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Structure-Activity Relationships Among Some *d*-N-Alkylated Amphetamines

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WOOLVERTON, W. L., G. SHYBUT AND C. E. JOHANSON. *Structure-activity relationships among some d-N-alkylated amphetamines*. PHARMAC. BIOCHEM. BEHAV. 13(6)869–876, 1980.—*d*-N-Alkylated amphetamines were synthesized in a series up to and including *d*-N-butylamphetamine and potencies of these compounds were compared in (1) rhesus monkeys allowed to respond for intravenous infusions of the drugs, (2) rats allowed to drink a milk solution for 15 minutes each day and (3) isolated, spontaneously beating guinea-pig atria. In the self-administration procedure, *d*-amphetamine (A), *d*-N-methylamphetamine (NMA), and *d*-N-ethylamphetamine (NEA) were self-administered above saline levels at two or more doses by all animals. For these three drugs, maximal response rates were found at similar doses in all animals. However, maximal rates were generally higher in animals maintained on pentobarbital than in animals maintained on cocaine under control conditions. *d*-N-propylamphetamine (NPA) was self-administered above saline levels by three of four animals at one or more doses. Maximal response rates for NPA were about 1/2 of that of A, NMA and NEA, and the dose-response curve was shifted to the right of these compounds by about 4 times. *d*-N-butylamphetamine (NBA) maintained responding above saline levels at two doses in only one of three animals. In rats, all of the compounds decreased milk intake in a dose-related manner. A, NMA and NEA were equipotent in disrupting intake, while NPA and NBA were, respectively, 1/4 and 1/6 as potent as the shorter-chain compounds. With the exception of NBA, all compounds increased the rate of beating of the guinea-pig atrium over the range of concentrations tested. In general, for substituents larger than ethyl, potency of *d*-N-alkylated amphetamines was inversely related to N-alkyl length.

Rhesus monkey Rat Guinea-pig atrium Amphetamine Self-administration Structure-activity

REPORTS of structure-activity relationships among amphetamine-like compounds have emphasized the importance of substituent size in modifying their behavioral and other pharmacological effects [2, 3, 28, 32, 33]. Thus, N-alkylation might be expected to alter some of the effects of *d*-amphetamine. *d*-N-methylamphetamine (NMA) and *d*-N-ethylamphetamine (NEA) are N-alkylated derivatives of *d*-amphetamine (A) which have behavioral effects similar to those of A in a number of test situations. All three compounds have been reported to increase general activity in rats, mice or monkeys [7, 23, 29, 32] as well as disrupt ongoing operant behavior [8, 9, 25, 37, 39]. Furthermore, these compounds have been shown to maintain responding that leads to intravenous delivery in rhesus monkeys [1,30]. Structural modifications, however, clearly alter the reinforcing properties in these compounds. For example, although NEA is a positive reinforcer, the addition of a meta CF_3 group to the ring produces a compound, fenfluramine, which is devoid of reinforcing properties and has few CNS effects [2, 11, 12, 17, 39].

Although the behavioral effects of A, NMA and NEA are similar, N-substitution appears to alter the potencies of these compounds. For example, A has been reported to be slightly more potent than NMA in the disruption of operant behavior [13,20] as well as in other CNS effects [19]. It has also been reported that the potencies of N-alkylated amphetamines in increasing locomotor activity in mice decrease with increasing substituent size [34]. In addition, biochemical investigations of several N-alkylated amphetamines have demonstrated their relative potencies in releasing H^3-NE from mouse heart to be A>NMA>NEA, while compounds with alkyl substituents larger than ethyl were reported to be in-

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active [5]. Similar potency relationships have been demonstrated for N-alkyl amphetamine derivatives in inhibiting accumulation of NE in rat brain and rabbit aorta [28]. These data are consistent with the hypothesis that the behavioral effects of these amphetamine-like compounds are mediated, at least in part, by the release of catecholamines [18, 25, 27]. If the hypothesis is correct, one would predict the relative potencies among N-alkylated amphetamines to be A>NMA>NEA>*d*-N-propylamphetamine (NPA)>*d*-N-butylamphetamine (NBA).

In the experiments to be described, *d*-N-alkylated amphetamines up to and including NBA were synthesized and their relative potencies in several systems were determined. In the first experiment, rate of responding for intravenous infusions of these drugs in rhesus monkeys was used as a measure of the reinforcing properties. In the second experiment, the potencies of these compounds in disrupting milk intake of rats were compared. Potencies were also compared when the compounds were added to a bath containing a spontaneously beating guinea-pig atrium, a preparation in which catecholaminergic mechanisms are more clearly involved. In general, for substituents larger than ethyl, the potency of these compounds in all three systems decreased with increasing N-alkyl length. Therefore, changes in catecholamine metabolism were implicated in the mediation of the behavioral effects of these compounds.

