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Behavioral characterization of alpha-ethyltryptamine, a tryptamine derivative with MDMA-like properties in rats

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Abstract. Several reports have speculated that the tryptamine-derived drug alpha-ethyltryptamine (AET) may have effects similar to those of the amphetamine-derived drug 3,4-methylenedioxymethamphetamine (MDMA). Indeed, the US Drug Enforcement Administration has recently placed AET on the Schedule I list because of its putative similarity to MDMA. The Behavioral Pattern Monitor, which quantifies locomotor and investigatory responses of rats, was used to characterize the effects of AET in a paradigm that distinguishes between the effects of traditional hallucinogens, amphetamine-like stimulants, and MDMA-like drugs. First, a dose-response study revealed that all doses of AET tested (5, 10, 20 mg/kg) significantly increased locomotor activity. Locomotor hyperactivity is produced by MDMA or amphetamine-like stimulants, but not by classical hallucinogens, such as LSD or mescaline. Additionally, AET significantly decreased measures of investigatory behavior. Similar decreases occur with MDMA or hallucinogen administration, but not with amphetamine-like stimulant administration. Second, as with MDMA, the locomotor hyperactivity induced by AET was attenuated by pretreatment (10 mg/kg) with the serotonin reuptake inhibitor fluoxetine. Thus, AET, a tryptamine-derived drug, appears to produce an MDMA-like profile of behavioral changes by virtue of releasing presynaptic serotonin.

Key words: Alpha-ethyltryptamine – Monase – Fluoxetine – MDMA – Locomotion – Rats – Serotonin

Recent interest in the compound alpha-ethyltryptamine (AET), a tryptamine derivative previously marketed as Monase, has been stimulated by its inclusion on the Schedule I list by the US Drug Enforcement Administration (DEA) (Federal Register 1993). The scheduling of AET was justified by the DEA because: AET has been substituted for 3,4-methylenedioxymethamphetamine (MDMA; Ecstasy) in street sales (Federal Register 1993); AET may produce serotonin neurotoxicity (Huang et al. 1991); and deaths have been reported after ingestion of AET (Daldrup et al. 1986; Federal Register 1993). Both in vivo and in vitro studies of AET have revealed that it inhibits monoamine oxidase activity and increases serotonin and dopamine release (Greig et al. 1959; Baker et al. 1980). Systematic behavioral studies of AET are few, however. The behaviors that have been examined, such as ejaculatory response (Renyi 1986), serotonin syndrome (Renyi and Ross 1985), and cage-leaving response (Renyi et al. 1986), have not been designed to evaluate AET in relation to other drugs with abuse liability, with the exception of amphetamine (Renyi and Ross 1985; Renyi 1986; Renyi et al. 1986). In order to test this drug in a paradigm that has been used extensively to profile hallucinogens and MDMA-like drugs, as well as stimulants, we performed a dose-response study of AET on rats tested in the Behavioral Pattern Monitor (BPM), a system for quantifying the locomotor and investigatory responses of rodents. Previous studies have shown that it is the serotonin-releasing properties of MDMA and related drugs that are responsible for their locomotor activating effects (Callaway et al. 1990, 1991). First, a derivative of MDMA, MBDB, that releases serotonin but not dopamine, has behavioral effects very similar to those of MDMA (Callaway et al. 1991). Second, the hyperactivity produced by MDMA is prevented by depletion of brain serotonin or pretreatment with serotonin antagonists (Callaway et al. 1990). Third, the locomotor activating effects of MDMA could be attenuated by pretreatment with fluoxetine or other inhibitors of serotonin uptake (Callaway et al. 1990). Hence, the locomotor hyperactivity produced by MDMA-like drugs is attributable to their actions as indirect serotonin agonists.

After observing that AET produced an MDMA-like profile of behavioral changes in the BPM, pretreatment with fluoxetine was used to further investigate the similarities between AET and MDMA. This experiment tested the hypothesis that, like MDMA, AET produces locomotor hyperactivity by virtue of an uptake carrier-dependent release of presynaptic serotonin.

