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Pharmacokinetic determinants of cocaine's differential effects on locomotor and operant behavior

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Abstract

Dose–response, effect–time and concentration–effect relations of intravenous cocaine (1–4 mg/kg) were investigated on contingency-controlled [fixed-ratio (FR) 70 performance] and unconditioned (locomotor activity) behaviors. Cocaine dose–response curves exhibited decreasing rates of response under the FR 70 schedule but increasing locomotor activity in a dose-related fashion. Effect–time profiles confirmed that these changes were time-dependent and provided additional clarity by mirroring the biexponential decay of cocaine concentrations with time. The duration of action of cocaine was comparatively shorter on locomotor activity than on FR performance. We integrated effect–time profiles of the two behaviors with concentration–time profiles simulated from our previously published pharmacokinetic parameters to derive cocaine's pharmacodynamic parameters. Classical inhibitory E_{max} and sigmoidal E_{max} models were used to describe cocaine's effects on FR performance and locomotor activity, respectively. Simultaneous pharmacokinetic–pharmacodynamic modeling reveals evidence of acute tolerance to cocaine in locomotor activity, as indicated by decreasing potency with dose, but not in contingency-controlled behavior.

Keywords: Fixed-ratio schedule; Cocaine, intravenous; Operant behavior; Pharmacokinetics; Pharmacodynamics; Locomotor activity, spontaneous

1. Introduction

Recently, we characterized the psychomotor stimulant effect of i.v. cocaine on a timing behavior and its relation to associated changes in serum cocaine concentration over time by pharmacokinetic–pharmacodynamic modeling (Lau et al., 1999). The i.v. route was used for its rapid onset and reliability of action which is without interference from absorption or first-pass effects. The behavioral paradigm used in that study was a differential reinforcement of low rate (i.e., DRL 45-s) schedule. This schedule of reinforcement results in low rates of responding, as only those responses that occur after a minimum time interval (in this case, 45 s) following a previous response are reinforced; responses that occur before an interval of 45 s has elapsed are not reinforced, and the timing interval is reset. We used two classes of responses as pharmacodynamic measures to study effects of cocaine: the rate at which reinforced responses occur (or density of reinforcement) and the shorter (or nonreinforced)-response rate. Following i.v. cocaine administration, the shorter-response rate increased to maximal effect immediately, while the density of reinforcement decreased to a minimum. As cocaine concentrations decreased biexponentially, the shorter-response rate returned toward baseline; at the same time, the density of reinforcement increased and returned to baseline level. Both behavior increases (i.e., shorter-response rates) and decreases (i.e., density of reinforcement) were readily described pharmacodynamically by the sigmoidal E_{max} and classical inhibitory E_{max} models, respectively.

The present study aimed to examine the role of cocaine's pharmacokinetics on other types of behaviors after i.v. administration. We used animals of the same species, age, and gender, and exposed to the same food-limited regimen as those under the DRL 45-s schedule. This enabled us to simulate cocaine concentration–time profiles from pharmacokinetic parameters published previously (Lau et al., 1999). Concentration–effect relations are well known to provide more accurate profiles of drug action than dose–response relations that are derived from time-course data

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collapsed into single points. To construct this concentration–effect relation, one must first analyze effect–time profiles in order to integrate them with the corresponding concentration–time profile. Integration of pharmacokinetics and pharmacodynamics permits the partitioning of pharmacokinetic and pharmacodynamic components and the identification of emerging events (e.g., acute tolerance) in drug action.

