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Caffeine Has Similar Pharmacokinetics and Behavioral Effects via the IP and PO Routes of Administration

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WANG, Y. AND C. E. LAU. *Caffeine has similar pharmacokinetics and behavioral effects via the IP and PO routes of administration.* PHARMACOL BIOCHEM BEHAV **60**(1) 271–278, 1998.—Caffeine administered intraperitoneally (IP) or orally (PO) decreased the reinforcement rate and increased the nonreinforced response rate in a dose-related fashion under a differential reinforcement of low rate schedule (DRL 45-s) in 3-h sessions. These effects were similar following both routes of caffeine administration. The parallel pharmacokinetics for IP and PO caffeine were each determined and related to the respective effects of caffeine on reinforcement rate. Serum caffeine concentrations were similar across the session after the absorption phase for a given dose. Consequently, the effect remained in approximately the same range within a dose, and no single dose possessed a full concentration–effect relation for the two routes. The effects of IP and PO caffeine on reinforcement rate plateaued at doses higher than 40 mg/kg, which produced a serum caffeine concentration of approximately 25 μg/ml regardless of the route of administration. The EC_{50} values were 7.34 and 9.93 μg/ml for IP and PO caffeine, respectively. This study as well as our previous studies demonstrated that the IP route is dependable for studying caffeine dose–response relations but not for studying other drugs (e.g., midazolam). The possible mechanism accounting for this difference is discussed.

Caffeine DMX DRL performance Pharmacokinetics Routes of administration

DIFFERENTIAL reinforcement of low rate schedules (e.g., DRL 45-s) produce low rates of responding, as only those responses that occur after a minimum time interval (≥45 s) following a previous response are reinforced. Responses that occur before this time has elapsed are not reinforced, and they reset the timing of the interval. In past research, we found that the DRL 45-s performance is objective, continuous, sensitive, and reproducible, and largely corresponded to the respective pharmacokinetics (PK) after drug administration (15–17). The effects of caffeine on performance under the DRL 45-s schedule and locomotor activity have been investigated in our laboratory (13,14,16). In these studies, caffeine was administered IP simply because it was the most common route used for caffeine in behavioral pharmacology (7,20–23) with other routes (e.g., SC, oral self-administration) used less extensively (10,11,13,25). Inasmuch as caffeine is consumed orally by humans and possesses high bioavailability (2), we also used the PO route to examine the acute and chronic effects of caffeine on performance under the DRL 45-s schedule (17,18). We found that caffeine has similar pharmacokinetics and behavioral effects via the IP and PO routes of administration (16–18), although other drugs such as midazolam are less effective (i.e., low bioavailability) via the oral route in comparison to other extravascular routes of administration (15,26).

Recently, we found that serum midazolam concentration–time profiles and behavior–time profiles were inconsistent following two successive 3 mg/kg doses administered IP and separated by 3–5 days (15). These results found for midazolam came as a surprise to us because this route was commonly used for studying the effect of midazolam; however, no justifying documentation was available. This led us to conduct the present study to reexamine the suitability of the IP route, and the effectiveness of the PO route, for caffeine for archival purposes, although no problem was detected in our previous studies (16–17). In those studies we focused on answering a specific question (i.e., interaction of alprazolam and caffeine)

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without considering the optimal route for caffeine administration. The present study—a replication of the two previous studies with respect to IP and PO caffeine (16–17)—investigated the effects of IP and PO caffeine on DRL performance in a within-subject design. The parallel pharmacokinetics of IP and PO caffeine and its active dimethylxanthine (DMX) metabolites (theobromine, paraxanthine, and theophylline) also were determined in animals under the same food regimen so that the relations between DRL performance and the respective pharmacokinetics could be delineated. Thus, the aim was to create an awareness concerning the choice of an optimal route of administration for the drug of interest to avoid possible misinterpretation.

