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A Comparison of *d*-Amphetamine, *l*-Amphetamine, and Methamphetamine Self-administration in Rhesus Monkeys[1]

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BALSTER, R. L. AND C. R. SCHUSTER. *A comparison of* d-*amphetamine,* l-*amphetamine, and methamphetamine self-administration in rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 1(1) 67–71, 1973.–Rhesus monkeys were trained to self-administer cocaine on a fixed-ratio 10 schedule of reinforcement during a daily 3 hr session. *d*-Amphetamine, *l*-amphetamine, and methamphetamine, at various dosages, were substituted for the cocaine for six consecutive sessions. The animals were returned to cocaine baseline between each test series. All three drugs were self-administered at rates higher than saline control levels. *d*-Amphetamine and methamphetamine were equipotent in maintaining self-administration behavior and both were approximately 4 times more potent than *l*-amphetamine.

Self-administration Substitution procedure *d*-Amphetamine *l*-Amphetamine Methamphetamine Cocaine Rhesus monkeys

THE TWO stereo isomers of amphetamine have been shown to have differential effects on both behavioral and neuropharmacological measures. On measure of psychomotor stimulation, *d*-amphetamine is 4 [7] to 10 [21] times as potent as *l*-amphetamine in the rat. However, *d*-amphetamine is only 1.4 times as potent as *l*-amphetamine on measures of stereotypy [22], and 2 times as potent in producing gnawing [21]. Similarly, on measures of psychotogenicity in man, *d*- is 1–2 times as potent as *l*-amphetamine [1]. These two isomers may also differentially affect catecholamine uptake in the CNS. In the rat, Taylor and Snyder [21] showed that *d*-amphetamine was 10 times more potent than *l*-amphetamine in blocking norepinephrine uptake but equipotent in blocking dopamine uptake. However, other investigators using rat *in vitro* preparations have shown in one case a 20-fold difference in blocking norepinephrine uptake [2] and in another case no difference [8] in blocking norepinephrine uptake.

Although there are some discrepancies these results in general suggest that the effect of the amphetamines on general activity is mediated by blocking norepinephrine uptake, whereas amphetamine produced stereotypy is mediated by blocking dopamine uptake. This conclusion is consistent with the work of Randrup and Munkvad [15,16] on the role of dopamine in drug-induced stereotypy.

This distinction between the two isomers of amphetamine offers a tool to assess the relative importance of the two catecholamines, norepinephrine and dopamine, in mediating the pharmacological effects of psychomotor stimulants [1,19]. One of the interesting pharmacological effects of the amphetamines is their ability to reinforce self-administration behavior in experimental animals [14,18] and in man [9]. The relative potencies of these two compounds in self-administration tests should provide suggestions as to the importance of norepinephrine and dopamine in the regulation of this behavior.

Methamphetamine is also effective in blocking the uptake of intracisternally administered norepinephrine [4] and is a potent agent for the production of an increase in general activity, being 2 [20] to 3 [5] times more potent than *d*-amphetamine. Therefore, methamphetamine was also tested for its potency in self-adminstration tests.

METHOD

Animals and Apparatus

One female (A019) and two male rhesus monkeys, *Mucaca mulatta,* weighing 4.2 to 5.5 kg were used. Animal A019 had an extensive history of cocaine self-administration prior to this experiment; animals A051 and A055 had no previous drug or experimental history. They were fed and watered ad lib throughout the experimental period.

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Each animal was fitted with a metal harness as described by Deneau, Yanagita, and Seevers [6] and a connecting arm constructed from a steel door spring. The arm was connected to the rear wall of a 4 x 4 x 3 ft top loading metal animal cage. This arrangement gave the animal relatively unrestricted movement about the cubicle. The front of the experimental cubicle contained a response lever and two stimulus lights. One light was mounted above the lever, the other in the center of the cage wall. All programming and recording was accomplished automatically with electromechanical equipment located in an adjacent room.

After the monkeys had adapted to the harness and experimental cubicles, they were surgically prepared with a chronic venous catheter of siliconized rubber. The catheter passed through the harness and arm to the outside of the cubicle where it was connected to a peristaltic infusion pump which could deliver solution at a fixed rate of 6 ml/min.

