Research Article

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Journal of Drug Abuse
2471-853X

2016
Vol. 2 No. 2: 14

DOI: 10.21767/2471-853X.100023

Relationship between the Dose to Produce Reinforcing Effect and that of Gross Behavioral Effects in Rhesus Monkeys

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Citation: Fujiwara A, Iino M, Sasaki M. Relationship Between the Dose to Produce Reinforcing Effect and that of Gross Behavioral Effects in Rhesus Monkeys. J Drug Abuse. 2016, 2:2.

Abstract

The selection of an appropriate range of doses is critical in drug self-administration, since the number of self-administrations and dose levels of a drug is interrelated, forming an inverted U-shape. The purpose of this study was to investigate the relationship between the dose to produce the reinforcing effect and that of gross behavioral effects, in order to determine dose ranges of a drug to assess the reinforcing effect. For assessing the reinforcing effect, the dose that was most frequently self-administered was explored in intravenous self-administration experiments in rhesus monkeys under a fixed ratio 5 schedule with a 1 min time-out after each self-administration for 2 h daily. For the gross behavioral effects, the minimum effective dose following cumulative dosing was observed. The most frequently self-administered dose levels were 0.016 and 0.064 mg/kg/infusion in cocaine, 0.25 and 0.5 mg/kg/infusion in pentobarbital, 0.016 and 0.063 mg/kg/infusion in pentazocine, 0.001 and 0.004 mg/kg/infusion in nicotine and 0.256 mg/kg/infusion in caffeine. These dose levels were 1/250-1/8 of the minimum effective doses in gross behavioral observations. Thus, it is suggested that a broad dose-range, less than the minimum effective doses in the gross behavioral observations, should be used in intravenous self-administration experiments for assessing the reinforcing effect of a drug.

Keywords: Self-administration; Reinforcing effect; Minimum effective dose; Rhesus monkey

Received: May 12, 2016; **Accepted:** May 19, 2016; **Published:** May 26, 2016

Introduction

The reinforcing effect of drug self-administration in animals is known to be useful in assessing the psychological dependence potential of drugs [1-3]. The number of drug self-administrations can be affected by variables such as the class of drugs, schedule of reinforcement, dose levels, and infusion speed of the dosing solutions [3-7]. Of these variables, the dose level is considered to be even more important when investigating the reinforcing effect. The relationship between the number of self-administrations and dose levels of a drug forms an inverted U-shape, with responses initially increasing as the dose is increased and finally decreasing as the dose is raised even further. These facts indicate that the reinforcing effect of drugs can be shown at optimum dose levels but not those set too high or too low. Ator and Griffiths [3] stated that the highest dose tested should be one that is unequivocally limited by, for instance, solubility or toxicity considerations, if the result for a particular assessment is negative in relation to the drug vehicle. As rationale for dose selection, Beardsley et al. [8] reported that a dose of SR141416 great enough to apparently suppress behavior, as evidenced by its engendering fewer infusions than those of the vehicle, was tested to maximize the likelihood that behaviorally active doses were included in the evaluation.

In this study, we observed dose-response relationships in gross behavioral observations and in intravenous self-administrations of cocaine, pentobarbital, pentazocine, nicotine and caffeine. We have shown that dose levels showing peak responses in intravenous self-administrations are less than the minimum dose levels required to produce gross behavioral effects of the drugs.

Materials and Methods

Subjects

In the gross behavioral observations, 2 male and 4 female rhesus monkeys (*Macaca mulatta*) between 6 and 18 years of

age and weighing 4.5 to 5.7 kg were used. These monkeys were individually housed in stainless steel monkey cages with high-pressure melamine facing plate walls (68W × 86D × 86H cm).

In the self-administration experiments, 3 male and 4 female rhesus monkeys between 9 and 13 years of age and weighing between 4.5 to 7.3 kg were used. All monkeys had a history of intravenous self-administration of drugs including cocaine, pentobarbital and pentazocine, but not nicotine or caffeine. These animals were restrained in individual stainless steel cages (75W × 90D × 100H cm) by metal harnesses and free-jointed metal arms in a monkey room [1]. Indwelling silicone catheters (OD: 2 mm, ID: 1 mm) were implanted into the jugular or femoral veins under pentobarbital anesthesia. Catheters exited from the midscapular region and were connected to silicone tubes passed through the restraining arm which was further connected to infusion apparatus located outside the cage.

All animals were fed 100-120 g of monkey chow (PS: Oriental Yeast Co., Ltd., Japan) once daily. Tap water was continuously available from a fountain nozzle. The room temperature and humidity were set at 25 ± 2 and 60 ± 20%, respectively. The room was illuminated from 7:00 AM to 7:00 PM.

All experimental procedures were approved and conducted in accordance with the Institutional Animal Care and Use Committee (IACUC) of Ina Research Inc., which is fully accredited by AAALAC International.

Apparatus

For the self-administration experiments, the experiment was conducted in the home cages fitted with one response lever and one red light approximately 5 cm above the lever. A predetermined volume of dosing solution or saline was automatically infused through the catheter when the monkey pressed the lever [1]. Scheduling of infusions and collection of data were controlled by a personal computer system (MED-PC, Med Association, USA).

