THE EFFECTS OF DELTA-9-TETRAHYDROCANNABINOL INJECTIONS TO THE NUCLEUS ACCUMBENS ON THE LOCOMOTOR ACTIVITY OF RATS

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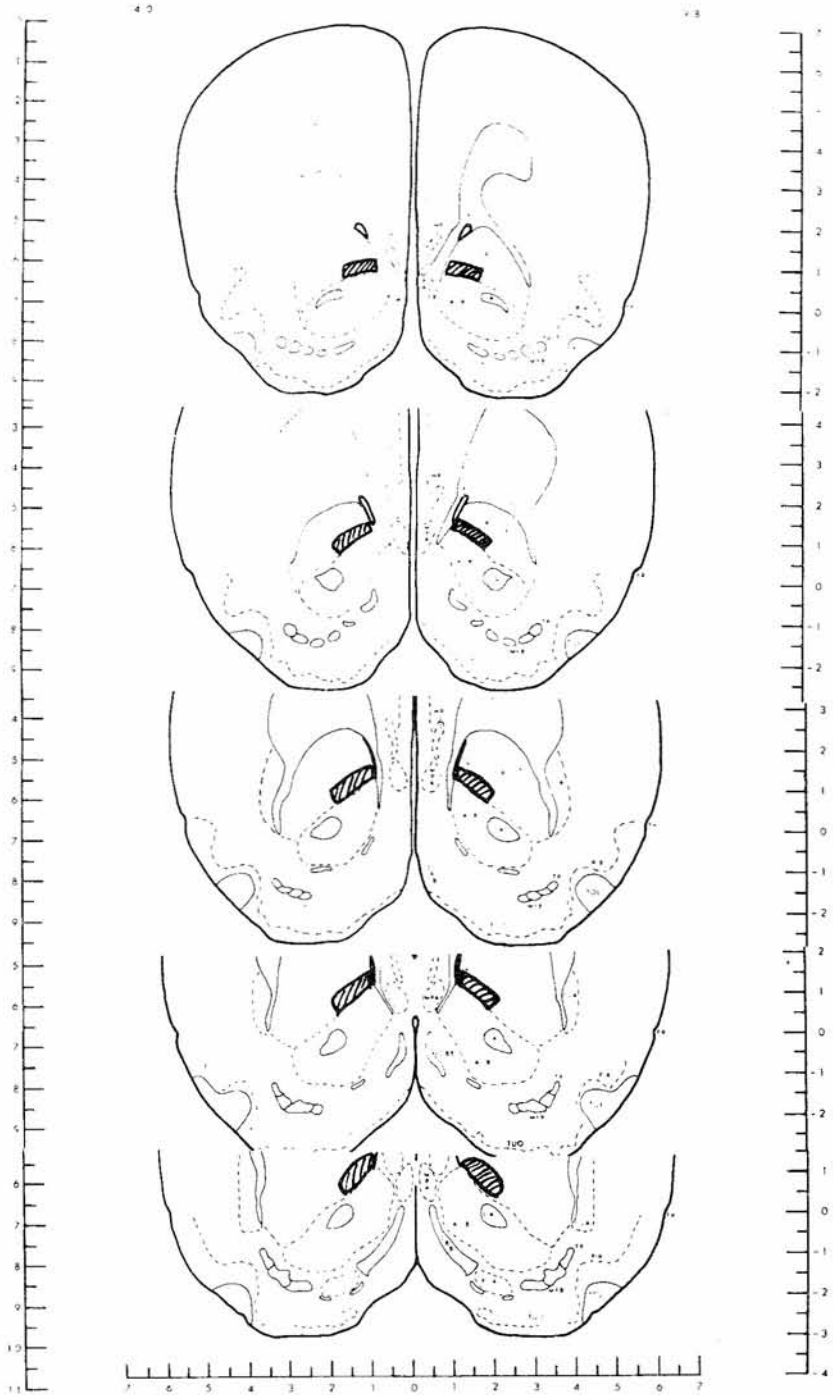
I. INTRODUCTION

The nucleus accumbens (NA) is a forebrain structure innervated by A10 dopaminergic neurons descending the medial forebrain bundle (1,2). Apart from the caudate nucleus, the NA contains the highest concentration of dopamine (DA) in the rat brain (3). The dopaminergic system of the NA has been shown repeatedly to be involved in the mediation of locomotor activity. The direct application of DA to this nucleus produces an increase in such activity (4,5). Furthermore, this effect can be blocked by an i.p. injection of pimozide (a dopamine antagonist) (6). It has also been demonstrated that those drugs which act as dopamine receptor agonists, such as apomorphine, ADTN, and ergometrine, as well as amphetamine, produce an increase in locomotor activity when injected directly to the NA (6).

