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# Reinforcing Properties of Intravenous Procaine in Rhesus Monkeys[1]

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FORD, R. D. AND R. L BALSTER. *Reinforcing properties of intravenous procaine in rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 6(3) 289–296, 1977. – The lever pressing behavior of rhesus monkeys was maintained by a fixed ratio 10 schedule of intravenous cocaine (3 monkeys) or codeine (2 monkeys) injections during 2 hour sessions. Saline or various doses of procaine hydrochloride were substituted for the baseline reinforcer for 6 consecutive sessions. Each substitution was separated by 3 or more days of cocaine or codeine reinforced responding. At one or more doses, procaine substitution resulted in response rates higher than saline control in all 5 animals. High response rates (greater than 30 injections per session) were obtained in 4 of the 5 monkeys. In addition, procaine self-administration was studied in two naive monkeys given 23 hour per day access to procaine following an initial 10 days of saline contingent operant level responding. At a dose of 0.3 mg/kg/injection, both animals initiated responding for procaine reinforcement. Drug intake varied widely from day to day, however each animal took over 1200 injections per day (over 360 mg/kg) at least once during the 30 days of access. With the exception of decreased food intake, there was little evidence for behavioral toxicity from these doses. Following a second 10 days of saline self-administration, both animals were given access to 3.0 mg/kg/injection procaine. A substantially greater intake of procaine was observed which was associated with marked toxicity.

Procaine Self-administration Substitution procedure Cocaine Codeine Unlimited access Rhesus monkeys

PROCAINE is a widely used local anesthetic. Since it was synthesized in 1905 it, along with subsequent synthetic local anesthetics, has largely replaced the naturally occurring compound cocaine in clinical practice. It is generally considered that procaine is unlike cocaine in not being subject to abuse because it lacks the sympathomimetic effects of cocaine [21]. Procaine, however, is not without central nervous system effects as evidenced by the wide variety of clinical purposes for which the compound has been given intravenously [9]. It has principally been utilized as an analgesic [17,18] or as an intravenous general anesthetic [14]. In addition, for the past 20 years, procaine has been promoted widely in Europe for the treatment of problems associated with senescence [1]. This latter use has been based upon apparent antidepressant properties of the drug in geriatric patients [4, 5, 23, 34]. A possible mechanism which may explain this antidepressant effect [4, 15, 23] is that procaine has been shown to be a monoamine oxidase inhibitor [12,15]. Monoamine oxidase activity is reportedly increased in the aged [22]. It has also been suggested [4,34] that the antidepressant properties of procaine may lie in its metabolite, diethylaminoethanol, which may have mild central nervous system stimulant effects similar to those of the closely related drug dimethylaminoethanol [19].

It is clear from the variety of suggested uses of procaine that it has a wide array of psychopharmacological effects. In spite of this, there have been very few studies of the behavioral pharmacology of procaine in laboratory animals [16]. Since procaine may possess many of the pharmacological properties common to drugs of abuse (i.e. analgesia, general anesthesia, and psychomotor stimulation) which are self-administered by laboratory animals [25], we studied the intravenous self-administration of this compound by rhesus monkeys. In the first study, the substitution of procaine was studied in animals maintained on cocaine or codeine reinforcement. In a second study, unlimited access to procaine was studied in experimentally naive animals.

## GENERAL METHODOLOGY

### *Animals*

Seven male rhesus monkeys *(Macaca mulatta)* weighing between 4.2 and 7.0 kg were used. Each monkey was housed individually for the duration of the study in an experimental cubicle. Each monkey was fitted with a

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stainless steel tubular harness [6] and connecting arm constructed from a steel spring. Under phencyclidine-pentobarbital anesthesia, the animals were surgically prepared with indwelling venous catheters (0.8 mm ID) of siliconized rubber. The catheter exited through the skin on the back and connected through the harness and arm to a peristaltic infusion pump (Cole-Parmer Masterflex) located outside the experimental cubicle.

*Apparatus*

The 0.8 × 0.8 × 1.0 m experimental cubicles were constructed of fiber glass with a clear plastic door. The door afforded a view of other similarly housed monkeys. The cages were sealed and the air supply was passed through a 3-stage filter designed to reduce particulate matter, odors and bacteriological contaminants.

Two response levers (BRS PRL-001) were mounted 40 cm apart and 30 cm above the cage floor. Three stimulus lights were located just above each lever. For Experiment 1 the left lever and associated stimulus lights were not used. All programming and recording was accomplished automatically with solid state equipment located in an adjacent room.