Procedures

Gross behavioral observation experiments

Two monkeys were used for each drug. Monkeys were restrained in primate restraining chairs. The dosing solutions were administered into the cephalic vein 2-4 times at an interval of 15 min. Doses of the repeated administrations were cumulatively increased until gross behavioral changes were noted. Immediately after each administration, the animals were returned to their home cages and gross behavioral observations were conducted immediately and 10 min after administration, according to the methods and criteria of our laboratory. Observation items included salivation, retching, vomiting, reactivity to external stimuli, posture, pupil size and motor function such as locomotor activity, slowed motion and ataxia. **Tables 1 and 2** show the test doses and schedule of each drug, respectively.

Self-administration experiment

Four to six monkeys were used for each drug. Intravenous self-administration of each drug or saline was observed for 2 h (11:00 AM to 1:00 PM) a day under a fixed ratio 5 (FR5) schedule of reinforcement. The beginning of the daily sessions was signaled by illumination of the red light above the lever. Each self-administration was followed by a 1 min time-out period, during which time the red light was extinguished and responses had no consequence. Monkeys were first allowed to self-administer cocaine 0.03 mg/kg/infusion until the daily number of self-administrations attained 11 or more for 3 consecutive days and then saline 0.25 mL/kg/infusion until the daily number of self-administrations attained 10 or less for 3 consecutive days. The number of self-administrations of cocaine was limited to 20 times per day to avoid over-dosing. After that, self-administration of the test drugs at 3-6 dose levels in descending order of dose level were observed for 4 days at each dose level. **Table 3** shows the test schedule of each drug.

Table 1 Dose levels of drugs in gross behavioral observation study.

Drugs	Cumulative dose (mg/kg)			
	1st	2nd	3rd	4th
Cocaine	0.25	0.5	1	2
Pentobarbital	0.5	1	2	4
Pentazocine	1	2	-	-
Nicotine	0.063	0.13	0.25	0.5
Caffeine	1	2	4	8

Table 2 Monkey information and test schedule of gross behavioral observation experiment.

Monkey	Test Schedule 1st	Test Schedule 2nd
No.32, Male, 6 years No. 1416, Female, 11 years	Cocaine	Pentazocine
No. 9, Female, 9 years No.26, Female, 8 years	Pentobarbital	-
No. 1309, Male, 18 years No.1314, Female, 18 years	Nicotine	Caffeine

Intervals of at least 1 week were set between the 1st and 2nd tests.

Drugs

Cocaine (Cocaine HCL, Takeda Pharmaceutical Industry, Japan), sodium pentobarbital (Nembutal, Dainippon Sumitomo Pharma Co., Ltd, Japan), pentazocine (Sosegon, Maruishi Pharmaceutical Co., Ltd., Japan), nicotine ((−)-Nicotine Sigma-Aldrich Co., Japan) or caffeine (Sigma-Aldrich Co. LLC, Japan) were dissolved or diluted in isotonic physiological saline (Otsuka Normal Saline, Otsuka Pharmaceutical Factory Inc., Japan) and kept in light-protected bottles at room temperature.

Data analyses

For self-administration experiments, the number of self-administrations over the last 3 days of cocaine, saline and the test drugs for each monkey was used in data analyses. A test dose of each drug was considered to be a positive reinforcer; 1) the mean number of self-administrations exceeded the mean number of saline self-administrations and their ranges did not overlap [9], and 2) the mean number of self-administrations for a dose was a statistically significant increase compared to that of saline. When the number of self-administrations was higher than that of saline

at only 1 drug dose level, the Student-t test was carried out. For 2 or more drug dose levels, the Dunnett test was carried out to determine statistical significance.

Results

Gross behavioral observation experiment

Gross behavioral changes observed were continual and rapid movement with cocaine, ataxia with pentobarbital, eye-closing and slowed motion with pentazocine, piloerection with nicotine and increased aggression to and decreased grimacing at the observer with caffeine. The minimal effective dose in the gross behavioral observations was 1 mg/kg for cocaine, 4 mg/kg for pentobarbital, 2 mg/kg for pentazocine, 0.25 mg/kg for nicotine and 4 mg/kg for caffeine **(Table 4)**.

Self-administration experiment

The mean daily number of self-administration of cocaine in the first self-administration periods was higher than that of saline in all animals **(Figure 1)**. The inverted U-shaped dose-response curve of cocaine was observed in all 6 animals. The most frequent mean daily number of self-administrations of cocaine was observed at 0.016 and 0.064 mg/kg/infusion and was obviously higher than that of saline in all animals. The inverted U-shaped dose-response curves were also observed in 5 of 6 monkeys with pentobarbital and in 3 of 5 monkeys with pentazocine. The most frequent self-administration was noted at 0.25 and 0.5 mg/kg/infusion in pentobarbital and 0.016 and 0.063 mg/kg/infusion in pentazocine **(Figures 2 and 3)**. Unlike cocaine, the mean daily number of self-administrations of pentobarbital and pentazocine were generally low at all dose levels in one monkey each and the most frequent self-administrations of these monkeys were barely higher than that of saline. The inverted U-shaped dose-response curve was observed with nicotine in 2 of 4 monkeys and with caffeine in 1 of 4 monkeys **(Figures 4 and 5)**. The most frequent self-administration was noted at 0.001 and 0.004 mg/kg/infusion with nicotine and at 0.256 mg/kg/infusion with caffeine.