METHOD

Effects of IP and PO Caffeine on DRL Performance

Animals. Four male, albino, Sprague–Dawley rats from HSD (Indianapolis, IN) were used. They were housed individually in a temperature-regulated room with a daily cycle of illumination from 0700–1900 h. They were reduced to 80% of their initial, adult free-feeding body weights (mean = 381 g; range: 380–382 g) by receiving limited daily food rations (5 g for the first day, 10 g for the next 5 days), and were then maintained at their 80% body weights by being given a daily food supplement (range: 14–16 g). Water was continuously available in the living cages. Experiments were executed in accor-

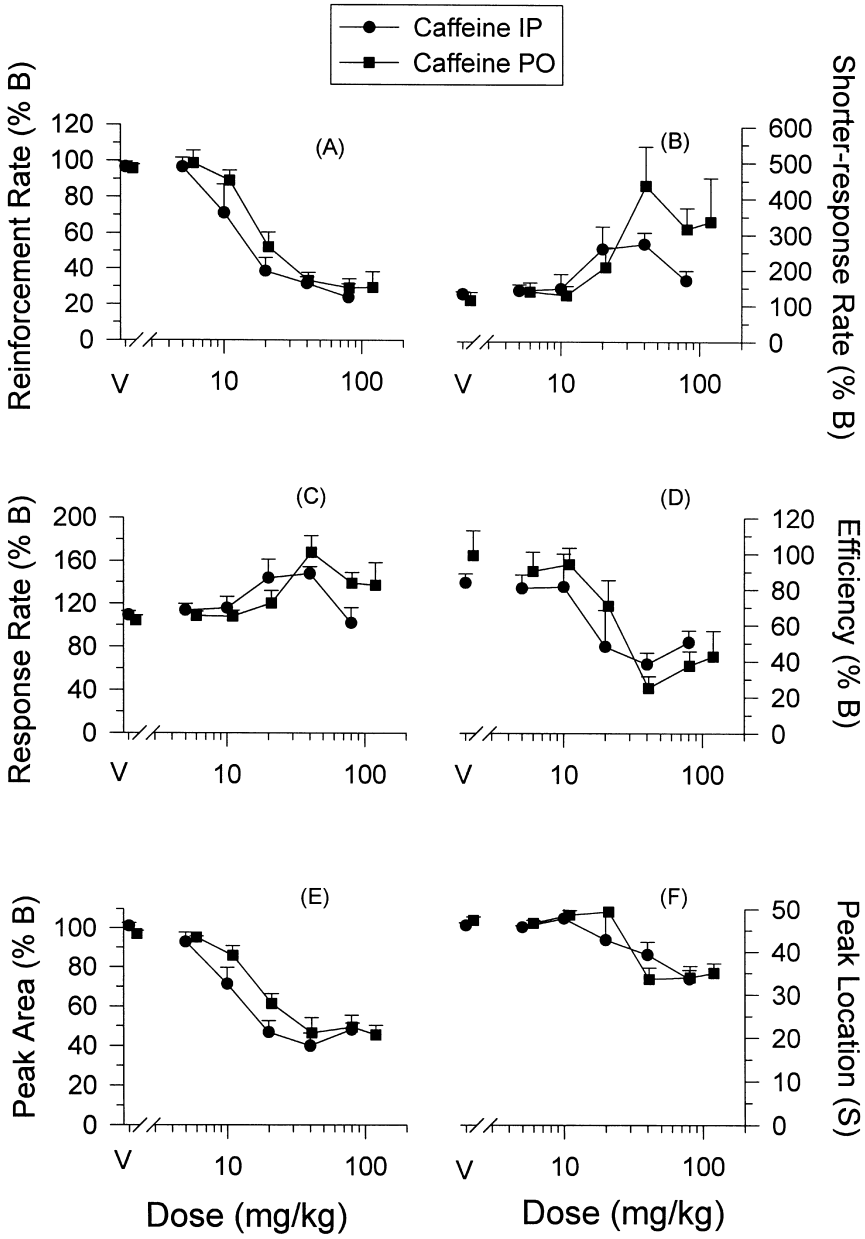

FIG. 1 Mean (SE) % baseline effects of caffeine for the 3-h sessions on: (A) reinforcement rate; (B) shorter-response rate; (C) response rate; (D) efficiency; (E) peak area. (F) peak location in second for IP and PO caffeine. V, vehicle; B, baseline.

dance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publ. No. 85-23, revised 1985).

Drugs. Caffeine was purchased from Sigma Chemical Co. (St. Louis, MO) and was dissolved in sodium benzoate (37.5 mg/ml) solution. It was administered either IP or PO by gavage, in an injection volume of 1 ml/kg body weight.

