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Discriminative Stimulus Properties of Substituted Amphetamine Derivatives

WILLIAM A. CORRIGALL,*†[1] KATHLEEN M. COEN,* FOUAD M. SAOUDA,* JAMES M. ROBERTSON* AND BRUCE A. LODGE‡

**Neurobiology Section, Addiction Research Foundation, Toronto, Ontario M5S 2S1, Canada*
†Department of Physiology, University of Toronto, Toronto, Ontario M5S 1A8, Canada
‡Pharmaceutical Chemistry Division, Bureau of Drug Research, Health and Welfare Canada, Ottawa, Ontario K1A 0L2, Canada

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CORRIGALL, W. A., K. M. COEN, F. M. SAOUDA, J. M. ROBERTSON AND B. A. LODGE. *Discriminative stimulus properties of substituted amphetamine derivatives.* PHARMACOL BIOCHEM BEHAV 43(4) 1117–1119, 1992.– Animals were trained to discriminate amphetamine (1 mg/kg) from saline in a fixed-ratio (FR 10), food-reinforced paradigm. Amphetamine-appropriate responding was engendered by the training dose, and by 3 mg/kg, while at lower doses there was a progressive decrease in the extent of responding on the drug-appropriate lever. The following three novel amphetamine derivatives were tested for their ability to produce amphetamine-appropriate responding: 2,5-dimethoxy-4-ethoxy-amphetamine (DMEA); 2,5-dimethoxy-4-methylthio-amphetamine (DMMTA), and 2,4,5-trimethoxy-amphetamine (TMA). DMEA produced only minimal (<20%) amphetamine-appropriate responding over a dose range of 0.1–10 mg/kg. Substantial decreases in response rate limited testing of the other amphetamines to a dose maximum of 3 mg/kg, but over the range of 0.1–3.0 mg/kg there was little evidence for generalization. At 3 mg/kg of either DMMTA or TMA, only 2 of 10 animals completed at least one uninterrupted FR 10 on either lever, and with either compound only 1 of these 2 animals responded more than 50% on the drug-appropriate lever. Of the three compounds tested, DMMTA had the greatest response rate-decreasing effect.

Amphetamine Discrimination 2,4,5-Trimethoxy-amphetamine 2,5-Dimethoxy-4-methylthio-amphetamine 2,5-Dimethoxy-4-ethoxy-amphetamine

ALTHOUGH amphetamine tends to produce predominantly stimulant effects on the CNS, the 4-methoxy-substituted derivative [paramethoxy-amphetamine (PMA)] has been reported to have both stimulant and hallucinogenic effects (7). However, in a recent study we found that neither PMA nor 4-ethoxy-amphetamine produce amphetamine-appropriate responding in drug discrimination testing (3). Recently, in Canada novel amphetamine derivatives have been seized; these include 2,5-dimethoxy-4-ethoxy-amphetamine (DMEA); 2,5-dimethoxy-4-methylthio-amphetamine (DMMTA), and 2,4,5-trimethoxy-amphetamine (TMA). The purpose of the present study was to extend our studies of the discriminative stimulus properties of substituted amphetamines to these derivatives, specifically, to test whether DMEA, DMMTA, or TMA show any amphetamine-like discriminative stimulus properties.

METHOD

Drug Discrimination Training and Testing

Subjects were male Long-Evans rats (Charles River, Lachine, Quebec) drug naive at the time experiments were begun. Animals were housed in a reversed light-dark cycle room (lights off between 0700 and 1900 h and initially maintained under ad lib feeding conditions.

After habituation to the colony room, animals were deprived of food for a period of 24–48 h and trained to press a lever on a schedule of continuous reinforcement to receive 45-mg food pellets. Response requirements were raised to a fixed ratio (FR) 10. At this stage of the protocol, discrimination training was begun (2). Essentially, animals were given a daily injection of either saline (1 ml/kg, IP) or amphetamine (1 mg/kg, IP) 15 min prior to the start of each daily operant session. Animals were trained to produce 10 consecutive responses on the left-hand lever after saline injections and the same FR on the right-hand lever after amphetamine to receive food pellets. The schedule requirement was such that responding on the incorrect lever reset the requirement for the correct lever, that is, each subject was required to complete an uninterrupted FR 10 on the correct lever. Session duration was 15 min. To eliminate possible olfactory cues, consecutive animals running in the same operant chamber received opposite training injections on some days and the same training injections

[1] To whom requests for reprints should be addressed.

on others. Choice of saline or amphetamine as the training injection was made according to a predetermined sequence that repeated every 4 weeks.