## EXPERIMENT 1

### PROCAINE SUBSTITUTION IN MONKEYS MAINTAINED ON COCAINE OR CODEINE SELF-ADMINISTRATION

*Method*

*Animals.* Five rhesus monkeys catheterized as described above were used. Each monkey had a varied history of use in substitution studies utilizing the present procedure. Three of the animals were maintained on cocaine reinforcement and two on codeine reinforcement. The codeine monkeys had been used for studies of opiate self-administration. All animals were given ad lib access to water and were fed about 30 Purina Monkey Chow biscuits and a vitamin supplement each day about 3–6 hr after the experimental session.

*Procedure.* The monkeys used in this experiment had been trained to respond for drug reinforcement on a fixed ratio 10 (FR 10) schedule during daily 2 hour experimental sessions. The session was signalled by the illumination of the two outside lamps of the three stimulus light display. During infusions these lights were turned off and the center lamp was illuminated. The infusion duration was 8 sec and resulted in the delivery of 1.0 ml. Responses during the infusion had no programmed consequence.

The substitution procedure was similar to that described previously [2,3]. It consisted of replacing the cocaine or codeine solution with a single dose of procaine solution for six consecutive daily sessions. Between each dose substitution, the animals were returned to their baseline drug for at least 3 days. The three cocaine monkeys were maintained on 0.1 mg/kg/injection cocaine hydrochloride and the two codeine monkeys were maintained on 0.4 mg/kg/injection codeine phosphate. These doses were chosen to produce roughly comparable baseline rates of responding. Procaine hydrochloride at doses ranging from 0.01–10.0 mg/kg/injection was tested. Generally, middle range doses were tested first and then larger and/or smaller doses were tested depending upon the results. In addition, saline (1.0 ml/injection) was substituted for six sessions before and after the procaine dose series.

Following the completion of the procaine dose series and the second saline substitution, two of the monkeys (B002 and B4110) were placed on a regimen of chronic procaine and saline substitution during which time they were not returned to their baseline drug (cocaine and codeine respectively). Each monkey was given access to saline (1.0 ml/injection) or procaine (3.0 mg/kg/injection) on alternate days for 30 days. Subsequently, in monkey B002 a 3.0 mg/kg/injection dose of procaine alternated with a 1.0 mg/kg/injection dose for 18 additional days and then access to the 3.0 mg/kg/injection dose alternated with a 0.3 mg/kg/injection dose for 15 more days. In the other monkey (B4110), the 30 day saline-drug alternation access was followed by 15 days of alternate access to 3.0 mg/kg/injection and 0.1 mg/kg/injection procaine. Following these extended substitutions in these two monkeys, they were returned to their baseline maintenance drug for three days and then again given a six day saline substitution.

*Drugs.* Cocaine hydrochloride, codeine phosphate and procaine hydrochloride were purchased commercially. They were dissolved in distilled water to produce concentrated solutions. These stock solutions were diluted with appropriate amounts of physiological saline to produce an injection volume of 1.0 ml/injection. New solutions were prepared at least once a week. The doses refer to the salts of each compound.

*Results*

The number of injections self-administered was recorded for four successive 30 minute segments of the 2 hour experimental sessions. For purposes of data analysis only the last three days at each test dose of procaine or of saline were used. Figure 1 shows the mean total number of injections per 2 hr session for saline and procaine substitution in each of the five animals. To the left of each plot is the overall mean number of injections of either cocaine (CA) or codeine (CO) self-administered during baseline. All the animals averaged between 35–55 injections of cocaine or codeine per session.

The values at $S_1$, $S_2$, and $S_3$ represent the results of saline substitution before the procaine dose series ($S_1$), after the procaine dose series ($S_2$) and after the extended substitution series ($S_3$). The right portion of each plot represents the results of procaine substitution at various unit doses.

In all five monkeys, the number of procaine injections self-administered was higher than the range of saline control days at at least one procaine dose. High response rates for procaine reinforcement were not obtained in monkey B002 at any dose, and in monkey B4108 at only one dose. In the other three monkeys relatively high rates of procaine self-administration were obtained at two or more of the unit doses tested. The effects of unit dose on response rate were fairly consistent at doses of 0.1 mg/kg/injection and higher. Except for monkey B002, a general tendency for response rates to decrease with increasing unit dose was obtained. Monkeys B4110 and B4108 who were tested at unit doses lower than 0.1 mg/kg/injection provide evidence for an inverted U-shaped dose-effect curve.

