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Cocaine-base smoking in rhesus monkeys: reinforcing and physiological effects

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Abstract. Four rhesus monkeys were trained to smoke cocaine-base under a progressive ratio (PR) schedule, with ten smoking trials available each day. Unit dose was varied from 0.25 to 3 mg/kg, and lidocaine (2 mg/kg) was substituted for cocaine. Number of responses and breakpoint on the PR schedule increased with dose while the number of smoke deliveries increased only slightly. Maximum daily smoke deliveries ranged from six to nine across monkeys. When lidocaine (2 mg/kg) was substituted for cocaine-base, responding decreased to approximately half of that maintained by cocaine, and when cocaine was reinstated, higher response rates returned. Cardiovascular changes associated with cocaine smoking were monitored with an indwelling radio transmitter. There was an initial decrease in heart rate (30 s) followed by a rapid rise and decline by the end of the 15-min trials. Blood pressure increased rapidly after trial onset and returned to pretrial baseline by 15 min. Over the eight trials completed during a session, heart rate and blood pressure steadily increased over presession baselines during the first four trials, but there was then a decline suggesting acute tolerance development. Observations of the monkeys after each trial revealed dilated pupils and slightly agitated, hyperactive behavior. These findings indicated that smoked cocaine-base was rapidly established as a reinforcer for monkeys, and the physiological effects were similar to those reported in studies of human subjects.

Key words: Cardiovascular effects – Cocaine-base – Monkeys – Self-administration – Smoking

Frequent cocaine use (weekly) increased by 33% from 1985 to 1988 (USPHS 1988) due in part to the use of smoked cocaine-base (crack) which has increased from 1 to 17% over the last 11 years. The increased use of smoked cocaine-base (crack) among cocaine users has been attributed to the immediacy of the effects and the lower costs of purchasing this form of the drug. Most of the animal (Johanson 1984; Woods et al. 1987) and human (Fischman 1984, 1988) cocaine research has employed the intravenous and intranasal routes of administration. There has been only one published study of cocaine-base smoking in monkeys (Siegel et al. 1976), and there are only two studies of cocaine-base smoking in humans. In one of these studies human subjects smoked coca paste (Paly et al. 1982). Controlled doses were not presented, since individuals had different smoking topographies. In the other study cocaine base was smoked through a specially designed glass pipe (Perez-Reyes et al. 1982); however, the investigators indicated that only 32% of the cocaine was inhaled. In addition, the cocaine may have been volatilized at such high temperatures that the cocaine molecule was broken down (Cook et al. 1985).

The purpose of the present experiment was to establish a primate model of cocaine base smoking. Smoking studies have been attempted with monkeys using tobacco (Jarvik 1967; Pybus et al. 1969; Ando and Yanagita 1981; Rogers et al. 1985), cannabis (Pickens et al. 1973) and DMT (Siegel and Jarvik 1980). However, for most of the animals in these studies the smoking behavior was not maintained by the reinforcing effects of the drugs, but by contingent delivery of water or food rewards. In many cases, control procedures that would demonstrate the reinforcing effects of the drug were omitted. Attempts were made in the present experiment to circumvent some of the technical difficulties encountered in the earlier human and animal studies, by developing a system to deliver precise quantities of cocaine and a training procedure that would maintain smoking behavior as its own reward.

The approach used in the present study was to apply methods that have been successful for rapidly establishing orally-delivered drugs as reinforcers for rhesus monkeys (Meisch and Carroll 1987; Caroll et al. 1990) to obtain smoking behavior. Additional objectives

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were to compare cocaine-base smoking across a wide range of doses and to a lidocaine placebo and to obtain measures of physiological changes during and after the smoking trials.

Materials and methods

Subjects Four male rhesus monkeys *(Macaca mulatta)* served as subjects. Three of the monkeys (M–S, M–V, and M–L) weighed 9 kg and M–O weighed 10 kg. Two monkeys (M–O and M–V) had experience with self-administration of orally-delivered phencyclidine and M–S and M–L were previously involved in a cocaine IV self-administration experiment in another laboratory. All monkeys were given free access to water, and they were maintained at 85% of their free-feeding body weight. This restricted feeding regimen was used because it was anticipated that cocaine self-administration would reduce food intake. This variable was controlled by reducing feeding by a fixed amount across subjects.

One subject, M–O was surgically implanted with a telemetry device (Data Sciences Inc., Roseville, MN) which transmitted physiological data about heart rate, diastolic blood pressure, and systolic blood pressure. A small probe was implanted into a branch of the femoral artery on the monkey's left side, and a transmitter was located subcutaneously on his left side above the hip. The implant procedure was considered minor surgery, and within 5 days of surgery the monkey's smoking performance returned to baseline levels.

