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Effects of Chlorpromazine on Continuous Avoidance Behavior in Mice

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DAVIDSON, A. B. *Effects of chlorpromazine on continuous avoidance behavior in mice.* PHARMAC. BIOCHEM. BEHAV. 17(3) 385–387, 1982.—Previous reports have indicated that self-trained appetitive operant schedules of reinforcement can be acquired readily by mice using an apparatus which detects head movement responses. Using a similar apparatus, suitably modified, the utility of this methodology has been extended to an operant schedule of reinforcement in which behavior is maintained by an aversive shock stimulus. As previously demonstrated with various other CNS active drugs in the appetitive mouse procedures, the effects of chlorpromazine in the mouse continuous avoidance procedure described here were similar to those obtained in analogous standard rat procedures. These results increase the opportunities for experimenters to avail themselves of the advantages offered by the use of mice, rather than rats, in operant behavioral pharmacology.

Chlorpromazine Continuous avoidance Mice Head-poke response

ALTHOUGH the rat appears to be the most commonly used species in studies in behavioral pharmacology, the mouse offers many advantages. Mice are cheaper, easier to house, require smaller amounts of drug, and are generally easier to handle than rats; a similar, large body of biological data is also available. The use of an apparatus which measures head movement responses of mice in an appetitive operant procedure has been reported [7,8] thereby overcoming problems associated with the use of conventional lever manipulanda in such procedures, including the labor intensive task of shaping the response. That prior study demonstrated that the effects of several CNS active drugs were similar in mice, self-trained on an appetitive multiple FI:FR schedule of reinforcement, to those obtained with rats and other species on a similar schedule of reinforcement in conventional operant apparatuses. Other investigators have successfully used this procedure to study the effects of CNS active drugs on DRL performance and also found that the effects obtained were similar to those obtained with rats [1,6]. However, there are no reports on the use of this methodology for aversively controlled operant behavior in mice.

We demonstrate in this report that an aversive schedule of reinforcement, continuous avoidance, is readily acquired by mice using a head movement response procedure. In addition, the sensitivity of this procedure to the characteristic effects of a standard pharmacological agent, chlorpromazine, on continuous avoidance responding is described.

METHOD

Animals

The subjects were male CD-1 mice (Charles River), weighing 15–20 grams upon their arrival. They were group housed in a standard polypropylene mouse cage and were given ad lib food and water in their home cage; testing was conducted during the normal work day.

Apparatus

Except that the experimental chamber was specially constructed and differed somewhat in dimensions, it was essentially similar to that reported previously [8]. The chamber was made of clear Plexiglas with a stainless steel grid floor, used for delivering footshock to the animals. The chamber was 15.25 cm long, 10 cm wide, and 10 cm high. The grid floor consisted of stainless steel rods (0.24 cm in diameter) set uniformly apart along the floor of the chamber such that the distance between their centers was 0.95 cm. The grids were connected to the scrambled output of a Grason-Stadler Model 700 shock generator. At one end of the chamber was a small "alcove." The alcove was approximately 3.8 cm wide, and 3.8 cm deep; it had a sloping roof which was 4.76 cm high at the alcove entrance and touched the grid floor at its rear. The shape and size of the alcove prevented the mice from escaping the shock by wedging themselves between the walls of the alcove. Mounted 1.8 cm deep within the alcove was a photocell and light pair approximately 1.25 cm above the grid.

The chamber was mounted on a wooden base and placed inside a larger sound attenuating chamber approximately 50 cm long, 43 cm wide, and 61 cm high, ventilated by a fan. Mounted on the ceiling and the back of the larger chamber were a 6-watt, 24-volt light bulb and a speaker, respectively.

Procedure

Training and testing were standardized for all mice and were conducted in daily one hour sessions, Monday through

