Review

Science review: The brain in sepsis – culprit and victim

Tarek Sharshar¹, Nicholas S Hopkinson², David Orlikowski¹ and Djillali Annane³

¹Attending Physician, Service de Réanimation Médicale, Hôpital Raymond Poincaré, Faculté de Médecine Paris Ile de France Ouest, Université de Versailles Saint-Quentin-en-Yvelines, Garches, France
²Attending Physician, Respiratory Muscle Laboratory, Royal Brompton and Harefield NHS Trust, Fulham Road, London, SW3 6NP, United Kingdom
³Head of ICU Department, Service de Réanimation Médicale, Hôpital Raymond Poincaré, Faculté de Médecine Paris Ile de France Ouest, Université de Versailles Saint-Quentin-en-Yvelines, Garches, France

Correspondence: Djillali Annane, djillali.annane@rpc.ap-hop-paris.fr

Published online: 8 September 2004
This article is online at http://ccforum.com/content/9/1/37
© 2004 BioMed Central Ltd

Critical Care 2005, 9:37-44 (DOI 10.1186/cc2951)

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 neuroendocrine 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, neuroendocrine 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 ambiguous 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 = adrenocorticotropic 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.
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 corticotropin-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 corticosterone level (adrenocorticotropic 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 neurohypophysis; these are, respectively, part of the hypothalamic and pituitary centres and the area postrema, which is close to the medullar 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 cyclooxygenase 2 and stimulation of the IxB-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 whetherTLRs 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-
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 neurons, 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 cyclooxygenase 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, neuron-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 individuals or in cardiogenic shock as a reference would have resulted in a higher rate of inappropriate vasopressin levels. 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].

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.