Apparatus. The subjects were housed in stainless steel chambers (Hoeltge HD–108) equipped with work panels on one of the side walls. The panels had a solid green stimulus light to indicate water availability, a flashing (10 Hz) red light to designate the lever pressing contingency, and a flashing green light to indicate the availability of smoke deliveries. Solenoid valve spouts mounted on the left side of the panel regulated water deliveries at 0.55 ml. The spouts were mounted on clear Plexiglas plates that had two small lights directly behind them which were illuminated when lip contacts were made on the spout. A smoking tube similar in shape to the drinking spout was mounted on the right side of the panel at the same height as the water spout. The smoking apparatus delivered volatilized cocaine-base to a monkey at doses up to 30 mg. This apparatus was a modification of a liquid drinking device previously described (Meisch and Henningfield 1977). This apparatus achieved the objective of delivering an accurate dose of cocaine base. Cocaine-base was dissolved in 95% ethanol (100 mg/ml) and stored in an airtight flask with a vacutainer top. Accurately measured amounts of this mixture were removed from the flask by a 1 ml syringe and deposited on a small coil of nichrome wire fastened to a fixture. The ethanol was allowed to evaporate for at least 24 h, leaving the cocaine base on the wire. The wires were weighed before and after coating and drying to verify that the exact dose had been placed on the wire. This fixture can be quickly and easily replaced allowing a succession of doses to be delivered to the animal. A set of these fixtures was prepared the day before for each session. The coil was inserted within the spout in close proximity to the monkey (but not so close that the monkey could touch the wire). A short air path to the monkey lessened the amount of cocaine base deposited on the wall of the apparatus rather than delivered to the monkey. This also lowered the transit time. The coil was heated with a short, high power pulse. This vaporized the cocaine-base without pyrolizing it. The coil was heated after the monkey was inhaling, ensuring that the smoke was entrained in the air stream rather than deposited on the wall.

The apparatus, shown in Fig. 1, consisted of a face plate with a chamber, a vacuum sensing switch, a spout, a heater fixture which carried the cocaine-base, a control housing with the stimulus lights, a contact sensor, and a relay that controlled a transformer that supplied the power for vaporizing the cocaine-base. The spout was made of a stainless steel tube 3.6 cm long with a 1.5 cm outer

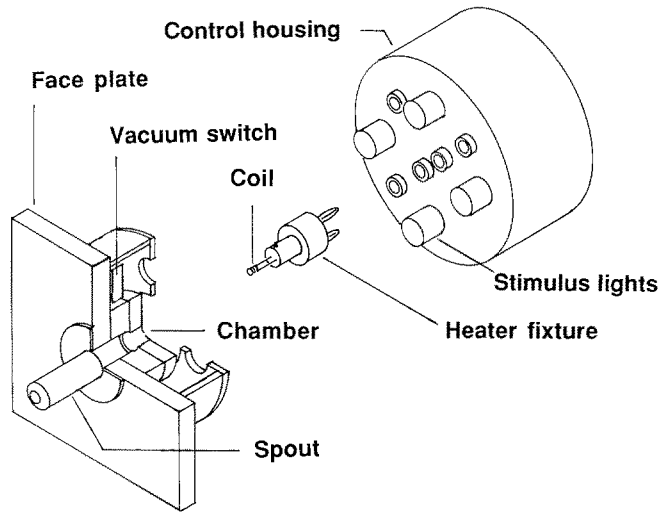

Fig. 1. Schematic of the smoking apparatus. The spout is where sucking or puffing responses are made. The coil is the area where a fixed dose of cocaine dissolved in ethanol (95%) is placed, and the ethanol is allowed to evaporate. The stimulus lights and control housing are mounted behind a clear Plexiglas plate (not shown) on the outside of the cage

diameter and a 1.2 cm inner diameter. The rounded tip had a 0.6 cm diameter hole which prevented the monkey from inserting its finger into the tube. In addition, a vertical bar was mounted across the tip of the spout to prevent the monkey from placing its tongue in the spout. The chamber fastened to the face plate just behind the spout, providing a mounting place for the vacuum switch and the heater fixture. The vacuum switch (Coventry Specialty Corp., Westfield, MA, model 505–3) was mounted on the upper part of the chamber. An air inlet hole 0.34 cm in diameter was drilled in the lower part of the chamber. The heater fixture was a machined Delrin plug with two pieces of brass tubing (0.15 cm OD × 5.5 cm in length) passing parallel through it. On the internal side, the brass tubes were crimped to a coil with a 0.3 cm inner diameter that consisted of nine turns of #24 Nichrome wire. The length of the wire was 17 cm. The coil stood off from the brass tubes about 0.6 cm. On the external side, the tubes were bent over and then around the two banana plug studs providing electrical connection between the coil and the transformer.

Before the trial, the heater fixture was inserted into the back of the chamber and given an eighth turn which held it in place. The control assembly was then mounted on the back of the face plate. The three outer banana jacks mated with three plugs on the face plate, while the inner jacks mated with the heater fixture. The transformer used to heat the coil was a Stancor RT–204, connected to provide 8 amp. Sucking on the spout activated a vacuum switch which sent a signal to the microcomputer control system used to control the experiment. The activation pressure was 1.0–2.0 in water. To register the puff the monkey was required to maintain the vacuum for a time determined by the experimenter. Values used in this experiment were 0.15–0.2 s. Five puffs or sucking responses (FR 5) were required to heat the wire. The program automatically switched to a puff time of 0.02 s on the last puff of the FR in order that the cocaine base was vaporized at the beginning of the monkey's puff rather than toward the end. Microcomputers (Micro Interfaces Inc.) located in an adjacent room controlled sessions and recorded data. In addition, lever pressing behaviors and cocaine deliveries were recorded on cumulative recorders (Ralph Gerbrands Co). There are prior descriptions of cages (Henningfield and Meisch 1976), drinking spouts (Meisch and Henningfield 1977), and microcomputers (Carroll et al. 1981). A complete description of a similar smoking apparatus that is used for human subjects was recently reported by Hatsukami and colleagues (1990), including results of

a test with tritiated cocaine base to determine the amount of cocaine base left in the apparatus after volatilization. Their results showed that at least 95% of the drug was delivered to the subject.

