Review
Science review: The brain in sepsis – culprit and victim
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Abstract

On one side, brain dysfunction is a poorly explored complication of sepsis. On the other side, brain dysfunction may actively contribute to the pathogenesis of sepsis. The current review aimed at summarizing the current knowledge about the reciprocal interaction between the immune and central nervous systems during sepsis. The immune-brain cross talk takes part in circumventricular organs that, being free from blood-brain-barrier, interface between brain and bloodstream, in autonomic nuclei including the vagus nerve, and finally through the damaged endothelium. Recent observations have confirmed that sepsis is associated with excessive brain inflammation and neuronal apoptosis which clinical relevance remains to be explored. In parallel, damage within autonomic nervous and neuro-endocrine systems may contribute to sepsis induced organ dysfunction.

Keywords apoptosis, autonomic nervous system, central nervous system, hormones, inflammation, neuromediators

Introduction

It is clear that septic shock can be associated with a spectrum of cerebral damage and dysfunction [1–3]. Reciprocal interactions between the immune and central nervous systems are now considered to be major components of the host response in septic shock. This is the case even though the brain is often thought of as a privileged organ – one that is anatomically sequestered from the immune system by the blood–brain barrier (BBB), lacking a lymphatic system and with low expression of histocompatibility complex antigens on its parenchymal cells. Because the central nervous system controls a wide range of physiological functions that are crucial to maintaining homeostasis and orchestrating the host response at behavioural, neuroendocrine and autonomic levels [4–7], disturbances in any of these adaptive functions may deleteriously influence the course of septic shock. For example, they may perpetuate immune-inflammatory responses and haemodynamic failure. Here we review the areas of the brain that are involved in the response to infection,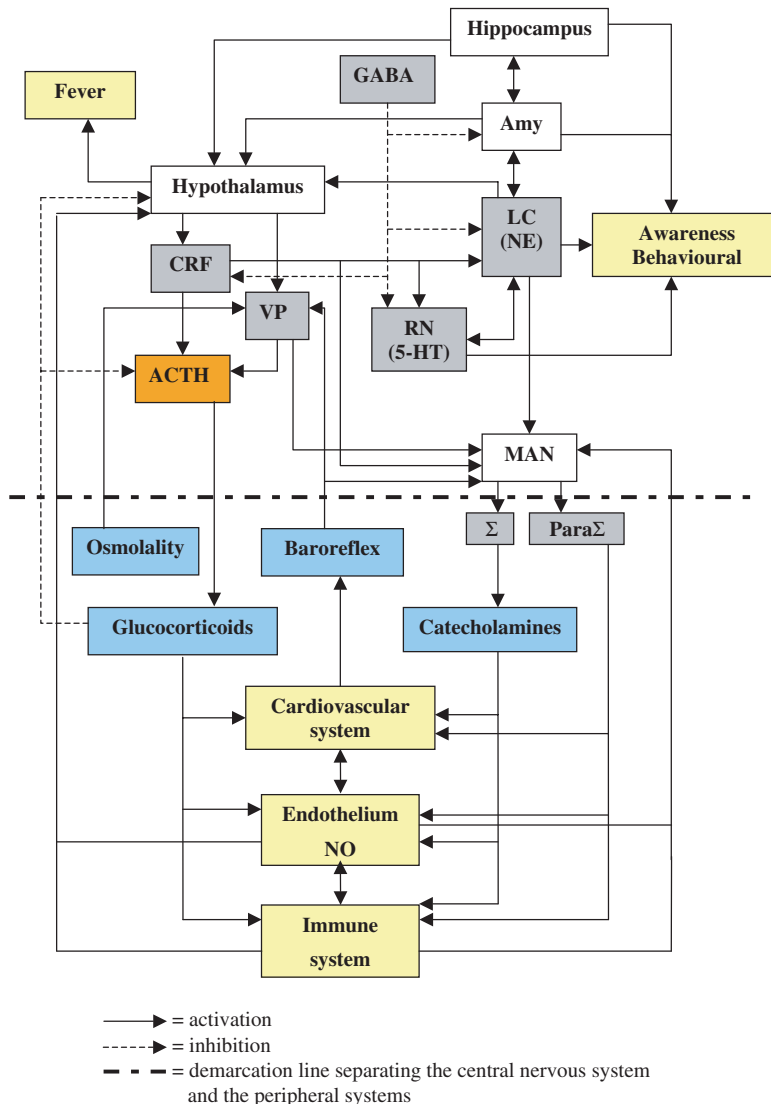 the pathways and mechanisms of immune–brain interaction during septic shock, and clinical aspects of cerebral dysfunction in human septic shock.