The range of the number of self-administrations and mean intake of each drug are shown in **Table 5**. At least one of the monkeys tested self-administered at least one dose of each drug beyond the range of saline self-administration. The doses beyond the saline range were 0.004-0.064 mg/kg/infusion in cocaine, 0.25-1 mg/kg/infusion in pentobarbital, 0.016-0.063 mg/kg/infusion in pentazocine, 0.00025-0.0016 mg/kg/infusion in nicotine and 0.064 mg/kg/infusion in caffeine. Total intake of each drug was related to the dose for each monkey. Maximal intake occurred at almost the highest dose tested resulting in an average of 1.7-4.2 mg/kg in cocaine, 6.7-17.3 mg/kg in pentobarbital, 1.8-3.8 mg/kg in pentazocine, 1.5-1.8 mg/kg in nicotine and 5.5 mg/kg in caffeine.

Comparison of the minimal effective doses (MED) in gross behavioral observations, the unit doses beyond the range of saline self-administration (SAD) and the unit doses of the most frequent mean daily number of self-administrations (PSAD) are shown in **Table 6.** SAD and PSAD were 1/1000-1/4 and 1/250-1/8 of the MED, respectively.

Discussion

In this study, it was demonstrated that the doses which were most frequently self-administered were 1/250-1/8 lower than the minimal effective doses in the gross behavioral observations.

Similarly to other studies [1, 10-12], cocaine, pentobarbital, pentazocine, nicotine and caffeine functioned as positive reinforcers at least one dose level and generally at several dose levels, and it is well know that the reinforcing effects of pentobarbital, pentazocine, nicotine and caffeine, in that order,

Table 3 Monkey information and test schedule of self-administration experiment.

Monkey	1st	2nd	3rd	4th	5th
No. 1, Male, 9 years	Cocaine	Pentobarbital	-	-	-
No. 3, Male, 9 years	Pentazocine	-	-	-	-
No. 5, Male, 9 years	Pentobarbital	Cocaine	Pentazocine	Nicotine	Caffeine
No.1396, Female, 13 years	Cocaine	Pentazocine	Pentobarbital	Nicotine	Caffeine
No.1398, Female, 13 years	Cocaine	Pentobarbital	Pentazocine	Nicotine	Caffeine
No.1405, Female, 12 years	Cocaine	Pentobarbital	Pentazocine	Nicotine	Caffeine
No.1414, Female, 12 years	Pentobarbital	-	-	-	-

Intervals of at least 2 weeks were set between each test.

Table 4 Minimal effective dose (MED) for gross behavioral observations in rhesus monkeys.

Drugs	No. of monkeys	MED (mg/kg)	Signs
Cocaine	2	1	Continual movement Rapid movement
Pentobarbital	2	4	Ataxia
Pentazocine	2	2	Eye-closing Slowed motion
Nicotine	2	0.25	Piloerection
Caffeine	2	4	Increased aggression to observer Decreased grimacing at observer

Drugs were administered intravenously by cumulative dosing at intervals of 15 min.