References

1. Papadopoulos MC, Davies DC, Moss RF, Tighe D, Bennett ED: Pathophysiology of septic encephalopathy: a review. Crit Care Med 2000, 28:3019-3024.
2. Sharshar T, Annane D, de la Grandmaison G, Brouland JP, Hopkinson NS, Gray F: The neuropathology of septic shock. Brain Pathol 2004, 14:21-33.
3. Sharshar T, Gray F, Lorin de la Grandmaison G, Hopkinson NS, Ross E, Dorandeu A, Orlikowski D, Raphael J-C, Gajdos P, Annane D: Apoptosis of neurons in cardiovascular autonomic centres triggered by inducible nitric oxide synthase after death from septic shock. Lancet 2003, 362:1799-1805.
4. Spyer KM: Neural mechanisms involved in cardiovascular control during affective behaviour. Trends Neurosci 1989, 12: 506-513.
5. Spirer CB, Broder CD: The neurologic basis of fever. N Engl J Med 1994, 330:1880-1886.
6. Chrousos GP, Gold PW: The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA 1992, 267:1244-1252.
7. Chrousos GP: The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995, 332: 1351-1362.
8. Seyle HA: A syndrome produced by diverse nocuous agents. Nature 1938, 138:22.
9. Carrasco GA, Van de Kar LD: Neuroendocrine pharmacology of stress. Eur J Pharmacol 2003, 463:235-272.
10. Bal-Pricc, Brown GC: Inflammatory neurodegeneration mediated by nitric oxide from activated glia-inhibiting neuronal respiration, causing glutamate release and excitotoxicity. J Neurosci 2001, 21:6480-6491.
11. Kim WG, Mohney RP, Wilson B, Jeohn GH, Liu B, Hong JS: Regional difference in susceptibility to lipopolysaccharide neurotoxicity in the rat brain: role of microglia. J Neurosci 2000, 20:6309-6316.
12. Jackson AC, Gilbert JJ, Young GB, Bolton CF: The ependymal cell of sepsis. Can J Neurol 1995, 12:303-307.
13. Bekter TP, Smith MC, Pierre-Louis SJ, Jaress J, Murray J, Hansen CA: Neurologic complications of critical medical illnesses. Can Med Assoc J 1993, 149:101-103.
14. Sharshar T, Gaykema RP, Hansen MK, Anderson K, Maier SF, Watkins LR: Vagal immune-to-brain communication: a visceral chemosensory pathway. Auton Neurosci 2000, 85:49-59.
15. Maier SF, Goehler LE, Flesher M, Watkins LR: The role of the vagus nerve in cytokine-to-brain communication. Ann N Y Acad Sci 1998, 840:289-300.
16. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchina GI, Watkins LR, Wang H, Abumrad N, Jawc JW, Tracey KJ: Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000, 405:458-462.
17. Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, Li JH, Yang H, Ulloa L, Al-Abed Y, et al.: Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature 2003, 421:384-388.
18. Goehler LE, Gaykema RP, Hamack SE, Maier SF, Watkins LR: Interleukin-1 induces c-fos immunoreactivity in primary afferent neurons of the vagus nerve. Brain Res 1998, 804:306-310.
19. Omar KM, Dorovini-Zis K: CD40 expressed by human brain endothelial cells regulates CD4+ T cell adhesion to endothelium. Neuroimmunol 2003, 134:166-178.
20. Wong D, Dorovini-Zis K: Expression of vascular cell adhesion molecule-1 (VCAM-1) by human brain microvessel endothelial cells in primary culture. Microvasc Res 1995, 49:325-339.
21. Hess DC, Thompson Y, Sprinkle A, Carroll J, Smith J: E-selectin on human brain microvascular endothelial cells. Neurosci Lett 1996, 213:37-40.
22. Riezmann P, Michel U, Albrecht M, Bruck W, Wockel L, Bistow A, Blomqvist A: Rat brain vascular distribution of interleukin-1 type-1 receptor immunoreactivity: relationship to patterns of inducible cyclooxygenase expression by peripheral inflammatory stimuli. J Comp Neurol 2004, 472:113-129.
23. Nadeau S, Rivest S: Effects of circulating tumor necrosis on the neuronal activity of the genes encoding the tumor necrosis factors receptors (p55 and p75) in the rat brain: a view from the blood–brain barrier. Neurosci 2001, 93:1449-1464.