Figure 2 represents the distribution of responding in successive 30 min segments of the session. The mean percentage of the total number of injections pictured in Fig. 1 which were self-administered in each segment is

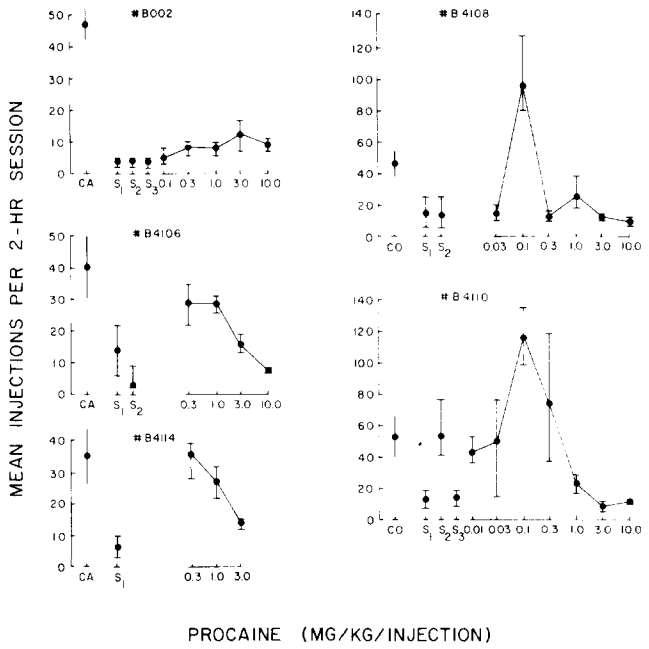


FIG. 1. Mean number of injections per session as a function of unit dose of procaine compared to saline and cocaine (CA) or codeine (CO) baseline in five monkeys. The points at CA and CO represent the mean number of injections of the baseline drug for each animal on the 3 days prior to each saline or procaine substitution ± 1 SD. The points at $S_1$, $S_2$, $S_3$ represent the results of saline substitution prior to the procaine dose series, after the procaine dose series and after chronic procaine substitution respectively. The saline and procaine values represent the means of the last 3 days of the six day substitution ± the range for each animal.

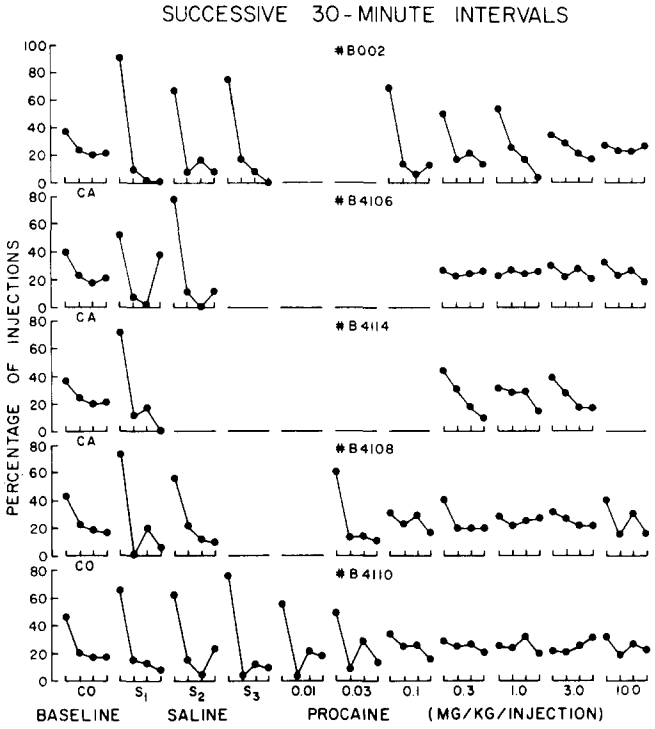


FIG. 2. The distribution of injections in successive 30 min segments of the 2 hr sessions for the 5 monkeys in Fig. 1. The data were obtained from the same sessions used for Fig. 1.

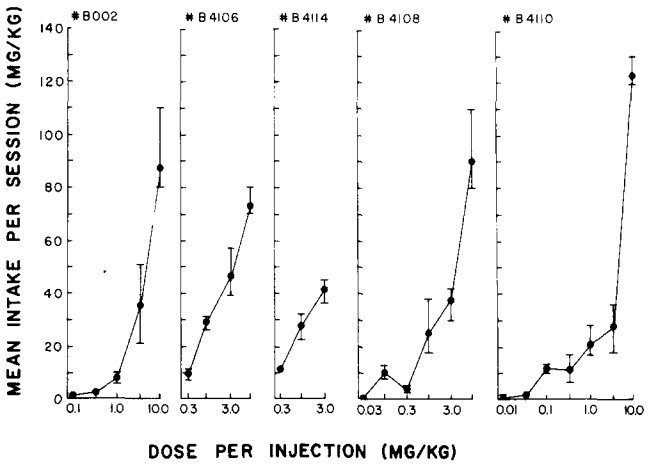


FIG. 3. Mean procaine intake per session as a function of unit dose for 5 monkeys. The data were obtained from the same sessions used for Fig. 1. Each point represents the mean of 3 sessions ± the range.

