Pharmacology Biochemistry & Behavior, Vol. 11, pp. 419–422. Printed in the U.S.A.

A Comparison of the Effects of Acute and Subacute Administration of β-Phenylethylamine and *d*-Amphetamine on Mouse Killing Behavior of Rats[1]

GORDON A. BARR,[2] JUDITH L. GIBBONS[3] AND WAGNER H. BRIDGER

Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY 10461

Received 30 May 1978

BARR, G. A., J. L. GIBBONS AND W. H. BRIDGER. *A comparison of the effects of acute and subacute administration of β-phenylethylamine and* d*-amphetamine on mouse killing behavior of rats.* PHARMAC. BIOCHEM. BEHAV. 11(4) 419–422, 1979.—β-Phenylethylamine (PEA) is an endogenous amine that in some instances acts biochemically and behaviorally like amphetamine. In the present experiments, the effects of PEA on mouse killing by rats were compared and contrasted with the effects of *d*-amphetamine on this behavior. When given acutely to experienced mouse killing rats, PEA (16 and 32 mg/kg) inhibited killing in a direct dose dependent manner. This is similar to the dose dependent inhibition of killing by amphetamine reported previously. However, *d*-amphetamine but not PEA showed physiologic tolerance following 8 days of twice daily administration. Cross tolerance between the two drugs only occurred when *d*-amphetamine was administered subacutely. It was concluded that PEA and *d*-amphetamine have similar acute effects but differed when given subacutely since PEA did not show tolerance and there was not bidirectional cross-tolerance. These data suggest that these drugs have different pharmacologic actions when given repeatedly. One possible difference may be the duration of action.

β-Phenylethylamine Amphetamine Mouse killing Muricide Predatory aggression Aggression Tolerance Food intake Stimulants

β-PHENYLETHYLAMINE (PEA) is an amine found in mammallian brain that is related structurally to amphetamine lacking only amphetamine's α methyl group. Like amphetamine PEA acts as an agonist in catecholamine (CA) systems by releasing CA neurotransmitters presynaptically [4], and by blocking reuptake of these transmitters into the presynaptic cell [16]. In addition, PEA probably has a direct, albeit brief, agonistic effect on postsynaptic dopamine receptors [1]. Behaviorally, both PEA and amphetamine increase motor activity, induce ipsilateral turning in unilateral substantia nigra lesioned rats, induce stereotypic behaviors, and maintain self-administration [1, 3, 4, 8, 10]. Furthermore, because of the structural, pharmacologic, and behavioral similarities between PEA and amphetamine and because PEA is found in brain tissue, PEA has been postulated to be a neuromodulator that affects behavior by acting through similar mechanisms as amphetamine, or as a mediator of amphetamine's behavioral effects [8,12].

There are, however, differences between the effects of PEA and the effects of amphetamine in some behaviors. For example, PEA results in a dose-dependent decrease in electrical self-stimulation from a medial forebrain bundle locus whereas amphetamine increases self-stimulation from this site [6], and stereotypy induced by PEA is affected differently by pretreatment with CA postsynaptic receptor blockers than is stereotypy induced by amphetamine [3].

In the present paper, we compared the effects of PEA and amphetamine on the aggressive response of a rat to a mouse. This behavior (mouse-killing, muricide) is potently and selectively inhibited by amphetamine [5,7], and tolerance may develop to this inhibition [2]. Further, in contrast to the facilitative effects of amphetamine on the other behavioral systems mentioned above, amphetamine inhibits the mouse-killing response. Both acute and subacute effects of PEA on muricide were studied and the possible development of a cross-tolerance to *d*-amphetamine was tested. The results showed similar inhibitory effects of both PEA and amphetamine following acute administration, but PEA, unlike amphetamine, showed no tolerance following subacute administration.

[1]Requests for reprints should be sent to Gordon A. Barr, Department of Psychiatry, Room G-50F, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461.

[2]Also at the Department of Psychology, Hunter College, City University of New York, NY, NY 10021.

[3]Presently at the Department of Psychology, St. Louis University, St. Louis, MO 63103.