METHOD

EXPERIMENT 1

Animals and Apparatus

The animals were 4 experimentally naive male rhesus monkeys (#5003, 5011, 5099, 6057) weighing between 5.1 and 7.1 kg. The apparatus and general procedures have been described previously [6]. Each animal was fitted with a stainless steel harness and spring arm for restraint. The animals were individually housed throughout the experiment in ventilated, sound-attenuating cubicles (83 cm deep×67 cm wide×75 cm high) where food (Purina Monkey Chow) and water were continuously available. In addition, each cubicle was equipped with a wide-angle lens for viewing the animal. On the inside front door of each cubicle were two response levers, each with two red and two white indicator lamps located above it. Additional white and red lights covered by translucent plastic were located on the ceiling of each cubicle. Cables connected the cubicles to solid state programming and recording equipment in an adjacent room.

PROCEDURE

Surgery

Following adaptation to the cubicle and restraint system, each animal was removed from the cubicle and injected with a combination of phencyclidine hydrochloride (1 mg/kg, IM) and atropine sulfate (0.04 mg/kg, IM) followed in 20–30 minutes by sodium pentobarbital (10–30 mg/kg, IV). When anesthesia was adequate, a silicone catheter (0.031 in. i.d., Ronsil Rubber Products, Belle Mead, NJ) was surgically implanted in a major vein. If a catheter became nonfunctional during the experiment, a new catheter was implanted as before following a 1–2 week period to allow any infection to clear.

The animal was returned to the cubicle after surgery. The catheter was threaded through the hollow arm to the back of the cubicle and connected to a peristaltic infusion pump which delivered drug solutions at a rate of 1 ml/10 seconds.

Training

Initially, each animal was trained in the presence of the white ceiling light and white lever lights to press the right lever for a 10 second infusion of 0.1 mg/kg cocaine hydrochloride. During an infusion the white ceiling light and lever lights were extinguished and the red ceiling light and lever light were illuminated. Responses occurring during the infusion as well as those occurring on the left lever were counted but had no other programmed consequence. Following acquisition of the lever-press response, the number of responses required for reinforcement was increased over the period of one 3 hour session to 10 (fixed ratio 10; FR 10). After responding during daily 3 hour sessions stabilized (2–3 days) a dose of 0.2 mg/kg/infusion cocaine hydrochloride was used to maintain responding in two animals (#5003 and #5009) and 0.25 mg/kg/infusion sodium pentobarbital was used to maintain responding in the other two animals (#5011 and #6057). Rates of responding cocaine tended to decrease over successive substitution periods and, later in the experiment, animals #5003 and #5099 were returned to 0.1 mg/kg/infusion cocaine to maintain response rates at a level comparable with those of the animals maintained on pentobarbital.

Baseline Conditions

Daily 3 hour sessions were signaled by the illumination of the white ceiling light and white lever lights. During each session, the animals received intravenous infusions of 0.1 or 0.2 mg/kg cocaine (#5003 and #5099) or 0.25 mg/kg pentobarbital (#5011 and #6057) by pressing the right lever on an FR 10 schedule. The number of infusions delivered, as well as the number of right and left lever responses, were recorded every 30 minutes.

Substitution Procedure

Following the establishment of stable rates of responding under baseline conditions (less than 10% variation in the total number of infusions per session for 3 consecutive sessions), 0.9% saline or a test dose of one of the *d*-N-alkylated amphetamines was substituted for at least 6 consecutive sessions. When responding was stable or after 14 sessions, whichever came first, the animal was returned to baseline conditions. The mean number of infusions over the last 3 days of a substitution period was used in the data analyses.

Test doses of the following drugs were substituted for the baseline drug in each animal: *d*-amphetamine, *d*-N-methylamphetamine, *d*-N-ethylamphetamine, *d*-N-propylamphetamine and *d*-N-butylamphetamine (See Table 1 for order of testing). Animal #6057 died before it could be tested with NEA or NBA. Drug doses were tested in nonsystematic order on an individual basis until a complete dose-response function was obtained for each drug. All doses of one drug were tested before testing another drug. Saline was substituted twice for at least six days in each animal irregularly in the series. A dose of a drug was considered to be a positive reinforcer if the mean rate of responding for the last three sessions of a substitution period was above the corresponding value for the last 3 sessions of a saline substitution and the ranges of these did not overlap. After the entire series

TABLE 1
ORDER OF SUBSTITUTION OF TEST DRUGS IN EACH MONKEY

Animal	Baseline	A	NMA	NEA	NPA	NBA
#5003	cocaine	4	2	1	3	5
#5099	cocaine	2	4	3	1	5
#5011	pentobarbital	1	4	5	2	3
#6057	pentobarbital	1	3		2	

had been tested, a dose of a drug tested early in the series was substituted in animals #5003 and #5009, to determine whether any change in sensitivity to the drug had resulted from repeated testing with similar compounds.

