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Effects of drugs of abuse on acquisition of behavioral chains in squirrel monkeys

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Abstract. The acute effects of various drugs of abuse on the acquisition of chains of behavior were assessed in squirrel monkeys trained to respond on three keys for food. Each new session the monkeys acquired a different four-response chain by responding sequentially on three keys in the presence of four different stimuli. Incorrect responses inactivated the keys and darkened the chamber for 10 s (time-out). Dose-effect curves were obtained by administering the drugs intramuscularly before the session and recording their effects on the rate and accuracy of responding. Cocaine, *d*-amphetamine, and Δ^9-tetrahydrocannabinol all decreased the accuracy and rate of responding within the dose range of 0.56–3 mg/kg. The highest dose of morphine tested (3 mg/kg) produced parallel decreases in the accuracy and rate of responding in some monkeys but had no effect at lower doses. These drugs decreased within-session accuracy though clearly acquisition did occur, but high doses of caffeine (30 and 56 mg/kg) prevented acquisition and recovery of performance and, furthermore, at 30 mg/kg these effects were observed in the absence of decreases in the rate of responding. The drugs of abuse tested all produced dose-related decreases in both the accuracy and rate of responding, and the decreases in accuracy were primarily observed only at doses that also decreased response rates. Therefore, based on these results from nonhuman primates each of these drugs has the potential to alter learning particularly when doses that disrupt other behaviors are administered.

Key words: Behavior – Cocaine – *d*-Amphetamine – Caffeine – Δ^9-Tetrahydrocannabinol – Morphine – Squirrel monkeys – Repeated acquisition – Response chains – Learning

In recent years a considerable research effort has been expended to identify both substances that facilitate and those that disrupt learning and memory. Much of this research concentrates on identifying which of the several thousand chemicals introduced into the environment each year, as well as the estimated 60 000 already in commercial use, may have deleterious effects on these processes (Peele and Vincent 1989). In that regard, due to the susceptibility of learning and memory to chemical insult, disease, and aging, others have focused on evaluating drugs for their potential to improve learning and memory (Nicholson 1990). However, in the past, often the assessment of the behavioral effects of a substance only included effects on a well-established performance. Consequently, there is a need to develop behavioral models to assess the effects of drugs and toxic chemicals on the acquisition of new behavior.

One such behavioral model, the repeated acquisition of behavioral chains, has been used to study acquisition behavior or "learning" and the function of variables such as drug administration (Sidman and Rosenberger 1967; Boren and Devine 1968; Thompson 1973). Under this behavioral paradigm, learning is defined as either a decrease in errors or as an increase in correct responses (accuracy) across trials within a session.

In the present research, we sought to condition repeated acquisition responding in the squirrel monkey. To the authors' knowledge, this represents the first report of the use of this schedule of reinforcement in the squirrel monkey. This nonhuman primate species was selected due to the extensive and successful use of the squirrel monkey in investigating the effects of drugs and toxic chemicals on previously learned behaviors. Moreover, the use of a nonhuman primate species facilitates the extrapolation of results to the human.

Materials and methods

Subjects. The subjects were five experimentally naive male squirrel monkeys *(Saimiri sciureus)* weighing between 530 and 583 g when given free access to food and water. The monkeys were maintained at 85% of their free feeding weights during the experiment. The monkey's diet consisted of Noyes formula L food pellets (P.J.

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Noyes Co. Inc., Lancaster, NH) received during the experimental session, and Purina Monkey Chow, fruit, and vitamins given after the daily behavioral session. Water was available continuously both in the home cage and the experimental chamber.

Apparatus. In the experimental chamber each monkey sat in a Plexiglas chair similar to the one described by Hake and Azrin (1963). Three translucent keys (G–6315, Gerbrands Corp., Arlington, MA) which could be transilluminated with colored lights were mounted horizontally on the transparent front wall. The keys were recessed 1.6 cm, and the center of each key was 35 cm above the chamber floor. Pressing a key with a force of at least 0.15 N opened the key contact and defined the response. A food pellet dispenser delivered 97 mg food pellets to a tray accessible through a 4.4 cm square aperture located in the front wall directly below the center response key. The food aperture could be illuminated by a 28 V d.c. lamp. A relay provided auditory feedback for response-key activation. The chair was enclosed in a ventilated, sound-attenuating chamber, and white noise was delivered to the room housing the enclosure to mask extraneous noises.

