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UPDATE ARTICLE

Septic encephalopathy: does inflammation drive the brain crazy?

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Sepsis and the multiorgan dysfunction syndrome are among the most common reasons for admission to an intensive care unit, and are a leading cause of death. During sepsis, the central nervous system (CNS) is one of the first organs affected, and this is clinically manifested as sepsis-associated encephalopathy (SAE). It is postulated that the common final pathway that leads to SAE symptoms is the deregulation of neurotransmitters, mainly acetylcholine. Thus, it is supposed that inflammation can affect neurotransmitters, which is associated with SAE development. In this review, we will cover the current evidence (or lack thereof) for the mechanisms by which systemic inflammation interferes with the metabolism of major CNS neurotransmitters, trying to explain how systemic inflammation drives the brain crazy.

Keywords: Sepsis-associated encephalopathy; acetylcholine; amines; GABA; inflammation

Introduction

Sepsis and the multiorgan dysfunction syndrome are among the most common reasons for admission to an intensive care unit, and are a leading cause of death.[1-4] During the last decades, advances have been made in our understanding of sepsis, but currently there is no target-directed, FDA-approved treatment for sepsis.

The pathophysiology of sepsis has been partially elucidated; it is a dynamic process, which involves components of the immune system, the coagulation pathway, parenchymal cells, and the endocrine and metabolic pathways.[5] Many factors have been postulated to trigger sepsis, including products released from bacteria as well as products from damaged cells. Toll-like receptor (TLR) signaling has been suggested to be a key pathway in sepsis pathophysiology, leading to the production of inflammatory mediators.[6] The activation of this pathway depends on the interaction between TLR and TLR ligands, which include those derived from bacteria in addition to host-derived products such as intracellular proteins, extracellular matrix components, and oxidized lipids.[7]

During sepsis, the central nervous system (CNS) is one of the first organs affected, and this is clinically manifested as septic encephalopathy (SE) or sepsis-associated delirium (SAD).[8-9] SE has been reported to occur in 8-70% of septic patients, with the wide variation attributable mainly to diagnostic criteria.[10] Reciprocal interactions between the immune system and the CNS are considered to be major components of the host response in sepsis (Figure 1). In addition, brain injury occurs during sepsis development, and proposed mechanisms to explain it include alterations in the blood-brain barrier (BBB), local generation of pro- and anti-inflammatory cytokines, amino acid metabolism disruption, brain ischemia, and imbalance of neurotransmitters[11] (Figure 2). Additionally, once inflammation persists, excitotoxicity and oxidative stress may further aggravate SE and contribute to neuronal dysfunction.[12] In animal models of sepsis, acute encephalopathy occurs, and survivors exhibit cognitive impairment that could be secondary to CNS damage.[13] Likewise, survivors from critical care, including septic patients, have well-documented persistent neurocognitive deficits and develop psychiatric disorders.[14-23]

The interaction between sepsis and the brain is an opportunity to study how systemic inflammation affects brain function. Most studies about the mechanisms of SE have used animals or cell cultures, and improved our understanding of how the CNS is affected by endotoxins and cytokines, but whether this is related to clinical SE remains unclear. It is postulated that the common final pathway that drives SE symptoms is the deregulation of neurotransmitters, mainly acetylcholine.[24] In this review, we will cover the current evidence (or lack thereof) for the mechanisms by which systemic inflammation interferes with the metabolism of the major CNS neurotransmitters, trying to explain how systemic inflammation drives the brain crazy.

Evidence that systemic inflammation is associated with brain dysfunction

Theoretically, systemic inflammation can reach the brain through at least four different routes: 1) peripheral organs

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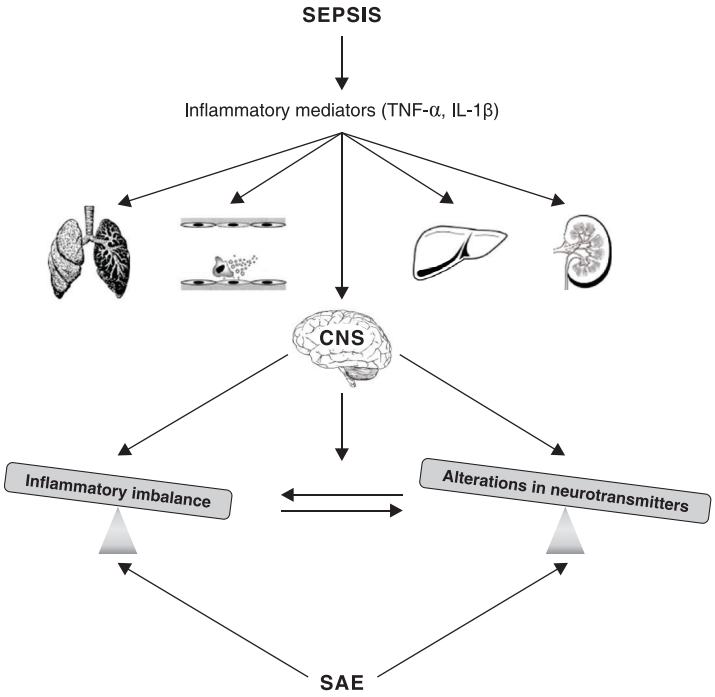

