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Preference for Cocaine by the Weight Pulling Method in Rats

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SUZUKI, T., Y. MASUKAWA, T. YOSHII, T. KAWAI AND S. YANAURA. *Preference for cocaine by the weight pulling method in rats*. PHARMACOL BIOCHEM BEHAV **36**(3) 661–669, 1990.—The purpose of the present study is to show the efficiency of the weight pulling method in evaluating quantitatively the positive reinforcing effect of cocaine. Rats were trained to pull the weight in order to eat the drug-admixed food (DAF). The experiments began with the preexposure of the drug through the repetition of CFF schedule. The schedule consisted of one choice trial (C) between the intake of normal food and DAF followed by two consecutive forced trials (F), in which the rats were forced to take the DAF only. The study consisted of Experiment I, where cocaine concentration in DAF was varied while the period of cocaine preexposure was kept constant and Experiment II, where the period of preexposure was varied while the cocaine concentration was kept constant. Results show that the reinforcing effect of cocaine was dependent on cocaine intake. On the other hand, the reinforcing effect of cocaine was independent of cocaine preexposure period. The effect of cocaine on the drug-seeking behavior was evident on the first day of cocaine exposure. It is concluded that the weight pulling method is sufficient to evaluate quantitatively the reinforcing effects of cocaine in rats, and this method may be useful for the prediction of dependence potential in man.

Weight pulling method Cocaine Morphine Codeine Preference Drug-admixed food Drug-seeking behavior Reinforcing effect Choice Rats

WE reported previously (18) that rats which had been exposed to morphine or codeine using constant dose for varying periods of time and then introduced to a task requiring pulling a weight performed this behavior to obtain the drug. The percentage of animals which did pull the weight to take the drugs was dependent on the period of drug exposure. In the case of these drugs, both positive reinforcing effects and physical dependence were produced. Weeks (23) reported that the reinforcing effects of morphine were intensified by withdrawal of morphine through the appearance of withdrawal signs. This indicates that morphine can also possibly reinforce drug-taking behavior by suppressing withdrawal signs resulting from its physical dependence. It was shown by Deneau and Seevers (4) that the degree of physical dependence is affected by three factors, namely dose of the drug, frequency of exposure and exposure duration. Yanagita (26) reported that for monkeys responding under a progressive ratio schedule, the breaking point for morphine was increased by preexposure to morphine which might produce physical dependence. We also reported (17) using the weight pulling method that the amount of weight in which rats would pull was greatly increased when they were made severely physically dependent on morphine by manipulating the drug dose and the period of drug exposure. It is possible that in the previous study (18) the weight pulling behavior of morphine preexposed rats, which was directly related to the duration of exposure, may have been determined not solely by its positive reinforcing effects, but also by its termination of withdrawal signs (negative reinforcing effects) caused by the presence of physical dependence. Although we did not test for this, the rats in the previous study (18) may indeed have been physically dependent on morphine, considering that the same schedule was used and physical dependence on morphine was produced (19).

The weight pulling behavior of codeine preexposed rats may also have resulted both from codeine's positive and negative reinforcing effects (ability to reinforce drug-taking behavior through termination of withdrawal signs), because codeine's reinforcing effects also generally were directly related to the length of exposure to codeine. Therefore, it can be suggested that the weight pulling method is effective in evaluating quantitatively the reinforcing effects of opioids such as morphine and codeine which have both *positive* and *negative* reinforcing effects.

Cocaine is taken by humans in a variety of routes, including the oral, intranasal, and intravenous, as well as by inhalation (8). It had been demonstrated that not only opioids but also cocaine has positive reinforcing effects through intravenous (6,13), intragastric (25) or oral (21) self-administration route and is chosen in a preference test using oral administration in animals (10).

To confirm that the weight pulling method is efficient to evaluate quantitatively the *positive* reinforcing effect of drug

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which has no ability to reinforce drug-taking behavior through termination of withdrawal sign (negative reinforcing effect), cocaine which does not produce physical dependence (11,24) was employed in the present study. Furthermore, the results obtained in the present study were compared with those in the previous study in which morphine and codeine were used (18).

METHOD

Animals

Male Sprague-Dawley rats aged 6 weeks (Tokyo Experimental Animal Ltd., Tokyo) were used in groups of eight. All rats were housed individually in a cage. Powder food (CA-1; Clea Japan Inc., Tokyo) and tap water were supplied ad lib. All rats in all groups were adjusted for age such that their weights were almost the same at the time of the experiment. The animal room was artificially illuminated daily from 8:30 a.m. to 8:30 p.m. and maintained at 21 ± 1°C.