Procedure

Initally each monkey was trained to press the lever for an injection of 200 μg/kg cocaine hydrochloride. Training took place three hours each day seven days a week, and the session was signalled by the illumination of the stimulus light mounted above the response lever. During infusions this light was turned off and the center light illuminated. Responses during infusion were recorded, but had no consequences.

Over the course of 1–2 weeks, the animal's response requirement was raised from 1–10 responses per injection (fixed-ratio 10). After the animal's lever-pressing behavior stabilized, the test drugs, at various dosages, were periodically substituted for 6 consecutive daily sessions; the animal was returned to cocaine baseline for at least 3 sessions between each test drug dosage. The following unit doses were tested in all three animals: 25, 50, and 100 μg/kg/inj *d*-amphetamine sulfate; 50, 100, 200 and 400 μg/kg/inj *l*-amphetamine sulfate; and 25 and 100 μg/kg/inj *d*-methamphetamine. (The *d*-amphetamine sulfate and *l*-amphetamine sulfate were graciously supplied by Smith, Kline, and French Laboratories, Philadelphia, Pennsylvania. The methamphetamine hydrochloride was graciously supplied by Abbott Laboratories, North Chicago, Illinois.) Two animals were also tested at 50 μg/kg/inj methamphetamine. Saline control tests were also run. The order of testing for the different compounds was balanced in a latin square design. The order of the dosages of a particular drug was random for each animal. Dosage refers to the salt of all the compounds used in this study. They were dissolved in physiological saline made up to allow the appropriate unit dose to be delivered in 0.2 ml/kg of animal weight. The infusion duration was adjusted for each animal and ranged from 8.4–11 sec.

RESULTS

The number of injections of cocaine on each of the three days just preceding each 6 day substitution test was recorded. The mean for each three-day series for each animal was calculated and the results are graphed in Fig. 1. The baseline for cocaine reinforcement remained fairly constant or slightly decreased (Animals A019, A051) over the duration of the experiment. If the animals were developing tolerance the baseline rate of responding would

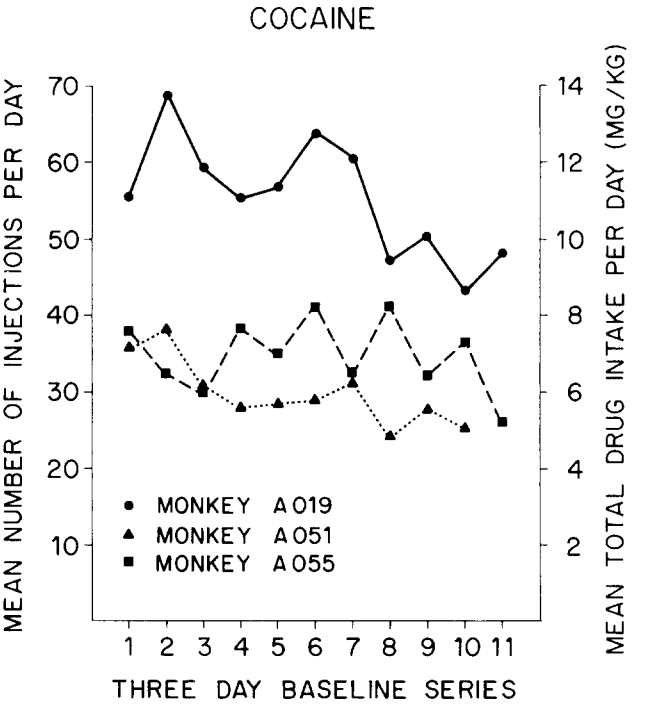

FIG. 1. The mean number of cocaine injections self-administered, and the mean total drug intake per day for each three-day baseline for three monkeys. These means are shown in the order they were tested for the entire experiment.

have increased since rate of cocaine self-administration is an inverse function of unit dose [23]. Monkey A019, who had a long prior history of cocaine self-administration, however, did self-administer more cocaine than the two experimentally naive animals, indicating that perhaps tolerance can develop to the response rate-limiting effects of cocaine.