Apparatus. Four operant Plexiglas chambers were used, and have been described previously (16,17). Each chamber, equipped with a response lever and a stainless steel food-pellet receptacle into which 45-mg dustless pellets (BioServ, Frenchtown, NJ) could be delivered, was enclosed in a sound-attenuating shell and was controlled by an IBM-type 486X computer. Session contingencies were programmed and data recorded using QuickBasic.

Procedure. Animals were magazine trained initially for 15 min on a noncontingent random-time schedule. Responses on the lever were shaped by successive approximations and were reinforced when interresponse times (IRTs) were greater than 3 s. The temporal requirement was slowly increased to an IRT of 45 s over 10–20 sessions. Once training was complete, a 3-h operant session was conducted at the same time every day. After intersession performance had stabilized (i.e., the performance did not vary by more than 5% from the baseline for each subject), animals first received an IP vehicle injection. This injection was followed by an IP caffeine dose–response determination: 5, 10, 20, 40, and 80 mg/kg. Ten noninjection sessions followed. The animals then each received a PO vehicle injection followed by a PO caffeine dose–response determination: 5, 10, 20, 40, 80, and 120 mg/kg. Caffeine doses were given in a random order. Caffeine and vehicle were each given immediately before the start of a session. All injections were separated by 3–5 days.

Data analyses. The IRT distributions for the administration of vehicle and those for caffeine were analyzed for 3-h sessions. The first 2 min of data, which allowed for the transient effects of handling, were not included in the analysis. Behavioral parameters were derived from the IRT distributions: shorter (nonreinforced)-response rate, reinforcement rate, total response rate, and efficiency. The total number of responses consisted of responses with IRTs $\geq$45 s and $<$45 s, which are the reinforced and nonreinforced responses, respectively. These responses were calculated as rates (responses per min). Efficiency was calculated as the ratio of reinforcement rate to the total response rate. Although we have found that the reinforcement rate in the 45–55-s bin, as well as in the $\geq$45 s bin, decreased as a function of dosage for drugs (e.g., alprazolam, caffeine), the 45–55 s bin function was more sensitive to drug effects than the total reinforcement rate was ($\geq$45 s). The 45–55-s bin function also required lower doses to reach the maximum effect than the total reinforcement rate measure did, and it has been used successfully to characterize the acute and chronic alprazolam–caffeine interactions (16–18). Thus, in the present study, the IRTs in the 45–55-s bin, rather than IRTs $\geq$45 s were used to calculate the reinforcement rate to facilitate comparison with our previous work; hereinafter, the term reinforcement rate refers to the rate of reinforcement in the 45–55 s bin.

Peak deviation analysis developed by Richards et al. (27) was used for characterizing the effects of caffeine with the parameters, peak area and peak location, which determine the size and the center of the IRT distribution peak, respectively. A reduction in peak area indicates that the IRTs are more disrupted, suggesting a decrease in temporal stimulus control.

Statistical analysis of the DRL performance was performed by repeated-measures, two-way ANOVA with route of administration and dose as the factors, followed by Newman–Keuls tests using SigmaStat (Jandel, San Rafael, CA).

Pharmacokinetics of IP and PO Caffeine

Animals. Three male, albino rats of the same strain were used under the conditions and food-limitation regimen mentioned above. The mean initial, adult free-feeding body weight was 381 g (range: 380–383 g).

HPLC determination of caffeine and DMXs. Serum microsample HPLC methods for the determination of caffeine and its active metabolites have been described previously (12). The separation of caffeine was performed on Beckman Ultrasphere C_{18} columns (5 μm particle size, 150 × 2 mm i.d.). Programmable absorbance UV detectors 785A (Applied Biosys-

