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Evaluation of Reinforcing Capability of Delta-9-Tetrahydrocannabinol in Rhesus Monkeys*

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Abstract. Harnessed rhesus monkeys, surgically prepared with indwelling jugular catheters, were given access by means of remotely controlled infusion pumps to unlimited quantities of delta-9-trans-tetrahydrocannabinol. Naive monkeys as well as monkeys which were automatically infused with THC for over 28 days did not self-administer THC. Monkeys which had a history of multiple drug self-administration also did not self-infuse THC.

Key words: Drug Self-Administration — Delta-9-THC; Monkey — Intravenous Route.

The procedure by which harnessed monkeys are permitted to intravenously self-infuse drugs has provided a reliable test of the reinforcing capability of many CNS active compounds (Deneau *et al.*, 1969). Although there is, as yet, no definitive analysis of the extent to which the reinforcing properties of drugs, as tested in animals, contribute to human drug dependence, there is increasing evidence that drugs which animals readily self-administer comprise the class of agents which human beings take compulsively and which produce strong dependence, e.g., opiates (Deneau *et al.*, 1964), stimulants (Deneau *et al.*, 1969) and barbiturates (Goldberg *et al.*, 1971). Further, drugs which animals do not self-administer to any considerable degree, e.g., psychedelics, tranquilizers, are of the type, generally, which human beings ingest sporadically, rather than chronically, and more for experimental or therapeutic reasons than for the drive states produced by narcotics or stimulants. These data suggest that the reinforcement potential of a drug contributes heavily to its addiction potential.

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The present study was designed to assess the reinforcing capability of delta-9-tetrahydrocannabinol (THC), the principal active ingredient of the marijuana plant (Gaoniand and Mechoulam, 1964). While marijuana has been smoked or ingested by millions of people and is not regarded as a drug which produces a very marked dependence (National Commission of Marijuana and Drug Abuse, 1972), it must be noted that the drug has been available only on the illicit market and, therefore, not on a regular basis or of a consistent quality. The prospective legalization of the drug in several countries would make available to the chronic marijuana user a regular supply of high quality drug. For this reason, an assessment of the reinforcing efficacy of standardized THC, at varied doses, appeared warranted. In the present study, several experimental procedures were utilized to assess the reinforcing capability of THC.

Materials and Methods

Subjects. Male Rhesus monkeys, weighing from 3.1 to 4.6 kg were used in each experiment. All were naive at the onset of the study with the exception of four used in one experiment. They were fitted with a steel harness (Deneau *et al.*, 1969), and a hollowed connecting cable permitted a silastic cathether to pass from automatic infusion pumps into the jugular vein.

Apparatus. The experimental cages were of a commercial housing type. A panel on the cage front contained two levers and a centered light which was controlled electrically. Depressions of one of the two levers activated an infusion pump for approximately 10 sec, depending upon the animal's body weight and delivered up to one ml of drug solution. Responses on the levers also produced onsets of lights above each lever for approximately 10 sec. An intensification of the house light signaled onset of each daily session. Delta-9-THC was obtained in ethanol solution from NIMH. Ethanol was removed and THC suspended in polyvinylpyrrolidone (PVP) by the method of Fenimore and Loy (1971). Drug solutions were changed every five days.

Analysis of Results. The basic datum of each experiment was the number of self-infusions of THC. These totals were compared with self-infusions of saline and PVP, collected from a control group of ten monkeys. Comparisons of THC and PVP/saline infusions were made both in naive animals (operant rate of self-infusion responding) and in animals previously trained to self-infuse cocaine (rate of extinction). For the PVP/saline group, the operant rate was, typically, two to four infusions per hour; and, the extinction rate 30 to 40 responses during the first hour dropping gradually to near operant rates by the fourth day (sessions length of four hours).

Procedure and Results

Spontaneous Self-Administration of THC in Naive Monkeys

Ten monkeys were given 12 h access per day, for 20 days, to THC at doses of 0.025, 0.05, 0.1, 0.2 and 0.3 mg/kg. Two monkeys, each, started at a particular dose and were changed to other doses every four days. The doses were selected on the basis of work with other monkeys which showed that 0.020 mg/kg was the minimal dose which could be discrimi-

nated in a "state dependent" learning test (unpublished data) and 0.3 mg/kg was an intoxicating dose. The purpose of this procedure was to determine if THC would be self-infused in the absence of other incentives.

The results were negative and are not presented graphically. No animal exceeded saline or PVP infusion rates. At the 0.2 and 0.3 mg/kg dose levels, this rate (2—3 infusions/h) was sufficient to produce a stuperous condition. To test if these doses were reinforcing, a schedule requirement of three responses per infusion was programmed for three monkeys at the 0.2 and 0.3 mg/kg dose levels. Again, response rates were maintained at the PVP/saline rate of only two or three per hour and the animals received only one or two infusions per day (four hour sessions).

