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Differential Effects of Imipramine in Rats as a Function of DRL Schedule Value[1]

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McGUIRE, P. S. AND L. S. SEIDEN. *Differential effects of imipramine in rats as a function of DRL schedule value.* PHARMAC. BIOCHEM. BEHAV. 13(5) 691–694, 1980.—Imipramine, a tricyclic anti-depressant, has selective effects on differential-reinforcement-of-low-response-rate (DRL) schedule performance as a function of schedule value. On a DRL 9-sec schedule of water reinforcement, imipramine at doses of 2.5 to 20.0 mg/kg resulted in no significant change in the number of reinforcements or responses. A dose of 5.0 mg/kg imipramine, given to rats performing on a DRL>72-sec schedule, produced a significant increase in the number of reinforcements and a concomittant decrease in responses. This effect was associated with a shift in the inter-response time (IRT) distribution to longer IRTs. Higher doses (20.0 and 40.0 mg/kg) decreased both response rate and reinforcement rate on the DRL 72-sec schedule. These findings demonstrate the importance of schedule parameters in determining the behavioral effects of imipramine.

Imipramine DRL Schedule parameters Operant behavior Drug-behavior interactions

ON differential-reinforcement-of-low-rate (DRL) schedules, a response is reinforced only if it occurs after a specified period of time since the last response [11]. The DRL schedule generates a pattern of responding characterized by low, stable response rates. Values of 15.0–22.0 sec have been the most extensively investigated especially in the assessment of drug effects on DRL performance [2, 9, 10]. DRL schedules of less than 15-sec and greater than 36-sec have received only limited investigation [1,5].

The importance of ongoing behavior as a determinant of drug effects is well established in the behavioral pharmacology literature [5,10]. We have previously reported the effects of imipramine on a DRL>18-sec schedule [8]. Imipramine administered to rats performing on this schedule increased reinforcement rate and decreased response rate at doses of 2.5, 5.0 and 10.0 mg/kg. To determine whether DRL schedule parameters are determinants of the effects of imipramine, we have compared the effects of imipramine on DRL schedules which differ in interresponse requirements. One group of rats received water reinforcement for responses occurring more than 9-sec apart (DRL>9-sec) and another group received water reinforcement for responses occurring more than 72-sec apart (DRL>72-sec). The effects of imipramine differed as a function of schedule value. On DRL>9-sec, imipramine had little effect on response or reinforcement rate; on DRL>72-sec, imipramine decreased response rate at all doses tested and increased reinforcement rate at a dose of 5.0 mg/kg.

METHOD

Animals

The experimental animals were 10 male Sprague-Dawley rats (Holtzman Co., Madison, WI), 90 days of age and weighing between 250 and 350 g at the beginning of the experiment. They were housed two to a cage in a temperature controlled (23°C) colony room and were water deprived for 23 hours before each one hour session. Standard laboratory chow was available at all times except during the experimental session. Following each session, water was available for an additional 10 minutes.

Apparatus

The experimental chambers were ten modified Gerbrands rat chambers (Model C). Each chamber was equipped with a white houselight and a LeHigh Valley response lever. A static force of 20–30 g was required to operate the lever. A solenoid-operated dipper delivered 0.05 ml of water. Each chamber was enclosed in a modified Coleman camping cooler equipped with a ventilating fan.

The experimental chambers were interfaced to a PDP-8E computer which controlled schedule contingencies and recorded responses, reinforcers and sequential interresponse times [13,14]. A interresponse time (IRT) is defined as the interval between two successive microswitch closures. Each IRT was recorded with a resolution of 0.1 sec. Data were analyzed off-line by the same computer.