Within the NA, dopamine and its agonists produce their effects on locomotor activity by inhibiting the dopaminergic neurons in that area. The spontaneous firing rate of single neurons in the NA is decreased by the application of either DA, ADTN or ergometrine to that site (7). This decrease in neural activity causes the release from inhibition of those neurons in the globus pallidus which subserve locomotion (8).

Among the demonstrated behavioral effects of delta-9-tetrahydrocannabinol (THC) are those which it produces on locomotor activity. The systemic administration of low doses of THC has been shown to increase locomotor activity, while



high doses have been demonstrated to decrease spontaneous locomotion (9-12).

The purpose of this study was to investigate whether THC is acting within the NA to produce its excitatory effects on locomotor activity. It can be hypothesized that locomotor stimulation produced by the application of a drug to the NA is mediated by the dopaminergic mechanism within the nucleus.

II. MATERIALS AND METHODS

Male, Long-Evans rats (Charles River Breeding Labs), weighing 250-350 g at the start of the experiment, were maintained on ad lib food and water until 24 hrs prior to surgery when they were deprived of food until post-surgery. The colony was on a 12 hr. light-dark cycle (7 a.m. - 7 p.m.).

Each rat was anesthetized with Sodium Pentobarbital and was administered Atropine Sulfate to maintain clear airways. Twenty-three gauge stainless-steel cannulae were bilaterally implanted to the nucleus accumbens at the stereotaxic coordinates of 3.4A, 1.5L, and 5.8V. Cannulae were kept patent with stainless-steel wire.

Seven to 10 days following surgery, the locomotor activity of each rat was assessed for a ten-minute, baseline period using a cylindrical activity chamber, which was housed in a sound-attenuating box containing a house light and ventilation system. The floor of the chamber was suspended on rubber mounts and vibrations of the floor were transduced by an accelerometer and converted into activity units. The cylinder measured 57 cm in diameter.

Immediately following the baseline period, the animal was taken from the chamber and injected with either one dose of THC (0.1, 0.5, 1.0, 2.0, or 10.0 mg/ml) or with vehicle solution (PVP) in a 1 mcl vol to each NA. Following the injection, each rat was tested in the activity chamber for a 50 min test session. Activity counts over the 50 min session were divided among 5 min bins on counters.

Animals were sacrificed for the purpose of histology. They were perfused with formal saline, and their brains were removed and kept in 10% formalin and saline for 24 hrs prior to being sectioned on a freezing microtone. Sections (50

FIGURE 1. Frontal sections of the rat brain taken from ref. 13. Cross hatched areas indicate areas of acceptable cannula placements, bilaterally. All placements outside these boundaries were rejected from the analysis.

microns) were mounted on microscope slides and stained. They were then read through a microscope in order to verify cannulae placements.

Activity counts during the 50 min test session were converted to a percentage of baseline activity for each rat. Grouppercentages were then submitted to a 2-way analysesof variance (drug dose x time). Appropriate t-tests were conducted following the analysis.