Self-Administration of THC after Training on Cocaine

Eight monkeys used in the previous spontaneous test were trained to self-infuse cocaine hydrochloride (unit dose: 0.2 mg/kg). Cocaine was dissolved in saline and added to a 3% PVP in saline solution to make up the unit infusion.

After ten days of training on cocaine (four hour sessions), THC was substituted at doses of 0.025, 0.05, 0.1 and 0.2 mg/kg. Each dose was tested for seven days with five days of cocaine availability intervening each dose change of THC. The purpose of this procedure was to determine if THC would be self-infused by well-trained animals. A second purpose was to determine if PVP was aversive to the monkeys by observing its effect on cocaine self-administration.

The high and regular self-infusions rates obtained with cocaine extinguished over a four-day period when THC was substituted. The extinction curves at the two lower doses of THC were similar to saline or PVP extinction curves. At the two higher doses, the curves were somewhat sharper, reflecting a slight toxicity from THC. These results are not presented graphically. The high rates of self-infusions for cocaine when mixed with PVP demonstrated that PVP is not aversive to Rhesus monkeys.

Self-Administration of THC Following Programmed Infusions of THC

Five monkeys were infused for 30 days with 2 mg/kg THC at a rate of 0.05 mg/kg every six min (four hour programmed infusions). Prior to these infusions, the animals had been trained to self-infuse cocaine. During the programmed infusion period, the self-infusion levers were activated to deliver a unit dose of 0.025 mg/kg THC if pressed. After 30 days, the four hour daily infusions of THC were terminated but the animal continued to have access to THC (0.025 unit dose) by the self-infusion route. The purpose of this procedure was to determine if an

abrupt withdrawal of relatively high dose of THC over a prolonged period would induce self-administration of the drug.

The results are negative and not presented graphically. The monkeys did not exceed random response rates. Over the 30 day programmed infusion period, a slight degree of tolerance developed to the 2 mg/kg dose of THC; however, the animals appeared (observation) to remain under drug influence for at least 10 h post-infusion over the entire 30 days. On the first day of drug withdrawal, the monkeys reacted to their environment in a manner typical of Rhesus monkeys. These observations were not systematically tabulated and do not include possible biochemical or pharmacological reactions to delta-9-THC or its withdrawal.

Self-Administration of THC Following Training on Cocaine-THC Mixture

Five naive monkeys were trained to self-infuse mixed solutions of cocaine and THC. Tests for self-infusions of THC followed each period of training on a mixed solution. From an initial mixture of 0.2 mg/kg cocaine—0.02 mg/kg THC, each successive mixture contained lesser doses of cocaine in quantities of 0.15, 0.1, 0.05 and 0.005 mg/kg. THC remained at a concentration of 0.02 mg/kg unit dose in all mixtures and in test periods where it was presented solely. Seven days of training on each mixed solution intervened each THC test period. The purpose of this procedure was to develop delta-9-THC as a secondary reinforcer by combining it with a primary reinforcer, cocaine. The procedure was also designed to measure any aversive or toxic characteristics of delta-9-THC by observing its influence on cocaine self-administration.

Cocaine-THC solutions were self-infused at a rate of between 100 and 150 infusions per four hour session at every dose level. There was no dose-response relationship and thus the results are not presented graphically. The absence of a dose related curve (cocaine schedule) undoubtedly can be attributed to the presence of THC in the solutions. Self-infusions at the rate of 100 to 150 per four hours resulted in the monkeys receiving between 2 and 3 mg/kg of THC, which, as shown with the previous animals who were injected with that dose, produced an intoxicated state for which only minor tolerance developed. When presented THC solely, the monkeys failed to respond beyond extinction levels. Extinction curved were slightly more prolonged than saline extinction curves; however, asymptomatic rates of 3 to 4 responses per hour were attained within five days. These results are not presented graphically.

Self-Administration of THC by Monkeys Trained to Self-Infuse Several Classes of Drugs

Four monkeys which had been used frequently in previous self-infusion studies were first given access to THC (0.02 mg/kg unit dose) and, second,

were retrained to self-infuse cocaine for seven days and then given access to THC. Two animals were provided with one of two doses of THC. Doses were 0.02 and 0.05 mg/kg. The monkeys had been drug-free for a period of eight weeks prior to this experiment. The purpose of this procedure was to determine if monkeys which had previously self-infused phenobarbital, phencyclidine, ethanol (irregularly) and *dl*-amphetamine would, after a dry-out period, self-infuse THC.