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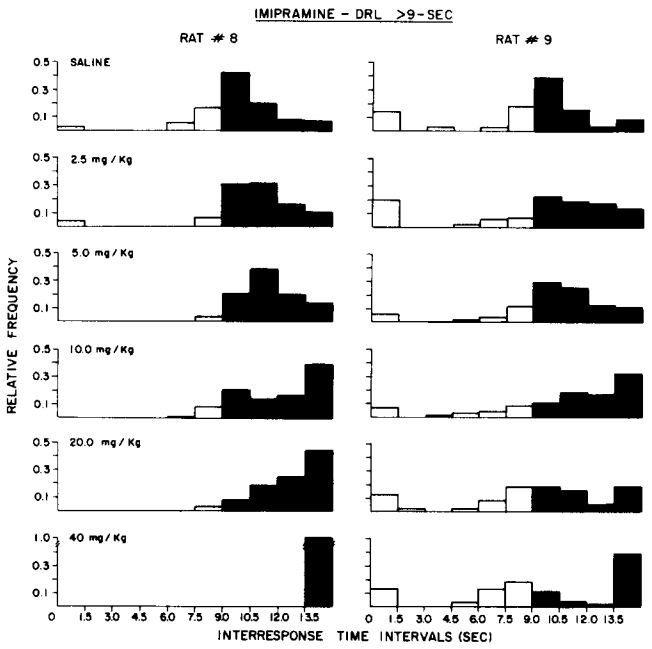

FIG. 1. The effect of saline and doses of imipramine on the IRT distribution of two rats performing on a DRL>9-sec schedule. Data are plotted as relative frequency. Each bar represents a 1.5-sec interval. Shaded bars represent reinforced IRTs.

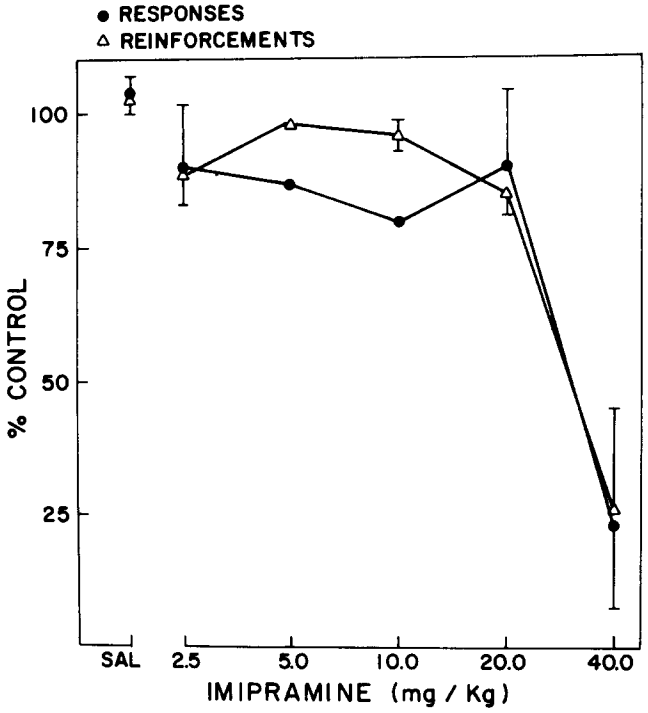

FIG. 2. The effect of imipramine on DRL>9-sec schedule performance. Filled circles (●) are responses: open triangles (△) are reinforcements. Brackets represent 1 ± SEM. All data are percent control. Control is defined as the mean of the three days before an injection.

Procedure

Following 5 days adaptation to the water deprivation schedule, rats were allowed to acquire the lever press response on a fixed ratio 1 schedule. After 3 days on this schedule, all rats had experience on a DRL 18-sec schedule. Subsequently, the schedule parameter was changed to DRL 9-sec for 5 rats and DRL-72 sec for 5 rats. On a DRL schedule only responses occurring after a specified time interval are reinforced. Responses occurring earlier than the minimum time reset a timer, reinitiating the interval. The experimental sessions lasted one hour per day and were conducted 7 days per week. Drug testing was initiated when responding had stabilized (approximately two months).

Drugs

Imipramine HCl (CIBA Pharmaceutical Co., Summit, NJ) was dissolved in 0.9% NaCl (1 ml/kg). 0.9% NaCl (1 ml/kg) was used for control injections. All injections were given IP one hour prior to the experimental session.

RESULTS

On the DRL>9-sec schedule, the rats typically responded predominantly after 9-sec. The response distribution was unimodal with the peak occurring between 9.1 and 10.5-sec. Very few short IRTs (0.1–1.5 sec) occurred (Fig. 1). Total responses across all animals for the one hour session ranged from 176–209.