Procedure. The transillumination of the response keys signalled the start of the behavioral sessions. Under the chain schedule, each step in the four-response chain was indicated by a different key color or duration of key illumination (stimulus). Each correct response within the chain produced a change in the key stimulus in the order of: flashing white-red-continuous white-blue. The order of stimulus presentation was constant throughout the experiment, and all three keys were always transilluminated with the same stimulus at the same time. The monkey's task was to learn a four-response chain by pressing the correct key (left, center, or right) in the presence of each stimulus. When the subject completed the four-response chain, the food aperture was illuminated, the key lights were extinguished, and a food pellet was delivered. After 10 s the food aperture lamp was extinguished and the response chain was reset. A press on one of the two incorrect keys resulted in a 10-s time-out during which all lights in the chamber were extinguished, and responses were of no programmed consequence. After the time-out, the response keys were transilluminated with the stimulus corresponding to the step in the chain where the error occurred, the chain did not reset. A session ended after 75 food presentations or two hours, whichever elapsed first.

A sequence consisted of a chain of four correct position responses. There were ten sequences in all, and sequences were changed in arithmetic progression each session. No sequences were used where the monkey could make correct responses by moving left to right or right to left across the three keys (e.g., right-center-left, RCL; or left-center-right, LCR). Also no sequences contained a response chain where two consecutive responses on the same position were correct (RR, LL, or CC). The ten sequences used were: (CLRC), (LRCR), (CRLR), (RCRL), (LCLR), (RLCL), (CRLC), (RLRC), (CLRL), and (LRLC).

Training. The monkeys were conditioned to press the response-keys by beginning with all three keys transilluminated with the last stimulus in the response chain (blue), and a response on any key resulted in delivery of a food pellet. Once key pressing was established, only a press on a predetermined blue key was reinforced. The monkeys were then trained to make a sequence of responses by the addition of another step in the chain. To begin a session the keys were transilluminated with continuous white lights and a response on any key changed the keys to blue. Only a response on the predetermined blue key produced a food pellet. A response on either of the other two keys produced a time-out period. Gradually the chain was extended in this manner (in reverse order) until all four steps of the chain were present. Following extensive training (6–8 months) performance in terms of the pattern of acquisition and overall accuracy stabilized.

Drugs. The drug forms administered and from which the doses were calculated were as follows: cocaine hydrochloride, *d*-amphetamine sulfate, caffeine sodium benzoate, morphine sulfate, and Δ^9-tetrahydrocannabinol (200 mg/ml in ethanol, supplied by the National Institute on Drug Abuse). All drugs were dissolved in physiologic saline (except Δ^9-tetrahydrocannabinol) to a concentration that permitted the desired dose to be injected in a volume of 1 ml/kg body weight. Δ^9-tetrahydrocannabinol, after evaporation of the alcohol, was suspended in 7 drops of Triton X–100, absolute ethyl alcohol in a 2% concentration (calculated as volume percent) and distilled water to a volume which permitted the administration of the desired dose in a volume of 1 ml/kg body weight. The drugs were administered by intramuscular injection into the thigh. Physiologic saline was used for control injections. The Triton X–100, ethyl alcohol solution was administered to determine the effects of the Δ^9-tetrahydrocannabinol vehicle. The session began after the elapse of the appropriate pre-session time allowing for the onset of the drug effect. The pre-session or onset times were: 5 min for cocaine, *d*-amphetamine, and morphine; 30 min for Δ^9-tetrahydrocannabinol and caffeine. The monkeys were tested between 08:30 and 17:00 hours, Monday through Friday. Drugs were tested on Tuesday and Friday with Thursdays used as a vehicle test day.

Dependent variables. Overall rates of responding were calculated by dividing the total number of responses, both correct and incorrect, by the total session time in seconds (session length minus time-out periods and access to the reinforcer). To construct learning curves and measure drug effects on within-session accuracy or within-session percent correct, percent correct, i.e., the number of correct responses divided by the total number of responses emitted (correct and incorrect) was plotted over blocks of reinforcers received. The session was divided into five blocks. Each of the first four blocks contained data for ten reinforcers. Block five contained data for the last 35 reinforcers received. To determine the effect of a drug on overall accuracy total percent correct was calculated by dividing the number of correct responses by the total number of responses emitted per session (random responding would yield less than 2% total percent correct). Following a given dose of a drug, when the rate of responding of a monkey was greatly decreased total percent correct from the session was not plotted nor included in the group mean if 25 or fewer responses per session were emitted, and within-session percent correct was not plotted nor included in the group mean for any one block if the total responses emitted in a block fell below ten responses. The number of monkeys contributing to each mean is indicated next to the appropriate data points. Absence of a number indicates all five monkeys contributed to the data points. Within-session percent correct and total percent correct were determined to be significant using the two sample rank test or Mann-Whitney *U* test ($P \leq 0.05$) (Goldstein 1964).