The transmitter signals were sent to a receiver mounted on the door of the monkey's chamber. The receiver was connected to an IBM PC AT used to store and analyze data. The software package used was Dataquest III (Data Sciences, Inc., Roseville, MN). The system sampled continuously and averaged values into intervals specified by the experimenter. A 30-s interval was used in this experiment. The telemetry system was synchronized with the microcomputer control systems so that the physiological data could be examined just prior to and immediately after cocaine deliveries.

Procedure. Subjects were first trained to perform licking responses on brass drinking tubes under concurrent FR 16 schedules for phencyclidine and water according to procedures that have been previously described (Carroll 1982). Next, the monkeys were trained to make sucking responses on the smoking tube. These responses resulted the burning of 1 mg/kg cocaine, and the smoke exited through the tip of the smoking tube. During initial acquisition, only lip contact behaviors were required for a smoke delivery. Subjects quickly learned to suck or inhale on the smoking tube. Once the subjects had learned to suck on the smoking tube for cocaine reinforcement, a lever press requirement was added. Following acquisition of this chained schedule, lever pressing and inhaling requirements were gradually increased. The inhalation response requirement was rapidly increased to five puffs, the maximum requirement. To aid the acquisition of lever pressing behavior, a brief stimulus (1 s illumination of the green light over the smoking tube) was introduced during the lever component according to a second order schedule FR (FR:S). Initially, the brief stimulus occurred after five lever presses of the necessary ten lever press response schedule FR 10 (FR 5:S). Subsequently, both response requirements and second order stimulus values were increased systematically (see Table 1).

There was a 1-h timeout starting at 7:30 a.m. each day. During this time water volumes for the previous day were recorded and fresh water was added for the session. Also, system checks and repairs, if necessary, were carried out during this time. Finally, the cocaine coils were weighed (to check quantity) and loaded into smoking tubes for the first trial of the session. Beginning at 8:30 a.m., consecutive trials were run restricting deliveries to a maximum number of ten per session. A trial consisted of a 30-min opportunity to finish the schedule requirements. Completed trials were followed by a 15-min timeout, but aborted trials were restarted immediately. Two consecutive aborted trials ended the session for the day. Each trial following a completed trial required a newly prepared coil to be loaded by the experimenter into the smoking tube during the previous timeout. The room was entered when subjects were in timeout or when there was a pause in responding. Following the end of the session, coils were prepaped for the next day. Subjects were fed at 1:00 p.m. each day.

Table 1. Training procedure: 10 trial/smoke limit; 15-min timeout after smoke delivery

Lever response FR	Brief stimulus FR (light over smoking tube)	Inhalation response FR
0	–	1
5	–	1
10	5	5
20	5	5
40	10	5
80	10	5
80	20	5
80	40	5
80	–	5

When behavior had stabilized at FR 80 with no brief stimuli, a progressive-ratio (PR) schedule was used. The PR schedule began at 20 lever presses and doubled after each completed trial during the session. Upon reaching the 1280 lever press requirement, the schedule increased to 2400 lever presses and then progressed at constant increases of 1200 lever presses thereafter. This schedule was chosen to be comparable to that used with previous cocaine IV self-administration in baboons (Griffiths et al. 1979), although in that experiment PR values were increased daily rather than after each trial. Once behavior had stabilized under the PR schedule, a dose-response curve was obtained. The following cocaine doses were tested in nonsystematic order across monkeys: 0.5 mg/kg, 1 mg/kg, 2 mg/kg, and 3 mg/kg. Two monkeys were also tested with a 0.25 mg/kg dose. Lidocaine was administered at the 2 mg/kg dose to insure that a comparable amount of smoke would be presented. Lidocaine was chosen as a control for cocaine because of its similar local anesthetic qualities to cocaine. Lidocaine has previously been used for control purposes with cocaine studies in humans (Fischman et al. 1983; Jaffe et al. 1989). Dependent variables included number of lever presses, licking and sucking behaviors on the smoking tube, and number of water deliveries. These categories were subdivided into intratrial, intertrial, and intersession periods. During the intrasession component, trial length, latency to first response and number of smoke deliveries were also collected.

During most trials the monkeys began responding immediately at the start of a trial; however, behavioral observations revealed that occasionally the subjects responded together or in close temporal proximity to each other. That is, sometimes one or more subjects delayed initiating responding, but they began responding when one or more other subjects started to lever press. The fact that the microcomputers recorded events in real time allowed for an analysis of the instances when two or more monkeys began responding contiguously in time. Two sets of data were compiled; one in which subjects delayed in responding and were apparently cued by another monkey to begin responding within a 3-min period, and one where subjects delayed responding and began lever pressing when no other monkeys had initiated responding (noncued). A delay in responding was arbitrarily defined as 3 min after trial onset, which is signaled by a red light over the lever.