The number of injections of each dosage of the test drugs on the last three days of the six day substitution was used for data analyses. The mean and range of the values for each animal are presented in Fig. 2. When saline was substituted for cocaine a low rate of self-administration not exceeding 20 injections per session was obtained. *d*-Amphetamine, *l*-amphetamine and methamphetamine all maintained response rates above the level for saline at at least 2 of the doses tested. The number of injections of these three compounds was inversely related to dosage per injection. Also, the figure shows *d*-amphetamine and methamphetamine have roughly identical rates of self-administration across the dose range tested. The dose response curve for *l*-amphetamine is shifted to the right by a ratio of 4.

Figure 3 presents the mean and range of total drug intake for each of the animals as a function of unit dose calculated from the same data as Fig. 2. For *d*-amphetamine and methamphetamine, drug intake remains constant at about 2–3 mg/kg daily, independent of unit dose of reinforcement. However, for *l*-amphetamine three animals showed a tendency for drug intake to increase with increasing unit dose.

Figure 4 presents a measure of the response distribution over the three hour session. The number of

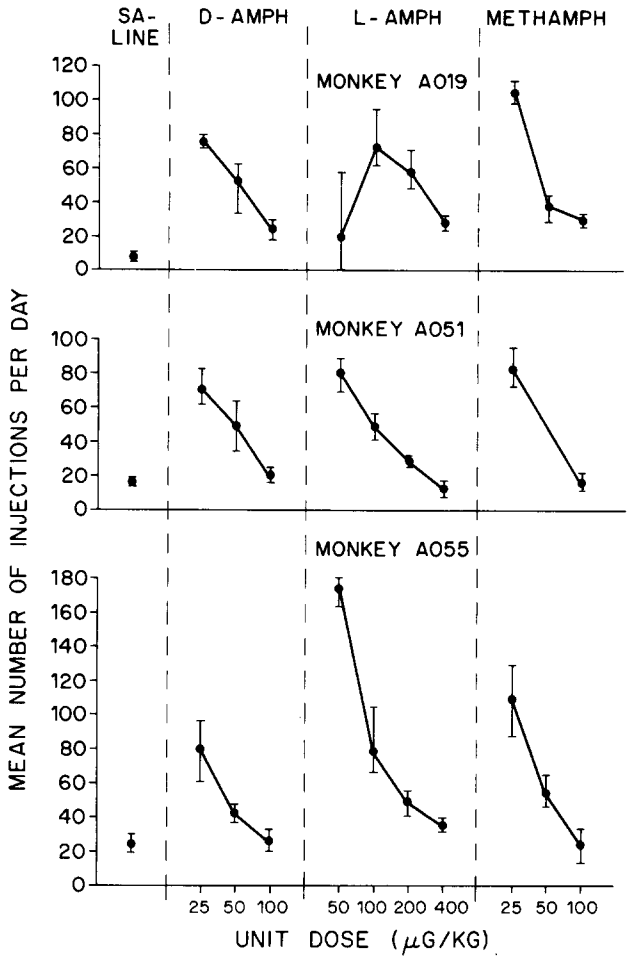

FIG. 2. The mean number of injections per day for *d*-amphetamine, *l*-amphetamine and methamphetamine at the various doses tested. The vertical bars indicate the range. Saline control levels are also shown.

