Research report

Influence of pre-exposure to morphine on cannabinoid-induced impairment of spatial memory in male rats

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**HIGHLIGHTS**

- Pre-training intra-CA1 injection of WIN55,212-2 decreased spatial memory acquisition.
- Amnesia induced by pre-training intra-CA1 of WIN55,212-2 was reversed in morphine-pretreated rats.
- Inhibition of amnesia in morphine-pretreated rats was suppressed by naloxone.

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**ABSTRACT**

In the present study, we investigated the effects of repeated morphine pre-treatment on impairment of spatial memory acquisition induced by intra dorsal hippocampus (intra-CA1) administration of the non-selective cannabinoid CB1/CB2 receptor agonist, WIN55,212-2 in adult male rats. 2-day version of Morris water maze task has been used for the assessment of spatial memory. On the training day, rats were trained by a single training session of eight trials and 24 h later a probe trial test consist of 60 s free swim period without a platform and the visible test was administered. Animals received pre-treatment subcutaneous (s.c.) injections of morphine, once daily for three days followed by five days drug-free treatment before training trials. The results indicated that bilateral pre-training intra-CA1 infusions of WIN55,212-2 (0.25 and 0.5 \( \mu \)g/rat) impaired acquisition of spatial memory on the training and test day. The amnesic effect of WIN55,212-2 (0.5 \( \mu \)g/rat) was prevented in rats previously injected with morphine (20 mg/kg/day \( \times \) 3 days, s.c.). Improvement in spatial memory acquisition in morphine-pretreated rats was inhibited by once daily administration of naloxone (1 and 2 mg/kg, s.c.) 15 min prior to injection of morphine for three days.

The results suggest that sub-chronic morphine treatment may produced sensitization to cannabinoids, which in turn reversed the impairment of spatial memory acquisition induced by WIN55,212-2 and mu-opioid receptors may play an important role in this effect.

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1. Introduction

Drug addiction is a chronic relapsing brain disorder, characterized by neurobiological changes leading to compulsive drug seeking and drug taking behaviors despite serious negative consequences [9]. Several groups of compounds that produce different pharmacological effects can lead to addictive behavior, including cannabinoids, opioids, psychostimulants, alcohol and nicotine [30]. The endocannabinoid system is an important neuromodulatory system involved in many of physiological functions [18,50]. This system consists of cannabinoid receptors, endogenous ligands and several proteins responsible for their synthesis and degradation [29]. Mammalian tissues contain at least two types of cannabinoid receptors, CB1 and CB2, both of which have been cloned [24]. CB1 receptors are conspicuously expressed in the perihellar and central nervous systems, particularly in the hippocampal...