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Review

Recent advances in the study of sepsis-induced depression

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ABSTRACT

Progress in medicine such as the use of anti-infective drugs and development of the advanced life support equipment has greatly improved the survival rate of patients with sepsis. However, the incidence of sepsis-related diseases is increasing. These include severe neurologic and psychologic disorders, cognitive decline, anxiety, depression, and post-traumatic stress disorder. Cerebral dysfunction occurs via multiple interacting mechanisms, with different causative pathogens having distinct effects. Because sepsis-related diseases place a substantial burden on patients and their families, it is important to elucidate the underlying pathophysiologic mechanisms to develop effective treatments.

Introduction

Sepsis is a life-threatening condition caused by a dysfunctional host response to infection and is a common cause of death in critically ill patients. As an increasing number of patients are now recovering from critical illnesses, physical dysfunction and organ failure after discharge as well as short- or long-term neurologic disorders such as cognitive impairment, decreased self-care ability, anxiety or depression, and post-traumatic stress disorder—collectively known as post-intensive care syndrome—are becoming more common.[1] Depressive symptoms are common in patients discharged from the ICU and adversely affect patients' quality of life. A systematic review showed that about 30% of ICU survivors had clinically significant depressive symptoms within the first 12 months after recovery from severe diseases. Given the complex pathogenesis and many complications of sepsis, there is considerable research interest in elucidating the mechanism underlying the association between sepsis and depression.

Depression is a common mental disorder in modern society and can impair physical functioning;[2,3] the emotional and neurocognitive manifestations include insomnia, overeating, obesity, diabetes,[4,5] and memory deficits, which can negatively impact daily work[6–8] and life activities of patients.[9,10] Numerous studies have used non-invasive neuroimaging approaches to investigate the pathologic changes in brain anatomy associated with depression. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have revealed significant changes in the frontal lobe, hippocampus, temporal lobe, thalamus, striatum, and amygdala in patients with severe depression exposed to negative vocabulary, a fearful environment, or sad scenes.[11,12] Although the mechanistic basis of these changes remains unknown, neuron loss, dendritic atrophy, abnormal activation of glial cells, and disruption of the neural network are thought to be involved.[13]

Studies on sepsis-induced brain injury have mostly focused on the destruction of the blood–brain barrier (BBB) and short- and long-term physiologic damage caused by metabolic disturbance and intestinal flora imbalance. In this review, we describe the mechanisms linking sepsis to emotional disorders, which can provide guidance for the development of effective interventions.

Sepsis Causes Depression-like Behavior by Disrupting the BBB

Pathogens activate nuclear factor kappa B (NF-κB) signaling to disrupt the BBB

The BBB, which is surrounded by adherent vascular cells and perivascular astrocytes, is an important physiologic barrier between the central nervous system (CNS) and peripheral circulation that regulates the exchange of molecules between blood

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vessels and brain parenchyma; its normal function is critical for the stability of the internal environment and signal transduction in the CNS.[14,15]

The pathophysiology of sepsis is related to the host immune response to infectious microorganisms.[16] The molecular patterns associated with pathogen signals such as lipopolysaccharide (LPS) are recognized by pattern recognition receptors expressed on host cells. Among the most important molecular patterns in the immune response in sepsis are those associated with the toll-like receptor (TLR) family. Pathogen recognition triggers a signal transduction cascade that culminates with the activation of the transcription factor NF-κB, which induces the expression of genes encoding proinflammatory cytokines and chemokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and IL-6. This leads to the recruitment and activation of leukocytes to the site of infection. In sepsis, pathogens cause damage at the CNS by inducing the release of cytokines from peripheral organs that penetrate the BBB.[17] Additionally, the production of TNF-α and IL-1β along with microbial peptides enhances the permeability of the BBB. It was also reported that leukocytes pass through the BBB into brain microvasculature in the early stages of sepsis, thereby causing damage to the brain.[18]

Another important mechanism contributing to the destruction of the BBB is the production of excess reactive oxygen species (ROS). Activated neutrophils and the electron transport chain are important sources of oxidizing molecules such as superoxide and hydrogen peroxide that can destroy macromolecules in the BBB.[19] Furthermore, ROS produced during sepsis can cause oxidative damage to proteins of the mitochondrial respiratory chain, resulting in mitochondrial dysfunction in neurons.[20] In preclinical studies, elevated levels of nitric oxide as well as lipid peroxidation and protein carbonylation were observed in the brain in the early stages (i.e., the first 48 h) of sepsis, which were associated with short-term damage. Additionally, long-term oxidative damage up to 60 days after sepsis induction was also reported.[21]

