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Enantioselective Behavioral Effects of *threo*-Methylphenidate in Rats

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ECKERMAN, D. A., S. S. MOY, A. N. PERKINS, K. S. PATRICK AND G. R. BREESE. *Enantioselective behavioral effects of* threo-*methylphenidate in rats*. PHARMACOL BIOCHEM BEHAV **40**(4) 875–880, 1991.—The relative potency of *d*- and *l-threo*-methylphenidate (*d*-MPH and *l*-MPH) was evaluated using three behavioral paradigms for rats: Responding maintained by a fixed-interval schedule of reinforcement (FI), responding maintained by a concurrent variable-interval schedule of reinforcement (Conc VI VI), and consumption of sweetened condensed milk during a 15-min free-access period. In each case the potency of the *d*-MPH enantiomer greatly exceeded that of the *l*-MPH enantiomer. Temporal control of responding was reduced (FI), choice responding was equalized for most rats (Conc VI VI), and milk consumption was suppressed by *d*-MPH and *dl*-MPH.

Methylphenidate enantiomers Schedule-controlled behavior Lever-press Anorexia Rats

THE classroom behavior of children diagnosed with attention deficit disorder (ADD) frequently improves with *dl-threo*-methylphenidate (*dl*-MPH, Ritalin®) therapy (20). The stimulant properties of *dl*-MPH diminish distractibility in the school environment but may also produce adverse effects, notably anorexia and possible suppression of growth (9). Though there are four diastereomers of the drug, only the *dl-threo* racemate is presently marketed. The *d*- and *l*-erythro isomers were removed from the formulation (23) because of toxicities and inefficacy (26). Little is known about the pharmacology of the separate *threo* enantiomers (Fig. 1) because a method for the preparative scale resolution of the racemic drug has only recently been developed (19). Therefore, any clinical advantage in the present practice of coadministering *d*- and *l*-MPH could not be gauged discerningly. One enantiomer may merely be isomeric ballast or it may contribute to side effects, and/or alter the pharmacokinetics of the opposite enantiomer.

Most of a therapeutic dose of *dl*-MPH is presystemically metabolized (4) through enantioselective deesterification, variably resulting in several-fold higher circulating concentrations of the *d*-isomer than the *l*-isomer (17). This isomeric distortion has not been considered in therapeutic drug monitoring studies and the clinical implications of metabolically altered isomeric ratios of MPH reaching the brain are not clear. Though both *d*- and *l*-MPH readily accumulate in rat brain (18), the *d*-isomer is more potent in inducing locomotor activity (19). The present behavioral studies extend the pharmacological characterization of the individual MPH enantiomers to explore the significance of the isomeric disposition of administered and centrally available MPH.

Effects of the two enantiomers were assessed for responding maintained by a fixed-interval schedule of reinforcement (FI). An FI schedule arranges reinforcement for a response emitted T-s following a stimulus, in our case the onset of a light. Responses emitted prior to time T are not penalized but do not produce the reinforcer. Typically, the interval starts with a pause in responding, and responding commences about half way through the time (i.e., at approximately T/2). Rate of responding typically accelerates for a short period and is then maintained at a steady rate for the remainder of the interval. Such a "pause-run" performance demonstrates control by the temporal pattern of reinforcement and thus attention to time. The loss of such a pattern demonstrates reduced attention to the temporal pattern of reinforcement. When administered *d*-amphetamine, for example, rats show a considerably shortened modal pause that is also more variable in length (13). In addition to the changes in pause, a change in motor activity is also induced by *d*-amphetamine. A reduced rate of responding is observed once responding starts in an interval. Separately measuring pattern and rate of responding allows one to separately characterize both changes in attention to temporal pattern and in motor activity. Eckerman et al. (7), using a variant of the FI procedure, found that *dl*-MPH also reduced pauses and diminished rate of responding. The present study thus assesses the degree to which these changes in attention and motor activity might be attributed to each of the two enantiomers.

A second behavioral paradigm (Conc VI VI) was selected to evaluate the impact of the two enantiomers on choice (the degree of preference for a more frequently reinforced response).

