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REVIEW

Pathogenesis of sepsis-associated encephalopathy: more than blood–brain barrier dysfunction

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Abstract

Sepsis-associated encephalopathy is a common neurological complication of sepsis and is responsible for higher mortality and poorer long-term outcomes in septic patients. Sepsis-associated encephalopathy symptoms can range from mild delirium to deep coma, which occurs in up to 70% of patients in intensive care units. The pathological changes in the brain associated with sepsis include cerebral ischaemia, cerebral haemorrhage, abscess and progressive multifocal necrotic leukoencephalopathy. Several mechanisms are involved in the pathogenesis of sepsis-associated encephalopathy, such as blood–brain barrier dysfunction, cerebral blood flow impairment, glial cell activation, leukocyte transmigration, and neurotransmitter disturbances. These events are interrelated and influence each other, therefore they do not act as independent factors. This review is focused on new evidence showing the pathological process of sepsis-associated encephalopathy.

Keywords Sepsis-associated encephalopathy · Blood–brain barrier · Cerebral blood flow · Glial cell activation · Leukocyte transmigration · Neurotransmitter disturbances

Abbreviations

SAE	Sepsis-associated encephalopathy
CNS	Cerebral blood flow
CSF	Cerebrospinal fluid
BBB	Blood–brain barrier
LPS	Lipopolysaccharide
GABA	Gamma-aminobutyric acid
AChE	Acetylcholinesterase
5-HIIA	5-Hydroxyindoleacetic acid

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Introduction

Sepsis and severe sepsis (sepsis accompanied by acute multiple organ dysfunction syndrome) are defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. This condition is the most common and leading cause of intensive care unit mortality worldwide. According to a recent international study, approximately 31.5 million sepsis deaths, 19.4 million severe sepsis deaths, and 5.3 million deaths have been reported annually [2]. Therefore, sepsis, especially severe sepsis, is an important public health problem and frequently a fatal condition of patients in intensive care units. Multiple organ system dysfunction, especially in the nervous system, occurs with sepsis. This indirectly increases the risk of sepsis-associated encephalopathy (SAE). A retrospective analysis showed that the incidence of neurological dysfunction in patients with sepsis is as high as 48.9%, second only to cardiac dysfunction [3].

Sepsis-associated encephalopathy, considered multifocal brain dysfunction because of a dysregulated host response without primary central nervous system (CNS) infection, is the most common cause of encephalopathy in intensive care units [4]. Survivors of SAE exhibit long periods of neurological sequelae, particularly neurocognitive deterioration [5], and the principal clinical manifestations of SAE may range

from mild symptoms, such as aprosexia and disorientation to delirium or coma [6]. Due to the lack of early diagnostic criteria, SAE patients are more serious, have a higher risk of death, and are prone to long-term cognitive dysfunction than non-SAE patients [7]. However, the pathogenesis underlying SAE remains unclear. Emerging evidence shows that some mechanisms, such as blood–brain barrier (BBB) dysfunction [5], cerebral blood flow (CBF) impairment [8], glial cell activation [9], leukocyte transmigration [10], and neurotransmitter disturbances [11], have been considered potential causative factors. The combination and synergism of all these contributors could be the underlying mechanism of SAE, but the exact interplay and connection between them is unclear.

BBB dysfunction

The BBB is a regulated interface separating the CNS from the peripheral circulation, which prevents the entry of toxic substances into the CNS and maintains CNS homeostasis [12]. The BBB is composed of vascular endothelial cells surrounded by the basal membrane, tight junction proteins, pericytes, end-feet of astrocytes and microglia [13]. During the early stages of sepsis, BBB alterations were observed among septic animal models [14]. Systemic inflammation and oxidative stress are crucial in mediating BBB integrity loss during sepsis.

