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Comparison of drug effects on the performance of two timing tasks in rats

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Abstract

Previous evidence suggests that different timing tasks are differentially sensitive to pharmacological manipulation, especially when different values for the temporal parameters are used. The present series of experiments compared the effects of physostigmine, caffeine, pentobarbital, morphine, and naloxone on the performance of a differential reinforcement of low rates with limited hold (DRL-LH) and a temporal response differentiation (TRD) task. In the DRL-LH task, rats were reinforced for responses that occurred 10–14 s from the end of the previous response. In the TRD task, rats were reinforced for responses with a duration of 10–14 s. The peak response time and peak spread of the initiation time distribution (for DRL-LH) or the response duration distribution (for TRD) were used as indices of temporal discrimination. Physostigmine, caffeine, and pentobarbital produced very similar effects on peak response time for both tasks, but the effects of morphine and naloxone were different for the two tasks. Effects on peak spread for the two tasks did not always correspond to changes in peak response time, suggesting that different processes may be measured by these two endpoints. Further, these effects were independent of changes in response rate suggesting that the effects were not due to gross disruptions in motivation or motor control. These results suggest that the effects of drugs on DRL-LH and TRD performance may differ, even when temporal parameters are identical.

Keywords: Time; Temporal; Operant; Behavior; Clock; DRL; TRD

1. Introduction

Several different operant behavioral tasks have been utilized to study time estimation in rats. These include, but are not limited to, the differential reinforcement of low rates with limited hold (DRL-LH) task [3,7], the temporal response differentiation (TRD) task [8], the interval bisection task [4], and the peak interval task [4]. In the DRL-LH task, subjects are required to withhold responding for a specific period of time to receive reinforcement. In contrast, the TRD task requires subjects to make a continuous response (for a specific period of time) to receive reinforcement. In the DRL-LH task, drug or toxicant-induced changes in time estimation are inferred from changes in the distribution of response initiation times (time intervals that separate each response). In the TRD task, changes in time estimation are inferred from changes in the distribution of the response durations. Leftward shifts in these distributions are thought to reflect an overestimation of the passage of time whereas rightward shifts are thought to reflect an underestimation of the passage of time.

Shifts in response distributions are also used as indices of time estimation in other types of timing tasks, such as the fixed-interval peak procedure and the interval bisection task [4]. In the peak procedure, rats are trained under a fixed interval schedule and then ''probe trials'' are inserted during which the rat is no longer reinforced. The rat's response rate generally peaks at the time of the fixed interval and changes in time estimation are inferred based on changes in this ''peak time.'' In the interval bisection task, rats are trained to discriminate a short from a long duration of a visual or auditory stimulus. Probe sessions in which stimuli of intermediate duration between the short and long duration stimuli are then presented, and changes in the bisection point (the duration yielding 50% responses fitting with the short stimulus and 50% responses fitting with long stimulus) are interpreted as changes in time estimation.

Studies aimed at determining the effects of a particular drug on time estimation using different timing tasks often

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produce conflicting results. Differing results can be a function of the timing task employed or the doses of drug administered. Particularly, with regard to the DRL-LH and TRD tasks, it has been previously demonstrated that the temporal requirements of the task (i.e., TRD 1–1.3 s vs. TRD 10–13 s) may account for differential drug effects on task performance [7,8]. Thus, if the effects of drugs on two timing tasks are to be directly compared, it is important that the doses of drug tested and the temporal requirements of the two tasks are identical.

The present series of experiments examined the effects of five drugs with different mechanisms of action on the performance of the DRL-LH and TRD tasks in rats. Drugs included: physostigmine, which acts by inhibiting the activity of acetylcholinesterase; caffeine, which acts by increasing cAMP and by interacting with adenosine receptors; morphine, which acts as an agonist at opioid receptors; naloxone, which acts as an antagonist at opioid receptors; and pentobarbital, which acts by potentiating chloride conductance at GABA receptors and by reducing glutamate transmission. For the DRL-LH task, subjects were required to withhold responding to an operant lever for at least 10, but not more than 14 s. The first response that was initiated within this 10–14 s window resulted in food delivery. Responses that were initiated either before or after this 10–14 s window were not reinforced and resulted in the initiation of a new trial. For the TRD task, subjects were required to hold the lever in the depressed position for at least 10, but not more than 14 s. Releasing the lever within this 10–14 s window resulted in reinforcer delivery. Releasing the lever either before or after this 10–14 s window had no programmed consequences. The peak response time and peak spread were derived from the distribution of initiation times (DRL-LH) or response durations (TRD) and were used as measures of temporal discrimination. The doses of drugs administered and the temporal requirements of each task (i.e., a 10–14-s "window" for reinforcement) were identical.

2. Methods

2.1. Subjects

Two groups of male Sprague–Dawley rats ($n = 8$ per group) from the National Center for Toxicological Research breeding colony served as subjects. Rats were approximately 8 months of age at the start of drug testing.

