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Self-Administration of Psychomotor Stimulant Drugs: The Effects of Unlimited Access[1]

CHRIS E. JOHANSON, ROBERT L. BALSTER[2] AND KATHRYN BONESE

The University of Chicago, Pritzker School of Medicine, Department of Psychiatry, 950 East 59th Street, Chicago, IL 60637

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JOHANSON, C. E., R. L. BALSTER AND K. BONESE. *Self-administration of psychomotor stimulant drugs: the effects of unlimited access.* PHARMAC. BIOCHEM. BEHAV. 4(1) 45–51, 1976. – Rhesus monkeys surgically prepared with intravenous catheters were given 23 hr daily access to injections of either cocaine, d-amphetamine, l-amphetamine, d-methamphetamine or diethylpropion on a fixed ratio 1 schedule of reinforcement for a maximum of 30 days. Responding was maintained by all these drugs but showed both day-to-day and hour-to-hour variability. The two animals self-administering 0.2 mg/kg/infusion cocaine died in less than 5 days. All 6 animals given access to 0.05 mg/kg/infusion d-amphetamine or 0.025 mg/kg/infusion d-methamphetamine also died, but tended to survive more days than animals exposed to cocaine. Three of the 5 animals whose responding was maintained by 0.5 mg/kg/infusion diethylpropion and one of the two animals whose responding was maintained by 0.05 mg/kg/infusion l-amphetamine survived the entire 30 days despite high rates of intake. Food intake was initially decreased, but often returned to predrug levels and was not related to level of drug intake.

Self-administration Rhesus monkeys d-Methamphetamine d-Amphetamine l-Amphetamine Cocaine Diethylpropion Unlimited access to psychomotor stimulants

ONE of the approaches which has been used to study the problems of drug abuse experimentally has utilized procedures involving the intravenous self-administration of drugs by infrahuman organisms. Animals will initiate and maintain lever press responding which is followed by an infusion of a wide variety of psychoactive drugs of abuse including opiates, barbiturates, alcohol and psychomotor stimulants (cf. [10]). Rate of responding is affected by such variables as the schedule of reinforcement, magnitude of reinforcement, level of drug deprivation or satiation, prior drug history and the duration of daily access [10]. With respect to the latter, it has been demonstrated that unlimited access to these drugs results in high intake which produces physical dependence and behavioral toxicity in the case of opiates, barbiturates and alcohol, and behavioral toxicity alone in the case of psychomotor stimulants [2]. In order to avoid these problems, most investigators have limited drug access to a few hours a day and employed schedules of reinforcement designed to reduce drug intake. In the case of psychomotor stimulants, reducing access to 3–4 hr/day results in stable rates of responding maintained by injections of cocaine, d-amphetamine, l-amphetamine, d-methamphetamine, and diethylpropion as well as other psychomotor stimulant drugs. Under these conditions, there were few observable signs of behavioral toxicity [1, 5, 12]. Rate of responding decreased as the dose per injection of each of these drugs was increased, resulting in relatively constant drug intake regardless of the unit dose [1, 5, 12].

Deneau *et al.* [2], in one of the few studies investigating the effects of unlimited access to psychomotor stimulant drugs, utilized rhesus monkeys fitted with harnesses and restraining arms and implanted with intravenous catheters to study the initiation and pattern of responding maintained by cocaine, d-amphetamine and caffeine infusions. They found that animals initiated and maintained responding for cocaine and d-amphetamine. Self-administration was cyclic with randomly alternating days of high and low intake and, in addition, the behavioral effects were characteristic of high dose amphetamine intoxication in monkeys [3,4] and man [7]. A similar pattern of d-amphetamine, d-methamphetamine and cocaine self-administration has been observed in the rat [8]. The study by Deneau *et al.* [2] showed that caffeine was less effective than the other stimulant drugs in initiating self-administration responding and the levels of intake did not produce any overt signs of drug effect or toxicity either during the period of access or when access was discontinued. Since an important defining component of the concept of the abuse potential of drugs is the toxic consequences of self- administration [2, 9, 10], it is important to study the effects of unlimited access to a wide variety of drugs. In the present study, the effects of continuous access to cocaine, d-amphetamine, l-am-

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[2] Now at the Department of Pharmacology, Medical College of Virginia, Richmond, Virginia 23298.

phetamine and d-methamphetamine were evaluated in order to confirm and extend the observations of Deneau *et al.* [2] on psychomotor stimulant self-administration. In addition, these results were compared to the effects of continuous access to diethylpropion (Tenuate®), a relatively new drug marketed for use as an anorexic agent. This drug has behavioral effects similar to other psychomotor stimulant drugs, but has not been extensively used non-medically [6,11].