Neuroanatomy of the brain response to infection

The systemic response to infection, an example of the response to noxious stress that was first described nearly 70 years ago by Seyle [8], involves a complex, organized and coherent interaction between immune, autonomic, neuro-endocrine and behavioural systems [4,7,9]. The brain structures involved in this response are, in roughly ascending order (Fig. 1), as follows:

1. The medullary autonomic nuclei (i.e. solitary tract nuclei, the dorsal motor nucleus of the vagus and the ambiguus nuclei), which control parasympathetic output directly and sympathetic activity indirectly, through the intermedio-lateral cell column in the thoracic spinal cord.
2. The parabrachial nuclei, A5 cell group and the area postrema, which are located in the brainstem and control the medullary autonomic nuclei.

ACTH = adrenocorticotrophic hormone; BBB = blood–brain barrier; CRF = corticotrophin-releasing factor; IL = interleukin; LPS = lipopolysaccharide; NF-κB = nuclear factor-κB; NO = nitric oxide; NOS = nitric oxide synthase; TLR = Toll-like receptor; TNF = tumour necrosis factor.

Figure 1


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                    = activation
- - - - - - - - ▶   = inhibition
━ ━ ━ ━ ━ ━ ━      = demarcation line separating the central nervous system
                      and the peripheral systems
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Main cerebral networks involved in the response to stress. ACTH, adrenocorticotrophic hormone; Amy, amygdala; CRF, corticotrophin-releasing factor; 5-HT, serotonin (5-hydroxytryptamine); LC, locus coeruleus; MAN, medullary autonomic nuclei; NE, norepinephrine (noradrenaline); NO, nitric oxide; ParaΣ, parasympathetic system; Σ, sympathetic system; RN, raphe nuclei; VP, vasopressin.

3   The midbrain raphe nuclei, which are the source of serotonergic fibre systems, and the reticular formation.

4   The locus coeruleus, which is both localized in the pons and the core of the noradrenergic network.

5. The hypothalamic paraventricular and supraoptic nuclei, which synthesize and release corticotrophin-releasing factor (CRF) and vasopressin.

6. The amygdala, which is located within the hippocampus and connected to the limbic system.

In addition to their neuroendocrine functions, CRF and vasopressin are both neurotransmitters with receptors that are expressed in the medullary autonomic nuclei and locus

coeruleus [9]. All of these structures are interconnected, notably the paraventricular nucleus, locus coeruleus and nuclei of solitary tract, which have reciprocal projections [9].

The CRF, vasopressin and noradrenergic networks (termed CRF/VP and LC-NA systems) are coactivated during the response to stress and modulate each other [7]. They are also influenced by cerebral facilitatory (serotonergic and cholinergic networks) and inhibitory (γ-aminobutyric acid and opioid networks) systems, as well as by peripheral feedback mechanisms such as circulating inflammatory mediators, baroreflex afferents (vasopressin and autonomic nuclei),

plasma corticosteroid level (adrenocorticotrophic hormone [ACTH] and CRF) and plasma osmolality (vasopressin).

There is an additional level of complexity, namely the interactive cellular organization of the brain, which includes endothelial cells, glial cells (astrocytes and microglia) and neurones. For example, astrocytes play a protective role in regulating local blood flow, transporting energy substrates from microvessels to neurones, preserving BBB properties, destroying pathogens, removing debris and promoting tissue repair [1,10]. However, activated glial cells acquire neurotoxic properties, notably by releasing nitric oxide (NO) and glutamate [10,11], in circumstances that include cerebral trauma, inflammation and infection.

Neuropathology of human septic shock

Neuropathological studies of human septic shock are scant, most of them being retrospective or performed in few patients [12,13]. In a recent prospective autopsy study of 23 patients who had died from septic shock, we found ischaemic lesions in all cases, haemorrhage in 26%, hypercoagulability syndrome in 9%, microabscesses in 9%, and multifocal necrotizing leucoencephalopathy in 9%, which was associated with both local expression and high circulating levels of proinflammatory cytokines [2]. This latter finding is of great interest because it shows that the brain can be damaged through purely inflammatory processes, as distinct from hypoperfusion or coagulation disturbances, during septic shock [14]. However, the incidence and features of brain lesions in the *ante mortem* period and in patients surviving septic shock remain to be assessed.