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Materials and methods

Animals. Male Sprague-Dawley rats (Harlan Industries, San Diego, Calif.) weighing 275–350 g were used. Animals were housed two or three per cage under a 12-h reverse light cycle (lights off: 0700 hours). Food and water were available ad libitum. Animals were allowed to acclimatize for approximately 1 week after arrival.

Behavioral testing. All behavior was measured in the BPM, a 30.5 × 61.0 cm black Plexiglas chamber housed in a wooden sound-attenuating box. Ten 2.5-cm holes are placed in the chamber (three in each long wall, one in one short wall, and three in the floor). Photocells in each hole detect investigatory holepokes. A touchplate, 15.2 cm above the floor, allows detection of rearings when contact is made by the animal between the metal floor and the metal touchplate. A 4 × 8 grid of infrared photobeams detects the animal's position in an X-Y plane. A computer continuously monitors all photobeams and the touchplate and stores the data for later analysis.

Analysis. The raw data were reduced to: the X and Y coordinates of the rat in the chamber; the occurrence of holepokes or rearings; and the amount of time spent at a particular coordinate or performing a particular behavior. Locomotor activity was quantified both by the total number of photobeam breaks in the BPM (movements) as a measure of total motor activity, and by the number of crossings between any of eight equal square sectors within the BPM (crossings) as a measure of horizontal locomotion. The number and duration of both holepokes and rearings were calculated. Data were first examined in 10-min time resolutions by two-way ANOVA with time as a repeated measure. When there were significant interactions with time (including Greenhouse-Geisser corrections for nonsphericity), further time resolutions were examined. Specific post hoc comparisons were done using Newman-Keuls. Significance was demonstrated by surpassing an alpha level of 0.05.

Procedure. Animals were tested in the dark and during the dark phase of their light cycle. Approximately 24 h before testing, animals were taken to the testing room, weighed, handled briefly, placed in a clear Plexiglas box (24 × 46 cm) for 30 s, and then returned to their cages in the animal room. On the day of testing, animals were brought to the testing room and allowed to sit for 60 min. Injections were administered under red lights in the testing room. Animals were tested for 120 min. In experiment 1, four groups (n = 7–10) of 35 rats received saline, 5, 10, or 20 mg/kg AET 10 min before testing.

Based on the results from experiment 1, 5 mg/kg AET was selected for further study because it had submaximal effects, but reliably increased activity. Because previous research with MDMA has demonstrated that only the locomotor activating effects of MDMA were attenuated by fluoxetine pretreatment (Callaway et al. 1990), we examined only locomotor activity in experiment 2. The most sensitive time resolution for activity was determined to be the second hour of the 2-h test. Four groups of ten rats each received pretreatments of either saline or 10 mg/kg fluoxetine 60 min before testing. Ten minutes before testing, rats were treated with either saline or 5 mg/kg AET. One rat, for unknown reasons, failed to respond throughout the test session and was omitted because it was more than two standard deviations below the group mean for several measures. Nevertheless, specific comparisons between groups were unaffected by this exclusion.

Drugs. Drugs used were: AET (Sigma Chemicals, St. Louis, Mo.) and fluoxetine (Lilly, Indianapolis, Ind.). Drugs were prepared fresh daily. AET (salt weight) was dissolved in nitrogen-purged 0.9% saline and injected subcutaneously in a volume of 1 ml/kg. Fluoxetine was dissolved in 0.9% saline and injected intraperitoneally in a volume of 2 ml/kg.