Drugs

NEA, NPA and NBA hydrochloride were synthesized for use in these experiments (details available on request from authors). Purity and identity of these compounds were verified by melting point, infrared spectroscopy, mass spectrometry and NMR analysis. Cocaine hydrochloride (Merck Co., Rahway, NJ) and sodium pentobarbital solutions were prepared at least once each week. Doses for these compounds refer to the salt. Doses for the amphetamine compounds refer to the base. All drugs were dissolved in sterile 0.9% saline for injection.

EXPERIMENT 2

Animals and Apparatus

The animals were 8 experimentally naive male Sprague-Dawley derived rats (Holtzman Co., Madison, WI) that weighed between 225–275 g at the beginning of the experiment. Water was available at all times except during experimental test sessions, and each rat was given 4–6 g of Teklad Rat and Mouse Diet (Winfield, IA) after each test session. Food was left in the cage until consumed.

The animals were housed individually in ceiling-suspended stainless steel cages (18×19×25 cm). During experimental sessions, a solution of milk (2 parts tap water and 1 part Borden's Sweetened Condensed Milk) was placed on the front of each cage in a graduated 50 ml Pyrex centrifuge tube fitted with a standard rubber stopper and drinking spout.

Procedure

Experimental sessions were conducted in the home cages at approximately the same time each day, 7 days a week. Initially, all rats were given IP injections of 0.9% saline (1 ml/kg) 15 minutes before every session. When milk intake stabilized for the group, dose-effect functions were determined for A, NMA, NEA, NPA and NBA, in that order. Doses of each drug were given IP and were tested in an ascending order, separated by at least 3 drug-free sessions. The doses tested ranged from a dose that had no effect on intake to a dose that eliminated intake for the entire 15 minute session. After each dose-effect function was completed, 1.0 mg/kg A was given to observe whether changes in the effect of this dose occurred as a result of repeated testing with other drugs, i.e., whether tolerance or increased sensitivity developed. In addition, when the testing of the entire series of drugs was completed, the dose-effect function of A was redetermined.

Drugs

Drugs were the same as those used in Experiment 1. Drug doses refer to the base. They were dissolved in 0.9% saline and the injection volume was 1 ml/kg.

Data Analysis

Milk intake was recorded and group means and standard errors were calculated. Least-squares regression lines were calculated for the dose-effect data and ED_{50} values (i.e., that dose required to reduce milk intake to 50% of control levels) as well as 95% confidence limits were estimated for each drug. Individual drugs were considered to differ in potency if the 95% confidence limits of the ED_{50}'s did not overlap. Control levels were defined as mean milk intake for the three sessions immediately preceding each test injection.

EXPERIMENT 3

Animals and Apparatus

Twenty-six male albino guinea pigs (Camm Research, Wayne, NJ) weighing between 250 and 450 g were used. Atria dissected from the hearts of freshly killed (by a blow on the head) guinea pigs were suspended in organ baths containing 15 ml of a standard Locke's solution saturated with 95% O_2–5% CO_2. The solution contained (in g/l) NaCl 9; KCl 0.42; $CaCl_2$ 0.24; $NaHCO_3$ 0.5; and anhydrous glucose 2, at a pH of 7.4. A temperature of 37°C was maintained throughout the experiments.

Procedure

Atria were attached to a strain-gauge transducer and spontaneous beats were recorded on an ink-writing oscillograph. The bath was changed every five minutes until a stable rate was reached (about 1 hour). Drugs were added only after the spontaneous resting rate of the atria changed by fewer than 5 beats/min during a 15 minute period of observation. Dose-response curves were obtained by a stepwise increase in concentration of the drugs in the organ bath. Concentrations of drugs were increased about 3-fold after rates had reached a new stable level.

Drugs

Drugs were the same as those used in the first two experiments. Concentrations refer to the base.

Data Analysis

Results are expressed as the mean atrial rate change from resting values. These values were calculated from separate values for each S.

RESULTS

Under baseline conditions in Experiment 1, the mean number of cocaine infusions per 3 hour session was 44.7 (±4.6 s.e.m.) while the animals maintained on pentobarbital took an average of 59.7 (±18.3 s.e.m.) infusions per session. When saline was substituted for either baseline drug, low rates of responding (usually<10 infusions/session) were observed by the sixth session in all animals (Fig. 1).

