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Research report

Animals with a schizophrenia-like phenotype are differentially sensitive to the motivational effects of cannabinoid agonists in conditioned place preference

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ABSTRACT

Cannabis is the most consumed illicit drug worldwide, but among patients with a diagnosis of schizophrenia, this consumption is higher suggesting that they are differentially sensitive to cannabis. We chose to study this problematic using a neurodevelopmental model of schizophrenia: neonatal ventral hippocampus lesions (NVHL). In a first study, we compared the locomotor response to novelty, a mild stress and two doses of amphetamine (0.75 and 1.5 mg/kg) in sham and NVHL rats at post-natal day 35 (PD35) or 56 (PD56). In a second study, we investigated the valence of the motivational effect of Delta-9-tetrahydrocannabinnol (THC, 0.5 mg/kg, i.p.) and the cannabinoid receptor agonist, WIN55,212-2 (WIN, 1 mg/kg, i.p.), using the conditioned place preference paradigm; we used a biased procedure that comprised 12 days of testing with 3 paired-conditioning. The effects of this dose of WIN were also measured on locomotor activity. Results confirmed that the adult NVHL animals displayed a stronger locomotor response to the two doses of amphetamine, but not to novelty and a mild stress. In adult NVHL, but not sham animals, WIN stimulated locomotor activity and produced a conditioned place aversion. At the dose tested, THC tended to produce an aversion in adult sham but not NVHL animals. Taken together these findings show that adult animals with a schizophrenia-like phenotype are differentially sensitive to the motivational effect of cannabinoids.

1. Introduction

Cannabis and schizophrenia are hardly to be found non-associated today. Indeed, cannabis consumption in schizophrenia patients is ten times higher than in the global population [1]. Moreover, recent studies suggest that the use of cannabis is associated with an earlier diagnosis of schizophrenia in vulnerable patients [2]. Initially, it was believed that cannabis was a kind of self-medication, used to alleviate some of the symptoms of the disease and/or side-effects of the medication [3]. Recent observations, however, suggest that this is unlikely because cannabis worsens rather than reduces psychotic symptoms and side-effects [4]. Since cannabis can induce both aversive and rewarding effects, and that these patients consume more cannabis than the global population, the following question arises: are they differentially sensitive to its rewarding effect and/or its aversive effect?

The literature on the motivational effects of cannabinoids is controversial. Some authors report rewarding effects with Delta-9-tetrahydrocannabinol (THC) and the non-selective cannabinoid receptor agonist, WIN 55,512-2 (WIN). Low doses of THC, for instance, decrease reward threshold for intracranial self-stimulation (ICSS) [5], induce a conditioned place preference (CPP) [6,7] and sustain intracerebroventricular self-administration in rats [7]. Rats can also be trained to self-administered intravenously WIN, and this behavior is associated with an increase in extracellular levels of ventral striatal dopamine, a reward-relevant neural event [8,9]. But others not only failed to find any rewarding effects of cannabinoids but reported aversive effects. Using the ICSS paradigm along with the curve-shift measurement method, Vlachou et al. [10,11,12] reported that systemic injections of WIN or THC produced a dose-dependent attenuation of reward. Several studies also reported a conditioned place aversion (CPA) with systemic injections of either low to high doses of THC [13,6,14,15] or low to medium doses of WIN [16].

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Adding to this complexity are some studies that failed to reveal either a rewarding or an aversive effect of cannabinoids. Fokos and Panagis [17] did not find any changes in ICSS reward threshold after systemic injection of low doses of THC and others did not observe a CPP nor a CPA with low doses of THC [13,12] or WIN [18].

The discrepancy between the results of so many studies suggests that the valence of the motivational effect of cannabinoids is dependent upon several variables such as the animal strain, the dependent variable associated with each behavioral paradigm, conditions such as food or water deprivation [19] and the duration of the wash-out period between each drug injection [6,20].

