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The additive effect of aging on sepsis-induced cognitive impairment and neuroinflammation

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ABSTRACT

Systemic inflammation is emerging as a significant driver of cognitive decline in the aged and vulnerable brain. In sepsis survivors animals low-grade brain inflammation occurs, suggesting that sepsis is able to induce in microglia a primed-like state. The purpose of this study is to analyze the role of sepsis-induced brain inflammation in the progression of the physiological process of brain aging. *Wistar* rats 2 month-old were subjected to sepsis and 60 and 90 days after were submitted to the new object recognition test and brain was removed to the determination of cytokines, myeloperoxidase (MPO) activity, amyloid-beta peptide (*A*β) and immunohistochemistry markers of microglial activation. In the hippocampus, from 60 to 90 days there was an increase in TNF-α and IL-1β levels in septic animals. This also occurred to the levels of IL-1β and IL-6 in the prefrontal cortex. This was associated with persistent increased in microglial activation and *A*β levels. In conclusion, neuroinflammation is persistent after sepsis and this could burst the usual inflammation that occurs during brain aging.

1. Introduction

Brain is commonly affected during sepsis. In animal models, acute brain inflammation and oxidative damage occur (Bozza et al., 2013) and survivors present long-term cognitive impairment (Barichello et al., 2005). It has also been shown that acute systemic inflammation is associated with an increase in the levels of amyloid-beta peptide (*A*β) in the central nervous system (CNS) leading to long-term cognitive deficits in sepsis survivors (Schwalm et al., 2014). In Alzheimer disease (AD), *A*β accumulates in the extracellular environment and forms amyloid plaques, which cause neuronal death (Haapasalo et al., 2010). *A*β is also able to trigger the activation of the receptor for advanced glycation endproducts (RAGE), a major event in the progression of neurodegeneration (Tan et al., 2009). Additionally, in the early stages of AD, brain microglia become activated by *A*β (Yu and Ye, 2015).

Schwalm et al., 2014 had already demonstrated an increase in *A*β in the hippocampus and prefrontal cortex late after sepsis. In this context, systemic inflammation is emerging as a significant driver of cognitive decline in the aged and vulnerable brain (Cunningham and Hennessy, 2015). Several different inflammatory comorbidities contribute to cognitive decline and increase the risk of AD (Cunningham and Hennessy, 2015). A growing body of clinical and preclinical evidence demonstrates that various peripheral inflammatory insults can exacerbate CNS inflammation (Cunningham et al., 2009; Pandharipande et al., 2013; Widmann and Heneka, 2014). Aging is a biological process that is characterized by a progressive deterioration in physiological functions and metabolic processes. These alterations are characterized by a gradual loss of cognitive performance and memory (Bishop et al., 2010), and this could be associated with low-grade persistent inflammation (Villeda et al., 2011).

Chronic comorbidities, aging and acute systemic inflammatory episodes can contribute to the progression of dementia, and in this context microglia seems to play a major role. Several experimental evidences demonstrate that different pre-morbid brain states make the