Under septic conditions, inflammatory cytokines such as IL-1β and TNF-α are systemically elevated [15]. Moreover, BBB damage and tight junction protein downregulation are closely related to the severity of sepsis and systemic inflammation [16]. The interaction of lipopolysaccharide (LPS) with TLR4 in endothelial cells can activate NF-κB through the MyD88 signalling pathway and GEF-H1-RhoA signalling pathway [17], and NF-κB is responsible for the activation of genes that encode proinflammatory cytokines and chemokines, such as TNF-α, IL-1β, and IL-6 [18]. LPS and proinflammatory cytokines can result in a significant decrease in occludin expression via the p38MAPK/JNK pathways and induce alterations in cell morphology and permeability [19]. Moreover, polymerase δ-interacting protein 2 has been reported to mediate LPS-induced BBB disruption by regulating NF-κB subunit p65 activation and Cox-2 as well as prostaglandin E2 induction [5]. In response to systemic inflammation, inflammatory mediators can disrupt the BBB and enter the brain to promote the activation of microglia [20]. Persistent microglial activation contributes to the generation of inflammatory cytokines and reactive oxygen species, which perpetuates a vicious cycle and aggravates BBB dysfunction in patients with sepsis [21] (Fig. 1).

In addition to the abovementioned factors, there are many other contributors to BBB failure under sepsis conditions,

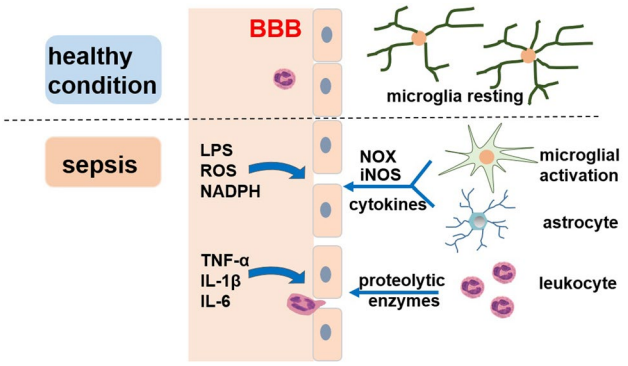

Fig. 1 Proposed pathological process of BBB dysfunction during SAE. The BBB plays an integral role in separating the CNS from the peripheral circulation under healthy conditions. In sepsis, systemic inflammation can destroy barrier functional integrity and promote the activation of microglia. Activation of microglial cells and astrocytes induces the generation of inflammatory cytokines and reactive oxygen species to aggravate BBB dysfunction. In addition, proteolytic enzymes derived from leukocyte transmigration into the brain parenchyma can induce BBB impairment

such as Drp1-Fis1-mediated mitochondrial dysfunction [22], alteration of sphingolipid metabolism in endothelial cells [23], tight junction downregulation mediated by matrix metalloproteinases [24] and detachment of pericytes from the basal lamina [14]. There is other evidence to indicate that the Omi/HtrA2 pathway manipulates LPS-induced endothelial cell apoptosis by translocating from mitochondria to the cytosol and inducing X-linked inhibitor of apoptosis protein degradation. In addition, Omi/HtrA2 also participated in the decline of occludin, claudin-5 and ZO-1 expression [25].

Taken together, various factors can result in BBB dysfunction, whereas BBB abnormalities in turn change amino acid transportation [26] and promote neuronal damage, apoptosis and brain oedema [27]. In addition, SAE can occur in the absence of BBB breakdown and is accompanied by increased water diffusion anisotropy and altered glial cell morphology in the white matter of the brain [28].

CBF impairment

CBF is strictly regulated to ensure energy and oxygen supply in the brain, which is determined by cerebral perfusion pressure, cardiac output and small cerebral vascular tone [29]. In the early phase of sepsis, cerebral microcirculatory impairment occurs even after restoration of adequate global haemodynamics [30]. Hypotensive episodes and dysregulated autoregulation also contribute to cerebral hypoperfusion [31], which occurs first in the cerebral cortex [28]. Decreased cerebral oxygenation leads to neuronal anoxia and apoptosis [32]. Furthermore, hypoperfusion of the brain can cause elevated $PaCO_2$. In hypercapnia, extracellular pH