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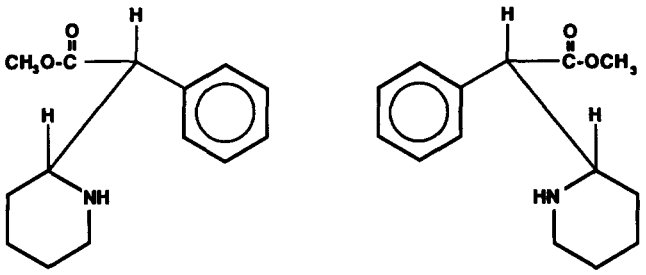

d - *threo* - Methylphenidate *l* - *threo* - Methylphenidate

FIG. 1. Stereochemistry of *d*-MPH and *l*-MPH depicted as saw-horse structures. Absolute configurations are (R, R) and (S, S), respectively.

Presses on each of two response levers were concurrently reinforced. The time when a reinforcer could be earned by either lever press was unpredictable since a variable-interval schedule of reinforcement was arranged for each. Five times more reinforcers, however, were provided for responses to one lever (the majority lever) than to the other (the minority lever). Rats typically intermix responses on the two levers and thereby increase the number of reinforcers earned. The proportion of responses to each lever, however, typically matches the proportion of total reinforcers provided for responses to that lever [the matching law (11)]. This matching of responses to reinforcers represents a close alignment between behavior and its maintaining environment. A shift away from such a match represents a disruption in this alignment. Responding may shift toward the majority lever ("overmatching") or responding may be distributed more evenly between the two levers ("undermatching"). In a prior study (24), *dl*-MPH was found to produce undermatching in normal adult human subjects. A concurrent schedule of reinforcement was, therefore, arranged in the present study to provide an assessment of the differential potency of the two enantiomers of MPH in producing such a reduced alignment between behavior and environment.

When given to attention-deficit-disordered (ADD) children, appetite suppression (AS) is an unwanted side effect of racemic MPH (9). The third behavioral paradigm was selected to evaluate the differential potency of the two enantiomers in suppressing appetite. Foltin (8) demonstrated that racemic MPH reduces the amount of sweetened condensed milk a rat will consume. Were this suppression even partially attributable to an isomer not involved in the therapeutic action, as inferred from the other behavioral effects, use of a single MPH isomer rather than racemic MPH for ADD would be advantageous.

METHOD

Subjects

Male Long Evans rats (Charles River, Raleigh, NC) were housed individually in wire-mesh cages with water freely available. Approximately 12 g of Purina Rat Chow (6 g for AS procedure) was made available immediately following training sessions. This feeding schedule maintained the rats stably at 340 to 400 g [425 to 500 g for the Appetite Suppression (AS) procedure]. A 6 a.m. to 6 p.m. light-dark cycle was maintained in the colony room with a constant temperature of 75 degrees. The following numbers of subjects were used for each procedure: FI: N=7, 20 months old at the start of the drug procedures; Conc VI VI: N=4, 3 months old at the start of the study, with drug procedures carried out when the rats were 4.5 to 16 months old; and AS: N=8, 8 months old at the start of the study. All rats were maintained in good health throughout the study.

Apparatus

FI and Conc VI VI procedures. Four rat chambers (30×30×24 cm, Coulbourn Instruments, Lehigh Valley, PA) were fitted with two rodent levers (Model E21-03) at a height of 4 cm above the floor rods and 5 cm on either side of the midline. A liquid feeder opening (Model E14-05 with a 0.2 cc cup) was centered at a height of 4 cm above the floor. Dim chamber illumination was provided by a No. 1829 incandescent lamp (voltage reduced) centered 5 cm above the liquid feeder. Sweetened condensed milk (Borden Eagle Brand, diluted 2:1 with water) served as the reinforcer. White noise provided sound masking in addition to that provided by a sound attenuating enclosure. Events were automatically controlled and recorded by computer with a precision of 0.01 s (29).

Drug Treatments

The MPH enantiomers were obtained as described in detail by Patrick et. al (19). Briefly, racemic MPH·HCl, generously supplied by Ciba Pharmaceutical Co. (Summit, NJ), was converted to diastereomeric binaphthyl phosphates and fractionated by repeated recrystallization. These salts were then decomposed and the HCl salts reformed. The degree of optical enrichment was quantified by gas chromatography after chiral derivatization using N-trifluoroacetyl-(*S*)-prolyl chloride. The procedure provided 99% isomerically pure *d*-MPH·HCl and 92% isomerically pure *l*-MPH·HCl.

