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Structural Variation and (+)-Amphetamine-Like Discriminative Stimulus Properties[1]

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OBERLENDER, R. AND D. E. NICHOLS. *Structural variation and (+)-amphetamine-like discriminative stimulus properties.* PHARMACOL BIOCHEM BEHAV **38**(3) 581–586, 1991.—Rats were trained to discriminate (+)-amphetamine sulfate (5.43 μmol/kg, 1 mg/kg) from saline in a food-reinforced, two-lever drug discrimination paradigm. Side chain variations of the amphetamine molecular structure were analyzed for their effects on the discriminative stimulus properties of this prototype central nervous system stimulant. Partial generalization was observed for the α-ethyl homologue of (+)-amphetamine, (+)-AEPEA, and for 2-aminoindan (AI), while 5,6-methylenedioxy-2-aminoindan (MDAI) elicited only saline-appropriate responding. By contrast, 2-amino-1,2-dihydronaphthalene (ADN) and 2-aminotetralin (AT) completely substituted for (+)-amphetamine. Relative to the training drug, ADN was ¼ as potent and AT was ⅛ as potent. The *S*-(−)-isomer of ADN was found to be responsible for the (+)-amphetamine-like discriminative properties of the racemate. The results suggest that constraining or extending the α-alkyl substituent of (+)-amphetamine has a deleterious effect on the ability of the resulting analogue to adopt the active conformation of (+)-amphetamine, thereby diminishing its characteristic discriminative stimulus properties.

Drug discrimination Stimulants (+)-Amphetamine (+)-α-Ethylphenethylamine 2-Aminoindan (AI) 5,6-Methylenedioxy-2-aminoindan (MDAI) 2-Amino-1,2-dihydronaphthalene (ADN) 2-Aminotetralin (AT)

A wide variety of biological interactions has been observed for drugs with molecular structures containing a basic nitrogen atom separated by 2 carbons from a phenyl group, the simplest example being phenethylamine (PEA). The addition of a methyl substituent to the α-carbon of PEA itself forms amphetamine. Most of the diverse behavioral effects of amphetamine seem to involve dopaminergic neurons, while norepinephrine (NE) and serotonin (5-HT) systems may exert modulatory influences (5,26). Although it elicits a variety of biological effects, the most outstanding pharmacologic characteristic of amphetamine is central nervous system (CNS) stimulatory activity (2). While it is well known that aromatic substituents may alter the type of activity observed in individual PEAs, less is known about the effects on activity from changes made to the side chain [e.g., see (26)]. Furthermore, although the stimulatory effects of amphetamine and its derivatives have been studied extensively, the diversity of procedures and techniques employed make it difficult to compare the results from different studies (2).

Evaluations employing the drug discrimination (DD) paradigm are particularly valuable for studies with congeneric series of compounds. The data obtained when the discriminative stimulus (DS) properties of two drugs are compared in this assay provide powerful and reliable estimates of their similarity and potency. Thus rats trained to discriminate saline from a specific drug at a specific dose can be challenged with various chemical analogues. Drug-appropriate operant responding only occurs when the test drug produces an interoceptive state similar to the training drug. The objectivity by which behavioral parameters are measured, and the relatively low doses required for many discriminable drug effects, facilitate the assessment of changes in psychopharmacological activity resulting from particular molecular modifications. The present study was directed, therefore, toward identifying the effects of selected molecular modifications on the DS properties of amphetamine itself, the "prototype" stimulant.