is reduced, and acid-sensing ion channel-1 A is activated by extracellular acidosis. The activation of acid-sensing ion channel-1 A is associated with CO_2-induced NO production as well as vasodilation and subsequent increases in CBF [33, 34]. Increased vascular bed perfusion leads to increased vascular hydrostatic pressure, which leads to cerebral oedema and aggravates brain injury [35]. In addition, studies have shown that severe hypercapnia ($PaCO_2$ 100-120 mmHg) can result in higher AQP4 levels and brain oedema, ultimately aggravating brain damage [36]. Cerebrospinal fluid (CSF) decreases to maintain stable intracranial pressure when CBF increases during hypercapnia [37]. CSF plays a vital role in transporting nutrients and protein clearance in the CNS [38]. Therefore, we hypothesized that decreased CSF in hypercapnia may lead to the accumulation of metabolites and ultimately aggravate the formation of encephalopathy (Fig. 2).

Glial cell activation

The neurovascular unit is composed of neurons, capillaries, microglia, oligodendrocytes and extracellular matrix [39]. In particular, microglia play an important defensive role in response to various pathogens and neuronal injury and are resident and immunocompetent cells of the CNS [40]. Increasing evidence indicates that endothelium–microglia interactions are associated with a variety of inflammation-associated brain diseases [41]. When the BBB is destroyed, resting microglia are activated swiftly after cellular damage appears, and subsequently some inflammatory cytokines such as TNF-α, IL-6 and IL-1β are released to eliminate toxins from the extracellular space [42]. This part mainly focuses on the mechanism of glial cell activation and its effect on brain dysfunction in sepsis.

Microglial cells, acting as antigen-presenting cells, express a variety of receptors, such as TLRs, major histocompatibility complex, CX3CR1 chemokine receptor and CD11b/CD45 [43]. Therefore, LPS, other pathogen components and inflammation in the peripheral blood can activate microglia when they pass through the increased permeability of the BBB [44] and then increase the levels of inflammatory factors in sepsis [45]. The combination of LPS and TLR4 on microglia can trigger a proinflammatory program, which includes the production of TNF-α and the increased secretion of glutamate through connexin channels and the cystine/glutamate antiporter system, finally promoting the deregulation of calcium influx and inducing neuronal dysfunction [46]. Moreover, TNF-α and glutamate can enhance the production of each other [47]. Microglial cell activation also induces the synthesis and upregulation of IL-6 and IL-1β via the expression of CD40 and ligand [48] as well as the activation of transcription factors such as NF-κB, contributing to the perpetuation of the inflammatory challenge [49]. IL-1β secreted by activated microglia might suppress axon development and synapse formation through activation of the p38-MAPK signalling pathway associated with memory impairments in septic patients [50]. Additionally, Rachid et al. showed that LPS could induce endothelial cell death

