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Facilitation of brain stimulation reward by Δ^9-tetrahydrocannabinol

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Abstract. The present experiment explored whether Δ^9-tetrahydrocannabinol (Δ^9-THC), the psychoactive ingredient in marijuana, shares with other drugs of abuse the ability to facilitate brain stimulation reward acutely, as measured by electrical intracranial self-stimulation (ICSS). Laboratory rats were implanted with stimulation electrodes in the medial forebrain bundle, and trained to stable performance on a self-titrating threshold ICSS paradigm. Δ^9-THC, at a dose believed pharmacologically relevant to moderate human use of marijuana, acutely lowered ICSS thresholds, suggesting that marijuana acts on similar CNS hedonic systems to most other drugs of abuse.

Key words: Marijuana – Cannabis – Cannabinoids – Δ^9-tetrahydrocannabinol – THC – Brain stimulation reward – Intracranial self-stimulation – ICSS – Reinforcement – Medial forebrain bundle – Rat

With the exception of the lysergic acid diethylamide (LSD)-like hallucinogens, all well-studied drugs of abuse have in common that they are voluntarily self-administered not only by humans but also by other mammals (Griffiths et al. 1978; Brady and Lukas 1984) and that they acutely facilitate electrical stimulation of brain reward loci (Esposito and Kornetsky 1980; Wise 1980, 1984), presumably deriving their euphorigenic properties and abuse potential therefrom (Wise 1980, 1984; Wise and Bozarth 1981; Kornetsky 1985). Whether delta-9-tetrahydrocannabinol (Δ^9-THC), the psychoactive constituent in marijuana, shares this brain-reward facilitating capacity or acts on other brain mechanisms to produce its abuse potential has remained unclear. We here report that Δ^9-THC acutely facilitates electrical brain stimulation reward of the medial forebrain bundle in the laboratory rat.

Materials and methods

For these experiments, male Lewis rats (Charles River) were implanted, by standard surgical and stereotaxic techniques, with chronic bipolar stimulation electrodes in the medial forebrain bundle [stereotaxic coordinates A3.7, L1.6, H-2.6, according to the brain atlas of Pellegrino et al. (1979)]. The animals were then trained to self-deliver rewarding electrical stimulation through the implanted brain electrodes by an adaptation of methods we have previously described (Seeger and Gardner 1979; Nazzaro and Gardner 1980). Training and testing was carried out in standard operant chambers equipped with two response levers. Microprocessor/brain-stimulator units were programmed to deliver titrating threshold decremental brain stimulation. Each response by the animal on the primary lever delivered a 250 ms stimulus train (60 Hz bipolar rectangular pulse-pairs) through the brain electrode. Initial current intensity was assigned to each animal on the basis of the lowest intensity supporting reliable responding at a rate of 1000 lever presses/30-min test session. The current decremented by $^1/_{16}$ of this initial intensity at every third press of the primary lever. At any time during this sequence of brain stimuli of decreasing magnitude, the animal could reset the current to maximum by pressing the second or "reset" lever, which reset the brain stimulation back to maximum for that animal and also activated a cue-signal tone but did not itself deliver brain stimulation. The current steps at which each animal reset were automatically recorded throughout each 30-min test session, and the mean of the resulting frequency distribution of reset levels was operationally defined as the brain reward threshold. The standard deviation of this frequency distribution was taken as a measure of performance stability, with a standard deviation of ± 1.5 current steps used as the criterion for stable performance and inclusion in the drug study. Brain reward threshold data were collated and analyzed in 15-min blocks. After training to stable performance, each animal was tested daily for a minimum of 6 weeks to ensure an absolutely stable baseline of brain reward threshold before drug trials began. Intraperitoneal (IP) saline injections (identical in volume, timing, and other parameters to the active Δ^9-THC and control PVP injections, below) were given before each daily baseline test.

Δ^9-THC was prepared for in vivo administration to the animals by the method of Fenimore and Loy (1971). The Δ^9-THC was first dissolved in a 20% solution of polyvinylpyrrolidone (PVP) (Aldrich Chemical Company) prepared in ethanol. This solution was then evaporated under nitrogen and the concentrated Δ^9-THC-PVP solution was suspended in saline at a Δ^9-THC concentration of 1.5 mg/ml. The Δ^9-THC was administered IP to the animals at a dose

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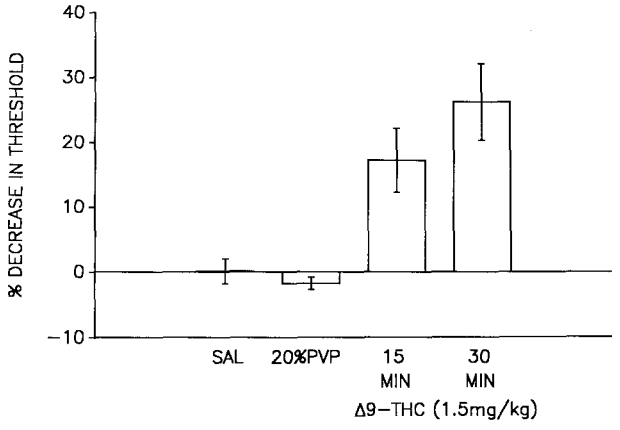