Immune–brain pathways

The immune system can be thought of as a diffuse sensory system that signals the presence of micro-organism constituents to the brain through three main mechanisms [15]. First are the circumventricular organs, which are composed of specialized tissue and located at a strategic position in the midline ventricular system. Because they are not protected by the BBB they can function as communicating structures between the brain and bloodstream. They encompass the pineal body, the subcommissural organ and the subfornical organ, but especially the organum vasculosum, the median eminence and the neurohypohysis; these are, respectively, part of the hypothalamic and pituitary centres and the area postrema, which is close to the medullary autonomic nuclei. The vagus nerve, by sensing peripheral inflammation (presumably through cytokine receptors on the nerve surface), conveys immune-related information to the medulla [16] and then suppresses the inflammatory response at the site of infection (through nicotinic acetylcholine receptors on monocytes) [17–19]. The third signalling pathway is via endothelial activation and leakage, which leads to release or passive diffusion of inflammatory and neurotoxic mediators.

Blood–brain barrier during infection

Diffuse endothelial activation, also termed panendothelitis, is considered to be the hallmark of septic shock. Both lipopolysaccharide (LPS) and proinflammatory cytokines induce the expression of CD40, vascular adhesion molecule-1 or intercellular adhesion molecule-1, and E-selectin on human brain microvessel endothelial cells [20–24]. They also cause transcriptional activation of the gene that encodes cyclo-oxygenase 2 and stimulation of the IκB-α/nuclear factor-κB (NF-κB) pathway [25–27]. Although brain endothelial cells do not express surface CD14, LPS also triggers the mitogen-activated protein kinase cascade through soluble CD14 [28]. LPS-activated brain endothelial cells exhibit IL-1 and tumour necrosis factor (TNF)-α receptors [29,30]; produce IL-1β, TNF-α and IL-6 [31–33]; and exhibit endothelial and inducible nitric oxide synthase (NOS) [34–37]. These mediators are able to interact with surrounding brain cells, relaying into the brain inflammatory response. This endothelial activation may result in alteration in the BBB [38–41]. Indeed, it has been shown that the BBB is rendered permeable in experimental models of septic shock [42–44], an effect that is attenuated by glial cells, dexamethasone, or NOS inhibition [42,45,46]. This endothelial activation may also result in cerebrovascular dysfunction. However, although a number of studies have assessed cerebral blood flow, endothelial reactivity and oxygen consumption during sepsis both in animal and human shock, they have yielded contradictory results, some showing impairment [47–49] and others not [50–53].

Cerebral immune system in infection

A coherent neuro–immune interaction requires that the brain can detect inflammatory mediators. Components of the innate and adaptive immune systems are expressed in the brain during experimental endotoxin shock [54]. Remarkably, their expression spreads from circumventricular organs to the deeper brain areas that control neuroendocrine and autonomic functions – a 'migratory' pattern of brain activation. Thus, LPS receptor CD14 is expressed sequentially, first in the circumventricular organs and then in hypothalamic and medullary autonomic nuclei during the very acute phase of experimental septic shock [55].

Toll-like receptor (TLR)2, TLR4 and TLR9 have been detected both in resting and LPS-activated animal or human glial cells (microglia, astrocytes and oligodendrocytes) [54,56,57], as may be expected because they are bone marrow derived monocytes. The issue of whether TLRs are expressed in neurones remains controversial, Lehnardt and coworkers [58] having recently shown that neuronal TLR remained undetectable after *in vitro* LPS stimulation. TLR4, which interacts with LPS-bound CD14, is constitutively expressed in circumventricular organs but also in the hypothalamus and medulla; in contrast to CD14, however, there is a downregulation of TLR4 mRNA in the brains of rats challenged by LPS [59]. There is also a strong and transient expression of the gene encoding TLR2 in the brains of LPS-

challenged mice [60]. Microglial cells also express TLR9 mRNA, and its ligand has been found to activate these cells both *in vitro* and in animal models [61]. CD14 and TLR both trigger cellular transcription of proinflammatory molecules through the NF-κB pathway. Thus, IκB mRNA follows a CD14 migratory-like transcription pattern in the brain of rats following intraperitoneal LPS administration [62].

It has been established that LPS stimulation induces NO synthesis [63,64], and the release of proinflammatory and anti-inflammatory cytokines and their receptors from neurones, astrocytes and microglial cells both *in vitro* [65–68] and *in vivo* [31,34–36,69–72]. The coexpression of proinflammatory and anti-inflammatory cytokines suggests the existence of a highly organized immune counter-regulation within the brain [73].