2.2. Operant training and testing procedure

Beginning on postnatal day 70, rats were gradually food-deprived to 85% of their free-feeding weights. On postnatal day 90, training for the timing tasks began. The subjects were divided into two groups of eight. One group was trained to perform the DRL-LH task and the other group was trained to perform the TRD task. For DRL-LH training, rats were initially reinforced for responses that occurred at least 0.5 s after the previous response. This temporal parameter was gradually increased in 0.5-s increments until the rats reached a lower time limit of 10 s, after which the upper limit was set at 14 s. Training at these final parameters continued until stable performance (defined below) was achieved. For TRD training, rats were initially reinforced for responses with a duration of at least 0.5 s. The required minimum lever hold duration was gradually increased in 0.5-s increments until lever holds of at least 10.0 s were achieved. The maximum lever hold duration was then set at 14.0 s, and rats were

Table 1
Sample size and drug doses included in the statistical analyses for each drug study

Drug	Dependent variable	*N*	Doses included in ANOVA (mg/kg)
Physostigmine	Peak response time (DRL-LH)	8	0.0, 0.2, 0.4, 0.6, 0.75
	Peak response time (TRD)	3	
	Peak Spread (DRL-LH)	8	
	Peak Spread (TRD)	3	
Caffeine	Peak response time (DRL-LH)	7	0.0, 10.0, 20.0, 40.0
	Peak response time (TRD)	8	
	Peak Spread (DRL-LH)	7	
	Peak Spread (TRD)	8	
Pentobarbital	Peak response time (DRL-LH)	7	0.0, 5.6, 10.0
	Peak response time (TRD)	8	
	Peak Spread (DRL-LH)	7	
	Peak Spread (TRD)	8	
Morphine	Peak response time (DRL-LH)	7	0.0, 1.3, 5.6, 7.5, 10.0
	Peak response time (TRD)	7	
	Peak Spread (DRL-LH)	7	
	Peak Spread (TRD)	7	
Naloxone	Peak response time (DRL-LH)	7	0.0, 3.0, 10.0, 30.0, 56.0, 75.0 (DRL-LH);
	Peak response time (TRD)	6	0.0, 3.0, 10.0, 30.0, 56.0 (TRD)
	Peak Spread (DRL-LH)	7	
	Peak Spread (TRD)	6	

trained at these final parameters until stable performance was achieved. As in previous studies from this laboratory [5,6,12,13], stable performance was defined as a standard error of not more than 15% of the mean for the percent task completed (reinforcers earned/reinforcers possible × 100, maximum reinforcers = 120). Behavioral sessions lasted 40 min. Once stable performance was demonstrated for a 2-week period, drug administration began.

2.3. Drug administration

All drugs were obtained from Research Biochemicals (Natick, MA) and were dissolved in sterile bacteriostatic 0.9% saline solution for a final injection volume of 1.0 ml/kg. Doses of each drug were administered by intraperitoneal injection in a semi-randomized order 15 min prior to operant testing on Tuesdays and Fridays of each week. Each dose was given on each of two separate test days. Testing without prior injection was conducted on Mondays and Wednesdays, and saline injections were administered on Thursdays. This dosing schedule ensured that drug administrations were separated by at least 2 days to reduce the likelihood that either tolerance or sensitization contributed to acute drug effects measured subsequently. The drug studies occurred sequentially in each of the two groups of rats as follows: physostigmine (postnatal days 250–300), caffeine (postnatal days 315–365), morphine (postnatal days 380–430), naloxone (postnatal days 445–495), pentobarbital (postnatal days 510–560). Drug studies were separated by a 2-week washout period during which subjects received daily injections of saline.

2.4. Behavioral endpoints

For the DRL-LH task, the initiation time (time between the end of the last response and the beginning of the next)