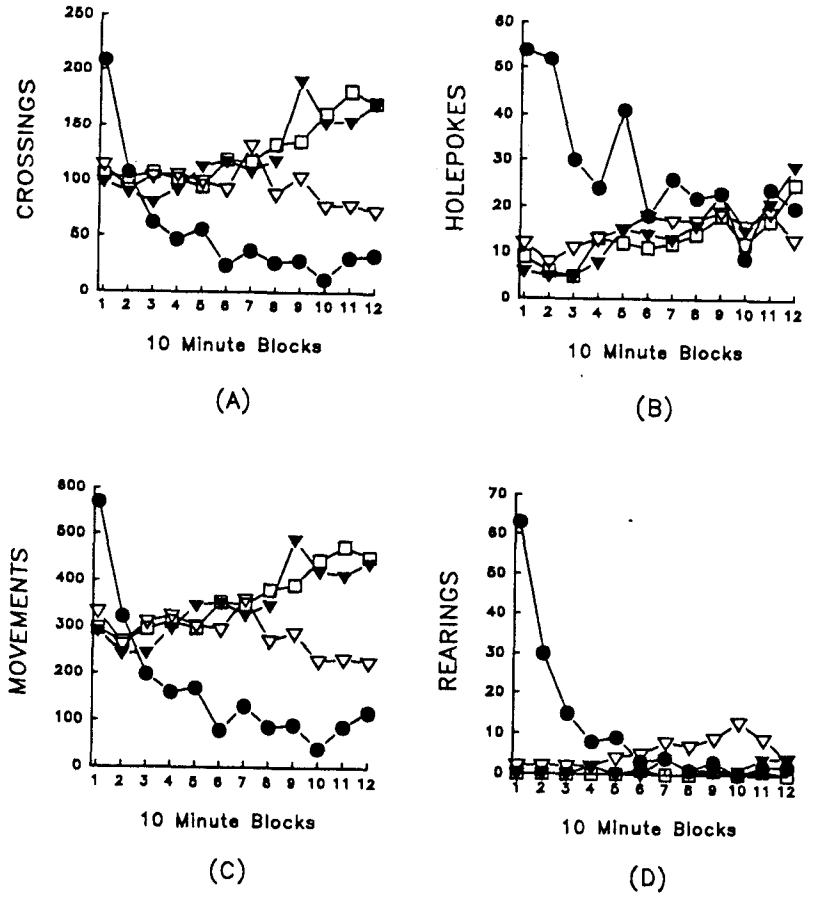

Fig. 1. All doses of AET (5, 10, 20 mg/kg) significantly increased horizontal locomotor activity (**A**) and global motor activity (**C**) over the 2-h test session. All doses of AET significantly decreased investigatory behaviors of holepokes (**B**) and rearings (**D**) over 2 h. Data are presented as group means for successive 10-min intervals. ● Saline; ▽ 5 mg/kg AET; ▼ 10 mg/kg AET; □ 20 mg/kg AET

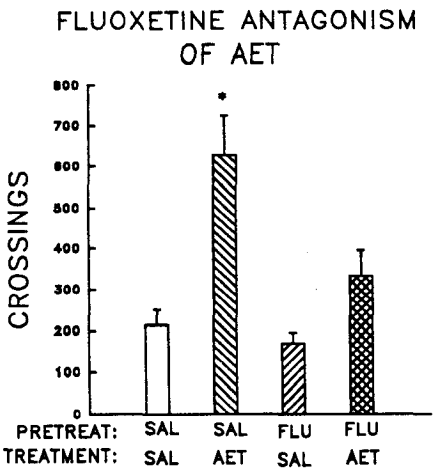

Fig. 2. Acute treatment with AET (*SAL/AET*) (5 mg/kg) significantly increased locomotor activity in the second hour of a 2-h test. This effect was attenuated by pretreatment with fluoxetine (*FLU/AET*). Data are presented as group means ± SEM. *Significantly different from all other groups, $P < 0.05$