shown for each of the animals. For the baseline drugs, cocaine (CA) or codeine (CO), about 40% of the injections were self-administered in the first 30 min of the session. Roughly 20% occurred in each of the succeeding three 30 min segments. A somewhat greater percentage of codeine injections were self-administered early in the session than was true of cocaine. During saline substitution the distribution of injections was markedly different. Most saline injections were self-administered in the first half-hour of the session, generally with successively fewer in each subsequent half-hour. With procaine substitution there is a dose-dependent shift in the distribution of injections from a saline pattern towards an increasingly even distribution of responding.

Figure 3 presents procaine intake as a function of dose for each of the animals. Total drug intake increased with increasing unit dose reaching as high as over 100 mg/kg/session in three of the animals tested at 10.0 mg/kg/injection. Even at these high intakes there were very little, if any, overt signs of behavioral toxicity. The animals did not appear similar to monkeys receiving cocaine or amphetamines. No hyperactivity, hyperreactivity or stereotyped behaviors were seen. If anything, the animals seemed sedated and less responsive to external stimuli, although systematic observational data were not obtained.

Figure 4 presents the results of the prolonged procaine and saline substitution in 2 of the 5 animals. In B002, the substitution of 4 of 5 procaine doses had produced more injections per session than that obtained in each of 3 saline substitution periods; however, these differences were quite small. B4110 had a high saline injection rate following the period of substituting various doses of procaine. Both monkeys were provided injections of saline and 3 mg/kg/injection of procaine on alternate days for 30 days. The results in Monkey B002 are shown at the top of Fig. 4. The number of injections of 3 mg/kg procaine (closed circles) were consistently higher than saline injections (open circles) throughout the 30 day period. Next in B002, the 3 mg/kg/injection dose alternated daily with 1 mg/kg/injection throughout Session 48, and then through Session 63 a 0.3 mg/kg dose alternated with 3 mg/kg/injection.

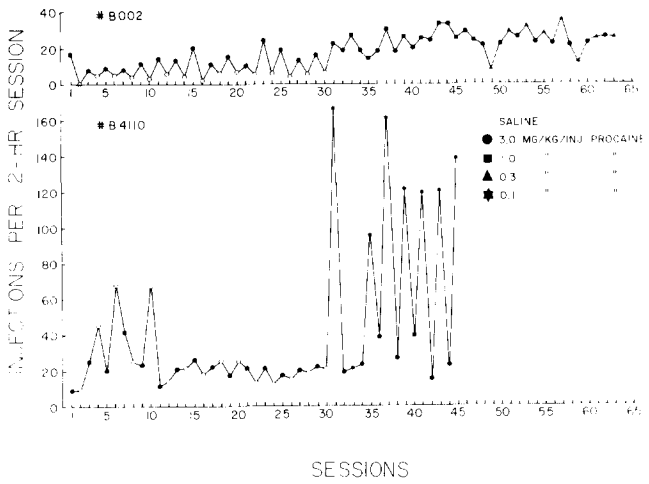


FIG. 4. Number of injections per session for 2 monkeys given extended procaine substitution. See text for details.

Thus, procaine was self-administered in this monkey above saline injection rates after more than 60 days without being returned to cocaine reinforced responding. However, injection rates were not markedly altered by changing the procaine injection dose. In Monkey B4110, indicated at the bottom of Fig. 4, the initial high saline injection rates decreased during the 30 days of alternating saline and 3 mg/kg/injection dose of procaine. Subsequently, a 0.1 mg/kg/injection dose of procaine alternated daily with 3 mg/kg/injection through Session 45. As shown, this lower dose of procaine markedly increased response rates. Again, significant rates of responding were maintained by procaine over an extended period of substitution. In addition, the procaine reinforced response rates over this period are consistently higher than a subsequent saline extinction in these two animals after they had been restabilized on their baseline drug ($S_3$ in Fig. 1).