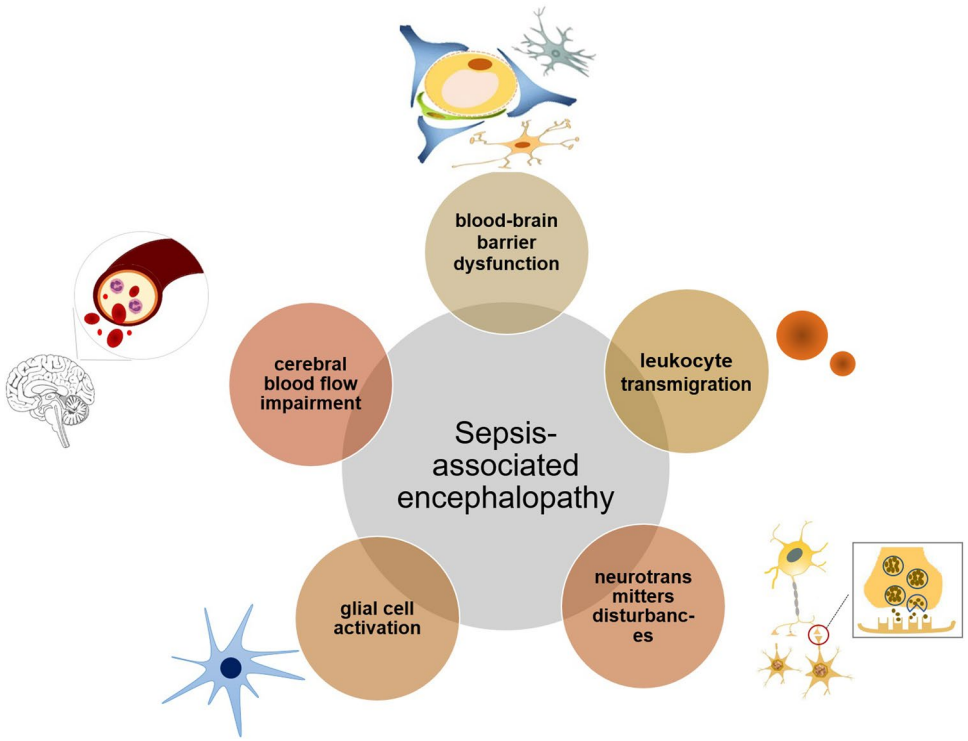

Fig. 2 Schematic view of pathological changes observed in SAE. They include BBB dysfunction, CBF impairment, glial cell activation, leukocyte transmigration and neurotransmitter disturbances

and increase BBB permeability by activating microglia. The mechanism of this effect appears to be mediated by NF-kB, JAK-STAT and JNK. These factors could then lead to the upregulation of iNOS and NADPH oxidase, which then generate NO and superoxide, respectively. These factors alone or together with peroxynitrite are cytotoxic to endothelial cells [51]. Therefore, inhibiting microglial activation could improve long-term cognitive performance in sepsis survivors [52].

In addition to microglia, astrocytes also play an important role in the onset of SAE. Under experimental sepsis conditions, mitochondrial biogenesis and ATP levels of astrocytes were significantly elevated to be suitable for the high-energy requirement and recover the ultrastructure of the mitochondria [53], which was mediated via the IL-6/AMPK signalling pathway [54]. Previous studies have clearly demonstrated that sepsis impaired astrocytic clearance of dehydroascorbic acid from the extracellular fluid and decreased the intracellular ascorbate concentration, which could upregulate iNOS and decrease glutamate uptake by astrocytes [55]. Hasegawa-Ishii et al. uncovered cytoskeletal and morphological alterations in hippocampal astrocytes after LPS injection, so astrocytes prepare for receiving cytokine signals via receptors expressed on the end-feet and then produce their own cytokines, including CXCL10, CCL11, and G-CSF, to change the hippocampal microenvironment [56]. For instance, astrocyte-derived CCL11 and G-CSF may stimulate microglia [57] and enhance the proliferation of microglia [56] in the hippocampus, resulting in learning and memory impairment [58]. Furthermore, the increased release of TNF-α and IL-1β by astrocytes aggravates inflammatory injury after the injection of LPS [59]. In the context of systemic inflammation, astrocytes can also regulate the phenotype of microglia. TLR4 stimulation and the costimulation of dopamine receptor D3 in astrocytes can promote the acquisition of proinflammatory features, ultimately promoting microglial activation (M1 microglia increase) and neuroinflammation [60].