Fig. 1. Per cent decrease (±SEM) in brain stimulation reward threshold in rat medial forebrain bundle produced by saline, 20% polyvinylpyrrolidone (PVP) vehicle, and 1.5 mg/kg Δ^9-tetrahydrocannabinol (Δ^9-THC). The effect of Δ^9-THC is shown at both 15 and 30 min post-Δ^9-THC

of 1.5 mg/kg. For control injections, a 20% PVP solution was used, with injection volumes and other parameters identical to the active drug injections.

After the 6-week baseline period, each animal was injected on the next day with PVP vehicle and tested on the brain reward paradigm. Two weeks of additional daily baseline testing then followed, and then, on the next day, each animal was injected with Δ^9-THC and tested on the brain reward paradigm. Daily baseline testing continued thereafter for an additional 2 weeks, and then a second Δ^9-THC dose was given and each animal tested on the brain reward paradigm. Some animals received repeated PVP vehicle injections, at the same intervals as the repeated Δ^9-THC injections, to test for possible sensitization effects with repeated vehicle injections. Significance of shifts in brain reward threshold between saline baseline, vehicle, and drug days was tested by analysis of variance for repeated measures followed by post-hoc comparisons (Winer 1962).

Results

Neither saline nor PVP vehicle significantly altered brain reward thresholds, either when administered singly or repeatedly. In striking contrast, Δ^9-THC significantly lowered brain reward thresholds in the medial forebrain bundle. This facilitation of brain reward was seen both 15 and 30 min following Δ^9-THC administration as compared to saline or PVP vehicle (analysis of variance for repeated measures: $F_{3,9}=16.5$; $P<0.0005$), was seen in every animal, and was consistent from first to second Δ^9-THC administration. These results are shown in Fig. 1. Individual post hoc comparisons, generated by t-test with adjustment in α for multiple comparisons (Winer 1962), showed the 15-min post-Δ^9-THC data point to be significantly different from saline and PVP vehicle by $P<0.005$ and the 30-min post-Δ^9-THC data point to be significantly different from saline and PVP vehicle by $P<0.001$. Significances of the individual comparisons between the Δ^9-THC, saline, and PVP data points were also computed using the Scheffé, Tukey A, Tukey B, and Newman-Keuls statistical procedures (Winer 1962). In every case, even using the extremely conservative Scheffé statistic, the 15-min post-Δ^9-THC data point proved significantly different from saline and PVP by at least $P<0.05$ and the 30-min post-Δ^9-THC data point proved significantly different from saline and PVP by at least $P<0.01$. In view of evidence that other drugs of abuse can cause permanent sensitization of brain reward systems, thus altering responsiveness to subsequent administrations of the same drug, it should be noted that in the present study the brain reward threshold shifts caused by the second Δ^9-THC administrations were *not* significantly different from those caused by the first Δ^9-THC administrations.

Discussion

These findings strongly suggest that Δ^9-THC shares with other recreational and abused drugs, with the exception of the LSD-like hallucinogens, the ability to facilitate brain reward mechanisms, and presumably derives its euphorigenic properties from such facilitation. Significantly, these present findings are at a dose of Δ^9-THC within a range believed to be physiologically and pharmacologically relevant to human recreational marijuana use (Rosenkrantz et al. 1975), an important point in view of criticisms (e.g., Harris and Stokes 1982) that previous laboratory studies of Δ^9-THC have used doses so high as to preclude behavioral and physiological relevance. The present robust and consistent findings of acute facilitation of brain stimulation reward by Δ^9-THC are in contrast to previous reports of inconsistent and contradictory effects of Δ^9-THC on brain reward (Wayner et al. 1973; Battacharyya et al. 1980). However, all previous studies used rate measures of brain reward, instead of the threshold paradigm we used, and rate measures are easily confounded by sedative and other motoric drug effects.