FI Procedure

Fixed-interval training. Subjects had previously received approximately 180 sessions of training on a partially reinforced fixed interval (FI) schedule [the peak procedure, e.g., (22)]. Training sessions were arranged five days per week during which 24 reinforcers could be obtained according to an FI 60-s schedule of reinforcement for lever pressing. Sessions were terminated at 60 min if 24 reinforcers had not been earned. Only presses to the right lever were consequated. The session began with a dark period of 30 s. Any press during the dark prevented onset of the next interval for the following 2 s. Light onset marked the start of the FI 60 s. The first press made 60 s after light onset darkened the chamber, illuminated the feeder opening, and raised the feeder cup for 3 s. Following this reinforcement period, an intertrial interval of 20 to 90 s (averaging 55 s) preceded onset of the next interval. Eighty sessions of training preceded the present drug test sessions.

Drug was injected IP 10 min prior to test sessions on Tuesdays and Fridays. Control injections (distilled water) were given on Thursdays. The isomeric MPH·HCl was administered in doses of 1, 3, and 9 mg/kg (salt) in injections of 1 ml/kg. Two to four administrations were given for each dose, with the order being nonsystematic. Following this series, 5 mg/kg injections of *d*-MPH and of *l*-MPH were given. Three to four administrations were given for each of these doses, with the order being nonsystematic.

Data analysis. Overall rate of responding, pausing at the start of intervals, and rate of responding following the initial pause (local rate of responding) were determined. Pause was defined as the time from onset of an interval (light onset) to the third response (such a definition excludes most cases where long

pauses follow the measured pause). A distribution of pause lengths was determined for each session analyzed, with any pauses longer than 60 s considered as a pause of 60 s. The mean pause length for each session was determined from these distributions. Total responding (excluding reinforced responses) was then used to determine mean overall response rate, local response rate (rate of responding following the pause), and mean pause for each experimental condition. A repeated-measures analysis of variance was carried out across conditions, considering rats as replications. Alpha level was set at 0.05.

Conc VI VI Procedure

Rats were trained to press both right and left levers, using sweetened condensed milk as a reinforcer. Reinforcement was then arranged according to a concurrent schedule such that both left-lever and right-lever presses were reinforced on a variable-interval schedule (Conc VI VI). In this schedule, reinforcers were made available once per minute on the average (5–250 s following the prior reinforcer). A random number generator assigned each reinforcer to follow either a left- or a right-lever press. Once assigned, the next press on the assigned lever that met a change-over-delay (COD) requirement produced the sweetened condensed milk. A COD of 5 s was used; that is, to produce the reinforcer, a response on the assigned lever had to follow the last response on the other lever by at least 5 s. This COD assured that responses on the nonassigned lever were not directly reinforced. This schedule thus assigned reinforcers for the left lever on the average of once per 75 s and for the right lever once per 300 s (Conc VI 75 VI 300 s). At maximum efficiency, left presses were reinforced at 48 reinforcers/hour and right presses at 12 reinforcers/hour. One-hundred twenty training sessions were given. Sessions, given on weekdays, continued until 40 reinforcers were earned. Effects of drugs were assessed following 30 training sessions on this procedure.

Drug procedures were the same as those used for the FI procedure, except that the 1 mg/kg of MPH·HCl was not given and only 1 administration of *d*-MPH and 2 administrations of *l*-MPH were given.

AS Procedure

Throughout the AS study, rats were given access to diluted sweetened condensed milk during 15-minute sessions between 10:00–11:00 a.m. on five days a week. The milk (one part Eagle Brand sweetened condensed milk to two parts tap water) was presented in bottles placed on the front of the home cages. Milk intake was first stabilized (less than 10% variation in mean intake for all rats for three consecutive sessions). A *dl*-MPH dose response function was then determined using the following dose sequence: 4 (n=6); 10 (n=6); 15 (n=6); 17.5 (n=6); 7.5 (n=6); 5 (n=3); 8 (n=2); and 12 mg/kg (n=1). The numbers in parentheses indicate the number of rats that had met the consumption stability criterion and were given that drug dose (the final three dose conditions were added to resolve those cases that were otherwise ambiguous). Drug was injected IP 20 min prior to test sessions. Upon completion of the dose response functions for *dl*-MPH, a single dose of *d*-MPH (10 mg/kg) and a single dose of *l*-MPH (10 mg/kg) was given to each rat.