Figure 1 During sepsis, inflammatory mediators (e.g., TNF-α, IL-1β) are released peripherally and can drive alterations in several organs, such as the liver, lung, kidney, cardiovascular system, and central nervous system. An imbalance between pro- and anti-inflammatory mediators interferes with the normal function of neurotransmitters. Furthermore, alterations in neurotransmitters can modulate the inflammatory balance, and are probably involved in the pathophysiology of brain dysfunction. CNS = central nervous system; IL-1β = interleukin 1β; SAE = sepsis-associated encephalopathy; TNF-α = tumor necrosis factor alpha.

synthesize and release cytokines that act on their receptors present in nerve fibers of the autonomic nervous system to modulate brain function; 2) circulating cytokines diffuse through the BBB; 3) cytokines might signal into the brain through specific areas that lack the BBB, such as the circumventricular organs; or 4) cytokines might enter the brain through a saturable transport mechanism.[25] There is no clear evidence to explain in detail how inflammation reaches the brain during sepsis, but both in animals and in humans, inflammation occurs in the CNS early and late after sepsis.[26-29]

The immune system is a complex, highly adaptive system,[29] and it is integrated with the CNS at several levels to maintain homeostasis.[30-32] However, it is possible that activation of the immune system may induce brain dysfunction, and, in fact, sepsis is a major risk factor for occurrence of delirium.[33] It is believed that pro-inflammatory cytokines, particularly interleukin (IL)-1β and tumor necrosis factor alpha (TNF-α), are generated in the periphery, communicate with the brain, and initiate cytokine synthesis in the CNS.[24] Fever and changes in behavior – such as anorexia, lethargy, and depression, collectively named sickness behavior – are observed as a response of neurons to cytokines in several different animal models.[34-38] In addition, studies in healthy volunteers have demonstrated that systemic inflammatory challenges impact the human brain.[39-41] A postmortem investigation found an association between brain dysfunction and astrocyte, microglia, and IL-6 activity in the human brain.[42]

However, excluding postmortem studies, a direct relation between inflammation and brain dysfunction in humans is limited because of the inaccessibility of the CNS. Thus, in general, investigations are limited to searching for a correlation between systemic inflammation markers and brain dysfunction.

High levels of procalcitonin and C-reactive protein (CRP) at intensive care unit (ICU) admission correlate with the duration of brain dysfunction, both in septic and non-septic patients.[43] Krabbe et al.,[41] using a human endotoxemia model, showed that a low-grade increase in the concentrations of TNF-α, its soluble receptor (sTNF-R), IL-6, and IL-1 receptor antagonist (IL-1RA) was inversely associated with declarative memory performance. This was independent of physical stress symptoms or activation of the hypothalamic-pituitary-adrenal (HPA) axis, suggesting that low-level systemic inflammation had a negative effect on some areas related to cognitive function. A recent study demonstrated that sTNFR was independently associated with delirium in general ICU patients.[44]

Pfister et al.[45] found a correlation between high plasma CRP levels, alterations in cerebrovascular autoregulation, and SE. The cerebral arterioles of patients with SE were less reactive to vasodilatory stimuli,[46] and this was