Pharmacodynamic analysis of i.v. cocaine in the present study employs a fixed-ratio (FR) food reinforcement schedule (i.e., FR 70). Like the DRL 45-s schedule, FR performance satisfies many of the criteria (i.e., objective, continuous, sensitive and reproducible) proposed as ideal for pharmacodynamic measurement (Laurijssens and Greenblatt, 1996). It is also a contingency-controlled behavior. Unlike the DRL 45-s schedule, however, the FR 70 schedule produces high rates of responding because a food pellet (45 mg) is delivered after the 70th lever press. A second objective of the study was the investigation of cocaine's effects on an unconditioned behavior by monitoring spontaneous locomotor activity following i.v. cocaine administration. Cocaine is known to decrease rates of responding under FR schedules with higher ratio values (e.g., > 30) but increase locomotor activity (Woolverton et al., 1978; Bedford et al., 1980; Reith et al., 1987; Falk et al., 1991; Lau et al., 1991). Examination of concentration–effect relations for these two behaviors will provide additional elucidation of cocaine's differential effects on noncontingent and contingency-controlled behavior and compare these with the aforementioned increasing and decreasing functions under the DRL 45-s schedule. Furthermore, integrated pharmacokinetic–pharmacodynamic analysis using effect–time data with concentration–time profiles rather than dose–response curves should enable real-time modeling of cocaine's pharmacological action at hypothetical effect sites. Although the effects of cocaine in animals have been investigated under various FR schedules, analyses were previously limited to dose–response rather than concentration–effect relations (Spealman et al., 1977; Smith, 1990; Kleven and Woolverton, 1991; Van Harren, 1992). In addition, pharmacokinetic–pharmacodynamic modeling has been applied to cocaine's effects on spontaneous locomotor activity in rats; however, the pharmacodynamic parameters were only derived from single dose of cocaine (Hutchaleelaha et al., 1997).

2. Materials and methods

2.1. Pharmacodynamics: FR 70 schedule and spontaneous locomotor activity

2.1.1. Animals

Eight male, adult, albino, virus-free rats of the Sprague–Dawley strain from HSD (Indianapolis, IN) with a mean, initial body weight of 413 g (range: 380–472 g) were used. They were housed individually in a temperature-regulated room with a 12 h light–dark cycle (lights on at 0700 h). Body weights were reduced to 80% of free-feeding levels by limiting daily food rations over a 2-week period as described previously (Lau et al., 1999), and held at these weights for the duration of the experiment. Water was continuously available in the living cages. Experiments were executed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publ. No. 85-23, revised 1985).

2.1.2. Drugs

Cocaine hydrochloride was obtained from the Research Triangle Institute (Research Triangle Park, NC) through the National Institute on Drug Abuse (NIDA). Drug doses of cocaine were expressed in terms of the salt. Cocaine HCl was dissolved in 0.9% NaCl and administered intravenously (i.v.) in a volume of 1 ml/kg body weight; cocaine solution was delivered in 15 s and was followed by 0.3 ml 0.9% saline in 15 s.

2.1.3. Catheterization

Right jugular vein cannulation was performed under sterile conditions as described previously (Lau et al., 1996; Ma et al., 1999). 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 0.9% saline containing 50 units of heparin per milliliter and was sealed with fishing line when not in use.

2.1.4. Apparatus

2.1.4.1. FR 70 schedule. Each of the four experimental chambers, 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 486 X computer as described previously (Lau and Wang, 1996). Session contingencies were programmed and data recorded using QuickBasic.

2.1.4.2. Spontaneous locomotor activity. Spontaneous locomotor activity was measured, as described previously (Lau and Falk, 1994), in a room isolated from other activities and noise. Animals were placed individually into stainless steel cages ($38.0 \times 25.5 \times 17.5$ cm) resting on Startle–Tremor Platforms (E45-10, Coulborn Instruments, Allentown, PA). The platforms were connected to individual activity monitors (E61-11) located in an adjacent room. Each monitor was threshold adjusted, by means of its sensitivity and separation controls. The threshold was adjusted so that the counter recorded locomotion and grooming movements, but not sniffing or head movements.

2.1.5. Procedure

2.1.5.1. FR 70 schedule. A 3-h behavioral test session was conducted daily. Rats ($N = 4$) were trained to respond under a FR 70 schedule, a pellet was delivered after the 70th lever press. After intersession performance had stabilized (i.e., the rate of reinforcement did not vary by more than 5% from the baseline for 5 consecutive days), right jugular vein catheters were implanted as described above.