24. Fabbry Z, Fitzsimmons KM, Herlaine JA, Moninger TO, Dobbs MB, Hart MN: Production of cytokines interleukin-1 and 6 by murine brain microvascular endothelium in smooth muscle pericytes. J Neuroimmunol 1993, 47:23-34.
25. Iwase K, Miyanaaka K, Shimizu A, Nagasaka A, Gotoh T, Mori M, Takiguchi M: Induction of endothelial nitric-oxide synthase in rat brain microvessels by system lipopolysaccharide administration. Proc Natl Acad Sci USA 1994, 91:1393-1397.
26. Nadel T, Fabry Z, et al.: Brain endothelial cell production of neuroprotective cytokine, interleukin-6, in response to noxious stimuli. Brain Res 1999, 210:215-220.
27. Fabbry Z, Fitzsimmons KM, Herlaine JA, Moninger TO, Dobbs MB, Hart MN: Production of cytokines interleukin-1 and 6 by murine brain microvascular endothelium in smooth muscle pericytes. J Neuroimmunol 1993, 47:23-34.
28. Iwase K, Miyanaaka K, Shimizu A, Nagasaka A, Gotoh T, Mori M, Takiguchi M: Induction of endothelial nitric-oxide synthase in rat brain microvessels by system lipopolysaccharide administration. Proc Natl Acad Sci USA 1994, 91:1393-1397.
29. Nadeau S, Rivest S: Effects of circulating tumor necrosis on the neuronal activity of the genes encoding the tumor necrosis factors receptors (p55 and p75) in the rat brain: a view from the blood–brain barrier. Neurosci 1999, 93:1449-1464.
30. Fabbry Z, Fitzsimmons KM, Herlaine JA, Moninger TO, Dobbs MB, Hart MN: Production of cytokines interleukin-1 and 6 by murine brain microvascular endothelium in smooth muscle pericytes. J Neuroimmunol 1993, 47:23-34.
31. Iwase K, Miyanaaka K, Shimizu A, Nagasaka A, Gotoh T, Mori M, Takiguchi M: Induction of endothelial nitric-oxide synthase in rat brain microvessels by system lipopolysaccharide administration. Proc Natl Acad Sci USA 1994, 91:1393-1397.
32. Nadeau S, Rivest S: Effects of circulating tumor necrosis on the neuronal activity of the genes encoding the tumor necrosis factors receptors (p55 and p75) in the rat brain: a view from the blood–brain barrier. Neurosci 1999, 93:1449-1464.
33. Fabbry Z, Fitzsimmons KM, Herlaine JA, Moninger TO, Dobbs MB, Hart MN: Production of cytokines interleukin-1 and 6 by murine brain microvascular endothelium in smooth muscle pericytes. J Neuroimmunol 1993, 47:23-34.
34. Iwase K, Miyanaaka K, Shimizu A, Nagasaka A, Gotoh T, Mori M, Takiguchi M: Induction of endothelial nitric-oxide synthase in rat brain microvessels by system lipopolysaccharide administration. Proc Natl Acad Sci USA 1994, 91:1393-1397.
35. Wong D, Borongio PB, al-Shekhlee A, Bongiorno PB, McCann SM, Gold PW, Licinio J: Inducible nitric oxide synthase gene expression in the brain during systemic inflammation. Nat Med 1996, 2:581-584.
36. Fabbry Z, Fabry Z, et al.: Brain endothelial cell production of neuroprotective cytokine, interleukin-6, in response to noxious stimuli. Brain Res 1999, 210:215-220.
37. Fabbry Z, Fabry Z, et al.: Brain endothelial cell production of neuroprotective cytokine, interleukin-6, in response to noxious stimuli. Brain Res 1999, 210:215-220.
38. Fabbry Z, Fabry Z, et al.: Brain endothelial cell production of neuroprotective cytokine, interleukin-6, in response to noxious stimuli. Brain Res 1999, 210:215-220.
39. Fabbry Z, Fabry Z, et al.: Brain endothelial cell production of neuroprotective cytokine, interleukin-6, in response to noxious stimuli. Brain Res 1999, 210:215-220.
40. Fabbry Z, Fabry Z, et al.: Brain endothelial cell production of neuroprotective cytokine, interleukin-6, in response to noxious stimuli. Brain Res 1999, 210:215-220.
41. Fabbry Z, Fabry Z, et al.: Brain endothelial cell production of neuroprotective cytokine, interleukin-6, in response to noxious stimuli. Brain Res 1999, 210:215-220.
70. Quan N, Stern EL, Whiteside MB, Herkenham M: Induction of pro-inflammatory cytokine mRNAs in the brain after peripheral injection of septic shock mRNAs of lipopolysaccharide in the rat. J Neuroimmunol 1999, 93:72-80.

