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Methylphenidate and *d*-Amphetamine: Effects and Interactions with Alphamethyltyrosine and Tetrabenazine on DRL Performance in Rats[1]

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SEIDEN, L S , J. ANDRESEN AND R. C MACPHAIL. *Methylphenidate and d-amphetamine Effects and interactions with alphamethyltyrosine and tetrabenazine on DRL performance in rats* PHARMAC BIOCHEM BEHAV. **10(4)** 577–584, 1979 —The effects of *d*-amphetamine and methylphenidate and their interactions with amine-depleting drugs were examined in rats trained to press a lever to obtain water reinforcement on a schedule that differentially reinforced responding at low rates (DRL) Both methylphenidate (2.5–20.0 mg/kg) and *d*-amphetamine (0.375–3 0 mg/kg) increased the rate of responding and decreased the frequency of reinforcement on the DRL schedule Both drugs also shifted the interresponse time (IRT) distributions to the left such that the modal IRT occurred well below the minimum IRT required for reinforcement (*d*-amphetamine was about eight times more potent than methylphenidate for each of these effects) The effects of both *d*-amphetamine and methylphenidate on DRL performance were attenuated by administration of alpha-methyltyrosine (AMT) (150 mg/kg) and both drugs attenuated the response rate-suppressing effects of tetrabenazine (TBZ) (4 0 mg/kg) The similarity of the drug interactions between methylphenidate or amphetamine and AMT or TBZ suggest that the doses of methylphenidate and *d*-amphetamine examined act on similar catecholaminergic pools with the central nervous system to influence DRL performance.

Drug behavior interactions Psychomotor stimulants Catecholamines DRL

STRIKING similarities exist between the behavioral effects of *d*-amphetamine and methylphenidate Both drugs produce anorexia [15,21], increase locomotor activity [3, 26, 42], elicit stereotypy [23], and increase operant responding maintained under schedules which engender low predrug rates of responding [4, 12, 16, 17, 19, 25, 30, 33, 34, 35] Pearl and Seiden [21] have recently demonstrated cross-tolerance between *d*-amphetamine and methylphenidate for the effects of these drugs on operant responding and milk consumption. The behavioral actions of both of these drugs appear to be mediated, at least in part, through the release of catecholamines (CA) from central neurons [6, 10, 11, 14, 20, 37, 38, 43]

Methylphenidate and *d*-amphetamine have been reported to differ in their behavioral effects following pretreatment with either alpha-methyltyrosine (AMT), a drug that inhibits CA synthesis) or reserpine (a drug that impairs intraneuronal CA storage). In rats, AMT has been shown to block the stereotypy induced by *d*-amphetamine but not by methylphenidate while reserpine, on the other hand, has been shown to block methylphenidate but not the stereotypy induced by *d*-amphetamine [23, 26, 27]. Amphetamine-induced increases in locomotor activity and continuous shock avoidance responding were blocked by AMT but not by reserpine pretreatment [25]. Since the behavioral actions of *d*-amphetamine were blocked after AMT-induced interference with CA synthesis and not after reserpine-induced interference with CA storage, it was inferred that the effects of amphetamine were mediated by a selective release of newly synthesized CAs.

On the other hand, because the behavioral actions of methylphenidate were blocked by reserpine but not by AMT, it was inferred that the effects of methylphenidate were mediated by the selective release of CAs from a granular storage pool [23, 26, 27]. In support of this notion, Chieuh and Moore [10,11] have found that reserpine enhanced, while AMT blocked, *d*-amphetamine-induced release of DA from central neurons.

Although previous studies have suggested a different mechanism of action for methylphenidate and *d*-amphetamine involving central CA neurons, the cross-tolerance between these two drugs for their effects on two specific

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behaviors [21] suggested a common site of action In an attempt to resolve this apparent discrepancy, the effects of drugs which differentially alter the metabolism of CAs, AMT and tetrabenazine (a reserpine-like CA storage inhibitor), on the action of methylphenidate and *d*-amphetamine on operant behavior have been examined [22,28]

The present experiments demonstrated that methylphenidate and amphetamine have similar actions on DRL behavior when given alone and in combination with other drugs; this is in contrast to the effect of methylphenidate and amphetamine effects on stereotypic behavior where the two drugs show dissimilar interactions with other drugs