Leukocyte transmigration

The transmigration of inflammatory leukocytes is a significant element of the innate immune response. Neutrophils are the predominant immune cells mediating much of the tissue injury during the progression of inflammation [61]. In the normal brain, there are no neutrophils in the brain parenchyma [62]. Under septic conditions, blood-borne proinflammatory mediators are produced, along with the activation of endothelial cells and the expression of ICAM-1 and VCAM-1; these outcomes contribute to neutrophil adhesion and recruitment into brain microvessels [63, 64]. The CXCR2 is a G-protein-coupled receptor for the well-known studied CXC chemokines including CXCL1, CXCL2, and CXCL5. It is widely expressed on hematopoietic cells and non-hematopoietic cells such as endothelial cells. Interactions between CXCR2 and its ligands play essential roles in leukocyte recruitment cascade in cerebral microvessels [65]. During CNS inflammation, astrocytes secrete significantly higher levels of CXCL1. Both endothelial CXCR2 and astrocyte-derived CXCL1 are crucial effectors mediating adhesion molecules expression on endothelial cells, resulting in robust neutrophil infiltration and leukocyte–endothelial cell interactions in the brain [66]. In addition, KC or MIP-2 produced by microglia also guide neutrophil transmigration into the brain parenchyma [67]. Subsequently, neutrophils accumulating in CNS jeopardize brain cells by increasing in cytokine levels, MPO activity and promoting oxidative damage [68]. Furthermore, neutrophils also generate many pro-inflammatory cytokines, ROS and proteolytic enzymes, including NOX, MPO, MMPs, elastase and cathepsins, which have hazardous effects on BBB integrity and allow passage of neutrophils into the brain [69]. It has been shown that ROS lead to junction proteins downregulation and the endothelial cytoskeleton reorganization through MLCK, PKC, MAPK, and Rho GTPases signaling pathways [70]. MMPs can dissolve the extracellular matrix, basal lamina and potentiate BBB disruption [71]. Persistent accumulation of neutrophils is related to cell death, brain oedema and tissue loss [72]. Therefore, the vicious cycle between neutrophil recruitment and BBB impairment aggravates neuronal dysfunction in sepsis.

In addition to neutrophils, other immune cells, such as inflammatory monocytes, are also recruited through the chemokine receptor CCR2, which plays an important role in SAE-induced long-term cognitive impairment [73].

Neurotransmitter disturbances

Most physiological and pathological processes in the brain involve multiple neurotransmitters. Inflammatory and metabolic alterations have been perceived as contributing to changes in cerebral neurotransmitters [74]. Thus, elucidating the role of different neurotransmitters could be beneficial to better therapeutic approaches to treat related diseases. Disorders of multiple neurotransmitters underlie the pathobiology of SAE. In the current research, a causal relationship has been demonstrated between the development of SAE and changes in neurotransmitter release or concentrations, such as acetylcholine [75], dopamine [76], serotonin [77], norepinephrine [78], gamma-aminobutyric acid (GABA) and its derivatives [79].

Acetylcholine dysfunction

Cholinergic signals mainly regulate cognitive function, movement, learning and memory by both nicotinic and muscarinic receptors [80]. The dysfunction of cholinergic signals could contribute to the occurrence of delirium, including inattention, confusion and perceptual disturbances [81]. Cholinergic signals also play a critical anti-inflammatory role, mainly suppressing endotoxin-inducible proinflammatory cytokines and TNF through interaction with peripheral α7 subunit-containing nicotinic acetylcholine receptors expressed on macrophages [82]. In 2010, Willem and colleagues demonstrated that peripheral inflammation could degenerate cholinergic neurons in the basal forebrain by activating microglia, while cholinergic inhibition of microglia could reduce neuronal dysfunction [74]. To study the effect of neuroinflammation on cholinergic transmission in the basal forebrain of sepsis patients, researchers examined cholinergic neuronal bodies in the basal forebrain and molecular cholinergic components in the cortex and hippocampus. They found that microglia were activated, and Iba1, IL-1β, and IL-6 gene expression in the cortex and hippocampus was upregulated. Choline acetyltransferase-positive neurons were significantly decreased in the basal forebrain of sepsis survivors. In the hippocampus, acetylcholinesterase (AChE) activity was enhanced, and the expression of the gene encoding the M1 muscarinic acetylcholine receptor, Chrm1, was decreased [75, 83]. As expected, microglial activation was associated with choline acetyltransferase protein expression and AChE activity. Consistent with a sepsis-induced cholinergic deficiency in the CNS, increasing acetylcholine receptor activity or using AChE inhibitors can prolong the lifetime of acetylcholine, thus attenuating proinflammatory cytokine release by microglia and improving the survival of sepsis patients [84]. The underlying mechanism is that increasing cholinergic activity can restore endotoxaemia-induced deficits in synaptic plasticity by decreasing small conductance calcium-activated potassium channels or decreasing calcium influx [85]. Therefore, cholinergic hypofunction and microglial activation may be significant underlying events leading to cognitive dysfunction among sepsis survivors. Furthermore, cholinergic signalling can protect neurons in the striatum, hippocampus, and cortex from neurotoxicity triggered by excitotoxic amino acids and other toxic substances [86]. Notably, plasma AChE activity can reflect acetylcholine levels in the brain; however, some studies have previously shown that serum AChE activity is not related to delirium in septic patients, and there are no clinical trials demonstrating the beneficial role of cholinergic agonists in the treatment of delirium [87].

