Receptor for advanced glycation endproducts mediates long-term neuroinflammation, neurodegenerative-like changes and cognitive impairment induced by sepsis

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Background: Patients that recover from sepsis present higher rates of central nervous system (CNS) morbidities associated to long-lasting impairment of cognitive functions. *In vivo* experimental models confirmed that sepsis induces long-term brain alterations after recovery of acute inflammation. Here, we investigated the role of the receptor for advanced glycation endproducts (RAGE) in the onset neuroinflammation, neurodegenerative-associated changes and cognitive dysfunction after sepsis recovery.

Methods: Sepsis was induced in adult Wistar rats by cecal ligation and perforation (CLP). In one set of experiments animals were killed at 1, 15 and 30 days, and the hippocampus was removed to the determination of cytokines, phosporilated tau, amyloid beta and RAGE content. In a second set of experiments the role of RAGE in changes observed in brain 30 days after CLP were investigated by selective blocking of RAGE in hippocampus with anti-RAGE antibody (RAGE*ab*). Additionally, cognitive performance was measured 30 days after CLP by the inhibitory avoidance and object recognition tasks.

Results: From one to fifteen days after CLP, IL-1β, IL-6 and TNF-α levels were increased in hippocampus, decreasing until 30 days. This was in parallel with an increase in the content of phosphorylated tau, amyloid beta (Aβ) and RAGE contents. At 30 days after CLP, the content of RAGE in hippocampus decreased in CLP-subjected animals receiving RAGE*ab*. IL-1β and IL-6 levels were also reduced by RAGE*ab*, as well as Iba-1 and GFAP content. RAGE*ab* also inhibited the increase in the content of hippocampal Aβ and tau phosphorylation. Finally, RAGE*ab* reversed sepsis-induced cognitive impairment.

Conclusion: These results suggest a prominent role of RAGE in biochemical and behavioral changes that might be associated to the onset of neurodegeneration and cognitive dysfunction following sepsis recovery.