None of the animals self-infused THC, either spontaneously or when transferred from cocaine. Extinction curves following cocaine transfer were considerably more rapid as compared to previous monkeys in the study, reflecting the prior training these animals had undergone in the extinction process. These results are not presented graphically.

Discussion

It may be concluded from these results that delta-9-tetrahydrocannabinol does not function as a reinforcing drug in rhesus monkeys. Both naive and experienced drug taking animals refused to self-administer THC. Probably the most conclusive assessment of the reinforcing capability of THC was provided by the group which was programmed with THC for 30 days, and the group which was trained for an equal period to self-infuse the drug in combination with cocaine, These two procedures could be expected to strengthen subtle basic reinforcing characteristics or secondarily reinforcing effects (conditioned by pairing with cocaine) of THC to a degree sufficient to maintain its self-administration. The negative results obtained in both tests can hardly be attributed to any aversive effects of THC as shown by the fact that cocaine self-infusions (mixture) were sustained at the 0.005 mg/kg unit dose level, normally, below the reinforcing threshold. It is also unlikely that the monkeys could not "feel" the unit dose of 0.025 or 0.02 mg/kg THC. In collateral studies (unpublished data) we have controlled choice responding for more than 60 days in state dependent learning paradigms with unit doses of THC as small as 0.02 mg/kg.

In comparison with drugs which are self-administered by animals, e.g. stimulants, narcotics, as well as others which are not, e.g. tranquilizers, psychedelics, several characteristics of THC are suggested which may account for its non-reinforcing capability. Principal among these would be the rather low profile of pharmacological activity induced by doses of the order employed in this study (Thompson *et al.*, 1971). Another effect of drugs shown to mitigate against their reinforcing potential is that of the induction of sufficiently severe central disturbances to be reported in man as hallucinogenic in nature. While modest as measured peripherally, i.v. doses of 2.0 mg/kg over a four hour period would induce

hallucinogenic activity in man. This factor would apply only to the two groups of monkeys which experienced such doses, of course, as the *ad lib* groups never initiated self-infusion of THC. Also, it would be a relevant condition only to the extent that the neurological correlates in monkeys of the hallucinogenic experience in man holds across different classes of drugs.

The absence of a negative reinforcing capability in THC, as shown by the refusal to self-infuse the drug in the two groups which experienced high doses for over 28 days before it was made available *ad lib*, was confirmed by observations of the behavior of the monkeys when THC infusions or self-infusions (cocaine solution) were terminated. Laboratory personnel, thoroughly familiar with these animals, could note no changes in appearance, activity, aggressiveness, or eating habits during the drug withdrawal period. The absence of severe withdrawal reaction to THC may be due to the lengthy duration of action of THC or its active metabolite 11-OH THC when given chronically.

One case of succesful training to self-infuse THC by a rhesus monkey was reported by Pickins and Thompson (1972). Using the same drug preparation and similar doses as used in the present study, these investigations obtained a steady rate of responding for THC by means of transferring the monkey on a very gradual schedule from phencyclidine self-infusions to THC. The response for THC was subject to extinction, however, which raises questions about the mechanisms underlying self-infusions of drugs when predicated on drug transfer procedures. When the substituted drug shares pharmacological effects with the parent drug, its self-infusion for some interval exceeding the typical saline extinction period is probably to be expected. However, unless those pharmacological effects, which would be viewed as latently reinforcing, possess a sufficient capacity to become reinforcing in themselves once the animal is sensitized to them, their self-administration would be only transient. The refusal to take THC by the four monkeys trained to self-infuse phencyclidine at an earlier period may be interpreted in this vein: a dry out period of several months was sufficient to diminish any carry over effects between the two drugs.

Estimates of the abuse potential of THC for man, predicated on the present results, obviously, are limited to its reinforcing capability and to its induction of somatic and behavioral toxicity, both when administered and withdrawn. The minimal reinforcing capability of THC in monkeys suggests that even at high doses, it is not likely to be taken for purely hedonistic purposes, i.e. "kick" induced by stimulants and narcotics, by very many individuals. The absence of marked withdrawal effects suggests that, again even at high doses, the drug is unlikely to be compulsively taken by man in order to forestall the distress of abstinence. As an

intoxicant, THC, and marijuana to the extent that they can be equated (Isbell *et al.*, 1967) appears to be fairly resistant to tolerance development. The programmed THC infused and cocaine-THC self-infused monkeys remained slightly stuperous throughout the four week drug periods. It may well be that the altered state of consciousness which is part of the intoxicated condition accounts, in the major part, for the continued use of marijuana by man.

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