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Relationship Between Minimum Reinforcing Doses and Injection Speed in Cocaine and Pentobarbital Self-Administration in Crab-Eating Monkeys

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KATO, S , Y WAKASA AND T YANAGITA *Relationship between minimum reinforcing doses and injection speed in cocaine and pentobarbital self-administration in crab-eating monkeys* PHARMACOL BIOCHEM BEHAV **28**(3) 407–410, 1987 —The relationship between minimum reinforcing doses and injection speed was investigated by using 2 levels of speeds in experiments on self-administration of cocaine or pentobarbital in 2 crab-eating monkeys each The experiments were conducted under a fixed ratio (FR) 1 schedule with 30-min time-out after each drug injection, wherein the drugs and saline were made available for alternate 5-day periods The minimum reinforcing doses at each injection speed were determined by the titration procedure in which the presence or absence of reinforcing effect at a particular drug dose was judged based on comparison of the self-administration rate at that dose with the rate in the preceding saline period The results showed that the minimum reinforcing doses of cocaine and pentobarbital tended to be higher in inverse proportion to the injection speed of the drugs

Cocaine Pentobarbital Minimum reinforcing dose Injection speed Crab-eating monkey

IT is believed by some that the subjective effects of dependence producing drugs such as opioids and stimulants are much stronger when the drugs are injected intravenously than by any other route In self-administration experiments using animals these drugs are known to be self-administered at very high rates when injected intravenously, while self-administration rates are generally low when injected intragastrically From this it may be speculated that the development of pharmacological action related to the reinforcing effect is weak by the intragastric route because the rise in blood concentrations of drugs is slow In rhesus monkeys, the self-administration rate of intravenous cocaine at the same dose was reported to show a tendency to decrease when injection time was lengthened [2]. In this experiment, change in the minimum reinforcing dose was not investigated as a function of the length of injection, but instead, attention was focused on the influence of injection speed on the reinforcing effect of cocaine by varying the length of injection time of the same unit dose of cocaine. The present authors have shown that the minimum reinforcing and discriminative doses of cocaine [4] and nicotine (to be published) are very close in monkeys and that the reinforcing effect of a drug is derived from the drug's subjective effects In the present study, the influence of injection speed on the minimum reinforcing doses of cocaine and pentobarbital were investigated in crab-eating monkeys. Cocaine and pentobarbital were selected from among the stimulants and depressants, respectively, because they are known to be relatively short acting and this feature of the drugs was though to conform with requirements of the experiment.

METHOD

Animals

Four adult crab-eating monkeys (*Macaca irus*, body weight 3.6–5 0 kg) were used in the present study. The monkeys were housed in individual cages and quarantined for 3 months They were then moved to open-fronted individual cages (85 cm width, 100 cm height, 95 cm depth) for self-administration experiments, where they were restrained by a free-jointed metal arm and metal harness, and conditioned for 1 month or longer before initiation of the experiment. The 2 crab-eating monkeys used in the intravenous self-administration experiment with pentobarbital had been used in drug discrimination experiments on CNS stimulants such as cocaine, but the other monkeys were experimentally naive. Rooms were air-conditioned at 25±2°C and 60±20% humidity, and the lighting was on from 7:00 a m. to 12·00 midnight or 1:00 a.m

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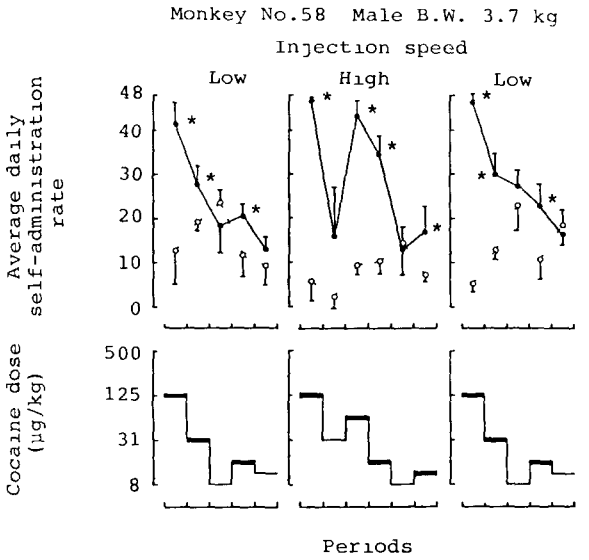