Inflammation disrupts the BBB, leading to depression

Although the relationship between the disruption of the BBB and depression is controversial,[6] the altered ratios of various molecules in the cerebrospinal fluid and serum of depressed patients suggest that the integrity of the BBB is compromised, and there is broad consensus that inflammatory factors in gut microbiome-associated diseases cause an imbalance of the brain–gut axis and act on the BBB to trigger depression.[22] In a mouse model of depression, mice that were stress-sensitive but not exposed to stress had lower expression of the tight junction protein claudin-5 (Cldn5) in the nucleus ambiguous (NAc) and abnormal morphology of the surrounding vasculature. Cldn5 expression was also found to be decreased in the NAc of depressed patients. Downregulation of Cldn5 was sufficient to induce depression-like behavior following subthreshold social stress, whereas chronic antidepressant treatment restored Cldn5 expression and promoted resilience. In mice with reduced BBB integrity or that were injected with adeno-associated virus expressing short hairpin RNA targeting Cldn5, the peripheral cytokine IL-6 infiltrated into the brain parenchyma and induced depression-like behavior. These findings suggest that chronic social stress promotes the penetration of peripheral IL-6 through the BBB and alters its integrity by reducing Cldn5 expression.[23] The astrocyte marker S100B has been detected in peripheral blood following BBB damage and thus serves as a serum marker of compromised BBB integrity.[24] In clinical studies, the S100B level was found to be elevated in the serum and cerebrospinal fluid of patients with major depressive disorder.[25,26] Real-time in vivo two-photon microscopy revealed that depression model mice had significant leakage of a 40-kDa fluorophore-conjugated dextran into the perivascular region, implying a loss of BBB integrity.[27] Inflammatory factors were shown to cross the BBB and induce depression in polycystic ovary syndrome.[28] At the same time, bovine serum albumin–cerium dioxide nanoclusters targeting ROS that could penetrate the BBB were effective in the treatment of depression.[29] These studies suggest that the destruction of the BBB and excess ROS production play an important role in the development of depression in patients with sepsis.

Abnormal Activation of Microglia Induced by Sepsis Leads to Depressive Behavior

Microglia are macrophage-like innate immune cells in the CNS. In a reactive state, microglia interact with neurons, astrocytes, and oligodendrocytes in response to changes in the CNS and coordinate immune mediators such as the proinflammatory cytokines IL-1β, IL-6, IL-18, IL-23, and TNF-α. In response to injury or pathogen-related molecular patterns, microglia coordinate the neuroinflammatory response and participate in the establishment of the CNS and clearance of dead cells, which play an important role in neurologic and psychiatric disorders.[30] In a mouse model of LPS-induced inflammation, activated microglia initiated a proinflammatory response, thereby directly modulating the function of neuronal circuits.[31] Peripheral inflammation in sepsis models caused extensive and intense microglia activation that induced nitric oxide production and increased the expression of the pro-apoptotic proteins B cell lymphoma 2 (Bcl-2) and Bcl-2–associated X protein (Bax), leading to apoptosis and sepsis-associated encephalopathy (SAE).[32] The high incidence of long-term brain damage caused by sepsis, including cognitive decline, anxiety, and depression and the occurrence of post-traumatic stress disorder, constitutes a substantial health burden in sepsis survivors.[33] Activated microglia were shown to enhance SAE, as demonstrated by studies in which microglia were inhibited by intracerebroventricular injection of dimethylamine tetracycline, which reduced acute cerebral oxidative stress injury, inflammation, and long-term cognitive impairment in sepsis survivors.[34]

Microglia exhibit abnormal function in neuropsychiatric disorders as a result of an overproduction of inflammatory mediators and increased neural phagocytosis, which may affect neural network remodeling and synaptic pruning, thereby impairing synaptic function and negatively impacting behavior.[35,36] In a mouse model of alcohol abuse, alcohol intake was shown to induce activation of Src tyrosine kinase, leading to anxiety-like behavior through overactivation of microglia-dependent Src/NF-κB/TNF signaling, which enhanced synaptic phagocytosis and impaired synaptic pruning.[37] A proteome-wide association study that incorporated genome-wide association data from subjects with depression identified potential causative genes

that were enriched in microglia.[38] In a clinical study, single-nucleus sequencing in the dorsolateral prefrontal cortex of 17 patients with major depressive disorder and 17 mentally healthy controls revealed 26 cell clusters in which microglia were the predominant cell type. The brain–gut axis theory posits that perturbation of gut flora balance can cause immune dysfunction, resulting in a cascade of events involving the release of inflammatory factors that reach the CNS through the circulation, activating microglia and triggering the emergence of depression-like behaviors.[39] Early-life inflammation was shown to impair microglia engulfment, leading to long-lasting maladaptation of glutamatergic neurons to stress and the development of depression during adolescence.[40] Collectively, the evidence to date suggests a close relationship between acute sepsis and long-term psychological and neurologic damage resulting from overactivation of microglia and impairment of neuronal function.