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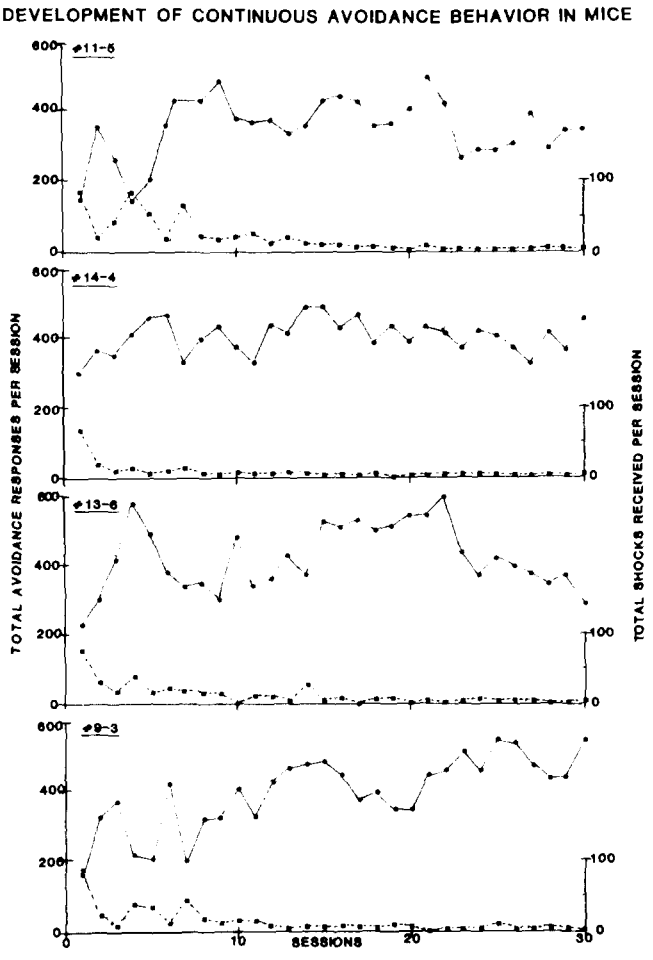

FIG. 1. Development of continuous avoidance behavior. For each of the mice used in this experiment, total avoidance responses (circles and solid lines; refer to scale on left) and total shocks received (squares and broken line; refer to scale on right) are shown for every session from the start of training through the 30th session. Values obtained on each day of drug administration and the immediately following day were omitted.

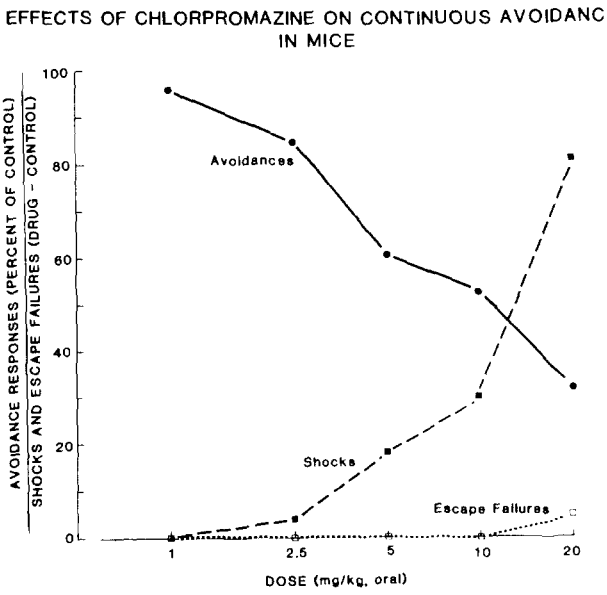

FIG. 2. Effects of chlorpromazine on continuous avoidance behavior. Group mean values are shown on the ordinate in terms of percent of control, for avoidance responses after drug administration, and differences between drug and control, for the number of shocks received and failures to escape shock.

Friday. The parameters employed in the continuous avoidance procedure [5] were a shock-shock (SS) interval of 20 seconds with a shock duration of 5 seconds and intensity of 0.5 mAmp, and a response-shock (RS) interval of 40 seconds. Each time a mouse placed its head within the alcove, the photocell beam was broken and a response was recorded. Each response was accompanied by an audible click delivered through the speaker. The mice could avoid the unsignalled shocks by responding prior to the elapse of the RS or SS interval and could terminate (escape) an ongoing shock by a response. During the course of the one-hour session the ceiling light remained on.

The experimental contingencies and the raw data (number of responses, number of shocks, and number of escape failures for each animal) were controlled and collected by means of a Data General Nova II computer and a BRS Interact experimental control system.

Two of six mice failed to acquire stable performance after 30 sessions and were dropped from the study. The remaining four mice achieved levels of stable performance, with less than 10 shocks per session, without any experimenter intervention, after 12–15 (mean=13.5) sessions.