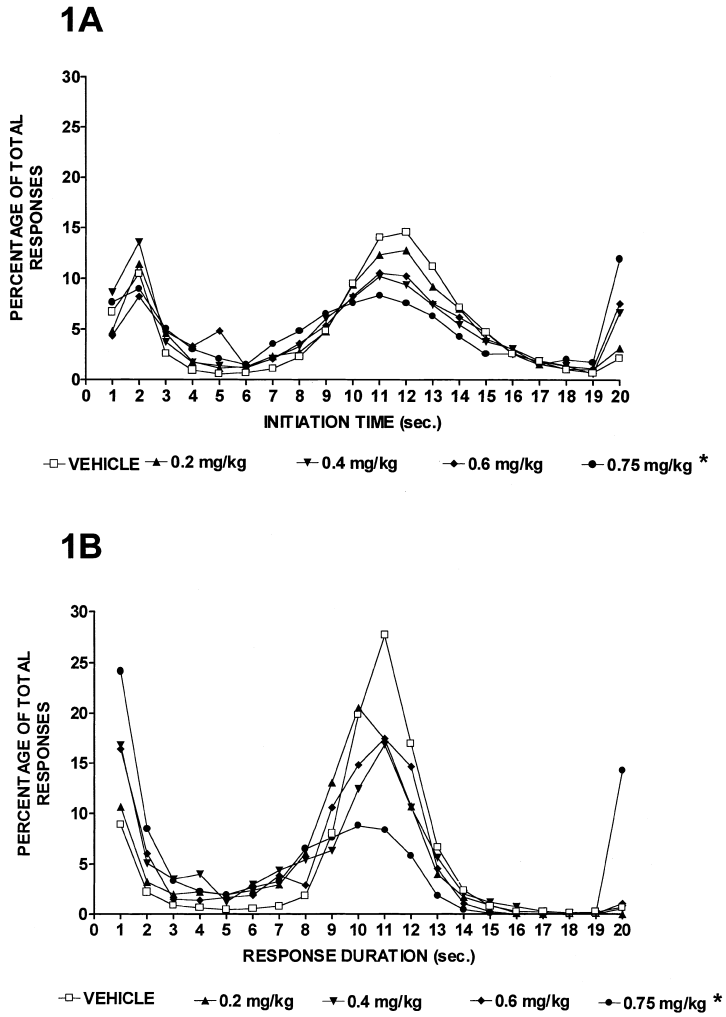

Fig. 1. Effect of physostigmine on the distribution of response initiation times for the DRL-LH task (A) and on the distribution of response durations for the TRD task (B). Data are presented as a percentage of total responses made. Responses with initiation times/durations of 0.01–1 s are shown in bin 1, 1.01–2 s in bin 2, etc., and all responses with initiation times/durations > 19.01 s are shown in bin 20. * Indicates significant difference in peak response time vs. vehicle by Dunnett's post hoc test.

Table 2
Effects of physostigmine, caffeine, pentobarbital, morphine, and naloxone on the peak response time for the DRL-LH and TRD distributions

Dose of physostigmine (mg/kg)						
	VEH	0.2	0.4	0.6	0.75	1.0
DRL-LH	11.51 (0.24)	11.46 (0.28)	11.21 (0.38)	11.44 (0.22)	10.63 (0.32)[a]	N/A
TRD	10.43 (0.12)	9.80 (0.21)	10.13 (0.26)	10.13 (0.18)	8.53 (0.58)[a]	N/A
Dose of caffeine (mg/kg)						
	VEH	10.0	20.0	40.0	80.0	120.0
DRL-LH	12.71 (0.27)	12.66 (0.75)	12.50 (0.66)	11.26 (0.56)[a]	N/A	N/A
TRD	10.89 (0.11)	10.41 (0.37)	10.11 (0.67)	9.69 (0.37)[a]	N/A	N/A
Dose of pentobarbital (mg/kg)						
	VEH	5.6	10.0	17.5	23.0	30.0
DRL-LH	12.87 (0.48)	11.29 (0.26)[a]	9.84 (0.43)[a]	N/A	N/A	N/A
TRD	10.79 (0.10)	9.84 (0.29)[a]	8.95 (0.34)[a]	N/A	N/A	N/A
Dose of morphine (mg/kg)						
	VEH	1.0	3.0	5.6	7.5	10.0
DRL-LH	12.10 (0.29)	12.30 (0.40)	12.30 (0.39)	14.31 (1.08)	13.06 (0.91)	13.76 (1.09)
TRD	10.80 (0.12)	10.97 (0.14)	10.83 (0.13)	9.67 (0.45)[a]	9.87 (0.24)	9.59 (0.50)[a]
Dose of naloxone (mg/kg)						
	VEH	3.0	10.0	30.0	56.0	75.0
DRL-LH	12.13 (0.29)	12.21 (0.27)	11.73 (0.31)	13.06 (1.12)	13.10 (0.91)	13.59 (1.05)
TRD	10.97 (0.10)	11.42 (0.37)	10.23 (0.22)	10.58 (0.16)	N/A	N/A

Data are expressed as the means, with S.E.M. in parentheses. N/A indicates that the majority of rats failed to produce a measurable peak response time at that dose.
[a] Indicates significant difference from vehicle.

Table 3
Effects of physostigmine, caffeine, pentobarbital, morphine, and naloxone on the peak spread for the DRL-LH and TRD distributions