METHOD

Animals

Male Sprague-Dawley rats (Holtzman Company, Madison, WI) which were sixty days old at the start of the experiment, were maintained at approximately 300 g body weight by adjusting their daily access to water Rats were housed 2 per cage in a room maintained at approximately 75°F and illuminated 14 hr per day (0800–2200 hr) Experimentation was conducted during the light phase of the illumination cycle (1700–2100 hr)

Apparatus

Lehigh-Valley operant conditioning chambers (Model No 1315) contained in sound-attenuating chambers were used Chambers were equipped with a ventilating fan that provided background masking noise and an 8-W houselight which illuminated the chamber during testing Reinforcement contingencies were programmed with use of Massey-Dickinson solid-state modules and the number of lever presses and reinforcement presentations were recorded Interresponse-time (IRT) data were recorded on magnetic tape and were later computer-analyzed by the method described by Seiden *et al* [32].

Experimental Procedure

Initially, rats were given access to water for 15 min per day for three days Prior to access to water on the fourth day, rats were placed in operant chambers and were trained to drink from a water-filled dipper (0.04 ml) presented periodically for approximately 15-min On two subsequent days, prior to access to water, rats were exposed to a fixed ratio of 1 (FR-1) schedule of water delivery, each exposure lasting until 60 reinforcers were delivered Rats were then exposed to a differential-reinforcement-of-low-rate (DRL) schedule [13] for the remainder of the experiment DRL schedules typically engendered low, stable response rates that are reliably increased by methylphenidate and by *d*-amphetamine [5, 16, 29, 34, 41] On this schedule, only responses which occurred at least 17 5 sec following the previous response (DRL 17 5) were reinforced Session duration was 30 min

When rats performing on the DRL schedule obtained 100 reinforcements per session, their behavior was considered stable All rats received each of the drug treatments tested, both ascending and descending dose series were tested in parallel in different rats Rats were exposed to the DRL schedule six days a week and were given sufficient daily access to water to maintain their body weights at 300 g Methylphenidate HCl (CIBA Geigy Corp., Summit, NJ) and *d*-amphetamine sulfate (Sigma Chemical Co , St Louis, MO) were administered 30 min prior to the experimental session Tetrabenazine methane sulfonate (Ro 1-9509, Hoffman-LaRoche Inc , Nutley, NJ) and *dl*-alpha-methyl-*para*-tyrosine (AMT, Regis Chemical Co , Morton Grove, IL) as free base were injected 60 min prior to the experimental session. Methylphenidate, *d*-amphetamine and tetrabenazine were dissolved in 0 9% saline solution and were injected IP in a volume of 1 ml/kg body weight; AMT was suspended in a solution containing equal volumes of 0 05% carboxymethylcellulose and 0.9% saline and was injected IP in a volume of 2 ml/kg body weight. Injections of saline or of saline-plus-carboxymethylcellulose served as control treatments All doses are expressed as the salt

Catecholamine Assays

Rats were sacrificed by decapitation and brain tissue was removed Brains were stored frozen in liquid nitrogen 2–4 weeks prior to assay Norepinephrine and dopamine were extracted from brain and isolated by the method of Bertler *et al* [1] NE and DA were oxidized to fluorescent compounds and were quantified by the methods of Bertler *et al* [1] and Carlsson and Waldeck [9], with the modifications of Carlsson and Lindqvist [8] and Seiden and Peterson [31] Amine values reported are expressed as μg CA per gram wet tissue weight and are corrected for recovery of 95% for NE and 80% for DA

Statistical

Each animal served as its own control Drug effects for each animal were expressed as a percentage of the average non-drug performance parameters seen after saline or saline-plus-carboxymethyl-cellulose Paired *t*-tests were used to determine the statistical significance of differences between treatment means. The statistical significance of correlations between data parameters were evaluated by linear regression analysis [36,44]

RESULTS

Effect of Methylphenidate and d-Amphetamine on DRL 17 5-sec Performance

The correlation between the rate of reinforcement and the dose of methylphenidate (0 84) and the correlation between the rate of reinforcement and the dose of *d*-amphetamine (0.87) were significant ($p<0$ 001) The correlation between the rate of responding and the dose of either methylphenidate (0) or *d*-amphetamine was not significant This was largely due to the fact that each individual animal showed an increase in the rate of responding at different doses of either methylphenidate or *d*-amphetamine (0 24) It is important to note however, that all animals showed an increase for at least one or more doses of both drugs However, at other doses, there was a decrease in response rate In spite of the decrease or increase in response rate, the IRT distributions were shifted to the left as shown in Fig 1