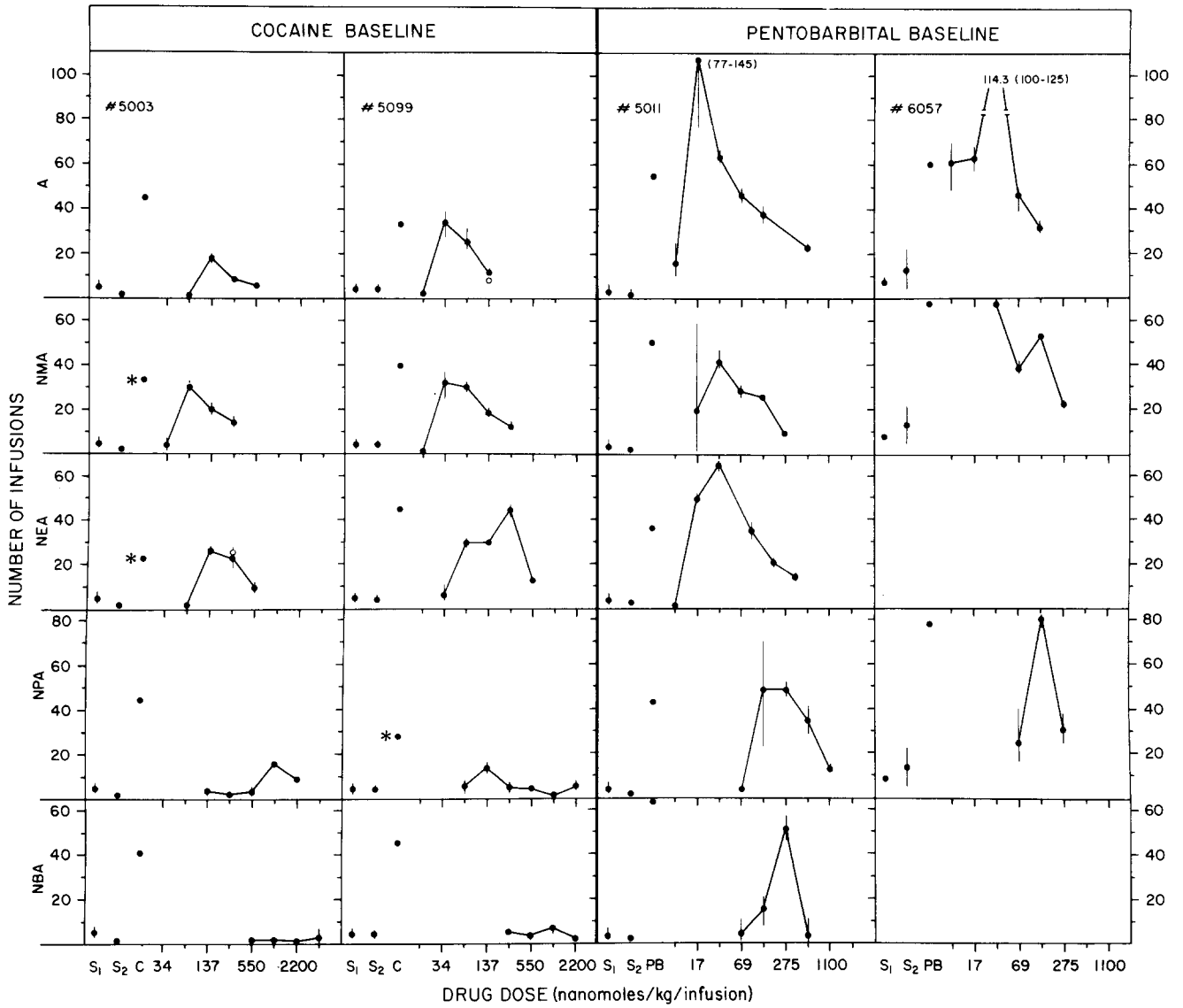

FIG. 1. Mean number of infusions of *d*-N-alkylated amphetamines for each animal during the last 3 sessions of each substitution period (vertical bars representing the range). The points above S_1 and S_2 represent the mean number of infusions of saline during the first and second saline substitution. The points above C and PB represent the mean number of infusions of cocaine and pentobarbital under control conditions during each drug substitution. (*During these periods, animals #5003 and #5099 were maintained on 0.2 mg/kg/infusion of cocaine during control periods.) Open circles (*d*-NEA, #5003 and *d*-A, #5099) represent redeterminations of the effects of these doses following completion of the entire series. Numbers in parentheses (animals #5011 and #6057) represent the range of infusions at that dose.

