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Effects of Caffeine on DRL Performance in the Mouse[1]

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WEBB, D. AND T. E. LEVINE. *Effects of caffeine on DRL performance in the mouse*. PHARMAC. BIOCHEM. BEHAV. 9(1) 7–10, 1978.—Mice were trained to stable and efficient DRL 18 sec performance utilizing a nose-poke as the operant. Caffeine, at doses less than 48 mg/kg, increased both response bursts (IRTs<3 sec) and longer IRTs, and shifted the IRT distribution towards shorter, nonreinforced IRTs. Auditory feedback for responses decreased the number of bursts emitted and produced performance more resistant to drug effects. These results are similar to those previously reported for caffeine on DRL in the rat, and for amphetamine on DRL in a variety of species.

Caffeine DRL Auditory feedback Nose-poke

NONMEDICALLY, caffeine is the most widely used central nervous system stimulant [2]. In addition, it has been used clinically in the treatment of hyperkinetic children [7, 8, 17]. However, it has received little attention in the operant literature. The first report of the effects of caffeine on schedule-controlled behavior was by Skinner and Heron in 1937 [21]. They found an increased rate of responding under a fixed-interval 4 min schedule of food reinforcement and during extinction in rats given 10 mg caffeine sodio-benzoate SC. The increase in rate of responding following caffeine administration has been confirmed in a variety of experimental paradigms and species. These include a two-lever fixed-interval and fixed number schedule in the rat [15], fixed-interval and Sidman avoidance schedules in the squirrel monkey [5], and fixed-interval schedules in the mouse [14].

The purpose of the present study was to expand the investigation of caffeine to another schedule of reinforcement which has proved sensitive to the effects of central nervous system stimulants, the differential reinforcement of low rates (DRL) schedule [6, 19, 20]. An additional purpose was to investigate the performance of a relatively unstudied species, the mouse, on the DRL schedule and to determine whether auditory feedback for responses would affect performance on this schedule.

METHOD

Animals

Four naive male laboratory mice (CD–1, Charles River, Wilmington, MA 01887) were used. Each was maintained at approximately 90% of free-feeding weight by restricting fluid intake. The mice were about 50 days old at the beginning of training.

Apparatus

The experimental apparatus was similar to one used by Wenger and Dews [24]. The chamber consisted of a 20×10×20 cm Plexiglas enclosure with a solid Plexiglas floor [12]. The floor and front panel were black; all other panels were clear. The front panel contained a circular aperture 2.2 cm in dia positioned to right of center and 0.5 cm above the floor. A response consisted of a nose-poke into this opening which interrupted a light beam falling on a photoresistor. A liquid dipper (BRS/LVE Model 114–02) delivered the reinforcer, 0.01 cc milk solution (equal parts evaporated milk and water) through a 1.4 cm dia hole in the floor centered 4 cm from the front of the chamber. The bottom of the milk trough was lined with sponge and the dipper arm was padded where it made contact with the stop screw to minimize auditory cues associated with lowering and raising the dipper, respectively. A loud clicking relay, mounted on the chamber ceiling, was used as an auditory stimulus. A houselight centered on the front panel 8 cm from the ceiling remained on during the experimental session. The chamber was contained within sound-attenuating housing, ventilated by an exhaust fan. Chamber events and data collection were controlled by a PDP8/e computer.

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Procedure

The mice underwent no systematic response-shaping; each was simply given 1 hr exposure to a continuous reinforcement schedule, i.e., every response reinforced. All animals acquired the nose-poke during this time and made more than 100 responses. Training on the DRL 18 sec schedule began the following day. Under this schedule, a response is reinforced only if at least 18 sec have elapsed since the animal's previous response; premature responses reinitiate timing of the 18 sec waiting period. On the DRL schedule, two mice (M6 and M7) received a relay click as auditory feedback for each response. For the remaining two (M0 and M1) no auditory feedback was provided. Experimental sessions were 45 min long and took place seven days a week. Animals were given 45 min access to water immediately after each session. Food was continuously available in the home cage.

After 28 hr of training on the DRL schedule, a series of caffeine injections was attempted, but as stable baseline performance between drug administrations proved difficult to recapture, it was decided to provide more training. Subsequently, the mice were transported to a different laboratory and given 55 hr of additional exposure to the DRL schedule with all parameters the same. Performance was stable in all animals at this time, and the series of caffeine administrations described below was then begun.