The cardiovascular monitoring device was implanted in only one monkey, due to the expense and to the fact that while these devices had been widely used in rats, they had not yet been extensively tested on monkeys. The monkey's behavior was allowed to stabilize for at least 10 days after implantation surgery before physiological data were collected for analysis. By comparing the physiological measures obtained by this device after cocaine smoking to pretrial baseline and to the same interval after lidocaine smoking, it was possible to verify inhalation of the cocaine base.

Blood samples were drawn from M–O immediately after the session for cocaine blood level analysis. The test days for blood levels were chosen on the basis of similarity to previous days when behavior (smoke deliveries) had stabilized. That is, once M–O's behavior had stabilized, the next day's session was allowed to continue until M–O took as many deliveries as during the prior period of stable behavior. Immediately following his last delivery (usually the eighth delivery), M–O was given an injection of Ketalar (0.1 ml/kg IM) and removed from the operant chamber to an adjacent room. Blood samples (3 ml) were taken at 5, 10, 15, and 30 min after smoking.

Results

Figure 2 shows the dose effect functions for the four monkeys. All doses of cocaine (0.25–3 mg/kg) maintained responding at higher rates than did lidocaine at the dose tested (2 mg/kg). Total responses generally increased as unit dose increased, with the exception of M–V who showed a decrease in responding at the

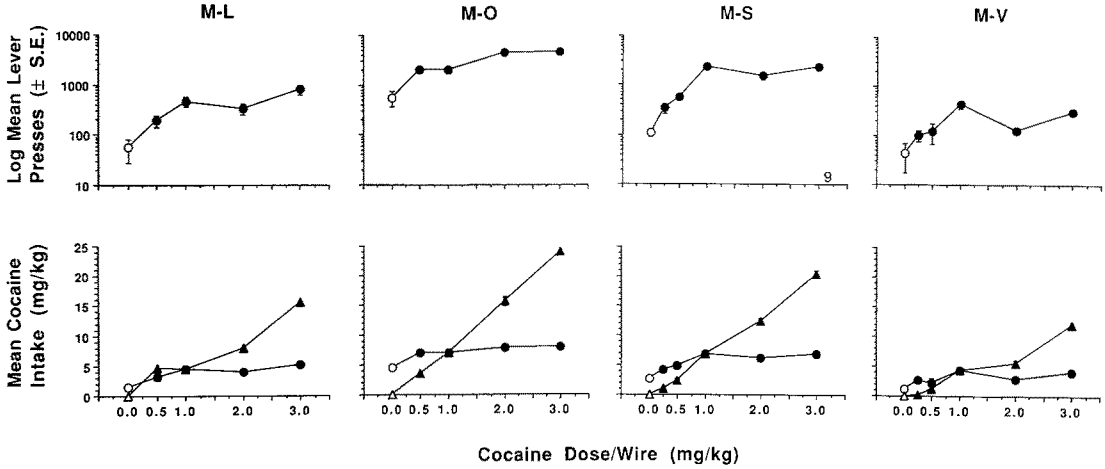

Fig. 2. Mean (±SE) total lever presses per session under the progressive ratio schedule smoke deliveries and cocaine intake (mg/kg) are presented on a log scale as a function of cocaine unit dose (0.25–3 mg/kg) for the four monkeys (*filled symbols*) and lidocaine at the 2 mg/kg unit dose (*open circles*). Each point represents the last 5 days of stable behavior at each dose. —●— Smoke deliveries; —▲— total cocaine delivered (mg/kg)

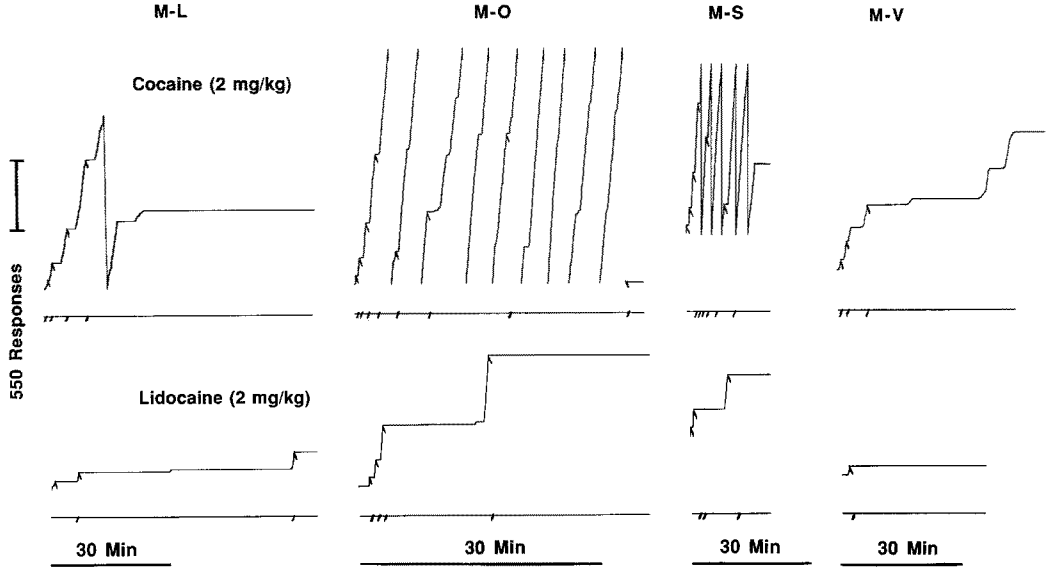

Fig. 3. Representative cumulative response records are presented for each of the four monkeys, M–L, M–O, M–S and M–V, during exposure to 2 mg/kg unit doses of cocaine (*upper record*) and lidocaine (*lower record*). Records were selected as those with the total number of smoke deliveries closest to that animal's mean for the dose. The time represented along the x-axis is represented by a horizontal line marking 30 min. Note that M–O's recorder ran at twice the speed of the other monkeys' recorders, and that the recorders did not move during the 15-min timeout after each smoke delivery. The stepping pen marked lever presses and downward deflections of the stepping pen represented smoke deliveries. The event pen also recorded smoke deliveries

