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EDITORIAL

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Hippocampus: a future target for sepsis treatment!

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The central nervous system orchestrates host response to an infection. It is commonly thought that blood borne cytokines and autonomic nervous afferent fibres signal the brain during an infection [1]. Intercommunications between brain stem nuclei, hypothalamus and limbic systems represent main circuits through which the stress response is mounted. Upregulation of inflammatory mediators within these important brain areas may be a major determinant of inappropriate stress response, progression of inflammation to the various organs, and death from sepsis [1]. Very early manifestation of brain activation during sepsis is changes in behaviour, including anxiety and loss of short-term memory and spatial recognition [1]. These symptoms are likely generated from the limbic system, the amygdala and the hippocampus. In this issue of *Intensive Care Medicine*, Dr. Wolff and co-workers using micro-array tools found that systemic administration of a non-lethal dose of LPS induced marked upregulation of pro-inflammatory mediators in the rats hippocampus, an effect that was aggravated by norepinephrine and almost not affected by inducible nitric oxide inhibition [2]. The hippocampus is one of the most vulnerable parts of the brain and is highly susceptible to ischaemia, anoxia and inflammation. It is well known that intravenous administration of LPS elicited expression of pro-inflammatory cytokines in the hippocampus and subsequently inhibited long-term potentiation [3, 4]. The CAP region of the dentate gyrus and the inner blade are the most susceptible areas, and following LPS injection, these regions are associated with large numbers of macrophages and perivascular microglial cells. It is likely that these cells produce pro-inflammatory cytokines triggering in excess the activity of the inducible nitric oxide, thereby causing neuronal DNA damage and a CD14 mediated phenomenon [5]. Therefore, the net effects of LPS are inhibition of neurogenesis and hippocampus function. Dr Wolff and co-workers used brain homogenate and thus could not dissect which cells were responsible for cytokines expression in their experiments [2]. They also did not investigate neuronal damages in the hippocampus to confirm cytokines induced damages to the limbic system. Nevertheless, the data showing that most of chemokines genes were upregulated before hypotension are in line with the concept that LPS directly affects the limbic system [3–6]. The limbic system and particularly the hippocampus contributes to the neural regulation of the stress system. In animals, hippocampus lesions may result in thymic atrophy and decreased lymphocytes counts suggesting immune-suppression [6]. Activation of the hippocampus suppresses corticotropin releasing factor synthesis [7]. Thus, it is possible that low activity of hippocampal regions during sepsis will result in decreased hypothalamic-pituitary adrenal axis (HPA) inhibitory outflow, thereby contributing to enhancement of the HPA activity known to be paramount to survive infection. In contrast, persistent activation of the hippocampus may blunt the HPA axis and normal immune response

to sepsis. Because no direct anatomical substrate between hippocampus/cortex and hypothalamic parvocellular neurons have yet been successfully identified, it is likely that cortico-hippocampal influences on hypothalamic hypophysiotropic neurons are indirectly achieved via subcortical relay neurons. Further investigations should examine whether sepsis induced anatomical and functional changes in the hippocampus and whether they correlate with the degree of HPA activation and survival.

On the other hand, a sustained inhibition of the hippocampus may account for long term cognitive sequels of sepsis. Interestingly, anti-inflammatory mediators like IL-10 may abrogate LPS induced hippocampus damages [3], and non-steroidal inflammatory blockade may restore neurogenesis and hippocampal functions [8]. Minocycline was shown to inhibits both caspase-dependent and independent apoptotic pathways and thus may protect against hippocampal damages [9]. A new class of drug is currently under investigation for the treatment of neuro-inflammation. This therapeutic approach is based on immune modulation via clearance of apoptotic cells, and was shown to prevent LPS-induced cell death in the hippocampus [10]. Treatment was associated with an increase in the concentration of the anti-inflammatory cytokine IL-10, and a decrease in activation of the stress-activated protein kinase, c-jun N-terminal kinase. This new treatment option may help manipulating brain response to sepsis and opens a new era in the management of critical illness associated acute inflammation.

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