Our laboratory has recently developed a considerable interest in the DS properties of the α-ethyl homologue of (+)-amphetamine, (+)-AEPEA (see Fig. 1), stemming from structure-activity relationship (SAR) investigations (10, 14–16, 18–21, 23) of 3,4-methylenedioxymethamphetamine (MDMA). This structural modification was evaluated in DD experiments utilizing rats trained to discriminate saline from (+)-amphetamine, MDMA, or N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), the α-ethyl homologue of MDMA. While symmetrical substitution occurred between MBDB and MDMA, no substitution was observed between MBDB and (+)-amphetamine (16,21). Most recently, the α-ethyl homologue of *p*-chloroamphetamine (PCA), 1-

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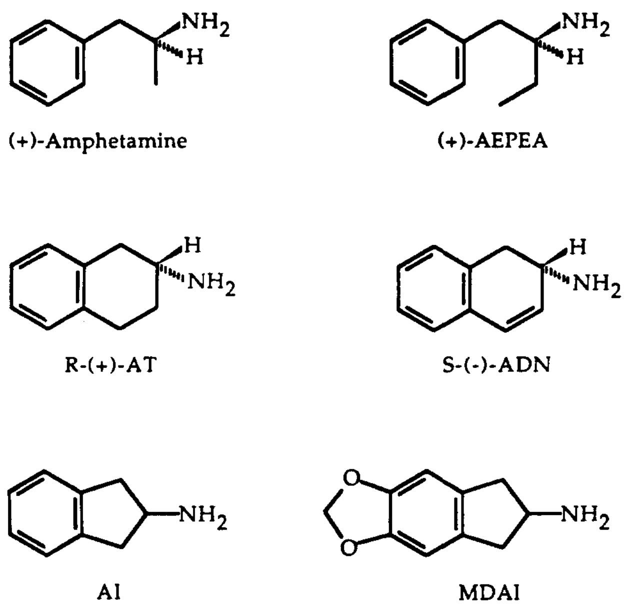

FIG. 1. Molecular structures of test drugs: (+)-amphetamine, (+)-α-ethylphenethylamine (AEPEA), 2-aminotetralin (AT), and 2-amino-1,2-dihydronaphthalene (ADN), 2-aminoindan (AI), 5,6-methylene-dioxy-2-aminoindan (MDAI).

(4-chlorophenyl)-2-butanamine (CAB), has also been found to exhibit pharmacology similar to its corresponding α-methyl homologue (11). However, in both these examples, a notable decrease in dopaminergic activity was observed in the α-ethyl substituted compounds (10, 11, 23). The retention of behavioral activities of MBDB and CAB, relative to MDMA and PCA, supports current thinking regarding the lack of a critical role for dopamine neurons in mediating the psychopharmacological effects of these primarily serotonergic agents (18–22). Since much evidence now exists for the dopaminergic mediation of the DS properties of (+)-amphetamine (7, 13, 26), it was anticipated that extension of the α-alkyl substituent of amphetamine itself might lead to more obvious changes in its DS properties. Therefore, (+)-AEPEA was prepared and evaluated in (+)-amphetamine-trained rats.

Several rigid analogues of amphetamine (shown in Fig. 1), in which the otherwise freely rotating, side chain is "tethered" to the phenyl ring, were also of interest. These included two six-membered ring derivatives of amphetamine, 2-aminotetralin (AT) and 2-amino-1,2-dihydronaphthalene (ADN). Previously, Glennon et al. (7) tested a series of conformationally restricted analogues of amphetamine in rats trained to discriminate 1 mg/kg (+)-amphetamine sulfate from saline. Complete generalization of (+)-amphetamine occurred with AT, which was about one-third as active as (+)-amphetamine. Curiously, when evaluated for its effect on spontaneous motor activity in mice, AT either produced a depressant effect (1,8), or only one-tenth the stimulant activity of amphetamine (24). The decrease in spontaneous motor activity was later found to be attributable to the effect of the *S*-(−)-isomer, while the *R*-(+)-isomer had very weak stimulant effects (17). By contrast, (±)-ADN clearly stimulated spontaneous motor activity in mice, in a dose-dependent manner, with one-fourth the potency of (+)-amphetamine (9). Thus an enhancing effect on stimulant activity resulted from the introduction of a double bond into the 3,4-position of AT. The *S*-(−)-isomer of ADN, which is of the same absolute configuration as *R*-(+)-AT (note in Fig. 1 that the priority numbers of the groups on the chiral carbon are different), was found to be solely responsible for the stimulant activity of the racemate. It was, therefore, of interest to determine whether ADN would elicit (+)-amphetamine-like DS effects. Each enantiomer of ADN was also tested in order to compare the DD results with the stereochemical evaluations obtained previously in mice (9).