71. Bredt DS, Hwang PM, Snyder SH: Localization of nitric oxide synthase indicating a neural role for nitric oxide. Nature 1990, 347:768-770.

72. Weng ML, Biogioni PB, Rettori V, McCann SM, Licinio J: Interleukin (IL)-1alpha, IL-1 receptor antagonist, IL-10, and IL-13 gene expression in the central nervous system during systemic inflammation: pathophysiological implications. Proc Natl Acad Sci USA 1997, 94:227-232.

73. Heyen JR, Ye S, Foskett JK, Johnson RW: Interleukin(IL)-10 inhibits IL-6 production in microglia by preventing activation of NF-kappaB. Brain Res Mol Brain Res 2000, 77:138-147.

74. Fontana A, Kristensen D, Fuchs R, Gamsa D, Weber E: Production of prostaglandin E and an interleukin-1 like factor by cultured astrocytes and G6 glioma cells. J Immunol 1992, 129:2413-2419.

75. Caggiano AO, Kraig RP: Prostaglandin E receptor subtypes in cultured rat microglia and their role in reducing lipopolysaccharide-induced interleukin-1beta production. J Neurochem 1999, 72:685-676.

76. Elmoquist JK, Scammell TE, Saper CB: Mechanisms of CNS response to systemic immune challenge: the febrile response. Trends Neurosci 1997, 20:565-570.

77. Kadoi Y, Saijo S: An alteration in the gamma-aminobutyric acid receptor system in experimentally induced septic shock in rats. Crit Care Med 1996, 24:298-305.