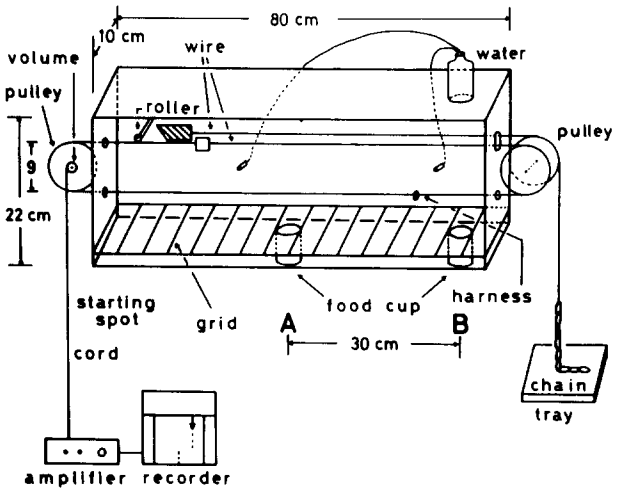
Drug

Cocaine hydrochloride (Takeda Chemical Industries, Ltd., Osaka) was mixed with animal powder food according to the method of Yanaura *et al.* (27). The drug-admixed food will be referred to as DAF. DAF was kept in cold storage (4°C) for a week. Any leftover food after a week was discarded.

Apparatus

The same apparatus as reported previously (18) was used. The apparatus was shown on the top half of Fig. 1. It was principally made up of a runway measuring 10 cm in width, 80 cm in length and 22 cm in height. The runway had a floor covered with cross grids and two food cups were placed 30 cm apart on the floor (at point A and B in Fig. 1). Endless wire mounted on pulleys placed outside at opposite ends ran lengthwise through the runway and could be pulled into motion. A stopper and a harness were fixed to the wire. Each rat had a collar put around its neck and the collar was connected to the harness during the trial. Another length of wire ran in parallel, mounted on another pulley placed outside near point B, and had a chain of links as weight at the outer end and a boat at the inner end.

At the start of the experiment, the rat held at the starting spot was released to move in the runway. The moment the rat passed point A, the stopper caught the boat and pushed it, pulling up the chain and causing a load to strain the rat. As the rat drew nearer and nearer to point B, it pulled the weight higher and higher, carrying an increasingly heavy load. The moment the rat reached point B, the boat pushed by the stopper touched the roller. Upon further advance of the stopper, the stopper caught the roller and set the boat free (see the bottom half of Fig. 1). When this happened, the rat was released from the load and was able to take the food in the cup at point B freely. If a rat went backward from B to A, then turned around and moved toward B again, the same process as above would be repeated: The load on the rat would increase as the rat moved away from point A. This relationship was correlative (Fig. 2). Each link of the chain weighed 30 g, and as constructed, the apparatus allowed addition of up to 17 links. To keep the length of wire inside the runway stretched taut, it carried one link at all times. Therefore, the rats pulled one link in all the experiments and an additional number of links in the test trials described behind (see the Procedure section). The location of each rat inside the apparatus was recorded by a potentiometer (Chino, Ltd., Tokyo, EH800-06) every 30 seconds for a 6-hr session. The



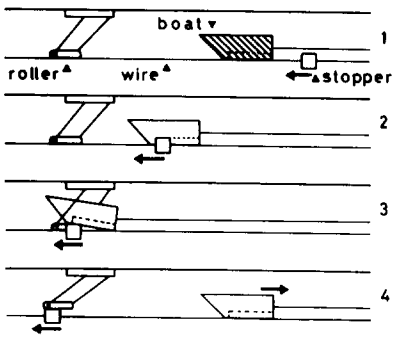


FIG. 1. Schematic diagrams of the apparatus and of the mechanism which releases a loaded weight.

number of times a rat approached point B within a given period of time or the span it stayed at point B was measured.

Procedure

The experiment was carried out in three steps: preliminary feeding, drug exposure and determination of the degree of drug preference. The rats were fed preliminarily in separate cages for a week. The intake of food was controlled during this period by feeding the rats only 6 hours a day, from 10:30 a.m. to 4:30 p.m. Water was given without restriction. A collar, which was connected to the harness during the following trials, was attached on each rat. One week later, drug was administered using the CFF schedule, which comprised one choice trial (abbreviated C) followed by two consecutive forced trials (abbreviated F). In the choice trial, normal food was placed in the cup at point A and the drug-admixed food (DAF) in the cup at point B so that the rat could choose either the normal or DAF. In forced trial, there is no food at point A and only the DAF was available in the cup at point B; hence the rat was forced to take the drug at the time of feeding. This CFF schedule was repeated 2 (in Experiment I) and 2 to 9 times (in Experiment II). After completion of this phase of the experiment using the CFF schedule, each group was subjected to four consecutive choice trials.

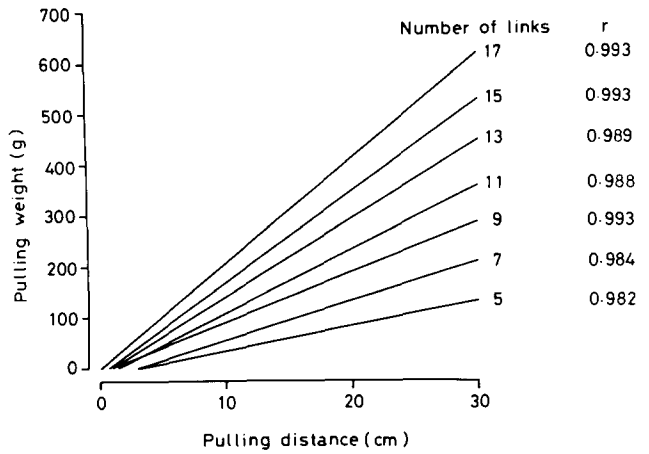


FIG. 2. The relation between the pulling distance and the load on rat (rat's pulling weight). Number of links: 5. $y=4.85x-14.95$; 7. $y=7.63x-21.68$; 9. $y=9.71x-5.98$; 11. $y=12.41x-17.37$; 13. $y=15.39x-14.62$; 15. $y=17.92x-12.72$; 17. $y=20.58x-3.70$.