A subject was considered trained to criterion level when no more than two incorrect responses were made before delivery of the first food pellet and, in addition, at least 90% of the total responding in the session was made on the correct lever. When these conditions were met, testing was begun.

Test sessions were carried out on Tuesdays and Fridays subject to sustained training criteria on intervening days. On test days, both levers were active and every uninterrupted FR 10 on either lever resulted in the delivery of a food pellet. During this phase, training sessions were carried out on intervening nontest days.

Drugs and Solutions

The following drugs were used: *d*-amphetamine sulphate; DMEA HCl, DMMTA HCl, and TMA HCl (all obtained from the Bureau of Drug Research, Health Protection Branch, Health and Welfare Canada, Ottawa). Solutions were prepared in sterile isotonic saline and injected at a volume of 1 ml/kg. All doses refer to the base.

Analysis

Data in all cases are presented as the group mean, and bars show the SEM. The sample size is 10 in all cases. Data from animals that did not complete at least one FR 10 during testing were not included in calculating the drug-appropriate response score; the number of animals not completing at least one FR 10 at any dose is shown adjacent to the relevant data point in each figure.

RESULTS AND DISCUSSION

Maximal selection of the drug-appropriate lever occurred at the training dose of 1 mg/kg (Fig. 1A); at this dose, the response rate was marginally reduced compared to the response rate following saline treatment (Fig. 1B). At a higher dose of amphetamine (3 mg/kg), selection of the drug-appropriate lever remained at 100% but the response rate was decreased substantially. Doses of amphetamine greater than 3 mg/kg were not tested in this study; in previous experiments, 10 mg/kg amphetamine would produce almost complete cessation of responding (2).

None of the substituted amphetamine derivatives engendered substantial amphetamine-appropriate responding at any dose (Fig. 1A). In the case of DMEA, there was no amphetamine-appropriate responding produced after doses between 0.1 and 10 mg/kg. The other two amphetamine derivatives, DMMTA and TMA, produced no amphetamine-appropriate responding between 0.1 and 1.0 mg/kg. At a dose of 3 mg/kg, both these amphetamine derivatives produced partial amphetamine-appropriate responding, but substantial decreases in response rate occurred after this dose of these compounds, preventing testing of higher doses (Fig. 1B). Indeed even at 3 mg/kg of either DMMTA or TMA only 2 of 10 subjects completed at least one uninterrupted FR 10; of the 2 animals that responded, only 1 produced greater than 50% amphetamine-appropriate responding after either drug. Whether these compounds would generalize at higher test doses if a paradigm with minimal response requirement was used is unknown.

Comparing response rates, there was considerable difference between the three amphetamine derivatives (Fig. 1B). DMEA appeared to have effects on response rate that were similar to those of amphetamine whereas DMMTA and TMA each produced substantial decreases in response rate at the 3-mg/kg dose and were therefore not tested at higher doses. The mechanism of the rate decreases could be sedation, induction of psychosis, or other drug-induced behavioral effects.