2 mg/kg dose. The greatest increase occurred between the 0.25 or 0.5 and the 1.0 mg/kg doses, and responding was relatively stable at the three highest doses (1, 2 and 3 mg/kg). The number of smoke deliveries was approximately the same at the three higher unit doses, and deliveries ranged from four to nine out of a possible ten. Smoke deliveries declined at the 0.5 and 0.25 mg/kg doses. Total session cocaine intake (mg/kg) increased steadily with increases in unit dose.

In Fig. 3 cumulative response records are presented for each monkey under conditions when the 2 mg/kg cocaine dose and lidocaine (2 mg/kg) were available. Records were selected as those with the number of smoke deliveries closest to the mean delivered per session for that dose. Generally, cocaine-maintained responding under the PR schedule began immediately at trial onset and proceeded at a high rate. Three of the four monkeys reached their break-point during the first 60–90 min of the 3-h session; however, M–O usually completed his eighth trial during the third hour. Responding maintained by lidocaine also began immediately at the start of each session, but it was later characterized by pauses in responding during the trials. Lidocaine-maintained responding had usually stopped by the end of the first hour.

Analysis of a 5-min blood sample on monkey M–O

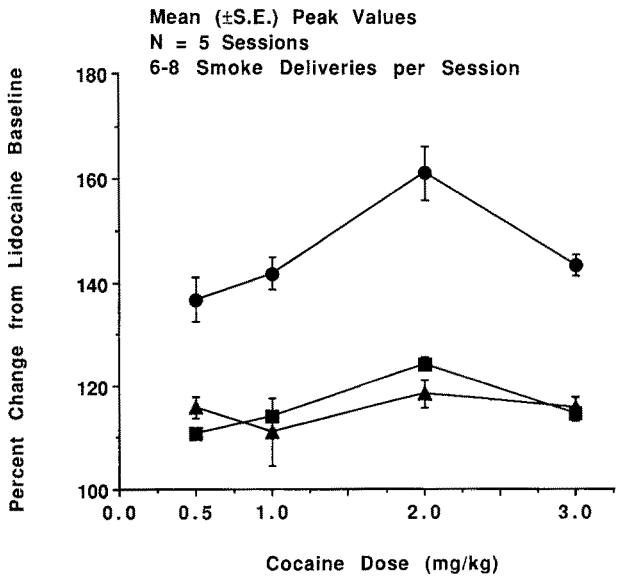

Fig. 4. Mean (± SE) peak values for heart rate and blood pressure are expressed as a per cent of values obtained during lidocaine (2 mg/kg) exposure as a function of cocaine-unit dose (0.5–3 mg/kg) for monkey M–O. Each point represents a mean (± SE) of the peak value (over the 6–8 trials/day) for the last 5 days of stable behavior at each condition. The lidocaine values were from the first five sessions of lidocaine exposure. The mean peak values for lidocaine were 130.3 bpm for heart rate, 118.7 mmHg for systolic and 78.6 mmHg for diastolic blood pressure. —●— Heart rate (bpm); —▲— systolic (mmHg); —■— diastolic (mmHg)

revealed a cocaine level of 124.7 ng/ml after the eight trial with a cocaine dose of 2 mg/kg. The 10, 15 and 30 min samples were 170.9, 130.3 and 102.6 ng/ml, respectively. The cardiovascular changes associated with cocaine smoking are summarized in Fig. 4. Mean peak heart rate, systolic and diastolic blood pressure were derived from the highest rates found during each of the last five sessions at each dose. These values are expressed as per cents of the mean peak values obtained with 2 mg/kg lidocaine. Eight trials were completed by this monkey at each dose, except for lidocaine when only six or seven trials were completed during the first five sessions. The mean for lidocaine sessions represents the first five sessions. Since lidocaine deliveries eventually diminished to 0, 1 or 2, the first 5 days were used to provide an accurate representation of the effects of lidocaine on cardiovascular functions. The results in Fig. 4 show a 37–60% increase (over values obtained with 2 mg/kg lidocaine) in peak heart rate across cocaine doses, with the 2 mg/kg cocaine dose producing the largest increase. Systolic and diastolic pressure were 10–20% higher during cocaine exposure compared to when lidocaine was smoked; however, there were no consistent differences across cocaine unit doses. It was not possible to present a no-drug comparison, as behavior extinguished after one trial when no drug was available. Data presented in Fig. 5 for lidocaine show physiological measures for a brief (2 min) drug-free period before the first daily trial.