METHOD

Animals

Twelve male and 3 female (A010, A013, and A021) rhesus monkeys weighing 4.1 to 5.7 kg with no prior experimental or drug histories were used. Each animal wore a stainless steel harness [2] connected to a flexible spring arm which was attached to the rear of the experimental cubicle [10]. After being adapted for 4–9 days to this semi-restraint, the animals, under pentobarbital anesthesia (30 mg/kg IV), were surgically prepared with indwelling venous catheters of siliconized rubber. The catheter was run subcutaneously and exited through the skin on the animal's back; it was then threaded through the harness and arm to the outside of the experimental cubicle where it connected to a peristaltic pump.

Apparatus

Each animal was housed in a sound-attenuated, wooden cubicle (1.3 × 1.3 × 1 m) that also served as the experimental environment. Two response levers and two stimulus lights were mounted on the front door of the cubicle. The entire ceiling of the cubicle was made of Plexiglas and could be transilluminated by either a red or white light.

The experimental cubicles were connected to electromechanical programming and recording equipment located in an adjacent room.

Procedure

After adaptation to restraint and catheterization, rate of saline self-administration (operant level of responding) was determined for 7–17 days for all animals except A021, A013 and A010. These three animals were given access to drug the day following catheterization. The white ceiling light and the stimulus light over the right lever (Lever 1) were illuminated 23 hr per day from 12:00 noon to 11:00 a.m. During this period, responses on Lever 1 resulted in an infusion of saline or drug. The infusion volume was 0.2 ml/kg and the infusion duration was approximately 10 sec. For those animals given access to diethylpropion where very large numbers of infusions were taken for several consecutive days, to restrict total fluid intake, the infusion duration was reduced to 5 sec, resulting in an infusion volume of 0.1 ml/kg. During infusions, the stimulus light and the white houselight were turned off and the red ceiling light was illuminated. Responses which occurred during the infusions and responses on the left lever (Lever 2) had no programmed consequence, but were recorded for all animals except A021, A013, A010 and 4034.

During the 23 hr session, each response on Lever 1 produced an infusion (fixed ratio 1; FR 1) except in the case of two animals where 10 responses were required for each infusion (FR 10). The response requirement for Animal A013 was increased to FR 10 on the first day of responding for methamphetamine in order to prevent overdosing within the first few hours of self-administration. The requirement for Animal A107 was raised to an FR 10 schedule of reinforcement in order to reduce the number of saline infusions during the predrug period.

From 11:00 a.m. until noon each day, the white ceiling light and the stimulus light were turned off and lever responding had no programmed consequence. During this time, the animals' food intake over the past 23 hr was determined by weighing the uneaten food in the food hopper and in the waste pan. The animals were then given their daily complement of food (Purina Monkey Chow) supplemented by a multiple vitamin preparation served on a sugar cube. Animals A010, A013 and A021 were given 125 g each day while the other animals were allowed to eat up to 200 g. Responses on each lever and the number of reinforcements obtained over the last 23 hr were recorded at this time.

Following the determination of operant rate of responding for saline infusions, the animals were given access to a psychomotor stimulant drug. Cocaine hydrochloride (0.2 mg/kg/infusion), l-amphetamine sulfate (0.05 mg/kg/infusion) and d-methamphetamine hydrochloride (0.025 mg/kg/infusion) were each tested in two animals. d-Amphetamine sulfate (0.05 mg/kg/infusion) was tested in 4 animals, and diethylpropion hydrochloride (0.5 mg/kg/infusion) was tested in 5 animals. All doses are calcualted from the salt. These doses are within a range which maintains response rates above saline operant level in a limited access substitution procedure [1, 5, 12]. The animals were given access to these drugs for 28–30 days or until they died or their physical condition indicated that death was imminent.