Results

In Fig. 1 is illustrated the effects of saline, Δ^9-tetrahydrocannabinol vehicle, and all drugs tested on total percent correct (overall accuracy) and the rate of responding. Low doses of cocaine (0.03–0.3 mg/kg) had no consistent effect on overall accuracy nor rate of responding (upper left panel). Higher doses (1.0, 1.8, and 3.0 mg/kg) decreased responding in all monkeys, and a parallel decrease in overall accuracy was observed.

In general, low doses of *d*-amphetamine (0.03 and 0.1) had no effect on the rate of responding nor overall accuracy (upper right panel). The higher dose of 0.3 mg/kg also had little effect on the rate of responding; however, this dose did produce significant decreases in the overall accuracy of responding. In converse, the dose of 0.56 mg/kg had no effect on overall accuracy while significant decreases in the rate of responding were observed. Only at the highest dose of *d*-amphetamine test-

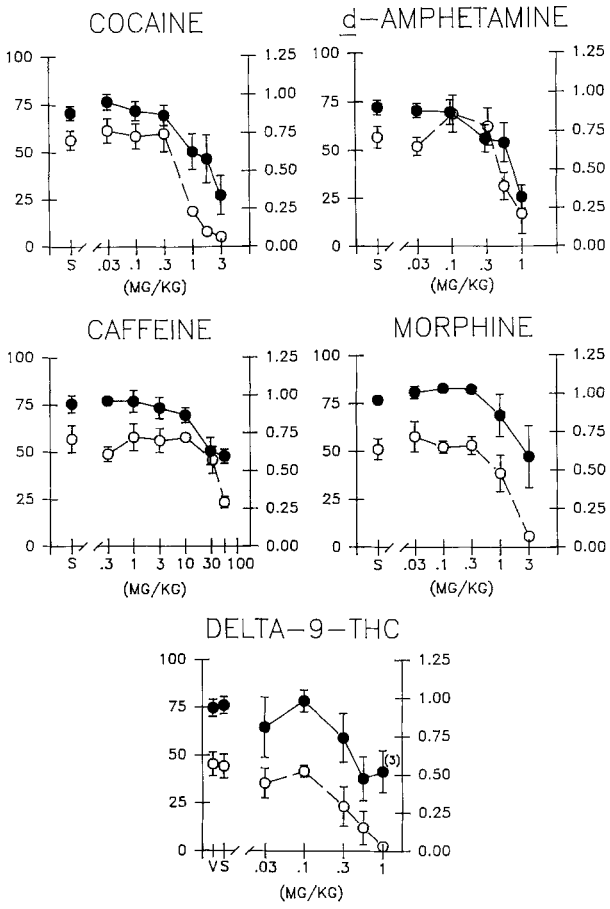

Fig. 1. Effects of various drugs and vehicles tested on total percent correct (●—●) and the rate of responding (○---○). *Abscissa:* dose of drug, log scale. *Ordinate: left axis;* percentage of total number of responses emitted per session that were correct; *right axis;* overall rate of responding. *Points* and *vertical lines* represent the mean ± SEM of single observations in five monkeys. Points above *S* represent the mean ± SEM from three to six saline sessions in each of five monkeys. *Points* and *vertical lines* above *V* represent the mean ± SEM from three Δ^9-tetrahydrocannabinol vehicle sessions in each of five monkeys

ed, 1.0 mg/kg, were significant decreases in both overall accuracy and response rate observed.

The dose response function for caffeine is uneventful in the 0.3–10 mg/kg dose range (center left panel). These doses had no significant effect on either overall accuracy nor response rate. The higher dose of 30 mg/kg caffeine had no significant effect on the rate of responding. However, this dose (30 mg/kg) produced significant decreases in overall accuracy, reflecting the substantial decrease in overall accuracy observed in the majority of subjects. In all subjects, increasing the dose of caffeine to 56 mg/kg resulted in significant decreases in both the rate and overall accuracy of responding.

