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Retardation of Discrimination Reversal by Δ^9-Tetrahydrocannabinol in Monkeys[1,2]

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GLUCK, J. P., D. P. FERRARO AND R. G. MARRIOTT. *Retardation of discrimination reversal by Δ^9-tetrahydrocannabinol in monkeys.* PHARMAC. BIOCHEM. BEHAV. 1(6) 605–608, 1973. Adult monkeys acquired a simultaneous 2-choice color discrimination after which they were given a series of ten successive discrimination reversals. Half of the monkeys received all of this discrimination training under the influence of a synthetic Δ^9-trans-tetrahydrocannabinol (Δ^9-THC), the major psychoactive constituent of marihuana, while the other monkeys served as nondrug controls. The drug states for the two groups were interchanged during the eleventh reversal. Although acquisition of the initial discrimination did not differ between the drug and control groups, subsequent discrimination reversals were markedly retarded for the drug group. Performance of the drug group on the initial reversals was characterized by perseveration to the previously reinforced stimulus. Introduction of the drug to the control group during the final reversal also produced an impairment of discrimination reversal performance.

Δ^9-tetrahydrocannabinol Discrimination reversal Monkeys Psychopharmacology

THE successive discrimination reversal procedure involves the repeated shifting of response contingent reinforcement between two invariant stimuli following the attainment of a specified performance criterion. Variations on this basic procedure have been useful in establishing a variety of findings including phylogenetic differences in learning [6, 15, 16], degrees of mental retardation [10], and actions of psychotropic drugs [8, 9, 11, 13]. The general utility of this relatively complex procedure is enhanced by its independence from perceptual-motor biases [1].

The majority of research dealing with the effects of marihuana on learned behavior has involved the use of simple behavioral tasks as represented, for example, by operant schedules of reinforcement [2]. By in large, this research has not served to delineate the behavioral mechanism of action for marihuana from that of other psychotropic drugs. Ferraro *et al.*, [3] have recently suggested that this delineation might be better accomplished through the use of more complex behavioral tasks such as those which incorporate a memory or conditional rule learning component. Accordingly, the present experiment investigated the effects of (-)Δ^9-trans-tetrahydrocannabinol, the major psychoactive constituent of marihuana, on the 2-choice nonspatial successive discrimination reversal performance of monkeys.

METHOD

Animals

Two adult male stumptail monkeys *(Macaca arctoides)* weighing approximately 11 kg, and two adult male rhesus monkeys *(Macaca mulatta)* weighing 9 kg were used. The monkeys had served in prior drug-behavior experiments [2], but had been drug free for 3 mo prior to the present study.

Apparatus and Materials

The experimental chamber was a sound attenuating cubicle equipped with a primate restraining chair and a stimulus-response panel containing two horizontally aligned plastic response keys. A stimulus projector was used to illuminate each response key with either white or green light. Reinforcement was a 0.3 g Noyes banana pellet delivered into a foodwell on the stimulus-response panel.

Synthetic (-)Δ^9-trans-tetrahydrocannabinol (96% Δ^9-THC, 3% Δ^8-THC, and 1% cannabinol; Batch No. SSC-66907) was obtained in a 0.2 g/ml solution with dehydrated alcohol from the National Institute of Mental Health. The Δ^9-THC was put into a 0.1 g/ml solution with sesame oil and stored in the dark under refrigeration. The

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drug vehicle used for oral administration was 3 cc of orange drink.

Procedure

The four monkeys were first trained to respond reliably to an illuminated response key and then were given 18 daily sessions of nondifferential reinforcement to the two color stimuli. A nondifferential reinforcement trial involved the simultaneous presentation of the green and white lights on the response keys with the left-right key positions of the two stimuli being randomly determined. A response to either of the two stimuli was reinforced with a probability of 0.5. Both reinforced and nonreinforced responses terminated the trial and produced a 10-sec intertrial interval during which no stimuli were presented. For this and subsequent conditions of the experiment, a daily session consisted of 100 trials. On the final two days of nondifferential reinforcement training, two monkeys (one stumptail and one rhesus) were given oral doses of 1 mg/kg Δ^9-THC 2.5 hr prior to the experimental session. The remaining two monkeys served as nondrug controls and were similarly administered the drug vehicle alone.

During the ensuing simultaneous discrimination condition the white light was specified as S^+ and the green light as S^-. Specifically, on each trial a response to S^+ was reinforced and produced the 10-sec intertrial interval; a response to S^- produced only the intertrial interval. Discrimination training was continued on a daily basis for each monkey until a performance criterion of three successive sessions of 90% correct responding was achieved. The discrimination was then reversed, that is, the white light was made S^- and the green light was made S^+, until the performance criterion was again achieved. In all, eleven such discrimination reversals were given.