RESULTS

Figures 1–6 present the number of drug infusions, the total drug intake and the amount of food consumed by the animals on each day of access to cocaine (Fig. 1), d-amphetamine (Fig. 2), l-amphetamine (Fig. 3), d-methamphetamine (Fig. 4), and diethylpropion (Figs. 5 and 6). In addition, for those animals that had saline available prior to drug access, the mean number of saline infusions and mean food intake calculated from the last 3 days of exposure are shown.

Responding on the FR 1 schedule of cocaine reinforcement (0.2 mg/kg/infusion) was maintained above operant levels on the first day of access for both Animals 2164 and 3097 (Fig. 1). Although drug intake increased on subsequent days, a decrease in intake occurred on Days 4 and 5 for Animal 2164 and on Day 3 for Animal 3097. Food consumption decreased to less than 32 percent of baseline intake on Day 1, and by Day 3, neither animal ingested any food. Both animals were found comatose within 5 days of access and, despite attempts to revive them, both died within 24 hr. These attempts to maintain life included IV administration of 5 percent dextrose in Ringer's solution, artificial respiration and placing the animal on an electric pad to maintain body temperature.

A dose of 0.05 mg/kg/infusion of d-amphetamine maintained responding above operant levels by the second or third day of access for each animal tested (Fig. 2). Animal 4032 died after receiving 11.8 mg/kg of drug and

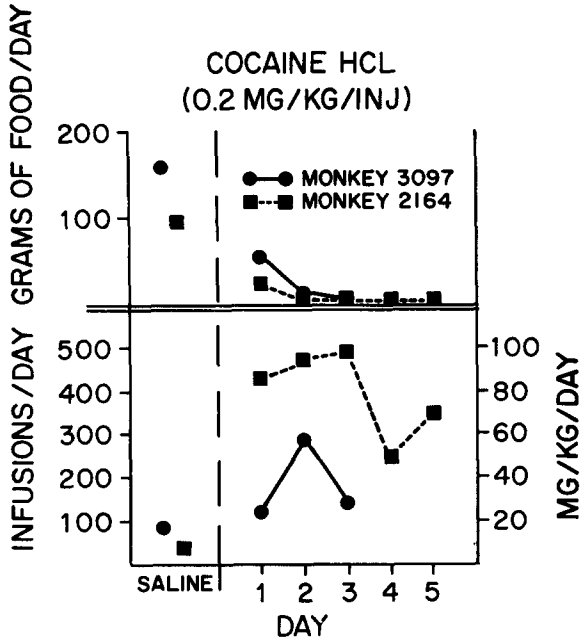

FIG. 1. Number of infusions and drug intake (bottom panel) and food intake (top panel) on each day of access to 0.2 mg/kg/infusion cocaine hydrochloride for Monkeys 3097 and 2164. Mean number of saline infusions and mean food intake for the 3 days prior to drug access are shown to the left of both panels.

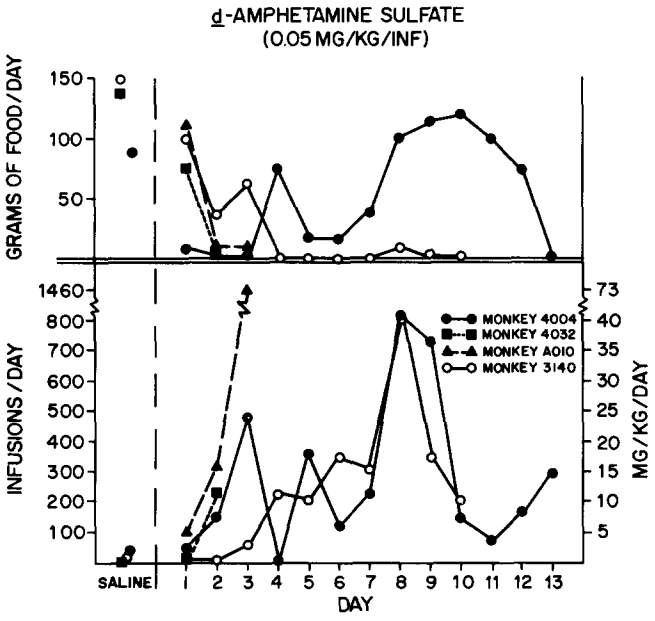

FIG. 2. Number of infusions and drug intake (bottom panel) and food intake (top panel) on each day of access to 0.05 mg/kg/infusion d-amphetamine sulfate for Monkeys 4004, 4032, A010 and 3140. Mean number of saline infusions and mean food intake for the 3 days prior to drug access are shown to the left of both panels for 3 of the monkeys.