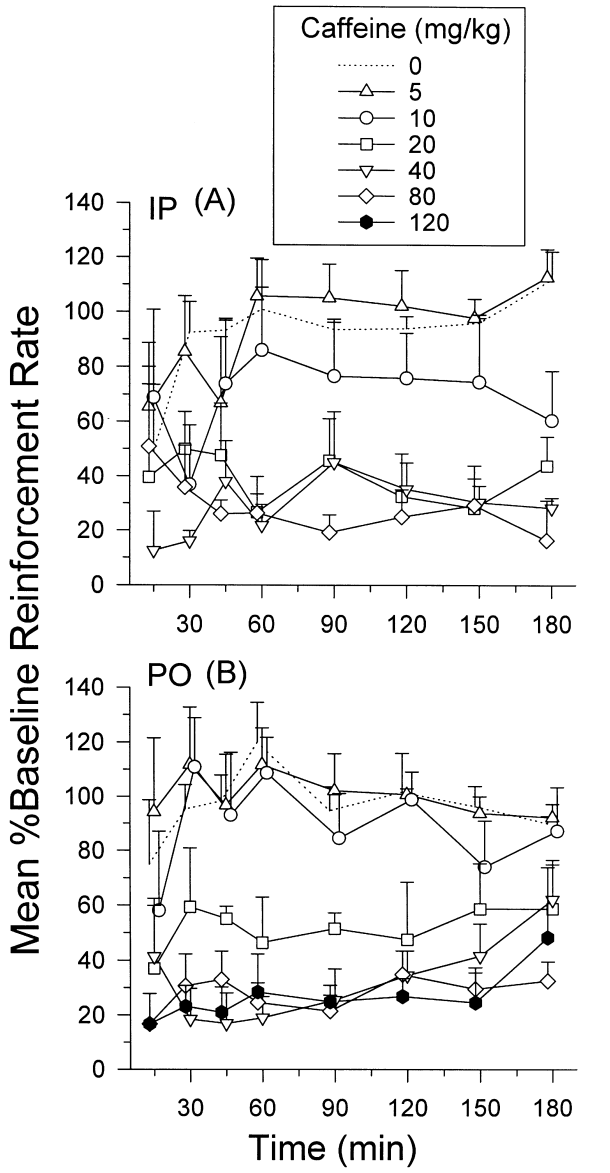

FIG. 2. Mean (SE) % baseline reinforcement rate-time profiles for caffeine: (A) IP route; (B) PO route.

tems Instruments, Foster City, CA), were operated at 270 nm. The capacity factors for theobromine, paraxanthine, theophylline, β-hydroxyethyltheophylline used as an internal standard, and caffeine were 1.31, 2.52, 2.97, 3.73, and 6.45, respectively.

Catheterization

Right jugular vein cannulation was performed under sterile conditions and has been described earlier (15). The proximal end of the silastic catheter was inserted into the jugular vein. The distal end of the catheter was threaded subcutaneously and exited through a small incision in the back of the animal. The catheter was flushed with 50 units of heparin in 0.9% saline and was sealed with fishing line when not in use.

Drug administration and blood sampling. The animals were allowed to recover for at least 2 days from the jugular vein catheterization prior to the drug administration series. The animals received IP doses of caffeine (10–80 mg/kg) followed by PO doses of caffeine (10–120 mg/kg). Drug doses were separated by 3–5 days.

Blood samples (100 μl) from the jugular catheter were obtained following drug administration at 5, 10, 15, 30, 60, 90, 120, 180, and 240 min postinjection. Drug doses were given 4 h prior to the feeding time because the feeding regimen needed to be maintained and the effect of food on drug pharmacokinetics avoided, especially for the oral route. Thus, the daily food supplements were given immediately after the last blood samples were taken.

Construction of concentration–effect curves. Concentration–effect curves for caffeine by the two routes of administration were constructed with the use of a four-parameter, logistic function of the following equation by the ALLFIT curve-fitting program written for the IBM PC (5,6):

$$y = [(a - d)/(1 + (x/c)^b)] + d$$

where y is the percent of baseline reinforcement rate and x is the serum caffeine concentration. The four-fitted parameters were a, the E_{min}, i.e., the % baseline reinforcement rate when x = 0; d, the E_{max}, i.e., the % baseline reinforcement rate for "infinite" concentration; b, the slope factor that determined