Dose of physostigmine (mg/kg)						
	VEH	0.2	0.4	0.6	0.75	1.0
DRL-LH	0.191 (0.010)	0.199 (0.014)	0.252 (0.029)	0.219 (0.020)	0.304 (0.039)[a]	N/A
TRD	0.128 (0.008)	0.139 (0.017)	0.178 (0.009)[a]	0.145 (0.001)	0.204 (0.005)[a]	N/A
Dose of caffeine (mg/kg)						
	VEH	10.0	20.0	40.0	80.0	120.0
DRL-LH	0.251 (0.008)	0.259 (0.011)	0.295 (0.020)	0.349 (0.016)[a]	N/A	N/A
TRD	0.166 (0.013)	0.188 (0.021)	0.206 (0.031)	0.233 (0.029)	N/A	N/A
Dose of pentobarbital (mg/kg)						
	VEH	5.6	10.0	17.5	23.0	30.0
DRL-LH	0.204 (0.009)	0.217 (0.017)	0.295 (0.031)[a]	N/A	N/A	N/A
TRD	0.136 (0.009)	0.158 (0.014)	0.233 (0.020)[a]	N/A	N/A	N/A
Dose of morphine (mg/kg)						
	VEH	1.0	3.0	5.6	7.5	10.0
DRL-LH	0.238 (0.017)	0.259 (0.027)	0.269 (0.020)	0.271 (0.040)	0.256 (0.023)	0.284 (0.017)
TRD	0.148 (0.011)	0.160 (0.008)	0.186 (0.029)	0.274 (0.033)[a]	0.245 (0.036)[a]	0.252 (0.032)[a]
Dose of naloxone (mg/kg)						
	VEH	3.0	10.0	30.0	56.0	75.0
DRL-LH	0.213 (0.011)	0.201 (0.017)	0.237 (0.023)	0.246 (0.033)	0.253 (0.016)	0.244 (0.042)
TRD	0.157 (0.013)	0.169 (0.021)	0.159 (0.016)	0.146 (0.013)	N/A	N/A

Data are expressed as the means, with S.E.M. in parentheses. N/A indicates that the majority of rats failed to produce a measurable peak spread at that dose.
[a] Indicates significant difference from vehicle.

Table 4
Effects of physostigmine, caffeine, pentobarbital, morphine, and naloxone on the response rates (responses/s) exhibited under the DRL-LH and TRD schedules

Dose of physostigmine (mg/kg)						
	VEH	0.2	0.4	0.6	0.75	1.0
DRL-LH	0.090 (0.005)	0.088 (0.010)	0.076 (0.013)	0.064 (0.005)	0.050 (0.013)[a]	N/A
TRD	0.068 (0.005)	0.065 (0.005)	0.064 (0.012)	0.057 (0.012)	0.034 (0.018)	N/A
Dose of caffeine (mg/kg)						
	VEH	10.0	20.0	40.0	80.0	120.0
DRL-LH	0.083 (0.003)	0.088 (0.010)	0.100 (0.013)	0.101 (0.009)	N/A	N/A
TRD	0.065 (0.003)	0.080 (0.007)	0.084 (0.013)	0.069 (0.010)	N/A	N/A
Dose of pentobarbital (mg/kg)						
	VEH	5.6	10.0	17.5	23.0	30.0
DRL-LH	0.075 (0.006)	0.093 (0.005)	0.115 (0.009)[a]	N/A	N/A	N/A
TRD	0.056 (0.003)	0.065 (0.006)	0.059 (0.006)	N/A	N/A	N/A
Dose of morphine (mg/kg)						
	VEH	1.0	3.0	5.6	7.5	10.0
DRL-LH	0.092 (0.005)	0.084 (0.008)	0.072 (0.013)	0.054 (0.013)	0.084 (0.016)	0.063 (0.008)
TRD	0.065 (0.002)	0.062 (0.003)	0.073 (0.008)	0.084 (0.010)	0.078 (0.007)	0.072 (0.013)
Dose of naloxone (mg/kg)						
	VEH	3.0	10.0	30.0	56.0	75.0
DRL-LH	0.082 (0.005)	0.087 (0.007)	0.092 (0.006)	0.077 (0.007)	0.063 (0.014)	0.052 (0.010)[a]
TRD	0.058 (0.003)	0.058 (0.004)	0.068 (0.007)	0.059 (0.004)	0.043 (0.007)	N/A

Data are expressed as the means, with S.E.M. in parentheses. Only subjects that were included in the analysis of peak response times and peak spread were included in the analysis of response rate.

[a] Indicates significant difference from vehicle.

was recorded. For the TRD task, the response duration (time between the onset and offset of each response) was recorded.

2.5. Data collection and analysis

Vehicle data for each drug study was combined with data collected during the subsequent washout period and was used to assess behavioral stability. Only rats that demonstrated stable performance during these vehicle sessions were included in the analysis of response distributions (see stability criteria outlined above). Paired *t* tests were used to examine changes in behavior under vehicle conditions across adjacent drug studies.

Response distributions were constructed by allotting each response in a given session to a one-s time bin that corresponded to the initiation time of the response (for DRL-LH) or the duration of the response (for TRD). Responses of 0.01–1.0 s were assigned to the first bin and all responses greater than 19.01 s were assigned to the last bin. Previous reports [7,8,11,14–16] indicate that data collected using DRL–LH and TRD schedules conform to a bimodal distribution with an initial burst of responding at 0.01–3.0 s followed by a second burst of responding at or near the temporal requirement for reinforcement (here, 10–14 s). Because responses with durations (TRD) or initiation times (DRL-LH) of less than 3.0 s have been shown to be insensitive to alterations in timing [11,14–16], data from bins 1–3 were omitted prior to statistical analysis for both tasks. SAS statistical software (version 6.12) was used to fit all remaining data (e.g., bins 4–20) to a Gaussian distribution using the ''corrected Akaike information criterion'' [2]. Data for doses of drug that failed to produce a Gaussian distribution were excluded from the ANOVAs. Rats that failed to produce a Gaussian distribution under vehicle conditions also were excluded from the ANOVAs. Table 1 summarizes the number of subjects and specific drug doses that were included in each statistical analysis after all exclusion criteria had been applied.