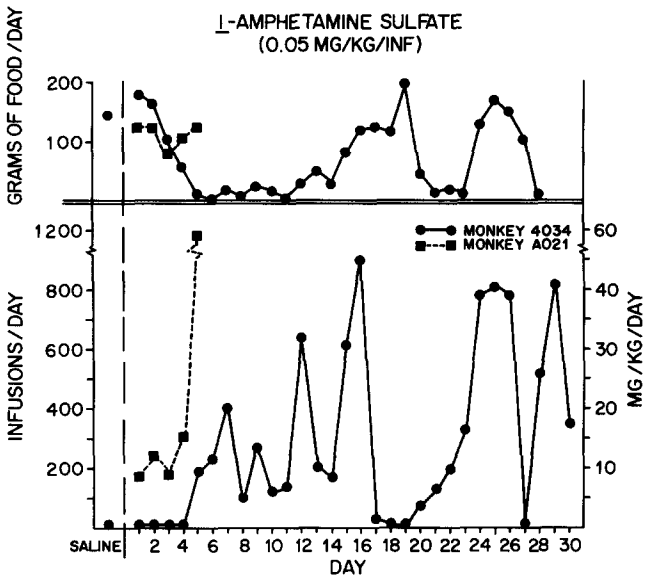

FIG. 3. Number of infusions and drug intake (bottom panel) and food intake (top panel) on each day of access to 0.05 mg/kg/infusion l-amphetamine sulfate for Monkeys 4034 and A021. Mean number of saline infusions and mean food intake for the 3 days prior to drug access are shown to the left of both panels for one of the monkeys.

consuming no food on the second day. Animal A010 increased her drug intake on each successive day of exposure and on the third day self-administered 72.6 mg/kg. On the fourth day of availability, this animal was comatose; attempts to revive her were successful. Animal 4004 survived a total of 13 days. Responding fluctuated considerably over the 13 day period with no apparent pattern. The maximum intake, 41 mg/kg, occurred on Day 8. Food consumption initially decreased, but by Day 8 has returned to predrug levels despite high levels of drug intake. However, 2 days prior to death, food intake again decreased. The data for Animal 3140 was similar to 4004 except that food intake never recovered. In addition, drug intake steadily increased over the first 8 days, but decreased on the next 2 days. Although the animal survived 10 days, he ate virtually no food after third day of access.

The results for Animal A021 whose responding was maintained by 0.05 mg/kg/infusion l-amphetamine (Fig. 3) are similar to those animals exposed to cocaine and d-amphetamine, except that food consumption decreased minimally on only one day. On Day 5 after receiving 59.5 mg/kg within a 24 hr period, this animal died during convulsions similar to those described by Deneau *et al.* [2]. Animal 4034, however, survived the entire 30 day access period to 0.05 mg/kg/infusion l-amphetamine. Drug and food intake were extremely erratic and unrelated.

Animal 4141, given access to 0.025 mg/kg/infusion d-methamphetamine (Fig. 4), only self-administered 5 infusions on the first day of access. However, on Day 3, intake increased to 5.4 mg/kg and the animal died. Food consumption was unaffected on Day 1, but on Day 3 was totally suppressed. On the first day of access, Animal A013 began to self-administer very large quantities of d-methamphetamine within a few hours. To prevent overdosage, the response requirement was raised to 10 responses per