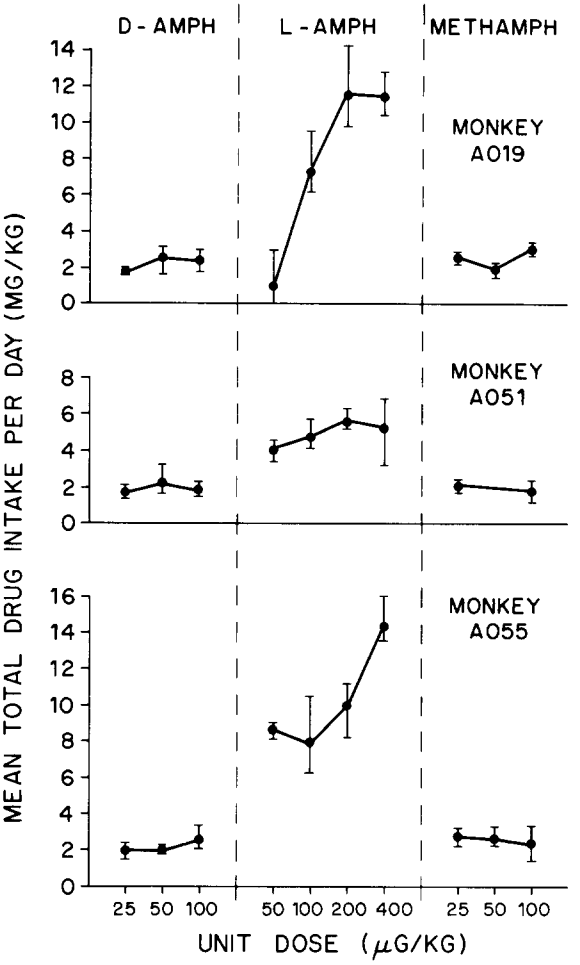

FIG. 3. The mean total drug intake per day (mg/kg) for *d*-amphetamine, *l*-amphetamine and methamphetamine at the various doses tested. The vertical bars indicate the range.

injections self-administered in the first 1.5 hr of the session was expressed as a percent of the total number of injections for that session. The mean of these values for the last three days at each unit dose was calculated. A similar measure was obtained for cocaine reinforcement except that the mean of all the three day baselines preceding each drug dosage tested was calculated. The distribution of injections for cocaine reinforcement remained quite stable for each animal and showed little variability between animals with about 55–66 percent of the injections self-administered in the first half of the session. This indicates a fairly stable rate of responding throughout the session. The slightly greater number of injections in the first half was accounted for by a burst of 4–6 injections taken within the first 5 min of the session.

When saline was substituted for cocaine, the animals self-administered virtually all the injections early in the session; in every case over 90 percent of the infusions were taken in the first 1.5 hr. This undoubtedly reflects extinction due to an ineffective reinforcer. The substitution of *d*-amphetamine, *l*-amphetamine and methamphetamine produced less consistent results. In general, at all unit doses tested, all the animals self-administered 70–80% of the injections of all three compounds in the first 1.5 hr. However, Animal A019 at 400 μg/kg/inj and Animal A051 at 200 and 400 μg/kg/inj self-administered *l*-amphetamine in a pattern similar to their saline pattern with over 90% of the injections in the first half of the session. With the exception of these two animals with *l*-amphetamine, the pattern of responding was not dose-dependent. The only clear conclusion which can be drawn from this data is that all the animals tended to distribute their injections early in the session to a much greater degree for the amphetamines than for cocaine, but not to the extent of saline, indicating some other explanation than extinction. It is likely that this difference can be accounted for by the longer duration of action of the amphetamines.

DISCUSSION

This study demonstrates that *d*-amphetamine, *l*-amphetamine, and methamphetamine at appropriate unit doses can maintain rates of self-administration above saline control levels when substituted on a cocaine baseline. This