The mean number of infusions per session for the last 3 sessions of each substitution period is also shown in Fig. 1. Several doses of A, NMA, and NEA maintained higher response rates than saline in all animals. In general, dose-response curves were the inverted "U" shaped functions typically observed for psychomotor stimulant drugs [35]. However, response rate differences were observed between animals as a function of baseline drug. As under baseline conditions, peak response rates were generally higher in the animals maintained on pentobarbital (#5011 and #6057) than in those maintained on cocaine (#5003 and #5099). For example, each animal maintained on pentobarbital self-administered more than 100 infusions of one dose of A while cocaine-maintained animals never exceeded 40 infusions per session during A substitutions.

When NPA or NBA was substituted, rates of responding above saline levels were less frequently observed. In the two animals maintained on cocaine, rates of responding for NPA were higher than saline rates at only one dose in #5099, and at two doses in #5003. Rates of responding for NBA overlapped the range of saline rates at all doses tested in these animals. On the other hand, when NPA was tested in the animals maintained on pentobarbital, response rates were maintained above saline levels at 4 doses in one animal (#5011) and at two doses in the other animal (#6057). When NBA was tested in animal #5011 (pentobarbital baseline),

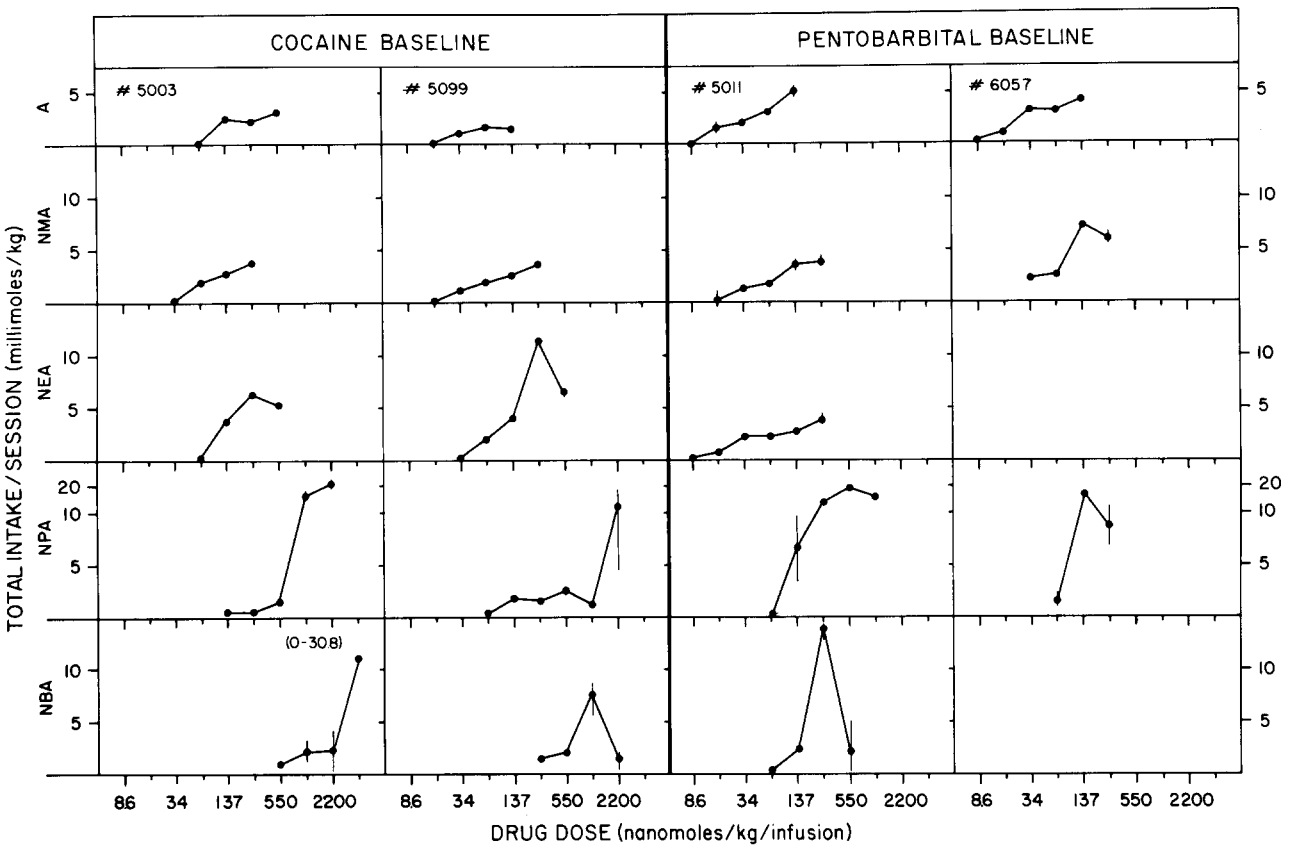

FIG. 2. The mean total intake of N-aklylated amphetamines for each animal during the last 3 sessions of each substitution period. Two animals (#5003 and #5099) were maintained on cocaine under baseline conditions and the other two animals (#5011 and #6057) were maintained on pentobarbital. Vertical bars represent the range of intake at that dose. Where they do not appear, the range lies inside the symbol. The numbers in parentheses (animal #5003, NBA) represent the range of intake.

responding was maintained at one dose. Substitution of a test dose of NEA (#5003) and A (#5099) after the entire series had been tested revealed no shift in the effects of these doses as a result of exposure to all the compounds.