On the DRL>9-sec schedule, although there were not statistically different changes in the overall response rate or reinforcement rate at doses of 2.5–20.0 mg/kg imipramine (Fig. 2), changes in response patterning consistent with our former experiment [7] were observed. Doses of 2.5–10.0 mg/kg imipramine decreased the frequency of IRTs less than 9.1-sec while the frequency of IRTs greater than 9.1-sec was increased (Fig. 2). This was typical of all rats tested. Mean pause length, defined as interresponse times greater than 1.5-sec, increased slightly at 2.5, 5.0, 10.0 and 40.0 mg/kg IMI.

On the DRL 72-sec schedule, 3 of the 5 rats displayed a bimodal IRT distribution with the first mode including short IRTs (0.1–12.0-sec) and the second mode occurring around 72-sec. For the other 2 rats, the distribution remained flat with the highest frequency of responding occurring in the 0.1–12.0 sec interval. Total responses for the session ranged from 60–139; reinforcements ranged from 4–25.

Doses of 5.0 and 10.0 mg/kg of imipramine resulted in a significant increase in reinforcements (paired t-test) on the DRL>72-sec schedule (Fig. 3). This was associated with a decrease in responses, an effect also seen with doses of 10.0, 20.0 and 40.0 mg/kg.

The IRT distributions for the rats performing on DRL 72-sec are shown in Fig. 4. Although patterning under saline control differed for the rats, nonreinforced responses were decreased while reinforced responses were increased at 2.0–10.0 mg/kg IMI for all animals. Higher doses of IMI (20.0 and 40.0 mg/kg) did not have consistent effects on DRL>72-sec performance. All doses tested increased mean pause length defined as interresponse times greater than 12.0-sec (Table 1). However, the mean increase never exceeded 70-sec.

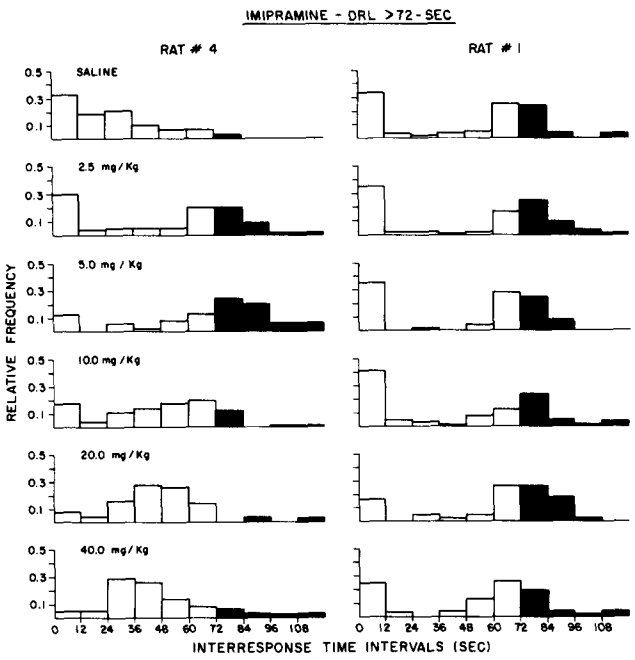

FIG. 3. The effect of imipramine on DRL>72-sec schedule performance. Filled circles (●) are responses; open triangles (△) are reinforcements. Brackets represent 1 ± SEM. All data are percent control. Control is defined as the mean of the three days before an injection.