In recent years, a large body of evidence has strongly implicated portions of the mesotelencephalic dopamine systems as specific neural substrates modulating direct brain reward (Corbett and Wise 1978; Seeger and Gardner 1979; Wise 1980; Wise and Bozarth 1981; Fray et al. 1983). Evidence exists that these dopaminergic neurons are connected "in series" to the neurons directly activated by rewarding electrical brain stimulation of the medial forebrain bundle (Wise 1980; Wise and Bozarth 1984). Congruent with this anatomical relationship, and congruent with the importance of dopaminergic function in these circuits to the rewarding properties of drugs of abuse (Spyraki et al. 1983), most drugs with dopamine agonist properties are euphorigenic (and have consequential abuse potential) while most dopamine antagonists are anhedonic (Wise 1981). Recently, we have demonstrated, using in vivo brain microdialysis and in vivo brain electrochemical techniques, that Δ^9-THC has dopamine agonist properties in portions of the mesotelencephalic dopamine circuitry which support brain stimulation reward (Ng Cheong Ton et al. 1988). Thus, there is now evidence from both in vivo neurochemical and in vivo brain stimulation reward studies suggesting that Δ^9-THC, the psychoactive ingredient in marijuana, may not be as anomalous a drug of abuse as formerly thought, and may in fact resemble other drugs of abuse in producing, as a final common neuropharmacological action, acute facilitation of the mesotelencephalic brain reward circuitry. Obviously, however, the cellular and/or molecular mechanisms by which Δ^9-THC accomplishes this may differ from those of other drugs of abuse, and such mechanisms remain to be explored.

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References

Bhattacharyya AK, Aulakh CS, Pradhan S, Ghosh P, Pradhan SN (1980) Behavioral and neurochemical effects of Δ^9-tetrahydrocannabinol in rats. Neuropharmacology 19:87–95

Brady JV, Lukas SE (1984) Testing drugs for physical dependence potential and abuse liability (Nat Inst Drug Abuse Res Monogr Ser, no 52). US Government Printing Office, Washington, DC

Corbett D, Wise RA (1978) Intracranial self-stimulation in relation to the ascending dopaminergic systems of the midbrain: a moveable electrode mapping study. Brain Res 185:1–15

Esposito RU, Kornetsky C (1978) Opioids and rewarding brain stimulation. Neurosci Biobehav Rev 2:115–122

Fenimore DC, Loy PR (1971) Injectible dispersion of Δ^9-tetrahydrocannabinol in saline using polyvinylpyrrolidone. J Pharm Pharmacol 23:310

Fray PJ, Dunnett SB, Iversen SD, Björklund A, Stenevi U (1983) Nigral transplants reinnervating the dopamine-depleted neostriatum can sustain intracranial self-stimulation. Science 219:416–420

Griffiths RR, Bigelow GE, Liebson I (1978) Experimental drug self-administration: generality across species and type of drug. Nat Inst Drug Abuse Res Monogr Ser 20:24–43

Harris RA, Stokes JA (1982) Cannabinoids inhibit calcium uptake by brain synaptosomes. J Neurosci 2:443–447

Kornetsky C (1985) Brain-stimulation reward: a model for the neuronal bases for drug-induced euphoria. Nat Inst Drug Abuse Res Monogr Ser 62:30–50

Nazzaro JM, Gardner EL (1980) GABA antagonism lowers self-stimulation thresholds in the ventral tegmental area. Brain Res 189:279–283

Ng Cheong Ton JM, Gerhardt GA, Friedemann M, Etgen AM, Rose GM, Sharpless NS, Gardner EL (1988) Effects of Δ^9-tetrahydrocannabinol on potassium-evoked release of dopamine in the rat caudate nucleus: an in vivo electrochemical and in vivo microdialysis study. Brain Res 451:59–68

Pellegrino LJ, Pellegrino AS, Cushman AJ (1979) A Stereotaxic Atlas of the rat brain, 2nd ed. Plenum Press, New York

Rosenkrantz H, Sprague RA, Fleischman RW, Braude MC (1975) Oral Δ^9-tetrahydrocannabinol toxicity in rats treated for periods up to six months. Toxicol Appl Pharmacol 32:399–417

Seeger TF, Gardner EL (1979) Enhancement of self-stimulation behavior in rats and monkeys after chronic neuroleptic treatment: evidence for mesolimbic supersensitivity. Brain Res 175:49–57

Spyraki C, Fibiger HC, Phillips AG (1983) Attentuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology 79:278–283

Wayner MJ, Greenberg I, Fraley S, Fisher S (1973) Effects of Δ^9-tetrahydrocannabinol and ethyl alcohol on adjunctive behavior and the lateral hypothalamus. Physiol Behav 10:109–132

Winer BJ (1962) Statistical principles in experimental design. McGraw-Hill, New York

Wise RA (1980) Action of drugs of abuse on brain reward systems. Pharmacol Biochem Behav 13 [Suppl 1]:213–223

Wise RA (1981) Brain dopamine and reward. In: Cooper SJ (ed) Theory in psychopharmacology, vol II. Academic Press, New York, pp 103–122

Wise RA (1984) Neural mechanisms of the reinforcing action of cocaine. Nat Inst Drug Abuse Res Monogr Ser 50:15–33

Wise RA, Bozarth MA (1981) Brain substrates for reinforcement and drug self-administration. Prog Neuropsychopharmacol 5:467–474

Wise RA, Bozarth MA (1984) Brain reward circuitry: four circuit elements "wired" in apparent series. Brain Res Bull 12:203–208

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