A preclinical study on the nootropic effects of ferulic acid through the heme oxygenase/carbon monoxide system

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Ferulic acid (FA) is a cinnamic-acid derivative abundant in some fruits and vegetables, as well as in plants of traditional Chinese medicine. Over the last years, several lines of evidence have unravelled the antioxidant and cytoprotective effects of FA due to both its free radical scavenging activity and ability to enhance the cell stress response. In light of this, FA supplementation has been proposed as a prophylactic treatment to prevent dementia. Heme oxygenase (HO) is a major player in the adaptive stress response and exists in two main isoforms, named HO-1 and HO-2, the former inducible under pro-oxidant conditions and the latter constitutively involved in the physiological turnover of heme. In the rat, HO-1 has been detected in few brain areas, such as hippocampus, hypothalamus and cortex, whereas HO-2 has been found in neurons populating cortex, hippocampus, hypothalamus, midbrain, basal ganglia, thalamus, cerebellum, and brainstem. Despite this differential distribution, both HO isoforms catalyze the transformation of heme into biliverdin (BV), ferrous iron and carbon monoxide (CO), this latter being a gaseous neuromodulator involved in the regulation of important brain functions, such as synaptic plasticity and neuropeptide release. Although several studies in literature have shown the neuroprotective effects of both FA and its congeners in preclinical models of Alzheimer's disease, characterized by the overproduction of free radicals, only scarce evidence is available supporting the possibility that FA regulates brain functions in laboratory animals exposed to psychological stress, whose main characteristic is the activation of the hypothalamus-pituitary-adrenal (HPA) axis. On these premises, this study was designed with the purpose to evaluate the possibility that FA (150 mg/kg), administered by intraperitoneal route to reduce the pre-systemic metabolism, might improve cognitive skills in male Wistar rats exposed to psychological stress, such as the novelty-induced emotional arousal, through the modulation of the HO system. Animals were randomly assigned to two experimental groups, namely not habituated or habituated to the experimental context, and the novel object recognition test was used to evaluate their cognitive performance. The lack of habituation to the arena has been shown to generate a stressful situation in the rat as demonstrated by the activation of the HPA axis. The administration of FA significantly increased long-term retention memory in not habituated rats. Ferulic acid increased the expression of HO-1 in the hippocampus and frontal cortex of not habituated rats only, whereas HO-2 resulted differently modulated in these cognitive brain areas. Ferulic acid activated the stress axis in not habituated rats as shown by the increase in hypothalamic corticotrophin-releasing hormone levels. Pre-treatment with the inhibitor of HO activity Sn-protoporphyrin-IX [0.25 µmol/kg, intracerebroventricular route (i.c.v.)], abolished the FA-induced improvement of cognitive performance only in not habituated rats, suggesting a role for HO-derived by-products. The CO-donor tricarbonyldichlororuthenium (30 nmol/kg i.c.v.) mimicked the FA-related improvement of cognitive skills only in not habituated rats, whereas BV did not have any effect in any group. In

conclusion, these results propose FA as a novel therapeutic agent to counteract stress-induced memory weakening in healthy subjects.