Low doses of morphine (0.03, 0.1 and 0.3 mg/kg) did not disrupt the rate nor overall accuracy of responding (center right panel). The higher dose of 1 mg/kg morphine did alter behavior in two subjects (not shown), though overall this dose had no significant effects on response rate nor overall accuracy. The highest dose of morphine (3 mg/kg) greatly decreased responding in all subjects; however, the trend toward a decrease in overall accuracy was not significant.

In most subjects low doses of 0.03 and 0.1 mg/kg Δ^9-tetrahydrocannabinol generally had no effect (bottom panel). As the dose was increased to 0.3 mg/kg a significant decrease in response rate was observed, although overall accuracy was unaffected. The effects of higher doses of 0.56 and 1.0 mg/kg Δ^9-tetrahydrocannabinol were consistent among subjects; severe decreases in both response rate and overall accuracy were observed.

In Fig. 2 are illustrated the effects of saline, Δ^9-tetrahydrocannabinol vehicle, and representative doses of all drugs on within-session percent correct (within-session accuracy). During a typical control session baseline performance rapidly improved for each monkey in a similar fashion as demonstrated by the superimposition of the saline control learning curves (lower right panel). For all the drugs tested the lower doses shown in Fig. 1 are not shown in Fig. 2, since they had no significant effect on within-session accuracy. Moderate to high doses of the psychomotor stimulants cocaine (1.0 mg/kg), *d*-amphetamine (0.3 and 0.56 mg/kg), and caffeine (30 and 56 mg/kg) all produced significant downward shifts of the relative position of the learning curves compared to the saline control curve. For cocaine, administration of the higher dose of 1.8 mg/kg did not result in any significant shift in the learning curve. For both cocaine and *d*-amphetamine the highest doses tested (cocaine, 3 mg/kg, *d*-amphetamine, 1 mg/kg) decreased within-session accuracy and consequently shifted the learning curves downward in the one subject able to respond in blocks 4 and 5 at these doses (not shown).

Comparison of the effects of the psychomotor stimulants on the pattern of within-session accuracy revealed cocaine and *d*-amphetamine affected the accuracy of responding in the first few blocks with performance either completely or partially recovering by the last block. For these drugs (cocaine and *d*-amphetamine), doses that affected within-session accuracy also greatly decreased the rate of responding as evidenced by the number of blocks where fewer than five monkeys contributed to each mean. In contrast, caffeine decreased within-session accuracy consistently in blocks 2 through 5 with no apparent recovery of performance. Furthermore, doses of caffeine which decreased within-session accuracy did not disrupt responding as severely as cocaine and *d*-amphetamine, since all monkeys met criteria for the accuracy calculations in each block.

No dose of morphine tested had any significant effect on within-session accuracy (effects of the two highest doses tested are shown in center right panel). However, in each subject 3 mg/kg of morphine produced large decreases in response rate with parallel decreases in within-session accuracy observed in at least one block (effects on overall response rate shown in Fig. 1). In two subjects large decreases were observed in the first block followed by no responding in the remaining blocks, and for the remaining subjects 3 mg/kg morphine decreased both response rate and within-session accuracy in block 5 (individual data not shown). The dose of 0.3 mg/kg Δ^9-tetrahydrocannabinol had no effect on within-session ac-