METHOD

Animals

Male hooded rats purchased from Blue Spruce Co. (Altamont, NY) were used. The rats weighed between 400–700 g and were 4–12 months of age at the time of testing. Spontaneous killers were determined by a single 24 hr mouse killing test. In our lab approximately 45% of all rats tested in this manner are killers. All animals were pretested for killing 20 min following a saline injection until they reach a criterion of 2 consecutive kills within 120 sec of the presentation of the mouse. Typically the number of saline pretests ranged from 2 to 8 with the majority of rats reaching criterion within 4 tests. Rats were housed singly in standard metal cages measuring 36×20×19 cm high, or in some experiments, in 10 gallon glass aquaria to enable observations by the experimenter. Mice were group housed and were of various strains and both sexes; pilot work had shown that neither the sex nor strain variables affected the killing response of practiced killers.

Drugs

β-Phenylethylamine HCl (PEA) (ICN Pharmaceuticals and *d*-amphetamine sulfate (Arenol Chemical Co.) were dissolved in distilled water and administered IP in a volume of 1 ml/kg. PEA was mixed immediately prior to injection and *d*-amphetamine mixed weekly. Doses refer to the weight of the base for both drugs.

Procedure

All experiments were conducted in a double-blind manner. For Experiment 1, which examined the effects of acute administration of PEA, rats were injected with either the vehicle or one of 4 doses of PEA (4, 8, 16, 32 mg/kg) in a replicated Latin Square Design. Five minutes following injection, a mouse was placed into the cage of the rat and the latency to sniff, attack and kill the mouse recorded. If no kill occurred within 30 min, the mouse was removed and the maximum latency of 1800 sec recorded.

In the second experiment, the development of tolerance following subacute administration of PEA and *d*-amphetamine was tested. For tolerance to PEA's inhibitory effect, rats were pretested with either 8, 16, or 32 mg/kg of PEA (N=8, 8, 9, respectively), given twice daily injections of PEA (32 mg/kg), without testing for killing, for 8 days, and tested with the same dose of PEA as on the pretest. *d*-Amphetamine tests followed the same procedure using pre- and posttest doses of 0.5, 1.0 and 2.0 mg/kg (N=8, 8, 15, respectively) and a subacute dose of 2.4 mg/kg. (The subacute dose was the same used in previous work [2].) For the highest test dose of PEA (32 mg/kg) and *d*-amphetamine (2.0 mg/kg), rats were given vehicle tests before and after the drug tests to assess the effect of subacute treatment with those drugs on baseline kill latencies. Rats were also tested with PEA (32 mg/kg; N=10) and *d*-amphetamine (20 mg/kg; N=10) prior to and after 8 days of twice daily saline injections.

The third experiment examined the possible development of cross-tolerance between PEA and *d*-amphetamine. To test the inhibitory effects of PEA following subacute amphetamine treatment, rats were tested for killing after 16 (N=8) and 32 mg/kg (N=10) of PEA, given twice daily injections of *d*-amphetamine (2.4 mg/kg) and retested with PEA.

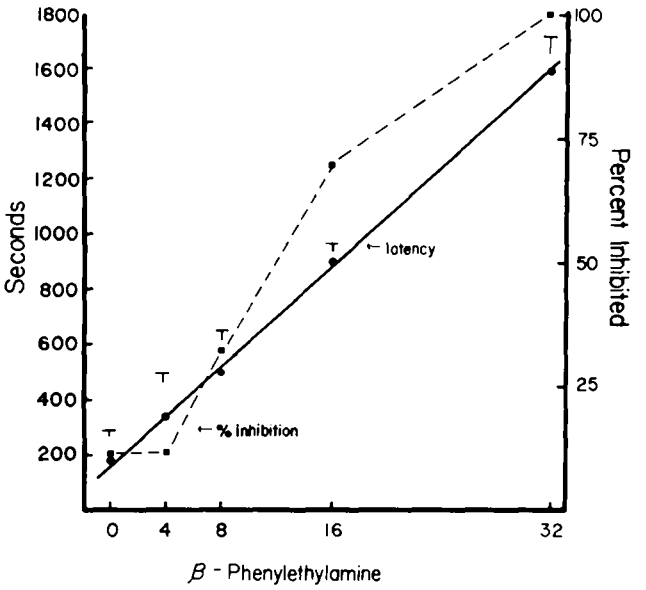

FIG. 1. The dose dependent inhibition of mouse killing by β-PEA. The solid line presents the data as latency to kill in seconds: the 8, 16, and 32 mg/kg doses are significantly greater than controls. The dashed line presents the data as the percent of animals not killing at 10 min after presentation of the mouse. The 16 and 32 mg/kg doses are significantly different from controls.