Finally, the set of test drugs for the present study was completed with the inclusion of two additional conformationally restricted derivatives. When evaluated in the previously cited DD study (7), complete generalization was observed for the 5-membered ring derivative, 2-aminoindan (AI), although on a molar basis it was less than one-fifth as potent as (+)-amphetamine. However, Witkin et al. (25) reported that AI decreased spontaneous motor activity in mice throughout the dose spectrum. By contrast, in a study employing (+)-MBDB-trained rats, we recently found that 5,6-methylenedioxy-2-aminoindan (MDAI) was equipotent to 3,4-methylenedioxyamphetamine (MDA), the open-chain analogue of MDAI (21). Similarly, in MDMA-trained rats, generalization occurred to MDAI which was equipotent to MDMA (15). Thus, in drugs believed to produce a serotonergic cue, an aminoindan appeared equipotent to the analogous amphetamine. We, therefore, included AI and MDAI in the present evaluation of (+)-amphetamine-like DS properties.

METHOD

Subjects

Twelve male Sprague-Dawley rats (Harlan Laboratories, Indianapolis, IN) weighing 200–240 g at the beginning of the study were used as subjects. None of the rats had previously received drugs or behavioral training. Water was freely available in their individual home cages and a rationed amount of supplemental feed (Purina Lab Blox) was made available after experimental sessions so as to maintain approximately 85% of the free-feeding weight. The temperature of the animal facility remained within the range of 22–24°C. The humidity was maintained at 40–50% and the lights were on between 6 a.m. and 8 p.m.

Apparatus

Six standard operant chambers (Coulbourn Instruments, Lehigh Valley, PA) consisted of modular test cages enclosed within sound-attenuated cubicles with fans for ventilation and background white noise. A white house light was centered near the top of the front panel of the test cage, which was also equipped with two response levers, separated by a food hopper, all positioned 2.5 cm above the floor. Solid state logic in an adjacent room, interfaced through a Coulbourn Instruments Dynaport to an IBM PC, controlled reinforcement and data acquisition with a locally written program.

Discrimination Acquisition, Training, and Testing

A fixed ratio (FR) 50 schedule of food reinforcement (Bioserv 45 mg dustless pellets) in a two-lever paradigm was used. Initially, rats were taught to lever press on an FR 1 schedule so that one food pellet was dispensed for each press. Half the rats were trained on drug-L, saline-R, and the other half drug-R, saline-L, to avoid positional preference. Training sessions lasted 15 min and were conducted at the same time each day, Monday through Friday. Levers were cleaned with a 10% ethanol solution in order to avoid olfactory cues (6). Both levers were present during all phases of training but reinforcements were delivered only after responses on the stimulus-appropriate lever. Presses on the incorrect lever were recorded but had no programmed consequence. After initially learning to lever-press for food, the training drug, (+)-amphetamine sulfate (5.43 mmol/kg, 1.0 mg/kg), or saline was administered IP 30 min prior to sessions. Saline and drug sessions were randomly ordered, with neither treatment given more than 3 consecutive sessions. As responding rates stabilized, the schedule of reinforcement was gradually increased from FR 1 to FR 50. Once at FR 50, training continued until an accuracy of at least 85% (number of correct presses × 100/number of total presses) was attained for eight of ten consecutive sessions.

Once criterion performance was attained, test sessions were interspersed between training sessions either one or two times per week. At least one drug and one saline session separated each test session. Rats were required to maintain the 85% correct responding criterion on training days in order to be tested. In addition, test data were discarded when the accuracy criterion of 85% was not achieved on the training sessions following a test session (3). Test drugs were administered IP 30 min prior to the session and test sessions were run under conditions of extinction, with rats removed from the operant box when 50 presses were emitted on one lever. If 50 presses on one lever were not completed within 5 min, the session was ended and scored as a disruption (D). Treatments were randomized at the beginning of the study and at least 8 rats were tested at each dose of a test drug.