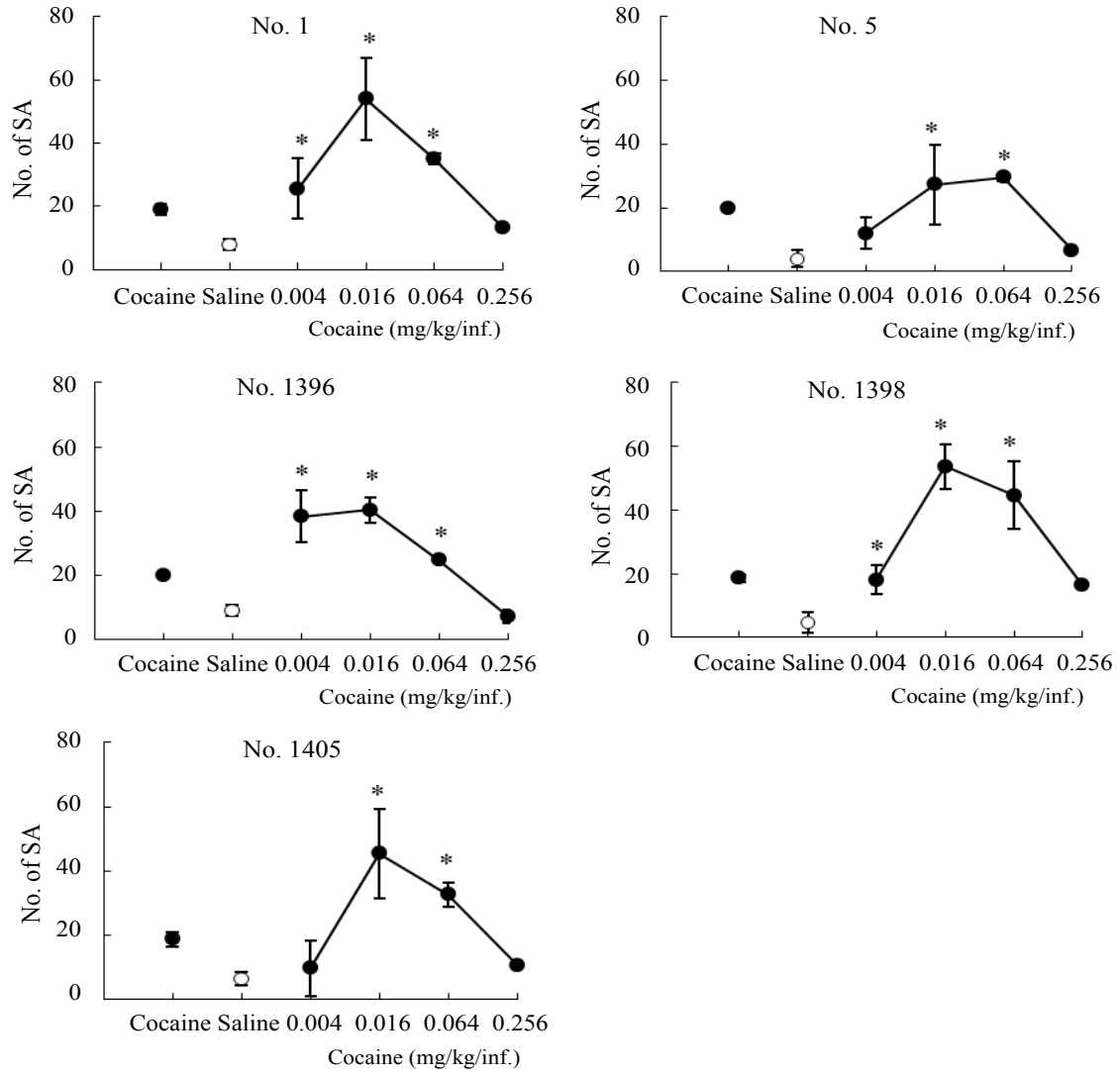

Figure 1 Intravenous self-administration of cocaine by each monkey.

Each monkey was allowed to self-administer cocaine (0.03 mg/kg/inf.), saline and the test drugs in descending order of dose levels under a FR5 schedule with time-out 1 min for 2 h/day. Each point represents the mean daily number of self-administrations (± S.D.) in the last 3 days. *: $p<0.05$ *vs.* saline.

are weaker than those of cocaine. [13-15]. The inverted U-shaped curves observed in other studies were also observed in all 6 monkeys with cocaine, in 5 of 6 monkeys with pentobarbital, in 3 of 5 monkeys with pentazocine, in 2 of 4 monkeys with nicotine and 1 of 4 monkeys with caffeine in this study. In the substitution procedure, pentobarbital, pentazocine and nicotine functioned as positive reinforcers in some, but not all of the monkeys tested [12, 16, 17]. Furthermore, methylenedioxymethamphetamine (MDMA) and 2-beta-propanoyl-3-beta-(4-tolyl)-tropane (PTT), considered to possess relatively weak reinforcing effects, did not function as positive reinforcers in any of the monkeys tested either [18, 19]. In addition, it is known that self-administration behavior is influenced by self-administration histories and/or baseline drugs [3]. For example, MK-801 was self-administered by monkeys when substituted for phencyclidine (PCP) but not cocaine [9]; and PCP, dexoxadrol and dextrophan were self-administered when substituted for ketamine but not when substituted for codeine [20]. Cocaine was used as a baseline drug in this study. Therefore, the reinforcing efficacy of each drug and the baseline drug selected may affect the number of monkeys that self-administered.

The dose levels with the greatest number of self-administrations with cocaine, pentobarbital and pentazocine in this study were comparable to other published substitution studies. The unit doses of self-administration were observed at 0.016 and 0.064 mg/kg/infusion with cocaine, at 0.25 and 0.5 mg/kg/infusion with pentobarbital and at 0.016 and 0.063 mg/kg/infusion with pentazocine in this study and the doses were reported at 0.012 to 0.25 mg/kg/infusion with cocaine [12], at 0.062 to 0.5 mg/kg/infusion with pentobarbital [12] and at 0.03 to 0.3 mg/kg/infusion with pentazocine [4]. On the other hand, the unit doses of nicotine (0.001 and 0.004 mg/kg/infusion) and caffeine

