ANTIHYPERALGESIC EFFECT OF A CANNABIS SATIVA EXTRACT IN A RAT MODEL OF NEUROPATHIC PAIN: MECHANISMS INVOLVED

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In recent years, some reports suggested that plant extracts consisting in combinations of cannabinoids and other minor components may provide benefits that surpass treatment with single ones and may be potentially useful in the treatment of many diseases, such as neuropathic pain, a debilitating chronic pain refractory to actual drugs. In the present study, the antinociceptive properties of a *Cannabis sativa* extract (H-CBD) containing cannabidiol (CBD) in large quantity, Δ^9tetrahydrocannabinol (THC), other minor cannabinoids and natural substances, was tested in a rat model of chronic constriction injury of sciatic nerve (CCI) and was compared with treatment with single compounds. Rats were orally treated daily for a week, starting from the 7th day following the injury. A group of animal was treated with H-CBD, a second and a third group with CBD or THC alone at the corresponding mixture dose (10mg/kg and 0.42mg/kg, respectively). Data showed that THC chronic treatment did not reduce thermal hyperalgesia (assessed by Plantar test, Ugo Basile, Varese, Italy), while CBD treatment partially relieved it. The treatment with H-CBD extract evoked a total relief of thermal hyperalgesia, suggesting an improving of the effects of single cannabinoids. In order to investigate whether this synergism could occur during pharmacodynamic phase, different antagonists were tested to study the involvement of cannabinoid and/or vanilloid receptors. Alterations in pharmacokinetic phase could be also responsible for H-CBD synergic effect observed. Hepatic cytochrome P450-mediated metabolism and intestinal P-glycoprotein-mediated transport, which cannabinoids are able to modulate and whose are substrates, were studied in CCI rats chronically treated with H-CBD extract and CBD alone, to evaluate whether they contribute to an increased bioavailability of CBD and/or other compounds contained in the plant extract tested. Data showed a marked decrease of total hepatic cytochrome P450 and an inhibition of P-glycoprotein activity. All together these findings suggest that natural extracts could represent a new pharmacological tool for the treatment of neuropathic pain. Natural extract contain substances such as terpenes and flavonoids that might increase cannabinoid bioavailability, probably by cytochrome P450-mediated metabolism inhibition. Moreover, both terpenes and flavonoids possess antioxidant and antinflammatory properties which could significantly contribute to the therapeutical effects.