2.1.5.2. Spontaneous locomotor activity. After the subjects' weights were stabilized, 2 h activity-monitoring sessions were conducted daily. Immediately before each daily session, animals ($N = 4$) were weighed, transported to the experimental room, and placed into their individual activity-monitoring cages at 1600 h and remained there overnight. At 0900 h, animals were returned to their home cages and given food rations to maintain their criterion weights. After 20 to 24 days of daily activity measurement, all animals displayed low intersession variability, right jugular vein catheters were implanted as described above.

The two groups of animals were allowed to recover for at least 2 days from the jugular vein catheterization before being returned to the daily operant or activity sessions. After intersession performance had restabilized, cocaine administration series began. Animals received i.v. doses of 1, 2 and 4 mg/kg cocaine as well as a vehicle injection. All injections were given immediately prior to a session, and were separated by 3–5 days in a random order.

2.1.5.3. Data analyses. Effects of cocaine (0–4 mg/kg) on the reinforcement rate under the FR 70 schedule and on locomotor activity were analyzed. Baseline performance for each session that immediately preceded each injection also was analyzed. For each rat, there were four baseline-day values that were averaged and treated as the mean baseline effect.

Regression analysis, paired *t*-test and repeated-measures (RM), one-way or two-way analysis of variance

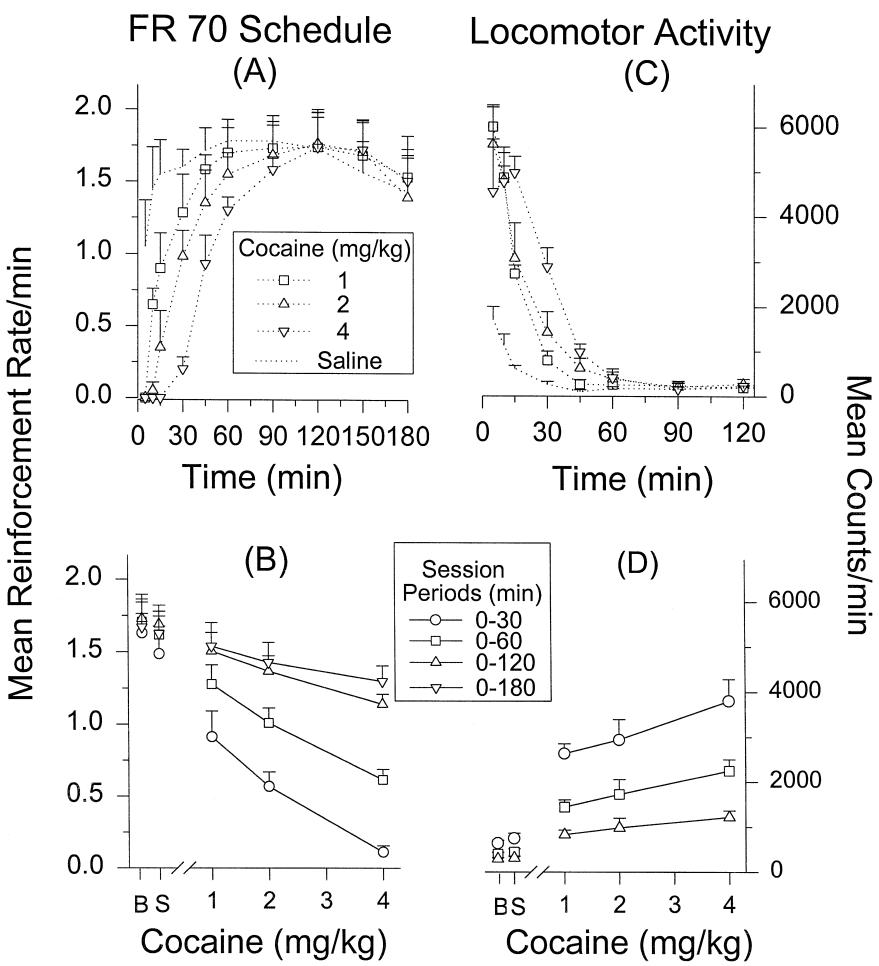

Fig. 1. Effects of i.v. cocaine (0–4 mg/kg) on reinforcement rate under the FR 70 schedule: (A) mean effect–time profiles (SE); (B) dose–response curves (SE) for the four session periods. Effects of i.v. cocaine (0–4 mg/kg) on locomotor activity: (C) mean effect–time profiles (SE); (D) dose–response curves for the three session periods. B and S denote baseline and saline, respectively.