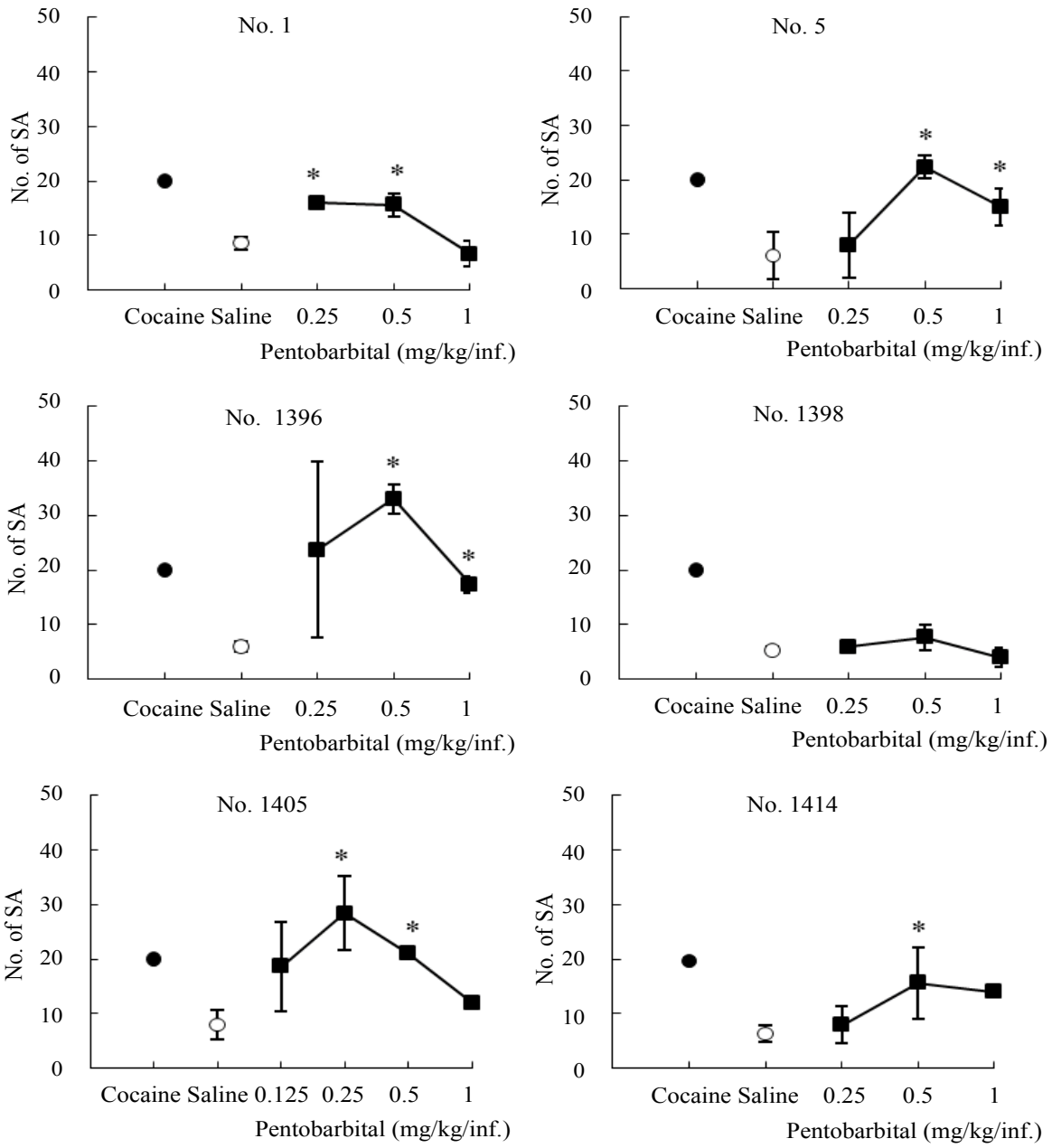

Figure 2 Intravenous self-administration of sodium pentobarbital by each monkey.

Each monkey was allowed to self-administer cocaine (0.03 mg/kg/inf.), saline and the test drugs in descending order of dose levels under a FR5 schedule with time-out 1 min for 2 h/day. Each point represents the mean daily number of self-administrations (± S.D.) in the last 3 days. *: $p<0.05$ *vs.* saline.

(0.256 mg/kg/infusion) were about 1/10 in comparison with the results of other substitution studies using rhesus monkeys with nicotine at 0.01 to 0.03 mg/kg/infusion [10] and baboons with caffeine at 3.2 mg/kg/infusion [21]. The reason for these differences is unclear, but Sekita et al. [11] demonstrated that the unit doses with the greatest number of self-administrations with caffeine were observed at 0.126 and 0.504 mg/kg/infusion the same procedure as ours. Therefore, it is suggested that these differences may be due to phenomena specific to our procedure. Taken together, the results of this study are almost consisted with those of other substitution studies, suggesting that our procedure may be suitable for evaluation of the reinforcing effects of drugs.

The number of drug self-administrations can be affected by the infusion speed of the dosing solutions. In other words, the speed of elevation in plasma levels of a drug and its peak level influence the number of self-administrations [5]. Since it is considered that gross behavioral changes appear rapidly following a rapid infusion, the same infusion speed was used for gross behavioral

