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RAPID COMMUNICATION

Effects of Methylphenidate and *d*-Amphetamine on Timing in the Rat[1]

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ECKERMAN, D A , D SEGBEFIA, S MANNING AND G S BREESE *Effects of methylphenidate and d-amphetamine on timing in the rat* PHARMACOL BIOCHEM BEHAV 27(3) 513–515, 1987 —Rats were trained to press a lever for food pellets provided according to a fixed interval 60-sec schedule of reinforcement Probe trials (peak trials) assessed responding over two-min periods with no pellet delivered The low rates of responding found early and late in probe trials were increased by methylphenidate and 1 0 mg/kg *d*-amphetamine (rate-dependent effect) Further, the mean time of responding (peak time) was shortened for both drugs (timing effect)

Temporal discrimination Rate-dependent effect Methylphenidate Amphetamine Psychoactive stimulant Rat

PSYCHOACTIVE stimulants change how behavior is distributed in time A fixed interval schedule of reinforcement (FI) arranges reinforcement for the first response emitted more than some criterion time following the last reinforcer Rate of responding increases during the interval, with a zero or low rate early and a higher rate as the criterion time is approached Moderate doses of *d*-amphetamine (*d*-A) (e g , [3]), methylphenidate (MP) [8], and cocaine [1], all *increase* the low rate of responding early in the interval while slightly decreasing or leaving unaffected the higher rate of responding near the end of the interval (the classic "rate-dependency" effect [2])

A potentially separate effect of psychoactive stimulants is that they shift temporal discriminations so that earlier times are treated as though they were later (e g , [4]) Meck (e g , [7]) has advocated the use of a variant of the FI schedule that provides an assessment of temporal discrimination as well as of rate-dependent effects In this "peak procedure," two kinds of trials are included (1) FI reinforcement trials in which the first response following a criterion time (T) is reinforced and (2) peak trials where rate of responding is merely recorded during an interval that is approximately 2T long and no reinforcement is provided Responding during peak trials increases to a point just beyond time T and then falls The point of maximum responding can be taken as the rat's estimate of the time of reinforcement Maricq, Roberts and Church [5] showed that a 1 9 mg/kg dosage of methamphetamine shifted the peak time of responding to lower values (a shift in temporal discrimination) while slightly increasing overall rate of responding (Experiment 2) This rate increase was proportionately greater for the lower rates both early and late in the peak trials (a rate-dependent effect)

Meck (e g , [6]) has ascribed the timing effect to a change in dopamine transmission While *d*-A affects both dopamine and noradrenergic systems, MP's effect is restricted to dopamine A direct comparison of the effects of MP to those of *d*-A, then, might yield information on the relative role of these two systems in producing rate-dependent effects and effects on temporal discrimination The present study offers such a comparison

METHOD

Subjects

Six male Sprague-Dawley rats (Charles River, Wilmington, MA), 60 days old at the start of training, were maintained at 80% of free feeding weight

Apparatus

Two 20×24×20 cm (h) operant chambers were used A response lever and food tray were located on one 20 cm

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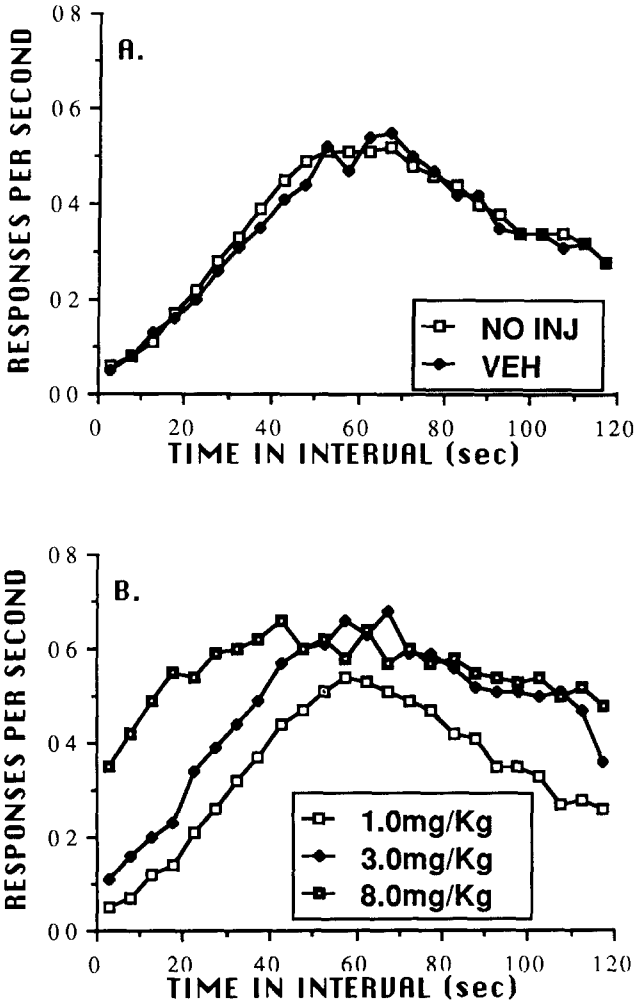