The mean of the response distribution (peak response time) was derived directly from the output of the fitting procedure. The coefficient of variation (peak spread) was derived by dividing the standard deviation of the distribution by its mean. Changes in these parameters were determined using repeated measures ANOVA followed by Dunnett's post hoc tests to compare the effects of each drug to its own control ($P < .05$). ANOVA also were used to examine the effects of each drug on overall response rates for each behavioral task. Previous studies have employed similar analyses of response distributions to describe behavior generated using TRD schedules [6].

3. Results

Physostigmine (Fig. 1; Tables 2–4) decreased the overall peak response time for the DRL-LH task [$f(4, 28) = 3.77$, $P < .05$], as well as for the TRD task [$f(4, 8) = 5.65$, $P < .05$]. For both of these tasks, the effects of the 0.75 mg/kg dose differed significantly from vehicle. Physostigmine also increased the overall peak spread for the DRL-LH task [$f(4, 28) = 4.60$, $P < .05$], as well as for the TRD task [$f(4, 8) = 12.65$, $P < .05$]. The 0.75 mg/kg dose significantly increased peak spread for the DRL-LH task, and the 0.4 and 0.75 mg/kg doses significantly increased peak spread for the TRD task. Physostigmine reduced overall response rates for the DRL-LH task [$f(4, 28) = 4.50$, $P < .05$], but did not alter response rates for TRD.

Like physostigmine, caffeine (Fig. 2; Tables 2–4) decreased the overall peak response time for the DRL-LH task [$f(3, 18) = 4.22$, $P < .05$], as well as for the TRD task [$f(3, 21) = 3.11$, $P < .05$]. For both tasks, the 40.0 mg/kg dose significantly decreased peak response time compared to vehicle. In addition, caffeine increased overall peak spread for the DRL-LH task [$f(3, 18) = 8.89$, $P < .05$] with the effects of the 40 mg/kg dose differing significantly from vehicle. The effect of caffeine to increase peak spread for the TRD task approached, but did not achieve, statistical significance [$f(3, 21) = 3.04$, $P = .052$]. Caffeine also had no effect on the overall rate of responding for either task.

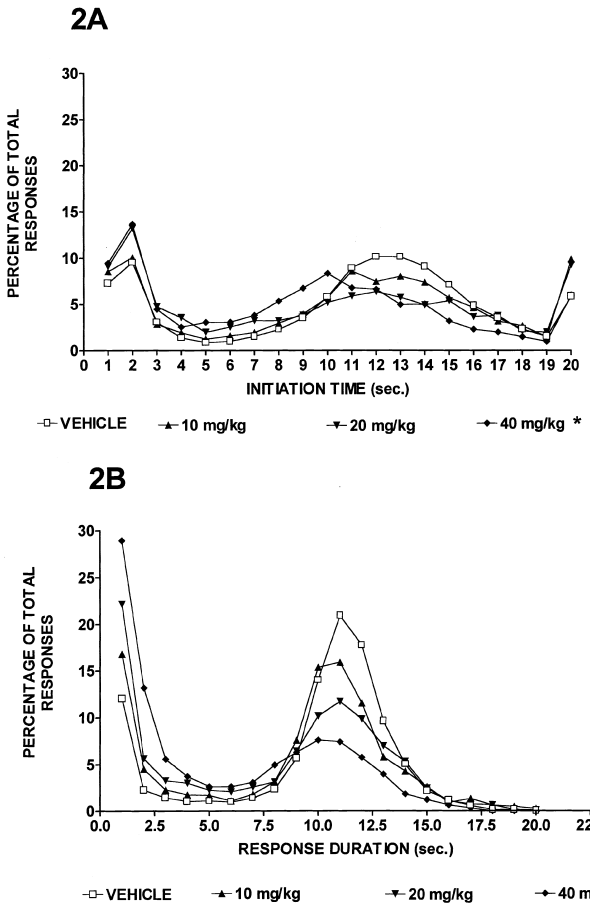

Fig. 2. Effect of caffeine on the distribution of response initiation times for the DRL-LH task (A) and on the distribution of response durations for the TRD task (B). Data expressed described in Fig. 1.

