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Daily l-Δ^9-tetrahydrocannabinol and pressing for hypothalamic stimulation

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Rats were fixed with chronically indwelling bipolar electrodes. After recovery from surgery they were trained to leverpress for intracranial stimulation (ICS). They pressed twice a day for three intensities of ICS for 5 min at each intensity. On each day for 10 days prior to tests with ICS, one group of rats was given THC (10 mg/kg, orally) and the other a placebo. The THC led to reduced pressing with initial doses but not with the later doses. Rats with electrode tips in the lateral hypothalamus near the entopeduncular nucleus of the internal capsule showed accelerated pressing toward the end of the 10 days of testing under THC.

A number of psychopharmacological agents that lead to verbal reports of euphoria also increase pressing for intracranial stimulation (ICS) of the hypothalamus in rats. Morphine, cocaine, and amphetamine, for example, are reported under certain circumstances to produce euphoria (Jaffe, 1975; McAuliffe & Gordon, 1974), and each under certain circumstances accelerates pressing for hypothalamic ICS (Adams, Lorens, & Mitchell, 1972; Crow, 1970; Stein, 1964). Marijuana, or its active ingredients, when assimilated under certain circumstances, is also reported to be euphorigenic (Jaffe, 1975; Peters, Lewis, Dustman, Straight, & Beck, 1976; Waskow, Olsson, Salzman, & Katz, 1970). Therefore, it is of interest to assess the effects of l-Δ^9-tetrahydrocannabinol (THC) on pressing for hypothalamic ICS.

Bailey and Pradhan (1972) tested rats for responsiveness to posterior hypothalamic ICS under the influence of THC in doses of 0, 1, 5, 10, 15, and 20 mg/kg. In general, rate of responding under THC was reduced. With testing at different intervals after injections of 10 mg/kg THC, suppression of responding was found to last 4 to 8 h. Tolerance to the depressant effects of daily doses of 10 to 20 mg/kg THC on responding for ICS developed within 7 days. Bailey and Pradhan (1972) also tested, concurrently, the effects of mescaline on pressing for ICS.

A pilot study (Taylor & Reid, Note 1) was done in which 5 and 10 mg/kg of THC in sesame seed oil were given intragastrically daily for 20 days 4 h before daily testing with hypothalamic ICS. The regimens for dosing and testing were determined using information from Rosenkrantz, Heyman, and Braude (1974) and Rosenkrantz (Note 2). The 5 mg/kg dose had little discernible effect 4 h after dosing. The 10 mg/kg dose initially depressed but subsequently led to accelerated pressing for ICS after about 5 to 10 days of administration. There was the possibility, however, that the sesame oil placebo by itself, in the quantities intubed, led to a reduction and instability in pressing. There was also the possibility that, as daily dosing continued, the time of acceleration in pressing occurred sooner after dosing, as it does in the case of morphine (Adams et al., 1972). Given these problems and the incompleteness of the extant data, the following study was done to retest the effects of THC on pressing for ICS. To avoid the complications associated with the pilot study and those associated with Bailey and Pradhan (1972), (1) less oil was used as the carrier for THC and for the placebo, (2) tests for pressing were conducted at different times after administration of THC (1 and 3 h), (3) the criterion used for stability in pressing was more conservative, and (4) only THC and a placebo were tested.

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METHOD

Subjects

Eleven adult (about 300 g) male Sprague-Dawley rats completed the procedures. Using standard techniques, each was fixed with a chronically indwelling bipolar electrode (Plastic Products No. 303) for ICS of the lateral hypothalamus. Each electrode was two strands of stainless steel wire (wire diameter = .02 cm), insulated except at the cross section of the tips. The strands were separated only by their insulation. Throughout the procedures, rats were individually housed with food and water always available.

Apparatus

The apparatus was a clear plastic chamber (30 x 24 x 35 cm) in a lighted, ventilated, sound-attenuating box. Through one wall of the chamber extended a lever, the depression of which yielded a single train of ICS. Each train of ICS was 60-Hz sine waves of .25-sec duration of varying intensities, but never over 50 microA, rms. ICS was delivered through light flexible leads connected to a commutator, allowing the rats unhampered movement. The number of ICSs delivered was automatically recorded for 5-min periods.

Procedure

After recovery from surgery (spanning at least 5 days), rats were trained to press for ICS. During initial testing, the intensity

of ICS was varied to select three intensities for each rat. There was a low intensity (limits of range were 5 to 17 microA), a medium intensity (ranging from 8 to 22 microA), and a high intensity (ranging from 15 to 30 microA). The low ICS was just intense enough to maintain low rates of pressing. The high ICS maintained high rates of pressing without behavioral disruption or seizures. The medium ICS was about halfway between the low and high ICS.