FIG 1 Responding during peak trials averaged across all subjects for the second methylphenidate series Separate averaged functions are shown in Panel A (top) for the nine non-injection sessions and the three water-vehicle injection sessions, separate averaged functions are shown in Panel B (bottom) for the three sessions at each drug dosage

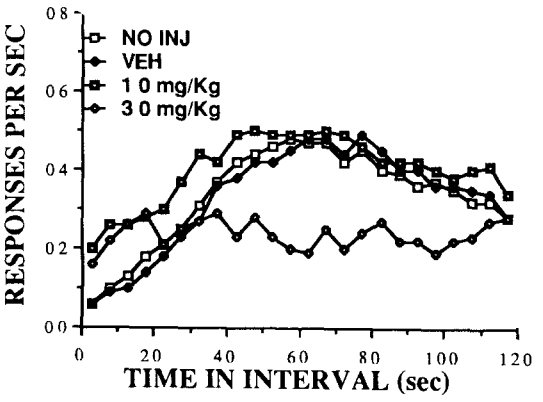

FIG 2 Responding during peak trial intervals averaged across all subjects given the *d*-amphetamine series Separate averaged functions are shown for the seven non-injection sessions, the three water-vehicle injection sessions, and the four sessions at each drug dosage

TABLE 1

MEAN PEAK TIMES FOR EACH DRUG CONDITION

		Methylphenidate Series One			
Pre*	No Inj	Veh	1 0	3 0	8 0 mg/kg
61 1	60 1	60 3	63 1	57 9	55 8 sec
		Methylphenidate Series Two			
	No Inj	Veh	1 0	3 0	9 0
	57 4	57 9	57 4	56 9	51 7
		d-Amphetamine Series			
	No Inj	Veh	1 0	3 0	
	57 1	58 6	54 5	50 4	

*Peak times for ten sessions preceding drug series

aluminum wall Lever presses (force of 0 2 and 0 3 N in the two chambers) were reinforced with 45 mg food pellets An indicator light was located above the feeder tray Experimental events were controlled by computer

Procedure

Behavioral training Following initial training with progressively longer FI schedules, training was given using the peak procedure In this procedure, a scrambled sequence of 18 FI trials and 12 peak trials were included in each training session The FI trials started with light onset and provided reinforcement for the first lever press that occurred after 60-sec Peak trials also commenced with light onset but lasted 120-sec, terminating without a pellet being presented A 10-sec dark period separated trials Training on this peak procedure continued for 70 sessions before the first drug evaluation series After a twenty session retraining period, the second and third drug series were given

Drug evaluations The first two drug series assessed the effect of MP (CIBA Pharmaceuticals) and the last assessed the effect of *d*-A (Sigma Chemical Co) During the first series, dosages of 0 0 (distilled water vehicle), 1 0, 3 0, and 8 0 mg/kg of MP were given Injections were given IP 10-min prior to the session, with drug sessions separated by a minimum of two days During the second series dosages of MP were 0 0, 1 0, 3 0, and 9 0 mg/kg Drug injections were given on Tuesdays and Fridays with vehicle injections given on Thursdays The sequence of dosages was scrambled The same arrangement was continued during the final series, where the dosages of *d*-A were 0 0, 1 0, and 3 0 mg/kg

Data analysis Lever press responses within successive 5-sec periods in peak trials were accumulated for a session Peak time was found by multiplying the number of responses for each 5-sec period by the time since trial onset These values were then averaged to yield peak time for responding

RESULTS

Rate of responding was low at peak trial onset, rose to a maximum at around 60-sec, and then fell again to 0 60–0 70 of this peak rate by 120-sec (Fig 1A, Fig 2) Responding for individual rats was well characterized by the mean rate of responding shown in the figures Also, data are shown for the second MP series only, as the first and second series

provided comparable data MP raised the low rates seen both early and late in peak trials This increase was dose-dependent for rates early in peak trials (Fig 1B) In addition to this general increase in low rates, there was a smaller increase in maximum rate Along with the general increase in responding, the peak time also shifted (Table 1) This leftward shift was confirmed through a one way within-subject analysis of variance [First series $F(5,20)=4\ 29$, $p<0\ 01$, Second series $F(4,20)=20\ 02$, $p<0\ 0001$] The observed shift in peak time was about 6 sec (10%)

The effect of 1 0 mg/kg of *d*-A was similar to that found for MP Low rates of responding both early and late in peak trials were increased (Fig 2) and peak time shifted to the left (Table 1) No increase was seen, however, in maximum rate The 3 0 mg/kg dosage of *d*-A reduced responding throughout the interval and appeared to eliminate all patterning of rates (Fig 2) The peak time was, however, shifted to the left even for this dose (Table 1) The shift in peak time was confirmed by a one way within-subject analysis of variance, $F(3,15)=8\ 47$, $p<0\ 01$

DISCUSSION

The present data confirm the rate-dependent effects previously shown for MP [8] as well as the rate-dependent and the temporal discrimination effects previously shown for methamphetamine [5] In addition, MP was shown to affect temporal discrimination That MP produced both rate-dependency and a shift in timing suggests that dopamine is implicated in both aspects of the stimulant effect

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