TIMING BEHAVIOR DURING PROLONGED TREATMENT WITH *dl*-AMPHETAMINE[1]

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Reports by Sidman (1955) and Dews and Morse (1958) describe the effects of acute administration of amphetamine compounds upon timing behavior generated by DRL schedules of reinforcement. This report describes the effects of chronic administration of *dl*-amphetamine on DRL performance and general activity.

EXPERIMENT I

Procedure

Two white rats performed daily on DRL 17.5 seconds. Lever responses spaced at least 17.5 seconds apart were reinforced with 0.1 cubic centimeter of sweetened condensed milk. A 3-minute blackout period followed a fixed number of reinforcements, so that from two to five blackout periods occurred in each daily 1-hour session. Both animals were injected intraperitoneally with physiological saline 5 minutes before each daily session. After base-line performance emerged, Rats A-1 and J-22 were given 1.0 milligram per kilogram of *dl*-amphetamine 5 minutes before each experimental session, and the drug regimen was continued until no further trends in the DRL performance were observed.

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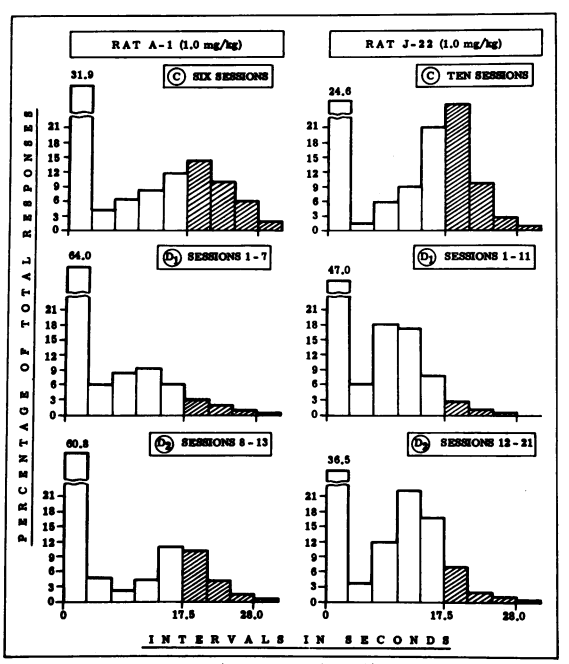

Fig. 1. Relative-frequency distributions of time intervals between successive lever-pressing responses averaged over: (C), control sessions; (D_1), the first half, and (D_2), the second half, of the chronic drug regimen. Shading indicates reinforced responses. Left distributions, Rat A-1; right distributions, Rat J-22.

Results

The predrug performances were those typically generated by DRL schedules. These are represented by the (C) distributions of Fig. 1. With *dl*-amphetamine injection (D_1), the IRT distributions showed a marked increase in the frequency of short IRT's compared with those in the control distributions. During the last half of the drug regimen (D_2), the modal values of the IRT distributions shifted towards the reinforced IRT's. The daily IRT data of both animals showed that the maximal drug effect occurred with the second and third drug injections. Following this, however, the performance gradually returned towards the predrug levels despite the continued drug injections.

Table 1

Average response rate per minute in DRL and blackout periods over: (C), saline control sessions; (D_1), the first half of the drug regimen; and (D_2), the second half of the drug regimen.

Animal No.	DRL (Average response per minute)			Blackout (Average response per minute)		
	(C)	(D_1)	(D_2)	(C)	(D_1)	(D_2)
A-1	4.9	9.1	6.4	1.5	6.2	4.8
J-22	5.7	10.6	7.4	5.6	10.6	9.7

Fewer reinforcements occurred as the *dl*-amphetamine shifted the distributions, but the number of reinforcements increased progressively towards predrug levels with continued *dl*-amphetamine injections.

Table 1 presents the average response rate per minute for the two rats over (C), the saline control sessions; (D_1), the first half of the drug regimen; and (D_2), the second half of the drug regimen. The response rates in the DRL periods and blackout periods are separately tabulated. With *dl*-amphetamine injection, (D_1), the response rates in both the DRL periods and blackout periods showed marked increments. During the last half of the drug regimen, (D_2), the rates declined but did not return to the predrug levels, (C). No differential effects of the drug on DRL responding and blackout responding were observed.