To test whether cross-tolerance to amphetamine's inhibition of killing occurred following subacute PEA administration, rats were tested for killing following 1.0 (N=8) or 2.0 mg/kg (N=9) of *d*-amphetamine, given twice daily injections of PEA (32 mg/kg) for 8 days, and then tested again with *d*-amphetamine.

The effects of PEA on food and water intake were measured in two ways. First, the effects of PEA on 24 hr food (powdered Teklad Rat Chow) and water intake were measured following injection of one of 3 doses of PEA (8, 16, 32 mg/kg) or the vehicle (N=12). Second, food and water intake were measured in 24 hour food-deprived animals following one of 3 doses of PEA (4, 8, 16 mg/kg) or vehicle (N=12). For the first paradigm, food and water intake were measured once 24 hr following injection. For the second paradigm, food and water intake was measured for 15 min periods, 5 and 30 min postinjection and for a 30 min period 1 hr postinjection. Spillage was minimal in these experiments and not routinely measured. Periodic examination of the amount of spillage that showed no obvious differences between drug groups.

Data are presented as the percent of animals killing and the latency to kill. Statistical analyses were done on both using non-parametric statistics for the former data and parametric analyses of variance or *t*-tests for the latter. The parametric analyses were done on transformations of the type $x' = \log_{10}(x + 10)$ where x was the original latency. This was done to minimize heterogeneity of variance between groups.

RESULTS

Experiment 1

In all experiments kill and attack latencies were highly correlated and hence attack latencies are not reported. The

data from Experiment 1 showed that PEA induced a dose-dependent inhibition of mouse killing (Fig. 1). An analysis of variance on kill latencies showed a highly significant drug effect ($p<0.001$) and subsequent comparisons of each dose with control injections using Dunnett's test showed a significant increase in kill latency at the 8, 16, and 32 mg/kg doses ($p<0.05$ for 8 mg/kg; $p<0.005$ for 16 and 32 mg/kg). Nonparametric analyses of the number of rats not killing at 10 min after presentation of the mouse by Wilcoxon sign-rank test showed inhibition by the two highest doses. This inhibition was short-lived, lasting the 30 min test session only for the highest test dose. Analysis of the latency to sniff the mouse showed no effect of the drugs.

Experiment 2

The data from the tolerance studies showed that there was tolerance as measured by a shift of the dose response curve of *d*-amphetamine to the right following repeated treatment (Fig. 2) (Wilcoxon sign-rank test; $Z=3.35$, $p<0.001$; Anova; $F(1,28)=20.51$; $p<0.01$). However, no tolerance developed to repeated PEA administration (Fig. 3). There were no changes for either *d*-amphetamine's or PEA's effect on the killing response following chronic saline treatment.

Experiment 3

The cross-tolerance data show that there was cross-tolerance between amphetamine and PEA when amphetamine was given subacutely but not when PEA was given subacutely (Figs. 4 and 5). The former effect was significant by the Wilcoxon sign-rank test ($Z=2.72$; $p<0.01$) and approached significance in the Anova ($F(1,16)=4.38$, $p=0.053$).

Food Intake

The data showed no effect of PEA on 24 hr food intake and only minimal effects in food-deprived rats. The nature of the latter effect was a slight inhibition of food intake by the highest dose tested (16 mg/kg) for 15 min immediately following PEA injections. By 30 min postinjection, food intake was the same for all groups. Water intake was not affected by PEA.

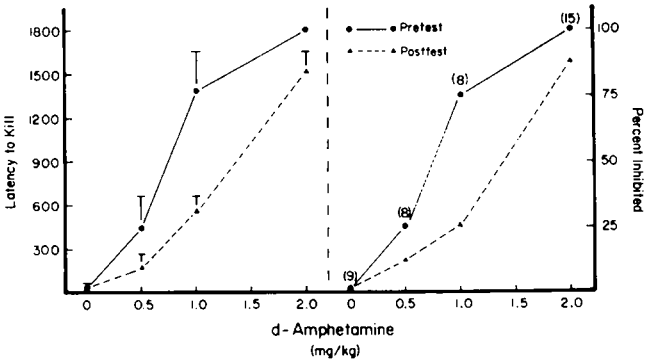

FIG. 2. The change in dose dependent inhibition of killing by *d*-amphetamine following subacute treatment. The left hand panel presents latency data in seconds while the right hand panel presents the data as the percent of animals not killing 10 min after presentation of the mouse. The numbers in parentheses are the N's.

