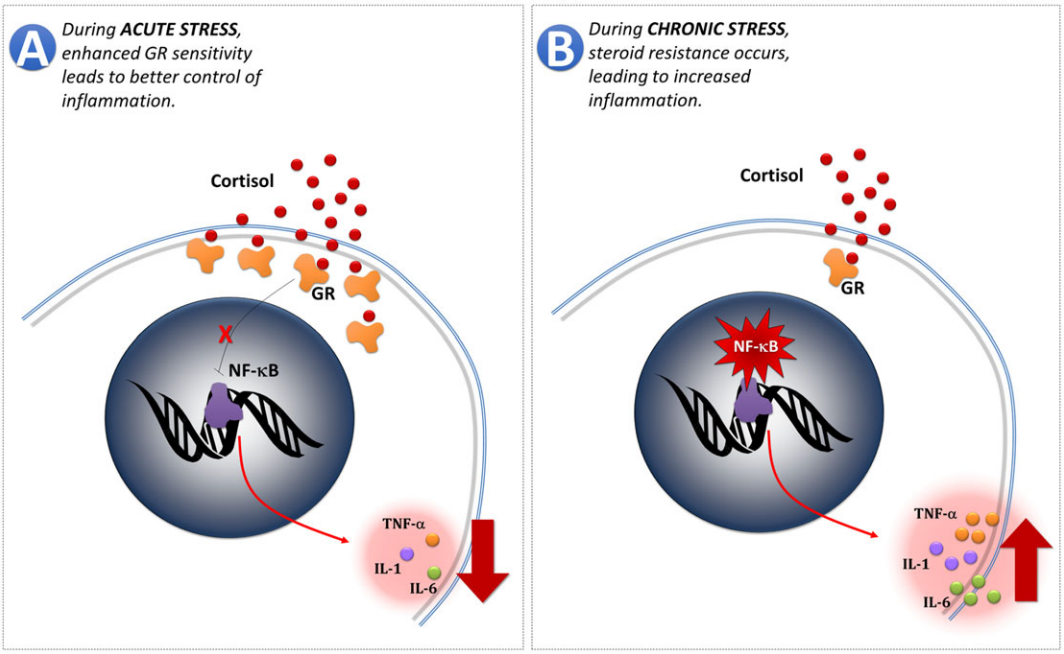

Figure 3. Psychosocial stress may induce anti-inflammatory or proinflammatory responses. Cells of the immune system are normally sensitive to increases in glucocorticoids (cortisol in humans) induced by stressors. Glucocorticoids regulate immune functions through binding to glucocorticoid receptors (GRs). Once activated, the GR translocates into the nucleus and represses inflammatory signaling pathways, including inhibiting NF-κB, a major transcription factor for proinflammatory cytokines. During acute stress, the increased GR sensitivity leads to better control of inflammation. However, chronic cortisol levels are observed during chronic stress and major depression. In this case, steroid resistance (e.g., lower GR numbers or reduced affinity) occurs, leading to increased inflammation by activating NF-κB and its target genes coding for proinflammatory mediators.

In addition, the constant exposure to high cortisol levels may lead to resistance (insensitivity) to the suppressive effects of steroids (Fig. 3).[48] Indeed, some studies reported that MDD patients had high cortisol concentrations, but decreased responsiveness to steroids after oral use of dexamethasone.[49] In the lack of adequate inhibitory control mediated by GC, the result is increased immune signaling as demonstrated by increased levels of activated cells and proinflammatory cytokines.[50,51] Indeed, the lymphocytes of MDD patients were remarkably resistant to the suppressive effects of dexamethasone *in vitro*.[52] In several studies with MDD, the common reported findings are inflammation and partial resistance to GC—in fact, these findings are more frequent than hypercortisolemia. Indeed, resistance to GC and high plasma proinflammatory cytokines were found in 85% of the studies in MDD.[53] Proinflammatory cytokines are known to induce GC resistance by disrupting GR expression and function, leading to unrestrained inflammatory responses.[54] Cytokine-dependent GR resistance also decreases the inhibitory feedback of hypothalamic corticotropin-releasing hormone, intensifying the stress-responsive system.[55] In addition, increased NF-κB signaling was also observed in healthy individuals following acute psychosocial stress, and it was dependent on NE-mediated adrenergic stimulation of peripheral blood mononuclear cells (PBMCs).[56] These data indicate that persistent GC/NE signaling, as shown in chronic stress disorders, contributes to exaggerated inflammatory responses by desensitizing GRs and activating transcription factors of proinflammatory genes.