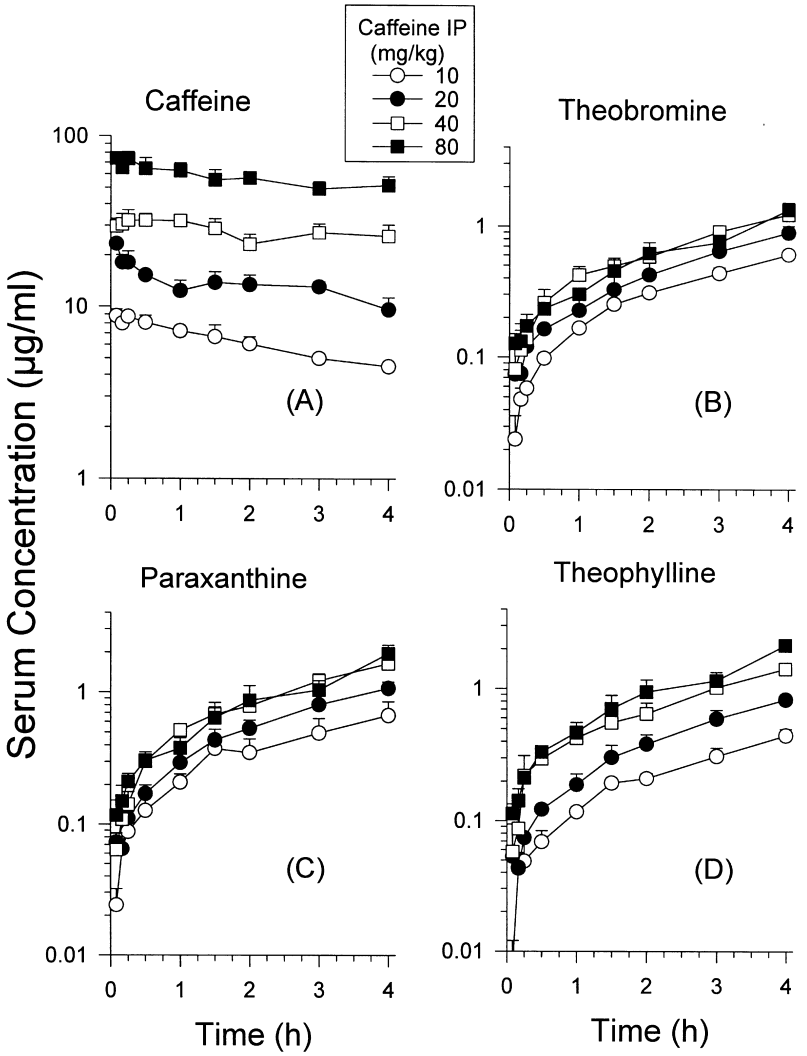

FIG. 3. Mean (SE) serum concentration–time profiles following IP caffeine administration: (A) caffeine; (B) theobromine; (C) paraxanthine; (D) theophylline.

the steepness of the curve; and c, the EC_{50}, i.e., the concentration resulting in an effect halfway between a and d.

Data analyses. Statistical analysis of the serum caffeine and DMXs concentration–time profiles was performed by repeated-measures, two-way ANOVA with route of administration and time as the factors, followed by Newman–Keuls tests using SigmaStat.

RESULTS

Effects of IP and PO Caffeine on DRL Performance

Figure 1A–F shows an overview of DRL performance for the 3-h session following vehicle and caffeine administration by the IP and PO routes. Decreases in reinforcement rate reached plateaus at higher caffeine doses regardless of the route of administration (Fig. 1A). The shorter-response rate exhibited an inverted U-shaped function for both IP and PO caffeine (Fig. 1B). The opposing relation between the reinforced and the nonreinforced response rate after caffeine administration resulted in a higher total response rate similar to the shorter-response rate (Fig. 1C). Consequently, efficiency was similar to the reinforcement rate function across doses after IP and PO caffeine administration (Fig. 1D). For both IP and PO caffeine, dose–response relations for the peak area measure were similar to those for reinforcement rate (Fig. 1E), whereas the center of the IRT distribution peak shifted to the shorter IRTs at higher caffeine doses, as shown by the peak location measure (Fig. 1F). It can be concluded that the effects of caffeine on these six performance indices of DRL performance were similar for the two routes of administration ($p > 0.05$).