*Discussion*

In at least three respects the results with procaine substitution are similar to those obtained with a number of drugs of abuse studied using a similar substitution procedure, including opioids [11,25], psychomotor stimulants [3], pentobarbital [7] and phencyclidine [2]. Procaine maintains response rates higher than saline control. There is some evidence for an inverted U-shaped function of response rate to unit dose and a dose-related increase in intake with increasing unit dose. Lastly, procaine differs from saline and resembles other drug reinforcers in the distribution of injections self-administered over the session.

We obtained fairly high response rates (30 or more injections per session) at one or more unit doses or procaine in four of the five animals. In the fifth monkey (B002), although rates higher than saline were obtained, they never exceeded 20 injections per session during the initial dose substitution. A comparison of the results for procaine substitution in cocaine baseline animals with those obtained in codeine baseline animals is limited by the small number of animals and that not all doses were tested in all the monkeys. It is clear, however, that procaine can maintain responding in animals with histories of both cocaine or opioid self-administration. Since procaine possesses some of the pharmacological properties of cocaine such as its local anesthetic effects, one might have concluded that procaine could maintain responding in cocaine baseline subjects due to the conditioned reinforcing properties of those effects procaine shares in common with cocaine. The observation that procaine reinforcement can result in high response rates in codeine maintained animals, demonstrates that a cocaine self-administration history is not necessary for procaine reinforcement.

A wide range of unit doses was not studied in all the animals, consequently it is not possible to state definitively the shape of the overall dose-response curve. There is some suggestion from these data, however, that response rate is an inverted U-shaped function of unit dose. Excluding Monkey B002 from consideration since high response rates were not reliably obtained in this monkey, the descending portion of the dose-response curve over the higher unit doses (0.1–10.0 mg/kg/injection) is evident in the remaining four animals, the only exception being monkey B4108 at 0.3 mg/kg/injection. Under limited access conditions similar to these, stimulants [3,27], opioids [11,25], barbiturates [8,29] and phencyclidine [2] all show response rate to be inversely related to unit dose over the upper range of doses studied. With stimulants, the adjustment in response rate is roughly proportional to the increase in unit dose resulting in relatively constant drug intake [3, 8, 27] and blood levels [33]. In this respect the results with procaine more closely resemble the results with opioids, barbiturates and phencyclidine [2, 8, 11, 25], in that drug intake increases markedly as a function of dose per injection. Only the two codeine baseline monkeys were tested at unit doses less than 0.3 mg/kg/injection. In both these animals response rate increased as a function of unit dose over the lower range of doses tested (0.01–0.1 mg/kg/injection). Over the entire dose range, therefore, response rate appears to be an inverted U-shaped function of dose per injection.

We also examined the within-session distribution of responses. The distributions of cocaine and codeine injections are very similar to those reported by Downs and Woods [7] with cocaine injections being somewhat more evenly spaced throughout the session than codeine injections. The negatively accelerating pattern of saline injections has also been seen in other studies [3, 11, 24]. This within-session decrease in response rate during the session with saline probably represents the extinction of responding for an ineffective reinforcer. With procaine there was a dose-related shift in the distribution of responding from a negatively accelerating pattern similar to saline to a more even distribution similar to cocaine and codeine. In fact, at intermediate doses, a constant rate of self-administration was seen in a number of the animals. Even Monkey B002, who never responded at high rates for procaine reinforcement, showed a stable within-session response rate at high doses. The failure of procaine reinforced responding to extinguish within-sessions at higher unit doses represents further evidence that it is serving as a reinforcer in this experimental situation.

## EXPERIMENT 2

### INITIATION OF PROCAINE SELF-ADMINISTRATION BY NAIVE MONKEYS GIVEN UNLIMITED ACCESS

Animals given relatively unrestricted access to drug reinforcement are well known to show markedly different

patterns of self-administration dependent upon the class of drugs studied. In addition, the behavioral toxicity associated with self-administered doses can be determined under these conditions. Psychomotor stimulants studied under conditions of unlimited access result in a marked behavioral toxicity occasionally resulting in death [13]. When the animals survive, daily intake is highly variable [6, 13, 20]. With unlimited access to opioids, drug intake increases progressively over days resulting in physical dependence development [6, 30, 31]. Very little overt behavioral toxicity is associated with opioid self-administration. Barbiturates have been less extensively studied, however in the case of pentobarbitol, the pattern and consequences of unlimited access appears to resemble the opioids, resulting in fairly stable responding and physical dependence development [6,32]. Unlimited access to ethanol, on the other hand, results in episodic high intake with periods of a few days of abstinence which are accompanied by withdrawal signs [6,28].

In the present study, two naive monkeys were studied under conditions of unlimited access to procaine.