In Fig. 5 mean heart rate and blood pressure during eight trials over the last five sessions at each dose are compared to the first five sessions of lidocaine exposure

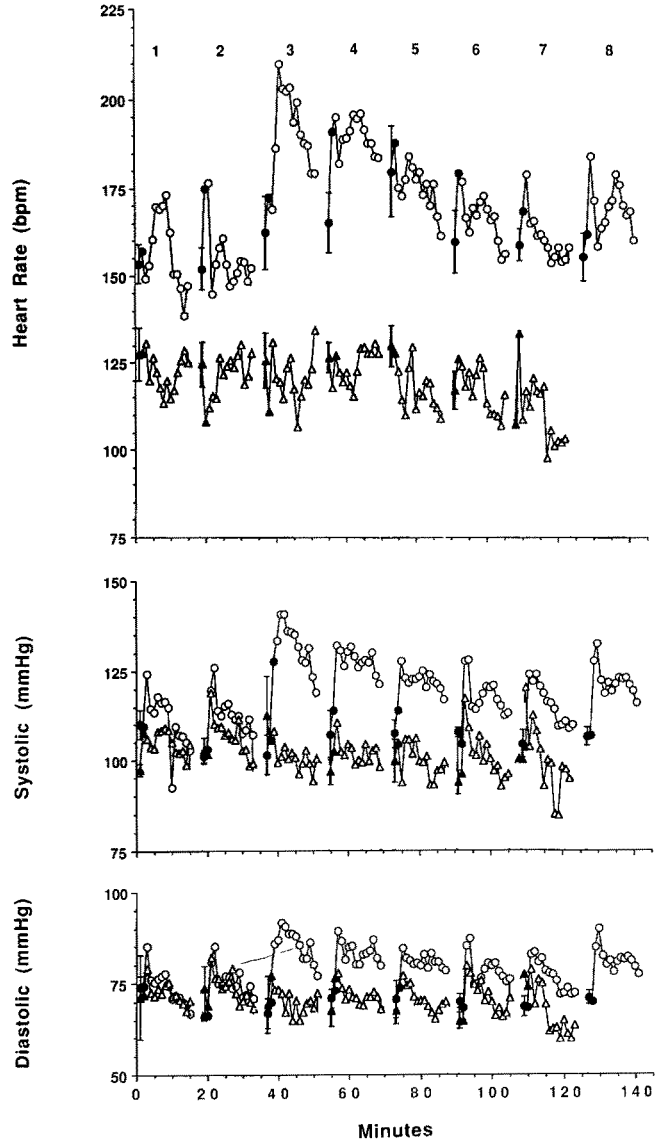

Fig. 5. Heart rate (bpm), systolic (mmHg) and diastolic (mmHg) blood pressure are presented in the upper, middle and lower frames, respectively, as a function of daily trials (6–8). Each point is a mean of five sessions, and vertical bars represent 2 SEs. *Circles* refer to the last five sessions at the 2 mg/kg cocaine dose, and *triangles* represent the first five sessions of lidocaine exposure. Each trial (indicated by the numbers within the frame) was divided into 1-min segments. The two *filled symbols* represent the last 2 min before the smoke delivery, and the *open symbols* show 13 min after smoke delivery. —○— Cocaine (2 mg/kg); —△— lidocaine (2 mg/kg)

(seven trials). A seventh trial was completed only on the first day of lidocaine exposure, and six trials were completed on the other 4 days. Thus, the apparant decrease in heart rate during the seventh trial may have been within the normal range of variability, or in fact a decrease explained by the extinction of responding. After lidocaine smoking there were no consistent increases in heart rate, and values obtained at 1-min intervals ranged from 105 to 135 beats per minute (b.p.m). The first trial presmoking baseline measures were slightly higher for cocaine than lidocaine. This may be due to the fact that the lidocaine mean represents the first 5 days while the

cocaine mean represents the last 5 days of stable responding. A history of cocaine-base smoking may have generated anticipatory physiological responses. After cocaine smoking, during the first trial, heart rate increased toward the middle of the trial. The subsequent within-trial changes in heart rate differed from trial to trial but generally, heart rate returned to pretrial (but not to presession) baseline by the end of the 15-min trial. This general within-trial pattern was consistent across the remaining seven trials. The peak heart rate after cocaine-base smoking continued to rise until the third (0.5 and 1.0 mg/kg doses) or fourth (2 and 3 mg/kg doses) trial and then there was a gradual decline in peak heart rate to levels of the second cocaine trial but not to presession baseline. This pattern of increased and then decreased heart rate across the eight trials did not appear to be due to the varying demands of the PR schedule, because an identical pattern was obtained in a preliminary experiment with an FR 160 schedule in monkey M–O that was tested with this schedule after the FR 80.

Systolic and diastolic blood pressure showed a consistent intertrial pattern across all cocaine doses. In Fig. 5 the 2 mg/kg cocaine dose is given as an example and compared to the 2 mg/kg lidocaine dose. There was typically a rapid rise in both systolic and diastolic pressure that occurred within the first minute after smoking, and it continued to rise and peak during the second and third minute. In the third or fourth minute there was a decline over the remainder of the 15-min trial. Blood pressure occasionally returned to presession values. The effects of lidocaine on blood pressure were minimal. During some trials there was a rise in blood pressure during the first minute, followed by a rapid decline to presession and pretrial levels. On other trials there was no measurable change due to lidocaine smoking.