The effects of IP and PO vehicle administration were close to baseline (>90%) on the reinforcement rate–time profiles except at the 15-min time point (Fig. 2A–B), which showed a vehicle effect. Caffeine decreased the reinforcement rate in a dose-related fashion. However, the decreases were approximately similar across the session for a given dose regardless of the routes of administration.

Pharmacokinetics of IP and PO Caffeine

The serum caffeine and its active three DMX concentration–time profiles after 4 IP (10–80 mg/kg) and 5 PO (10–120

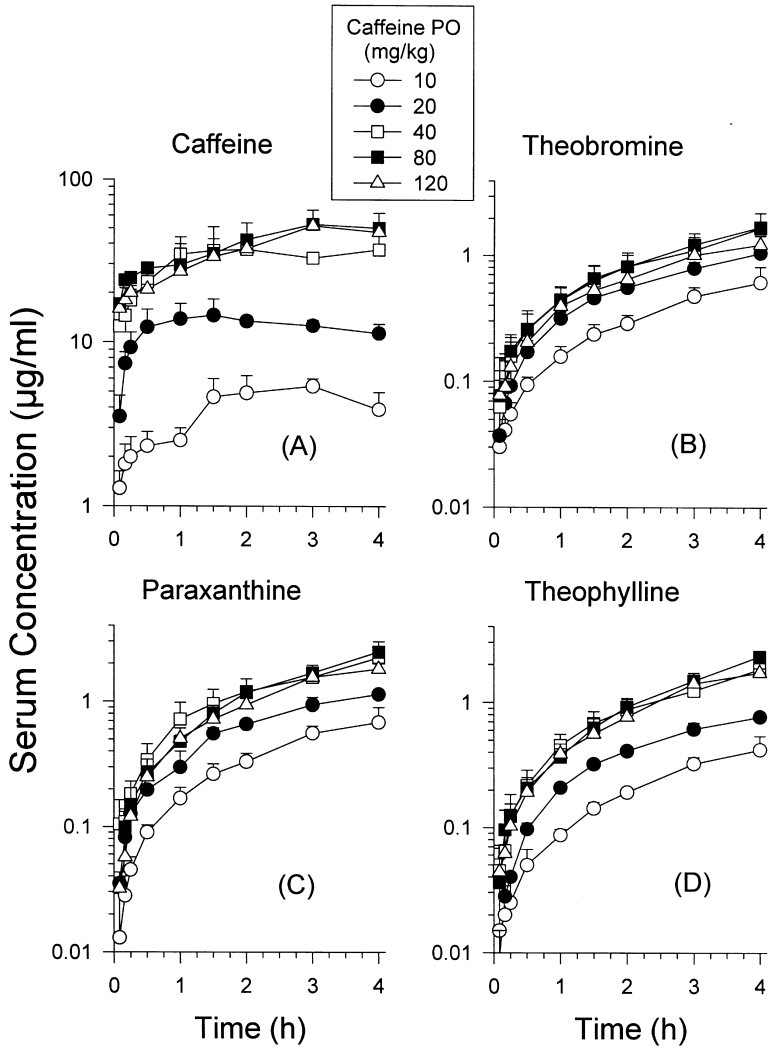

FIG. 4. Mean (SE) serum concentration–time profiles following PO caffeine administration: (A) caffeine; (B) theobromine; (C) paraxanthine; (D) theophylline.

mg/kg) caffeine doses are shown in Figs. 3A–D and 4A–D, respectively. Following IP caffeine doses, serum caffeine concentration reached maximum levels (C_{max}s) at 5 min and then slowly decreased across time in a dose-related fashion (Fig. 4A). For the PO doses, the C_{max}s were attained after the absorption phase and serum caffeine concentrations remained high for the duration of the blood sampling (Fig. 4A). For the first hour, the caffeine concentration increases differed considerably as a function of route by repeated measures two-way ANOVAs ($p < 0.01$, 0.01, 0.05, and 0.005 for 10, 20, 40, and 80 mg/kg, respectively). Serum caffeine concentration–time profile increased as a function of IP dose but plateaued at PO caffeine doses higher than PO 40 mg/kg (Figs. 3A–4A). Caffeine metabolizes to the three DMXs, in approximately equal amounts, and the formation of the three DMXs continues to progress at the fourth hour, as shown in Figs. 3B–D and 4B–D. No significant differences in the formation of the three DMX serum concentration–time profiles were found between the two routes ($p > 0.05$).