Figure 2 presents the mean total intake per session of each drug during the last 3 sessions of each substitution period. In general, for A, NMA, NEA, and NPA no more than a 2-fold increase in intake was observed with a 4–8 fold increase in dose per infusion over the range of doses that maintained responding above saline levels. A notable exception was NEA in animal #5099, where intake was substantially higher at the 275 nanomoles/kg/infusion dose than at other doses. Although intake of NBA was occasionally high, this was due to a few injections of high unit doses.

In addition to the response rate differences noted above, the pattern of responding over the session differed for the two baseline drugs (Fig. 3). Responding for cocaine was relatively evenly distributed over the session, with slightly more than 50% of the total taken in the first half. In contrast, animals responding for pentobarbital took 70–80% of their infusions in the first half of the session. When saline was substituted for either baseline drug, approximately 90% of the total number of infusions occurred during the first part of the session. For test drugs, there was no systematic difference in the distribution of responding over the session as a function of dose or baseline drug, so all doses were combined for this measure. When A, NMA and NEA were sub-

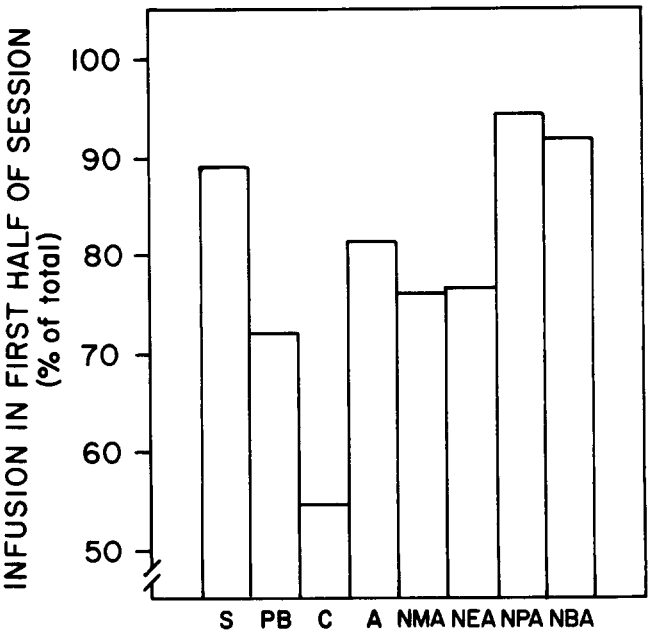

FIG. 3. Percent of total infusions taken in the first half of the session for saline (S), pentobarbital (PB), cocaine (C) and each test drug. Each bar represents the median percent for all animals and all doses of each drug.