(ANOVA), followed by Newman–Keuls tests using SigmaStat (Jandel, San Rafael, CA) for the evaluation of effects of cocaine were performed as appropriate.

2.2. Pharmacokinetic–pharmacodynamic analysis

We used the SAAM II software system (SAAM Institute, 1997) for the integration of FR 70 performance or spontaneous locomotor activity with cocaine concentration–time profiles as described previously (Lau et al., 1999); however, cocaine concentration–time profiles (1–4 mg/kg) were simulated using the pharmacokinetic parameters of i.v. cocaine. Model parameters were estimated by numerical optimization using Akaike's information criterion (AIC) as the objective function (Akaike, 1974).

Because effect–time profiles of the decrease in reinforcement rate following cocaine administration under the FR 70 schedule were similar to those of the density of reinforcement under the DRL 45-s schedule (Lau et al., 1999), the effect-linked, classical inhibitory E_{max} model is used, which is expressed in terms of Ce such that

$$E_{rr} = E_o\left[1 - \frac{Ce^i}{Ce^i + IC_{50}^i}\right]$$

where E_o, IC_{50}, and Ce are the baseline response, the cocaine concentration required to produce 50% maximal inhibition, and the concentration in the reinforcement rate compartment, respectively, and i is the Hill factor. The subscript ''rr'' denotes reinforcement rate. Cocaine effect compartment kinetics was defined by the loss rate constant, k_{eo}. One set of pharmacodynamic parameters (IC_{50}, i, E_0, $k_{eo,rr}$) was estimated for the three cocaine doses.

Because effect–time profiles of the increase in locomotor activity were similar to those of the shorter-response rate under the DRL 45-s schedule (Lau et al., 1999), the effect-linked sigmoidal E_{max} model is used, which is expressed in terms of the serum cocaine concentration in the locomotor activity compartment (Ce) such that

$$E_{la} = E_o + \frac{E^*_{max}Ce^n}{EC_{50}^n + Ce^n}$$

where E_o, E_{max} and EC_{50} are the baseline response, the maximal response and the concentration required to produce 50% maximal response, respectively, and n is the Hill factor. The subscript ''la'' denotes locomotor activity.

Three pharmacodynamic models, one for each dose, were used to describe effects of cocaine for each behavioral measure. Each model receives a different dose for fitting and prediction of the respective data associated with that dose for the four animals as described previously (Lau and Heatherington, 1997; Lau et al., 1999).

3. Results

3.1. Pharmacodynamics: FR 70 schedule and spontaneous locomotor activity

Fig. 1A shows cocaine significantly decreasing the FR 70 reinforcement rate (min^{-1}) in both a time- and dose-related fashion as indicated by a two-way RM ANOVA

Table 1
Cocaine pharmacodynamic parameters (CV%) estimated by simultaneous PK–PD modeling of serum cocaine concentrations and reinforcement rates under the FR 70 schedule or locomotor activity after administration of i.v. bolus cocaine (1–4 mg/kg). The subscripts ''rr'', ''la'' and ''x'' denote reinforcement rate, locomotor activity and 1, 2 or 4 mg/kg doses, respectively. Summary statistics:

FR 70 schedule: four adjustable parameters (AIC = 0.17).
Spontaneous locomotor activity: six adjustable parameters (AIC = 8.23).