The drug condition initially assigned to each monkey during nondifferential reinforcement training was maintained throughout acquisition of the initial color discrimination and the subsequent ten discrimination reversals. On the first day of the eleventh and final discrimination reversal the drug states for the monkeys were interchanged. The previously nondrug control monkeys were administered 1 mg/kg Δ^9-THC and the previously drug monkeys were given the drug vehicle alone. Training in these interchanged drug states continued until the performance criterion for the eleventh discrimination reversal was achieved.

RESULTS

The administration of Δ^9-THC did not produce differential effects during nondifferential reinforcement training or during acquisition of the initial color discrimination. Responding for both the drug and nondrug groups was evenly divided between the two color stimuli during the last two days of nondifferential reinforcement and both groups acquired the initial discrimination at the same rate. The mean number of sessions needed to meet the 90% performance criterion on the initial discrimination for the non-

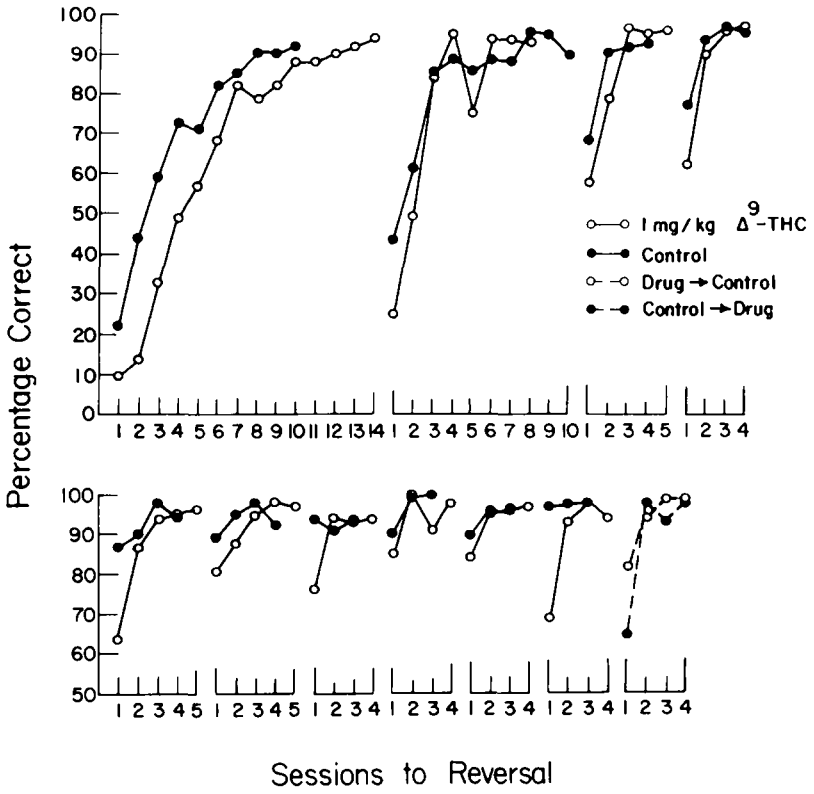

FIG. 1. Percentage correct responding during each session across successive discrimination reversals for the nondrug control and 1 mg/kg Δ^9-THC stumptail monkeys. The dashed lines in the final reversal signify that the drug states were interchanged during this reversal.