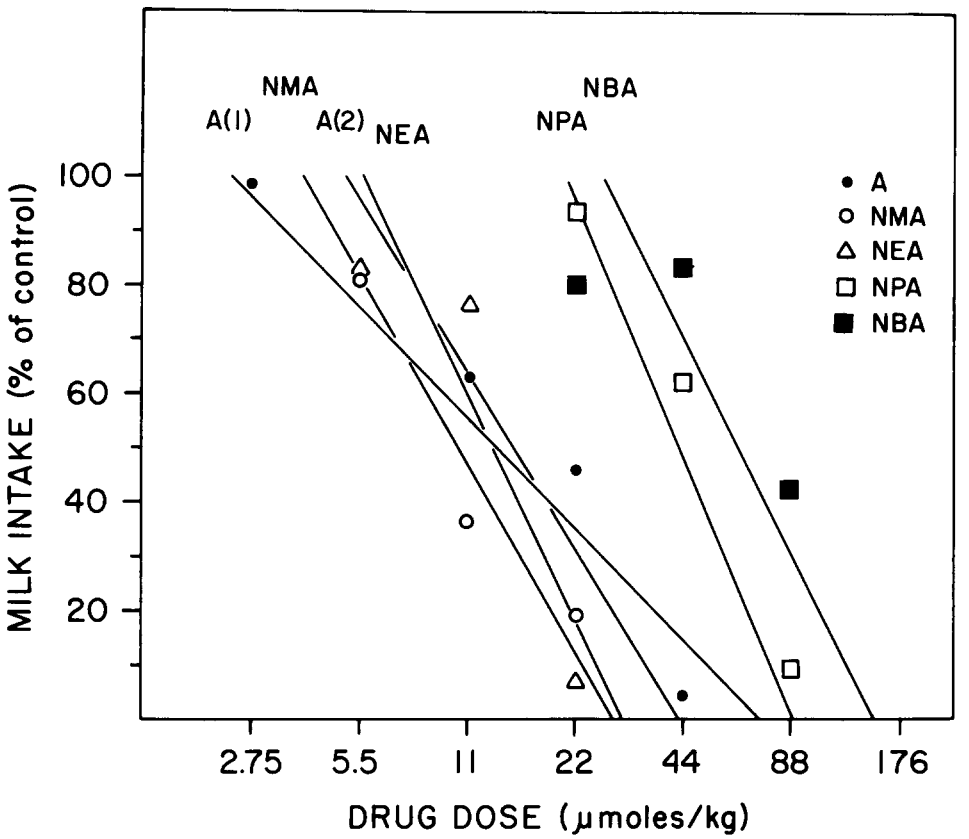

FIG. 4. Effects of N-alkylated amphetamines on milk intake of rats, expressed as percent of control. Control values were the mean intake for the three days immediately preceding each test dose (range—25.5-32.8 ml). The solid lines represent the calculated regression lines for the raw data represented by symbols ● A; ○ NMA; △ NEA; □ NPA; ■ NBA. A(1) and A(2) are the initial A dose-effect function and the redetermination, respectively.

stituted for baseline drug, 75–80% of the total number of infusions were taken in the first half of the session. In contrast, when NPA and NBA were substituted, more than 90% of the infusions were taken in the first half of the session in a pattern similar to that observed during saline substitution.

In Experiment 2, mean milk intake ranged between 25.5 and 32.8 ml for the group under control conditions. There was no change in intake under control conditions during the experiment. Dose-effect data for all of the compounds are shown in Fig. 4. *d*-Amphetamine decreased milk intake in a dose-related manner, and when the dose-effect function was redetermined at the end of the series, it had not changed as a function of repeated testing. In addition, the periodic tests with 1.0 mg/kg A revealed no change in the effect of this dose during testing of the series. Each of the other compounds decreased milk intake in a dose-related manner and the dose-effect functions were parallel to A and each other. When high doses of each drug were given, stereotyped behaviors including sniffing, gnawing, and head-bobbing were observed. ED_{50} values for all compounds are shown in Table 2. The compounds with N-alkyl groups of ethyl or smaller were approximately equipotent and were more potent than NPA. NBA was the least potent of the series.

In the third experiment, the rate of beating in untreated atria stabilized after about one hour at 168±6 beats/min (s.e.m., N=26). Each of the compounds except NBA was effective in increasing the rate of the spontaneously beating atria (Fig. 5). Although the regression lines for A, NMA, and NEA were parallel, slopes over the dose range tested decreased with increasing size beyond NEA, precluding the calculation of exact EC_{50}'s. The potency of these compounds was inversely related to substituent size: A>NMA>NEA>NPA>NBA.

DISCUSSION

Over a wide range of doses, intravenous delivery of A, NMA and NEA contingent upon lever pressing maintained responding in rhesus monkeys. This is consistent with data reported for all three of these compounds in monkeys [1, 6, 30] and for A and NMA in rats [21,22]. On the other hand, responding was maintained over a narrow dose range in three of four animals by NPA and in only one of three animals by NBA. It could be argued that response rates at or below saline levels for NPA and NBA were due to suppression of responding by high doses rather than a lack of reinforcing effects. This possibility is obviated by the fact that responding on the first day of a substitution period was not suppressed relative to saline substitution, except at the highest doses. In addition, it is unlikely that responding was suppressed at lower unit doses where total intake was often 1/10 that seen at higher unit doses (Fig. 2). Repetitive, stereo-

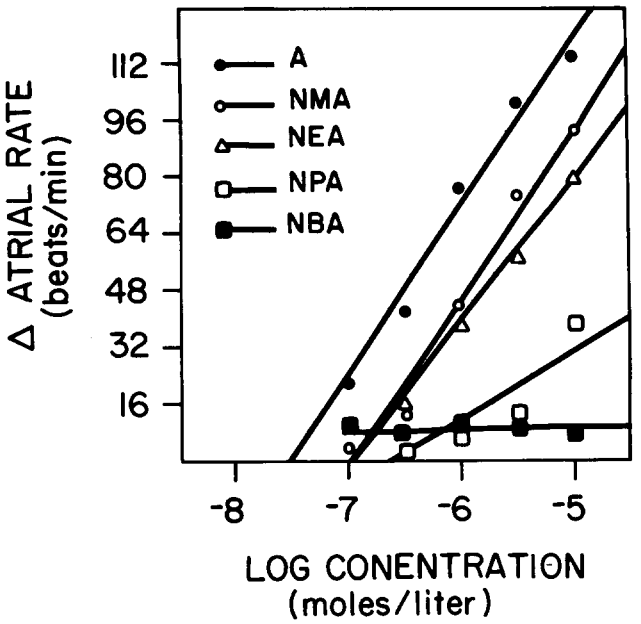

FIG. 5. Effects of N-alkylated amphetamines on guinea pig atrial rate. Ordinate: Change in atrial rate (beats/min); abscissa: $\log_{10}$ concentration (moles/liter) of each test compound. Symbols represent: ● A; ○ NMA; △ NEA; □ NPA; ■ NBA.