Relation Between Reinforcement Rate and Serum Caffeine Concentration

Figure 5 shows the relations between mean serum caffeine concentration ($n = 3$ rats) and mean reinforcement rate ($n = 4$ rats) as constructed by using ALLFIT. The first 15-min effects of IP and PO caffeine on reinforcement rate were not included in these analyses, owing to the slight but short-lived disruptive effects of even vehicle administration (Fig. 2A–B). For any of the caffeine doses, the serum concentration remained little changed during the session time. Thus, construction of the caffeine concentration–effect function for the 3-h session length required all the doses (10–120 mg/kg) for both routes of administration; no single dose possessed a full concentration–effect relation (Fig. 5). Nevertheless, the decreased reinforcement rate plateaued at serum caffeine concentrations higher than 25 μg/ml regardless of the route of administration. It was apparent that there was little difference in the effectiveness of IP and PO caffeine in changing DRL performance as reflected by the IP and PO caffeine EC_{50} values, 7.34 and 9.93 μg/ml, respectively (Table 1). Inferential statistical analysis could not be performed with respect to a difference between the two curves because mean data, rather than individual animal data, from parallel groups were used to estimate the EC_{50} values. Nevertheless, the two curves closely approximated each other.

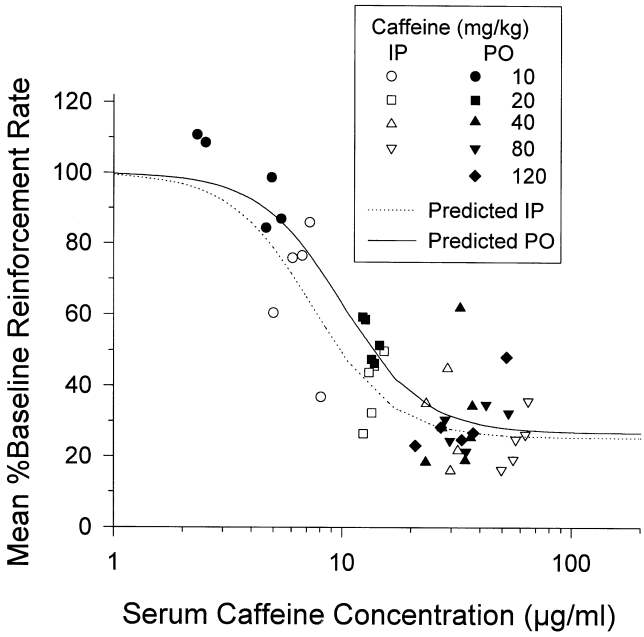

FIG. 5. Mean % baseline reinforcement rate vs. mean serum caffeine concentrations. Lines are the curves fitted by ALLFIT.

DISCUSSION

We investigated the effects of caffeine via the IP and PO routes of administration from the standpoint of dose– and concentration–effect relations. Caffeine exhibited dose-related effects on DRL performance as shown by the 3-h collapsed data and the reinforcement rate-time profiles for both routes of administration (Figs. 1–2). Likewise, serum caffeine concentration–time profiles, following the IP and the PO caffeine administration, were dose proportional, although the PO caffeine concentration–time profiles plateaued at higher doses. There was no occasion detected of unpredictable DRL performance– and concentration–time profile following the IP and PO caffeine doses. The present study as well as the previous studies clearly reveal that both routes of caffeine administration are valid for studying caffeine dose– and concentration–effect relations.

We found no literature pertaining to the undependability of using the IP route for drug administration, despite informal recognition that this route can be problematic (unpublished observations). For example, it is commonly known that rats occasionally remain completely or partially unanesthetized following an anesthetic IP drug dose—e.g., pentobarbital, or ketamine plus xylazine. However, such observations are neither documented nor investigated in the literature. A drug's molecular structure and its physicochemical properties (e.g., lipophilicity, pKa value), and their interactions with the physiological factors associated with the route of administration largely determine the drug's pharmacokinetic processes—absorption, distribution, metabolism, and elimination. It has been found that the lipophilic β-adrenoceptor blockers are not only rapidly absorbed but also have a large first-pass effect in comparison to the hydrophilic β-adrenoceptor blockers (24). Following both IP and PO routes of administration, certain drugs are subject to first-pass effects. For caffeine, there is no important hepatic first-pass effect detected in humans or