The majority of previous studies have investigated neuroendocrine and immune responses at baseline, and stress reactivity is largely unknown in mood disorders. Recently, we reported the neuro-immune responses in euthymic BD patients subjected to the Trier Social Stress Test, a psychosocial stress task commonly used to describe biological changes evoked by a controlled stress exposure.[57]

We found that BD patients had impaired stress responses, as shown by reduced salivary cortisol levels and attenuated heart rate, in comparison with healthy controls.[57] Patients also had reduced proportions of regulatory T cells, but higher proportions of activated T cells compared with controls. In contrast to controls, patients with BD had higher levels of the mitogen-activated protein kinase (MAPK) p-ERK and of p-NF-κB in lymphocytes after the stress challenge, but exhibited lymphocyte resistance to dexamethasone. In conclusion, failure to mount adequate neuroendocrine responses under stress could be associated with detrimental overshooting of immune responses and hence could be underlying the immune imbalance observed in BD.

Inflammation leads to depression-like behavior: mechanistic pathways

The use of inflammatory stimuli was associated with the development of depression-like behavior in experimental and clinical studies. Indeed, LPS, vaccination, and proinflammatory cytokines may lead to important changes in behavior, including fatigue, depressed mood, and impaired cognition.[58] These behavioral changes were named "sickness behavior" and constitute a group of changes engaged in by mammals in order to enhance host survival following infection. Exposure to cytokines was associated with sickness behavior in humans. Up to 50% of patients under IFN-α therapy developed clinically defined depression. The IFN-α–induced depressive syndrome is responsive to antidepressants and clinically overlaps with idiopathic MDD.[59]

How do circulating cytokines trigger depression-like behavior? Peripherally released cytokines may reach the brain via humoral and neural routes, driving CNS inflammation and modulating key brain areas involved with depression. The humoral route includes the leaking of cytokines into the brain parenchyma through the blood—brain barrier—notably, via the circumventricular organs and via active transport through receptors. Cytokines may also signal the brain through binding to receptors expressed in peripheral afferent fibers (e.g., the vagus nerve)—this transmission was called the "neural route." Cytokines alter the metabolism, production, and transport of neurotransmitters involved in regulating mood (i.e., dopamine, glutamate, and serotonin).[60] For instance, cytokines may activate indoleamine 2,3-dioxygenase (IDO), an enzyme that alters tryptophan metabolism. IDO is involved in breaking down tryptophan into kynurenine, a tryptophan metabolite. Tryptophan is an essential amino acid (i.e., that must be obtained through diet) and the primary precursor of serotonin. This pathway induces depression by reducing the production of serotonin and augmenting levels of kynurenine. In the brain, kynurenine is further metabolized by the following cellular pathways: (1) neural progenitor cells and microglia, generating 3-hydroxykynurenine (3-HK) and quinolinic acid (QA); and (2) astrocytes, producing kynurenic acid (KA). 3-HK is an oxidative stressor, whereas QA is an agonist of the *N*-methyl-D-aspartate (NMDA) receptor, inducing the release of glutamate and blocking glutamate reuptake by astrocytes.[61] Interestingly, increased levels of QA were found in the brain and CSF of suicide victims/attempters.[62,63] QA has been associated with oxidative stress and lipid peroxidation. These activities, in combination, can lead to excitotoxicity and neurodegeneration. In contrast to QA, KA can reduce glutamate and dopamine release, both of which can lead to impaired cognition.[61]

In addition, IDO can also be induced/activated by multiple inflammatory signaling pathways, including STAT1, interferon regulatory factor-1, NF-κB, and p38 MAPK.[60] Importantly, blocking NMDA glutamate receptors (with ketamine) or inhibiting IDO activity protects mice from experimentally induced depression-like behavior.[64,65] Based on these preclinical findings, ketamine has proven to have rapid antidepressant effects in humans.[66] Drugs that block IDO may also be useful for patients with depression and high inflammatory markers.

Cytokines may also interfere in the synthesis of dopamine. IFN-α injection in rats resulted in a significant decrease in the levels of tetrahydrobiopterin (BH_4) and dopamine in the amygdala and raphe areas. BH_4 is an important cofactor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis.[60] The impact of cytokines in dopaminergic pathways may lead to decreased motivation (anhedonia), an important symptom of depression.