## Method

*Animals and apparatus.* Two experimentally naive rhesus monkeys weighing 5.8 and 7.0 kg were used. They were catheterized and housed in self-administration cubicles as described in the general procedure. For this experiment, both levers and stimulus arrays were used.

*Procedure.* The animals were adapted to the harnesses and restraining arms prior to surgery. The experimental procedure was initiated after the animals had fully recovered from the catheterization surgery (5–6 days).

Each daily experimental session lasted 23 hr from 11:00 a.m. until 10:00 a.m. the following morning. During the session the two outer stimulus lights over each lever were illuminated. One lever was arbitrarily designated as correct and the other incorrect. Correct lever responses resulted in an 8 sec infusion during which the outer stimulus lights over that lever were turned off and the center light illuminated. Responses during the infusion had no consequence. Incorrect responses resulted in a comparable 8 sec change in the stimulus lights over that lever, however no infusion occurred. Responses during the light change had no consequences and were not recorded.

Each of the two animals was exposed to the following sequence of conditions: During the first 10 days each correct response resulted in 1.0 ml saline injections, for the next 30 days each correct response resulted in 0.3 mg/kg procaine hydrochloride injections. This was followed by an additional 10 days of access to saline. Following the second saline access period, the animals were again given access to procaine, this time at a unit dose of 3.0 mg/kg. One animal died during the fourth day of high dose access. The other animal had continued access to 3.0 mg/kg/injection procaine for 29 days, followed again by saline for 9 days.

Each day from 10:00 a.m. to 11:00 a.m. the animals' cages were cleaned, the number of food biscuits remaining in the food trough and excreta pan were counted and the number of correct and incorrect responses for the preceding 23 hr were recorded. At this time the animals were given a vitamin supplement on a sugar cube and their daily allocation of 250 g of Purina Monkey Chow was placed in the food trough. They were given ad lib access to water.

## Results

Figure 5 presents the results obtained during both saline access periods and the intervening access to 0.3 mg/kg/injection procaine. During operant level determination for saline reinforcement (left panel) neither animal exceeded 26 responses in a 23 hr period on either lever. During the initial saline period both animals consumed their entire food allotment of 250 g except on Day 5. We have no explanation for this decreased food intake on this day.

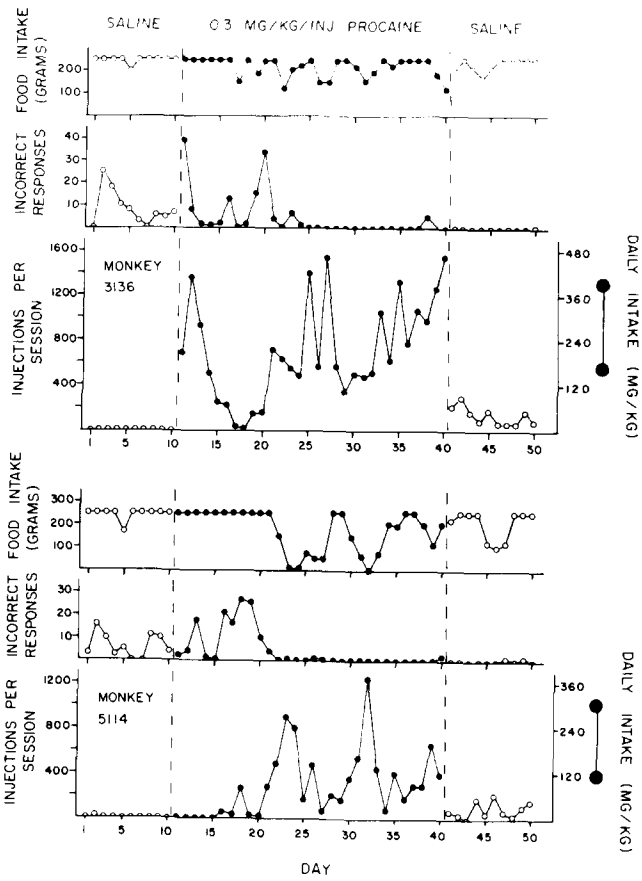


FIG. 5. Daily food intake, incorrect response rate and number of injections (open and closed circles) and procaine intake (closed circles only) during 23 hr per day access to saline and 0.3 mg/kg/injection procaine in 2 monkeys.

Both monkeys initiated high rate responding for procaine reinforcement during the 30 day access period. Monkey 3136 self-administered 684 injections on the first day of access. Monkey 5114 did not initiate high rate responding until the 8th day of access. Response rate for procaine reinforcement varied widely from day to day. Monkey 3136 consistently self-administered more procaine than Monkey 5114.