Pharmacokinetic parameters[a]		Pharmacodynamic parameters		
V_c (l/kg)	0.69		(A) FR 70 schedule: reinforcement rate	
V_{ss} (l/kg)	2.24		E_0 (counts/min)	1.626 (1.60)
Cl (l h^{-1} kg^{-1})	8.31		IC_{50} (μg/ml)	0.125 (9.54)
$k_{(0,1)}$ (min^{-1})	0.202		$k_{eo,rr}$ (min^{-1})	1.03 (160.23)
$k_{(2,1)}$ (min^{-1})	0.335		i	3.55 (14.66)
$k_{(1,2)}$ (min^{-1})	0.146		(B) Spontaneous locomotor activity	
α (min^{-1})	0.637		E_{max} (counts/min)	6170 (5.88)
$t_{1/2\alpha}$ (min)	1.09		$k_{eo,la}$ (min^{-1})	0.332 (35.06)
β (min^{-1})	0.046		n	1.95 (8.27)
$t_{1/2\beta}$ (min)	14.93		Dose-dependent parameter	
			EC_{50} (μg/ml)	Relative potencies ($EC_{50,la}^{1\,mg/kg}/EC_{50,la}^{x\,mg/kg}$)
		Dose		
		1 mg/kg	0.149 (13.58)	1
		2 mg/kg	0.238 (14.03)	0.626
		4 mg/kg	0.335 (13.72)	0.444

[a] Pharmacokinetic parameters of cocaine (Lau et al., 1999).

($P < 0.001$). Subsequent statistical comparisons indicate the magnitude of cocaine's effects ordered as 4 > 2 > 1 mg/kg ($P < 0.05$). Furthermore, the reinforcement rates returned to saline level 120 min after cocaine administration (1–4 mg/kg). Although there was a decreasing trend in reinforcement rate after this time for both saline and cocaine doses, it was not statistically significant ($P > 0.05$). The effect of session length on dose–response relations of cocaine was additionally investigated by dividing the 3-h sessions into four-session periods (i.e., 0–30, 0–60, 0–120 and 0–180 min). Cocaine produced significant dose-related decrements in reinforcement rate compared against those of baseline and vehicle treatment regardless of the length of session period ($P < 0.001$), with the greatest decrease in the magnitude of reinforcement rate during the 0–30 min session period (Fig. 1B). Dose–response curves also became flatter with increasing session periods, while effects of cocaine were always significantly greater than those of the respective saline injections ($P < 0.05$), except for the 1 mg/kg cocaine dose in the 0–180 min session period.

Cocaine increased locomotor activity significantly in a time- and dose-related fashion according to a two-way ANOVA ($P < 0.05$; Fig. 1C). Subsequent comparisons revealed that effects of the 4 mg/kg dose were significantly greater than those of the 1 mg/kg dose ($P < 0.01$), but effects of cocaine between doses of either 1 and 2 mg/kg or 2 and 4 mg/kg did not vary significantly ($P > 0.05$). The maximal effects of cocaine attained at 5 min were similar in magnitude for the three doses ($P > 0.05$). Effects on locomotor activity were short-lived (approximately 60 min). Cocaine produced significant dose-related increases in locomotor activity for the three session periods (i.e., 0–30, 0–60 and 0–120 min), $P < 0.001$, with the greatest effect during the 0–30 min session period (Fig. 1D). In addition, enhanced locomotor activity following cocaine administration (1–4 mg/kg) for the three session periods were all significantly greater than the respective saline treatments ($P < 0.05$). Effects of vehicle administration were not different from those of baseline for both behaviors (Fig. 1B and D).

3.2. Relation between pharmacodynamics and pharmacokinetics

For FR 70 performance, one set of pharmacodynamic parameters (E_o, IC_{50}, k_{eo} and i) could account for effects of cocaine across the three drug doses (Table 1A). Results following cocaine administration were compared against those of baseline and saline in evaluation of both reinforcement rate and locomotor activity (Fig. 2A–B). In addition, vehicle treatments did not vary significantly from baseline ($P > 0.05$). The FR 70 reinforcement rate attained E_{max} with cocaine concentrations greater than 0.45 μg/ml at the effect site and then returned toward baseline as concentrations progressively decreased (Fig. 2A). With respect to locomotor activity, while E_o, E_{max}, and n could be shared