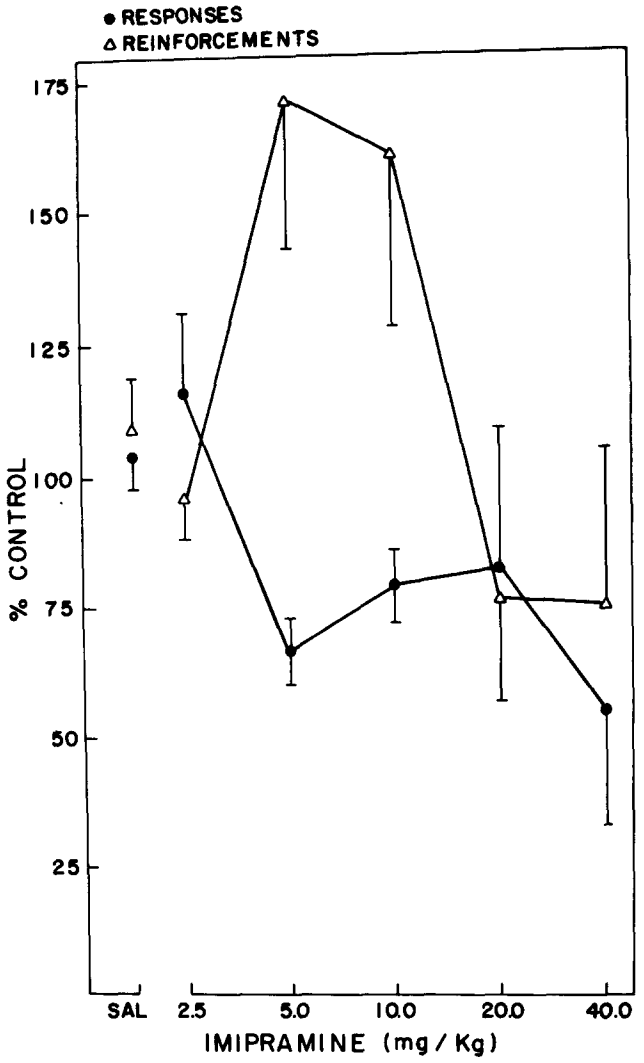

FIG. 4. The effect of saline and doses of imipramine on the IRT distributions of two rats performing on a DRL>72-sec schedule. Data are plotted as relative frequency. Each bar represents a 12-sec interval. Shaded bars represent reinforced IRTs.

DISCUSSION

These experiments have compared the effects of the tricyclic antidepressant, imipramine, on differential-reinforcement-of-low-rate schedules which differed in schedule parameters. Imipramine has a selective effect on performance as a function of schedule value. DRL>9-sec, is a short interval which generates a pattern of responding where approximately 60% of all responses are reinforced. Administration of imipramine to rats performing on DRL>9-sec had no effect upon response and reinforcement rates over doses ranging from 2.5 to 20.0 mg/kg. In contrast, performance on DRL>72-sec schedules is characterized by low density of reinforcement with only approximately 20% of all responses reinforced. Imipramine at two doses, increased the number of reinforced responses while nonreinforced responses were decreased.

Investigations of drug effects on DRL schedules have

TABLE 1

MEAN PAUSE LENGTH (sec)

	Saline	2.5	5.0	10.0	20.0	40.0
				Dose (mg/kg)		
DRL>9-sec*	10.6 ± 0.09	12.1 ± 0.20	11.1 ± 0.08	12.5 ± 0.29	10.0 ± 0.06	26.4 ± 6.9
DRL>72-sec†	47.3 ± 1.5	54.6 ± 1.9	69.9 ± 1.8	60.8 ± 2.9	62.5 ± 7.8	58.5 ± 8.3

*Pause length is defined as all interresponse times greater than 1.5-sec. Each value is the mean ± SEM for five animals.

†Pause length is defined as all interresponse times greater than 21.1-sec. Each value is the mean ± SEM for five animals.

concentrated on DRL values in the range of 15.0–40.0 sec [3, 6, 7]. A partial explanation for the selection of these parameters may be related to the pattern of responding generated. Typically, the IRT distribution is either bimodal with one mode consisting of short IRTs (0.1–3-sec) and the other mode occurring near the required schedule value or unimodal in which case few short IRTs occur. DRL values of 15, 18 and 20-sec have been employed in the investigation of the behavioral effects of imipramine [3,6]. McGuire and Seiden [8] have reported an increase in reinforcements and a decrease in responses when rats performing on a DRL>18-sec were treated with 5.0 and 10.0 mg/kg imipramine. The largest increase produced by imipramine in the present study with DRL>72-sec is greater than the effect on DRL>18-sec. The absence of a similar effect of imipramine on DRL 9-sec supports the importance of baseline response patterning as a determinant of imipramine's effect.

Comparing doses of imipramine across varying DRL parameters suggests that the effect of imipramine is a function of the schedule value rather than a non-selective rate decreasing effect. For example, administration of imipramine to rats performing under a DRL>9-sec schedule resulted in a maximum increase in mean pause length of 26.4 sec at 40.0 mg/kg, the highest dose tested. The maximum increase in mean pause length on the DRL>72-sec occurred at 5.0 mg/kg imipramine. At this dose, mean pause length was increased to 69.9 sec. If the effect of imipramine was non-selective, perhaps a sedative effect, pauses of equal duration, would be expected regardless of schedule value.

