AN EXTRACT OF HYPERICUM PERFORATUM L. COUNTERACTS HISTONE MODIFICATIONS ELICITED BY PROLONGED COCAINE ADMINISTRATION IN MOUSE HIPPOCAMPUS AND PREFRONTAL CORTEX

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Hypericum perforatum, also known as St. John's wort, is a member of the family Hypericaceae and a herbaceous perennial plant native Europe, western Asia, and northern Africa. Nowadays it has a worldwide distribution. Hypericum species contain biologically active secondary metabolites belonging to at least ten different classes, with prevalence of naphthodianthrones (hypericin and pseudohypericin), phloroglucinols (hyperforin), flavonoids (rutin, hyperoside, isoquercitrin, quercitrin, quercetin, amentoflavone) and phenylpropanoids (chlorogenic acid).

Hypericum perforatum has been used as a medicinal plant for centuries, for the treatment of several disorders. The most investigated pharmacological effects have been the antidepressant properties. In vitro studies suggest that an antidepressant activity may be due to hypericin, through the inhibition of the monoamine oxidase (MAO) enzyme. Further studies show that hyperforin is capable of inhibiting the reuptake of serotonin, dopamine, noradrenaline, GABA, and L-glutamate. It is also well established the increased neurotransmission of monoamines, including 5-hydroxytryptamine (5-HT), noradrenaline, dopamine, gamma amino butyric acid and L-glutamate. Furthermore, it is also known that 5-HT plays a significant role in the mechanisms of analgesia and opioid dependence. Previous findings reinforce the use of herbal medications to prevent drug addiction: H. perforatum extract has been reported to attenuate heroin and morphine withdrawal syndromes, respectively.

Epigenetic processes that regulate histone acetylation play an essential role in behavioral and molecular responses to drugs of abuse. In drug addiction, for instance, repeated cocaine administration elevates global histone acetylation levels in reward-related brain regions, such as the nucleus accumbens (NAc). Furthermore, manipulations of histone acetyltransferases (HATs) and histone deacetylases (HDACs) by pharmacological inhibitors of these enzymes, viral mediated gene transfer, and/or knock-out models, have confirmed that histone acetylation is critically involved in behavioral responses to prolonged administration of cocaine.

The aim of this study was to provide molecular basis of the use of a dried Hypericum perforatum extract (containing 0,3% of hypericin) that proved to be able to reduce anxiety, alteration in social behavior associated with withdrawal manifestations and cocaine reinforcement effects on reward pathways. 49 male OF1 mice (35-40 g) were treated with incremental doses of cocaine: 5 mg/kg (2 days), 15 mg/kg (3 days) and 25 mg/kg (5 days), to induce drug dependence. Three different doses of Hypericum perforatum were included in the experimental design, considered as dried extract (mg/kg body weight): each dose was co-administered with cocaine, and in addition, the maximal dose of 300 mg/kg was administered once as acute exposure, after the induction of cocaine dependence. Firstly, we evaluated histone acetylation levels in prefrontal cortex, striatum and

hippocampus. We observed by Western Blot analysis a global increase in H3 acetylation levels in hippocampus and prefrontal cortex. Hypericum perforatum treatment was able to prevent this increase in a statistically-dependent manner, in both cerebral areas.

Results of this study show that an Hypericum perforatum extract can be effective in decreasing signs of cocaine dependence and counteracting epigenetic effects elicited by this drug of abuse in discrete brain areas.