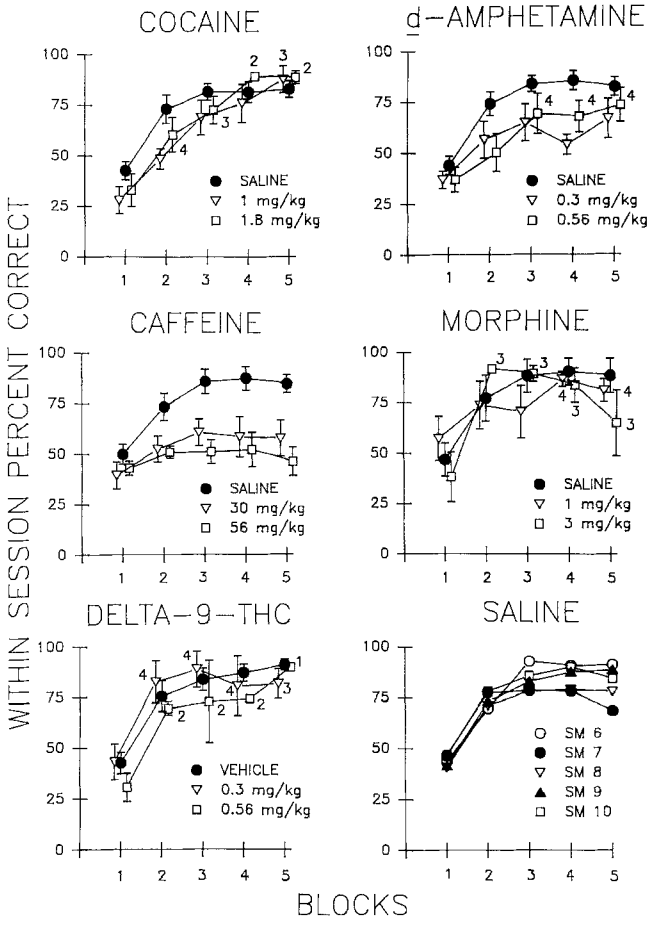

Fig. 2. Effects of the various drugs and vehicles tested on within-session percent correct. *Abscissa:* blocks of reinforcers per session, 10 reinforcers for each block 1 through 4, 35 reinforcers in block 5. *Ordinate:* percentage of total responses emitted per block that were correct. *Drug plots: points* and *vertical lines* represent the mean ± SEM of single observations in five monkeys. *Saline plot: points* represent the mean of five saline sessions for each monkey

curacy, while 0.56 mg/kg disrupted performance, resulting in a significant shift in the relative position of the learning curve downward compared to the saline control curve. Following administration of 1 mg/kg Δ^9-tetrahydrocannabinol within-session accuracy was decreased in SM 6 (not shown), the only subject which completed the session at this dose.

Discussion

The present research clearly shows that a behavioral baseline of repeated acquisition responding can be established in the squirrel monkey. Clearly each monkey when presented with a new sequence would reliably and in a consistent fashion acquire the sequence. This is illustrated by the pattern of improvement in the accuracy of responding subsequent to vehicle administration (Fig. 2, lower right panel).

The psychomotor stimulants examined in this experiment are often abused in the belief that they possess performance enhancing properties. The three psychomotor stimulants tested in the present experiment, cocaine, *d*-amphetamine, and caffeine did not improve performance; moreover, they produced detrimental effects on the accuracy (within-session and overall accuracy) of responding of squirrel monkeys. The present results and other experiments performed in pigeons responding under a repeated acquisition schedule illustrate the inability of these drugs to increase accuracy (Thompson 1973, 1974, 1977; Evans and Wenger 1990). Unlike caffeine, both *d*-amphetamine (Harting and McMillan 1976; Thompson and Moerschbaecher 1980) and cocaine (Thompson and Moerschbaecher 1980; Evans and Wenger 1990) slightly and infrequently increased the accuracy of pigeons responding under a repeated acquisition schedule. As stated previously (McMillan 1979; Thompson and Moerschbaecher 1980), the discrepancies in regard to the ability of cocaine and *d*-amphetamine to increase accuracy or in general terms the sensitivity of the baseline to drugs may depend on the baseline error rate or baseline accuracy. Nevertheless, these experimental differences aside, the majority of studies have demonstrated that in both avian and nonhuman primate species responding under various schedules measuring acquisition, cocaine and *d*-amphetamine have failed to increase the accuracy of responding (Thompson 1973, 1974, 1977; Moerschbaecher et al. 1979; Thompson and Moerschbaecher 1979; Moerschbaecher and Thompson 1980; Thompson et al. 1983). Furthermore, the inability of cocaine and *d*-amphetamine to improve the accuracy of performance does not appear to be limited to acquisition schedules. In experiments designed to measure the effects of these drugs on memory (matching-to-sample), these drugs produced either no effect or decreased matching accuracy at doses which produced marked decreases in the rate of responding (McMillan 1981; Branch and Dearing 1982; Wenger and Wright 1990). Lastly, it should be noted in acquisition schedules where cocaine and *d*-amphetamine increased accuracy these increases were small, demonstrating the limited efficacy of these substances to improve performance (Harting and McMillan 1976; Thompson and Moerschbaecher 1980; Evans and Wenger 1990).