Prostaglandins are key mediators in the brain response to inflammatory stimuli, their role in fever having been extensively investigated. Thus, following LPS stimulation astrocytes release significant amount of prostaglandin E [74], whereas microglia express prostaglandin receptors [75] and express cyclo-oxygenase 2 [76]. Finally, a number of other mediators are involved in the cerebral brain response to immune challenge including, among others, chemokines, macrophage migrating inhibitory factor, platelet activating factor, superoxide radicals and carbon monoxide.

Consequences of cerebral immune activation

There is a body of evidence that NO, cytokines and prostaglandins modulate brain neurotransmission [77–82], especially the β-adrenergic system, the production and release of CRF, ACTH and vasopressin, as well as medullary autonomic centre output [83,84]. Inversely, neurotransmitters and neurohormones also modulate cerebral expression of inflammatory mediators [85,86]. These effects have been described elsewhere [66,87]. The final neuroendocrine and autonomic response is variable because it depends on a highly complex and spatiotemporally changing process that involves both stimulatory and inhibitory factors, which themselves depend on interactions between glial, endothelial and neuronal cells. Disturbances in these relationships may lead to maladaptive responses, as illustrated by a recent experimental study [88] that showed that heart failure associated sympathetic hyperactivity was linked to decreased NO production in the paraventricular nucleus. The opposite phenomenon may occur in septic shock, which is associated with reduced sympathetic output [89].

At an intracellular level, various phenomena have been reported, including activation or inhibition of mitochondrial respiration [10,90], activation of mitogen-activated protein kinase and NF-κB pathways [91] and release of cytotoxic agents such as calcium and reactive oxygen species [92,93], as well as protective ones such as heat shock proteins [94]. However, although sepsis-related mitochondrial dysfunction has been extensively assessed in various human organs [95],

it remains to be documented in the human brain, but it is of course the case that genetic mitochondrial diseases are well described causes of brain dysfunction in humans.

Clearly, an important aspect of cerebral dysfunction is brain cell apoptosis, which occurs as a consequence of multiple factors that are in play during septic shock, including ischaemia, glial cell activation, TNF-α, IL-1β. interferon-γ and NO [96–99]. LPS challenge is associated with either glial or neuronal apoptosis [99,100] and it appears that NO is the main apoptotic mediator, although the TLR4 pathway may also be involved [101]. On the other hand, recent experimental studies have suggested that IL-10 and cyclo-oxygenase inhibition attenuate LPS-induced apoptosis [97,102,103]. We recently found apoptotic microglial and neuronal cells in the hypothalamus and cardiovascular autonomic centres in the brains of patients who had died from septic shock [3]. Of note is that, in that study, neuronal apoptosis was closely correlated with endothelial cell inducible NOS expression [3].

Encephalopathy, neuroendocrine and autonomic dysfunction in septic shock
Septic encephalopathy

The prevalence of encephalopathy in severe sepsis varies from 9% to 71%, depending on the definition, which can be based on clinical criteria [1,104–106], electroencephalographic criteria [107,108], or, more recently, on sensory evoked potentials [109,110]. An important advantage of the latter technique is that it is not influenced by sedation [109,110]. The severity of encephalopathy has been found to correlate with the global severity of illness, as assessed by Acute Physiology and Chronic Health Evaluation II score or organ failure scores, and with mortality [104–106]. As described above, the pathophysiology of encephalopathy is multifactorial, including the following: cerebral endothelial dysfunction, with BBB disruption and cerebral blood flow impairment, fostering translocation of neurotoxic molecules and brain hypoperfusion/ischaemia, respectively [1]; neurotoxic amino acids (such as ammonium, tyrosine, tryptophan and phenylalanine), whose plasma levels are increased in sepsis because of muscle proteolysis and reduced hepatic clearance [1,77,111–114]; and endotoxin and inflammatory mediators, which alter glial and neuronal metabolism, as was described previously [1]. Renal and hepatic failure, metabolic disturbances and neurotoxic drugs may also contribute to the development of brain dysfunction. Finally, neurone-specific enolase, a marker of brain injury, may be a predictor of death in septic shock patients [115].

Neuroendocrine dysfunction and autonomic failure

The endocrine response to sepsis is complex, and in this review we focus only on the hypothalamic–pituitary–adrenal axis and on vasopressin. Briefly, disruption of the hypothalamic–pituitary–adrenal axis is a common feature in severe sepsis and may be unmasked by a short Synacten

test, when cortisol level increases by less than 9 µg/dl after an intravenous bolus of 250 µg corticotrophin [116]. It is now recognized that, in sepsis, adrenal insufficiency partly accounts for reduced vascular sensitivity to vasopressors [117] and an increased risk for death [116]. Moreover, in septic shock, correcting this disorder by cortisol replacement therapy improves haemodynamic status and survival [118].