In rats, DRL 17 5-sec schedules of reinforcement engender a biomodal interresponse time (IRT) frequency distribution, the rats used in this experiment showed a bimodal IRT distribution One mode consisted of short IRTs (0 1 to 2.5 sec) and the second mode consisted of much longer reinforced IRTs (e g , between 17 5 and 19 9 sec, see Figs 2a and 3a) At certain doses, methylphenidate and *d*-amphetamine shifted the distribution of IRTs to the left, that is, the 17 5–

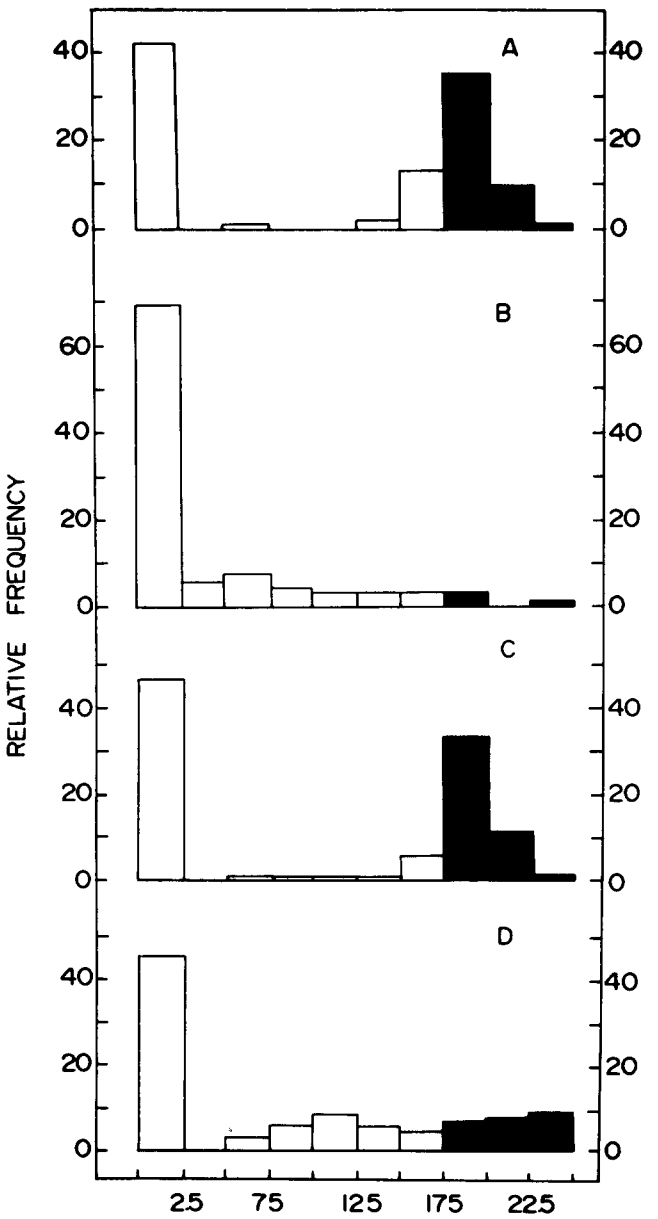

FIG 1 Interresponse time (IRT) distributions for the performance of one representative rat (R38) under DRL 17 5 sec A, nondrug control performance, B, 20 mg/kg methylphenidate, C, 20 mg/kg methylphenidate following pretreatment with 150 mg/kg AMT, D, 20 mg/kg methylphenidate following pretreatment with 4 0 mg/kg TBZ Darkened bars represent reinforced IRTs