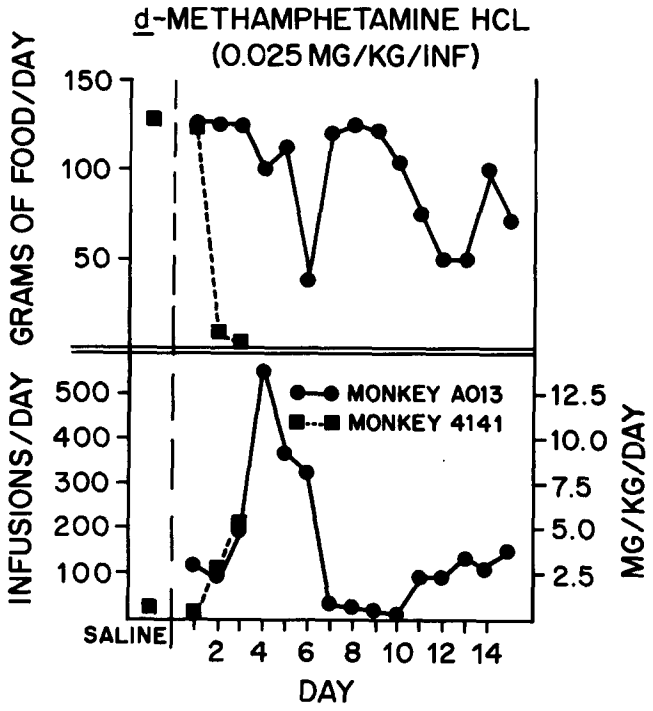

FIG. 4. Number of infusions and drug intake (bottom panel) and food intake (top panel) on each day of access to 0.025 mg/kg/infusion d-methamphetamine hydrochloride for Monkeys A013 and 4141. Mean number of saline infusions and mean food intake for the 3 days prior to drug access are shown to the left of both panels for one of the monkeys.

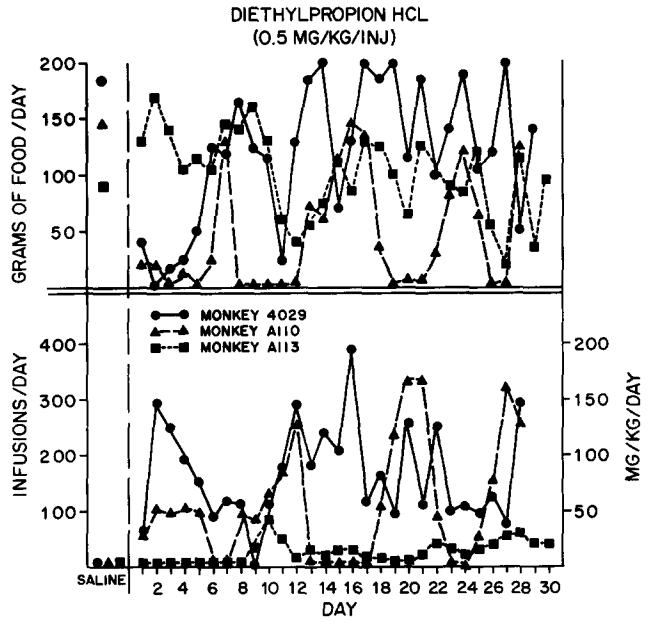

FIG. 5. Number of infusions and drug intake (bottom panel) and food intake (top panel) on each day of access to 0.5 mg/kg/infusion diethylpropion hydrochloride for Monkeys 4029, A110 and A113. Mean number of saline infusions and mean food intake for the 3 days prior to drug access are shown to the left of both panels.

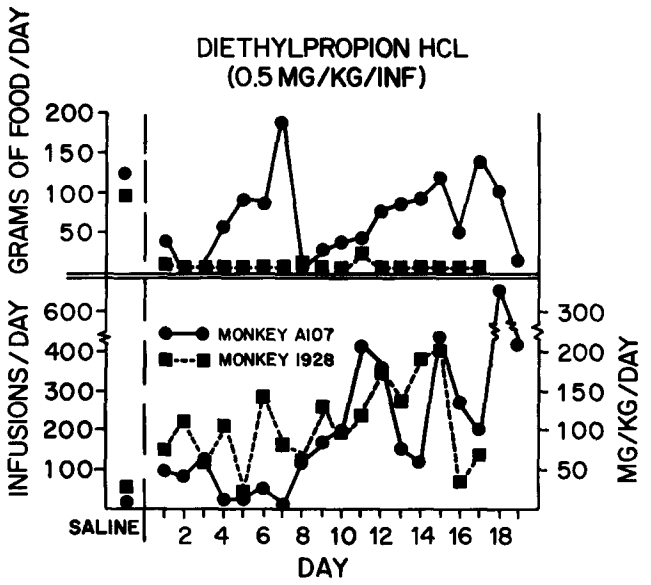

FIG. 6. Number of infusions and drug intake (bottom panel) and food intake (top panel) on each day of access to 0.5 mg/kg/infusion diethylpropion hydrochloride for Monkeys A107 and 1928. Mean number of saline infusions and mean food intake for the 3 days prior to drug access are shown to the left of both panels.

infusion (FR 10). The rate of drug infusions decreased. From that point on, responding showed day-to-day variability and even dropped to 0 on Day 10. Maximum intake occurred on Day 4 when the animal self-administered 561 infusions. On the fifteenth day of access, the animal died after self-administering 155 infusions. Food consumption was not initially affected even when drug intake was maximal on Day 4. By Day 13, however, food intake had decreased, but not to the extent seen with cocaine or d-amphetamine.