Amine abnormalities

Dopamine is a neurotransmitter with multiple functions, and it is considered a major regulator of inflammation via D1-like DA receptors (D1 and D5) and D2-like receptors (D2, D3 and D4) [88, 89]. In the brain, dopamine is critical for the maintenance of working memory and the regulation of emotion [90], and substantial evidence demonstrates that an overdose of dopamine has been associated with the development of SAE [91]. In 1985, Freund et al. observed high levels of dopamine in the hippocampus, striatum and pons-medulla, along with low levels of breakdown products (HVA and 3MT), suggesting decreased turnover of dopamine during sepsis [77]. Compared with non-SAEs, severely septic animals and encephalopathy exhibited obviously lower levels of dopamine [92]. In contrast, the findings of the Oytun Erbass study exhibited an evident increase in brain HVA levels in septic animals compared with the sham group, confirming an increase in brain dopamine turnover during sepsis. It was also indicated that there was a significant positive correlation between brain dopaminergic activity and stereotypic behavioural scores [76]. Shimizu found that the concentrations of dopamine in the hypothalamus and striatum did not differ significantly between the septic group and the control group. Striatal dopamine metabolites tended to decrease 48 h after the induction of sepsis [93]. In addition, dopamine receptor D3 expressed in astrocytes but not microglia can regulate the dynamics of the acquisition of pro-inflammatory and anti-inflammatory phenotypes by astrocytes and microglia. Upon systemic LPS challenge, TLR4 stimulation and the costimulation of dopamine receptor D3 induced astrocyte activation and decreased the production of the anti-inflammatory protein Fizz1 by M2 microglia, thus favouring the function of M1 microglia and promoting neuroinflammation [60]. The data in Nolan's study showed that dopamine could activate the NF-κB pathway in macrophages and prime the NLRP3 inflammasome, eventually inducing the production of inflammatory cytokines. These effects may be a vital mechanism for neuroplasticity in dopaminergic brain regions [94]. Additionally, recent research suggested that administration of a small dose of L-dopamine at an early stage in sepsis can limit neuroinflammation, improve neuroplasticity and reverse sepsis-induced decreases in hippocampal dopamine levels [95]. Clearly, there are inconsistent opinions on changes in dopamine activity in sepsis pathology. It is possible that dopamine activity may be related to the severity of sepsis. Combined with the above findings, these findings indicate that dopaminergic alterations are at least partly responsible for the progression of SAE.

Serotonin, or 5-hydroxytryptamine, a modulator of various functions in the CNS, is associated with prosocial behaviour and affective disorders [96]. The role of serotonin in the pathogenesis of encephalopathy has been extensively

studied. According to reports, concentrations of brain and plasma tryptophan were increased in septic rats, which is the basis of increased brain serotonin metabolism in sepsis [92]. In addition, Herbert R. Freund et al. discovered that concentrations of the serotonin precursor and its metabolite 5-hydroxyindoleacetic acid (5-HIIA) were initially increased in most tissues in mild septic animals. The 5-HIIA/serotonin ratio was also increased significantly, indicating an increased turnover of serotonin [77], but eventually declined with the progression of severe sepsis [92]. In 1999, Shimizu also proposed that the level of 5-HIIA and the 5-HIIA/serotonin ratio were increased in sepsis compared with the sham group in the cortex, striatum, and hippocampus both 24 and 48 h after the operation, whereas the hypothalamic 5-HIIA did not change significantly [93]. In addition, in contrast to the increase in the serotonin synthesis rate observed in the above reports, Finn Bengtsson's experiment demonstrated that there were no major changes in the CNS serotonin synthesis rate following 12 or 24 h of sepsis [97], and it has been demonstrated that serum serotonin levels can be used as a peripheral indicator for central serotonin levels, but there are no correlations of serum serotonin levels with delirium [87]. It is difficult to explain why there are regional differences in changes in serotonergic activity.

