Disturbed sensitive equilibrium led by stress-induced inflammation in psychiatric illness

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INTRODUCTION

The internal environment of an organism is in dynamic equilibrium homeostasis, but abnormal conditions can shift certain equilibrium parameters, resulting in a stress response. Inflammation is triggered by noxious stimuli and involves the transmission of vascular cells and immune cells, coordinated by a large number of mediators forming a complex regulatory network with basic pathways consisting of inducers, sensors, mediators and effectors.[1]

Inflammation can remove disturbances and expand homeostasis and adaptive capacity.[2] However, inflammation is accompanied by a non-adaptive outcome of expedient balance at the expense of many other physiological processes, which may become maladaptive in the chronic phase.[1] Changes in conditions may alter homeostasis and increase the deleterious effects of non-adaptive traits. Therefore, inflammatory responses are often associated with pathological conditions, including sadness, pleasure deficiency, fatigue, decreased libido and food intake, altered sleep and social withdrawal behaviour.[3]

Tissue stress or dysfunction can induce paraneoplastic inflammation, which can become chronic when it persists.[1] The shift from short term to long term can lead to a breakdown in immune tolerance. Social, psychological and environmental factors promote low-grade, non-infectious systemic chronic inflammation (SCI),[4] which can gradually cause collateral damage to tissues, such as through the induction of oxidative stress.[2] SCI can lead to various major modern diseases whose causes include lack of physical activity, poor diet, environmental and industrial toxins, and psychological stress.[5]

HIGH IMMUNE AND NEUROLOGICAL CROSSOVER

The nervous and immune systems are highly interoperable.[6] Immune processes play a crucial role in the central nervous system (CNS) homeostasis, resilience and brain reserve. Microglial, astrocytes and mast cells are the main components of the innate immune system within the CNS, monitoring its local environmental homeostasis through fine motor processes. The microglial has a vital role in neural development, maintaining synaptic loop homeostasis through synaptic pruning. It also senses neural activity, contacts neurons and indirectly influences their firing, which is associated with activity-dependent synaptic plasticity, learning and memory. Systemic inflammation activates the microglial, which releases pro-inflammatory mediators and induces phagocytosis by macrophages.[7]

CNS and the peripheral immune system are closely linked, and immune cells are also present at the brain border: antigen-presenting cells and T cells, which protect the blood–brain barrier (BBB) and CNS function. T cells can respond to peripheral inflammatory signals and release cytokines that affect CNS function.[8] The meningeal lymphatic system transports CNS immune cells and molecules to lymphoid organs to trigger the immune response, including the subsequent migration of immune cells into the brain. Innate and adaptive immunity play an important role in CNS homeostasis, and disturbances in the balance of neuronal, glial and immune cell interactions can affect cognitive performance.[9]

NEUROGENIC NEUROINFLAMMATION INDUCED BY STRESS

In contrast to peripheral inflammation, the complex response system of the CNS is neuroinflammation. The latter involves a coordinated defence of innate and adaptive immune cells, vascular cells and neurons to maintain tissue integrity in response to

pathogens, trauma and degeneration.[10] Macrophages and perivascular cells replace the function of resident dendritic cells. The blood–CNS barrier reduces microvascular permeability to macromolecular and blood cell extravasation. Its intrinsic immune cells deal directly with pathogens and tissue damage, but inflammatory cells are involved only in severe cases.[11]

Neuroinflammation exists in a graded degree from mild to severe. The adaptive response maintains homeostasis and includes the release of gliotransmitters, neurotrophic factors and cytokines in addition to vasodilation and phagocytosis.[12] This maintains synaptic plasticity and the protection, repair and regeneration of neurons. However, maladaptation includes the release of pro-inflammatory factors and plasma extravasation, resulting in dysfunction: hyperexcitability, impaired inhibition and reduced computational power.[13] In more severe cases, neurotoxicity may occur, including excitotoxicity, apoptosis and blood–CNS barrier breakdown, which cause neurodegeneration, loss of function and increased potential for chronic disease. Anti-inflammatory mechanisms may be triggered simultaneously to terminate neuroinflammation and reduce pathological outcomes.[14]