Rats were allowed to press for the three selected intensities, 5 min at each intensity, during a daily testing session. Each test with an intensity was preceded by 10 presses or 10 experimenter-initiated trains of ICS given while shaping the rat to press. The order of tests with the intensities always started with the low and ended with the high ICS. Rats were allowed to press for the three selected intensities twice daily for 43 days to stabilize pressing rates.

Subsequent to the stabilization period, the rats were run at 5 days at the selected intensities, the days of baseline, at times subsequently corresponding to 1 and 3 h after administration of THC or placebo (about 12:00 a.m. and 2:00 p.m.). Following baseline, rats were randomly assigned to one of two groups, six rats in one group and five in the other. Across 10 days, six were intubed daily with 10 mg/kg of THC (NIMH ADL-16792-14 in sesame oil) and others were intubed with equal volumes (.5 ml/kg) of THC's carrier, sesame seed oil. After days under THC or placebo, there were another 5 days of tests with ICS.

The rats were sacrificed under large doses of anesthesia followed by intracardial perfusions of saline and Formalin. Ninety-micron frozen slices of each brain were inspected to determine the sites of the electrode tip. Slices were treated as photographic negatives, and the resulting images were enlarged and photographically recorded as aids in inspecting the sites of ICS (Guzman-Flores, Alcarez, & Fernandez, 1968).

To summarize, the rats were tested at three intensities of ICS, 5 min at each intensity twice daily for 43 days to stabilize pressing rates. Then responding was tabulated twice daily for 5 days, the baseline performance. The rats were then randomly assigned to one of two groups and tested twice daily 1 and 3 h after dosing for 10 days. One group got 10 mg/kg of THC, while the other got a placebo. At the end of the 10 days, testing without dosing continued for 5 days.

RESULTS

Analyses of the data of initial baseline and of the 5 days following dosing indicated that the groups did not differ reliably (Fs < 1), which suggests that any differences between groups seen with dosing is apt to be due to THC. There was, of course, a reliable effect noted with intensity of ICS [$F(2,18) = 7.1$, $p < .0001$]. Mean presses/5 min on days of initial baseline were 59, 272, and 459, respectively, for low, medium, and high ICS.

To assess the effects of THC, difference scores were calculated for each rat. A difference score was obtained by subtracting a mean baseline score from each comparable score obtained after baseline, that is, difference score equals number of presses under THC or placebo minus mean presses of baseline for a given intensity and time of testing. These difference scores were then submitted to a 2 by 2 by 3 by 10 analysis of variance (ANOVA), with repeated measures on the last three factors. There were factors of the two groups (those of THC and no THC), the three intensities, the two tests following drug administration, and the 10 days of dosing. That ANOVA yielded for the factor of group an $F(1,9) = 4.56$, $p = .06$; for the factor of days an $F(9,81) = 3.95$, $p = .0001$, and for the interaction of Groups by Days an $F(9,81) = 3.95$, $p = .0003$ (Figure 1). None of the associated factors indicated that time after dosing was a reliable source of variance.

There were reliable effects associated with intensity of ICS (Figure 2); however, these effects were probably

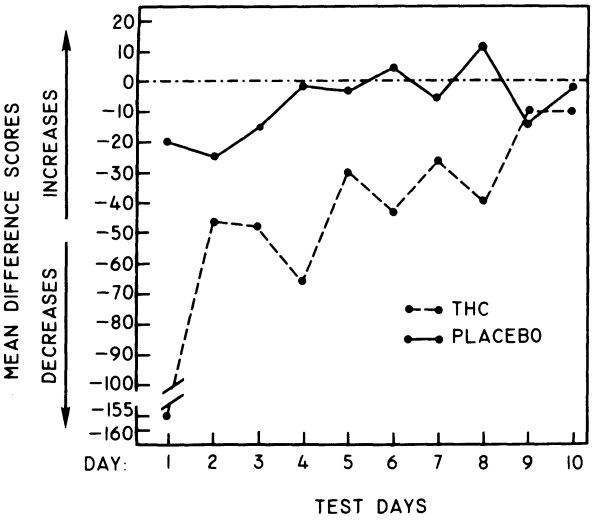

Figure 1. Mean difference scores for rats receiving either THC or placebo. Each score is collapsed across intensities and the two times of testing after dosing.