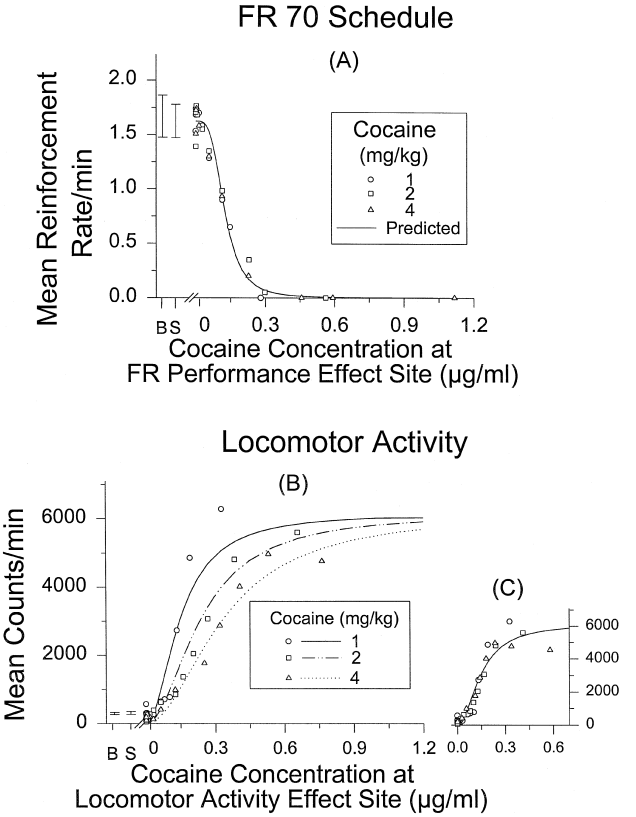

Fig. 2. (A) Predicted (lines) and mean observed (open symbols) reinforcement rates plotted against cocaine concentrations at FR performance effect sites after cocaine administration (1–4 mg/kg; solid line). (B) Predicted (lines) and mean observed (open symbols) concentration–effect relations for locomotor activity after cocaine administration (1–4 mg/kg). (C) Predicted concentration–effect relations for locomotor activity after 1 mg/kg cocaine administration (solid line) and the mean observed locomotor activity plotted against cocaine concentrations at locomotor activity effect sites corrected for potencies of cocaine relative to the i.v. 1 mg/kg dose. B and S denote baseline and saline, respectively.

across doses, values of EC_{50} increased as a function of dose (Table 1B). A single value of EC_{50} could not appropriately describe the data as reflected by visual examination and the goodness of fit of the data (AIC = 8.58) which was greater than that shown in Table 1. As a result, analysis of EC_{50} reveals that the potencies for the three doses relative to the lowest dose (i.e., 1 mg/kg) decreases as a function of dose (e.g., the relative potency of the 4 mg/kg dose was 0.44), Table 1B. Fig. 2B shows the predicted concentration–effect curves for all three doses using the pharmacodynamic parameters shown in Table 1 (solid, mixed, dotted lines). The open symbols are observed effects of locomotor activity plotted against concentrations at the respective effect sites. Fig. 2C shows mean observed effects for all doses plotted against concentrations, once corrected for their corresponding relative potencies (Table 1B). The resulting curve matches the predicted concentration–effect curve for the 1 mg/kg dose. In this way, the concentration–effect relation of the 1 mg/kg dose describes those of cocaine across doses.

4. Discussion

Cocaine's effects differed markedly on the two behavioral paradigms examined in this study: reinforcement rate under the FR 70 schedule, and spontaneous locomotor activity. That is, while cocaine decreases FR performance (Fig. 1A–B), it increases levels of spontaneous locomotor activity (Fig. 1C–D). These effect changes are reflected in concentration–effect and effect–time profiles as well as in the magnitude of the reference concentrations (i.e., IC_{50} or EC_{50}). Although dose–response relations presented for the two behaviors clearly are informative (Fig. 1B and D), effect–time and concentration–effect profiles are more accurate in characterizing cocaine's in vivo effects (Figs. 1A,C and 2A–C). Effect–time profiles describe ongoing behavioral changes and reflect cocaine concentration–time curves, whereas pharmacodynamic parameters numerically define and predict behavioral endpoints with the pharmacodynamic models. Furthermore, concentration–effect relations demonstrate the differential effects of cocaine on contingency-controlled vs. unconditioned behavior.