Norepinephrine, acting as a critical neuromodulator, is known to play important roles in regulating multiple brain functions, including attention, learning, and memory. The hippocampus receives noradrenergic innervation and expresses β-adrenergic receptors, which are involved in modulating the induction of long-lasting forms of synaptic potentiation [98]. Dysfunctional noradrenergic signalling is correlated with a number of cognitive impairments, such as Alzheimer's disease [99] and depression [100]. In 1984, Freund found that brain norepinephrine decreases with sepsis and SAE [92]. Instead, in 1985, he discovered that most of the dopamine in the striatum is converted to norepinephrine, which leads to high levels of norepinephrine [77]. As with serotonin, there were also regional differences in norepinephrine expression. Hypothalamic norepinephrine was decreased at 24 h after septic operation. Cortical norepinephrine was increased 48 h after the septic operation; however, there was no significant change in hippocampal norepinephrine [93]. Research shows that both increases and decreases in norepinephrine might cause dysregulation of norepinephrine-dependent functions and lead to a pathological state under sepsis conditions [78]. On the other hand, researchers observed that the levels of hippocampal β2-adrenoceptor were significantly decreased after sepsis, accompanied by increased proinflammatory cytokines and downregulated CREB/BDNF and synaptic protein expression; eventually, septic mice exhibited cognitive deficits. Intriguingly, β2-adrenoceptor activation alleviates sepsis-induced cognitive impairments by modulating microglial phenotypes and reversing neuroinflammation and synaptic plasticity [101]. In summary, abnormalities in the noradrenergic transmission system play a vital role in SAE.

GABA alteration

GABA, a nonprotein amino acid formed by decarboxylation of glutamic acid [102], is the principal brain inhibitory neurotransmitter that regulates inflammatory and neurodegenerative diseases [103]. In a previous study, it was reported that GABA receptor density in the brain was altered in animal studies of metabolic encephalopathy [104]. In septic patients, elevated IL-1β together with a reduced release of IL-1α increases Akt-mediated GABAergic activity, which contributes to the alteration of synaptic strength and cognitive dysfunction [105]. In an acute inflammation model, increased tonic α5 $GABA_AR$ current and surface levels in hippocampal neurons by IL-1β through a p38-MAPK signalling pathway are critical for inflammation-induced memory deficits [106].

In summary, these alterations in neurotransmitter metabolism may be an important reason for the development of SAE. Notably, it would probably be incorrect to interpret that any single neurotransmitter dysfunction should be responsible for SAE, which involves multifactorial mechanisms and multiple neurotransmitter interactions [77].

Conclusions

Sepsis-associated encephalopathy is a common and detrimental neurological complication of sepsis but lacks diagnostic criteria and target-directed treatments, additionally, it is prone to be overlooked in clinical practice. The pathogenesis of SAE is complex and multifactorial. The increased understanding of pathogenesis is beneficial for developing new preventive and therapeutic strategies to reduce sequelae of sepsis. This paper summarizes the pathogenesis of SAE as mentioned above. The pathomechanisms of SAE are parallel, influence each other, and contribute to neuronal dysfunction. A thorough understanding of the pathogenesis of CNS dysfunction is helpful to reduce the incidence of SAE. Future efforts should be directed towards understanding the crosstalk of these mechanisms, not each of them alone.

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Declarations

Conflict of interest The authors have no relevant financial or nonfinancial interests to disclose.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Consent for publication Not applicable.

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