Effects of cannabinoid compounds on memory consolidation in rats

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Cannabis sativa is the most widely used illicit and recreational drugs in Western countries. The psychoactive constituents of the drug, such as Δ^9- tetrahydrocannabinol (Δ^9-THC), regulate a multitude of brain functions including learning and memory processes. Although cannabinoids have been shown to have a wide range of potential therapeutic effects (e. g. antiemetic actions, analgesia, anxiolysis, appetite regulation), the psychomimetic side effects, as well as the potential for abuse and dependence, have restricted their clinical use and development.

Our recent studies showed that the endocannabinoid system is crucially involved in the control of emotional states and memory processes (1, 2, 3). However, contrasting findings have been reported regarding the effects induced by pharmacological manipulation of the endocannabinoid signaling on cognitive function and emotional behaviors. Pamplona et al reported that systemic administration of the non-selective CB receptor agonist WIN 55,212-22 facilitated the extinction contextual fear memory. On the other hand, Chhatwal et al found that systemic administration of the same compound did not affect extinction process (4, 5). Fernandez-Espejo and Galan-Rodriguez showed that administration of the indirect CB1 agonist AM404 disrupted Prepulse Inhibition (PPI) and enhanced the startle response while Bortolato et al reported a lacking effects for the same drug on PPI and startle reflex (6, 2). Moreover, intra-BLA infusion of WIN55,212-22, a non selective cannabinoid receptor agonist, has been shown to induce an enhancing effect on memory consolidation in the inhibitory avoidance task or totally lack any effect in rats trained in the same behavioral test (1, 7). Several confounding variables could be responsible of the opposite data reported in literature, among them the time of administration (after or before the training) seems to be of crucial importance. Following a pre-training administration cannabinoid drugs could strongly alter pain perception and locomotor activity at the time of training, thus adding important potential confounds that occur when a drug or other treatment is given before the training. In order to reduce the impact of such confounding variables we trained rats in an inhibitory avoidance apparatus and administered immediately post-training with several cannabinoid receptor (CB) agonists or antagonists in order to fully characterize in the same project and under the same experimental conditions, the effects induced by systemic administration of these drugs on memory consolidation. In particular, male adult Sprague Dawley rats (350-450 g at the time of testing) were trained in an inhibitory avoidance task in which they received an inescapable mild footshock (aversive event, 1 sec, 0.35 mA) upon entering the dark compartment of the apparatus. On the retention test, 48 h later in drug-free conditions, the latency to enter the dark compartment was recorded and taken as a measure of memory retention (longer latencies were interpreted as indicating better retention). To better clarify the involvement of diverse receptors in mediating the action of cannabinoid coumpounds, we evaluated whether the observed effects could be due to activation of cannabinoid receptors as well as Peroxisome proliferator-activated receptors (PPARα) and the transient receptor potential vanilloid receptors (TRPV1) by co-administration of the cannabinoid drug together with non-impairing doses of CB, PPARα or TRPV1 receptor antagonists.

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