RESULTS

FI Procedure

Distribution of postreinforcement pauses. Figure 2 shows the distribution of pauses to the third response for each condition.

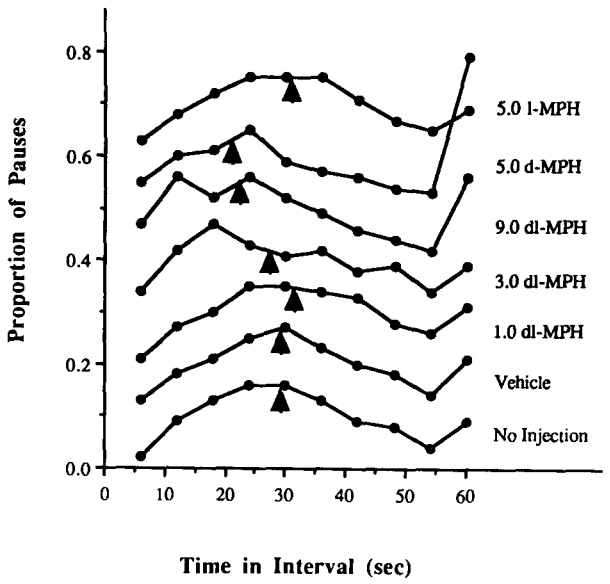

FIG. 2. Relative frequency of pause termination in successive 6-s segments across the fixed interval. The mean relative frequency for the seven rats is shown under control, vehicle and drug conditions. Pause terminations were defined as the time of the third response in the interval. Intervals with less than three responses are included at 60 s. Individual functions were separated for this display by adding a constant to all values. These constants increased by 0.1 for each successive function. The triangle is located below each function at the mean pause, calculated with pauses of 60 or more seconds excluded.

Intervals with fewer than three responses are included at 60 s. Curves for the control, vehicle, and 1.0 mg/kg drug dose are similar, with values distributed around 30 s (note the mean pause, excluding no-response intervals, is indicated by a triangle on the figure). The curves for 3.0 mg/kg, 9.0 mg/kg, and the 5.0 mg/kg *d*-MPH, however, are shifted to the left, indicating that fewer long pauses occurred than under control and vehicle conditions. The exception to this trend was that more intervals with less than three responses occurred with the highest drug dose and, most notably, with *d*-MPH.

A repeated measures ANOVA confirmed the significance of the overall drug effect, $F(6,36)=3.31$, $p<0.01$. Individual a priori contrasts found that the *l*-MPH and vehicle mean pause lengths were not significantly different, $F(1,6)=0.00$, $p>0.9$, and that the values for the *d*-MPH and 9.0 mg/kg *dl*-MPH were not significantly different, $F(1,6)=0.24$, $p>0.6$. The difference between the *d*-MPH and *l*-MPH only approached significance in this analysis, $F(1,6)=2.75$, $p<0.10$, perhaps because of the increased incidence of no-response intervals for the higher drug doses and for *d*-MPH.

Local and overall rates of responding. Figure 3 depicts the overall and local (following termination of the pause) rates of responding, averaged across the interreinforcer interval, for each drug dose. The two curves show similar trends, with local rates about twice the overall rates for control and vehicle and at the lowest drug dose. Decreases in both rates were observed with increasing drug dose and with *d*-MPH, while administration of *l*-MPH led to rates most comparable to the vehicle values. The

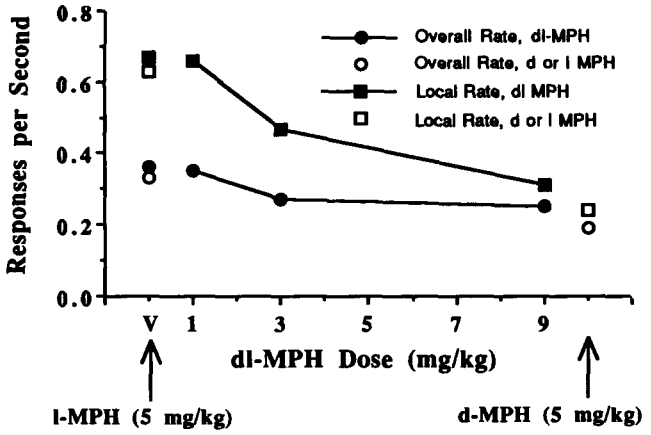

FIG. 3. Overall and local rates of responding under the fixed interval procedure for seven rats under control, vehicle, and drug conditions. Local rate was defined as responding after the third response in the interval. The horizontal axis shows dose of *dl*-MPH, with data for vehicle (V) and the separate enantiomers shown at the points indicated (see text for explanation).