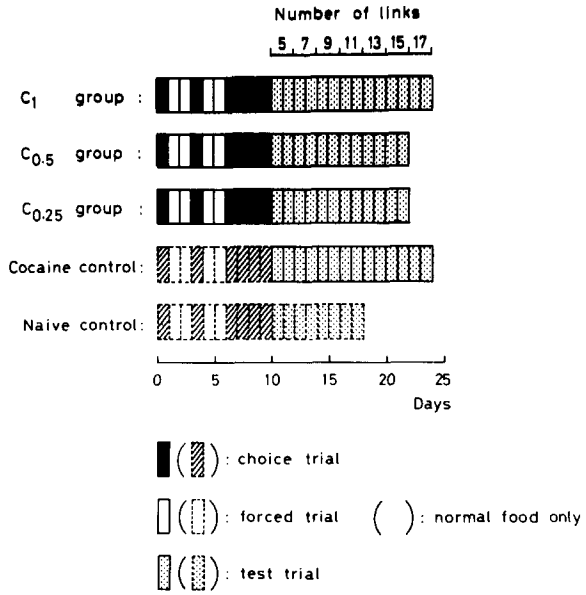


FIG. 3. Schedule of Experiment I.

Up to this point, only a single link of chain was attached to the wire (to insure that it remains taut). Then, to determine drug preference, the following test trials were conducted. Normal food was placed in the cup at point A and the DAF in the cup at point B like in the choice trial. The rat was able to take normal food in the cup at point A freely, however, the moment the rat passed point A and moved toward point B, the weight of the chain links began to strain its neck. Unless the rat pulled this weight, it could not reach point B and hence could not take the DAF. The initial load was at 5 links (150 g) and increased by 2 links (60 g) after every two days (two trials) until the rat terminated its weight pulling behavior to reach point B. The test was repeated twice for each number of links. The apparatus was constructed in such a manner as to allow addition up to 17 links. In the last two trials of 4-day choice (one link) and test trials (5–17 links), the number of rats that reached point B was recorded, and the proportion of this number to the total number ($n=10$–12) was calculated. This proportion was obtained by multiplying the number of rats in one group ($n=5$–6) with the number of repeated tests (2 consecutive days).

All the experiments were carried out, one trial a day, between 10:30 a.m. and 4:30 p.m. After completion of the trial for the day, the rats were returned to their home cages and only water was given. After each trial, the normal food and DAF intake were determined, and drug intake and preference rate were calculated. Calculating preference rate was performed as follows:

$$\text{Preference rate (\%)} = \frac{\text{DAF intake (g)}}{\text{Normal food intake (g)} + \text{DAF intake (g)}} \times 100$$

Rats were weighed before and after trials. Additionally, the movement of each rat in the apparatus for the 6-hour experimental period from 10:30 a.m. to 4:30 p.m. was recorded by a potentiometer in the test trials. Maximum pulling weight divided by the body weight of each rat was calculated from the weight pulling distance in all approaching behavior of each rat to DAF during test trials using the relationship, shown in Fig. 2, between the rat's weight pulling distance and the load carried (rat's pulling weight).

Experiment I. The schedule of Experiment I is shown in Fig. 3. The period of cocaine exposure was kept constant, with the CFF schedule implemented twice. Cocaine was mixed with the food in three concentrations, 0.25 mg, 0.5 mg and 1.0 mg/g of food. Thus, three groups , $G_{0.25}$, $G_{0.5}$ and $G_{1.0}$ (the subscript designates the concentration of cocaine in mg/g of food), were trained.

Two groups served as control groups, a cocaine group and a naive group. The cocaine control group was subjected to the CFF schedule twice, to the daily choice trial for four days, and finally to the test trials. The choice trial was run with normal food at point A and also normal food at point B, and the test trial with normal food at point A and cocaine-admixed food (0.5 mg/g of food) at point B. Therefore, this group had no preexposure to cocaine. On the other hand, the naive control group went through the same procedure as the cocaine control group, except with the placement of normal food at point B even in the test trial. This group was therefore completely free from cocaine exposure.

Naive group was a control reflecting the animal's food deprivation condition. The rats in this group, as well as cocaine-exposed groups, limited their feeding only to the described 6 hours experimental a day. The food cup position might be learned by the repetitions of forced trial. Naive control group is also used for removing the possibility that the weight pulling behavior in the cocaine-exposed rats is caused by position learning.

Cocaine control group was employed to confirm that the reinforcing effect of cocaine did not need preexposure to cocaine.