Neuronal activity may also trigger an inflammatory response in the CNS known as neurogenic neuroinflammation.[10] It has beneficial effects, such as increasing computational capacity and promoting regeneration.[15] But when it lasts too long, it can become maladaptive, associated with various conditions such as pain, psychological stress and seizures.[10]

Psychological stress is one of the primary triggers of neurogenic neuroinflammation. Social and physical living environments and lifestyles are key stress and chronic inflammation triggers. Specifically, industrialisation has led to living environments that differ significantly from those earlier in the evolutionary process, such as demanding work settings. These differences result in an evolutionary mismatch that triggers changes in social interaction and sleep quality.[16] The influence of psychological stress involves not only neurohormonal responses but also neuroinflammation. An example is chronically elevated cortisol levels that lead to decreased sensitivity, disrupting glucocorticoids that effectively downregulate inflammatory activity.[17]

In psychiatric pathology, excessive upregulation or downregulation of microglial function can have a negative impact.[9] Genetic defects in signalling pathways lead to abnormal development of brain circuits and neuropsychiatric symptoms. Psychosocial factors may cause the disruption of microglial function in later life. Chronic stress and depressive behaviour are associated with the loss of microglia in the hippocampus (HPC) of mice,[18] which means that the homeostasis of CNS maintained by microglia is disrupted. Depression and schizophrenia (SCZ) are associated with increased microglial activity,[19] which represents increased levels of neuroinflammation, suggesting a link between neuroinflammation and mental illness.

Chronic stress can also disrupt the integrity of the blood–CNS barrier and lead to the release of inflammatory mediators in the CNS. Nitric oxide, cyclo-oxygenase-2 and excess pro-oxidants in different brain regions play a role in neuronal functional and structural damage. The activation of their biochemical pathways depends on the activation of N-methyl-D-aspartate receptor (NMDAR) and nuclear factor-κB (NF-κB). Stress can alter the oxidative or nitrosative pathways of inflammatory mediators.[20] In conclusion, neuronal activity patterns encoding psychological stress responses and peripheral immune responses may act synergistically to trigger neuroinflammation.[10]

STRESS AFFECTS THE BRAIN AND ITS FUNCTIONS

Chronic stress-induced effects on the brain and its function can be analysed at micro, mesoscopic and macro levels, in order of molecular, circuit, neuroarchitecture and large-scale brain network levels.[21] Impact aspects include synaptic (especially glutamatergic) structure and function, the hypothalamic–pituitary–adrenal (HPA) axis,[15] etc.

Stress triggers changes in the synaptically active pathway, with the mechanistic target of rapamycin complex 1 (mTORC1) at its core.[22] Brain-derived neurotrophic factor (BDNF) is released upon activation by glutamatergic neurons. Chronic mild (unpredictable) stress can sequentially lead to decreased or increased BDNF in different brain regions, decreased mammalian target of rapamycin (mTOR) activation and downstream effectors, decreased glutamate release, decreased synaptic plasticity, decreased prefrontal synaptic spine density, and ultimately, maladaptive outcomes like pleasure-deficit behaviour.[23] At the circuit level, increased or decreased activation of selected neuronal projections between different areas triggers depression-like or anxiety-like behaviours.[24] Chronic stress also alters neural architecture. In mice, it decreases apical dendrite length and branching in the medial prefrontal cortex (PFC) and HPC CA3 pyramidal neurons while increasing dendrite density in the basolateral amygdala.[24] These are biologically relevant for stress-related neuropsychiatric disorders. Macroscopically, the brain is organised into coherent large-scale functional networks. Abnormally low connectivity or hyperconnectivity within and between networks plays a role in neuropsychiatric disorders, such as major depressive disorder (MDD),[25] involving overall dysregulation of cognitive and/or emotional information processing.[26]