Furthermore, glutamate may also bind to extrasynaptic NMDA receptors, leading to lowered production of brain-derived neurotrophic factor (BDNF), thus impairing neuroplasticity.[67] BDNF is a neurotrophin with important roles in the neurogenesis

and is essential for an antidepressant response; it was found to be reduced by TNF-α and IL-1β and their intracellular signaling pathways, including NF-κB in animal models of depression.[68]

Early-life stress leads to chronic inflammation

Childhood maltreatment (CM) is a major risk factor for developing psychopathology during lifetime. Of note, maltreated children are more likely to develop MDD (OR 2.6), BD (OR 3.3), anxiety disorders (OR 2.5), substance abuse (OR 3.5), or PTSD (OR 4.4) during adulthood.[69,70] CM encompasses emotional, physical, and sexual abuse, neglect, and the witnessing of domestic violence. Exposure to early-life stress (ELS) leads to long-lasting neuro-endocrine-immune changes that predispose to higher vulnerability to psychiatric disorders later in life, known as developmental programming.[71]

ELS is associated with an immune phenotype characterized by increased inflammation, impaired cell-mediated immune responses, and premature immunosenescence.[72] Higher basal or stress-induced levels of plasma cytokines, including IL-6, IL-1β, and serum TNF-α, have been described in healthy adults exposed to ELS.[73] Also, previous studies reported altered cell-mediated immune markers in adults with ELS, including expansion of activated T cells ($CD4^+$ and $CD8^+$), natural killer cells, and higher CD4/CD8 T cell ratios.[74] Large epidemiological cohorts reported that ELS is an independent risk factor for inflammation later in life.[75] The current literature suggests that ELS accelerates telomere attrition in peripheral PBMCs, as well as leading to the accumulation of age-related epigenetic changes.[72] Although it is well established that adults with ELS have immune changes associated with cellular activation and inflammation, it is largely unknown whether these changes precede the onset of neuropsychiatric disorders.

Recently, we reported the effects of ELS on immune and endocrine pathways in healthy adolescents without previous or current psychopathology.[76] The adolescents with history of ELS had increased proportions of activated and senescent T cells. Following stimulation *in vitro*, it was found that immune cells (lymphocytes) of adolescents with a history of ELS (CM) produced more (up to 5×) inflammatory cytokines (IL-2, IFN-γ, and IL-17) which were associated with increased MAPK ERK and NF-κB signaling. In addition, CM was linked with increased hair cortisol levels (50% increase), reflecting cumulative cortisol levels, in parallel with increased cellular resistance to steroids as well as low plasma BDNF levels. These data may suggest that healthy adolescents with history of CM had an overt immune activation profile before any psychopathology is established. It was speculated that this altered neuroimmune profile could importantly contribute to enhanced vulnerability to trauma-related neuropsychiatric disorders later in life. Further prospective studies should investigate whether these changes may indeed predispose to psychopathology during one's lifetime.

Conclusions and future perspectives

Patients with neuropsychiatric disorders exhibit many of the features of chronic (low-grade) inflammation, including higher plasma levels of inflammatory inducers (PAMPs or DAMPs), activated sensors (TLRs and inflammasome), and inflammatory mediators (cytokines and chemokines) targeting all tissues. Future clinical studies should identify new inflammatory inducers and sensors that may prove useful as drug targets. Also, new preclinical studies are welcome to describe the underlying mechanisms involved in stress-induced changes in microbiota (providing PAMPs) or alarmins (providing DAMPs).

Higher levels of inflammatory mediators have been linked with the etiology and clinical progression of neuropsychiatric disorders. Peripherally released cytokines reach the brain and drive neuroinflammation by modulating key brain areas involved with depression, and, notably, impairing plasticity and neurochemistry and activating neuroendocrine axes (Fig. 2). Indeed, higher levels of cortisol and catecholamines are commonly described as a consequence of the activated sympathetic nervous system (SNS) and HPA axis. Despite its regulatory effects, chronic exposure to high cortisol levels may lead to resistance to steroids at both central (i.e., hypothalamic) and peripheral (i.e., lymphocyte) levels. Immune cells resistant to steroids acquire an inflammatory profile, and inflammation may contribute to cellular steroid resistance. Based on this knowledge, clinical trials confirmed the clinical efficacy of using anti-inflammatory agents for treating BD and MDD. Future studies will investigate whether these

treatments are also effective in attenuating premature senescence, including increased oxidative stress and shortened telomeres.

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Competing interests

The authors declare no competing interests.

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