Results

Experiment 1

AET significantly increased locomotor activity over the 2-h test session, as measured both by crossings [$F(3, 31) = 6.54$] (Fig. 1A) and movements [$F(3, 31) = 7.27$] (Fig. 1C). AET also significantly decreased investigatory activity, as measured by holepokes [$F(3, 31) = 8.02$] (Fig. 1B) and rearings [$F(3, 31) = 25.42$] (Fig. 1D) over the 2-h test session. Because activity measures had significant time-by-AET interactions [$F(33, 341) = 8.97$–10.43], data were examined for the first and second hour. The second hour was the more sensitive measure of AET's locomotor activating effects. AET significantly increased activity, as measured by both crossings [$F(3, 31) = 14.81$] and movements [$F(3, 31) = 16.89$]. Post hoc analyses revealed that all doses were significantly different from saline. For movements, post hoc analyses also demonstrated dose-dependent effects of AET because between doses, 5 mg/kg AET was significantly different from saline and both 10 mg/kg and 20 mg/kg. Lower doses of AET (1.25–2.5 mg/kg) produce qualitatively similar, but diminished, effects (K.M. Krebs and M.A. Geyer, unpublished observations).

Experiment 2

There was a significant interaction between fluoxetine pretreatment and AET treatment for crossings [$F(1, 35) = 4.51$] and for movements [$F(1, 35) = 7.04$] for the second hour of testing (Fig. 2), indicating that the increase in both crossings and movements produced by AET was reduced by fluoxetine pretreatment. Post hoc analyses revealed that, for both crossings and movements, the fluoxetine-pretreated/AET-treated group was different only from the saline-pretreated/AET-treated group.

Discussion

The behavioral profile produced by AET is strikingly similar to that of MDMA and is readily distinguishable from the effects of either traditional hallucinogens or amphetamine-like stimulants. The present studies of the effects of acutely administered AET demonstrated that all doses of AET significantly increased locomotor activity over the 2-h test session. The ability of AET to closely mimic the effects of MDMA-like drugs, despite its dissimilar structure, may provide a tool that could shed light on the structure-activity relationship mediating the common behavioral effects of these disparate compounds. Similar effects are also seen in rats treated with MDMA (Gold et al. 1988; Callaway et al. 1990, 1991) and amphetamine (Callaway et al. 1990), but not in rats treated with classical hallucinogens, such as LSD or mescaline (Adams and Geyer 1985; Geyer and Krebs 1993). Additionally, AET significantly decreased measures of investigatory behavior. Again, similar effects are observed with MDMA administration (Gold et al. 1988; Callaway et al. 1990, 1991) and with hallucinogen administration (Adams and Geyer 1985; Geyer and Krebs 1993; Krebs and Geyer 1993), but not with stimulant administration (Callaway et al. 1990). Therefore, the pattern of results observed with AET administration, namely increased locomotor activity and decreased investigatory behavior, is remarkably similar to the pattern produced by MDMA, but not by traditional hallucinogen or stimulant administration.

Experiment 2 demonstrated that the serotonin reuptake inhibitor fluoxetine attenuated the locomotor hyperactivity produced by AET. A similar effect was also seen with MDMA (Callaway et al. 1990), indicating that serotonin release is necessary for MDMA-like drugs to exert their locomotor activating effects. Accordingly, the fluoxetine-induced attenuation of AET's effects on locomotor hyperactivity indicates that AET acts via serotonin release.

Thus, in the present studies in rats, AET has been found to be similar to MDMA-like drugs in two respects: (1) AET increases locomotor activity and decreases investigatory activity; and (2) AET's effects on locomotor activity can be attenuated by pretreatment with fluoxetine. These results lead to the conclusion that AET exerts these effects through serotonin release. This apparent similarity in the effects of AET and MDMA in rats is consistent with reports that AET has been sold on the street as an MDMA-like drug (Federal Register 1993).

These observations of AET's similarity in effects to MDMA are especially interesting when we consider the differences in structure between these compounds. MDMA and its related drugs are amphetamine derivatives, whereas AET is a tryptamine derivative that is much more closely related to serotonin. This observation could be important in the understanding of the nature of the structure-activity relationships of these drugs. Further studies should now be undertaken to provide converging evidence for the relevance of presynaptic serotonin release to the effects of AET and to determine whether related derivatives of tryptamine have similar effects. If

there is a common mechanism for producing the locomotor activating effects seen with both AET and the methylenedioxy-substituted phenalkylamines, then the combined study of both classes of compounds could provide critical insights into the pharmacological actions subserving the subjective effects of indirect serotonin agonists.

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