An in-depth mechanism for the sustained effects of stress is the epigenetic regulation of gene expression.[27] Stress changes epigenetic markers of gene fine-tuning involved in brain plasticity. Stress-induced epigenetic modifications of HPA axis-related genes control homeostatic levels of glucocorticoids,[28] as well as many other genes essential for neuronal function. These can determine stress adaptation or maladaptation, resulting in a trajectory of health or disease.[29] Changes in epigenetic enzymes induced by stress result in aberrant DNA

methylation and histone modifications of specific genes and alterations in microRNAs in brain regions, including the prefrontal cortex (PFC), ventral tegmental area (VTA) and hippocampus (HPC).[30] Thus, the transcription and translation of molecules involved in the stress response, synaptic plasticity and neuromodulator signalling are disrupted, leading to maladaptive changes and stress-related psychiatric disorders.[24]

INFLAMMATION IN PSYCHIATRIC DISORDERS

Psychiatric disorders, including depression and MDD, anxiety disorders, bipolar disorder (BD), autism spectrum disorder (ASD), SCZ, post-traumatic stress disorder (PTSD), addiction and obsessive-compulsive disorder, are affecting the lives of hundreds of millions of people worldwide. Despite the enormous resources invested in various types of psychiatric research over the past decades, molecular mechanisms of the illnesses remain elusive. Psychiatric disorders are more heterogeneous than most neurological diseases because multiple substances and different pathway alterations can cause a single symptom. This heterogeneity dictates that pathological data sampled from patients with a specific diagnosis are only valid for comparison with data from healthy controls. Furthermore, phenotypes are often shared due to symptom overlap between diagnoses.[31]

A growing number of studies have shown that not only classic neuroinflammatory diseases are caused by immune dysregulation, but also similar processes are involved in the various psychiatric disorders described above; the common pathways involved include microglia activation, pro-inflammatory cytokines, molecular mimicry, anti-neuronal autoantibodies, self-reactive T cells and disruption of the BBB.[9] Major features of inflammation, such as elevated levels of pro-inflammatory cytokines in peripheral blood and cerebrospinal fluid, the development of innate or adaptive cellular responses and activation of glial cells, have been detected in all of these psychiatric disorders, and levels of inflammatory markers are reduced in patients after treatment.

Peripheral inflammatory signals can infiltrate the brain parenchyma through damaged BBB or cerebrospinal fluid and activate microglia and trigger an inflammatory cascade response. Glial cells also release cytokines (interleukin (IL)-1β, IL-6, IL-8, tumour necrosis factor-α, interferon-γ, and so on), chemokines, inflammatory mediators, and reactive nitrogen and oxygen species (RNS and ROS). These newly released substances amplify inflammatory signals within the CNS,[32] thereby inducing neurotoxicity and neurodegeneration and affecting various aspects such as neurogenesis, synaptogenesis, neurotransmitter and receptor expression.[33] Ultimately, neural structures, circuit connections and higher-order networks are altered,[24] and psychiatric illness occurs.

Stress-induced inflammation is considered to be involved in various psychiatric disorders by affecting neuronal signalling, altering neurotransmitter