Caffeine was administered IP in an isotonic saline solution at a volume of 0.01 cc/g body weight. Dosages were 6, 24, 3, 12, 0, and 48 mg free base/kg body weight and were given in that order for each animal. A control injection consisted of saline alone and is designated as "0" above and on figures. On drug days the mice were injected and then placed in a holding cage for 30 min prior to the experimental session. Each successive dose was administered when stable day-to-day performance was evidenced. Stability was defined as less than 5% difference between the day preceding the injection day and the current four-day mean with respect to both responses (excluding IRTs<3 sec) and number of reinforcements. At least seven experimental sessions intervened between each drug injection.

RESULTS

Figures 1 and 2 show separately the effects of caffeine on the two distinct classes of interresponse times (IRTs) which characterize performance on the DRL schedule. The first of these (Fig. 1) involves very short IRTs, termed bursts of responding [20]. The second (Fig. 2) comprises longer IRTs, the distribution of which typically shows a mode at or near the minimum reinforced IRT. In general, both classes of IRTs showed increases in frequency with increasing drug dose to a maximum at between 12 and 24 mg/kg, and decreases at higher doses (as probable toxic doses were reached). There were no overt behavioral effects, i.e., ataxia or hyperactivity at any of the doses tested.

Some differences are apparent, however, between the curves for M6 and M7 (the mice that received auditory feedback for responses) and those for M0 and M1. M0 and M1, the nonfeedback group, emitted many more short IRTs than M6 and M7 on nondrug days. Figure 1 shows the mean and range of the number of IRTs<3 sec per session for control days for each of the four mice. The control values are based on the days immediately preceding each drug day (a total of 6 days per mice). On control days, the mean number of IRTs

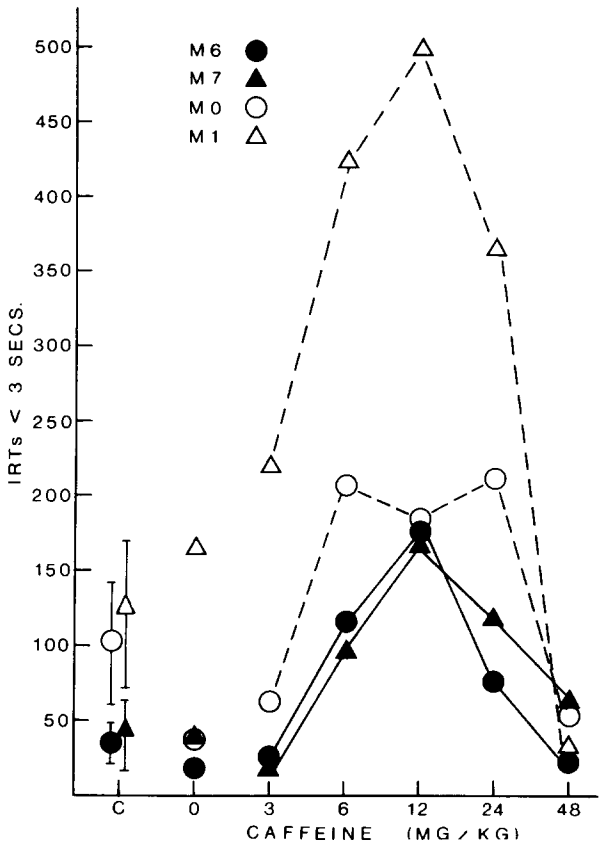

FIG. 1. IRTs<3 sec per session for each caffeine injection (3–48 mg/kg), for the saline injection (O), and the mean and range of six nontreatment days (C). The nontreatment control consists of the day immediately preceding each injection day. Data for each subject are plotted individually.

<3 sec per session is 3–4 times larger for M0 and M1 than for M6 and M7. The range is also wider for the nonfeedback animals, evidencing greater day-to-day variability in the number of short IRTs emitted. This contrast between the two groups became even more pronounced under the drug. Note that even at the lowest dose (3 mg/kg), some increase was in evidence for M0 and M1. There was also a difference between the two groups with respect to the emission of longer IRTs (Fig. 2). As the drug dose was increased, the mice without the feedback (M0 and M1) displayed a smaller and more gradual rise in the frequency of these longer IRTs than did the other two mice. The peak effect on long IRTs occurred at 12 mg/kg for the feedback group, whereas for the nonfeedback group, 24 mg/kg was maximally effective.