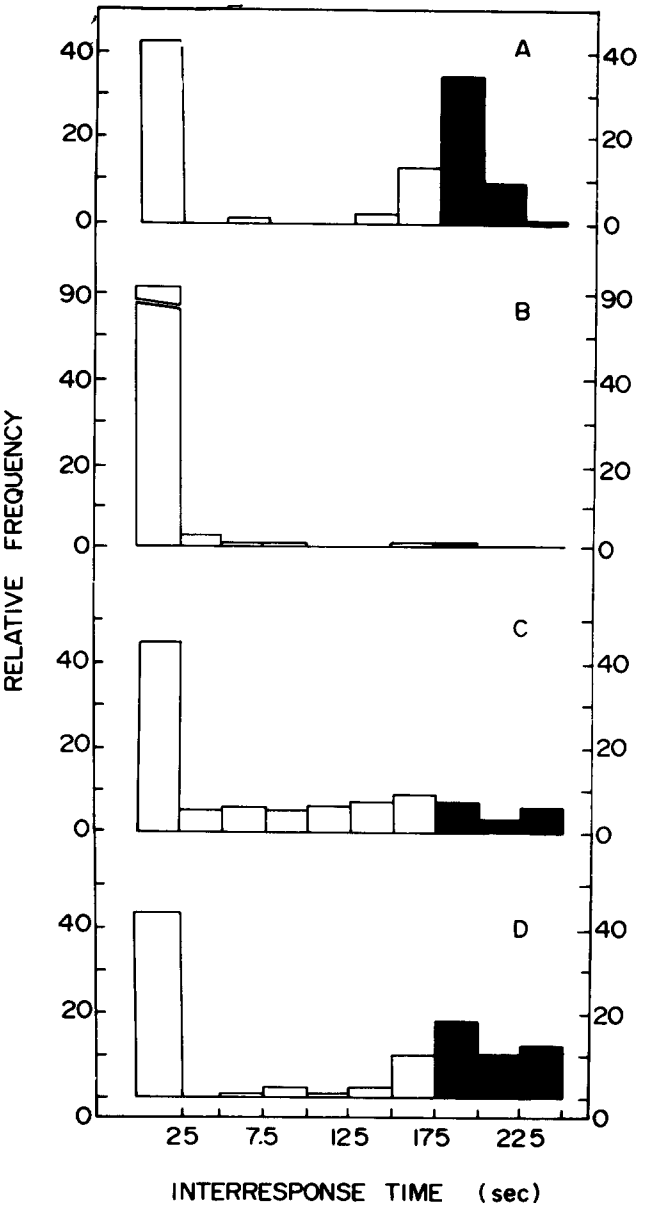

FIG 2 Interresponse time (IRT) distributions for the performance of one representative rat (R38) under DRL 17 5 A, control performance, B, 1 5 mg/kg *d*-amphetamine, C, 1 5 mg/kg *d*-amphetamine following pretreatment with 150 mg/kg AMT, D, 1 5 mg/kg *d*-amphetamine following pretreatment with 4 0 mg/kg TBZ Darkened bars indicate reinforced IRTs

19 9 sec mode decreased while the 0 1–2.5 sec mode increased (Figs. 1b and 2b). Shifts in the IRT distributions were similar for *d*-amphetamine and methylphenidate except for the difference in potency. *d*-Amphetamine was approximately 8 times more potent than methylphenidate (Fig 3) The effects of these two drugs on DRL performance are similar to those reported by Pearl and Seiden [21]

Effect of Tetrabenazine on DRL 17 5-sec Performance and on Brain CAs

Tetrabenazine caused a dose-related decrease in response rate on the DRL 17.5-sec schedule (Fig 4). There was a correlation between the dose of tetrabenazine and reinforcement rate (0 88), as well as between the dose of TBZ