An inspection of individual records for each trial revealed that during the first 30 s after smoke exposure there was a rapid decline in heart rate, followed by an increase that lasted for approximately 6–8 min and then a return to baseline by the end of the 15-min trial. Systolic and diastolic blood pressure (mmHg) characteristically increased immediately after smoking, followed by a brief decline when heart rate began to increase and then a more sustained increase (7–8 min) followed by a return to baseline by the end of the 15 min trial. Similar relationships between heart rate and blood pressure changes were found with lidocaine during the first few minutes of the smoke trial; however, there were no sustained increases in these measures over the 15 min trial, and the baseline heart rate and blood pressure measures were lower during lidocaine exposure.

Behavioral observations indicated that monkey M–V became very agitated and excitable when smoking cocaine. M–V's state became more severe and incidents of self-mutilation behavior occurred, specifically biting the upper leg area. At the end of the study, M–V's access to cocaine was terminated because of bleeding in the nose and, respiratory problems. His condition significantly improved over the course of 2–3 weeks after the study was terminated. Another subject, M–S, intensely groomed and picked at himself in a non-injurious manner. Generally during the daily sessions, the subjects sat quietly; however, they showed some hyperactivity and increased agitation immediately after obtaining their cocaine deliveries. Behavioral observations after lidocaine exposure revealed no changes from presession behavior. Although it has been noted that lidocaine can cause sleepiness (Stecher 1968), this was not observed under these dose and testing conditions. The 3 h daily access to cocaine or lidocaine smoking did not reduce the monkeys' food intake below the allotted amount necessary to maintain their weights at 85% of free-feeding. After this experiment when the monkeys were allowed free access to food, their food intake was comparable to that of monkeys not self-administrating cocaine-base. Other than the temporary problem with M–V, the monkeys remained in excellent health throughout the experiment (approximately 1 year).

One observation regarding the monkeys' smoking behavior was that occasionally the initiation of responding appeared to be cued by responding of other monkeys. During most of the trials the monkeys began responding immediately at trial onset and continued until a smoke delivery was obtained; however, occasionally, a monkey did not respond immediately at trial onset and began

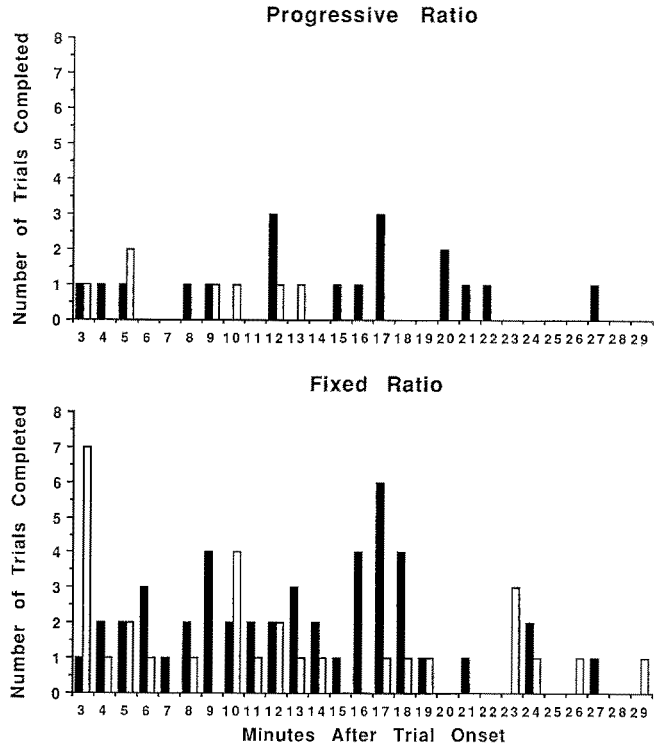

Fig. 6. The total number of trials completed for four monkeys over ten consecutive days were distributed on the basis of the number of minutes after trial onset that responding (leading to trial completion or a smoke delivery) was initiated. These data were collected during the training period when an FR 80 schedule *(lower frame)* was used and later after performance stabilized under the progressive ratio schedule *(upper frame)*. A delay in responding was defined as a period of 3 min or more between trial onset and responding. A cued trial was defined as responding that was initiated by a monkey after the 3-min delay from trial onset and within 3 min of when another monkey began responding. The *filled* bars represent the number of cued trials and *open* bars refer to noncued trials. ■ Cued trials; □ noncued trials

only when another monkey initiated a trial. The four monkeys were housed in the same room facing each other, and trial onset time was not synchronized across monkeys; it was dependent upon the monkey's behavior. In order to test the hypothesis that delayed (defined as > 3 min after trial onset) initiation of responding during trials was cued by responding during trial onset of another monkey, all late trials for all monkeys were analyzed for a 10-day period during the training phase when the monkeys were responding under an FR schedule and later during a 10-day period when the PR schedule was in effect. Figure 6 shows that there were many more late trials (44 versus 27) during the training phase (FR) than during the PR phase; however, this may have been due to a greater probability of synchronization of trials under the FR schedule. A comparison of cued and noncued late trials indicated that 30 of the 46 trials (65%) were cued during the FR schedule while 17 of the 24 trials (72%) were cued when a PR schedule was in effect. There was a relatively even distribution across monkeys with respect to the total number of late trials, total number of cued trials and the number of occasions a specific monkey's responding at trial onset appeared to cue another monkey. Almost all of the cued responding occurred within 1 min of the time that another monkey initiated responding.