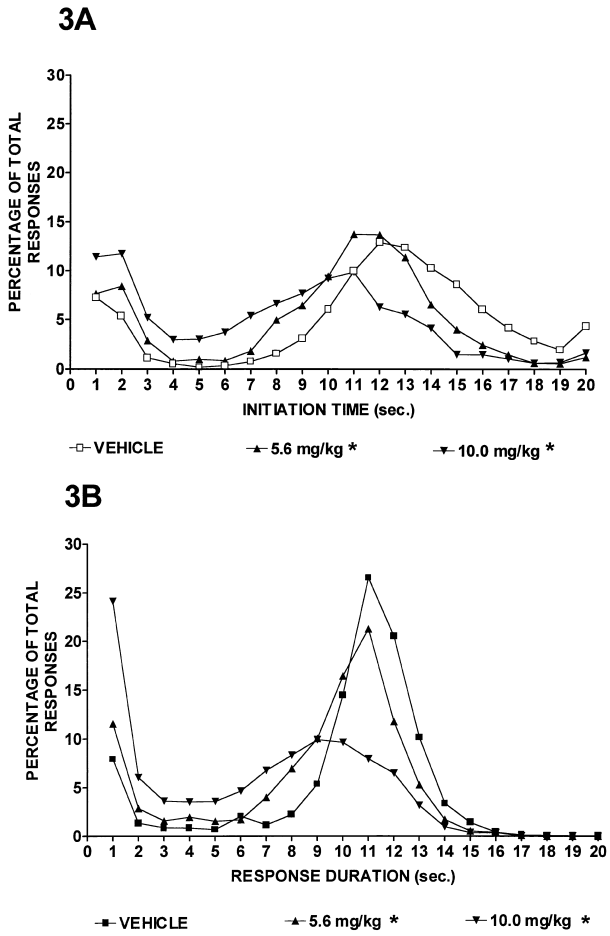

Fig. 3. Effect of pentobarbital on the distribution of response initiation times for the DRL-LH task (A) and on the distribution of response durations for the TRD task (B). Data are expressed as described in Fig. 1.

Pentobarbital (Fig. 3; Tables 2–4) reduced overall peak response time for both the DRL-LH task [$f(2, 12) = 19.56$, $P < .05$] and for the TRD task [$f(2, 14) = 17.72$, $P < .05$]. For both tasks, the effects of 5.6 and 10.0 mg/kg differed significantly from vehicle. Pentobarbital also increased peak spread both for the DRL-LH [$f(2, 12) = 9.45$, $P < .05$] and for the TRD tasks [$f(2, 14) = 29.16$, $P < .05$]. For both tasks, the effects of the 10.0 mg/kg dose on peak spread differed significantly from those measured under vehicle conditions. Pentobarbital reduced overall response rates for the DRL-LH task [$f(2, 14) = 11.38$, $P < .05$], but did not alter response rates for TRD.

Morphine (Fig. 4; Tables 2–4) had a marginally significant effect to increase peak response time for the DRL-LH task [$f(5, 30) = 2.07$, $P = .098$], but there was no effect on

peak spread. For TRD, on the other hand, morphine reduced overall peak response time [$f(5, 30) = 6.60$, $P < .05$] and also increased overall peak spread [$f(5, 30) = 4.83$, $P < .05$]. The effects of 5.6 and 10.0 mg/kg morphine were significantly different from vehicle for peak response time, while the effects of 5.6, 7.5, and 10.0 mg/kg morphine were significantly different from vehicle for peak spread. Morphine did not alter the overall rate of responding for either task.

Naloxone (Fig. 5; Tables 2–4) failed to produce an overall significant effect on peak initiation time or peak spread for either behavioral task. However, naloxone significantly reduced response rates for both DRL-LH [$f(5, 30) = 3.49$. $P < .05$] and for TRD [$f(4, 20) = 3.49$, $P < .05$].

In addition to analyzing acute drug effects on timing, paired t tests were used to examine behavior under vehicle conditions across adjacent drug studies. For the DRL-LH task, there was a significant difference between the physostigmine vehicle and caffeine vehicle conditions for peak spread ($t = -5.88$, $P < .05$) and between the physostigmine and caffeine vehicle ($t = -9.58$, $P < .05$), the caffeine and morphine vehicle ($t = 4.37$, $P < .05$), and the naloxone and pentobarbital vehicle conditions ($t = -3.19$, $P < .05$) for peak response time. For the TRD task, there was a significant difference between the physostigmine and caffeine vehicle conditions for peak response time ($t = -6.15$, $P < .05$), but there were no differences in vehicle values for peak spread. Response rates differed between the naloxone and pentobarbital vehicle conditions for DRL-LH ($t = 3.12$, $P < .05$) and between the physostigmine and caffeine vehicle conditions for TRD ($t = 5.04$, $P < .05$).

