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Cannabinoids Prevent Cocaine-induced Psychomotor Stimulation through CB_1 Cannabinoid Receptor

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INTRODUCTION

Cannabinoid agonists and endocannabinoid modulators have been shown to have complex effects on psychomotor function. Many recent studies have reported that CB_1 cannabinoid agonists have an excitatory action in low doses and an inhibitory action, together with serious motor dysfunction, in higher doses on locomotor activity. Furthermore, Δ^9-tetrahydrocannabinol, the main psychoactive component of cannabis, seems to have a triphasic effect, decreasing the locomotor activity or stimulating movements and causing catalepsy, depending on the dose administered. This profile differs from the one already described on the locomotor actions of other drugs of abuse, such as cocaine, amphetamine and morphine.

METHODS

In the present study, we examined the effects of the direct CB_1R/CB_2R agonist WIN 55,212-2 and the indirect cannabinoid agonist/endocannabinoid (EC) neurotransmission modulator AM-404 on spontaneous motor activity and hyperlocomotion caused by cocaine. Rats were injected ip with WIN 55,212-2 (0.3, 1 and 3mg/kg) or AM-404 (3, 10 and 30 mg/kg). We also examined whether WIN 55,212-2 (1 mg/kg) or AM-404 (10, 30 mg/kg) affected the hyperlocomotive action of cocaine (5, 10 mg/kg), and whether the CB_1R antagonist SR141716A (0.02 mg/kg) could block the tentative effects of WIN 55,212-2 and AM-404 on motor activity and on cocaine-induced hyperlocomotion.

RESULTS

WIN 55,212-2 decreased spontaneous locomotor activity at the two highest doses tested, while AM-404 had no effect on motor function *per se*. Cocaine caused a significant, dose-dependent increase in locomotor activity. WIN 55,212-2 reduced hyperlocomotion caused by both doses of cocaine (5 and 10 mg/kg), while AM-404 (10 mg/kg) blocked the 5mg/kg dose and AM-404 (30 mg/kg) the 10mg dose of cocaine. SR141716A blocked the effects of WIN 55,212-2 and AM-404 on motor activity and on the hyperlocomotion induced by cocaine, while it had no effect on motor function *per se*.

DISCUSSION

The present results indicate that cannabinoid agonists and EC neurotransmission modulators either decrease or have no effect on locomotor activity. Importantly, these compounds counteract the hyperlocomotor actions of cocaine at doses that either decrease spontaneous locomotion or have no effect by themselves. These effects are probably mediated via CB_1 receptor stimulation. Our data suggest that compounds that affect EC neurotransmission may play an important role in the treatment of pathological states associated with psychomotor overexcitability.

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