Data Analysis

The data were scored in quantal fashion with the lever on which the rat first emitted 50 presses in a test session scored as the "selected" lever. The percentage of rats selecting the drug lever (%SDL) for each dose of test compound was determined. If that drug was one which completely substituted for the training drug (at least one dose resulted in the %SDL = 80% or higher), the method of Litchfield and Wilcoxon (12) was used to determine the ED_{50} and 95% confidence interval (95% C.I.). This method also allowed for tests of parallelism between the dose-response curves of the test drugs and that of (+)-amphetamine.

Drugs

Doses refer to the salt forms for each drug and are expressed in terms of μmol/kg. The training dose of (+)-amphetamine sulfate, 5.43 μmol/kg, was 1.00 mg/kg. The molecular weight and the source for each compound used in the study are as follows: (+)-amphetamine sulfate (184, Smith, Kline and French), 2-aminoindan hydrochloride, AI (170, Aldrich), 2-aminotetralin hydrochloride, AT [184, (1)], and 2-amino-1,2-dihydronaphthalene, ADN [182, (9)]. (+)-AEPEA sulfate was prepared in this laboratory using standard methods described previously (16). The melting point was 124–125°C, the optical rotation was +13.6° (c = 2, MeOH), and the NMR spectrum was consistent with the assigned structure. All solutions were prepared by dissolving the compounds in saline at a concentration that allowed the appropriate dose to be given in a volume of 1 ml/kg, identical to the volume of the saline injections.

RESULTS

The (+)-amphetamine-saline discrimination was successfully acquired by all twelve rats. The average number of sessions to criterion was 45 ± 3 (± SE), with a range of 23–65 sessions. The response rate after (+)-amphetamine (112 ± 10 presses/min) was not significantly different ($p > 0.05$, Student's *t*-test) from the response rate after saline (102 ± 9 presses/min). Of the 8 rats tested

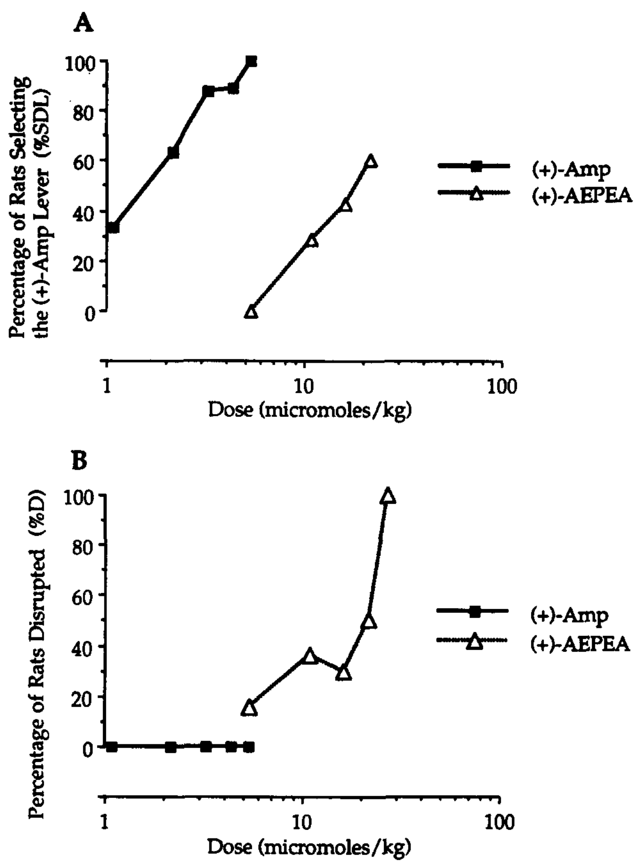

FIG. 2. Results of tests with (+)-amphetamine and (+)-AEPEA in (+)-amphetamine-trained rats. The top panel, A, shows the dose-response curves for the percentage of rats selecting the drug lever (7–10 rats responding at each dose). The percentage of the total rats tested that were disrupted (failed to finish 50 presses on one lever in 5 min) over the doses tested is given in B, the bottom panel.

with saline, none selected the drug lever. The test data for (+)-amphetamine and (+)-AEPEA are illustrated in Fig. 2.