78. Kadoi Y, Saijo S, Kunimoto F, Imai T, Fujita T: Impairment of the brain beta-adrenergic system during experimental endotoxemia. J Surg Res 1995, 57:495-500.

79. Dawson VL, Dawson TM, London ED, Bredt DS, Snyder SH: Nitric oxide mediates glutamate neurotoxicity in primary cortical cultures. Proc Natl Acad Sci USA 1991, 88:6368-6371.

80. Dunn AJ: Endotoxin-induced activation of cerebral catecholamine and steroid metabolism: comparison with interleukin-1. J Pharmacol Exp Ther 1992, 261:964-969.

81. Dunn AJ: Cytokine activation of the HPA axis. Ann N Y Acad Sci 2001, 917:608-617.

82. Matsuoku Y, Furuyashiki T, Bito H, Ushikubi F, Tanaka Y, Kobayashi T, Muro S, Sato N, Koyama T, Higashi M, et al: Impaired adrenocorticotropic hormone response to bacterial endotoxin in mice deficient in prostaglandin E receptor EP1 and EP3 subtypes. Proc Natl Acad Sci USA 2003, 100:4132-4137.

83. Taniura S, Hong JS: Regulation of the hypothalamic-pituitary-adrenocortical axis by lipopolysaccharide-induced interleukin-1beta production in the rat. J Pharmacol Exp Ther 2000, 298:305-310.

84. Persson PB: Modulation of cardiovascular control mechanisms and their interaction. Physiol Rev 1996, 76:193-232.

85. Weidenfeld J, Kahbha K, Reches A, Shohami E: Role of the cerebral adrenergic system in the regulation of prostaglandin biosynthesis in rat brain. J Neurochem 1992, 58:694-699.

86. Garthwaite J: Glutamate, nitric oxide and cell-cell signalling in the nervous system. Trends Neurosci 1991, 14:60-67.

87. McCann SM, Kemura M, Karanth S, Yu WH, Mastronardi CA, Rettori V: The mechanism of action of cytokines to control the release of hypothalamic and pituitary hormones in infection. Ann N Y Acad Sci 2000, 917:14-18.

88. Li Y-F, Patel KP: Paraventricular nucleus of the hypothalamus and elevated sympathetic activity in heart failure: the altered inhibitory mechanisms. Cytokine 2003, 17:17-26.

89. Annane D, Trabold F, Sharshar T, Jarin I, Blanc A, Raphael JC, Gally J-P, Sebille V, Mege JL, de Jongh P: Inappropriate sympathetic activation at onset of septic shock: a spectral analysis approach. Am J Respir Crit Care Med 1999, 160:459-465.

90. Kramer BC, Yabut JA, Cheong J, JnoBaptiste R, Robakis T, Olanow CW, Mytilineou C: Lipopolysaccharide prevents cell death caused by glutathione depletion: possible mechanisms of protection. Neuroepidemiology 2002, 13:361-372.

91. Kramer BC, Glodek J, Cornish P, Scandellieri V, Zito P, Hopfer U, Paz P, Putt M, Arzt E, Stalla GK, Renner U: Lipopolysaccharide directly stimulates the intrapituitary interleukin-6 production by folliculostellate cells via specific receptors and the p38 mitogen-activated protein kinase/NF-kB pathways. Endocrinology 2000, 141:4457-4466.

92. Zhan RZ, Fujimori H, Shimoji K: Regionally different elevation of intracellular free calcium in hippocampus of septic rat brain. Shock 1996, 6:293-297.