Three of the 5 animals tested with 0.5 mg/kg/infusion diethylpropion survived the 28–30 day regimen (Fig. 5). For Animal 4029, drug intake varied over the 29-day access period, but did not seem to increase with continued access. Although food intake was initially suppressed, it returned to predrug levels by Day 13. Food consumption continued to fluctuate from 50 to 200 g over the next 16 days; however, food and drug intake were not systematically related. Responding maintained by diethylpropion by Animal A110 also varied from day to day. Periods of low drug intake were longer in duration and the number of infusions was lower compared to 4029. However, the number of infusions self-administered during periods of peak intake were just as high. Except on the last day of access, food and drug intake were inversely related. Animal A113 took relatively few infusions of diethylpropion compared to the other animals given access to this drug, although responding was increased relative to responding maintained by saline. Food consumption initially increased when drug was available but teneded to fluctuate; this variability, however, did not seem to be related to level of drug intake.

Two animals died during diethylpropion access (Fig. 6). The data from Animal A107 were similar to the data from 4029 who survived the regimen, in terms of the erratic pattern of both drug and food intake. However, on Day 18,

TABLE 1

CORRELATION BETWEEN RESPONSE RATE ON LEVER 1 AND LEVER 2

Animal	Drug	r
2164	Cocaine	0.90*
3097	Cocaine	N/A†
3140	*d*-Amphetamine	0.41
4004	*d*-Amphetamine	0.64*
4032	*d*-Amphetamine	N/A
4141	*d*-Methamphetamine	N/A
A110	Diethylpropion	0.42*
A113	Diethylpropion	0.66*
4029	Diethylpropion	0.23
A107	Diethylpropion	0.64*
1928	Diethylpropion	0.61*

*$p \leq 0.05$
†Statistic not applicable since animal survived less than 4 days

two days before he became comatose, the animal self-administered 328.5 mg/kg diethylpropion, which was 50 percent more than ever taken previously and is greater than the amount self-administered by any other animal given access to diethylpropion in the present experiment. After the animal was found comatose, extensive attempts were made to revive him by administering 5 percent dextrose, 45 percent NaCl and antibiotics to treat pneumonia. In addition, this animal was given 15–20 cc of Sustagen® each day for 7 days at which time he was sacrificed. Animal 1928 died after 17 days of access although his drug intake never exceeded 202 mg/kg. However, not only was food intake initially suppressed when access to drug began, but consumption never returned to more than 20 percent of predrug levels.

The number of responses occurring on Lever 2 was recorded for all animals except A021, A013, A010 and 4034. In all cases, rates of responding were higher on Lever 1 than on Lever 2 ($z = 8.6$; $p \leq 0.0001$), despite considerable fluctuations in both measures. Table 1 shows the correlation between the level of responding on the two levers. For 6 animals, there was a significant positive correlation between the two rates. For two animals, the measures were unrelated.

The behavioral changes observed following 1–2 days of access were similar for the animals exposed to cocaine and the amphetamines. These animals became hyperactive, restless and often threw themselves against the walls of the cubicle when the door was opened by the experimenter. Most animals engaged in repetitive picking and scratching