Discussion

Cocaine-base smoking was rapidly established in four rhesus monkeys. All of the monkeys had a history of lip-contact responding on a similar device for orally-delivered PCP and water under concurrent FR 16 schedules. The training procedure was further accelerated in two monkeys (M–L and M–S) that also had a history of IV cocaine self-administration. Cocaine smoking behavior was established within the first session for these monkeys compared with several weeks with the cocaine-naive monkeys. In all four monkeys it was cleary demonstrated that smoked cocaine-base was functioning as a reinforcer, as lidocaine (2 mg/kg) did not maintain responding at levels comparable to those maintained by several doses of cocaine base. The total session dose (2–24 mg/kg) that maintained responding over a unit dose range of 1–3 mg/kg in these monkeys was comparable to that reported by Siegel and colleagues (1976) from interviews with human cocaine-base users (4–7 mg/kg over an average 4-h period). The dose-response function obtained with the PR schedule was similar to that reported by Griffiths and coworkers (1979) with intravenously-delivered cocaine HCl in baboons. Responding and cocaine intake (mg/kg) increased with unit dose. In the earlier study a similar progressive ratio sequence was used except the ratio value was changed each day rather than with each trial as it was in the present experiment. However, the range of break points across animals was similar in the previous (Griffiths et al. 1979) and present experiment at the 1 mg/kg dose and results were comparable at the 0.4 and 0.5 mg/kg doses across the two studies.

The self-administration data obtained in this experiment also concur with results of an earlier experiment by Siegel and colleagues (1976). They trained monkeys to puff on lettuce cigarettes loaded with three 10 mg plugs of cocaine base, a total dose that was similar to that given to the monkeys in the present study at the 3 mg/kg unit dose. Although their experimental design allowed the monkeys to receive up to 30 smoke deliveries per session, the average number of cigarettes smoked was 7.28 across monkeys and conditions, which was comparable to the mean of 5.5 deliveries obtained at the 3 mg/kg dose in the present study.

The cardiovascular changes reported in this experiment indicate that cocaine was absorbed; however, there is not unequivocal verification that absorption was by the lungs or oral and nasal mucosa. A comparison of heart rate and blood pressure measures during cocaine and lidocaine smoking revealed substantially higher values for cocaine than lidocaine. A small rise in blood pressure during the first minute of some lidocaine trials may have been attributed to the inhalation behavior, to the direct effects of lidocaine or to a combination of effects. On some of the cocaine trials there was an increase in heart rate during the minute prior to the inhalation of cocaine. This may have been a conditioned anticipatory response to cocaine, as it extinguished rapidly when lidocaine replaced cocaine. Blood levels obtained in the present experiment also verify that cocaine-base was absorbed, and levels were comparable to those reported in human subjects after a 20 mg exposure to cocaine-base smoke using an identical delivery system (Hatsukami et al. 1990). The mean increase in peak heart rate in the human subjects that smoked 20 mg cocaine-base was 19.5 bpm and it was 18 bpm after the first 20 mg dose in the monkey. Mean increase in peak systolic pressure was 17.7 in the human subjects compared to 15 for the monkey. The mean peak blood level after a 20 mg dose in human subjects was 110 ng/ml, and it was 170 ng/ml in the monkey after the eighth 20 mg dose. Thus, the animal model provides a close representation of the physiological effects of cocaine-base smoking in humans.

The cardiovascular data obtained in the present experiment after the first cocaine delivery of the session were also comparable to those obtained in human subjects when cocaine and lidocaine were administered by IV injection (Fischman et al. 1976, 1983; Resnick et al. 1977). Peak heart rate increases in human volunteers increased by 26 bpm at the 48 mg dose (0.6 mg/kg), which was comparable to a peak heart rate increase of 20 bpm in M–O at the 0.5 dose and 15 bpm at the 1 mg/kg dose in the present experiment. Similarly, lidocaine produced peak heart rate increases ranging from 6 to 9 bpm in human subjects (Fischman et al. 1983) and 5 bpm in the monkey, M–O. Blood pressure changes showed similar relationships between cocaine and lidocaine across human and animal studies.

Tolerance development to the cardiovascular effects of smoked cocaine-base was difficult to assess because of the daily variability in dosing regimen which was determined by the animal's performance on the PR schedule. The peak increases in heart rate (bpm) were generally reached within the first hour of the session, and these

measures declined and stabilized during the remainder of the session, while the monkey continued to earn smoke deliveries. The magnitude and time course of this apparent acute tolerance was very similar to that reported in human subjects receiving repeated IV deliveries of cocaine HCl over a 4-h period (Ambre et al. 1988).

In conclusion, the present results show that cocaine-base smoking can be reliably established in rhesus monkeys that have first been trained to self-administer orally-delivered drugs. The response rates and dose response curves were comparable to those obtained by others using the IV route of cocaine self-administration in nonhuman primates. Cardiovascular measures and/or blood analysis revealed that cocaine-base was absorbed by the monkeys, and that acute tolerance developed. These measures were consistent with those obtained from studies of smoked and IV cocaine use in human subjects. This animal model will be useful for pursuing research questions regarding the abuse of smoked cocaine-base.

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