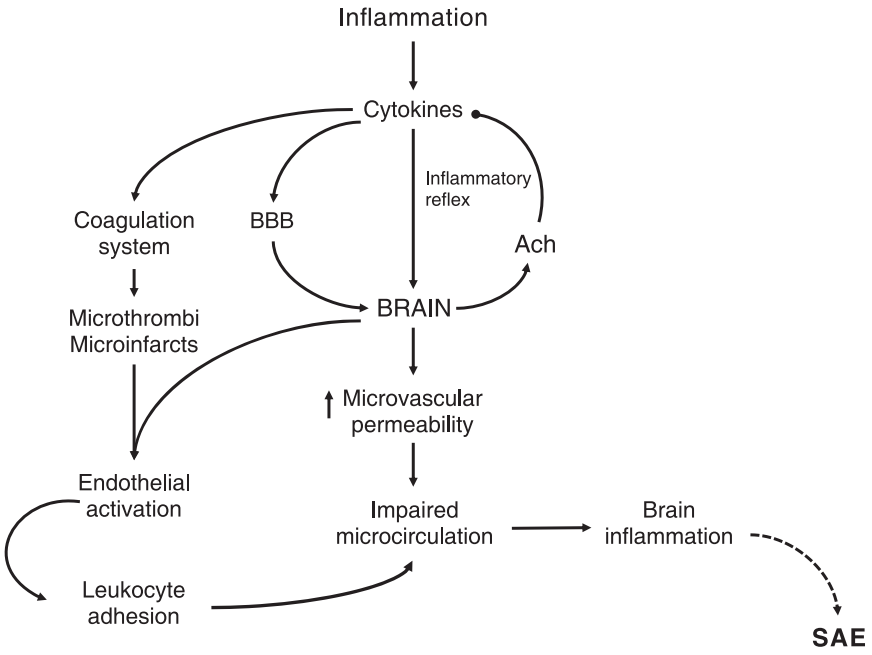

Figure 2 Cytokines produced in the infection site activate afferent signals to the brain, and the subsequent vagal activation inhibits cytokine synthesis through the "inflammatory reflex" of the cholinergic pathway. Inflammation changes the structure and function of the blood-brain barrier (BBB), increasing microvascular permeability, impairing microcirculatory blood flow, and producing brain inflammation. During sepsis, alterations in the coagulation system results in microthrombus formation and microinfarcts. Endothelial activation also impairs the microcirculation and worsens brain inflammation, which in turn is related to brain dysfunction. Ach = acetylcholine; BBB = blood-brain barrier; SAE = sepsis-associated encephalopathy.

independently associated with acute brain dysfunction.[47] Healthy volunteers injected with endotoxin had decreased cerebral blood flow, and this was associated with peak serum concentrations of TNF-α.[48] Recently, it was demonstrated that patients with lower vascular reactivity had increased duration of brain dysfunction.[47] The mechanisms behind endothelial dysfunction and acute brain dysfunction remain unclear, but inflammation could drive structural and functional alterations in the BBB, increasing microvascular permeability and impairing microcirculatory blood flow.[49-52] These alterations could be secondary to a decrease in the activity of endothelial nitric oxide synthase induced by inflammation[53] or to alterations in the coagulation system, resulting in microthromboses and microinfarcts.[54] Endothelial activation in the brain microvasculature has been observed after sepsis in animal models, and this was associated with leukocyte adhesion and brain inflammation.[26] In addition, BBB dysfunction induced by metalloproteinase (MMP) activation was also associated with brain inflammation and cognitive impairment in an animal model of sepsis.[55] This is supported by the fact that MMP-9 content was associated with delirium in the general ICU patient.[44]

It is supposed that systemic inflammation can lead to neuronal or glial damage; however, at least in experimental endotoxemia in humans, there is no correlation between acute systemic inflammation and plasma levels of brain specific proteins (S-100β, neuronal enolase [NSE], glial fibrillary acidic protein [GFAP]) nor deterioration of cognitive function.[56] In contrast, S-100β is associated with SE,[45] and NSE is associated with delirium in general ICU patients.[57] Sharshar et al.[27] demonstrated that septic shock is associated with neuronal and glial apoptosis in autonomic centers in humans, but brain TNF-α expression did not differ between septic shock and control patients. Whether neuronal and glial apoptosis is sufficient to induce clinically relevant brain dysfunction remains unknown.

Thus, to date, there is evidence that brain inflammation occurs during sepsis both in animals and in humans. Inflammation is probably related to alterations in cerebral blood flow and neuronal/glial cell damage, but a direct link between these and SE is still lacking.

Evidence linking systemic inflammation and deregulation of neurotransmitters

Since inflammation and alterations in neurotransmitters are the major theories trying to explain brain dysfunction we explore the evidences that links inflammation and major neurotransmitters system deregulation (Figure 3).