Our results demonstrate that all the psychomotor stimulants tested have the propensity to decrease the accuracy of responding. Most often these drugs decreased accuracy at doses that also decreased responding. Infrequently, caffeine (30 mg/kg) and *d*-amphetamine (0.56 mg/kg) decreased accuracy without affecting the rate of responding. A distinction between the behavioral effects of cocaine and *d*-amphetamine and those of caffeine can be identified by examining their disruptive effects on the pattern of acquisition. Cocaine and *d*-amphetamine do decrease within-session accuracy, though clearly acquisition does occur as indicated by the shape of the learning curve (positive slope) and recovery of performance. In contrast, very little or no acquisition occurs following the administration of high doses of caffeine with no apparent recovery of performance (flat learning curves) during the experimental session. In addition, cocaine and *d*-amphetamine only affected within-session accuracy or acquisition at doses that either de-

creased or eliminated responding of the monkeys. This was not observed for caffeine. Consistent decreases in acquisition were observed in the absence of decreases in rate of responding. This is particularly evident at 30 mg/kg caffeine where the response rate was unaffected in four of the five subjects while within-session accuracy was decreased in all subjects. In a previous study, administration of these psychomotor stimulants to pigeons had little or no detrimental effects on within-session percent correct (Evans and Wenger 1990). In the pigeon these drugs generally eliminated responding before decreases in within-session accuracy were observed. These differences in results may be attributed to differences in species or baseline error rates.

In the squirrel monkey morphine did not significantly decrease accuracy at any dose administered, although the data of individual subjects clearly reveal at the highest dose tested (3 mg/kg) parallel decreases in overall accuracy and response rate. In the present study, the inability of morphine to decrease accuracy unless the rate of responding was significantly decreased is in agreement with studies testing the drug under other procedures measuring the accuracy of responding. In conditional and FR discrimination studies conducted in patas and rhesus monkeys, morphine had no effect on accuracy unless response rates were substantially decreased (Moerschbaecher and Thompson 1983; Moerschbaecher et al. 1984). Like the monkey, the accuracy of pigeons responding under a repeated acquisition or matching-to-sample schedule also was not affected until doses which produce substantial decreases in response rate were administered (McMillan 1981; Thompson and Moerschbaecher 1981). In addition, under a repeated acquisition procedure other μ agonists, heroin and methadone, in patas monkeys (Moerschbaecher et al. 1983) and methadone in pigeons (Cleary et al. 1988) did not disrupt acquisition behavior unless doses which produced large decreases in responding were administered. However, in rats the accuracy of FR discrimination was decreased at doses (1–5.6 mg/kg) which had no effect on the rate of responding (Moerschbaecher et al. 1984). Therefore, unlike pigeons and monkeys, rodents appear to be more sensitive to the disrupting effects of morphine on response accuracy. Overall, this report in squirrel monkeys and others using patas and rhesus monkeys suggest morphine can decrease accuracy at a dose that significantly decreases response rates but has little or no effect at lower doses.

Δ^9-Tetrahydrocannabinol administration significantly decreased the accuracy of responding or the learning of new sequences by squirrel monkeys at doses (0.56 and 1.0 mg/kg) that decreased response rates. Others, injecting Δ^9-tetrahydrocannabinol (0.5 mg/kg) intramuscularly to squirrel monkeys, also observed decreases in accuracy (Branch et al. 1980). However, in patas and rhesus monkeys Δ^9-tetrahydrocannabinol had no effect on the accuracy of repeated acquisition responding (Thompson and Winsauer 1985; Schulze et al. 1988). This contrast in the effects of Δ^9-tetrahydrocannabinol between squirrel monkeys and old world monkeys indicates a dissimilarity in drug sensitivity. In support of this view, differences in drug effects on the accuracy of repeated acquisition responding between squirrel monkeys and old world monkeys were also observed for the stereoisomers of N-allyl-normetazocine (a PCP-like drug) (Moerschbaecher and Thompson 1983; Fu and Moerschbaecher 1990). This differential sensitivity of squirrel monkeys as compared to old world monkeys to the behavioral effects of certain drugs may be useful in identifying facets of the pharmacology of these drugs not observable in other species. In that regard, similar to the effects in squirrel monkeys, acute administration of Δ^9-tetrahydrocannabinol can impair a variety of human behaviors including the ability to acquire new behavior (see review by Hollister 1986); however, it has never been determined whether the observed decrements represent direct effects on learning.

The results of this investigation revealed a novel effect of caffeine and indicated squirrel monkeys to be differentially sensitive as compared to other nonhuman primates to the effects of Δ^9-tetrahydrocannabinol on acquisition behavior. These findings provide new insights into the effects of drugs on learning and therefore promote the squirrel monkey as a valuable species to investigate the effects of drugs and chemicals on learning.

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