Experiment II. The schedule of Experiment II is shown in Fig. 4. The concentration of cocaine was kept constant at 0.5 mg/g of food, which was the middle concentration in Experiment I. Three groups of rats, G_4, G_6 and G_9, were used, each differing in the period of cocaine exposure, as indicated by the subscript, which designated the number of repetitions of the CFF schedule. These three groups and the $G_{0.5}$ group of Experiment I (referred to as G_2 group in this Experiment II) together provided four groups differing in the period of cocaine exposure (the number of repetitions of the CFF is 2, 4, 6 or 9).

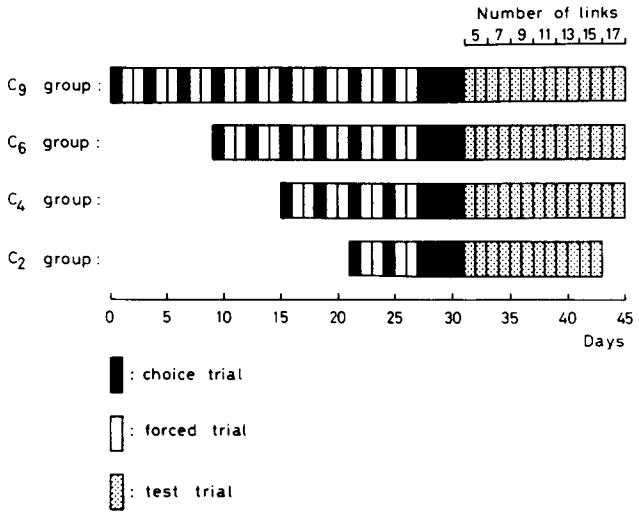


FIG. 4. Schedule of Experiment II.

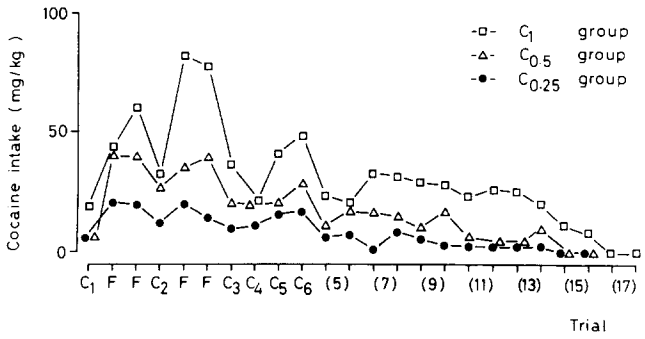


FIG. 5. Cocaine intake during Experiment I. Each plot represents the mean of 6 rats.

Statistical Analysis

The proportion of the total number of rats in each group that reached point B pulling a given number of links and obtained DAF, and the preference rate were calculated. The results of these calculations were transformed according to an inverse sine function, and thereafter subjected to an analysis of variance (ANOVA). ANOVA was also utilized to analyze the drug intake. The Wilcoxon test was used to determine whether an individual experimental group produced a significantly greater maximum pulling weight than the naive control ($p<0.05$). Dose-response curve of maximum pulling weight was analyzed using a one-way random factorial ANOVA. The Student's *t*-test was used in the statistical evaluation for locomotor activity and food intake.

RESULTS

Experiment I

Figure 5 shows the average cocaine intake per subject, based on the results obtained in three groups, $G_{0.25}$, $G_{0.5}$ and $G_{1.0}$ group. The cocaine intake was dependent on the cocaine concentration in the test trials, $F(2,240)=7.110$, $p<0.001$. As shown in Fig. 6, the number of rats taking the DAF as weight was increased tended to fall more gently as cocaine concentration increased. The effect of cocaine on the proportion of rats in each group that obtained DAF significantly was dependent on the concentration of cocaine, namely cocaine intake, $F(2,8)=4.459$, $p<0.05$. The preference rate in the test trials exhibited a similar pattern, $F(3,240)=3.864$, $p<0.01$ (Fig. 7). Prior to the test trials, both control groups were trained with normal food, not DAF, at point B, as described above. The preference rate here refers to the ratio of the normal food taken at point B to the normal food taken at point A. In the test trials, the preference rate in the cocaine control group refers to the ratio of DAF to normal food, whereas in the naive control group it refers to the ratio of normal food taken at point B to normal food taken at point A. Both groups, after the first choice trial and before the start of the test trial, took the normal food both at point A and at point B about 50% rate. In the test trials which followed, the cocaine control group took some DAF at point B in relation to the weight, like the cocaine-exposed groups, even though this group had no prior exposure to cocaine. On the other hand, the naive control group in the test trials showed rapidly decreasing intake of the normal food at point B in relation to the weight.

As shown in Fig. 7, the cocaine control group took more food at point B (cocaine-admixed food) on the first day of test trial (first day of cocaine exposure) than on the previous day when the group had only the normal food at point B. On the other hand, the naive control group took less food at point B (normal food) on the first day of test trial than on the previous day. The difference between food intake on the first test trial day and on the previous day in the cocaine control group is significantly greater than in the naive control group. Frequency of approaching behavior to DAF at point B tended to fall as the weight was increased. However, total time spent at point B after releasing the load was opposite.