The forms of the IRT distributions can be seen in Fig. 3. This figure shows the proportion of the total experimental session time consumed by IRTs of various lengths, dwelling time [22]. This measure weights IRTs of different lengths more equitably than does a relative frequency distribution and prevents larger changes in the frequency of short IRTs from diminishing the remainder of the distribution. The distributions for the saline injections were typical of those for noninjection days and displayed a mode at about the minimum reinforced value. As can be seen, caffeine shifted this mode to progressively shorter IRT values, decreasing the incidence of reinforced IRTs. The contrast between M7 and

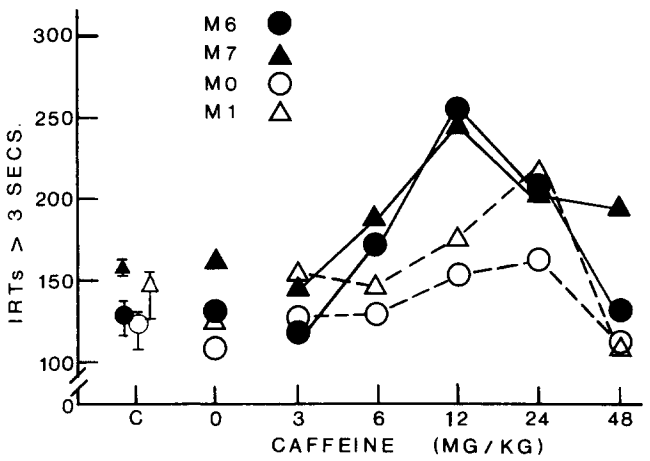

FIG. 2. IRTs<3 sec per session for each caffeine injection (3–48 mg/kg), for the saline injection (O), and the mean and range of six nontreatment days (C). The nontreatment control consists of the day immediately preceding each injection day. Data for each subject are plotted individually.

M1 (also between M6 and M0, not shown) in the size of the first bin illustrates the effect of the presence or absence of the auditory feedback in controlling the response bursts which comprise this bin. While all animals showed dose-dependent changes in the frequency of these short IRTs, the magnitude of the change was much greater for M0 and M1 (no feedback) than for M6 and M7 (feedback). At the two highest doses (24 and 48 mg/kg), M7 continued to show a distribution with a well-defined mode, albeit at IRT values below the minimum reinforced value. For M1, on the other hand, the distribution completely flattened out at 24 mg/kg and was characterized by many long IRTs at 48 mg/kg, as responding was greatly reduced. M6 and M0 exhibited flattened distributions at 24 mg/kg and a large number of very long IRTs at 48 mg/kg, similar to the distribution for M1.

DISCUSSION

The results reported above indicate that mice are capable of stable DRL performance comparable to that found in rats, monkeys, and humans. This extends the results of Wenger and Dews [24] with FI and FR performance in mice to another schedule of reinforcement. It has previously been reported that mice perform poorly on DRL schedules [4,13]. Carlsson *et al.* [4] only monitored performance of their mice on a DRL 8 sec schedule for 15 days, a short training time for this schedule. Maurissen [13], however, failed to produce temporal patterning on a DRL 30 sec despite 90 hr of training. As we did not extend our DRL requirement past 18 sec, we cannot comment on whether this difference in performance is due to the DRL requirement, the strain of mouse used, or the numerous other methodological differences between the two studies (lever press vs. nose poke, solid vs. liquid reinforcer).

The effects of caffeine on DRL performance in the mouse are similar to those reported for amphetamine and other stimulants in rats on the same schedule: an increase in response rate corresponding to a greater amount of bursting and a shift of the distribution toward short IRT values [1, 16, 18, 19]. Ando [1] found a similar effect of caffeine, although