Septic shock may also be associated with a relative vasopressin deficiency, a concept that is worthy of clarification. Indeed, it is one rationale for treating septic shock with vasopressin infusion, the optimal start, duration and target plasma vasopressin concentration of which remain unresolved [119–121]. First, deficiency implicitly suggests that plasma vasopressin levels are abnormally reduced. Landry and coworkers [122] originally reported significantly lower plasma vasopressin levels in late septic shock than in cardiogenic shock (3.1 ± 1.0 versus 22.7 ± 2.2 pg/ml). The latter observation, together with the demonstration of high vasopressin levels in experimental early endotoxic shock [123,124], suggests that circulating vasopressin levels wane as the course of septic shock progresses. Indeed, this pattern was confirmed in patients with septic shock [125].

Second, 'inappropriately low' means that the observed plasma vasopressin level does not match the expected value for a given level of plasma osmolality or a given degree of hypotension. It is highly difficult to apply such a criterion in septic shock. For instance, circulating vasopressin levels were inappropriately low in a third of patients with septic shock, mainly after the 36 hours from the onset of shock [125]. Vasopressin levels were thought to be inappropriate when they were 3.6 pg/ml or less (the upper limit for normonatraemic and normotensive healthy individuals) and sodium concentration was 145 mmol/l or more, or systolic blood pressure was less than 100 mmHg. One may argue that using the upper limit observed in hypernatraemic or hypotensive healthy individual or in cardiogenic shock as a reference would have resulted in a higher rate of inappropriate vasopressin levels. The latter issue concerns the limits of natraemia and systolic blood pressure to which one should refer. In such a life-threatening and complex condition as septic shock, it is conceivable that the osmo- and baro-thresholds of vasopressin secretion are respectively shifted to an upper level of natraemia and a lower level of systolic blood pressure, simply because vasopressin reserve must be preserved or vasopressin concentrations are appropriate for other physiological factors.

Keeping this in mind, it is noteworthy that, in patients with septic shock and adrenal insufficiency, plasma vasopressin levels were significantly higher in nonsurvivors [125]. It is therefore plausible that secretion of vasopressin, which is known to modulate ACTH release and to be regulated by circulating cortisol [7], was adapted to adrenal function. In addition, this observation may also suggest that plasma vasopressin deficiency is not associated with poorer outcomes. So, why should plasma vasopressin be normalized?

In an opposing and provocative view, one may argue that vasopressin secretion should be limited in some patients, particularly those with adrenal insufficiency. However, vasopressin infusion, if not beneficial in normalizing vasopressin deficiency, might be useful because of its haemodynamic properties [119–121]. The various mechanisms underlying inappropriately low circulating vasopressin levels may include increased vasopressin clearance from plasma, depleted vasopressin stores after the initial release, impaired baroreflex or osmoreceptor sensitivity, cytokines, or NO-induced decreased vasopressin synthesis or release [126–129]. We found normal vasopressinase activity, empty vasopressin neurohypophyseal stores on magnetic resonance imaging [130] and impaired baroreflex activity in some patients [125]. However, interpretation of baroreflex sensitivity is difficult because it is directly influenced, through the medullar V1b receptor, by plasma vasopressin level [131].

Autonomic failure was initially described in endotoxin challenged animals before it was documented in patients with septic shock, particularly by using spectral analysis of heart rate variability [89,132]. Impaired autonomic function is associated with an increased risk for death from critical illness [133,134].

Conclusion

Septic shock is often complicated by encephalopathy, neuroendocrine dysfunction and cardiovascular autonomic failure, all of which worsen patient outcomes. The mechanisms of these dysfunctions are highly complex and involve inappropriate immune–brain signalling, which results in brain cell activation; deleterious production of NO; dysfunction of intracellular metabolism; and cell death. Areas of the brain that are responsible for cardiovascular homeostasis appear to be specifically vulnerable during sepsis, creating a vicious cycle. The central role played by NO suggests that inhibition of inducible NOS expression would be beneficial but this needs to be demonstrated experimentally, especially because inhibition of endothelial NOS might worsen brain ischaemia. It may prove difficult to manipulate the complex and inter-related processes involved.

Competing interests

The author(s) declare that they have no competing interests.

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