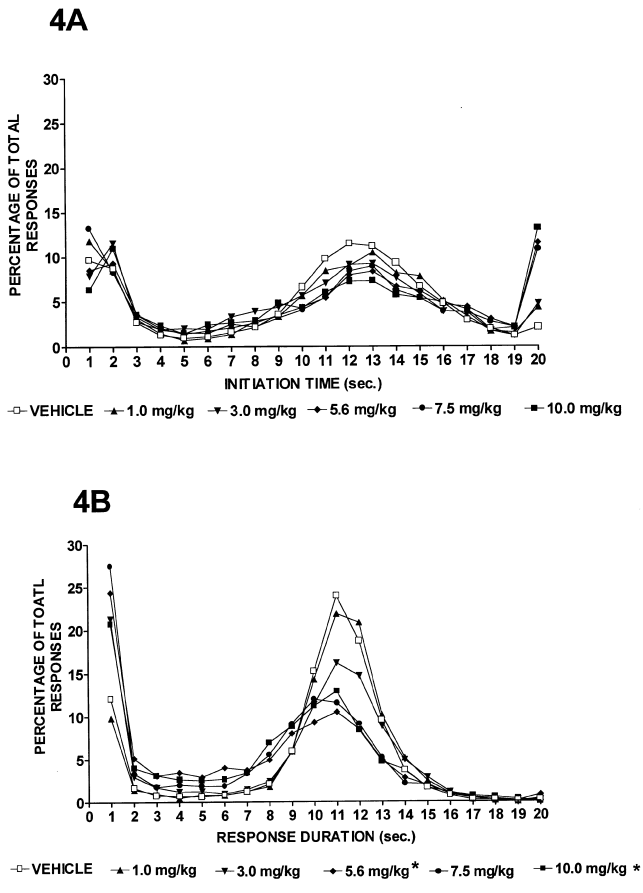

Fig. 4. Effect of morphine on the distribution of response initiation times for the DRL-LH (A) task and on the distribution of response durations for the TRD task (B). Data are expressed as described in Fig. 1.

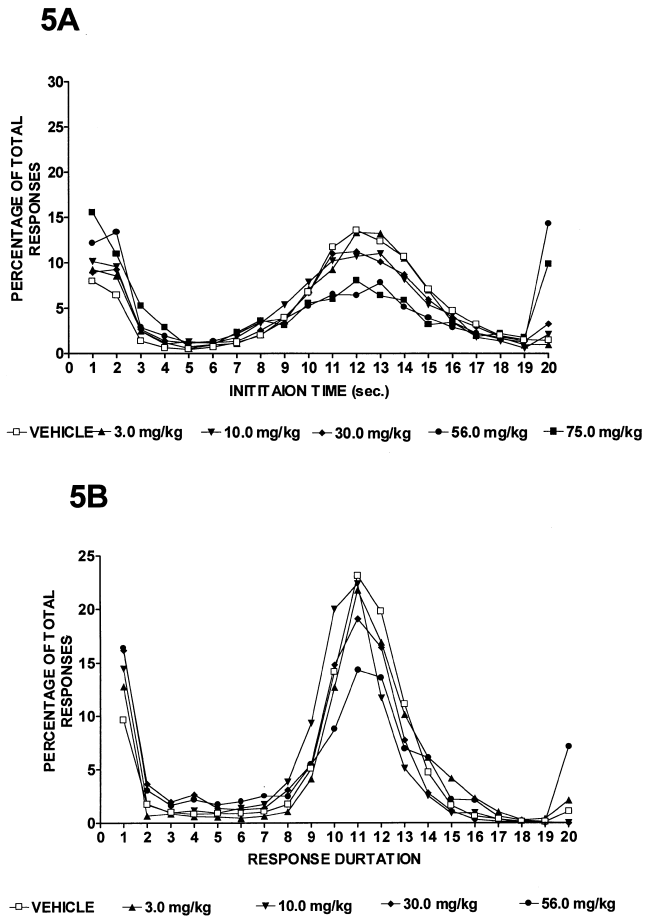

Fig. 5. Effect of naloxone on the distribution of response initiations for the DRL-LH task (A) and on the distribution of response durations for the TRD task (B). Data are expressed as described in Fig. 1.

4. Discussion

The present experiment examined the effects of five drugs with different mechanisms of action on the performance of two different timing tasks in rats. Drugs included: physostigmine, which acts by inhibiting the activity of acetylcholinesterase; caffeine, which acts by increasing cAMP and by interacting with adenosine receptors; morphine, which acts as an agonist at opioid receptors; naloxone, which acts as an antagonist at opioid receptors; and pentobarbital, which acts by potentiating chloride conductance at GABA receptors and by reducing glutamate trans-

mission. Physostigmine, caffeine and pentobarbital each shifted the peak of the initiation time distribution (for the DRL-LH task) and the peak of the response duration distribution (for the TRD task) to the left. Morphine shifted the mean of the response duration distribution for TRD, but had no effect on the initiation time distribution for DRL-LH. Naloxone failed to alter the peak of the response distribution for either task. Effects on peak spread for the two tasks were similar for pentobarbital and naloxone, but differed for each the other drugs tested. The fact that the effects of these drugs manifest differently in each of these behavioral tasks highlights the need to employ several different types of tasks when assessing the effects of drugs on timing. Further, the fact that a marked dissociation exists between changes in these distribution parameters and changes in overall response rate suggests that the DRL-LH and TRD tasks provide specific information that is fundamentally different from that derived using simple measures of motivation or motor performance.