In both monkeys, the number of incorrect responses increased somewhat during the early period of initiation of procaine self-administration, however, during the last 10–15 days of procaine access incorrect responding fell to negligible levels. This indicates that increases in lever pressing were not the result of a generalized increase in behavior caused by procaine administration and is further evidence that the drug is acting as a primary reinforcer under these experimental conditions.

In spite of high levels of procaine intake, often exceeding 200 mg/kg/day especially in Monkey 3136, there was little if any overt evidence of toxicity. Both animals appeared essentially normal throughout the procaine access period with the following exceptions. On Day 32, Monkey 3136 had a convulsive seizure after self-administering only 49 injections in the preceding 3 hr. The seizure lasted only about 1 min. Since this seizure did not follow a period of particularly high intake we questioned the animal care technicians in the holding facility where the monkey was kept prior to this experiment. It was determined that this monkey had a history of unaccountable seizures. A number of instances were witnessed in which this animal spontaneously developed seizures, fell off the perch and evidenced the clonic phase of grand mal convulsions. The history of seizure activity makes the role of procaine in the seizure seen on Day 32 difficult to determine.

The best documented evidence for procaine effects during this phase of the experiment is the decreased food intake corresponding roughly to the period of high procaine intake in both animals (Fig. 5). The relationship between food intake and procaine self-administration is particularly evident in Monkey 5114. On the 3 days during which this animal self-administered the most procaine, food intake was negligible. In addition, loose stools often accompanied these periods of decreased food intake.

Beginning on Day 41, access to procaine was terminated and correct lever responding resulted in saline infusions. Response rate decreased in both animals as a consequence of saline substitution (Fig. 5, right panel). No overt signs of withdrawal were seen. Both animals failed to consume their entire food allotment on various days during the withdrawal period. This was particularly true of Monkey 5114 on Days 45–47. These periods of decreased food intake during saline substitution did not occur on the same days in both animals and were not accompanied by any other behavioral or autonomic signs of withdrawal.

After the 10 day saline substitution, both animals were again given access to procaine at a 10-fold increase in dose per injection. During the first 3 days of access to this dose Monkey 3136 self-administered 374, 100 and 121 injections respectively for daily intakes of 1122, 300 and 363 mg/kg. This monkey was found dead on the morning of the fourth day of access to this dose. Sixty infusions had been self-administered prior to death. Prior to this, Monkey 3136 appeared normal although food intake was again decreased. This is the monkey with a history of a seizure disorder and it is tempting to conclude that this monkey died from convulsions.

The number of injections self-administered at 3.0 mg/kg/injection and the daily procaine and food intake for Monkey 5114 are presented in Fig. 6. Incorrect lever responses continued to occur infrequently and therefore are not presented in this figure. The largest number of incorrect responses in any day was 37. On the first two days of access to 3.0 mg/kg/injection procaine, this monkey self-administered 285 and 404 injections respectively. After this, the rate of procaine self-administration stabilized around 100 injections per session. This intake of around 300 mg/kg/day was consistently higher than what this animal self-administered during the first access period to 0.3 mg/kg/injection procaine. As a consequence of this higher procaine intake, toxicity was markedly increased.

Food intake was suppressed almost throughout this second procaine access (Fig. 6, upper panel). After a

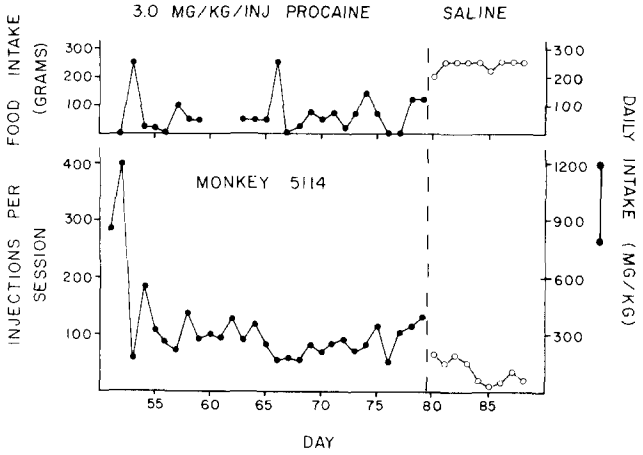


FIG. 6. Daily food intake and number of injections (open and closed circles) and procaine intake (closed circles only) during 23 hr per day access to saline and 3.0 mg/kg/injection procaine in 1 monkey.

number of days of eating very little the monkey became very weak. This monkey would reject regular monkey chow placed in his hand but would consume highly preferred food such as banana flavored chow. This supplementary food is not included in the food intake in Fig. 6, but never amounted to more than a few grams a day.