The average locomotor activity per subject, recorded by potentiometer, was about 10 meters for all groups. There was no significant difference among these groups. However, the rats in cocaine-exposed groups and cocaine control group showed much more movement accompanied with pulling weight than those in the naive control group. It was reflected in the maximum pulling weight of each rat calculated from the weight pulling distance in all approaching behavior of each rat to DAF. The maximum pulling weight was dependent on the cocaine intake, $F(1,19)=$

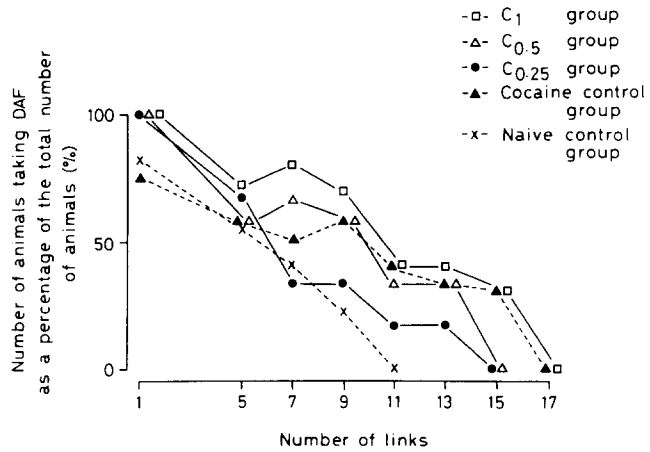


FIG. 6. The relation of the percentage of animals taking cocaine-admixed food against the number of chain links in Experiment I.

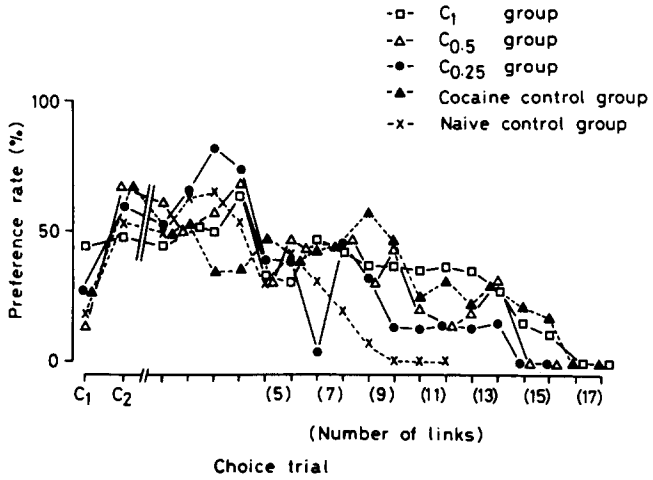


FIG. 7. Preference rate for cocaine-admixed food in choice trials and trials in Experiment I. Each plot represents the mean of 6 rats.

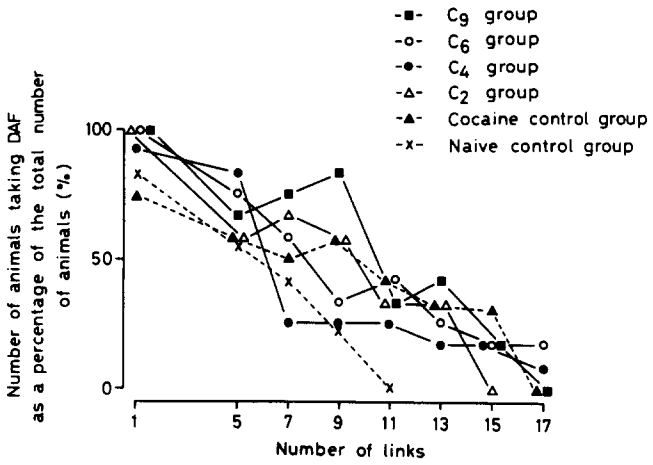


FIG. 9. The relation of the percentage of animals taking cocaine-admixed food against the number of chain links in Experiment II.

8.185, $p<0.01$. The results for the cocaine control group are also shown in Fig. 8 because this group was subjected to the experiment under the same conditions as the $G_{0.5}$ group except for the absence of preliminary cocaine exposure. Significant differences of maximum pulling weight from naive control were shown in all cocaine-exposed groups and cocaine control group. Cocaine control group showed much the same maximum pulling weight as shown by $G_{0.5}$ group. As it is apparent from Fig. 8, regardless of whether or not cocaine was exposed prior to the test condition, the dose-response relationship was uniform. The same tendency was shown in Figs. 6 and 7.

Experiment II

The average cocaine intake per subject in all groups of Experiment II tended to be the same as shown in $G_{0.5}$ of Experiment I, and constant irrespective of the period of cocaine preexposure.