Both compounds produced a parallel, dose-dependent increase in drug-appropriate responding with approximately an order of magnitude difference in potency. The ED_{50} and 95% C.I. calculated for (+)-amphetamine was 1.57 (0.99–2.49) μmol/kg; 0.29 (0.18–0.46) mg/kg. All of the rats tested with the various doses of (+)-amphetamine finished 50 presses within the 5-min test period, i.e., %D = 0 across the entire dose range. However, the α-ethyl derivative, (+)-AEPEA, produced accompanying increases in the percentage of disruptions and only partially substituted for (+)-amphetamine (maximum %SDL = 60). For example, a significant number of rats (4/11) tested with 10.85 μmol/kg of (+)-AEPEA (twice the training dose of (+)-amphetamine) were scored as disrupted. This dose did not appear to mimic the drug cue since only 29% of the responding rats selected the drug lever. The maximum percentage of rats selected the drug lever after a dose of 21.7 μmol/kg of (+)-AEPEA. Of the 10 rats tested at that dose, 5 were disrupted, 3 selected the drug lever and 2 selected the saline lever. The highest dose tested, 27.1 μmol/kg [which is 5 times the training dose of (+)-amphetamine] disrupted 100% of the rats tested.

Figure 3 shows the results of substitution testing of the two six-membered ring analogues, ADN and AT, both of which fully

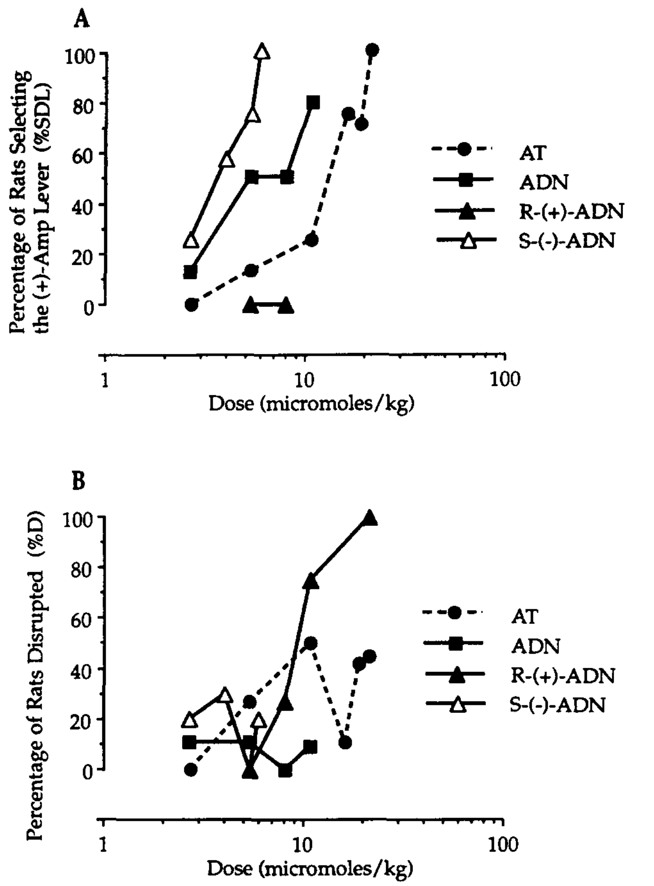

FIG. 3. Results of substitution tests with AT and ADN in (+)-amphetamine-trained rats. Panels A and B as in Fig. 2.