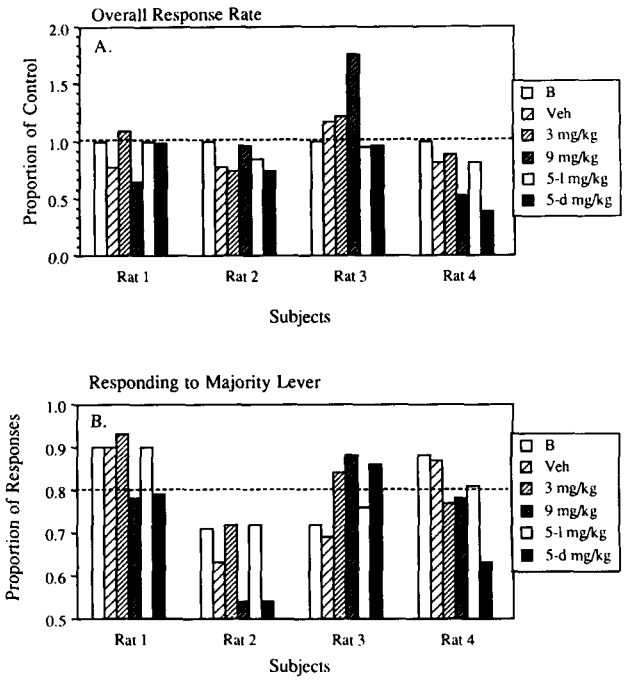

FIG. 4. Effects of methylphenidate on choice behavior. Overall rate of responding is expressed as a proportion of the rate observed during non-injection baseline sessions (panel A) and left lever responding (the lever more frequently reinforced, see text) is shown as a proportion of the total responding that was emitted (panel B). The dashed line in panel A indicates no effect and the dashed line in panel B indicates the "matching line," i.e., the proportion that matched the proportion of reinforcers obtained on the left lever (0.8). Data are separately shown for each of the four subjects.

drug effect observed in the local rates of responding was found with a repeated measures ANOVA to be highly significant, $F(6,36)=7.87$, $p<0.001$. While *d*-MPH was not significantly different from 9.0 mg/kg *dl*-MPH, $F(1,6)=1.13$, $p>0.3$ and *l*-MPH was not significantly different from vehicle, $F(1,6)=1.98$, $p>0.2$, the local rate of responding with *d*-MPH was significantly lower than that with *l*-MPH, $F(1,6)=9.08$, $p<0.05$. The same pattern of results was found when the overall rates of responding were tested. The drug effect proved significant, $F(6,36)=3.06$, $p<0.05$. No significant difference was found between the overall rates for *d*-MPH and the highest drug dose of *dl*-MPH, $F(1,6)=1.33$, $p>0.2$, nor the rates for *l*-MPH and vehicle, $F(1,6)=1.17$, $p>0.3$. Rates were significantly lower with *d*-MPH when compared with *l*-MPH, $F(1,6)=6.17$, $p<0.05$.

Conc VI VI Procedure

Both *dl*-MPH and *d*-MPH altered the proportion of responses to the two levers (choice) in the Conc VI 75 VI 300 s schedule (see Fig. 4B).

Again, *l*-MPH did not affect behavior. Effects were consistent within rats, but differed across rats. For three of the four (R1, 2, and 4), *dl*-MPH and *d*-MPH but not *l*-MPH moved these proportions closer to equal responding, a loss of differentiation between the two levers. For the remaining rat (R3), however, responding became more concentrated on the lever producing more reinforcers with *dl*-MPH and *d*-MPH but not with *l*-MPH, that is, an increased differentiation of responding was seen. Of potential interest, this increased differentiation was seen for the one rat that showed an increased overall rate of responding with 9 mg/kg of *dl*-MPH.