The percentage of rats in each group that pulled the weight to point B is shown for the test groups in Fig. 9. All of the test groups and even the cocaine control group, which had no CFF with cocaine, showed roughly the same tendency. An addition of 17 links (510 g) was necessary to bring the number down to about 0%. Effects of cocaine on the proportion of rats obtaining DAF was not dependent upon the length of the CFF-exposure period at the constant concentration of cocaine (0.5 mg/g of food). The naive control group in the test trials for intake of the normal food at point B needed 11 links (330 g) to abandon weight pulling.

The preference rates for G_2 ($G_{0.5}$ group in Experiment I), G_4, G_6 and G_9 in Experiment II were plotted in Fig. 10. They tended to fall as the weight was increased, however, they were roughly constant irrespective of period of cocaine exposure. The frequency of approaching behavior to DAF at point B and total time spent at point B after releasing the load exhibited a similar pattern. The average locomotor activity per subject in the test trials was about 10 meters in all of the groups in Experiment II. There was no significant difference between naive control and cocaine-exposed groups. However, the rats in cocaine-exposed groups showed much more movement accompanied with pulling weight than

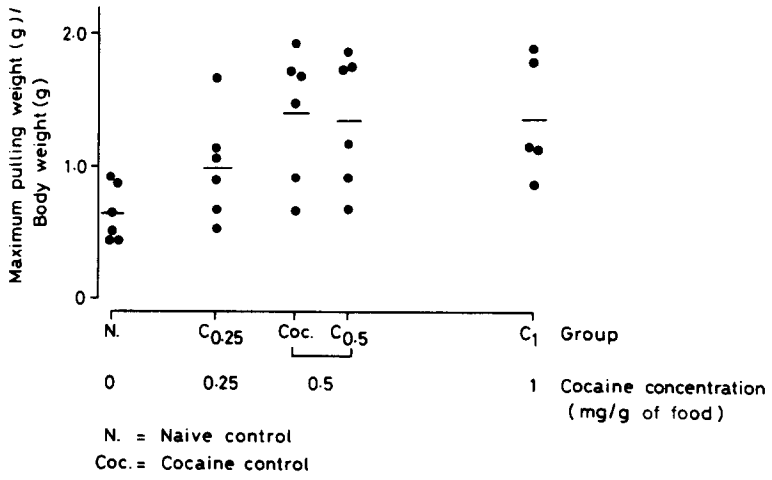


FIG. 8. Maximum pulling weight of each rat in test trials in Experiment I.

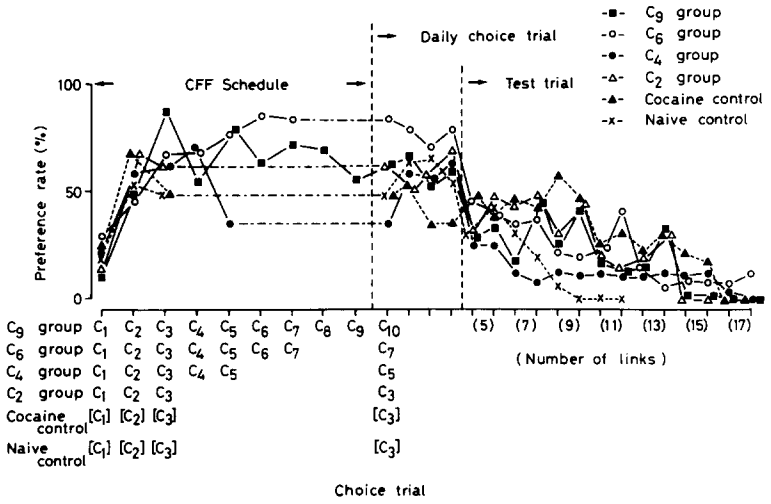


FIG. 10. Preference rate for cocaine-admixed food in choice trials and test trials in Experiment II. Each plot represents the mean of 6 rats.

those in the naive control group. Maximum pulling weights in G_2, G_4, G_6 and G_9 groups were significantly greater than those in the naive control group (Fig. 11). They were roughly constant irrespective of cocaine-exposure period.

DISCUSSION

The preference for cocaine, which has no negative reinforcing effect, was examined in rats using the weight pulling method and the results were compared with those of morphine and codeine obtained in a previous report (18).

As previously mentioned, cocaine is taken by humans in a variety of routes. It is well known that cocaine is absorbed from all sites of application, including mucous membranes and the gastrointestinal mucosa (14). Furthermore, Van Dyke *et al.* (22) reported that similar peak plasma cocaine values were found after oral and intranasal application of the same dosage, and subjective "highs" were greater after oral than after intranasal administration in humans. On the other hand, Tang and Falk (21) reported that serum cocaine values obtained by oral self-administration test in rats were similar to those producing subjective "highs" in coca-leaf chewers and experienced users of cocaine. The maximum concentration of cocaine in food in this study was 1.0 mg/g of food, and cocaine intake was about 40 mg/kg/day, which is similar to the results of oral cocaine self-administration in rats reported by Tang and Falk (21). It was expected that the cocaine intake would be sufficient in producing psychopharmacological effects.