On the second day of this procaine access period, during which the monkey self-administered over 1.2 g/kg, two convulsive episodes occurred. They were terminated with intravenous diazepam (1.0 mg/kg). No other seizures were seen throughout the remainder of the experiment. Over the last 10–15 days of this procaine access period, this monkey developed severe tremors. These tremors were mostly intention tremors which were most noticeable when the monkey reached for food biscuits or other objects. The appearance of these tremors occurred simultaneously with the development of severe muscle weakness and while the monkey was eating very little. It is difficult to determine if these neuromuscular effects were directly the result of procaine toxicity or secondary to malnutrition.

After 29 days of access to this higher dose of procaine, saline was again substituted (Fig. 6, right panel). Response rates decreased steadily and food intake returned rapidly to normal. During this period the monkey's tremors disappeared and by the 10th day the animal was almost fully recovered. No behavioral or autonomic signs of withdrawal were seen. One month after the experiment the monkey appeared normal and healthy with no evidence for residual toxicity.

*Discussion*

Procaine can clearly serve to reinforce lever pressing behavior in naive rhesus monkeys given unlimited access on an FR 1 schedule. Responding occurred almost exclusively on the procaine reinforced lever indicating that the response rate increases were specific to the procaine contingency and not the result of a general increase in behavioral activity which would be expected to affect responding on both levers equally.

The pattern of responding for a relatively low dose of procaine (0.3 mg/kg/injection) was highly erratic from day to day. In this respect the pattern of procaine intake

resembles the pattern of psychomotor stimulant [6, 13, 20] and ethanol [6,28] self-administration when studied under similar conditions of unlimited access. On the other hand, at a higher unit dose (3.0 mg/kg/injection) the pattern of intake was more stable.

The severity of the toxicity accompanying these self-administered doses of procaine also seems to depend upon the unit dose. Although food intake was decreased at both unit doses, it was more markedly affected at the higher dose. Convulsions occurred in both animals, although one of them had a history of a seizure disorder. In the other animal, convulsions only occurred during the day of highest procaine intake. Other signs of toxicity were only observed at the high unit dose. Intention tremors and muscle weakness may have been secondary to malnutrition. Convulsions are a commonly reported side effect of high blood levels of local anesthetics [21], but this represents the first suggestion we have been able to find of neuromuscular effects. They may only occur with chronic administration.

## GENERAL DISCUSSION

Intravenous procaine can serve as a reinforcer under conditions of both limited and unlimited access in both drug experienced and naive rhesus monkeys. This is perhaps surprising since it is generally considered that procaine is devoid of reinforcing efficacy in man. This latter conclusion is based principally upon the fact that procaine appears to have little abuse liability in humans despite fairly easy access. There is even reason to believe that the drug using subculture has had experience with intravenous procaine since it is commonly misrepresented as cocaine or mixed with cocaine sold in street samples.

Intravenous self-administration studies using monkeys and rats have shown a good correlation between a drug's ability to act as a reinforcer in animals and its abuse by humans. This correlation has led to the use of self-administration procedures in the preclinical assessment of drug abuse liability [25,26]. Procaine appears to be an exception to this correlation. This suggests that additional research be carried out to assess the reasons for this discrepancy. Some of the questions which this study raises include the following:

(1) Is procaine devoid of reinforcement efficacy in man? Only the general recognition that procaine is subject to little abuse bears upon this question. Experimental studies of the abuse potential of procaine in man have not been carried out.

(2) Is the reinforcing efficacy of procaine related to its metabolism? Procaine is metabolized very rapidly in man. This occurs principally in the blood by plasma esterases (perhaps cholinesterase) and one of the products of procaine metabolism is diethylaminoethanol [10]. The rapid hydrolysis of procaine results in an extremely short duration of action, consequently, effective concentrations may only be reached under conditions such as were present in these experiments in which repeated injections (spaced as close as 8 sec apart) could result in accumulation. Repeated small injections would not be likely to occur in a human use situation. An alternative possibility is that the reinforcing efficacy of procaine lies in its metabolite diethylaminoethanol which bears a marked structural similarity to the central nervous system stimulant dimethylaminoethanol. The conversion into an alcohol is true only of the local anesthetics with an esteratic linkage (e.g. procaine, proparacaine, tetracaine); the others are principally dealkylated (e.g. lidocaine), and have a longer duration of action [10]. Studies comparing the reinforcing efficacy of various local anesthetics as well as studies of their metabolic products would help to answer some of these questions.

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