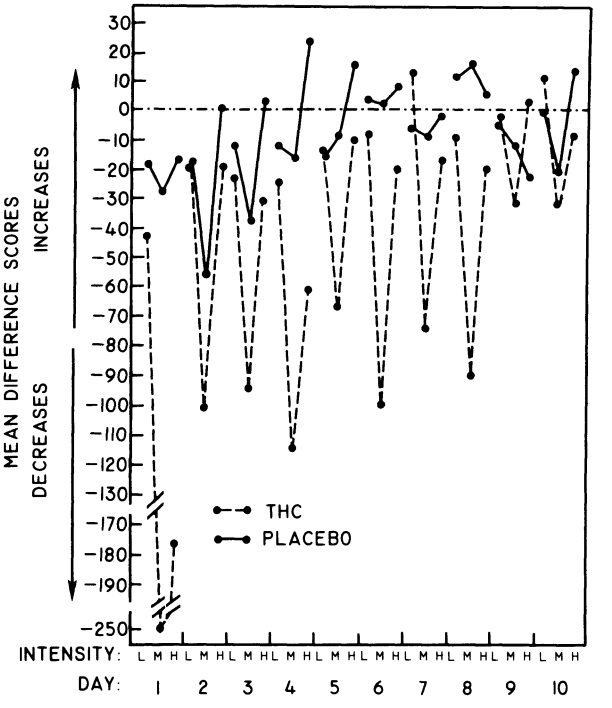

Figure 2. Mean difference scores on test days showing effects of intensity on rats receiving either THC or placebo.

due to the fact that there was a higher "floor" to the amount of decrease for the low intensity. Similar analyses using ratio scores rather than difference scores failed to yield strong intensity effects. Since the factors associated with time after dosing were not reliable sources of variance and since factors associated with intensity effects are due to the nature of difference scores, the relationships of interest are those of the Groups by Days interaction (Figure 1).

As can be seen in Figure 1, THC initially suppressed responding. With continuance of dosing, however, the rats of THC pressed, on the average, nearly as much as rats of placebo. Mean pressing between groups was reliably different ($ps < .05$) on Days 1 and 4 of dosing but not on other days.

The rats' responsiveness under THC was quite variable. All THC rats' scores were depressed across the first 4 days of dosing compared to baseline. Subsequently, however, some rats' pressing was markedly depressed but others' was accelerated. The largest increase of any rat of the placebo group compared to baseline on Day 10 was 24 presses (averaged across intensities and time after dosing). Yet, three of the six rats of THC had scores greater than 24, one of the three pressing more than 50 presses greater than baseline.

The sites of ICS also varied. All sites were in the lateral hypothalamus about 1.5 mm lateral to the midline, but they varied in the anterior-posterior plane and somewhat in depth. The rats of THC were ranked according to their electrode placement along the anterior-posterior plane. The rank order correlation between site of ICS (ant-pos) and difference scores under THC on the last day of dosing was .96 ($p < .05$). Rats of placebo had a similar rho of .10. The sites that led to increased pressing were just lateral or slightly posterior to the entopeduncular nucleus of the internal capsule. The other sites were just anterior to those placements but still in proximity to the medial forebrain bundle.

DISCUSSION

The studies (Bailey & Pradhan, 1972; the pilot study; and this study) assessing THC's effects on pressing for ICS all demonstrate (1) with initial dosing a suppression of pressing and (2) relatively rapid development of tolerance to the suppressive effects. If it is presumed that the depressive effects reflect a dysphoria, then the presumed dysphoria is relatively common with large doses but wanes with continued dosing. The widely held view (e.g., Becker, 1953) that one has to "learn" to "appreciate" the positive effects of THC could merely be a rationalization (attribution) of a pharmacological property of THC, namely, tolerance to its initially dysphoric effects.

The studies assessing the effects of THC on pressing for ICS do not provide strong evidence that THC can accelerate pressing for ICS. This study leads to the suggestion that, although the depressive effects of initial large doses of THC are common to all electrode sites (rats), pressing can be accelerated with dosing for certain ICS. Research with morphine (e.g., Esposito & Kornetsky, 1977; Farber & Reid, 1976; Rossi & Reid, 1976) has shown that even though an agent may produce a general behavioral depression, pressing for certain ICS is accelerated. Furthermore, the accelerated pressing, when seen, may reflect the euphorigenic properties of the opioids (Rossi & Reid, 1976). This small study leads to the suggestion that further research with THC and pressing for ICS could lead to the specification of those sites of ICS that are especially responsive to THC as reflected by acceleration of pressing for ICS.

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