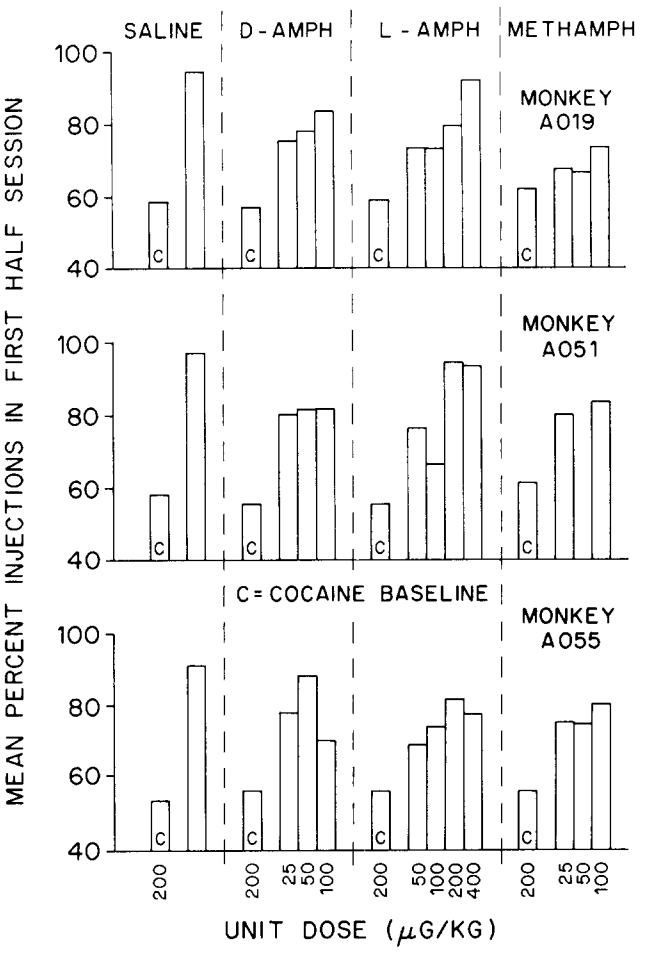

FIG. 4. The mean percent injections occurring in the first half (1.5 hr) of the session for *d*-amphetamine, *l*-amphetamine and methamphetamine at the various doses tested. The mean percent for the cocaine baseline preceding each drug series is indicated by the bar labelled C. Saline control levels are also shown.

confirms the results with *d*-amphetamine in monkeys [6,17] and rats [11], with methamphetamine in monkeys [6] and rats [12] and with *l*-amphetamine in rats [24]. These results indicate that *l*-amphetamine can also serve to reinforce self-administration behavior in rhesus monkeys. That self-administration rates of these three compounds are inversely related to unit dose also confirms a large number of studies with these and other psychomotor stimulants [11, 13, 23].

Of primary interest in the present study was the finding that *d*-amphetamine and methamphetamine were equipotent in maintaining self-administration behavior and that both were roughly four times as potent as *l*-amphetamine. Before discussing this result in relation to other differential potencies of these compounds, it is important to understand what factors control rate of responding for drug reinforcement. Drugs, in addition to their reinforcing properties, also have the ability to nonspecifically disrupt all ongoing behavior. Consequently, the dose-dependent pause following drug reinforcement may be due to either a form of drug-satiation or it may be due to the inability of the animal to perform the required response as a result of behavioral disruption. Pickens and Thompson [13] demonstrated that an intravenous infusion of cocaine disrupted lever-pressing behavior in rats working for food reinforcement. The duration of the disruption was a positive function of dosage of cocaine administered. Owens [10] in a study of the effects of *d*-, *l*-amphetamine, and methamphetamine on fixed-ratio responding for liquid food reinforcement in rats demonstrated *d*-amphetamine and methamphetamine to be roughly equipotent and both to be about 4–5 times as potent as *l*-amphetamine. These results are similar to those obtained in the present study. Consequently, it could be possible that the difference between *d*- and *l*- found in the present study simply reflects the relative potencies of these drugs to disrupt operant behavior. This suggests that the upper limits of drug self-administration are determined by nonspecific behavioral toxicity rather than a function of reinforcement efficacy.

One of our major interests in undertaking this study was to gain some suggestion as to the role of dopamine and/or norepinephrine as mediators of the reinforcing actions of the amphetamines. The differences in the potency of *d*- and *l*-amphetamine in their effects on blockage of uptake of dopamine and norepinephrine has been used as a tool for analyzing the importance of each in the control of a given behavioral action of amphetamine [1,19]. We believe, however, that the results of the present experiment cannot be used in this manner for several reasons. As previously discussed, from a behavioral viewpoint rate is a confounded measure of the reinforcing efficacy of drugs. In addition there are objections from the neurochemical point of view. First, the potency differences in the effects of *d*- and *l*-amphetamine on biogenic amines have been limited to studies of blockade of uptake in the rat. Clearly, amphetamines cause the release of norepinephrine and dopamine as well [3]. The reinforcing actions of amphetamines could as well be related to this action of the drug rather than to a blockade of uptake. Further, these biochemical studies have been done in the rat and it would be unjustified to extrapolate the findings to the rhesus monkey. We are currently investigating the effects of intravenously administered amphetamines on brain biogenic amines in the rhesus monkey. The neurochemical implications of the current study must await the outcome of these studies.

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