TABLE 1

CONCENTRATION–EFFECT PARAMETERS (±SD) FOR IP AND PO CAFFEINE

			(% Baseline)	
	EC_{50} (μg/ml)	Slope	E_{min}	E_{max}
Caffeine IP				
	7.34 (±0.91)	2.4	100	25.35 (±3.79)
Caffeine PO				
	9.93 (±1.45)	2.4	100	26.73 (±3.88)

animals (1–3); thus, it is not surprising that the concentration–time profiles were similar following the two routes of administration in the present study (Figs. 3–4).

Midazolam is much more lipophilic than caffeine based on their partition coefficient values (4,26). For drugs undergoing first-pass metabolism such as midazolam, a bioavailability of approximately 5–50% was found when midazolam was given by extravascular routes of administration in humans and rats (8,9,15,19). We are the first, to our knowledge, to report that IP midazolam produced more sporadic within-subject variability in both serum concentration–time profiles and behavior–time profiles than did PO midazolam (15). Although between-subject variability in first-pass metabolism is commonly observed, we suspect that the unpredictable within-subject serum midazolam concentration-time profiles after IP administration may additionally result from variability in the locus in the peritoneal cavity where the drug solution is injected; no such consideration is needed for the PO route. Although midazolam (pKa = 1.7 and 6.51) has a faster onset of action than caffeine (pKa = 1 and 14) as reflected by their pKa values (4,26), we do not believe the pKa values play an important role in determining the unpredictability of the IP route; pKa values mainly determine the rate and extent of absorption and distribution.

The minimal first-pass effects of caffeine resulted in high bioavailability that accounted for its effectiveness via the oral route in humans or animals (1–3). In the present and our previous studies, we did not determine its bioavailability, but caffeine has similar pharmacokinetics and behavioral effects via the IP and PO routes of administration in rats (16,17). The terminal elimination half-life of caffeine is about 3 h, the volume of distribution and the clearance are 0.89 l/kg and 0.29 l/h/kg, respectively, in rats (1,4,17). The oral route is useful for chronic dose regimens because it avoids any possibility of skin necrosis produced by a daily SC dose (18).

On the basis of the six indices (Fig. 1A–F), we concluded that the effects of IP and PO caffeine on 3-h DRL performance were similar. These results were consonant with those reported for caffeine in other schedules of DRL (20,28,29). There are two reasons accounting for the fact that the time courses of the behavioral effects of caffeine appear to be similar by the PO and IP routes, whereas the establishment of caffeine serum concentrations differed as a function of route. First, the effect of vehicle administration on the reinforcement rate for the first 15-min time point somewhat masked the initial differences in serum caffeine concentration for the two routes (Fig. 2); however, the decreases in reinforcement rate were still greater following 10 mg/kg IP caffeine administration than those following the 10 mg/kg PO caffeine administration because the serum caffeine concentrations were greater for the former than for the latter (Fig. 5). Second, the effects of IP and PO caffeine on reinforcement rate plateaued after a serum caffeine concentration of approximately 25 μg/ml (Figs. 1A, and 5). It is evident that for all the caffeine doses the caffeine concentration–effect relation remained in approximately the same range within a dose (Fig. 5). The EC_{50} value for PO caffeine was 9.93 μg/ml (Table 1), which was consonant with that found in a previous study, 8.07 μg/ml (17). The formation of the three active DMX metabolites for the first 3 h was independent of the two routes of administration (Figs. 3 and 4).

For both routes of caffeine administration, not only the serum caffeine concentration–time profiles but also the effects on reinforcement rate approximately mirrored those found previously (16,17). The effects of caffeine on reinforcement rate can be immediately interpreted as a function of serum caffeine concentrations, regardless of the route of administration. The intent of this study was to create an awareness concerning the choice of an optimal route of administration for the drug of interest. In addition, we hope this report will encourage others to document optimal route(s) of administration for psychoactive drugs, thereby facilitating research in psychopharmacology.

ACKNOWLEDGEMENTS

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