Chlorpromazine (Smith Kline and French Labs) was administered orally in aqueous solution, by intubation, one hour before the experimental session. Doses of 1, 2.5, 5, 10, or 20 mg/kg were administered to each mouse on a Thursday with a minimum of one week between druggings. For each mouse, results on the day of drug administration were compared to its mean control values from the previous three days. A difference which exceeded 2 standard deviations from the mean was considered significant.

RESULTS AND DISCUSSION

At the beginning of the self-training procedure, the mice responded to the shocks by running about the chamber, jumping, and attempting to enter the alcove containing the response photocell. Interruption of the light beam by the last of these activities terminated the shock. The frequency of head insertions into the alcove, and subsequently of more discrete head movements within the alcove, increased over the next few sessions resulting in fewer and eventually only occasional shock presentations. Total responses and shocks for the mice used in this experiment are shown in Fig. 1 for all non-drug sessions from the start of training through the 30th session to illustrate the development and maintenance of this behavior. Shock rate, the more sensitive measure of drug activity in such continuous avoidance procedures [4], was more stable in all mice than avoidance rate. Avoidance rate was reasonably stable but showed some cyclic variation. Every mouse terminated every shock delivered within 5 sessions after the start of training.

The effects of chlorpromazine, in this group of mice, are summarized in Fig. 2. There was a continuous essentially

monotonic decrease in avoidance response rate with increasing doses. Shock delivery increased at a positively accelerated rate. The median Minimum Effective Doses (MEDs) for significantly decreasing avoidance responding and increasing shocks were 3.75 and 2.5 mg/kg, respectively, based on effects in each animal.

In a similar situation in which rats exhibited no instances of escape failure in control sessions, other investigators arbitrarily selected a value of 4 escape failures to indicate a significant difference from control [4]. These investigators proposed that escape failure was a measure of an impaired capacity to respond and that the ratio of escape failure MED to shock increase MED (dose-range-ratio) was an estimate of the "effective dose range" of a drug. Since two of the mice in this experiment did not fail to escape, even at the highest dose tested, the median dose-range-ratio for chlorpromazine could not be determined, but was at least 6.

Conclusions

The procedure and apparatus described here permitted reasonably rapid training of mice to stable levels of performance on a continuous avoidance operant schedule without the need for response shaping or other experimenter involvement. The resultant behavior was sensitive to the effects of chlorpromazine, a standard reference drug in avoidance procedures. The effects of chlorpromazine in this mouse procedure were similar to those reported previously [4] using the same parameters in a similar procedure in rats. Indeed, the sensitivity of this procedure to the potency of chlorpromazine, based on changes of shock rate, was somewhat greater than that reported in that study. The wide effective dose range of chlorpromazine measured in this procedure agrees with its high specificity (i.e., avoidance block without escape block) in more discriminating discrete avoidance procedures (e.g., [2,3]).

These results extend the utility of the apparatus and head movement response, using mice as experimental animals, to operant schedules based on aversive reinforcement in addition to the appetitively reinforced operant schedules previously reported.

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REFERENCES

1. Balster, R. L. and J. B. Baird. Effects of phencyclidine, *d*-amphetamine and pentobarbital on spaced responding in mice. *Pharmac. Biochem. Behav.* **11:** 617–623, 1979.
2. Cook, L. and E. Weidley. Behavioral effects of some psychopharmacological agents. *Ann. N.Y. Acad. Sci.* **66:** 740–752, 1957.
3. Davidson, A. B. and E. Weidley. Differential effects of neuroleptic and other psychotropic agents on acquisition of avoidance in rats. *Life Sci.* **18:** 1279–1284, 1976.
4. Heise, G. A. and E. Boff. Continuous avoidance as a base-line for measuring behavioral effects of drugs. *Psychopharmacologia* **3:** 264–282, 1962.
5. Sidman, M. Avoidance conditioning with brief shocks and no exteroceptive warning signal. *Science* **118:** 157–158, 1953.
6. Webb, D. and T. E. Levine. Effects of caffeine on DRL performance in the mouse. *Pharmac. Biochem. Behav.* **9:** 7–10, 1978.
7. Wenger, G. R. and P. B. Dews. The effects of some CNS active drugs on schedule-controlled behavior maintained by food presentation in the mouse. *Fedn Proc.* **34:** 766, 1975.
8. Wenger, G. R. and P. B. Dews. The effects of phencylidine, ketamine, *d*-amphetamine and pentobarbital on schedule-controlled behavior in the mouse. *J. Pharmac. exp. Ther.* **196:** 616–624, 1976.