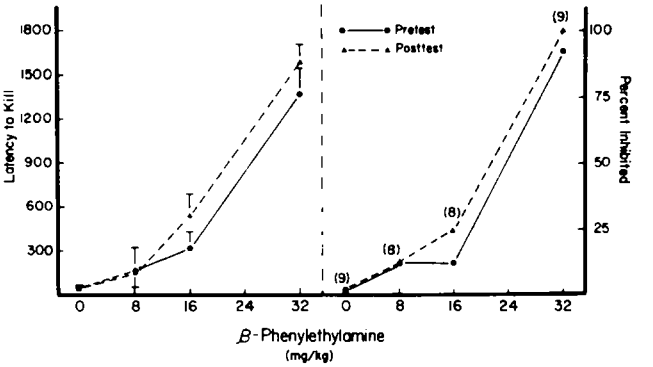

FIG. 3. The lack of change in the dose dependent inhibition of killing by β-PEA following subacute treatment. See Fig. 2 for further description.

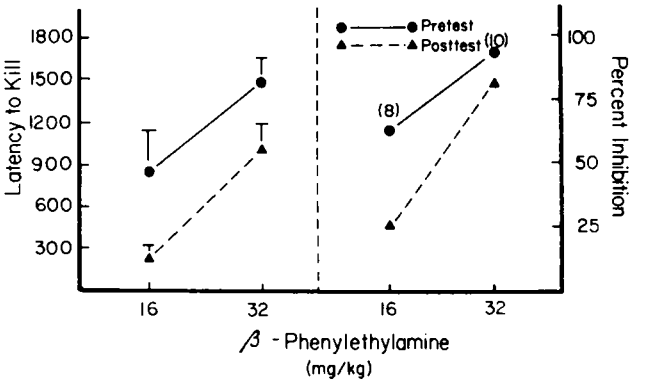

FIG. 4. The dose response curve of β-PEA when *d*-amphetamine was given subacutely. See Fig. 2 for details.

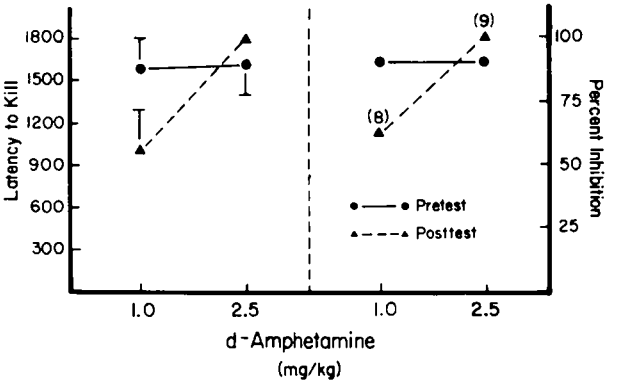

FIG. 5. The dose response curve of *d*-amphetamine when β-PEA was given subacutely. See Fig. 2 for details.

DISCUSSION

The data from these experiments demonstrated that PEA and amphetamine both inhibited killing in a dose-dependent fashion. Unlike *d*-amphetamine, however, tolerance did not develop to PEA's effects and two-way cross-tolerance did not occur between PEA and amphetamine. These latter data

suggest that the pharmacologic mechanism by which PEA and amphetamine act to inhibit killing may be different.

One major difference between *d*-amphetamine and PEA is the duration of action in the central nervous system. The time course of amphetamine's effects on predation, on locomotor activity and in inducing stereotypy are measured in hours ([15], unpublished observations) whereas the behavioral effects of PEA rarely last more than one hour [1, 3, 6]. This short duration of action of PEA may account for the lack of tolerance to its inhibitory effects, and it is possible that more frequent administration or treatment with higher doses might induce tolerance to PEA.

Observations of other behaviors such as food and water intake, stereotypy and activity point to other similarities and differences between PEA and amphetamine. First PEA, unlike amphetamine, had little effect on food and water intake, with only a brief and mild decrease in food intake induced by the highest dose of PEA. In contrast, PEA induced stereotypies similar to those of amphetamine but with greater autonomic effects, such as piloerection. The intensity of the stereotypy also increased with chronic treatment in agreement with Borison *et al.* [3].

In humans, PEA has been suggested to play a role in the mediation of a variety of psychiatric disorders including both affective disorders and psychosis [3,12]. A recent study has shown that phenylacetic acid, the oxidative metabolite of PEA, is higher in violence-prone psychopaths than in other convicts matched on a variety of parameters [14].