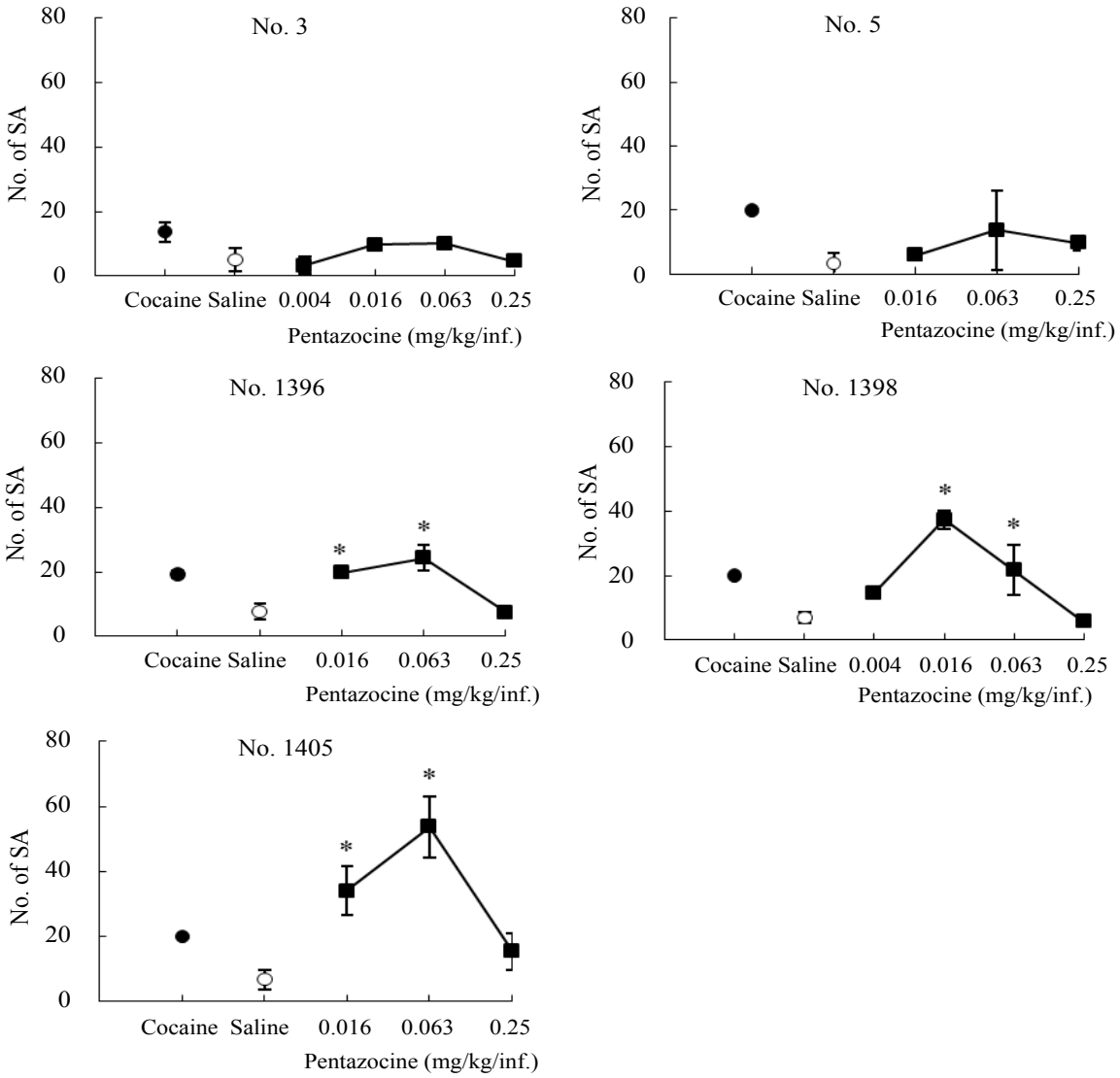

Figure 3 Intravenous self-administration of pentazocine by each monkey.

Each monkey was allowed to self-administer cocaine (0.03 mg/kg/inf.), saline and the test drugs in descending order of dose levels under a FR5 schedule with time-out 1 min for 2 h/day. Each point represents the mean daily number of self-administrations (± S.D.) in the last 3 days. *: $p<0.05$ *vs.* saline.