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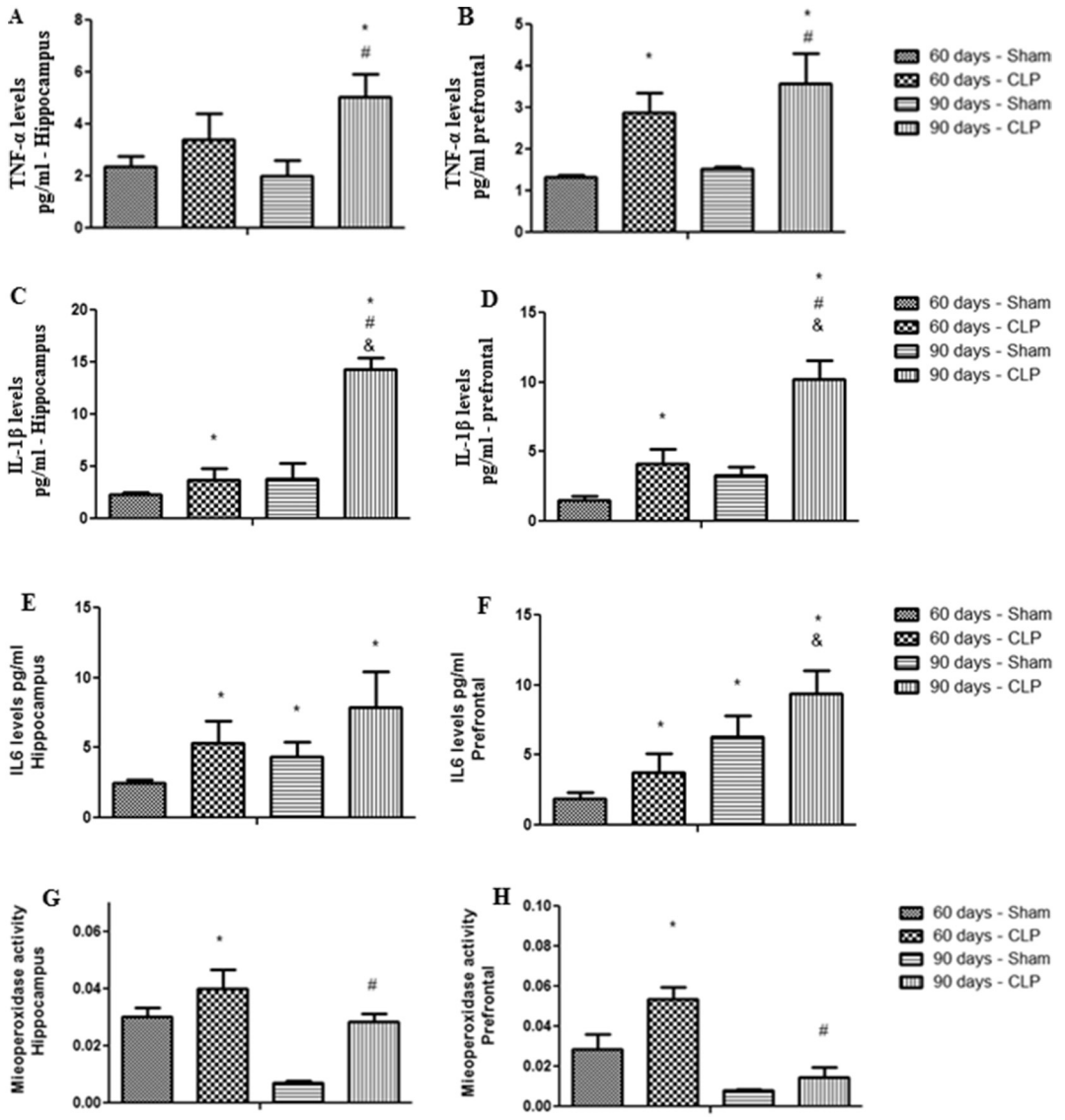

Fig. 1. Inflammatory parameters in the hippocampus and prefrontal cortex late after sepsis induction. Animals were submitted to CLP or sham-operated and 60 or 90 days after surgery animals were euthanized and the hippocampus and prefrontal cortex were removed to the determination of: A) TNF-α – Hippocampus; B) TNF-α – prefrontal; C) IL-1β – Hippocampus; D) IL-1β– prefrontal; E) IL-6 – Hippocampus F) IL-6 – prefrontal; G) myeloperoxidase levels – Hippocampus and H) myeloperoxidase levels - prefrontal. Data were expressed as mean ± SD. n = 8 each group. $p < 0.05$ denoted statistically difference between groups. *Different from sham 60 days; #Different from sham 90 days, & different from CLP 60 days.

brain more susceptible to an acute systemic inflammatory challenge (Cunningham et al., 2005, 2009; Cunningham and Hennessy, 2015). This susceptibility is associated with the induction of a primed microglia state that can be over activated inducing long-lasting and more severe brain inflammation and dysfunction (Cunningham et al., 2005, 2009; Cunningham and Hennessy, 2015). We had previously demonstrated that cognitive deficits occur in young (60-days old) rats survivors, these deficits peaked 30 days after sepsis induction and progressively improved from 30 to 60 days (Tuon et al., 2008). Despite of this improvement low-grade brain inflammation persists (Steckert et al., 2013) suggesting that sepsis is able to induce in microglia a primed-like state. Thus, it is hypothesized that sepsis could induce sustained brain alterations that would exacerbate the effects of aging on brain function.

Thus the purpose of this study is to analyze the role of sepsis-induced brain inflammation in the progression of the physiological process of brain aging.

2. Methods

2.1. Ethics

The experimental procedures involving animals were performed in accordance with the National Institutes of Health (Bethesda, MD, USA) Guide for Care and Use of Laboratory Animals and with the approval of our institutional ethics committee (protocol number: 041-2016/1).

2.2. Sepsis induction – cecal ligation and perforation (CLP) model

Wistar rats 2 month-old were subjected to CLP as previously described (Fink and Heard, 1990). Briefly, animals were anesthetized using a mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg) given intraperitoneally. Under aseptic conditions, a 3 cm midline laparotomy was performed to expose the cecum and adjoining intestine. The cecum was ligated with a 3.0 silk suture at its base, below the ileocecal valve, and was perforated once with a 14-gauge needle. The cecum was then squeezed gently to extrude a small amount of feces through the perforation site. The cecum was then returned to the peritoneal cavity, and