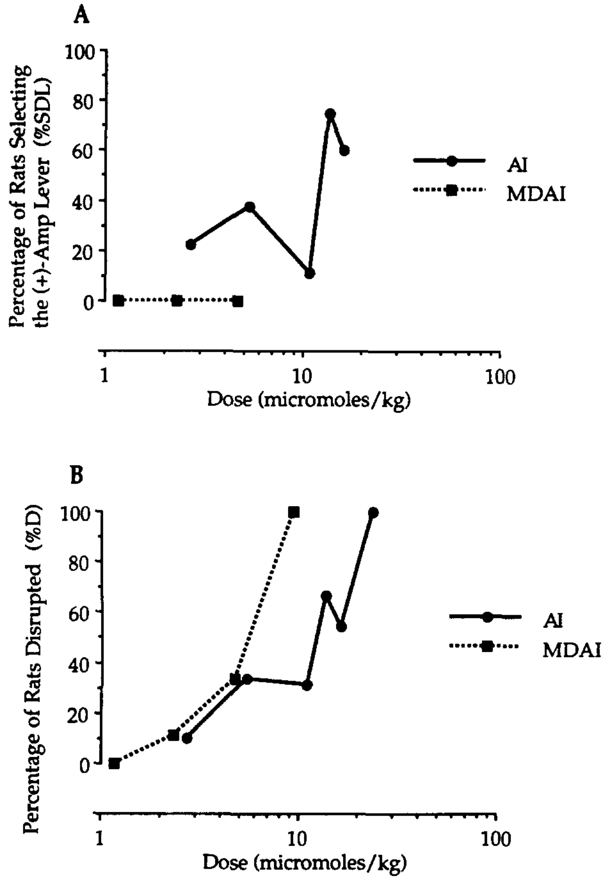

FIG. 4. Results of substitution tests with AI and MDAI in (+)-amphetamine-trained rats. Panels A and B as in Fig. 2.

substituted for (+)-amphetamine. Of the two, ADN elicited (+)-amphetamine-like DS properties that appeared less complex since it produced very few disruptions. The ED_{50} (95% C.I.) for (±)-ADN was 6.40 (4.09–10.0) μmole/kg, about ¼ the potency of (+)-amphetamine. The enantiomers of ADN were found to differ significantly with respect to mimicking (+)-amphetamine. In contrast to the complete lack of (+)-amphetamine-like DS properties observed for the *R*-(+)-isomer, *S*-(−)-ADN potently substituted for the training drug with an ED_{50} (95% C.I.) of 3.63 (2.86–4.63) μmole/kg. Rats tested with higher doses of the *R*-(+)-isomer did not finish 50 presses within the 5-min test period. AT also disrupted large percentages of the rats tested, although complete substitution for (+)-amphetamine was observed with a calculated ED_{50} (95% C.I.) value of 11.91 (8.68–16.4) μmoles/kg. Thus the potency of AT was approximately one-eighth the potency of (+)-amphetamine and about half that of ADN. Both ADN and AT produced dose-response curves that were parallel to that of (+)-amphetamine.

Generally, the 5-membered ring derivatives were much less (+)-amphetamine-like than the 6-membered ring compounds. As shown in Fig. 4, AI produced an erratic increase in %SDL but, similar to (+)-AEPEA, it caused significant numbers of rats to be disrupted and only partially substituted for (+)-amphetamine. The maximum %SDL (75%) occurred at 13.6 μmoles/kg, three times the training dose of (+)-amphetamine. In contrast to the partial substitution of AI, the introduction of a methylenedioxy substituent in MDAI had the dramatic effect of completely abolishing the (+)-amphetamine-like DS. None of the rats tested with any dose of MDAI selected the drug lever. Yet, MDAI was the most potent rigid analogue in causing disruptions, which occurred in a dose-dependent fashion.