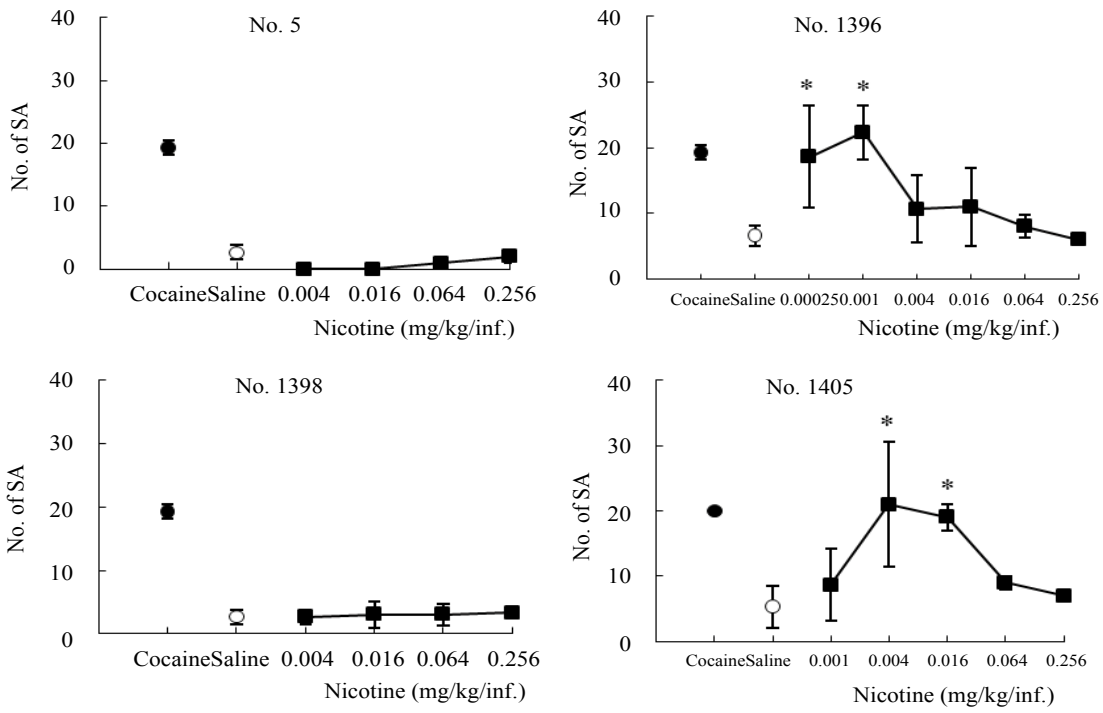

Figure 4 Intravenous self-administration of nicotine by each monkey.

Each monkey was allowed to self-administer cocaine (0.03 mg/kg/inf.), saline and the test drugs in descending order of dose levels under a FR5 schedule with time-out 1 min for 2 h/day. Each point represents the mean daily number of self-administrations (± S.D.) in the last 3 days. *: p<0.05 *vs.* saline.

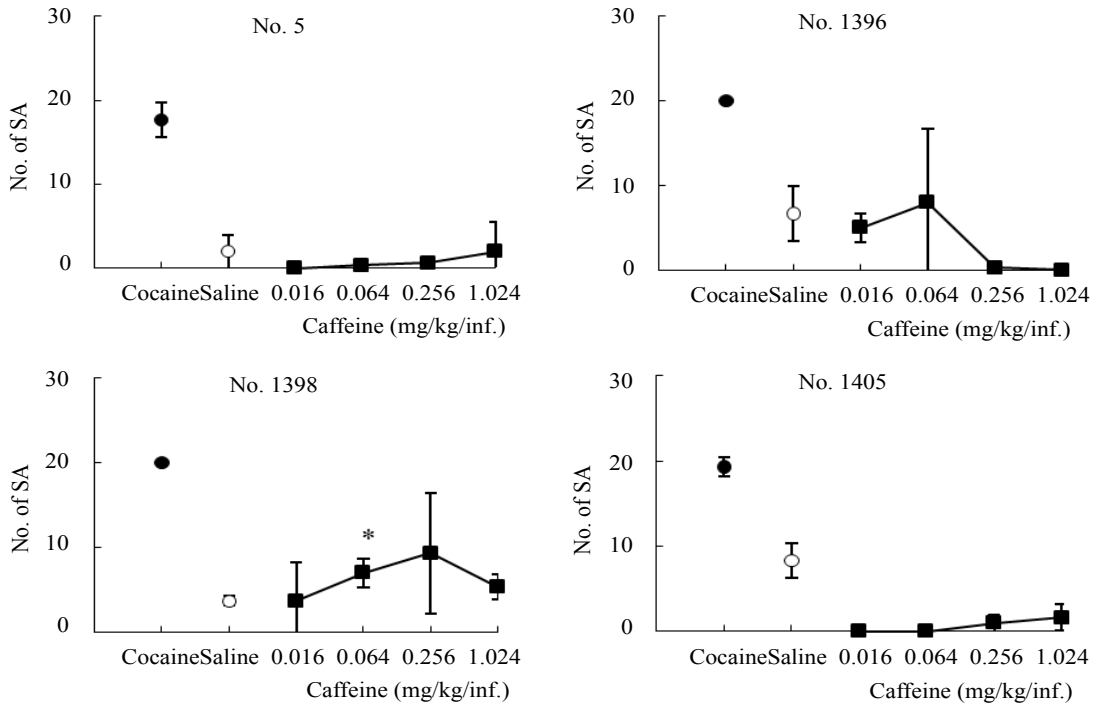

Figure 5 Intravenous self-administration of caffeine by each monkey.

Each monkey was allowed to self-administer cocaine (0.03 mg/kg/inf.), saline and the test drugs in descending order of dose levels under a FR5 schedule with time-out 1 min for 2 h/day. Each point represents the mean daily number of self-administrations (± S.D.) in the last 3 days. *: p<0.05 *vs.* saline.

Table 5: Range of the number of self-administrations and mean intake of cocaine, pentobarbital, pentazocine, nicotine and caffeine.