Acetylcholine (Ach)

A widely postulated mechanism to explain delirium is cholinergic failure.[83] The first evidence for this hypothesis

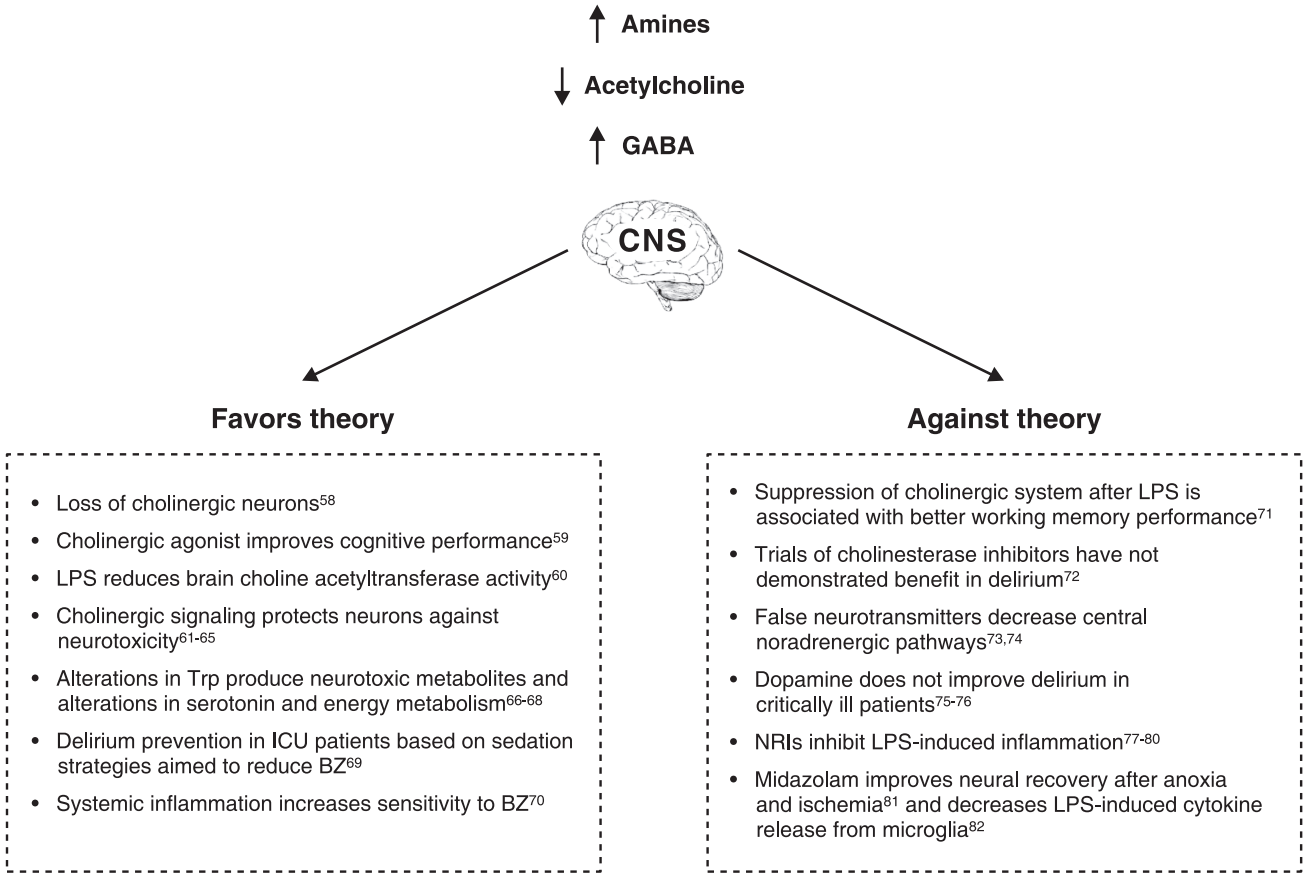

Figure 3 Facts that favors or are against the theory of neurotransmitters imbalance in the genesis of sepsis-associated encephalopathy. LPS = lipopolysaccharide; Trp = tryptophan; ICU = intensive care unit; BZ = benzodiazepines; NRI = norepinephrine reuptake inhibitors; GABA = gamma-aminobutyric acid; SAE = sepsis-associated encephalopathy.

came from case reports linking delirium to acute poisoning with anticholinergic drugs and the reversal of delirium with cholinergic drugs. Cholinergic signaling by both nicotinic and muscarinic receptors modulates cognitive function, arousal, learning, and memory, the major brain functions affected in delirium. Thus, sepsis-induced inflammation is presumed to affect cholinergic signaling and contribute to the genesis of SE.