metabolism and initiating oxidative stress. In depression, for example, chronic stress activates NF-κB and the nucleotide-binding oligomerization domain(NOD), leucine-rich repeats (LRR) and pyrin domain-containing protein 3 (NLRP3) inflammasome.[34] NF-κB and NLRP3, in turn, stimulate the release of various pro-inflammatory cytokines. Elevated levels of pro-inflammatory cytokines can enhance indoleamine 2,3-dioxygenase (IDO) activity. IDO activation leads to the degradation of tryptophan to kynurenine and other derivatives,[35] which is a precursor of 5-hydroxytryptamine, and decreased tryptophan levels affect monoamine synthesis and delivery.[36] Activated microglia can convert kynurenine to quinolinic acid, which can bind to the NMDAR and act in conjunction with increased glutamate release and reduced reuptake from astrocytes (due in part to the induction of RNS and ROS), leading to glutamate accumulation.[32] Excess glutamate leads to a significant decrease in *BDNF* gene expression in the PFC and HPC, affecting neurogenesis, long-duration enhancement and dendritic sprouting.[34] Also, because BDNF constitutively controls nuclear translocation of the master redox-sensitive transcription factor (Nrf2), when BDNF levels are low, translocation of Nrf2 is prevented, and detoxification/antioxidant enzymes are not activated, leading to the generation of sustained oxidative stress and, thus, increased susceptibility to depression.[37] Cytokine effects on the neurotransmitter system can inhibit multiple aspects of the lack of reward motivation and pleasure in cortical striatal circuits involving the basal ganglia, PFC and cingulate cortex while also activating circuits regulating anxiety, arousal, alertness, and fear involving the amygdala and HPC.[38]

Interestingly, the aforementioned inflammatory pathways are not specific to depression. Increased levels of pro-inflammatory cytokines mediated by NF-κB activation and the kynurenine pathway involving IDO and its downstream pathways all play critical roles in the pathogenesis of BD, SCZ, ASD and PTSD.[33] An obvious question then follows: why does stress-induced inflammation lead to different pathogeneses, given the high degree of overlap in the pathways involved in various common psychiatric disorders? The answer to this question remains inconclusive, but we can moderately speculate through the available evidence. For example, overexpression of IL-6 has been reported in various psychiatric disorders and is thought to be associated with cell adhesion, migration and synaptic modifications.[33] High levels of IL-6 have been associated with poorer cognitive performance, even in undiseased populations, while another cytokine, IL-1β, is associated with memory and negative emotions such as sadness.[39] These findings suggest that multiple and diverse cytokines each act at different concentrations in different brain regions. So we propose a question of our own: could these variations lead to the development of psychiatric disorders with different symptoms through permutation?

It is also worth noting that inflammation does not lead to the development of psychiatric disorders in all
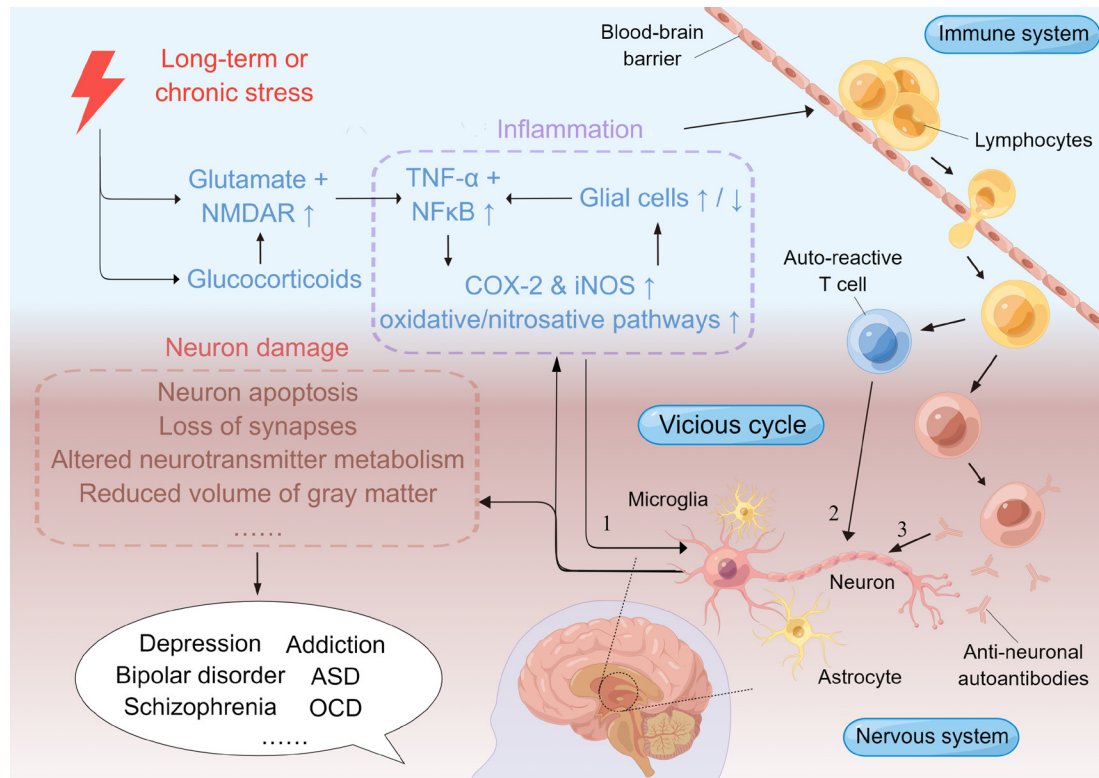
Figure 1 Biological mechanisms of psychiatric disorders led by stress-induced inflammation. The + in the figure means 'release', and ↑/↓ means 'activation/inactivation'. The arrows labelled 1, 2, 3 represent the three ways neuroinflammation damages neurons: (1) pro-inflammatory cytokines, (2) auto-reactive T cells and (3) anti-neuronal autoantibodies. ASD, autism spectrum disorder; COX-2, cyclo-oxygenase-2; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor-κB; NMDAR, N-methyl-D-aspartate receptor; OCD, obsessive-compulsive disorder; TNF-α, tumour necrosis factor-α. By Figdraw.