TABLE 2

ED_{50}* VALUES FOR EACH TEST COMPOUND IN RATS

Compound	μ moles/kg	95% c.l.	mg/kg	95% c.l.
A(1)	14	10.2– 20.5	2.6	1.9 – 3.8
A(2)	12	9.4– 14.4	2.15	1.7 – 2.6
NMA	10.0	7.1– 12.6	1.9	1.35– 2.4
NEA	12	9.5– 15.5	2.4	1.9 – 3.1
NPA	48	42.6– 55	10.3	9.1 –11.8
NBA	71	55 –111	16	12.3 –25

*Approximate dose required to reduce intake to 50% of control levels, as determined by least squares linear regression.

typed movements were observed in all animals during periods of self-administration of A, NMA and NEA as well as with NPA and NBA during the first session of a substitution period when intake was high.

Although A, NMA and NEA functioned as positive reinforcers in all 4 animals, average response rates for these compounds differed as a function of baseline drug condition. Animals whose responding was maintained by pentobarbital under control conditions self-administered test drugs at a higher rate than did those animals whose responding was maintained by cocaine. The fact that baseline drug conditions were not reversed makes it possible that individual differences between animals could account for this finding. However, several additional explanations might account for these differences. It is well known that the rate and pattern of responding under control conditions are critical determinants of the effects of a drug [16]. In addition to the fact that the overall response rates maintained by 0.1 mg/kg cocaine were slightly lower than those maintained by 0.25 mg/kg PB, the patterns of responding during control sessions were substantially different. Responding maintained by cocaine was relatively stable throughout the session, while responding maintained by PB tended to occur in bursts followed by long pauses. These patterns are consistent with previous descriptions of cocaine and barbiturate-reinforced responding [1, 36, 38]. It is possible that the higher rates as well as the pattern of bursting observed in the PB-maintained animals under control conditions shaped similar rates and patterns of responding for test compounds. It is also possible that metabolic changes contributed to rate differences. PB is known to be a potent inducer of the liver microsomal enzyme system, a system involved in the inactivation of amphetamines and related compounds [10,14]. In animals whose responding was maintained by PB, sufficient intake under baseline condition could result in an increase in the synthesis of metabolic enzymes and a more rapid destruction of amphetamines. Such an effect, though not measured in the present experiment, might explain a decreased disruption of ongoing responding by the test drugs, and consequent higher response rates for amphetamines in barbiturate-maintained animals. In any case, these data are in contrast to observations by others [24] that higher rates of responding for A were observed in cocaine-maintained animals compared to PB- or codeine-maintained animals. It remains for future research to reveal the sources of differences between these divergent experimental results.

When *d*-N-alkylated amphetamines were administered to rats allowed to drink milk, there was a dose-related decrease in intake. In addition, typical sympathomimetic effects (e.g., increased motor activity and stereotypy) were observed following high doses of each compounds. This is consistent with data reported elsewhere for A, NMA and related compounds [4, 15, 40]. In addition, the potencies of the N-alkylated amphetamines in disrupting milk intake were similar to their potencies in the self-administration procedure. That is, with substituents larger than ethyl, potency diminished rapidly as N-alkyl length increased. In the milk intake tests, it might be argued that potency differences could be accounted for by the development of tolerance to the disruptive effects of the compounds due to repeated testing. However, the redetermination of the effects of doses of the first compound tested after the entire series had been tested makes this unlikely. This possibility is made even more remote by the data from the guinea-pig atrium. That is, since fresh atria were used each time, previous drug exposure could not have contributed to observed potency relationships.

Daly *et al.* [5] reported a decrease in activity of N-alkyl amphetamines with substituent groups larger than ethyl in releasing H^3-norepinephrine from mouse heart. This observation together with data from the experiments presented here are consistent with the hypothesis that the behavioral effects of amphetamine and related compounds are mediated by the release of catecholamines [1,14]. That N-alkylated amphetamines with substituent groups larger than ethyl are less potent behaviorally than smaller compounds may be due to diminished ability to release catecholamines centrally.

ACKNOWLEDGEMENTS

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