In an animal model of LPS-induced long-term cognitive deficits, neuronal loss in the hippocampus and the prefrontal cortex occurs mainly due to reduced cholinergic innervation at postrolandic cortical areas. This is consistent with the fact that the hippocampus is particularly sensitive to systemic inflammation.[84] We demonstrated that the use of cholinergic agonists improves cognitive performance in septic animals,[58] and that endotoxin is able to reduce brain choline acetyltransferase activity.[59] Thus, it is possible that cholinergic neurons are particularly sensitive to systemic inflammation. This is the major theory behind SE, but to date there is no direct evidence to support it.

Endotoxin administration to healthy individuals increases plasma acetylcholinesterase (AChE) activity, which is associated with better performance in evocative memory tasks, but worse performance in working memory.[60] In addition, patients that respond to endotoxin by suppressing the cholinergic system have a better working memory performance as compared with patients that enhance cholinergic activity, indicating that limited cholinergic activation may be beneficial for cognition.[60] To date, human trials of cholinesterase inhibitors have not demonstrated benefit to prevent or treat delirium.[71]

The cholinergic pathway may be involved indirectly in the pathogenesis of delirium. The cholinergic pathway acts as a predictor of individual variation in systemic inflammatory response to infection; thus, by modulating systemic inflammation, the cholinergic system can indirectly affect brain function.[60] High plasma levels of an alpha-7 nicotinic Ach receptor agonist correlated with lower cytokine levels in endotoxin-treated volunteers.[72] Cholinergic signaling protects striatal, hippocampal, and cortical neurons against neurotoxicity induced by excitotoxic amino acids as well as other toxic insults. Several mechanisms have been postulated to explain these effects, from the production of growth factors[61,85] to a decrease in superoxide anion generation[62] to antioxidant actions.[63,64] In addition, resembling the peripheral cholinergic anti-inflammatory pathway, ACh and nicotine[65] have been reported to modulate LPS-induced TNF-α release from microglia through activation of α-nAChR.

Thus, it is possible that the decrease in cholinergic neurons during systemic inflammation decreases the availability of an ''anti-inflammatory'' signal in the brain. This is consistent with the decrease of cholinergic neurons observed with aging[86] that occurs in parallel to microglia activation.[87]

Amines

Dopamine, norepinephrine, and serotonin have a role in arousal and the sleep-wake cycle.[83] In addition, the D2 dopamine receptor subtype has been associated with hallucinations, stereotypic behavior, and thought disturbances,[88] and norepinephrine plays an important role in modulating attention, anxiety, and mood.[89] Thus, amines could be involved in several different symptoms associated with brain dysfunction. In fact, excess dopamine and norepinephrine has been associated with hyperactive delirium.[89] Experimentally, this is supported by the fact that the administration of dopamine agonists results in frontostriatal abnormalities that correlate with delirium, and dopamine antagonists are classically used to treat hyperactive delirium.[90,91] Furthermore, elevated CNS serotonin activity is postulated to occur in hepatic encephalopathy, and serotonin syndrome secondary to the withdrawal of serotonin reuptake inhibitors resembles the clinical picture of SE.[92,93]

Brain serotonin synthesis depends on the availability of tryptophan (Trp), and dopamine and norepinephrine production requires tyrosine (Tyr) and phenylalanine (Phe).[94] Despite the fact that most delirium theories suggest that an increase in amines drives delirium, in healthy volunteers the administration of LPS increases the cerebral delivery and influx of Phe.[95] This can be associated with the synthesis of ''false'' neurotransmitters, such as phenylethanolamine, which in turn can decrease central noradrenergic pathways.[73,96] An elevated Phe/large neutral amino acids (LNAA) ratio during acute febrile illness is associated with delirium in hospitalized elderly patients.[74] The systemic inflammatory response is associated with a decrease in the ratio of branched-chain (valine and isoleucine) and aromatic amino acids (mainly phenylalanine). This is associated with an increase in the cerebral delivery and unidirectional cerebral influx of phenylalanine, an abolished influx of leucine and isoleucine, and an ammonia-independent cerebral efflux of glutamine.[95] In this context, both low and high levels of Trp/LNAA are associated with delirium in the general ICU patient.[94] Alterations in Trp concentrations could lead to delirium due to the production of neurotoxic metabolites or alterations in serotonin/melatonin synthesis. In fact, increased activation of the kynurenine pathway (a neurotoxic metabolite of Trp) is associated with mortality and brain dysfunction in ICU patients.[97] Besides its neurotoxic effect, the accumulation of kynurenine or quinolinic acid can compromise immune functions.[66] In addition, the excessive degradation of tryptophan, as seen in septic patients, could lead to NAD+ depletion.[67] In this context, neurons may become functionally hypoxic (due to Krebs cycle impairment) even in the presence of oxygen, and cellular hibernation may, in part, reflect an underlying tryptophan shortage.