FIG 1 Titration of the minimum reinforcing doses of cocaine in a crab-eating monkey under the FR1 schedule with 30-min time-out and 2 levels of injection speed Thick horizontal lines indicate the reinforcing effect was positive In the above graphs solid lines and dotted lines indicate data on cocaine and saline respectively *$p<0$ 05, Low, 1 ml/23 sec/4 kg, High, 1 ml/5.8 sec/4 kg

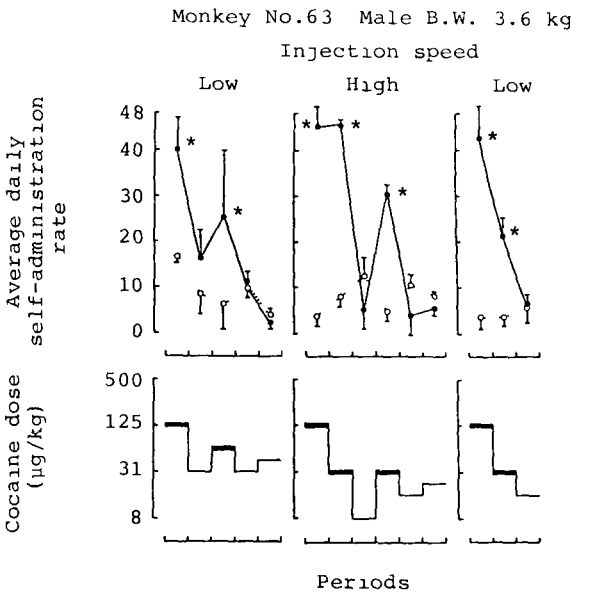

FIG 2 Titration of the minimum reinforcing doses of cocaine in a crab-eating monkey under the FR1 schedule with 30-min time-out and 2 levels of injection speed For further explanation, cf Fig. 1

Food and Water

Monkeys were fed 120 g/day solid-type monkey chow (Oriental Co or Nihon Clea) with added vitamin C (30 mg/100 g). Tap water was available ad lib from a fountain nozzle activated at pressure by the tongue.

Drug Preparation

Cocaine HCl (cocaine) and pentobarbital Na (pentobarbital) as used in this study were dissolved in physiological saline to the necessary concentrations To the pentobarbital solutions was added Na_2CO_3 at $^1/_5$ the amount of pentobarbital to prevent crystalization out by the rapid change in pH when the solution entered the blood The doses of the drugs were changed by adjusting the concentration of the drug solution

Procedure

The catheter which had been intravenously implanted was connected via tubing passing through the restraining arm to a lever-activated, automatic injector located outside the cage that allowed a predetermined unit dose of a drug or saline (infusion volume: 0 25 ml/kg, infusion speed 1 ml/23 sec) to be automatically infused through the catheter when the monkey pressed a lever switch in the cage [3] Two monkeys each were initially trained to self-administer cocaine at a unit dose of 125 μg/kg and pentobarbital at 1000 μg/kg under a fixed ration (FR) 1 schedule. The schedule was changed to a FR1 schedule with 30-min time-out after each drug injection in order to avoid the cumulative effects of the drugs. After the monkeys showed frequent and stable self-administration under the FR1 schedule with 30-min time-out, saline was substituted for the drugs. The drugs and saline were thereafter made available alternately for periods of 5 days at a time After a clear difference between the self-administration rates for saline and for the drugs had been observed by this procedure, titration was conducted as follows under the same schedule to determine the minimum reinforcing doses of the drugs. Whenever the average self-administration rate per day in a 5-day period of a drug at some unit dose was significantly higher than the rate in the preceding 5-day saline period, that particular unit dose of the drug was assumed to have a reinforcing effect, and the unit dose was decreased for the next 5-day drug period. Likewise, whenever the self-administration rate of each drug at a certain unit dose was not significantly higher than the rate in the preceding saline period, this dose was assumed to have no reinforcing effect and the unit dose was then increased in the next drug period The self-administration data during the first day in each session were excluded from the calculations of the average daily self-administration rates because the self-administration frequency on any first day is often susceptible to strong influence by the condition of the preceding period. As a statistical method, Student's t-test (two-tailed, $p<0.05$) was used to evaluate for significant differences between self-administration rates in saline and drug periods.