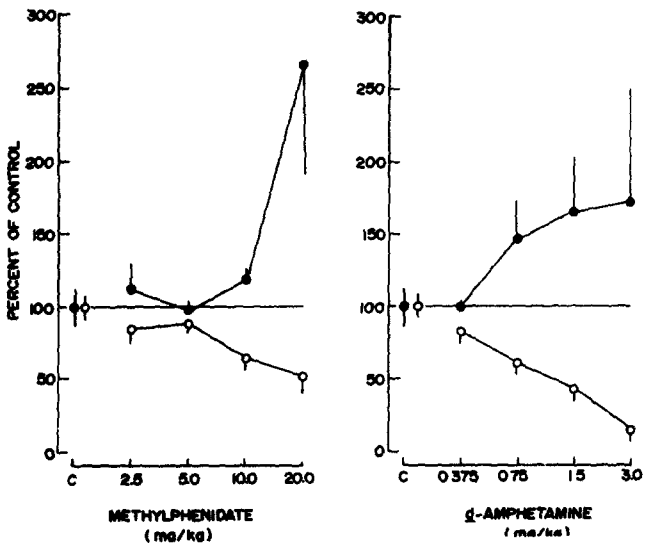

FIG 3. Effects of methylphenidate (left panel) and *d*-amphetamine (right panel) on the response rate (●) and reinforcement rate (○) of rats performing under a DRL 17 5-sec schedule of reinforcement. Symbols above C represent the effects of treatment with saline vehicle, 100% (± SEM) equals 3 33 (± 0 04) responses per minute and 2 20 (± 0.18) reinforcements per minute Each symbol represents the average effect of five rats and vertical lines represent 1 SEM

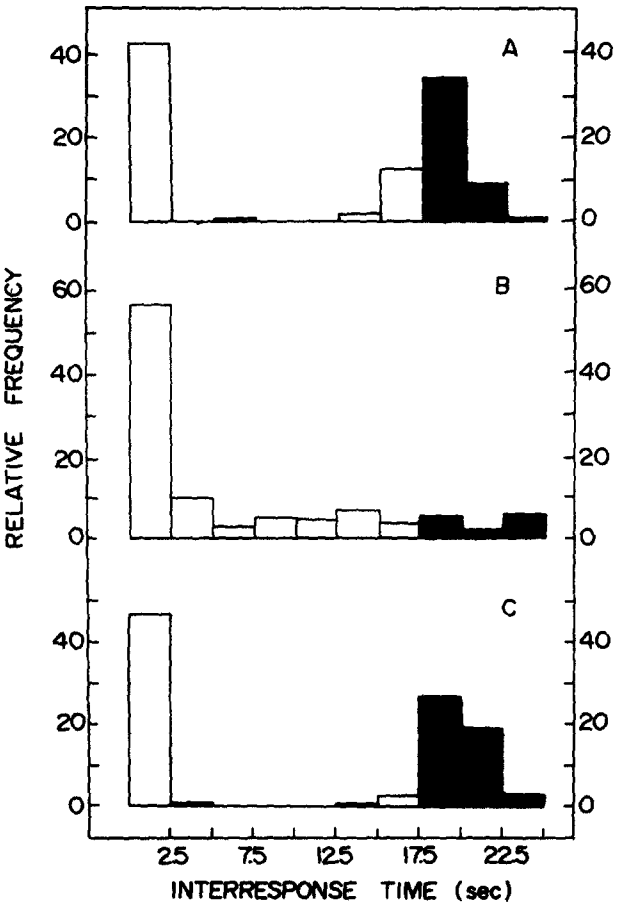

FIG 5 Interresponse time (IRT) distributions for the performance of one representative rat (R38) under DRL 17 5-sec A, nondrug control performance, B, 4.0 mg/kg TBZ, C, 150 mg/kg AMT Darkened bars represent reinforced IRTs

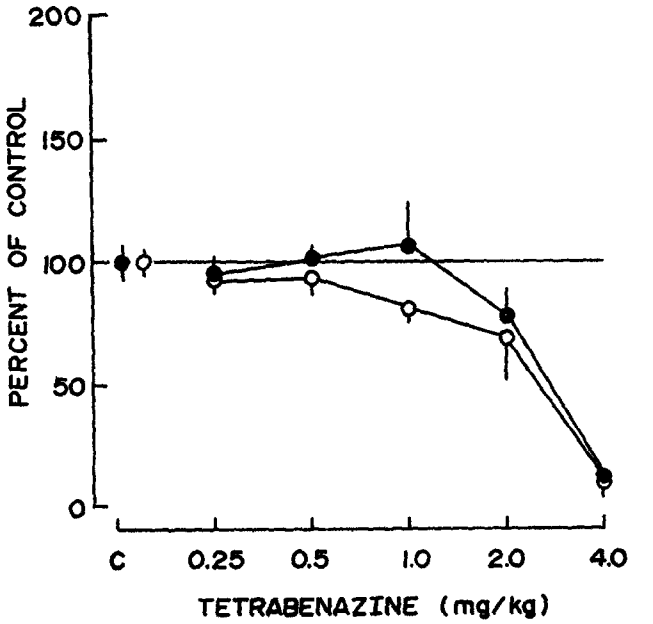

FIG. 4 Effects of TBZ on the response rate (●) and reinforcement rate (○) of rats performing under a DRL 17 5-sec schedule of reinforcement

and response rate (0.81) ($p<0.001$). Response rate was decreased by approximately 20% and 90% at 2.0 mg/kg and 4.0 mg/kg, respectively. Reinforcement rate was also decreased at 2 0 and 4.0 mg/kg. No dose of tetrabenazine increased response rate or reinforcement rate. At a dose of 1 0 mg/kg, the reinforcement rate was decreased while the response rate remained at control values (Fig. 4).