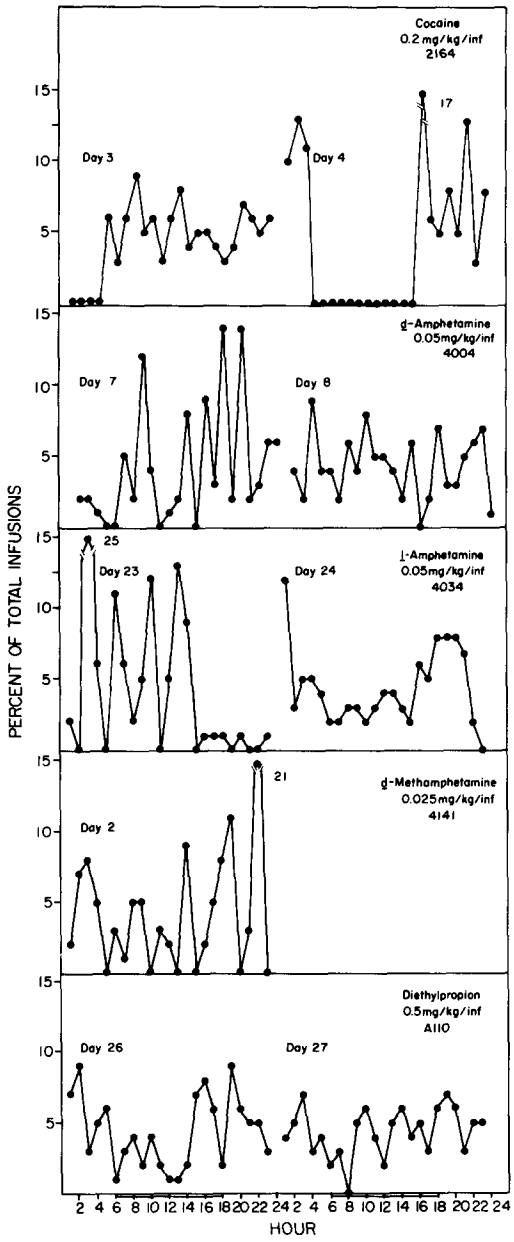

FIG. 7. Percent of total daily infusions during each hour of access to cocaine, d-amphetamine, l-amphetamine, d-methamphetamine and diethylpropion on 2 consecutive days. Night hours are indicated by the black bar on the abscissa.

and extended their legs away from their bodies in a bizarre posture. They rocked back and forth for considerable periods of time and often appeared to be staring intently. In addition, tremors, mydriasis and pilo-erection were observed. During periods of high drug intake, animals were unable to grasp pieces of food offered by an experimenter, although they often made an attempt. Animals who survived at least a week lost considerable muscle mass. Except just prior to their death, the animals were extremely difficult to handle due to their hyperactivity. The behavioral changes seen after 2–3 days of access to diethylpropion appeared less severe, but by the third week of

access, the animals were very hyperactive and uncoordinated and showed abnormal posturing similar to that seen with cocaine and the amphetamines.

Figure 7 shows hourly intake of each drug on 2 consecutive days of moderate to high drug intake for representative animals. As can be seen, intake was erratic and unrelated to a day-night cycle. Similar results were found with all animals.

DISCUSSION

Rhesus monkeys given unlimited access to a variety of psychomotor stimulant drugs self-administer them in amounts sufficient to result in death after less than 3 weeks of availability. Most of the animals whose responding was maintained by cocaine, d-amphetamine, l-amphetamine and d-methamphetamine survived less than 5 days on the 23 hr/day regimen and never more than 15 days except for one animal on l-amphetamine. Three of the 5 animals whose responding was maintained by diethylpropion, however, survived for the duration of the 28–30 day experiment, despite, in 2 of the animals, high levels of daily intake up to 196 mg/kg. Even the 2 animals who died survived longer than any animal tested with cocaine, d-amphetamine, or d-methamphetamine. In fact, Animal A107 died on Day 19 only after receiving 2 days of massive doses totalling 542.5 mg/kg diethylpropion. It may very well be that diethylpropion is a less toxic drug, although the present results should only be considered preliminary. One problem with this study is the use of only one dose of each drug. However, in studies where animals have limited access to these same drugs, total daily intake is relatively independent of the dose per injection [1, 5, 12]. It seems likely, therefore, that the same results would have been obtained in the present experiment, even if somewhat different doses had been used.