cases, and not all patients with psychiatric disorders have detectable markers of inflammation in their bodies. Inflammation and psychiatric illness are not in a simple include-and-be-included relationship, but inflammation-mediated illnesses are still an important subset of all psychiatric disorders. This discrepancy may be related to the heterogeneity of the disorders and inspires future differentiation of different subtypes of psychiatric disorders (figure 1).

DISCUSSION

Emergence and advances in the field of immunoneuropsychiatry offer novel ideas for breaking through current bottlenecks in treating psychiatric disorders. Microglia and astrocytes are likely effective targets for developing new drugs for psychiatric disorder therapy. In previous clinical treatments, some patients with various psychiatric disorders were unresponsive or weakly responsive to conventional medications, which may be associated with glial cell-mediated neuroinflammation.[40] Therefore, the application of adjuvant immunomodulatory therapy, that is, the use of microglia inhibitors, the inhibition of pro-inflammatory cytokines or their downstream signalling pathways, and the enhancement of anti-inflammatory mediator activity, may have a promising medical future.

Since stress is an important aetiological factor in the induction of neuroinflammation, using non-pharmacological means to intervene and alleviate mental stress may be an effective route to treat neuroinflammation and psychiatric disorders. Twelve weeks of aerobic exercise has been shown to significantly reduce serum levels of inflammatory markers and improve cognitive processing speed in individuals with a history of drug dependence. In addition, diet, music and family interventions have all been documented to improve neuroinflammation-related psychiatric disorders.

Nonetheless, current treatments for inflammation-involved psychiatric disorders are mainly based on their clinical efficacy, and the exact mechanisms remain to be elucidated. For example, diagnostic and treatment difficulties occur because the classification of neuropsychiatric disorders primarily depends on their manifest symptoms rather than pathogenic mechanisms. The ongoing development of immunoneuropsychiatry is expected to promote the transfer of research from phenomenology to pathology, offer direction for classifying patients into inflammatory and non-inflammatory groups according to pathogenic mechanisms, and guide the prescription of specific medications for different illness subtypes. These achievements would considerably decrease clinical

therapy challenges while simultaneously making great strides in neuropsychiatry.

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