Effect of AMT on DRL 17 5-sec Performance and Brain CAs

Response rate, reinforcement rate and IRT distributions were not affected by AMT (Fig. 5). Dopamine and norepinephrine were depleted by AMT (150 mg/kg) by 22 5 ± 6.2% and 6 9 ± 7.2%, respectively, when the drug was given 60 min prior to sacrifice, and by 36.9 ± 3.4% and 9.2 ± 9 1%, respectively, when given 90 min prior to sacrifice.

Interaction of Methylphenidate and d-Amphetamine with TBZ

For both methylphenidate and *d*-amphetamine, the IRT distribution approached normal (Figs. 1d and 2d) following TBZ pretreatment. It should be noted that low doses of tet-

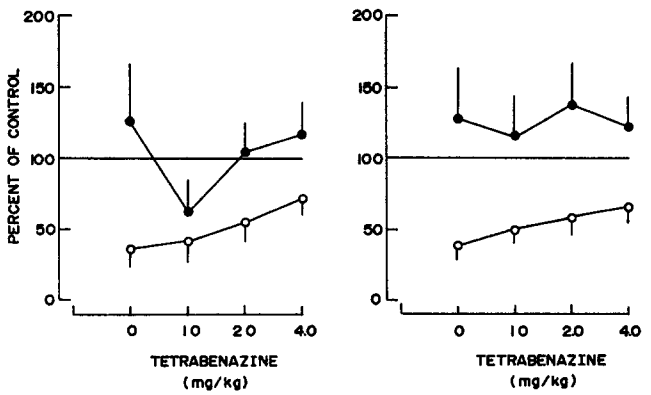

FIG 6. Effects of methylphenidate (20 0 mg/kg, left panel) and *d*-amphetamine (1 5 mg/kg, right panel), given alone and following pretreatment with TBZ on the response rate (●) and reinforcement rate (○) of rats under a DRL 17 5-sec schedule of reinforcement. Methylphenidate and *d*-amphetamine were given 30 min presession and TBZ was given 60 min presession

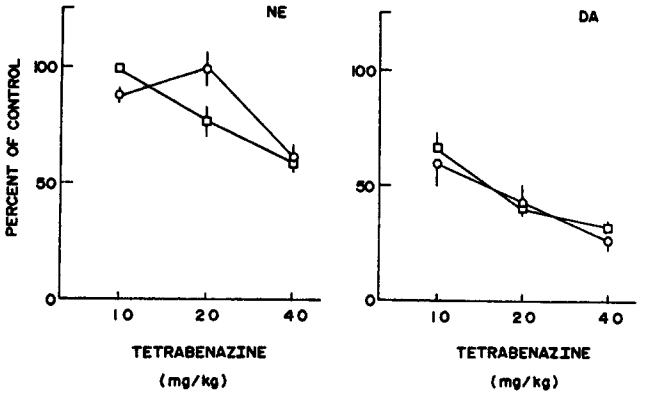

FIG 7 Effects of TBZ on whole brain levels of norepinephrine (left panel) and dopamine (right panel) Drug was given 60 (○) or 90 (□) minutes prior to sacrifice. Groups of control animals (n+4) received saline vehicle 60 or 90 min prior to sacrifice Average control values (± 1 SEM) for norepinephrine 0 29 ± 0 02 μg/g (○) and 0 39 ± 0 02 μg/g (□); and for dopamine. 0 72 ± 0 04 μg/g (○) and 0 68 ± 0 06 μg/g (□) Remaining symbols represent average effects in groups of 4 rats, and bars represent ± 1 SEM