Behavioral endpoints expressed as time-course data collapsed into single points have been widely used to study drug dose–effect relations in behavioral pharmacology. However, limited attention has been given to effect–time profiles and to their associated pharmacokinetics. A single dose–response curve can only clarify whether cocaine's effect is dose related. For a short-acting drug such as cocaine, it takes many dose–response curves to relate the effects to the corresponding pharmacokinetics (Fig. 1B and D). For example, dose–response curves became flatter with increasing session length for both behavioral paradigms, not only indicating that cocaine's effects are time-dependent, but also suggesting that the ED_{50} increases with session length. However, discrepancies among studies arise from misinterpreting dose–response relations when different session lengths were used in investigations. For instance, effects of the 2 mg/kg cocaine dose in the 0–30 min session period were much greater than those of the 4 mg/kg dose in session periods of 0–120 and 0–180 min in length (Fig. 1B). However, the effect at each time point was greater for the 4 mg/kg dose than the 2 mg/kg dose as shown in effect–time profiles (Fig. 1A). Thus, estimation of cocaine's effects on reinforcement rate or locomotor activity becomes greatly confounded and inaccurate using sessions of differing lengths. Only equal session lengths or session segments in the same portion of the pharmacokinetic profile can be compared, and these must include any drug post-administration time delay as well. The effect–time profile is the method of choice for investigation of drug effects on behavior because it permits analysis of these effects regardless of session length.

In our previous pharmacokinetic and pharmacodynamic studies of psychomotor stimulants and benzodiazepines (Lau and Heatherington, 1997; Lau et al., 1997, 1998, 1999), drug pharmacodynamics were measured by performance under the DRL 45-s schedule which produces ''spaced responding'' or ''timing behavior''. Inter-response time (IRT) profiles and the number of responses were also recorded throughout the session. Drug-induced alterations in IRT distribution and disturbances in sequential patterning enable characterization of the drugs' putative actions from their effect–time profiles. For example, short IRTs are followed by further short IRTs with high probability as described by observed sequential dependencies (Weiss et al., 1966). Increases in short IRTs constituted the stimulatory effect reported for cocaine in this context. Only when cocaine concentrations fell below the EC_{50} value for the shorter-response rate did the density of reinforcement begin to return toward baseline (Lau et al., 1999). Thus, the density of reinforcement constitutes an index for evaluating drug-induced deficits in timing performance, because the IC_{50} value for the density of reinforcement is smaller than the EC_{50} value. This is also reflected in the duration of cocaine's effects on these two measures; disruption of density of reinforcement persists longer than the change in shorter-response rate.

Cocaine-induced deficits in the reinforcement rate as indicated by dose–response curves under the FR 70 schedule (Fig. 1B) supports the results of many previous cocaine studies under FR schedules (MacPhail and Seiden, 1975; Harris et al., 1978; Woolverton et al., 1978; Bedford et al., 1980). The time course of reinforcement rate decreases under the FR 70 schedule which resembles the effect–time profile of density of reinforcement under the DRL 45-s schedule (Fig. 1A; Lau et al., 1999). Both DRL and FR performance, like many other operant behaviors, require conduct that fulfills a required and objectively defined contingency, whereas locomotor activity is an unconditioned behavior that involves no behavioral contingency. With respect to this contingency requirement, then, the density of reinforcement under the DRL 45-s schedule is somewhat analogous in measure to reinforcement rate under the FR 70 schedule used in the present study. The contingency-controlled behavioral component (i.e., reinforcement rate or density of reinforcement) is distinct from the shorter-response rate previously measured for DRL performance, as shorter-response rate more closely resembles an unconditioned activity. Both the shorter-response rate and locomotor activity possess similar psychomotor stimulant characteristics, which are immediate and shorter-lived than the disruption of the behavior required to satisfy the programmed contingency following i.v. administration. An advantage of DRL over FR schedules is that both stimulatory effects and contingency-controlled performance are measurable; FR only measures the latter.