Suzuki *et al.* (17,20) evaluated the reinforcing effects of opioids using "frequency of approaching behavior to DAF" and "total time spent at the point where DAF was placed" as parameters of reinforcing effect by the "original" weight pulling method. Only these parameters were used at the time because there was no releasing mechanism available in the previous apparatus. There was a possibility that rats might choke and the subsequent behavior of rats might be affected by the limitation of taking DAF, which was due to the excessive load. Therefore, we developed the "new" apparatus which had a loaded weight releasing mecha-

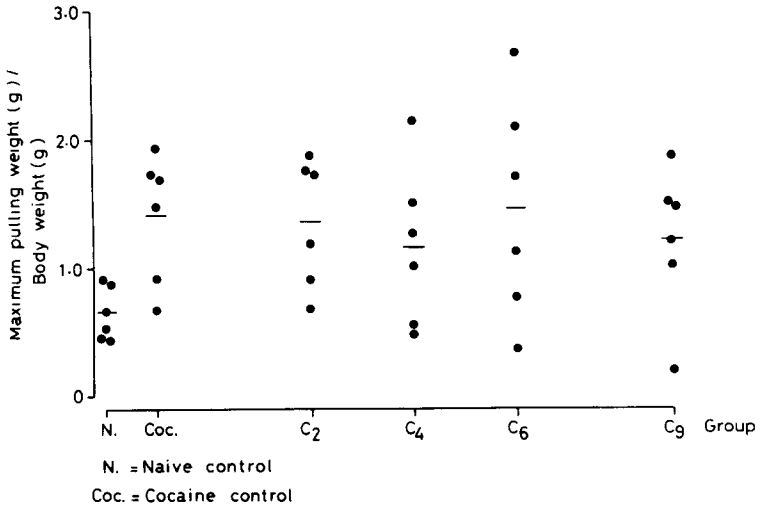


FIG. 11. Maximum pulling weight of each rat in test trials in Experiment II.

nism. The possibility of choking the rats and limiting DAF intake were avoided. However, it became impossible to use the previous parameters, because rats could substitute increasing the "total time spent at the point where DAF was placed" for the "frequency of approaching behavior to DAF" which was decreased by increasing the load.

On the other hand, rats in cocaine-exposed groups showed much more movement accompanied with weight pulling than those in the naive control group. Therefore, maximum pulling weight of each rat was calculated from the weight pulling distance in all approaching behavior of each rat to DAF during test trials using the weight load and weight pulling distance's relationship. The maximum pulling weight was dependent on the concentration of cocaine. Furthermore, cocaine intake was dependent on the concentration of cocaine. It is suggested that the more cocaine the rats took, the more weight they pulled. The maximum pulling weight was a parameter of rat's approaching behavior to DAF, however, not of DAF-taking behavior. Therefore, the number of rats that reached point B pulling the weight and took DAF, and percentage of DAF intake to the total food intake (preference rate) in the test trials were calculated as parameters of the latter. These parameters as well as the maximum pulling weight were significantly dependent on the concentration of cocaine, namely cocaine intake. The rats in the naive control group took the food at point B even with nine links of weight. Weight pulling behavior in the naive control group might be due to the learning of food cup position (point B) through the repetition of forced trials when the food cup was placed only at point B. Its augmentation can be a reflection of the animal's food deprivation. However, the maximum pulling weight, proportion of number of animals taking DAF and preference rate, which were used as the parameters of weight pulling behavior, were greater in cocaine-exposed group than in naive control group. Furthermore, these parameters were increased in a dose-dependent manner with statistical significance. It is suggested that orally administered cocaine had psychopharmacological effects and one of these is weight pulling behavior.

On the other hand, cocaine is well known to stimulate the central nervous system and enhance the spontaneous motor activity (5,12), and these actions may induce the weight pulling behavior. Consequently, the naive control group, completely free from cocaine, was compared with other groups for locomotor activity, calculated from the records of potentiometer within a unit trial time (6 hr) in the test trials. The rats under study moved about 10 meters for naive control in weight free area and for cocaine-exposed groups in weight pulling area, and there was no significant difference in movement of each rat.

These findings suggest that the weight pulling behavior is not caused by the position learning or the enhancement of spontaneous motor activity but by the positive reinforcing effect of cocaine and the effect depends on the cocaine intake. The dosage-dependent effects of cocaine in the present study are consistent with what Yanagita (26), Bedford *et al.* (2) and Roberts *et al.* (15) found using the progressive ratio schedule, and also with that of Johanson and Schuster (9), Balster and Schuster (1) and Brady and Griffiths (3) findings using the choice procedure. These findings suggest that the weight pulling method is sufficient as a method to evaluate quantitatively the reinforcing effects of cocaine.

