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BRIEF COMMUNICATION

Anxiogenic Effect of Phenylethylamine and Amphetamine in the Elevated Plus-Maze in Mice and Its Attenuation by Ethanol

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LAPIN, I. P. *Anxiogenic effect of phenylethylamine and amphetamine in the elevated plus-maze in mice and its attenuation by ethanol.* PHARMACOL BIOCHEM BEHAV 44(1) 241-243, 1993.—In previous experiments β-phenylethylamine (PEA), like the standard anxiogens caffeine, pentylenetetrazole, and yohimbine, has exhibited an anxiogenic effect in the two animal models of anxiety: the social interaction test and the conflict situation test. In the present study, PEA acts as an anxiogen in an elevated plus-maze, diminishing (compared to controls) the ratio of entries into open arms over the total number of entries and shortening the time spent in the open arms. DL-Amphetamine sulfate (AMPH) also had a similar action. These data support the previous suggestion that PEA may belong to the group of endogenous anxiety-inducing compounds. Pretreatment with ethanol prevented the effects of both PEA and AMPH.

Phenylethylamine Amphetamine Anxiety Ethanol Elevated plus-maze

β-PHENYLETHYLAMINE (PEA)—a neuroactive trace monoamine, has recently (1-3,5) been demonstrated to share activities characteristic of standard anxiogens like caffeine, pentylenetetrazole, and yohimbine in mice by: a) reducing the number and duration of active contacts (in the social interaction test) and b) reducing the number of transitions between dark and light compartments (in the conflict situation test). The purpose of the present study was to test the activity of PEA in the elevated plus-maze, a model of anxiety (4,6). Preliminary observations made in our laboratory have shown that in this model not all standard anxiogens are active in contrast to their action in other models, for example, yohimbine appeared to be inactive in mice (2). This test has been introduced to study anxiogens and anxiolytics in the rat (6) and mouse (4). There are numerous publications in the last few years about the use of this model in both species. DL-Amphetamine sulfate (AMPH), which is structurally methyl-PEA, was taken for comparison with PEA as its close derivative.

METHOD

Subjects

Adult, albino, male SHR mice (bred from Swiss) from Rappolovo farm (near St. Peterburg) weighing 19-20 g, about 6 weeks old, were used. Animals were housed in groups of 35-40 and received standard diet and cow milk ad lib. In the laboratory, mice were kept in groups of eight in 20 × 15 × 10-cm cages. C57BL/6 mice, which were successfully used in other models of anxiety (3,5), did not respond to either PEA or AMPH in the elevated plus-maze. For this reason, they were not used in the present study. In the social interaction test, ethanol attenuated the anxiogenic effect of PEA in C57BL/6 mice (5).

Elevated Plus-Maze

The apparatus was made of wooden arms (crossed school rulers) and cardboard walls of enclosed arms. Dimensions of the maze were as follow: open arms, 5 × 27.5 cm; closed arms, 5 × 27.5 × 15 cm. The closed arms had no roof. The maze was elevated to a height of 40 cm. Illumination over open arms was 80-90 lux and in the middle of the closed arms 15-17 lux.

Drugs

PEA (Sigma Chemical Co., St. Louis, MO) and AMPH (manufactured in Russia) were freshly dissolved in physiological saline. Solutions in a volume of 1% of the body weight

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were injected IP. Control treatments were made with saline. Ethanol was also freshly added to saline and administered orally only once in a volume of 1% of the body weight. Pretreatment with ethanol was made 15 min prior to PEA or AMPH injection. Mice were tested in the maze 5 min after the second treatment. The interval was chosen on the basis of previous experiments (2) that showed that this interval is optimal for measuring the anxiogenic effect of PEA.

Procedure

The mouse was placed at the center (intersection of arms) of the maze with its nose to one of the open arms. Each session lasted 4 min. The following parameters were recorded: number of entries into both open arms, number of entries into both closed arms, the ratio of the number of entries into the open arms over total number of entries into all arms, and total time (seconds) in both open arms. Number of entries was counted by means of digital calculators and total time in the open arms by a cumulative sport stopwatch. This ratio is considered (6) to reflect the fear-induced inhibition to enter the open arms and is probably related to the level of "anxiety" and "fear." Locomotion and rearings were measured in all groups of mice in a 20 × 20 × 15-cm chamber 2 min before placing the mouse into the maze by methods described elsewhere (2).

Statistical Analysis

Comparisons of groups were made by the Mann-Whitney *U*-test.

RESULTS

PEA and AMPH dose dependently diminished the ratio of the number of entries into the open arms over the total number of entries into all arms, as well as total time spent in open arms (Table 1). AMPH was more potent than PEA in diminishing total time spent in open arms. Pretreatment with a small dose of ethanol (0.1 g/kg) blocked the effects of PEA and AMPH. In control experiments, neither PEA nor AMPH altered locomotion. In doses of 1 and 5 mg/kg AMPH significantly reduced the number of rearings. Both doses increased movement time in control However, these two parameters were not used in the present study. Ethanol (0.1 g/kg, PO, prior to AMPH), which was per se not changing those two parameters, did not alter the action of AMPH.

DISCUSSION

Data show that in the elevated plus-maze PEA possesses an activity typical of standard anxiogens. The same was true for AMPH. These observations support the previous suggestion (1-3,5) that PEA can be an endogenous anxiogen. It seems probable that anxiety appeared as a typical symptom of AMPH intoxication and addiction (7) is mediated via PEA-related mechanisms. Anxiety induced in the animal models by PEA is particularly (comparing with those induced by other anxiogens) susceptible to the protective action of ethanol (2).

Formally speaking, the fact that C57BL/6 mice did not respond to PEA or AMPH in the plus-maze test can be interpreted as the anxiogenic action of PEA and AMPH is not a general phenomenon. However, PEA is active in C57BL/6 mice in other models of anxiety (1-3,5). Moreover, it is also known that even anxiogens of humans (e.g., yohimbine) are not active in all models of anxiety in laboratory animals (2). We do know that there are numerous behavioral phenomena that are strain and species specific, for example, apomorphine aggressiveness (only in rats, not mice), amphetamine group toxicity (only in mice, not rats), and alcohol preference (only in C57BL/6 mice, not other mouse strains), to mention a few. That is why it seems reasonable that one merely describes a phenomenon and does not make any extrapolations to other species nor any generalizations (confirming once again how right the French writer Dumas' father was saying "Every generalization is wrong including this one").

TABLE 1

ANXIOGENIC EFFECT OF PEA AND AMPH IN THE ELEVATED PLUS-MAZE AND ITS ATTENUATION BY ETHANOL

Drugs (mg/kg)		Means		
PO	IP	Total Number of Entries	Ratio Open to Open + Closed	Time (seconds) in Open Arms
Saline	Saline	21	0.73	18.7
Saline	PEA (1)	20	0.62	15.8
Saline	PEA (5)	25	0.51*	15.0
Saline	PEA (10)	26	0.46*	13.2*
Ethanol (100)	Saline	23	0.58	22.9
Ethanol (100)	PEA (10)	22	0.67†	29.2†
Saline	Saline	23	0.67	21.7
Saline	AMPH (0.5)	20	0.60	16.0
Saline	AMPH (1)	25	0.55*	11.0*
Saline	AMPH (5)	27	0.31*	6.3*
Ethanol (100)	Saline	26	0.59	29.2
Ethanol (100)	AMPH (5)	20	0.63‡	18.8‡

Groups of 16 mice. Statistical significance of the differences between groups: *with control group (saline + saline); †with group saline + PEA (10); ‡with group saline + AMPH (5).

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