Typically, the proportion of total presses made to a lever in a Conc VI 75 VI 300 s schedule is found to approximate the proportion of reinforcers earned by presses on that lever (this would imply that 0.8 of the total responses should have been made to the left lever in the present study). While the average of all four rats approximates this matching value, the observed baseline proportions for two rats (rats 2 and 3) were less extreme than this "matching" value (undermatched) and the proportions for the other two rats were more extreme than this value (overmatched). The effect of MPH (loss of or increase in differentiation) was not consistently different for rats that undermatched or overmatched.

MPH did not consistently affect overall rate of responding in the Conc VI 75 VI 300 s schedule (see Fig. 4). While overall rate was suppressed below baseline levels for rat 4 (9 mg/kg *dl*-MPH, 5 mg/kg *d*-MPH), it was increased for rat 3 (9 mg/kg *dl*-MPH). For the remaining two rats, no effect was seen on overall rate of responding. Unaccountably, vehicle injections appeared to change overall rate of responding slightly.

Appetite Suppression Procedure

Data for two rats were excluded during the course of the experiment: rat 4 died and data for rat 7 failed to show consistent amounts of drinking from day to day. Milk intake for the remaining subjects stabilized within 19 days (range: 7–19 days) with an average of 27 grams of milk (range: 22–32 g) consumed per subject. Racemic MPH produced dose-dependent decreases in milk drinking (see Fig. 5), while equal doses of the *threo* racemate had differential effects on drinking: the 10 mg/kg *l*-MPH dose (data point above L in Fig. 5) reduced milk intake slightly, whereas the 10 mg/kg *d*-MPH dose (data point above D in Fig. 5) reduced intake to levels similar to those seen after the highest dose of *dl*-MPH. The data points for 10 mg/kg *d*-MPH are located at the 20 mg/kg value and the *dl*-MPH scale to test the hypothesis that all of the appetite-suppressant effects of *dl*-MPH might be attributed to the *d*-enantiomer. Since ap-

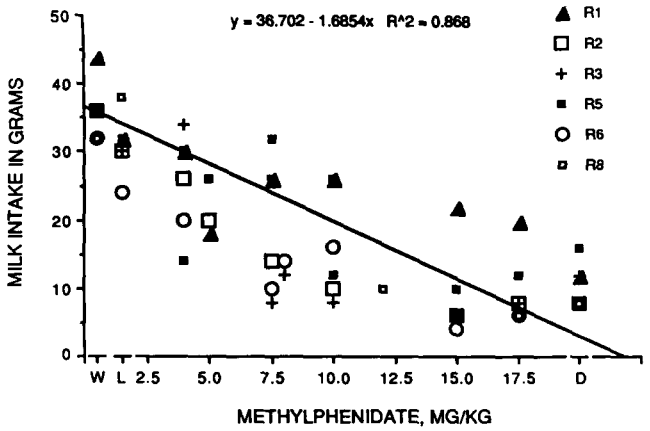

FIG. 5. Milk intake during test sessions after administration of MPH (4.0–17.5 mg/kg), 10 mg/kg *l-threo*-MPH and 10 mg/kg *d-threo*-MPH. Symbols represent single determinations for individual subjects. The regression line is based on responding to both racemic MPH and the separate enantiomers. The line predicts that 22 mg/kg MPH would maximally decrease milk intake. The data points for 10 mg/kg *d-threo*-MPH are located above "D" at 20 mg/kg on the scale. The data points for 10 mg/kg *l-threo*-MPH are located above "L," placed adjacent to values for the control water injections located above "W" at 0 mg/kg MPH.

proximately equal amounts of the *d*-enantiomer occur in both 17.5 mg/kg *dl*-MPH and 10 mg/kg *d*-MPH, the results shown in Fig. 5 imply that the *d*-enantiomer does account for all of the appetite suppressing qualities of *dl*-MPH. The slight reduction in milk intake seen after injections of the *l*-enantiomer, in turn, might be attributed to the presence of a small amount of the *d*-enantiomer in the *l*-compound (see the Procedure section). Note that the data shown in Fig. 5 are single-session consumption values. The significance of the relation is shown by the correlation ($r = .932$, $p<0.001$). No evidence of tolerance was seen across repeated doses.