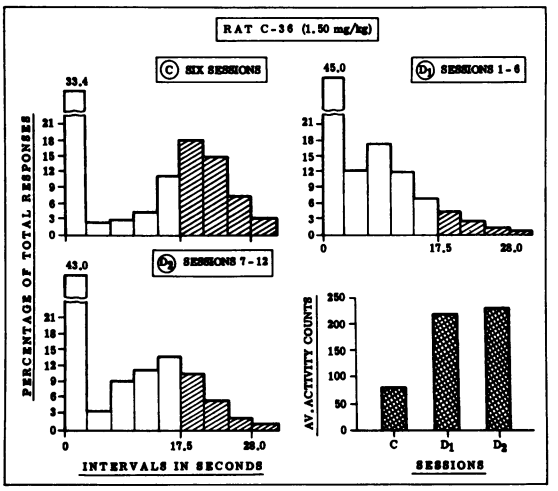

Fig. 2. Relative-frequency distributions of time intervals between successive lever-pressing responses averaged over: (C), control sessions; (D_1), the first half, and (D_2), the second half, of the chronic drug regimen. Shading indicates reinforced responses. Bottom curve presents averaged activity counts from the same subject over the same period of time.

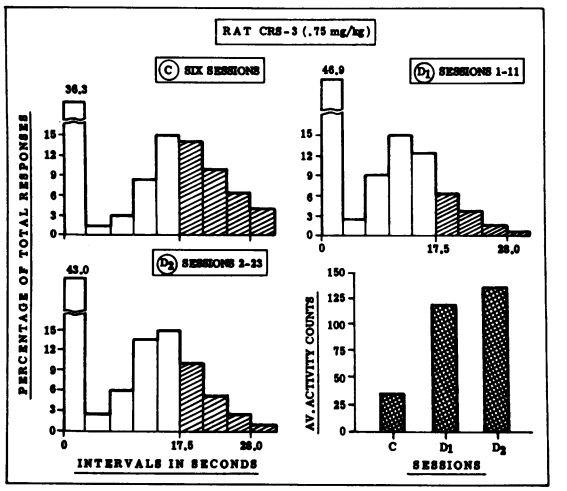

Fig. 3. Relative-frequency distributions of time intervals between successive lever-pressing responses averaged over: (C), control sessions; (D_1), the first half, and (D_2), the second half, of the chronic drug regimen. Shading indicates reinforced responses. Bottom curve presents averaged activity counts from the same subject over the same period of time.

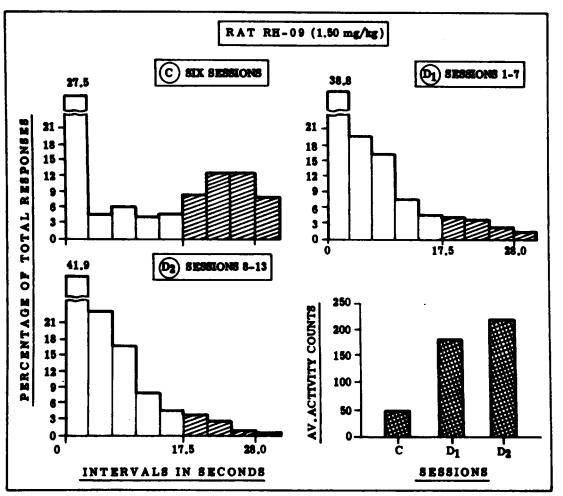

Fig. 4. Relative-frequency distributions of time intervals between successive lever-pressing responses averaged over: (C), control sessions; (D_1), the first half, and (D_2), the second half, of the chronic drug regimen. Shading indicates reinforced responses. Bottom curve presents averaged activity counts from the same subject over the same period of time.

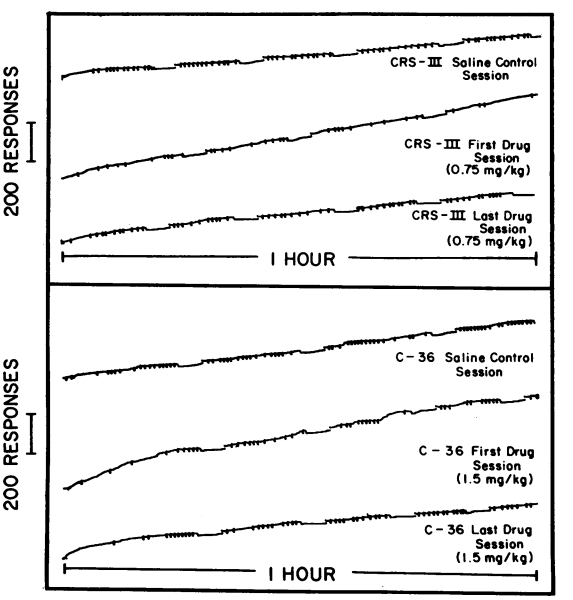

Fig. 5. Cumulative records of DRL performance for Rats CRS-3 and C-36.