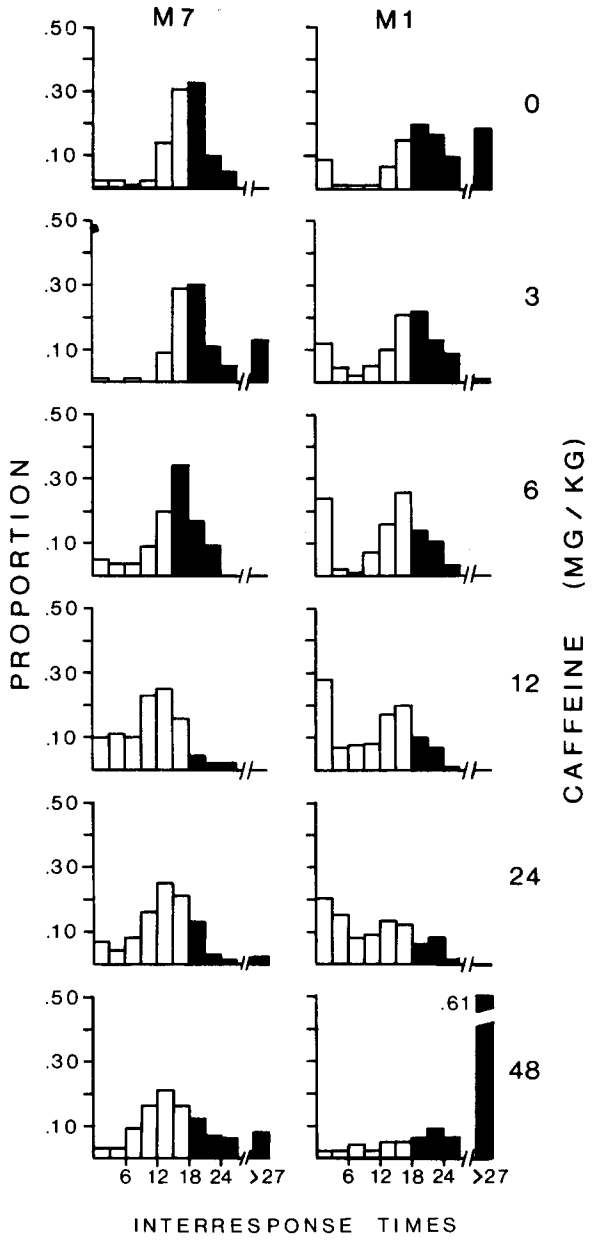

FIG. 3. IRT distributions showing the proportion of total experimental session time consumed by IRTs of various lengths. Data are included for one feedback subject (M6) and one nonfeedback subject (M1) for each dose of caffeine (3–48 mg/kg) and for the saline injection (O). IRT bins are 3 sec wide. Shaded bars indicate reinforced IRTs. The last bin accumulates all IRTs>27 sec.

less marked, on DRL performance in the rat. The smaller effect may have been due to the dose range chosen, the short (5 min) pretreat time, and the subcutaneous route of administration. Mechner and Latranyi [15] and Davis *et al.* [5] found that caffeine increased response rate on FI at doses of 3 mg/kg or less—the former with rats, the latter with squirrel monkeys.

Short IRTs are never reinforced on DRL and a satisfactory explanation for their occurrence is at present lacking. Kramer and Rilling [9], however, noting that response bursts

occur almost exclusively following nonreinforced responses, suggest that a nonreinforced response may fail to inform the animal unambiguously that a criterion response has been emitted. Our data are consistent with such an interpretation, since clear exteroceptive feedback for responses greatly diminished response bursts. The feedback also attenuated the rate-increasing effects of caffeine for M6 and M7. This attenuation is consistent with several studies reporting that behavior under the control of exteroceptive stimuli is more resistant to the effects of certain drugs than behavior under the control of interoceptive stimuli [10, 11, 23]. The selective changes in short IRTs on DRL suggests that it may be more meaningful to evaluate bursts and longer IRTs separately when looking at drug effects and other experimental manipulations on this schedule. Such an analysis of response rate, in terms of its component IRT classes, has previously been reported for the effects of water deprivation and amphetamine on fixed-interval, fixed-ratio, and variable-interval behavior [3].

In summary, mice can acquire stable and efficient DRL 18 sec performance. Auditory feedback for responses decreases the number of short IRTs emitted and produces performance more resistant to drug effects. Caffeine has very similar effects on the DRL schedule in the mouse to those previously reported for caffeine and amphetamine in the rat: increases in short IRTs and a shift of the IRT distribution towards shorter, nonreinforced IRTs. The prevalent use of caffeine, both clinically and nonmedically, warrants increased behavioral investigation of this compound. The present results suggest that the mouse is a suitable species for such behavioral work.

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