To better understand the neurobiological bases of cannabis use in schizophrenia, it is essential that studies be carried out with a valid animal model of the disease. There have been several behavioral studies carried out with different animal models of psychosis or schizophrenia (for review, [21]), but none of them has investigated the motivational effects of cannabinoids. In this study, we addressed this later issue using the neurodevelopmental model developed by Lipska and Weinberger [22]. This model consists of lesioning the ventral hippocampus early after birth and testing the animals at different lifetime periods; it has excellent face and predictive validities as several behavioral abnormalities are homologous to those observed in schizophrenia patients and become evident only at the early period of adulthood (for review, [23]). The present study was thus aimed at investigating the valence of the motivational effect of THC and WIN in animals that had neonatal lesions of the ventral hippocampus (NVHL). Studies were carried at two time periods, at post-natal days 28 to 40 (PD28-40, adolescence) and at PD56 to 68 (adulthood).

2. Materials and methods

2.1. Animals

Female Sprague–Dawley rats (Charles River breeding farm, St-Constant, Quebec) were purchased at 15–17 days of gestation. They were housed individually in Plexiglass cages in a room with a constant temperature (20–22 °C) and humidity (40–45%), and a 12-h light:12-h dark cycle (6 am/6 pm). They had free access to food and water. Each dam gave birth to 6–18 pups; female pups were culled just before surgery, at PD6-7 to keep males at a weight between 15 and 18 g at the time of surgery. All experimental procedures were in accordance with the Canadian Council on Animal Care and all efforts were made to minimize the number of animals used.

2.2. Neonatal surgical procedure

The surgical procedure was based on the description by Lipska and Weinberger [22]. 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. An incision was made to the skin overlying the skull 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 into the tissue. After the second injection, 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 animals, 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. Fourteen days after surgery, at PD21, animals were weaned and housed 2–3/cage; each group contained at least one sham and one NVHL animal.

2.3. Experimental procedure

2.3.1. Locomotor activity test

Experiments were performed during the light cycle between 8 am and 5 pm with adolescent and adult rats beginning at PD35 and PD56 respectively. Locomotor activity was measured using an Opto-Varimex Auto Track System (Columbus Instruments, Columbus, OH, USA) that consists of Plexiglass cages (43 cm × 43 cm × 33 cm) equipped with two arrays of 15 infrared photocells located 1.5 and 14.5 cm above the wire-mesh floor to detect horizontal and vertical movements respectively. Computer software quantified ambulatory activity by calculating the distance traveled beyond a virtual box of 9.6 cm × 9.6 cm drawn around the animal; the location of the animal within the box was determined ten times per second. Movements detected within the virtual box were considered as non-ambulatory and were quantified as time (s) during which photocell beam interruptions were detected. Vertical activity was quantified as the total number of photocell beam interruptions produced by rearing [24] (for validation data on these measures of activity).

On the test day, unhabituated animals were weighted and placed into the cage for 30 min to measure their locomotor responses to a novel environment. They were then injected with a 0.9% NaCl solution (1 ml/kg, i.p.) and placed again into the cage for 30 min for monitoring locomotor responses to a mild stress. Following this second test, they were injected with one of two doses of D-amphetamine (0.75 or 1.5 mg/kg, i.p.) and their locomotor responses were measured for 90 min. All these tests were performed in the dark and in the presence of a white noise (70 dB) to mask external noises.

In different groups of sham and NVHL adolescent and adult animals, the effects of the CB1 agonist, WIN, was tested on locomotor activity. On the first day of testing each animal was injected with vehicle or 1 mg/kg (i.p.) of WIN and placed in the activity box for 30 min. Four days later the animals previously injected with WIN received the vehicle and the others WIN and locomotor activity was measured for 30 min.

2.3.2. Conditioned place preference test

The conditioned place preference (CPP) apparatus consisted of a three compartments box: a black compartment (27 cm × 22 cm × 26 cm) with a stainless steel grid rod floor, a white compartment (27 cm × 22 cm × 26 cm) with a stainless steel mesh floor and a central gray compartment (14 cm × 22 cm × 26 cm) with a gray plexiglass floor. The white and black compartments were separated from the center gray compartment with a guillotine door and each compartment was equipped with infrared photo-beams to detect motor activity (Med Associates Inc., VT, USA). Each box was encased into a sound-attenuating ventilated black melamine box.

On the first two days, the animals were placed into the center compartment of the CPP apparatus and were allowed free access to the entire box for 30 min. On day 3, they were placed into the apparatus and the time spent in each compartment was measured for 15 min to establish the baseline preference. The conditioning phase began on the fourth day and consisted in a 3-day cycle: On the first day of a cycle, the animals were injected with the drug or vehicle