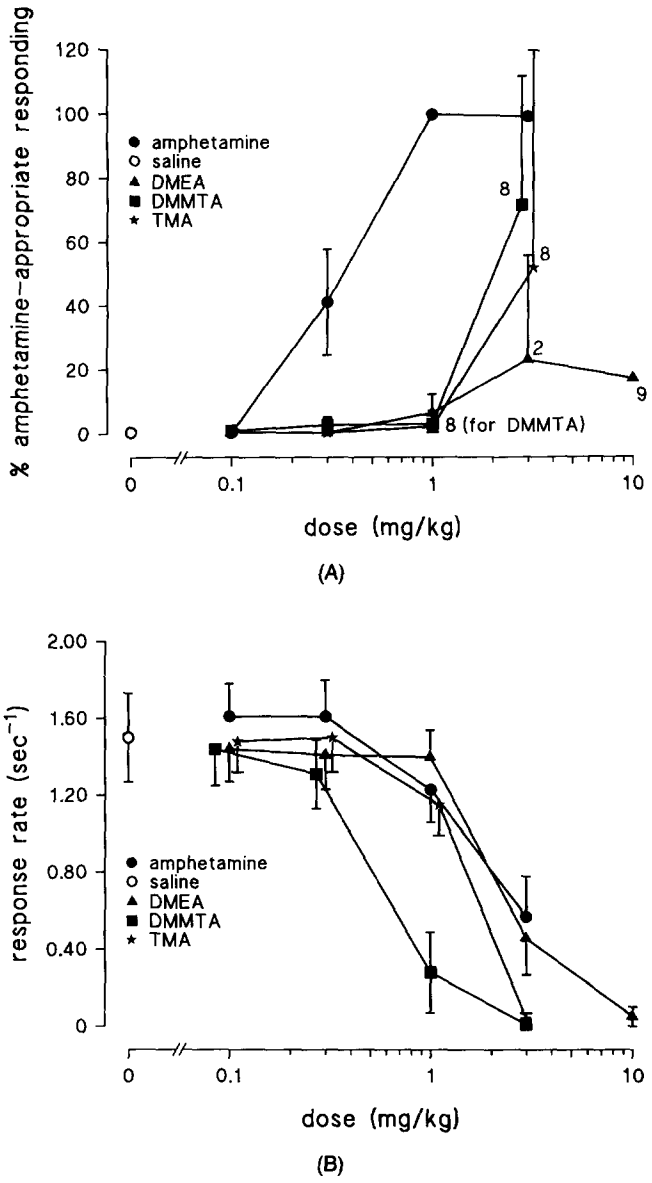

FIG. 1. (A). Selection of the amphetamine-appropriate lever by animals following different doses of amphetamine, 2,5-dimethoxy-4-ethoxy amphetamine (DMEA), 2,5-dimethoxy-4-methylthio-amphetamine (DMMTA), 2,4,5-trimethoxy-amphetamine (TMA), or saline. Numbers beside certain data point indicates the number of animals that did not complete at least one uninterrupted fixed ratio (FR) 10 at that dose during the 15-min session. Only DMEA was tested at a dose of 10 mg/kg because the other two derivatives produced substantial decreases in responding after a dose of 3 mg/kg. Data in this and Fig. 1B derive from the same sample of subjects (n = 10). Points represent mean values and bars SEM. For clarity, some data points have been shifted slightly to the left or right to avoid overlap of error bars. (B). Average response rates after amphetamine, saline, or substituted amphetamine derivatives (mean ± SEM).

This research shows that the amphetamine derivatives DMEA, DMMTA, and TMA have essentially no amphetamine-like discriminative stimulus properties; in the absence of overt response decreases, a maximum of approximately 20% amphetamine-appropriate responding was produced. However, Glennon and colleagues (5) have shown that TMA produces partial amphetamine-appropriate responding in animals trained at a somewhat higher dose of amphetamine (1 mg/kg amphetamine sulphate, dose as the salt). In addition, both TMA and DMEA generalize fully to the hallucinogen 4-methyl-2,5-dimethoxy amphetamine [(DOM) (4)]. These examples raise two points. First, the compounds appear to be more hallucinogenic than stimulant is profile. Second, lack of generalization of the amphetamine cue to DMEA, DMMTA, or TMA in this study may be a function of the training dose of amphetamine used. We have previously observed limited generalization of the amphetamine cue to PMA and para-ethoxy-amphetamine (3) whereas others (5,6) who have used a somewhat higher amphetamine dose to train subjects have observed greater, although still partial, generalization to PMA. It may be that animals trained at a higher dose of amphetamine are trained to a set of drug cues sufficiently different to permit generalization to these compounds (18). This would suggest that other than the stimulant properties of amphetamine might be important in establishing generalization.

This data provides the first information about the behavioral pharmacology of DMEA, DMMTA, and TMA. Detailed interpretation will require additional research into potential mechanisms of action of the drugs within the CNS.

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