

FERULIC ACID AFFECTS MEMORY CONSOLIDATION IN RATS EXPOSED TO EMOTIONALLY AROUSING EXPERIENCES: EVIDENCE FOR THE INVOLVEMENT OF HEME OXYGENASE SYSTEM

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Emergent studies from nutritional neuroscience has been focused on the neuroprotective role of bioactive nutraceuticals that display an astonishing capacity to attenuate or mitigate various oxidative and proinflammatory processes involved in the pathogenesis of neurological diseases. The potential therapeutic value of phenolic compounds, and in particular of the ferulic acid (FA), has been the object of study in a large number of preclinical studies that suggested the possible role of FA in ameliorating learning and memory processes and reducing depressive-like behaviours (Kim et al. 2007, Zeni et al. 2012, Chen et al. 2015). However, these pieces of evidence were obtained either in laboratory animals exposed to neurotoxins and redox disruptors, or in Alzheimer disease-transgenic models (Hamaguchi et al. 2009, Catino et al. 2016, Mori et al. 2013). The first aim of our study was to examine the role of FA in the regulation of complex brain functions independently of brain damage due to an increased production of free radicals. To address this issue, we investigated whether FA, administered intraperitoneally (i.p) in order to minimize the hepatic first-pass effect, could affect locomotor, exploratory or cognitive skills in intact male Wistar rats exposed to low and high levels of emotional arousal induced by training experience to the experimental apparatus. Our data showed that rats exposed to high levels of emotional arousal spent more time exploring the experimental apparatus during training, as displayed by the higher locomotion, rearing and wall-rearing frequencies compared to rats exposed to low levels of emotional arousal. The administration of FA (150 mg/kg i.p) or vehicle did not affect any of the abovementioned parameters, independently from the experimental condition. Moreover, results obtained during the training trail of the novel object recognition test demonstrated that the total exploration time for the objects was significantly lower in rats that were not previously exposed to the experimental context. Interestingly, the administration of FA (150 mg/kg i.p) immediately after training and tested 24-h later, increased the discrimination index only in the experimental group exposed to high levels of emotional arousal, while no preference for the novel object were revealed in vehicle-treated animal of both experimental conditions. From a mechanistic point of view, we aimed to investigate whether the FA-induced behavioural outcomes could be mediated by the heme oxygenase/biliverdin reductase (HO/BVR) system, which plays a crucial role in the adaptive response to stress. Our data revealed a higher expression of HO-1 in the hippocampus and frontal cortex of FA-treated rats exposed to high levels of emotional arousal only, whereas no significant effect was evidenced in the BVR expression among experimental groups and conditions. Pre-treatment with Sn-protoporphyrin-IX (0.25 μ mol/kg, intracerebroventricular route, 4h before training), a well known inhibitor of HO activity, counteracted the FA-induced improvement of object recognition performance, without affecting locomotor and exploratory behaviour, only in animals not previously exposed to experimental context. Taken together, our data suggest that the neuropharmacological effects of FA under conditions of high emotional arousal involve the activation of the HO system.

Kim et al. (2007) Biosci Biotechnol Biochem 71,1063-8

Zeni et al. (2012). Eur J Pharmacol 679,68-74

Chen et al. (2015). Metab Brain Dis 30,129-36

Hamaguchi et al. (2009). Am J Pathol 175,2557-65

Catino et al. (2016). Front Pharmacol 6,305

Mori et al. (2013) PLoS One 8,e55774