REVIEW OF CLINICAL PHARMACOLOGY AND
PHARMACOKINETICS INTERNATIONAL
EDITION 24: 110-111 (2010)

Antagonism of Cannabinoid CB1 Receptors Modulates the Effects of Amphetamine on Locomotor Activity and Dopamine and Glutamate in the Nucleus Accumbens *in vivo*

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Key words: Dopamine, glutamate, amphetamine, cannabinoids, motor activity

S u m m a r y. The endocannabinoid system (ECS) modulates many neurotransmitter systems and is implicated in reward, addiction and the effects of psychostimulants. The psychostimulant d-amphetamine (d-amp) is well known to modulate locomotor activity as well as dopamine and glutamate function; however, it is yet unclear how the ECS is able to intervene in these effects of d-amp. Thus, the aim of the present study was to investigate the effects of CB1 antagonism on d-amp-induced behavioural and neurochemical effects. Sprague- Dawley rats were either observed for locomotor activity after administration of vehicle, d-amp, SR or SR and d-amp or underwent surgery for probe implantation and administered the same treatments in microdialysis experiments measuring dopamine and glutamate in the nucleus accumbens. Our results showed that d-amp on its own induced hyperlocomotion and increased dopamine and glutamate. When coadministered with SR, these effects on locomotor activity and neurotransmitter levels were modulated. This study provides further evidence for the role of the ECS in d-amp- induced behavioural and neurochemical effects in vivo, and furthermore, emphasizes the importance of this modulatory neurotransmitter system in psychostimulant addiction.

INTRODUCTION

The ECS modulates many neurotransmitter systems and thus it is implicated in many physiological processes including reward and cognition. This interaction can also be extended to pathological states such as drug dependence and addiction. Interestingly, the ECS has been implicated in psychostimulant addiction and has even been considered a potential target for treatment, however, at present, this phenomenon is not completely understood. The effects of drugs of abuse such as cannabinoids and the psychostimulant d-amp on the brain and on behaviour are not only mediated by the mesolimbic dopaminergic system but also by the excitatory glutamatergic neurotransmitter system. Amphetamine, an indirect dopamine agonist, is universally known to modulate locomotor activity and extracellular dopamine and glutamate. Evidence demonstrates that cannabinoids also modify locomotor activity as well as the neurotransmitters dopamine and glutamate, mainly via their action on the CB1 receptor in the brain. In the present study, we chose to investigate the effects of SR, a CB_1 receptor antagonist, coadministered with the psychostimulant, d-amp on locomotor activity, in vivo extracellular dopamine levels and glutamate levels in the nucleus acccumbens, the epicentre of reward.

METHODS

Male Sprague-Dawley rats were divided into two groups; the first group was intraperitoneally (i.p.) administered one of four treatments and locomotor activity was measured. The second group of rats underwent surgery and a microdialysis probe was implanted in the nucleus accumbens. Sample collection began 24 h later. Once baseline samples were collected, the rats were injected i.p. with one of four treatments and sample collection resumed. All samples were then measured for dopamine and glutamate using High Performance Liquid Chromatography with electrochemical detection. The four treatment groups were as follows: vehicle, d-amp, SR or SR + d-amp.

RESULTS

Our results show that d-amp- administered rats exhibited increased motor activity and this effect was modulated by coadministration with SR. Likewise, increased extracellular dopamine and glutamate observed after d-amp administration in the nucleus accumbens, were also modified by SR.

DISCUSSION

This study addresses the effects of the CB1 antagonist, SR, on the universally known stimulatory effects of d-amp on locomotor activity as well as dopamine and glutamate release in the nucleus accumbens. Our results show that SR was indeed able to modulate both locomotor activity and neurotransmitter release induced by d-amp, thus providing us with further evidence for a role of the ECS in the effects of d-amp. On a larger scale, these results contribute to the expansively growing literature on the significance of the ECS in reward and addiction.

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