Drug	Dose (mg/Kg/ inf.)	Monkey													
		No. 1		No. 3		No. 5		No. 1396		No. 1398		No. 1405		No. 1414	
		Range	Intake	Range	Intake	Range	Intake	Range	Intake	Range	Intake	Range	Intake	Range	Intake
Cocaine	0.004	15-33	0.1	-	-	7-17	0.05	29-43	0.2	14-23	0.1	2-19	0.04	-	-
	0.016	45-69	0.9	-	-	15-40	0.4	36-44	0.6	47-61	0.9	32-60	0.7	-	-
	0.064	33-36	2.2	-	-	29-31	1.9	24-26	1.6	38-57	2.9	30-37	2.1	-	-
	0.256	12-15	3.4	-	-	6-8	1.7	5-9	1.8	16-17	4.2	9-11	2.6	-	-
	Saline	6-9	-	-	-	1-5	-	7-10	-	1-7	-	4-8	-	-	-
Pentobarbital	0.125	-	-	-	-	-	-	-	-	-	-	13-28	2.3	-	-
	0.25	15-17	4.0	-	-	2-14	2.0	7-39	5.9	6	1.5	23-36	7.1	4-10	2.0
	0.5	14-18	7.8	-	-	20-24	11.2	31-36	16.5	5-9	3.8	21	10.5	9-22	7.8
	1	4-8	6.7	-	-	13-19	15.0	16-19	17.3	3-6	4.0	11-13	12.0	13-15	14.0
	Saline	8-10	-	-	-	1-9	-	5-7	-	5-6	-	5-10	-	5-8	-
Pentazocine	0.004	-	-	1-6	0.01	-	-	-	-	14-16	0.1	-	-	-	-
	0.016	-	-	9-10	0.2	5-7	0.1	19-20	0.3	34-39	0.6	27-42	0.5	-	-
	0.063	-	-	9-11	0.6	5-28	0.9	18-20	1.5	13-28	1.4	46-64	3.4	-	-
	0.25	-	-	4-5	1.2	7-11	2.4	6-9	1.8	5-6	1.4	9-20	3.8	-	-
	Saline	-	-	2-9	-	1-7	-	5-10	-	6-9	-	6-10	-	-	-
Nicotine	0.00025	-	-	-	-	-	-	10-25	0.005	-	-	--	-	-	-
	0.001	-	-	-	-	-	-	18-26	0.02	-	-	5-15	0.01	-	-
	0.004	-	-	-	-	0	0.0	5-15	0.04	2-4	0.01	15-32	0.1	-	-
	0.016	-	-	-	-	0	0.0	5-17	0.2	1-5	0.05	17-21	0.3	-	-
	0.064	-	-	-	-	0-2	0.1	6-9	0.5	2-5	0.2	8-10	0.6	-	-
	0.256	-	-	-	-	1-3	0.5	6	1.5	3-4	0.9	7	1.8	-	-
	Saline	-	-	-	-	2-4	-	5-8	-	2-4	-	3-9	-	-	-
Caffeine	0.016	-	-	-	-	0	0.0	3-6	0.1	1-9	0.1	0	0.0	-	-
	0.064	-	-	-	-	0-1	0.02	2-18	0.5	5-8	0.4	0	0.0	-	-
	0.256	-	-	-	-	0-1	0.2	0-1	0.1	3-17	2.4	0-2	0.3	-	-
	1.024	-	-	-	-	0-6	2.0	0	0.0	4-7	5.5	0-3	1.7	-	-
	Saline	-	-	-	-	0-4	-	3-9	-	3-4	-	6-10	-	-	-

The ranges of the number of self-administrations and mean intake (mg/kg/2- hr session) of drugs obtained during the last 3 days at each dose by each monkey.

Table 6 Relationship among the minimal effective doses (MED) in gross behavioral observations, the unit doses of self-administration beyond the range of saline self-administration (SAD) and the most frequent mean daily number of self-administrations (PSAD).

Drugs	Dose			Ratio	
	MED (mg/kg)	SAD (mg/kg/inf.)	PSAD (mg/kg/inf.)	MED/SAD	MED/PSAD
Cocaine	1	0.004-0.064	0.016-0.064	1/250-1/16	1/63-1/16
Pentobarbital	4	0.25-1	0.25-0.5	1/16-1/4	1/16-1/8
Pentazocine	2	0.016-0.063	0.016-0.063	1/125-1/32	1/125-1/32
Nicotine	0.25	0.00025- 0.016	0.001-0.004	1/1000-1/16	1/250-1/63
Caffeine	4	0.064	0.256	1/63	1/16

observations and drug self-administration experiments in this study. Cumulative dose levels were used in this study, and it is possible that the MED would be even lower in a single dose study; however, for cocaine and pentobarbital at least, the MED was the same for both cumulative and single doses (data not shown). Therefore, it is suggested that applying the same dose route and infusion speed in both gross behavioral observation and self-administration experiments can be extremely helpful in the selection of an optimal dose range.

In summary, the most frequently self-administered dose levels in this study were lower than the minimal effective doses in the gross behavioral observations, with the ratios varying for each drug. These results suggest that self-administration experiments should be carried out at dose levels below the MED for gross behavioral observation experiments.

Acknowledgement

The authors wish to thank Dr. Yoshio Wakasa for valuable feedback. The authors also thank Mr. Takahiro Ootsuka and Mr. Mitsuru Hoshino for providing technical assistance.

Conflicts of Interest

None.

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