TABLE 1

EFFECTS OF AMT PRETREATMENT ON THE METHYLPHENIDATE AND *d*-AMPHETAMINE-INDUCED CHANGES IN PERFORMANCE UNDER DRL 17 5 SEC EACH ENTRY REPRESENTS THE AVERAGE EFFECT (± SEM) AS PERCENT OF CONTROL FOR 5 RATS NONDRUG CONTROL VALUES ARE 3 33 ± 0 04 RESPONSES PER MIN AND 2 20 ± 0 18 REINFORCEMENTS PER MIN AMT (150 mg/kg) AND AMT VEHICLE WERE GIVEN 60 MIN PRESESSION, AND SALINE, METHYLPHENIDATE (20 mg/kg) AND *d*-AMPHETAMINE (1 5 mg/kg) WERE GIVEN 30 MIN PRESESSION

Treatment	Response Rate	Reinforcement Rate
	(% Control)	
AMT vehicle - Saline	101 ± 4	106 ± 5
AMT-Saline	108 ± 6	98 ± 2
AMT vehicle - Methylphenidate	267 ± 77*	52 ± 12
AMT vehicle - *d*-amphetamine	176 ± 29*	43 ± 11
AMT-*d*-amphetamine	124 ± 16	58 ± 11
AMT-Methylphenidate	101 ± 38	55 ± 21

*$p<0$ 05

rabenazine between 0.25 and 0.5 mg/kg had no effects on response or reinforcement rates Even a 2 mg/kg dose of TBZ only slightly decreased response and reinforcement rates. The effects of methylphenidate or amphetamine in combination with these low doses of TBZ were the same as the effects of methylphenidate or amphetamine when given alone. Larger doses of TBZ caused a decrease in response and reinforcement rates but both methylphenidate and *d*-amphetamine could antagonize the rate suppressing effects on reinforcement rate and response rate (Fig 6) seen with a large dose of tetrabenazine (4 mg/kg). The effects on reinforcement are significantly different ($p<0$ 05) at 4 mg/kg of tetrabenazine from those of TBZ in combination with either amphetamine or methylphenidate. The effects of methylphenidate and amphetamine on response rate were not significant although the effects on reinforcement rate showed similar effects to the dose response curve depicted in Fig. 3. The lack of a statistically significant increase in response rate may have to do with either the repeated administration of amphetamine or the fact that tetrabenazine was given to the animals between the first and the second determination of the dose. The major point is that methylphenidate and amphetamine acted similarly with regard to their interactions with both high and low doses of TBZ.

Dopamine and norepinephrine were depleted from brain and the depletion was proportional to the dose of tetrabenazine (Fig. 7) Dopamine was depleted more than norepinephrine at all doses.

Interaction of Methylphenidate and d-Amphetamine with AMT

AMT pretreatment blocked the rate-increasing effects of

methylphenidate (20 mg/kg) and partially blocked those of *d*-amphetamine (1 5 mg/kg) AMT was effective in blocking drug-induced increases in response rate but not in blocking drug-induced decreases in reinforcement rate (Table 1) The rate-enhancing effects of methylphenidate and *d*-amphetamine were attenuated by AMT and the IRT distributions were partially normalized (Figs 1c and 2c)

DISCUSSION

The results of these experiments indicate that methylphenidate and *d*-amphetamine produce similar effects on DRL performance These results are similar to those reported by Pearl and Seiden [21]; see also [5,41] Furthermore, the two drugs interact with alpha-methyltyrosine (AMT), an inhibitor of catecholamine biosynthesis, in a similar way. AMT pretreatment partially blocks the rate increasing effects of methylphenidate and *d*-amphetamine on DRL performance The effects of the two drugs seems more complex following pretreatment with tetrabenazine (TBZ) Following pretreatment with a low dose of TBZ, which alone produces minimal changes in DRL performance, methylphenidate and *d*-amphetamine disrupted DRL-reinforced responding Higher doses of TBZ alone decreased response rate and reinforcement rate on the DRL schedule, both methylphenidate and *d*-amphetamine antagonized the rate-suppressant actions of TBZ The major conclusion of these behavioral studies indicate that both methylphenidate and *d*-amphetamine when given alone have similar effects on DRL behavior When given after pretreatment with either AMT or tetrabenazine, the effects of methylphenidate and *d*-amphetamine are also similar