Aberrant Activation of Hypothalamic–pituitary–adrenal (HPA) Axis in Sepsis-related Depression-like Behavior

HPA axis and depression-like behavior

The limbic system comprises the cingulate cortex,[41,42] amygdala, and hippocampus. Corticotropin-releasing hormone (CRH) secreted by neurons activates the pituitary gland and modulates the HPA axis, which regulates homeostasis, stress response, energy metabolism, and neurologic functions and plays an important role in the pathophysiology of mood and cognitive disorders. The hypothalamus secretes stimulatory or inhibitory factors that act on the pituitary gland, which in turn secretes hormones (namely, corticotropin-releasing factor [CRF], adrenocorticotropic hormone, and cortisol) that act on target organs.

Overactivation of the HPA axis leading to the emergence of depression-like behaviors is one of the main hypotheses regarding the pathogenesis of depressive illness,[43] and some studies have demonstrated that excessive stimulation of the HPA axis in chronic and persistent high-stress states (e.g., inflammation, post-trauma, or prolonged hypertension) is linked to the emergence of depression.[44,45] CRF is a key factor in the regulation of the stress response and has been implicated in a number of psychiatric disorders; overproduction of CRF can lead to depression, anxiety, and anorexia nervosa whereas CRF deficiency is related to neurodegeneration in Alzheimer disease, Parkinson disease, and Huntington disease.[27] Sleep deprivation can lead to dysfunction of the limbic system, increased CRH release in the amygdala, and hyperactivation of the HPA axis, resulting in cognitive dysfunction and depression-like behavior in mice.[46]

Abnormalities in the HPA axis have been observed in a large proportion of depressed patients ranging from 35% to 65%, and typically involve the excessive release of glucocorticoids or increased expression of adrenocorticotropin-releasing hormone.[47] Overexpression of the postsynaptic protein postsynaptic density 93 (PSD-93) was shown to be associated with depression-like behavior in mice; whereas, PSD-93 depletion had an antidepressant effect. Additionally, postmortem examination of brain samples from patients with depression revealed increased colocalization of PSD-93 and CRH in the paraventricular nucleus of the hypothalamus, suggesting synaptic regulation of the HPA axis in depression.[48] The HPA axis plays an important role in the brain–gut axis; patients with depression show altered immune cell activity in the gut, an imbalance of gut microbial composition, and abnormal gut microbial function.[49] This dysregulation is associated with decreased levels of anti-inflammatory factors (e.g., IL-10, transforming growth factor beta [TGF-β]) as well as increased levels of proinflammatory factors (e.g., IL-1, IL-6, TNF-α, interferon alpha [IFN-α]) that further activate the HPA axis to induce hypercortisolism while reducing brain serotonin levels and interfering with glutamatergic neuron metabolism, leading to the development of depression. However, additional studies are needed to validate these findings.

Sepsis and the HPA axis

Sepsis-induced brain dysfunction (SIBD) has high morbidity and mortality.[33] It has been proposed that impaired autonomic regulation in the brain results in insufficient brain perfusion and neuronal damage, leading to SIBD.[50] In a prospective neuroimaging study of patients with SIBD with sepsis-induced neurologic dysfunction, MRI and stereoscopic pixel-based brain morphometry (VBM) analysis suggested neuronal loss in the insula, cingulate cortex, frontal lobe, precuneus, and thalamus.[51,52] In sepsis mice, expression of HPA axis-related circadian rhythm-regulated genes and circadian fluctuation of glucocorticoid level were abolished. Mice with cecal ligation and puncture-induced sepsis showed a stress-induced decline in cFos mRNA and protein levels in the ventral hippocampus, which coordinates emotional behavior, and reduced HPA axis activation with a corresponding increase in the glucocorticoid receptor-mediated immune response and negative emotional behavior.[53] Thus, overactivation of the HPA axis caused by dysfunction of limbic system regulation may be a key mechanism underlying depression in SIBD.

Dysfunction of the reward system in sepsis

The brain reward system comprises the substantia nigra, striatum, and mesencephalic marginal cortex dopamine pathways.[54] The dopamine system is involved in reward and affective functions, which are perturbed in schizophrenia, addiction, and depression; dopaminergic neuron fibers in the substantia nigra and ventral tegmental area (VTA) of the midbrain project to the striatum, cortex, and other brain areas.[55] A chemical genetic approach has been used to activate the dopaminergic system in the VTA of sepsis mice, leading to excitation of the sympathetic nervous system and an increase in the level of catecholamine neurotransmitters acting on mononuclear macrophages and B cells; this was associated with increases in the phagocytic bactericidal capacity of macrophages and number of IgM+ B cells and enhanced intrinsic and adaptive immunity, suggesting a causal relationship between the immune response to bacterial infection and VTA activation.[56] Activation of the reward system by a chemical genetics approach in tumor-bearing mice reduced sympathetic nervous system-mediated noradrenergic input, resulting in decreased immunosuppression of myeloid immune cells and reduced tumor volume and mass, demonstrating that antitumor immune