DISCUSSION

For each of the present experiments, *d*-MPH was the behaviorally active enantiomer while *l*-MPH showed very little behavioral activity. Mechanistic studies indicate that response to *dl*-MPH depends upon the *d*-enantiomer facilitating dopaminergic and/or noradrenergic transmission through a cocaine-like competitive inhibition of catecholamine uptake (19). Similarly, only one enantiomer of cocaine exhibits significant behavioral activity (10). Conversely, both *d*- and *l*-amphetamine isomers are efficacious in the treatment of different subpopulations of ADD children (2). Amphetamine putatively acts by a catecholamine releasing mode (16,19), subject to different receptor and behavior stereoselectives (28).

The *l*-isomer of MPH appears to exist as an inefficacious by-product of the manufacturing process. Accordingly, the presence of the *l*-isomer in the circulation may confound attempts to correlate blood concentrations of MPH with clinical response (1). In view of the pronounced and variable enantioselective metabolism of *dl*-MPH (17), the present behavioral results indicate that definitive therapeutic drug monitoring studies will require the stereospecific determination of *d*-MPH and *l*-MPH blood concentrations rather than detecting only the sum of both isomers as reported in the literature.

The present data confirm the appetite-suppressant effects previously shown for repeated administrations of MPH via IP injection (8), as well as extending these results to find that the *d*-enantiomer of MPH is responsible for the decrease in milk intake which occurs following administration of racemic MPH. Support for this conclusion arises from the different effects on milk drinking seen following equal doses of the *threo*-racemate: 10 mg/kg *l*-MPH produced only a small decrease in milk intake, while 10 mg/kg *d*-MPH produced reductions in intake similar to those seen following 17.5 mg/kg racemic MPH.

Using the rat as a model, the *l*-isomer in racemic MPH thus appears to have a benign presence in so far as anorexia and pressor effects (19) are concerned. Whether it contributes to other common *dl*-MPH side effects such as insomnia, nervousness, and stomach pain is not known. However, the appropriateness of administering any multiple isomers of a drug for pharmacotherapy is dubious (6) considering the manifold stereoselectivities of the biological system.

The two main effects of MPH observed with the FI procedure were (1) to shorten the modal length of the postreinforcement pause, while increasing the frequency of intervals that had less than 3 total responses (increasing pause variability) and (2) to decrease the local rate of responding. These effects demonstrate a reduced temporal control and a decreased motor activity. The mechanism for these changes is not clear. This shift has often been described as part of a larger "rate dependency" effect of psychoactive drugs (14), whereby low rate performances are increased and high rate performances are decreased. On the other hand, the shortened pause might also be described as resulting from a speeded internal clock (5,15). Still further, the shortened pause could be part of an increased "focus" of behavior on the bar that might also involve decreased competition from other behavior (and thus be similar to the behavioral stereotypy observed at higher doses). "Attention" describes a controlling relation between a stimulus and behavior [(3), p. 131–132]. In this functional sense, the diminished control represented by the shortened and more variable pauses represents "reduced attention to time" regardless of the mechanism(s) responsible for the effect. Thus *d*-MPH and *dl*-MPH reduced attention to the temporal patterning of reinforcement in the present study.

For three rats, the effect of MPH on choice was to equalize responding [consistent with effects previously found (24, 25, 27), but see (12) for the opposite effect with a different kind of choice schedule]. The equalized choice resulted, in this case, from a relatively greater reduction of responding for the favored lever. Surprisingly, *d*-MPH and *dl*-MPH increased the asymmetry of responding for the fourth rat, the only rat in the present study that showed an increased local rate of responding under either *dl*-MPH or *d*-MPH (*l*-MPH, of course, did not alter rate for any rat in the present study). This increased responding also was seen on the favored lever. In all cases, therefore, the primary effect of the drug was on the favored choice.

The published literature confirms that performance reinforced according to variable-interval schedules sometimes shows rate increases and sometimes shows rate decreases following administration of psychoactive stimulants [e.g., *d*-amphetamine (14,21)]. To date, no account has been brought forward that predicts which effect will be seen. The present study, by finding a 3:1 mix, therefore, is in line with the published literature.

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