Discussion

Certain of the sympathomimetic effects of the amphetamines have long been known to decrease, with repeated administration (Torme & Lasagna, 1960), reflecting the development of a physiological tolerance to the drug. Our results also fit the classic definition of drug tolerance, *i.e.*, a decrement in the effect of a drug with repeated administration.

The question remained: Was the development of tolerance to chronic administration of *dl*-amphetamine independent of the specific behavioral situation? In order to investigate the behavioral specificity of this form of tolerance, a second investigation was undertaken.

EXPERIMENT II

Procedure

Three white rats performed every other day on the DRL 17.5-second schedule used in Experiment I. On alternate days, the animals were placed in a standard photocell activity chamber for 15 minutes. The amount of general activity in the 15-minute sessions was measured by the number of times movement of the animal interrupted the photocell circuit. Saline was administered 5 minutes before the DRL sessions and 15 minutes before the general activity sessions. Following stabilization of each animal's behavior in both situations, *dl*-amphetamine at dosages of 0.75 or 1.5 milligram per kilogram was substituted for the saline and continued until no further trends in the DRL performance were observed.

Results

Figures 2, 3, and 4 present averaged IRT distributions and averaged activity counts for Rats C-36, CRS-3, and RH-09 for (C), the saline control sessions; (D_1), the first half of the drug regimen; and (D_2), the second half of the drug regimen. With *dl*-amphetamine injection, the IRT distributions (D_1) showed a marked increase in the frequency of short IRT's compared with that in the saline control distributions, (C). With Rats C-36 and CRS-3, the modal values of the IRT distributions shifted towards the reinforced IRT's during the last half of the drug regimen, (D_2). These results corroborate the findings in Experiment I. In contrast, the general activity level of Rats C-36 and CRS-3 remained consistently elevated over the entire course of the drug regimen. Rat RH-09 failed to show any improvement in the DRL performance during the drug regimen; and its activity level also remained consistently elevated over the same period of time.

Table 2 presents the average response rate per minute for the three rats over sessions (C), (D_1) and (D_2). The response rates in the DRL periods and blackout periods are tabulated separately. With *dl*-amphetamine injection (D_1), the response rates in both DRL and blackout periods showed marked increments. For both Rats C-36 and CRS-3, the response rate decreased from (D_1) to (D_2); however, Rat RH-09 showed no decrement in response rates from (D_1) to (D_2).

Table 2

Average response rate per minute in DRL and blackout periods over: (C), saline control sessions; (D_1), the first half of the drug regimen; and (D_2), the second half of the drug regimen.

Animal No.	DRL (Average response per minute)			Blackout (Average response per minute)		
	(C)	(D_1)	(D_2)	(C)	(D_1)	(D_2)
C-36	3.5	8.5	5.9	2.5	7.3	4.6
CRS-3	3.5	6.8	5.8	3.6	7.4	5.4
RH-09	2.8	7.4	9.0	2.1	7.8	7.0

Figure 5 presents the cumulative records for Rats CRS-3 and C-36 for the last saline session, and the first and last drug sessions. These records show that although the response rate fell from the first to the last drug sessions, the number of reinforcements earned increased.

Discussion

The results of Experiment II corroborate the findings of Experiment I concerning the development of tolerance to repeated administrations of *dl*-amphetamine. Torme and Lasagna (1960) have recently reported that general activity does not reflect the development of tolerance to *dl*-amphetamine, and our results are in accord with their findings. What variables account for determining which components of an organism's behavioral repertoire will reflect the development of tolerance to *dl*-amphetamine cannot at present be specified. However, further research is currently underway to investigate the specific role of the reinforcement contingencies in the development of behavioral tolerance to repeated administration of a drug.

CONCLUSIONS

Animals trained on a DRL schedule of reinforcement and treated with *dl*-amphetamine chronically show the development of tolerance to the drug. Activity measures in the same animals over the same period of time do not reflect the development of tolerance to the drug.

REFERENCES

Sidman, M. Technique for assessing the effects of drugs on timing behavior. *Science*, 1955, **122**, 925.

Dews, P. B., and Morse, W. H. Some observations on an operant in human subjects and its modification by dextro-amphetamine. *J. exp. Anal. Behav.*, 1958, **1**, 359-364.

Tainter, M. L. Effects of certain analeptic drugs on spontaneous running activity of the white rat. *J. comp. Psychol.*, 1943, **36**, 143-155.

Torme, J., and Lasagna, L. Relation of thyroid function to acute and chronic effects of amphetamine in the rat. *J. Pharmacol. & exp. Therap.*, 1960, **128**, 201-209.

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