After the minimum reinforcing doses were investigated at the injection speed of 1 ml/23 sec/4 kg (low speed) Next, the injection speed was changed to 1 ml/5 8 sec/4 kg (high speed) by changing the injectors. After the minimum reinforcing doses were investigated at these two speeds, the injection speed was returned to the low speed and the minimum reinforcing doses of the drugs were reinvestigated. Although experiments with the injection speed of 4 mg/92 sec/4 kg were conducted immediately after the initial experiments at the low speed, the data are omitted from this report, because the injection speed is thought to be substantially the same as the low speed.

Control of the automatic injector as well as recording of

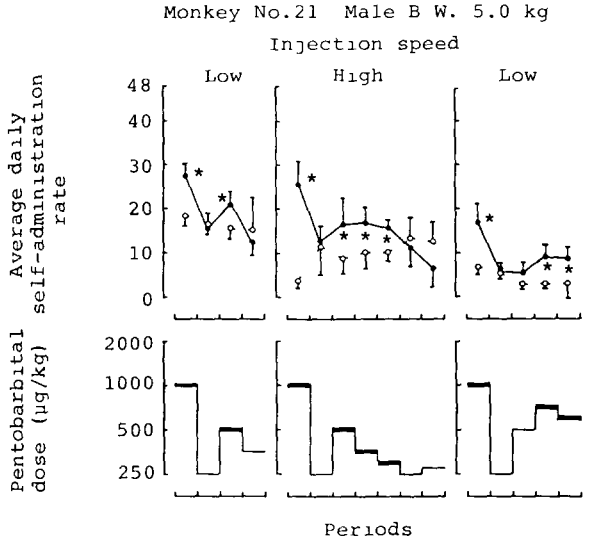

FIG 3 Titration of the minimum reinforcing doses of pentobarbital in a crab-eating monkey under the FR1 schedule with 30-min time-out and 2 levels of injection speed In the above graphs solid lines and dotted lines indicate data on pentobarbital and saline respectively For further explanation, cf Fig 1

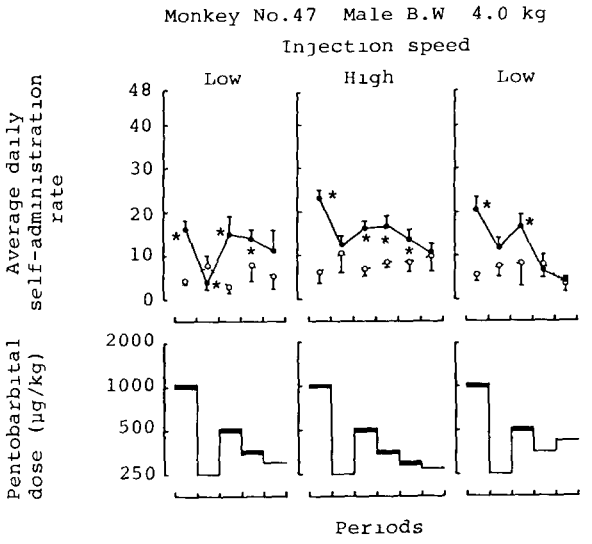

FIG 4 Titration of the minimum reinforcing doses of pentobarbital in a crab-eating monkey under the FR1 scedule with 30-min time-out and 2 levels of injection speed In the above graphs solid lines and dotted lines indicate data on pentobarbital and saline respectively For further explanation, cf Fig. 1

the number of self-administrations was handled by a microcomputer system (SAS-80) specifically developed for the purpose at the present institute

RESULTS

In 1 out of 2 monkeys used in the experiments on cocaine (No. 58), a reinforcing effect at the low speed was observed at 31 μg/kg/inj and as low as 16 μg/kg/inj. With the high-speed injection, the reinforcing effect of cocaine was observed at 12 μg/kg/inj but not at 8 μg/kg/inj. In the final experiments again at the low speed, reinforcing effect was observed at no lower than 16 μg/kg/inj (Fig 1)

In the other monkey which was used in the experiments on cocaine (No. 63), the reinforcing effect stopped being observable when the unit dose was decreased to 31 μg/kg/inj at the low speed but it was again observed when the unit dose was increased to 63 μg/kg/inj The minimum reinforcing dose at the high speed was 31 μg/kg/inj. In the final experiment at the low speed, the minimum reinforcing dose was 31 μg/kg/inj (Fig 2)

In 1 out of 2 monkeys used in the experiments on pentobarbital (No. 21), reinforcing effect was observed at as low as 500 μkg/inj at the low speed. The minimum reinforcing dose of pentobarbital at the high injection speed in this monkey was 313 μg/kg/inj. In final experiment at the low speed, reinforcing effect of the drug was observed at as low as 625 μg/kg/inj (Fig. 3)

In the other monkey used in the experiments on pentobarbital (No. 47), the minimum reinforcing dose of the drug was 375 μg/kg/inj at the low speed. At the high speed, reinforcing effect was observed at as low as 313 μg/kg/inj In the final experiment at the low speed, the minimum reinforcing dose was 375 μg/kg/inj (Fig. 4).