Plasma levels of Tyr/LNAA are also associated with delirium. Patients with high levels of tyrosine could have excess dopamine or norepinephrine, which is consistent with a neurotoxic effect of norepinephrine.[68] Despite this, the use of dopamine antagonists in critically ill patients does not consistently improve delirium severity and duration,[75,98] and the use of vasoactive drugs is not independently associated with increased incidence of delirium.[76] Furthermore, as described with Ach, norepinephrine seems to have anti-inflammatory properties. The administration of norepinephrine reuptake inhibitors (NRIs) inhibits LPS-induced expression of cytokines, chemokines and endothelial activation,[99] probably increasing norepinephrine availability to glial cells. In addition, α2-adrenoceptor stimulation decreases vascular endothelial cell permeability[77] and reduces production of inflammatory mediators.[78] Supporting this view, dopexamine, an α2-adrenoceptor and dopamine 1 and 2 receptor agonist, protects against cerebral edema induced by sepsis, and the co-administration of an α2-adrenoceptor antagonist blunted this effect.[79] In humans, there is preliminary evidence that dexmedetomidine, an α-agonist, exerts protective effects in septic patients,[80] but this is not supported by animal models of primary brain injury.[100] The lack of a consistent effect is also observed with the β-adrenergic receptor; β2-adrenoceptor activation can induce[101] or protect against brain inflammation.[102,103]

Gamma-aminobutyric acid (GABA)

The most compelling evidence about delirium prevention in ICU patients comes from sedation strategies aimed to reduce benzodiazepine (BZ) use.[104] Despite this, little is known about GABA neurotransmission under inflammatory conditions, or of the exact mechanisms whereby increased GABA signaling drives delirium. The cortical type A GABA (GABA-A) and corticotrophin-releasing factor systems are major regulatory factors of the behavioral response to stress.[69] Acute stressors such as restraint, infection, hypoxia or combined mild stressors influence the GABA-A complex at two different levels: by altering BZ-1 binding sites and modulating the expression of selective GABA-A receptor subunits.[105] Inflammatory mediators increase the insertion of GABA-A receptors in the neuron membrane,[106] and an increase in GABA-A receptor activity has been observed in septic rats.[107,108] Thus, it could be presumed that increased sensitivity to BZ occurs during systemic inflammation. In fact, GABA-A agonists worsen postoperative pain only in the presence of inflammation.[109] Cerebral synaptic activity is decreased in SE, and because GABA-A receptor regulates synaptic transmission in most cerebral inhibitory synapses, it is possible that GABA-A could be a target for new therapeutic strategies aimed to treat or prevent delirium. Indeed, increased GABAergic neurotransmission has been reported in patients with hepatic encephalopathy.[70]

On the other hand, while the expression of GABA-A receptors is found normally in glial cells, BZ receptor non-associated with GABA-A expression, which is low in normal glial cells, is increased during inflammatory conditions.[110] In this context, the BZ midazolam improves neural recovery after anoxia and ischemia.[111] Midazolam decreases LPS-induced cytokine release from microglia via non-GABA-A BZ receptors.[81] This seems to be a specific effect, as propofol has no such protective effect *in vitro*.[82] Thus, if systemic and brain inflammation leads to delirium, it is expected that BZ could improve delirium in the critically ill patient.

Concluding remarks

Despite the fact that SE and brain dysfunction are highly prevalent in ICU patients and are associated with worse prognosis, surprisingly little is known about their pathophysiology. The most cited theory – neurotransmitter deregulation – lacks solid evidence to be widely accepted, and this may partly account for the lack of effect of clinical interventions designed to treat acute brain dysfunction, mainly strategies based on cholinergic drugs. Thus, the hypothesis that neurotransmission and inflammation are connected and are major players in brain dysfunction pathophysiology requires further critical assessment in the future.

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Disclosure

The authors report no conflicts of interest.

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