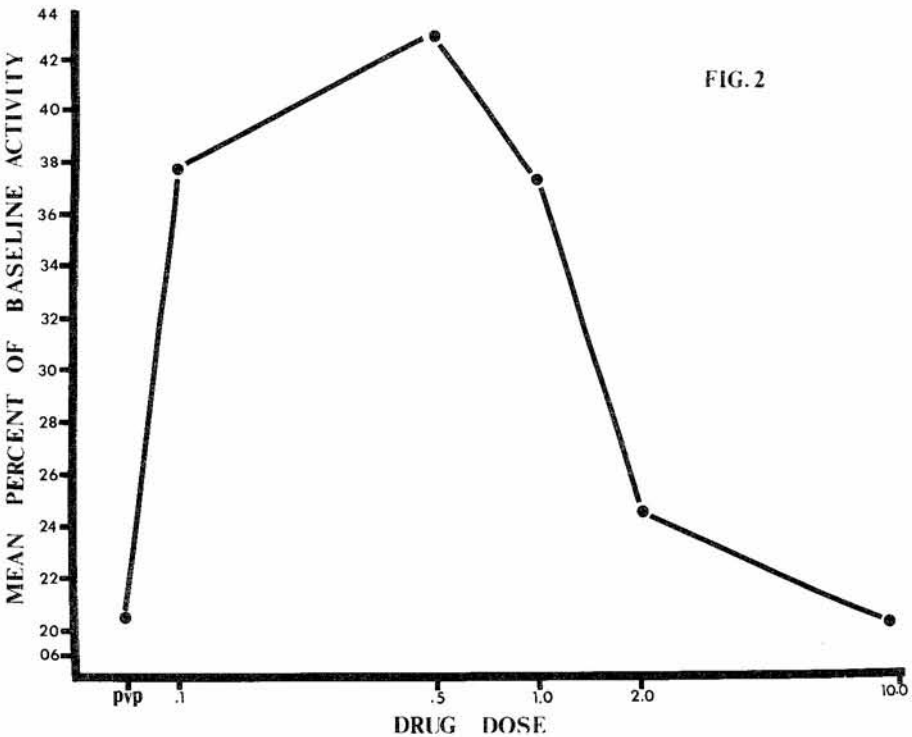


FIGURE 2. Mean percent of baseline activity plotted as a function of THC dose per cannula (two doses per animal). PVP is the vehicle alone. This control value is less than 100 per cent because activity decreases as a function of time.

III. RESULTS

The injection sites which were considered acceptable upon histology are circumscribed in Figurel. Those cannulae placements lying outside of these areas were not considered acceptable and the data from animals having such placements were not used in the analysis.

THC produced a significant increase in locomotor activity above that produced by vehicle injections for the first 20 min post-injection based on a 2-way analysis off variance (drug dose x time), $F(5,36) = 3.34$, $p < 0.02$, (see Figure 2). The results of comparisons between drug doses revealed that the 0.5 mcg group had a significantly elevated locomotor activity score when compared to the vehicle control group, $t(12) = 2.70$, $p < 0.01$, the 2 mcg group, $t(12) = 2.04$, $p < 0.05$, and the 10 mcg group, $t(12) = 2.22$, $p < 0.02$.

IV. DISCUSSION

Low doses of THC, bilaterally administered to the nucleus accumbens of rats, produced an increase in locomotor activity above that displayed by vehicle controls. The peak effect was observed at 20 min post-injection. While statistical analysis revealed that there was a significant difference among the groups at 25 min post-injection, the effect was of a lesser magnitude than that which was observed at 20 min post-injection.

The effect of injections of 10 mcg THC was virtually the same as the effect of the control injections. This suggests that higher doses administered directly to the nucleus accumbens produced a locomotor response similar to that produced by high doses upon systemic administration.

The increase in locomotor activity produced by THC in this study could be indicative of an effect upon dopaminergic mechanisms in the nucleus accumbens. Neurons with dopamine receptor sites in the NA project to the globus pallidus where they release GABA. Jones and Mogenson have shown that stimulation of the nucleus accumbens produces an inhibition of the firing of neurons in the globus pallidus (14). This inhibition is abolished by the application of picrotoxin (a GABAantagonist) to the globus pallidus. Furthermore, these investigators found that the application of GABA to the globus pallidus attenuates the increase in locomotor activity caused by the injection of dopamine to the nucleus accumbens.

Based on the evidence obtained in this study that low doses of THC are acting within the NA to produce an effect

similar to that produced by dopamine agonists, investigations of the effects of THC application to the NA on the firing rate of single units there is warranted.

Those drugs which increase locomotor activity upon injection to the nucleus accumbens decrease the spontaneous firing rate of neurons there. The effect of inhibiting these neurons is to inhibit the transmission of GABA to the globus pallidus. Thus, the neurons in the globus pallidus which mediate locomotor activity are released from the inhibitory effect of GABA there.

Also of interest in the investigation of the site of action via which THC effects locomotor activity is the globus pallidus itself. Should local application of THC to the globus pallidus produce an effect on locomotion, it would seem possible that GABAnergic system there is directly involved in the effect. If however, no effect on locomotion results from the injection of THC to the globus pallidus the possibility that the drug is acting upon the dopaminergic neurons of the NA to produce its effects on locomotor activity would be reinforced.

Finally, further evidence that THC is acting upon dopamine receptors in the NA would be indicated if its effect on locomotor activity could be blocked by a dopamine receptor antagonist. Studies are being conducted in our laboratory to test these hypotheses.

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