By definition, the DRL schedule produces low rates of responding on the DRL>9-sec schedule, the average response rate ranged from 2.9–3.5 responses/min. The DRL>72-sec schedule produces an average rate of 1.0–2.3 responses/min. Thus, it might be predicted that imipramine would increase response rates on DRL schedules. None of the doses tested produces an increase in response rate, in fact, imipramine decreased response rates on the DRL>72-sec schedule. Examination of the IRT distributions for both schedules, however, does suggest rate dependency within each schedule. The IRT distributions show a slight decrease in short IRTs (which occur with a higher frequency) and some increase in long IRTs, (which occur at a lower frequency) especially on the DRL>72-sec schedule and as such suggests rate dependent effects when local response rates are considered.

The interaction of response rates and patterns of response distribution is necessarily complex and an issue which deserves further experimental investigation. These authors feel that the effects of imipramine and other tricyclic antidepressants may not, in fact, be determined solely by response rate and that the effects may be significantly affected by the pattern of responses generated and the density of reinforcement. Density of reinforcement suggests itself as a critical variable in determining the effects of imipramine and manipulation of density may provide an important approach in elucidating the behavioral mechanisms of the tricyclic antidepressants.

Interestingly, tricyclic antidepressants administered to pigeons produce rate increases comparable to those seen with amphetamine [4]. Similar rate increases have not been reported in rats. As Dews [4] has pointed out, this may reflect species differences between rats and pigeons in responsiveness to the tricyclic antidepressants. Comparisons across species in this case may be meaningless until an understanding of the underlying mechanisms of the tricyclic antidepressants and the brain biochemistry of the species has been more clearly elucidated.

REFERENCES

1. Ando, K. Development of temporally spaced responding in relation to schedule value in rats. *Jap. Psychol. Rec.* **15:** 159–163, 1973.
2. Campbell, A. B. and L. S. Seiden. The effect of relative and absolute reinforcement magnitude on operant responding. *Physiol. Behav.* **12:** 843–849, 1974.
3. Carlton, P. L. Potentiation of the behavioral effects of amphetamine by imipramine. *Psychopharmacologia* **2:** 364–376, 1961.
4. Dews, P. B. A behavioral output enhancing effect of imipramine in pigeons. *Int. J. Neuropharmac.* **1:** 265–272, 1962.
5. Kelleher, R. T. and W. H. Morse. Determinants of the specificity of behavioral effects of drugs. *Ergebn. Physiol. biolog. Chemie exp. Pharmac.* **60:** 1–56, 1968.
6. Kornetsky, C. A comparison of the effects of desimipramine and imipramine on two schedules of reinforcement. *Int. J. Neuropharmac.* **4:** 13–16, 1965.
7. Malott, R. W. and W. W. Cumming. Schedules of interresponse time reinforcement. *Psychol. Rec.* **14:** 211–252, 1964.
8. McGuire, P. S. and L. S. Seiden. The effects of tricyclic antidepressants on a differential-reinforcement-of-low-rates schedule in rats. *J. Pharmac. exp. Ther.*, in press, 1980.
9. Pearl, R. and L. S. Seiden. The existence of tolerance to and cross tolerance between *d*-amphetamine and methylphenidate for their effects on milk consumption and on differential-reinforcement-of-low-rate performance. *J. Pharmac. exp. Ther.* **198:** 481–486, 1977.
10. Seiden, L. S. and L. Dykstra. *Psychopharmacology: A Biochemical and Behavioral Approach.* New York: Van Nostrand Reinhold Publishing Company, 1977.
11. Sidman, M. Technique for assessing the effects of drugs on timing behavior. *Science* **122:** 925, 1955.
12. Sidman, M. Time discrimination and behavior interaction in a free operant situation. *J. comp. physiol. Psychol.* **46:** 469–473, 1956.
13. Snapper, A. G., J. Z. Knapp and H. K. Kushner. Mathematical description of schedules and reinforcement. In: *The Theory of Reinforcement Schedules,* edited by W. N. Schoenfeld. New York: Appleton-Century-Crofts, 1970, pp. 247–275.
14. Snapper, A. G., K. R. Stephens, R. I. Cobez and F. VanHaaren. *The SKED Users Group,* Kalamazoo, MI, October, 1974.