DISCUSSION

Rhesus monkeys have been the most widely used species in self-administration experiments in monkeys, and much background data on self-administration experiments has been obtained in this species However, crab-eating monkeys were used in the present study because the international supply of rhesus monkeys had become limited at the beginning of this study. The minimum reinforcing doses of cocaine at the low injection speed in crab-eating monkeys in the present study were found to be almost the same as those in rhesus monkeys at a similar injection speed [6,7]. It is also known that the minimum discriminative doses of cocaine are close to each other in both species [1,4]. Accordingly, the sensitivity to the CNS action of cocaine is thought to be similar between crab-eating and rhesus monkeys

In the initial experiments at the low speed, the minimum reinforcing doses of cocaine were 16 and 63 μg/kg/inj in each monkey At the high speed the minimum reinforcing doses of cocaine decreased to 12 and 31 μg/kg/inj, respectively. Although the difference between 12 and 16 μg/kg/inj in Monkey No. 58 may not seem so significant, increase in average self-administration rate of the drug at 16 μg/kg/inj at the high speed compared to the rate at the low speed supports the view that the reinforcing effect is strengthened when injection speed is raised. The experiments at the low speed were repeated after completing the experiments at the high speed, to control both the influence of experiment order and the change in sensitivity to cocaine and pentobarbital accompanying repeated intake of the drugs. The minimum reinforcing doses of cocaine at the low speed were the same in the initial and final experiments in Monkey No 58, but in Monkey No. 63 the minimum reinforcing dose in the final experiment was lower than in the initial experiment at the low

speed and the same as the minimum reinforcing dose at the high speed These results may suggest that the decrease of the minimum reinforcing doses at the high speed is not attributable to the injection speed However, the average self-administration rates of cocaine at 31 μg/kg/inj were much higher at the high speed than at the low speed in the final experiment in Monkey No 63. Accordingly it can be assumed that the reinforcing effect of cocaine becomes stronger as the injection speed is increased. The minimum reinforcing doses of pentobarbital were 375 and 500 μg/kg/inj in each monkey at the low speed. The minimum reinforcing doses in the monkeys were decreased to 313 μg/kg/inj at the high speed In the final experiments at the low speed, some increase of the minimum reinforcing doses was observed, which may indicate that tolerance to the action of pentobarbital had developed. However, the minimum reinforcing doses were lowest in the experiments at the high speed which were conducted after the initial slow-speed experiment Accordingly, the degree of influence due to tolerance development was not thought to exceed the influence of the injection speed, even considering that tolerance to the action of pentobarbital had developed

In the present study, the FR1 schedule with 30-min time-out was used in order to avoid the cumulative effects of the drugs. The duration of the effects of cocaine is known to be very short. For example, the effect of intravenous cocaine at 0.1 mg/kg has been suggested to be diminished within 10–20 min after administration in drug discrimination experiments in rhesus monkeys [1] The duration of the effects of pentobarbital at the doses used in the present study are also thought to be relatively short, so that the cumulative effects of the drug may be almost negligible.

For the evaluation of significant differences between self-administration rates in saline and drug periods, Student's *t*-test was used as a statistical method Theoretically, it may be inappropriate to apply the *t*-test to such dependent numbers which can influence each other. However, some criterion was necessary to judge promptly whether the reinforcing effect was positive or not during the course of the titration for minimum reinforcing doses, so the convenient *t*-test was chosen arbitrarily in these experiments.

The titration procedure used in the present study may seem unsystematic compared with usual procedures in psychophysics [5] However, it was thought reasonable to conclude from above results and discussion that the minimum reinforcing doses of cocaine and pentobarbital tend to become higher in inverse proportion to the injection speed of the drugs In a past study [2], it was suggested that reinforcement efficacy of cocaine at particular doses becomes weaker when the infusion duration of the drug becomes longer, i e , when the injection speed becomes slower. Thus, for the development of reinforcing effect of the drugs, it was thought necessary that the drugs enter into blood stream at doses higher than a certain threshold level and at equal to or faster than a certain criterion of speed

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