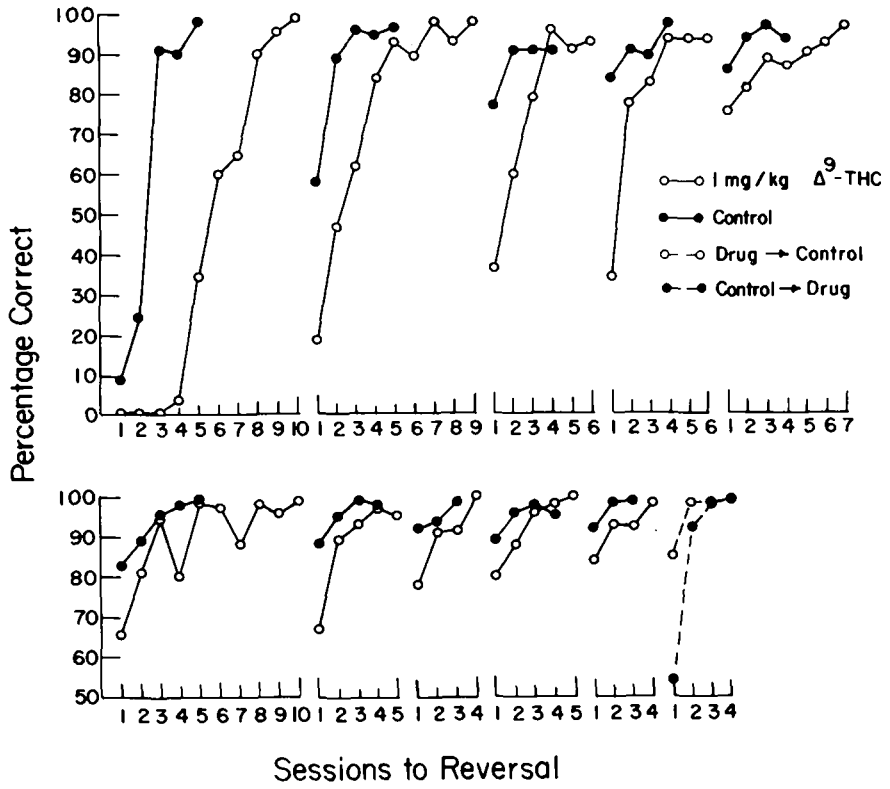

FIG. 2. Percentage correct responding during each session across successive discrimination reversals for the nondrug control and 1 mg/kg Δ⁹-THC rhesus monkeys. The dashed lines in the final reversal signify that the drug states were interchanged during this reversal.

drug control and drug groups was 13.0 and 13.5 sessions, respectively.

A well defined Δ⁹-THC effect was observed on discrimination reversal performance. Figures 1 and 2 present percentage correct responding across the eleven discrimination reversals for the two species of drug and control monkeys. The number of sessions required to meet the performance criterion decreased across successive reversals for both the drug and control animals. In other words, both groups acquired a comparable discrimination reversal learning set. However, further analysis of the first 10 reversals presented in Fig. 1 and 2 supports the conclusion that Δ⁹-THC retarded discrimination reversal performance. This conclusion emerges from two basic findings: (1) Performance of the drug animals was markedly below that of the control animals on the first day of each reversal, and (2) within each reversal the drug animals consistently required a larger number of sessions to reach the performance criterion than did the control animals.

Further evidence of the impairment in discrimination reversal produced by Δ⁹-THC may be seen in the eleventh reversal where the drug states of the individual monkeys were interchanged. The administration of Δ⁹-THC to the control monkeys sharply attenuated discrimination performance on the first reversal day and, thereafter, had no observable effect. In comparison, the removal of the drug from the drug monkeys occurred with minimal effect throughout the reversal. In this context it is conceivable that these monkeys had developed a drug tolerance which could have minimized the effects of the change to the nondrug state [5]. It should be further noted that the observation of asymetrical transfer effects between drug states is not uncommon in the literature pertaining to state dependent learning [14].

DISCUSSION

The obtained data suggest that the effects of Δ⁹-THC on discrimination behavior depend, in part, on the complexity of the behavioral task. Whereas daily administration of Δ⁹-THC did not interfere with performance on a nondifferential reinforcement schedule or with the acquisition of a simultaneous color discrimination, the drug did impair performance on successive reversals of the discrimination. Our failure to find a Δ⁹-THC effect on the acquisition of a simple discrimination is in accord with other reports that Δ⁹-THC does not disrupt the ongoing performance of previously learned color or form discriminations in primates [2,4].

The Δ⁹-THC produced retardation of discrimination reversal performance observed herein was particularly characterized by a perseveration of responding to the previous S^+ on the first day of each reversal. At least two explanations of this drug-induced perseveration seem viable. On the one hand, Δ⁹-THC may have retarded the process of extinction to the previous S^+. Alternatively, counter conditioning to the previous S^- may have been impeded by the drug state. Two lines of evidence tend to implicate the

latter explanation. Gonzales and Carlini [7] have reported that a marihuana extract did not affect the rate of extinction of a previously reinforced instrumental response. Furthermore, data from a recent stimulus generalization experiment by Lyons *et al.* [12], suggest that Δ^9-THC may act to increase the aversiveness of a negative discriminative stimulus. If Δ^9-THC similarly affected the S in the present forced choice discrimination situation then the observed response perseveration to the previous S^+ could be tentatively viewed as an active avoidance of the previous S^-.

The observed retardation of discrimination reversal performance by Δ^9-THC apparently sets this drug apart from other pharmacological classes of drugs. Previous experiments have been consistent in showing that drugs of the stimulant [9,11], tranquilizer [8], and barbiturate [13] classes facilitate discrimination reversal performance. Taken together these data may be related to the finding that Δ^9-THC is alone among psychotropic drugs in selectively affecting short-term memory in nonhuman primates performing on a complex delayed matching-to-sample task [3]. However, further research, particularly with complex behavior tasks, will be necessary before the behavioral mechanism of action for Δ^9-THC can be definitively elucidated.

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