Under vehicle conditions, responding on both the DRL-LH and TRD tasks conformed to a bimodal distribution with an initial burst of responding at 0.01–3.0 s followed by a second burst of responding at or near the temporal requirement for reinforcement (here, 10–14 s). Previous work with DRL schedules suggests that the initial burst of responses (0.01–3.0 s) is insensitive to the temporal requirements of DRL schedules [11,14–16]. Therefore, changes in temporal discrimination are best determined by examining changes in the peak response time (mean) and the peak spread (coefficient of variation) of the upper mode of the distribution. Previous authors have interpreted peak time and peak spread for DRL-LH as providing indices of accuracy and precision of the temporal discrimination, respectively [15,16]. Because the peak response time (mean) is used as a factor in deriving the peak spread (coefficient of variation), one might assume that they are simply different representations of the same behavioral process or that changes in peak spread can be entirely accounted for by changes in peak time. As the present data illustrate, however, drug-induced changes in peak spread do not always correspond to changes in peak time, suggesting that different behavioral processes are be measured by each of these two endpoints. Future behavioral and pharmacological studies will be necessary to better understand the significance of these endpoints with regard to the performance of these two tasks.

It is interesting to compare the effects seen in the current study with previous work [7,8] that examined drug effects on DRL-LH and TRD tasks with very similar temporal requirements (10–13-s "window" rather than the 10–14-s "window" used here). Although different statistical analyses of the distributions were used, those studies demonstrated leftward shifts in the distributions for the DRL-LH and TRD tasks in response to methamphetamine, phencyclidine, and Δ-9-THC. Leftward shifts in both tasks were also seen for physostigmine, caffeine and pentobarbital in the current study. Thus, leftward shifts in the peak response times for DRL-LH and TRD with these particular temporal requirements appear to be a common response to drugs of several different pharmacological classes. Further studies will be necessary to determine whether other classes of agents are capable of producing rightward shifts in peak response times for these two tasks.

A detailed analysis of the effects of pentobarbital, caffeine, morphine, or naloxone on time estimation in rats has not been previously reported. Meck [9] has postulated the existence of an "internal clock" mechanism that is responsible for changes in time estimation in response to drugs. According to this hypothesis, leftward shifts produced by drugs in timing tasks reflect an increase in clock speed and an overestimation of the passage of time. Conversely, rightward shifts in timing tasks reflect a decrease in clock speed and an underestimation of time passage. In the light of this hypothesis, the current data suggests that pentobarbital and caffeine alter timing function by producing an overestimation of the passage of time. Naloxone appears to have no significant effects on timing function using the current temporal parameters. The effects of morphine on timing function are unclear given the present results and require further investigation.

Previous investigations of physostigmine's effects on timing have yielded somewhat inconsistent results. Meck et al. reported that low doses of physostigmine (0.01–0.09 mg/kg, ip) can produce a leftward shift in timing functions using the peak-interval procedure [10] and the interval bisection task [9]. Bizot [1], on the other hand, reported no effect of physostigmine in an interval bisection task using slightly higher doses (0.06–0.12 mg/kg) and different temporal requirements. In the present experiment, physostigmine shifted the peak response times for both tasks, but only at relatively high doses (i.e., 0.75 mg/kg). The apparent inconsistencies in the effects of physostigmine on timing may reflect differences in the relative sensitivities of the various timing tasks to cholinergic stimulation or differences in the temporal parameters used.

Finally, it is important to comment on differences in behavioral performance which occurred between vehicle conditions in several of the adjacent drug studies. Although these differences were not evident for every endpoint or between every dose–response determination, the possibility that changes in vehicle values may have contributed to effects of subsequently administered drugs cannot be ruled out. Such differences in baseline values may reflect an effect of prior drug exposure, an effect of subsequent behavioral experience, or some combination of the two. Alternatively, these differences may reflect random variation in baseline behavior that emerged over the animals' life span and that is independent of the present experimental manipulations. Regardless of which of these hypotheses is true, the fact that differences in behavior exist under vehicle conditions highlights the importance of re-establishing an independent vehicle value for each drug study conducted in sequence.

In conclusion, the present series of experiments demonstrates that the DRL-LH and TRD tasks can be differentially sensitive to the effects of drugs, even when identical temporal parameters are used. This finding extends the work of previous studies [7,8] to include agents from several unique pharmacological classes. Specifically, the current work suggests that GABA agonists such as pentobarbital and adenosine antagonists such as caffeine can produce leftward shifts in timing functions indicative of an overestimation of the passage of time. Opioid drugs such as morphine produce differential effects on the performance of these two timing tasks. The fact that the effects of these drugs can manifest differently in each of these behavioral tasks highlights the need to employ several different types of tasks when assessing the effects of drugs on timing. Further, the fact that changes in these parameters often occurred in the absence of changes in response rate suggests that the DRL-LH and TRD tasks can provide specific cognitive–behavioral information that is inaccessible using simple measures of motivation or motor performance. Future studies using these and other pharmacologic agents will provide additional understanding of the pharmacology of time estimation.

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