DISCUSSION

The analogues tested in this DD experiment exhibited various degrees of diminished (+)-amphetamine-like activity. The simple extension of the α-alkyl substituent from methyl to ethyl resulted in a dramatic decrease in potency. Furthermore, the inability of (+)-AEPEA to completely substitute for (+)-amphetamine indicates that a change in the qualitative nature of the behavioral effect may also have resulted from this molecular modification. These results suggest that the α-alkyl substituents strongly influence the degree to which amphetamine analogues share DS stimulus properties with (+)-amphetamine itself. Presumably, this reflects the decreased ability of (+)-AEPEA to interact with dopaminergic pathways (see introduction). If that is the case, this particular side chain modification can be viewed as an especially relevant one in the comparison of (+)-amphetamine-like and MDMA-like activities, as discussed previously (18–22). It is apparent that the extension of the α-methyl group of MDMA to an ethyl does *not* lead to analogous changes in MDMA-like behavioral activity (18–21). In fact, MBDB, the α-ethyl homologue of MDMA, has effects in man (16) and animals (18–21) that closely resemble those of MDMA. Although no studies have been reported of dopamine releasing, or dopamine uptake inhibition activity of (+)-AEPEA, a dramatic attenuation of the dopaminergic effects of MDMA and PCA occurs in their α-ethyl homologues, MBDB and CAB, respectively (10, 11, 23). Thus the effect on dopaminergic mechanisms resulting from the increased size of the α-alkyl substituent may be critical in the loss of stimulant-like DS properties by (+)-AEPEA while exerting a relatively minor effect on drugs with indirect agonist activity that is primarily associated with serotonergic neuronal systems.

The most potent amphetamine-like compound tested in the present study was 2-ADN which seemed to exert a stereospecific activity. The four-fold potency difference observed between (+)-amphetamine and racemic 2-ADN is consistent with the results from experiments measuring spontaneous motor activity in mice, as reported in our original study (9). Also consistent with those earlier results, the *S*-(−)-isomer of 2-ADN appeared to be responsible for the behavioral effects of the racemate. In previous studies, 2-AT either did not stimulate spontaneous motor activity in mice (1,8), or it had 10% of the activity of amphetamine (24). Yet, in the present study, it mimicked (+)-amphetamine as a DS in rats, in agreement with the results of Glennon et al. (7). However, 2-AT was one-half as potent as (+)-amphetamine in that study but only one-eighth as potent as (+)-amphetamine in the present experiment.

The results of the AI substitution tests are also comparable to those reported previously (7). The relatively high level of partial substitution observed here (maximum %SDL was 75%) is well within the range of the relatively low level of complete substitution of 2-AI for (+)-amphetamine observed previously [maximum amphetamine-appropriate responding was 83%, (7)]. However, AI produced a greater level of disruptive effects in the rats employed in the present study. For example, 6/6 rats were disrupted with 4 mg/kg (24 μmol/kg) of AI, the dose that produced complete substitution for (+)-amphetamine in the study by Glennon et al. (7). Procedural differences may account for these discrepancies. Interestingly, the methylendioxy-substituted indan derivative MDAI elicited only saline-like responding in (+)-amphetamine-trained rats in contrast to the complete substitution previously observed in rats trained to discriminate saline from either MDMA (15) or (+)-MBDB (21) (at doses reflecting a potency similar to the training drugs and which did not produce significant disruptions). These results provide additional support for the distinctive pharmacological activities of (+)-amphetamine-like stimulants and MDMA-like compounds. It should be emphasized that while AI and MDAI are not chiral, other rigid analogues in this study, such as AT and ADN, exist in their racemic forms as half *R* and half *S*. Therefore, based on kinetics, the apparent potency of 2-AI is higher than might be observed if enantiomers existed for this compound.

In conclusion, unlike MDMA-like activity, (+)-amphetamine-like DS properties are significantly decreased by an α-ethyl substituent in the side chain, or when the α-methyl group is tethered back to the ring, as in 2-aminoindan. Incorporating the side chain into a 6-membered ring containing a double bond, as in ADN, leads to a compound that is very much amphetamine-like. However, in the same compound without the double bond (AT), a decrease in (+)-amphetamine-like DS properties is observed. The conformations of amphetamine, AEPEA, 2-AT and 2-ADN were studied by deJong et al. (4), using ^{13}C-NMR techniques. They found differences in the angles between the planes of the phenyl ring and side chains and concluded that potency differences were attributable to the conformational allowance of simultaneous access of the ammonium and phenyl groups to a flat receptor surface (4). Similar arguments could apply to the behavioral results obtained in the present study, suggesting that MDMA and (+)-amphetamine may possess different active conformations.

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