Animals exposed to cocaine and the amphetamines survived fewer days than those described by Deneau *et al.* [2]. Although the cocaine doses used in the study by Deneau *et al.* [2] were higher (0.25 mg/kg/infusion or 1.0 mg/kg/infusion) and the amounts self-administered greater (up to 180 mg/kg), animals survived about 30 days. A discrepancy is also evident with the amphetamines for which Deneau *et al.* [2] report that 9 mg/kg was the maximum daily amount self-administered by any animal even though the unit dose (0.1 mg/kg) was higher. The animals in the present experiment self-administered as much as 72.6 mg/kg of d-amphetamine. The animal which survived 13 days of access to this drug self-administered more than 9 mg/kg on 6 of those days while the animal which survived 10 days self-administered more than 9 mg/kg on the last 7 days. In the Deneau *et al.* [2] study, none of the animals given access to d-amphetamine died. These differences may very well have been due to the fact that in the study by Deneau *et al.* [2] drug infusions were limited to approximately one per min since the duration of the infusion was about 5 times longer than in the present study. This limitation may have helped to avoid toxicity resulting from several rapid infusions. However, it is difficult to compare the two studies since we are uncertain as to the procedural details of the original study. There are some indications that cocaine and d-amphetamine intake were sometimes restricted to 1 dose per hr in the study by Deneau *et al.* [2], although it is never clear when this occurs. For instance, the authors state that animals given access to 0.1 mg/kg d-amphetamine increased their rate of responding "until a maximum daily dosage of 9 mg/kg was attained in 2–3 weeks." Whether this maximum was determined by the experimenter or the animal is unclear. If the intake was limited by the experimenter, the differences in toxicity are easily explained. A further difficulty in comparing the two studies is that in the study by Deneau *et al.* [2] the results are reported in general terms; original data only appear in the figures. Therefore, there is no way of determining variability. Since the variability in the present study was so great, it is difficult to believe that it did not occur in the original study.

Another difference between the results of the present study and those reported by Deneau *et al.* [2] is the level of Lever 2 responding. They state that during periods of high drug intake, the animals responded equally on both levers. In the present study, Lever 1 responding was always greater than Lever 2 responding, indicating that the animals were able to discriminate between them. However, for many of the animals, there was a significant positive correlation between rates of responding on the 2 levers.

Deneau *et al.* [2] state that the pattern of cocaine and amphetamine intake is cyclic with days of relatively high intake alternating with days of little or no self-administration, a pattern also seen in human intravenous users [7]. To a certain extent, the present study confirms these findings; animals who died early in the present study showed variability in intake from day to day, but evidence for regular cyclicity is minimal. Even animals who survived for longer periods never ceased taking drug for more than 24 hr which is not true with humans [7] who often cease injecting these drugs for much longer time periods. Nevertheless, relative to morphine, pentobarbital and ethanol [2,13], day-to-day variability as well as hour-to-hour variability in intake is much more evident with the psychomotor stimulants, and the gradual development of tolerance over a 30 day period is difficult to demonstrate.

Despite these differences, the behavioral changes produced by cocaine in the present study were similar to those reported by Deneau *et al.* [2]. These include restlessness, stereotypic movements, dysmetria, tremors, mydriasis, pilo-erection and ataxia. However, access to the amphetamines also produced these effects to the same degree; in the study by Deneau *et al.* [2], the authors did not observe such severe toxicity with this drug, but again, this may have been due to restricted intake. These effects have also been reported to occur in monkeys which have been administered large quantities of d-methamphetamine [3,4]. Diethylpropion, on the other hand, took longer to develop the level of toxicity seen with the other psychomotor stimulant drugs. This result lends further support to the conclusion that diethylpropion is relatively less toxic than these drugs.

Although there were some exceptions, most animals decreased their food intake when they initially began self-administering drug. However, in most cases, food consumption returned to near baseline levels within 7 days of drug self-administration if the animal survived. In general, food and drug intake were not correlated. Although there are indications that differences exist between drugs in terms of their ability to produce anorexia, additional doses and animals need to be tested before any definitive statement is possible. Nevertheless, 6 of the 7 animals who died in 10 days or less of drug access had

consumed very little food, a factor which may have contributed to their demise.

In conclusion, then, it can be seen that rhesus monkeys will initiate responding for IV injections of a number of psychomotor stimulant drugs. When given unlimited access, these animals self-administer highly toxic doses often resulting in death within a few days of availability. Since the toxicity associated with self-administered doses of drugs is an important component of their abuse potential [2, 9, 10], we conclude that the psychomotor stimulants are particularly dangerous in this regard, a conclusion borne out by the consequences of IV abuse of these drugs by man.

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