In conclusion, the data from these experiments and from other experiments suggest that amphetamine and PEA act similarly for some behaviors. The acute actions of these drugs are similar for the induction of stereotypy, the induction of rotation in unilateral substantia nigra lesioned rats and the inhibition of muricide but appear to be different for electrical self-stimulation and drug-induced anorexia. Whether amphetamine's actions are mediated by PEA may depend on factors such as the particular behavioral effect, the neurotransmitter system, and the anatomical loci of action. Furthermore, differences and similarities between subacute as well as acute effects may point to similarities and differences between PEA and amphetamine. For example, PEA and amphetamine show cross-sensitization of stereotyped behavior following chronic treatment [3]. If stereotypy is mediated by dopaminergic systems then PEA and amphetamine may act via the same mechanisms in this system. However, PEA and amphetamine did not show cross-tolerance for the inhibition of mouse killing behavior. This might be due to PEA's short duration of action, or could be due to other different modes of pharmacologic action. Thus, while PEA has been suggested to have a functional role in depression, schizophrenia and migraine [1, 12, 13], the nature of that role and its relationship to amphetamine's action remain to be explicated.

ACKNOWLEDGEMENTS

We thank Gregg Tyler Schimmel for expert technical assistance and Beth Ann Malone for help in preparation of this manuscript. This research was supported in part by NIH grants MH-06418 and RR-05397.

REFERENCES

1. Antelman, S. M., D. J. Edwards and M. Lin. Phenylethylamine: evidence for a direct, postsynaptic dopamine-receptor stimulating action. *Brain Res.* **127:** 317–322, 1977.
2. Barr, G. A., J. L. Gibbons and W. H. Bridger. Inhibition of rat predatory aggression by acute and chronic *d*- and *l*-amphetamine. *Brain Res.* **124:** 565–570, 1977.
3. Borison, R. L., H. S. Havdala and B. I. Diamond. Chronic phenylethylamine stereotypy in rats: A new animal model for schizophrenia? *Life Sci.* **21:** 117–122, 1977.
4. Carlsson, A. Amphetamine and brain catecholamines. In: *Amphetamines and Related Compounds*, edited by E. Costa and S. Garattini. New York: Raven Press, 1970, pp. 289–300.
5. Horovitz, Z. P., J. J. Piala, J. P. High, J. C. Burke and R. C. Leaf. Effects of drugs on the mouse-killing (muricide) test and its relationship to amygdaloid function. *Int. J. Pharmac.* **5:** 405–411, 1966.
6. Howard, J. L., G. T. Pollard, K. W. Rohrback and N. E. Harto. Effect of β-phenylethylamine and *d*-amphetamine on electrical self-stimulation of brain. *Pharmac. Biochem. Behav.* **5:** 661–664, 1976.
7. Malick, J. B. Differential effects of *d*- and *l*-amphetamine on mouse killing behavior in rats. *Pharmac. Biochem. Behav.* **3:** 697–699, 1975.
8. Mantegazza, P. and M. Riva. Amphetamine like activity of β-phenylethylamine. *J. Pharmac.* **15:** 472–478, 1963.
9. O'Boyle, M. Rats and mice together: The predatory nature of the rat's mouse-killing response. *Psychol. Bull.* **81:** 261–269, 1974.
10. Risner, M. E. and B. E. Jones. Characteristics of β-phenethylamine self-administered by dog. *Pharmac. Biochem. Behav.* **6:** 689–696, 1977.
11. Rossi, A. C. The "mouse-killing" rat: Ethological discussion of an experimental model of aggression. *Pharmac. Res. Communs.* **7:** 199–216, 1975.
12. Sabelli, H. C. and A. D. Mosnaim. Phenylethylamine hypothesis of affective behavior. *Am. J. Psychiat.* **131:** 695–699, 1974.
13. Sandler, M., M. B. H. Youdim and E. Hanington. Phenylethylamine oxidising defect in migraine. *Nature* **250:** 335–337, 1974.
14. Sandler, M., C. R. J. Ruthuen, B. L. Goodwin, H. Field and R. Mathews. Phenylethylamine overproduction in aggressive psychopaths. *Lancet* **2** (8103): 1269–1279, 1978.
15. Segal, D. S. Behavioral characterization of *d*- and *l*-amphetamine: Neurochemical implications. *Science* **190:** 475–477, 1975.
16. Sulser, F. and E. Sanders-Bush. Effect of drugs on amines in the CNS. *Ann. Rev. Pharmac.* **11:** 209–230, 1971.