The intensity and time course of drug effects were shown to be dependent on drug concentration changes over time either in serum or at hypothetical effect sites (Lau and Heatherington, 1997; Lau et al., 1997, 1998, 1999; Wang and Lau, 1998). A significant correlation was also found between locomotor activity–time profiles and serum or

brain cocaine concentration–time profiles in rodents (Benuck et al., 1987; Reith et al., 1987; Falk et al., 1991; Lau et al., 1991); however, no explicit pharmacodynamic models were used in these studies. A sigmoidal E_{max} model was recently used to characterize single dose effects of i.v. cocaine (5 mg/kg) on locomotor activity in rats (Hutchaleelaha et al., 1997). The EC_{50} for that study was somewhat greater (i.e., 0.57 μg/ml) than the value of 0.335 μg/ml derived for the highest dose (4 mg/kg) in the present study (Table 1B), which can be explained by the increase in EC_{50} with increasing dose with respect to locomotor activity. During model formulation, we also used a linear model to describe locomotor activity by integrating pharmacodynamic and pharmacokinetic data, yielding a greater AIC value (i.e., 8.33). This indicated that the sigmoidal E_{max} model was more appropriate than a linear model for approximating the time course of locomotor activity. In addition, although cocaine concentrations were dose proportional at the 5-min time point across the three doses (Lau et al., 1999), the maximum effect values were similar (Fig. 1C), suggesting that levels of locomotor activity had reached a plateau. Nevertheless, the increase in slope values with dose in the linear model also reiterated the decrease in relative potency with increasing dose observed in our sigmoidal E_{max} model of concentration–effect data (Table 1B).

The use of reference concentration as an indicator of acute tolerance was first suggested by Hudson et al. (1983). In this context, then, the increase in EC_{50} and associated decrease in relative potency across doses may be explained by the phenomenon of acute tolerance. Reference concentration may be considered an index for the sensitivity of a behavioral endpoint to a drug, and the relative potency an index for extent of acute tolerance across doses. In this way, the extent of acute tolerance to cocaine varies directly with reference concentration but inversely with relative potency of cocaine under the locomotor activity paradigm; that is, as reference concentration increases, acute tolerance increases as well since relative potency has decreased. This bears direct application to estimating the extent of acute tolerance as acute tolerance increases with dose size. Acute tolerance to cocaine has been previously shown to the chronotropic and subjective effects of cocaine in humans (Ambre et al., 1988; Noe and Kumor, 1991), but not in rats under a spontaneous locomotor activity paradigm. The absence of a required behavioral contingency in locomotor activity measurement may account for the occurrence of acute tolerance observed under this paradigm. In contrast, one set of parameters could account for DRL and FR performance; that is, no acute tolerance observed in contingency controlled-behavior. Drug dose–response relations are best examined under conditions where a preceding dose has no residual effect on succeeding doses during both pharmacokinetic and pharmacodynamic studies. Analyzing steady-state performance under the DRL 45-s schedule, we have found no mutual interference between doses (e.g., tolerance, sensitization) for midazolam, alprazolam, cocaine and caffeine when doses were separated by 3–5 days (Lau et al., 1996, 1997, 1998, 1999).

In summary, this study indicates cocaine's differential effects on contingency-controlled behavior vs. spontaneous locomotor activity by pharmacokinetic–pharmacodynamic modeling. A unique concentration–effect relation of cocaine is presented here for FR performance (Fig. 2A). While cocaine decreases the reinforcement rate under the FR 70 schedule, it increases levels of spontaneous locomotor activity. Furthermore, the unique concentration–effect relation for cocaine's effects on locomotor activity across the three doses can be determined only after cocaine concentrations at the effect site are adjusted with relative potencies (Fig. 2C). The effect–time profiles for both behaviors mirror pharmacokinetic profiles. Effect–time profile is the method of choice for investigation of drug effects on behaviors and, with incorporation of the drug's pharmacokinetics, provides a better understanding of the role of drug concentrations on the three behavioral paradigms, as seen in the present study. The temporal dichotomy of cocaine's effects on different behavioral measures is clarified by a comparative study incorporating pharmacokinetic and pharmacodynamic data, an approach which can add considerable power to the delineation of drug effects.

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