

## Commentary

# Sepsis-associated delirium: the pro and con of C5a blockade

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## Abstract

The intimate mechanisms of sepsis-induced delirium are unknown. Among the potential contributing factors, the breakdown of the blood-brain barrier is considered a key determinant of brain dysfunction. The complement activation is paramount to an appropriate activation of the central nervous system during stress. C3a and C5a have been extensively studied and may be involved in sepsis-induced delirium. Here we discuss the pro and con for inhibiting C5a to attenuate brain damage during sepsis. In particular, we discuss the hypothesis that C5a increased blood-brain barrier permeability may ease the brain to mount an appropriate response to sepsis. Thus, blockade of C5a may be detrimental, resulting in an attenuated response of the stress system.

Flierl and colleagues showed recently in mice that systemic administration of neutralising anti-C5a antibody prevented caecal ligation and puncture-induced damage to the blood-brain barrier (BBB) and dysfunction of the pituitary gland [1]. These data are in line with the well-established role of the complement anaphylatoxin C5a in brain signalling during inflammation [2].

C5 is constitutively expressed in neuronal and non-neuronal brain cells. Following endotoxin administration, the C5a receptor becomes upregulated in a time-dependent manner within the cerebral endothelium, then in microglial cells neighbouring the endothelium and, finally, in deeper brain parenchyma. The complement activation has been demonstrated in numerous inflammatory and degenerative, acute and chronic, diseases of the brain [3]. Following C5a upregulation, microglial cells are recruited and activated to release proinflammatory cytokines, and their phagocytosis capacity is enhanced, and astrocytes are also activated [4]. Subsequently, C5a contributes to the activation of the stress system. Indeed, systemic blockade of C5a reduced lipopolysaccharide-induced neuronal activation in the paraventricular nuclei and amygdala [5]. Similarly, in Flierl and colleagues'

study, C5a blockade almost fully blunted the pituitary response to caecal ligation and puncture-induced sepsis [1].

## The pro side for inhibition of C5a

Adequate neuronal function requires a highly regulated extracellular environment, wherein the concentrations of ions such as sodium, potassium and calcium must be maintained within very narrow ranges. The brain accounts for approximately 20% of oxygen consumption in humans, and is also extremely sensitive to a wide range of chemicals that are circulating without harm to peripheral organ systems. It is therefore paramount that the interface between the central nervous system and the peripheral circulatory system (that is, the BBB) functions as a dynamic regulator of ion balance, as a facilitator of nutrient transport, and as a barrier to potentially harmful molecules.

Intuitively, the disruption of this barrier may flood the brain with neurotoxic substances. Subsequently, it is commonly thought that the breakdown of the BBB is a key causative factor of sepsis-associated delirium [6-8]. The stimulation of cerebrovascular endothelial cells with septic plasma induced dissociation of tight junction proteins such as occludin from the cytoskeletal network, and subsequently increased the size-selective transendothelial solute flux [9].

In patients, vasogenic oedema can be demonstrated by magnetic resonance imaging within the Virchow-Robin spaces, within the posterior cerebral hemispheres and, less frequently, as diffuse white matter oedema. Various mediators cause BBB hyperpermeability, such as bradykinin, IL-1 $\beta$ , TNF $\alpha$  and complement [6]. Recent experiments suggest that upregulation of C3 induced a breakdown in the BBB and increased gliosis, increased the water content, and up-regulated Toll-like receptor 4 with subsequent alterations in TNF, inducible nitric oxide synthase and aquaporin 4 [10].

BBB = blood-brain barrier; IL = interleukin; TNF = tumour necrosis factor.

Extending these findings, Flierl and colleagues were able to prevent the damage to the BBB by systemic administration of an anti-C5a neutralising antibody [1]. Unfortunately, they did not look at neuronal activation or damage to confirm any neuroprotection. Of note, interfering with complement activation either by blocking C5a or its receptor [11], or by inhibitor of the alternative complement pathway, attenuates neuronal death in experimental traumatic brain injury [12].

### The con side of blocking C5a

To survive stress, the brain must be alerted, must identify the stressors and must mount an appropriate response. The limbic system, the hypothalamic–pituitary axis and the locus coeruleus/noradrenergic system are tightly interconnected to orchestrate homeostasis in stress. These structures are all behind the BBB. The circulating inflammatory mediators may reach these brain areas via the circumventricular organs that lack a BBB or by active transport across the BBB [6].

It is also possible that specific systems are in place to open the BBB as a normal response to severe infection. Indeed, by increasing the BBB permeability, C5a may ease pathogen-associated molecular pattern access to brain sensing areas such as paraventricular and amygdala cells. Upregulation of C5a therefore allows the stress system to mount an appropriate response. This assumption is supported by at least three major facts. Firstly, blockade of C5a markedly reduced the activation of the hypothalamic–pituitary cells [5] and decreased the corticotrophin and corticosterone levels [1]. This effect correlated with decreased expression of pathogen-associated molecular pattern [5] and of cytokines [1,5]. The resulting inappropriate hypothalamic–pituitary adrenal axis is probably detrimental in sepsis [13]. Secondly, in patients with sepsis, magnetic resonance imaging studies showed that increased BBB permeability is an early, common, and transient phenomenon [8]. Patients who did survive to sepsis recovered a normal brain. Thirdly, C5-deficient mice or those pretreated with a C5a receptor antagonist are unable to mount a febrile response to intraperitoneal endotoxin challenge [14].

Furthermore, C3 is also broadly upregulated during sepsis, and may act as a gatekeeper – protecting the brain from any live circulating microorganisms while the BBB is rendered permeable. Neuronal excitation involving the excitatory glutamate receptors may be an important underlying mechanism in sepsis-induced altered neurotransmission [6]. Recent reports suggested that C5a induced neuroprotection against glutamate-mediated apoptosis through inhibition of caspase 3 activity, through the mitogen-activated protein kinase transduction pathway, and through regulation of the glutamate receptor GluTR2 [15]. C5 blockade may therefore inhibit select neuroprotective actions of the complement cascade, and may possibly exacerbate neuro-excitatory mechanisms.

Future studies should investigate neuron survival in the stress system following C5a antibodies, or C5a receptor antagonists or blockade of the alternative complement pathway in experimental sepsis.

### Competing interests

The author declares that they have no competing interests.

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