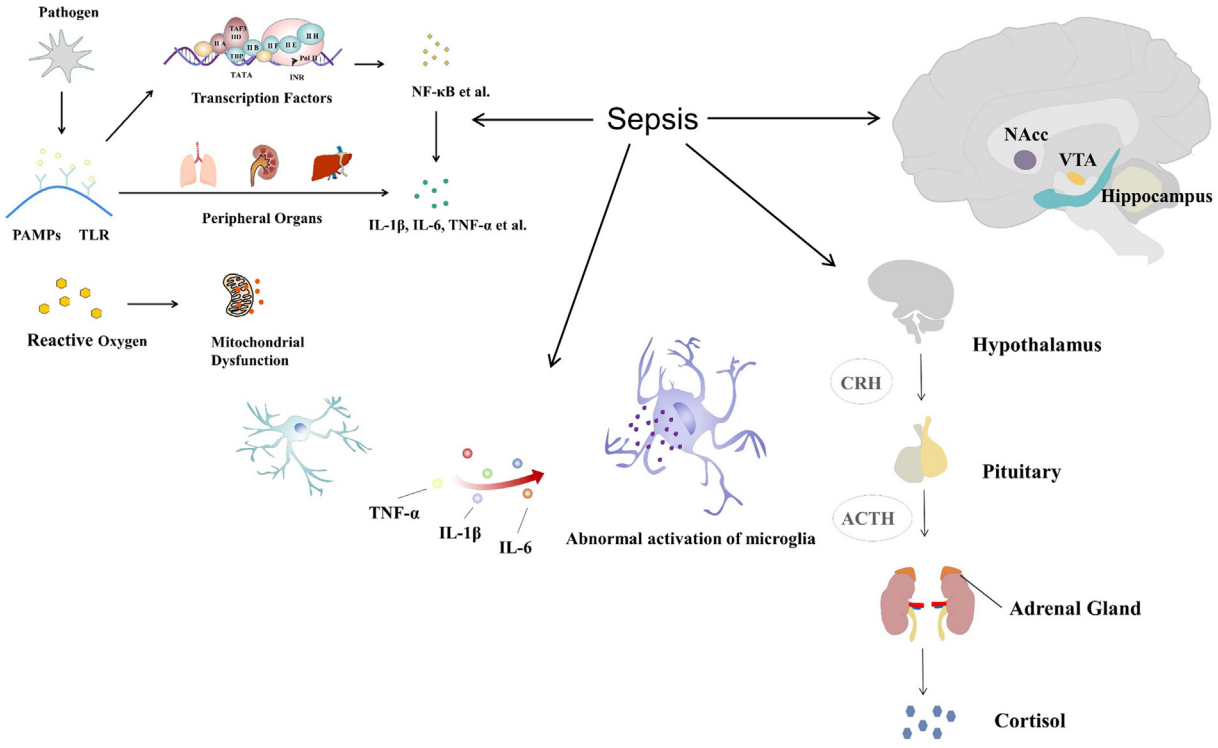

Figure 1. Possible mechanisms of sepsis-induced depression. ACTH: Adrenocorticotropic Hormone; CRH: Corticotropin-releasing hormone; INR: International normalized ratio; IL: Interleukin; NAcc: Nucleus accumbens; NF-κB: Nuclear factor kappa B; PAMPs: Pathogen-associated molecular patterns; TLR: Toll-like receptor; TNF: Tumor necrosis factor; VTA: Ventral tegmental area.

responses can be modulated by the brain reward system, which is a key neural circuit for emotional responses.[57] These findings suggest that peripheral and CNS dysfunction is closely linked to immune responses caused by the cytokine storm in sepsis.

Conclusions and Outlook

Sepsis is associated with depression-like behavior resulting from the disruption of the BBB, systemic immune dysfunction, and uncontrolled neuroinflammation. Depression can worsen the prognosis of patients with sepsis. Using brain imaging techniques such as fMRI and PET[58] combined with chemical genetics and photogenetics, it has been demonstrated that overactivation of glial cells, reduced integrity of the BBB, dysregulation of the HPA axis caused by limbic system dysfunction, and disorder of the brain reward system caused by abnormal neurotransmitter secretion and excessive release of peripheral inflammatory factors can individually or jointly contribute of the occurrence of sepsis and depression (Figure 1). The detailed mechanisms linking these processes must be clarified in order to develop targeted and effective interventions for preventing the occurrence of depression in patients with sepsis.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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