Sub-chronic celecoxib treatment prevents sAβ-induced neuroinflammation: underlying cognitive and behavioral dysfunctions

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Several findings have proposed a link between experiences of depression and the consequent progress of dementia later in life, suggesting a link on neuroanatomical resemblances (Kessing & Andersen, 2004). Studies which employed DSM-IV criteria for the diagnosis of major depressive disorder found elevations in plasma Aß levels in non-demented elderly (Pomara et al. 2006), in young and elderly depressives (Kita et al. 2009). Interestingly, a new orientation of the amyloid cascade hypothesis has evidenced that the presence of soluble rather than the aggregated forms of Aß may explain the early memory deficits and psychiatric symptoms revealed (Rowan et al. 2005). However, findings regarding the cellular and molecular mechanism underlying the link among soluble Aß (sAß) and these disorders are unclear. The process of neuroinflammation has been shown to be a key factor in depression as well as in cognitive impairments. One enzyme that plays a crucial role in this process is the cyclooxygenase-2 (COX-2) enzyme, which is rapidly induced upon inflammatory stimulation in astro-glial cells and has been shown to enhance Aβ neurotoxicity and oligomerization (Hüll et al. 2006; Nagano et al. 2004). The first aim of this study was to investigate mechanisms through which the soluble form of Aβ affects neuroinflammatory pathways implicated in the pathophysiology of neurodegenerative diseases and depression. Given the implications of cytokines and COX-2 in memory consolidation and depression, the second aim of this study was to investigate if the selective COX-2 inhibitor, celecoxib, is able to reverse the sAβ-mediated effects. Thus, in the present study, Wistar male rats were treated with an intracerebroventricular (icv) injection of sAβ and biochemical, behavioral and neurochemical parameters were evaluated 7 days after injection. In particular, bio- and neuro-chemical experiments were used to examine the effects of sAβ on astro-glial markers, content of monoamines and COX-2 expression in the hippocampus (HIPP). Novel object recognition and the forced swimming tests were used to evaluate possible cognitive and behavioral dysfunctions. Our results demonstrate that icv injection of sAβ significantly increases COX-2 protein expression in the HIPP of treated-rats compared to controls. The occurrence of an immune response was further confirmed by microglial and astrocytic activation. Interestingly, hippocampal protein expression, the number of both total and hypertrophic microglia cells, as well as reactive astrocytes were up-regulated in sAβ-treated rats. Moreover, sAβ-treated rats show a depressive-like profile and cognitive deficits, as confirmed by an increased time of immobility and a significant reduction in the discrimination index, respectively. As expected from the behavioural analysis, we found a decrease of serotonin and an increase of noradrenaline levels in the HIPP of treated rats compared to controls. Systemic administration of celecoxib prevents the behavioral dysfunctions, as well as the bio- and neuro-chemical alterations observed between experimental groups. In conclusion, our results might open new insights into novel biomarkers of the inflammatory cascades and potentially provide innovative therapeutic approach to counterbalance sAβ-induced effects.

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