We reported previously (18) that the reinforcing effects of opioids such as morphine and codeine, which have both positive and negative reinforcing effects, can be evaluated quantitatively by the weight pulling method and that the reinforcing effects of these drugs depends on the period of drug preexposure. On the other hand, it was suggested that the reinforcing effect of psychostimulant cocaine, which has only positive reinforcing effect, can also be evaluated quantitatively in the present study. Therefore, we attempted to discriminate qualitatively between the reinforcing effects of opioids and that of psychostimulant cocaine. The period of drug preexposure was varied and the concentration of drug contained in food was kept constant according to previous report (18). The concentration of cocaine was kept constant at 0.5 mg/g of food, which was the middle concentration in dose-response curve in Experiment I. The maximum pulling weights in all of cocaine-exposed groups were significantly greater than those in naive control group. However, the weight pulling behavior was roughly constant irrespective of the length of cocaine-exposure period. The reinforcing effect like that in morphine and codeine which depended on the length of drug-exposure period was not shown in the case of cocaine by using "proportion of number of animals pulling weight and taking DAF" and "preference rate," as well as "maximum pulling weight," as parameters. To confirm that reinforcing effects of cocaine do not depend on the preexposure period, cocaine control group which has no preexposure to the drug was utilized. Rats in the cocaine control group pulled 5 links and took some food at point B similarly to naive control rats due to learning of food cup position and its augmentation by the reflection of the animal's food deprivation in the first weight pulling test. However, the difference between food intake on the first test trial day and on the day before for the cocaine control group is significantly greater than in the naive control group. "Proportion of number of animals pulling weight and taking DAF" and "preference rate" showed a tendency similar to those of the test groups in the following trials with weight increment. Furthermore, the maximum pulling weights in the rats of cocaine control group were significantly greater than those in the naive control rats. These results seem to indicate that the reinforcing effect of cocaine on drug-seeking behavior was produced on the first day of cocaine exposure, without a long preexposure. Fischman and Schuster (7) reported that that subjective positive effect of cocaine in man is pronounced at the time of first injection, which is consistent with the results of the present study. These findings suggest that the reinforcing effect of cocaine, which does not produce negative reinforcing effect caused by physical dependence, remains invariable irrespective of the length of cocaine preexposure. Yanagita (26) reported that, when tested by the progressive ratio schedule, morphine produces a stronger reinforcing effect on the drug-seeking behavior of monkeys with preliminary exposure which might produce physical dependence; however, cocaine does not. These data are consistent with our results. It is suggested that we could discriminate qualitatively between the reinforcing effect of opioids and that of psychostimulant cocaine by the weight pulling method.

A diagram summarizing the results obtained with morphine and codeine in the previous study (18) and cocaine in this study is shown in Fig. 12. It depicts the effects of the period of CFF drug exposure and the concentration of drug which is related to drug intake, on the reinforcing effect of drug, with the number of rats taking the DAF against the weight as the measure of drug-seeking behavior. Each hatched area in the x-y plane represents the drug-seeking beheavior for a particular drug; a larger hatched area means a stronger drug-seeking behavior. For the group given morphine or codeine in the previous study, the area increases as the period of CFF drug exposure increases. Long exposure is required in codeine-exposed rats in order to produce the similar area to morphine-exposed rats. These results suggest that the reinforcing effect of morphine or codeine, which produces both positive and negative reinforcing effects, depended on the length of the drug-exposure period. On the other hand, as stated above, the reinforcing effect of cocaine, which does not produce negative reinforcing effects, remains invariable irrespective of cocaine preexposure period.

In conclusion, quantitative evaluation of the reinforcing effects of opioids such as morphine and codeine and of psychostimulant

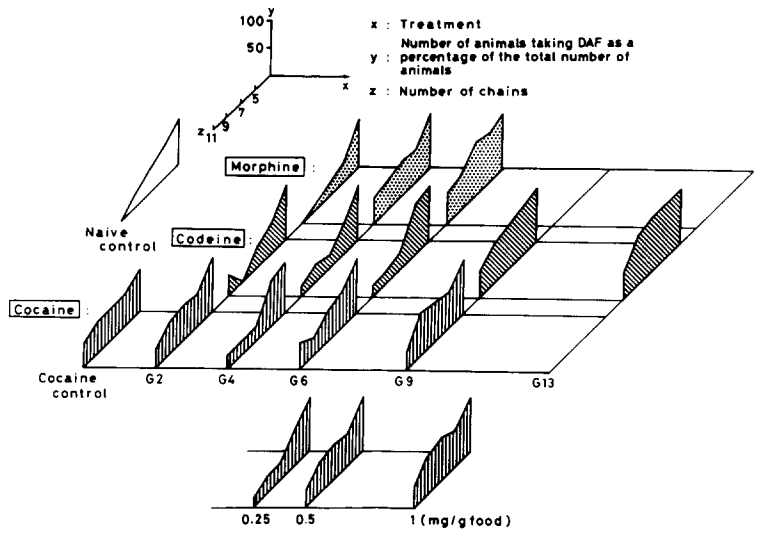


FIG. 12. The summarized diagrams show the effect of the exposure period or the effect of concentration of drug on the drug-seeking behavior for drug-admixed food by the weight pulling method.

cocaine, and qualitative discrimination of the reinforcing effects of these drugs classified as different types are possible by using the weight pulling method. It is suggested that the weight pulling method may be useful for the prediction of dependence potential in man, because this method requires no surgery, and as simple as the conditioned place preference (16) and the oral self-administration method (21). Furthermore, the weight pulling method, like the progressive ratio lever-press method (26), is available for evaluating the reinforcing effects of drugs qualitatively and quantitatively.

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