93. Wang T, Qin L, Liu B, Liu Y, Wilson B, Eling TE, Langenbach R, Taniura S, Hong JS: Role of reactive oxygen species in LPS-
induced production of prostaglandin E2 in microglia. J Neurochem 2004, 88:939-947.
94. Feinlein DL, Galea E, Aquino DA, Li GC, Xu H, Reis DJ: Heat shock protein 70 suppress astroglial-inducible nitric-oxide synthase expression by decreasing NF-kappaB activation. J Biol Chem 1996, 271:17724-17732.
95. Bresley D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, Davies NA, Cooper CE, Singer M: Association between mitochon- drial function and severity and outcome of septic shock. Lancet 2002, 360:219-223.
96. Yuan J, Yankner BA: Apoptosis in the nervous system. Nature 2000, 407:802-809.
97. Lynch AM, Walsh C, Delaney A, Nolan Y, Campbell VA, Lynch M, O’Keeffe T: Induction of nitric oxide synthase and nitric oxide mediated apoptosis in neural PC12 cells after stimulation with tumor necrosis factor-alpha/lipopolysaccha- ride. J Neurochem 1998, 71:88-94.
98. Lee J, Hur J, Lee P, Kim JY, Cho N, Kim SY, Kim H, Lee MS, Suk K: Dual role of inflammatory stimuli in activation-induced cell death of mouse microglial cells. Initiation of two separate apoptotic pathways via induction of interferon regulatory factor-1 and caspase-11. J Biol Chem 2001, 276:32956-32965.
99. Heneka MT, Loschmann PA, Gleichmann M, Weller M, Schulz JB, Walter G, O’Keeffe T: Induction of nitric oxide synthase and nitric oxide mediated apoptosis in neural PC12 cells after stimulation with tumor necrosis factor-alpha/lipopolysaccha- ride. J Neurochem 1998, 71:88-94.
100. Lehndt S, Massilion L, Follet P, Jensen FE, Ratan R, Rosen- berg PA, Volpe JJ, Vartanian T: Activation of innate immunity in the CNS triggers neurodegeneration through a toll-like receptor 4-dependent pathway. Proc Natl Acad Sci USA 2003, 100:8514-8519.
101. Shibata H, Katsuki H, Nishikawa M, Kume T, Kaneko S, Akaike A: Lipopolysaccharide-induced dopaminergic cell death in rat midbrain slice cultures: role of inducible nitric oxide synthase and protection by indomethacin. J Neurochem 2003, 86:1201-1212.
102. Monje ML, Toda H, Palmer TD: Inflammatory blockade restores function to the hippocampal neurogenesis. Science 2003, 302:1760-1765.
103. Young GB, Bolton CF, Austin TW, Archibald YM, Gonder J, Wells GA: The encephalopathy associated with septic illness. Clin Invest Med 1990, 13:297-304.
104. Prendini C, Buzzoni PN, Shinay CH, Schein RMH, Wilson MF, Sheagren JN, Hinshaw LB, The Veterans Administration Systemic Sepsis Cooperative Study Group: Impact of encephalopathy on mortality of sepsis. Crit Care Med 1990, 18:801-806.
105. Edelman LA, Putterman D, Putterman C, Sprung CL: The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. JAMA 1996, 275:470-473.
106. Straver JS, Keunen RW, Stam CJ, Tavy DL, de Ruiter GR, Smith SJ, Thijis LG, Schellens RG, Gielen G: Nonlinear analysis of EEG in septic encephalopathy. Neurul Res 1998, 20:100-106.
107. Young GB, Bolton CF, Archibald YM, Wells GA: The electroencephalogram in sepsis-associated encephalopathy. J Clin Neurophysiol 1992, 9:145-152.
108. Zauner C, Gendo A, Kramer L, Kranz A, Grimm G, Madl C: Metabo- lic encephalopathy in critically ill patients suffering from sepsis or septic multiple organ failure. Crit Care Med 2000, 28:1310-1315.
109. Zauner C, Gendo A, Kramer L, Funk GC, Bauer E, Schenk P, Ratheipser K, Madl C: Impaired subcortical and cortical sensorimotor pathways in septic patients. Crit Care Med 2002, 30:1136-1139.
110. Freund HR, Muggia-Sullam M, Peiser J, Melamed E: Brain neuro- transmitter profile is deranged during sepsis and septic encephalopathy in the rat. J Surg Res 1985, 38:267-271.
111. Freund HR, Muggia-Sullam M, LaFrance R, Holroyd J, Fischer JE: Regional brain amino acid and neurotransmitter derange- ments during abdominal sepsis and septic encephalopathy in the rat. The effect of amino acid infusion. Arch Surg 1986, 121:209-216.
112. Winder TR, Minuk GY, Sargeant EJ, Seland TP: γ-Aminobutyric acid (GABA) and sepsis-related encephalopathy. Can J Neurol Sci 1988, 15:23-25.
113. Sprung CL, Cerra FB, Freund HR, Schein RM, Konstantinides FN, Marcal EH, Pena M: Amino acid alterations and encephalopathy in the sepsis syndrome. Crit Care Med 1991, 19:753-757.
114. Weigand MA, Volkmann M, Scmidt H, Martin E, Bohrer H, Bar- denheuer HU: Neurop-specific enkephalin as a marker of fatal outcome in patients with severe sepsis or septic shock. Anes- thesiology 2000, 92:901-907.
115. Sprung C, Peduzzi PN, Shatney CH, Schein RM, Wilson MF, Young GB, Bolton CF, Austin TW, Archibald YM, Gonder J, Wells GA: Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal func- tion reserve. Br J Clin Pharmacol 1998, 46:589-597.
116. Annane D, Bellissant E, Sebille V, Lessieur O, Mathieu B, Raphael JC, Gadjo PS: Effect of treatment with low doses of hydrocortisone and flu- drocortisone on mortality in patients with septic shock. JAMA 2002, 288:862-871.
117. Landry DW, Levin HR, Gallant EM, Ashtown RC, Seo S, D’ Alessand- rini D, Oz MC, Oliver JA: Vasopressin pressor hypersensitivity in vasodilatory septic shock. Crit Care Med 1997, 25:1279-1282.
118. Mutlu GM, Factor P: Role of vasopressin in the management of septic shock. Int Care Med 2004, 30:1276-1281.
119. Russell JA: Vasopressin in septic shock: clinical equipoise mandates a time for restraint. Crit Care Med 2003, 31:2707-2709.
120. Landry DW, Levin HR, Gallant EM, Ashtown RC, Seo S, D’ Alessan- rini D, Oz MC, Oliver JA: Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997, 95:1122-1125.
121. Wilson MF, Brackett DJ, Hinshaw LB, Tompkins P, Archer LT, Benjamin BA: Vasopressin release during sepsis and septic shock in baboons and dogs. Surg Gyn Obstet 1981, 153:869-872.
122. Brackett DJ, Schaeffer CF, Tompkins P, Fagareus L, Peters LJ, Wilson MF: Evaluation of cardiac output, total peripheral vascular resistance, and plasma concentrations of vasopressin in the conscious, unrestrained rat during endotoxemia. Circ Res 1985, 17:273-284.
123. Sharshar T, Blanchard A, Paillard M, Ramm P, Jullien P, Jaffe A, Kuznetsova A, Deynailler D, Bonduelle M: Subcortical and cortical dysfunction in septic shock. Eur J Neurosci 1995, 7:592-596.
124. Landgraf R, Neumann I, Holabofer F, Pittman QJ: Interleukin-1β stimulates both central and peripheral release of vasopressin and oxytocin in the rat. Eur J Neurosci 1995, 9:259-262.
125. Reid IA: Role of vasopressin deficiency in vasodilation of septic shock. Crit Care Med 1997, 25:1109-1110.
126. Sharshar T, Carlier R, Blanchard A, Feydy A, Gray F, Paillard M, Raphael JC, Gadjo PS, Annane D: Depletion of neurohypophysyal content of vasopressin in septic shock. Crit Care Med 2002, 30:497-500.
127. Luk J: Role of V1 receptors in the action of vasopressin on the baroreflex control of heart rate. Am J Physiol 1993, 265:R524- R529.
128. Goldstein B, Kempski MH, Stair D, Tipton RB, DD, De Asla R, Cox C, Lund N, Wolff PD: Autonomic modulation of heart rate variability during endotoxin shock in rabbits. Crit Care Med 1998, 26:1694-1702.
129. Winchell RJ, Hoyt DB: Spectral analysis of heart rate variability in the ICU: a measure of autonomic function. J Surg Res 1996, 63:11-16.