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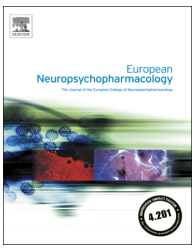

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Cannabinoids reward sensitivity in a neurodevelopmental animal model of schizophrenia: A brain stimulation reward study

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Abstract
The comorbidity schizophrenia and cannabis has a high prevalence. The consumption of cannabis is ten times higher among schizophrenia patients, suggesting that these patients could be differentially sensitive to its motivational effects. To study this question, we investigated the motivational effects of cannabinoid agonists using the brain stimulation reward paradigm and a neurodevelopmental model of schizophrenia: neonatal ventral hippocampus lesions (NVHL). Using the curve-shift paradigm, we first compared the effect single dose (0.75 mg/kg) of amphetamine in sham and NVHL rats on reward and operant responding. Then, in different groups of NVHL and sham rats, we studied the effect of delta-9-tetrahydrocannabinol (THC, 0.5 mg/kg, i.p.) and WIN55,212-2 (WIN, 1 and 3 mg/kg, i.p.) Rats were initially trained to self-administer an electrical stimulation to the posterio-medial mesencephalon. Once responding was stable, reward threshold defined as the frequency required to induce a half maximum response rate was measured before and after injection of the drug or the vehicle. Results show that amphetamine enhanced reward in sham and NVHL rats, an effect that was shorter in duration in NVHL rats. THC produced a weak attenuation of reward in sham rats while WIN produced a dose-dependent attenuation in NVHL; the attenuation effect of WIN was blocked by the cannabinoid antagonist, AM251. WIN also produced an attenuation of performance in sham

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and NVHL rats, and this effect was partially prevented by AM251. These results provide the additional evidence that the motivational effect of cannabinoids is altered in animals with a schizophrenia-like phenotype.

1. Introduction

The prevalence of drug use among schizophrenia patients is more than 50% and for cannabis it is ten time higher than the global population (Koskinen et al., 2009). According to the self-medication hypothesis, these patients consume cannabis to alleviate their symptoms and reduce the unpleasant secondary effects of their medication. This hypothesis, however, has received weak empirical support and it was observed that cannabis aggravates rather than improves their psychotic symptoms (Voruganti et al., 2001). Some recent studies have shown that the endocannabinoid system is dysregulated in schizophrenia (Potvin et al., 2008) (for review (Muller-Vahl and Emrich, 2008)) suggesting that schizophrenia patients may be differentially sensitive to the psychotropic effects of cannabis.

Studies carried out with normal naïve animals have demonstrated that cannabinoids induce either a rewarding or an aversive effect (for review, (Vlachou and Panagis, 2013)), results that are consistent with human studies (Green et al., 2003). Rats can be trained to self-administer intravenously the potent cannabinoid agonist, WIN55, 212-2 (WIN); this operant response is accompanied by an increase in ventral striatal dopamine release, a neurochemical effect that is most often associated with reward (Fattore et al., 2001; Lecca et al., 2006). Consistently, delta9-tetrahydrocannabinol (THC), the major psychoactive component of cannabis, enhances reward induced by brain electrical stimulation (Gardner et al., 1988; Lepore et al., 1996). Other studies, however, have reported that WIN produced a significant attenuation of brain stimulation reward (Vlachou et al., 2003, 2005). It was also reported that THC and WIN induce either a conditioned place-aversion (Chaperon et al., 1998; Cheer et al., 2000; Mallet and Beninger, 1998; Sanudo-Pena et al., 1997) or a conditioned place-preference (Lepore et al., 1995). The lack of consistency between studies is generally attributed to differences in methodology, rat strains, doses and the type of cannabinoid agent used.

In view of this, it can be hypothesized that schizophrenia patients consume cannabis because they are differently sensitive to its rewarding and/or aversive effects. Although the comorbidity schizophrenia and cannabis has been widely investigated in human, only one study has been carried out to investigate the motivational effect of cannabinoids using an animal model of schizophrenia (Gallo et al., 2014). In the present study, we further addressed this issue using the neonatal ventral hippocampus lesion (NVHL) model developed by Lipska et al. (1993). We investigated the valence of the motivational effect of THC and WIN in adult NVHL rats using the brain stimulation reward paradigm. Since it was consistently found that NVHL rats were more sensitive to the hyperlocomotion effect induced by amphetamine, we also compared the reward enhancing effect of amphetamine in sham and NVHL rats. Results show that the reward enhancing effect of amphetamine is shorter in duration in NVHL rats, and that WIN is acting at CB1 receptors to produce a significant attenuation of reward in NVHL but not in sham rats. These results provide additional evidence that rats with a schizophrenia-like phenotype are more sensitive to the aversive effect of CB1 receptor activation.

2. Experimental procedures

2.1. Animals

Female Sprague-Dawley rats (Charles River Canada) were purchased at 15–17 days of gestation and housed individually in breeding cages in temperature and humidity-controlled room with a 12 h light/dark cycle (22 °C, 40%, 6 am/6 pm). They have free access to food and water. Six to 18 pups were obtained per litter. Female pups were culled just before surgery to keep male pups between 15 and 18 g at PD6–7. All experimental procedures were performed in accordance with the Canadian Council on Animal Care Guide.

2.2. Surgery

2.2.1. Neonates

On the 6th or 7th day of age, male pups were anesthetised by isoflurane inhalation (induction 5%, maintenance 1–2%, 1–2 L/min O_2) and placed on a stereotaxic instrument adapted for small animals. The skull was exposed and a burr hole was made at the point of entrance of the injection cannula (0.3 mm o.d.) in each hemisphere. The injection cannula was lowered into the left and right ventral hippocampal formation at the following stereotaxic coordinates: 3.0 mm posterior to bregma, 3.5 mm lateral to the sagittal line and 4.5 mm below the surface of the cranium. It was connected with polyethylene tubing to a 10 μl microsyringe and a volume of 0.3 μl of a solution containing 5 μg/μl of ibotenic acid was injected with a micro-infusion pump over a period of 2 min; the injection cannula was left in place for an additional minute to allow diffusion of the solution into the tissue. The incision was closed with Vetbond (CDMV, Canada) and the pups were allowed to recover on a heating pad; upon awakening they were returned to their mother. For sham rats, identical surgical procedures were applied with the exception that the injection cannula was not inserted into the brain to prevent damage to the brain and to control for stress related to the procedures. Animals were weaned at PD21 and housed 2–3/cage; each group contained at least one sham and one NVHL rat.

2.2.2. Adults

At PD40–46, sham and NVHL rats were anesthetised by isoflurane (2.5–3.5%, 0.6 L/min O_2) and placed on a stereotaxic apparatus. A burr hole was made at the point of insertion of the stimulation electrode and four stainless steel screws were threaded into the skull to wrap a stainless steel wire that served as the inactive electrode. A moveable stimulation electrode (Miliaressis, 1981)