Methylphenidate and *d*-amphetamine have previously been differentiated on the basis of their interactive effects with amine-depleting drugs on locomotor activity and stereotyped behavior It has been reported that AMT pretreatment blocked *d*-amphetamine-induced stereotypy, but did not block methylphenidate-induced stereotypy [21] Other investigators have reported that reserpine pretreatment does not block amphetamine-induced increases in locomotor activity [7,39] or the amphetamine-induced increase in non-discriminated continuous avoidance responding [25, 40, 43] Scheel-Kruger [26,27] has proposed that the behavioral effects of amphetamine depend on the release of catecholamines from a newly synthesized pool in the CNS, since blockade of CA synthesis by AMT antagonized amphetamine effects whereas blockade of CA storage by reserpine did not On the other hand, the behavioral effects of methylphenidate have been proposed to depend on release of catecholamines from a granular storage pool in the CNS since its effects were blocked by reserpine but not by AMT [26,27]

The results of the drug interactions presented in this behavioral study using a DRL schedule of reinforcement differ from the results of Scheel-Kruger [26,27] described for similar drug interactions but measuring stereotypic behavior rather than operant behavior In the present study, data have been presented showing that AMT partially blocks methylphenidate and *d*-amphetamine-induced disruptions of DRL performance, and that tetrabenazine (a reserpine-like drug with a short duration of action) does not block the effects of methylphenidate or amphetamine These results indicate that methylphenidate and amphetamine have a similar profile when interacted with AMT or TBZ While these findings [26,27] are not in convergence with those reported in this paper, other results seem more consistent. They also showed that this antagonism could be reversed when the rats were pretreated with AMT following reserpine Pearl and Seiden [21] have found that methylphenidate and *d*-amphetamine show cross tolerance on both milk drinking and DRL behavior

In general, the effects of methylphenidate and amphetamine are similar, however, there are a few exceptions to this generalization in the data that have been presented in this manuscript Treatment with the two psychomotor stimulants antagonizes the rate decreasing effects of tetrabenazine However, there is a marked difference between the effects of 1 mg/kg of tetrabenazine as it is affected by methylphenidate (20 mg/kg) or amphetamine (3 mg/kg) At a 1 mg/kg dose of tetrabenazine, methylphenidate causes a decreased response rate, but amphetamine causes an increase in response rate Although a few differences exist between the effects of methylphenidate and amphetamine when they are combined with amine-depleting drugs, the similarities are greater than the differences

The results presented in these studies suggest that methylphenidate and *d*-amphetamine act on similar intracellular CA pools insofar as storage pools can be inferred from drug-drug interaction studies Studies of release of pulse-labeled CAs by methylphenidate and *d*-amphetamine [10] are consistent with the interpretations of Scheel-Kruger [27] and Randrup and Munkvad [23]

The differences in results reported in this and other studies [3,21] and the results of Scheel-Kruger [27] may be related to one or several variables First, the relative doses of methylphenidate and *d*-amphetamine required to modify behavior differ The dose-range for modifying DRL performance was between 0 75 and 3 mg/kg and between 2 5 and 20 mg/kg for *d*-amphetamine and methylphenidate, respectively These dose ranges are the same for producing changes in milk drinking behavior [21] On the other hand, the dose range for inducing stereotyped behavior is between 2 5 and 10 mg/kg and between 25 and 100 mg/kg for *d*-amphetamine and methylphenidate, respectively The highest dose used to modify DRL behavior is nearly equivalent to the lowest dose that engenders stereotypy It is possible, therefore, that the drug interaction and inferred catecholamine release from different pools depends on the dose of the drug Second, drug-induced disruptions of DRL performance are different from drug-induced stereotypy The behavioral response pattern may be an important consideration in the differences between methylphenidate and *d*-amphetamine interactions with AMT or TBZ It is a common observation that drugs have multiple chemical effects and that the preponderance of one effect is more important in the mediation of a behavior [2,18] Third, the use of TBZ instead of reserpine may have partially contributed to differences in drug-drug interactions, the similarity of the biochemical response to TBZ and the similar effects of amphetamine make this explanation appear unlikely

It appears then that methylphenidate and amphetamine are similar to each other when their effects on a DRL schedule of reinforcement are measured; furthermore, their interactions with TBZ and AMT are also very similar This would support the idea that methylphenidate and *d*-amphetamine (i e , those drugs which play a role in DRL performance) may act on the same transmitter pools in the CNS The fact that the two drugs show cross tolerance to their effects on two different types of behavior [21] is consistent with this idea

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