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Hypodipsia, Stereotypy and Hyperactivity Induced by β-Phenylethylamine in the Water-Deprived Rat

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COOPER, S. J. AND C. T. DOURISH. *Hypodipsia, stereotypy and hyperactivity induced by β-phenylethylamine in the water-deprived rat.* PHARMACOL BIOCHEM BEHAV **20**(1) 1–7, 1984.—β-Phenylethylamine (PEA) is an endogenous constitutent of human, rat and other mammalian brain tissue. It is rapidly metabolised by type B monoamine oxidase, and there is evidence for specific binding sites for PEA in rat brain. In the first experiment, the effects of systemically-administered PEA (3.125–50.0 mg/kg) on water consumption in water deprived male rats were investigated. PEA produced a depression of drinking within the first 15 min following its administration, with a strong linear relation between drug dose and the degree of depression. In the following 45 min, there was evidence of a dose-related recovery in the drinking. In the second experiment, the effects of PEA on activity in water-deprived rats were investigated. PEA at 12.5 m/kg produced behavioral stimulation, which was particularly evident in measures of total horizontal activity. At higher doses, 25.0 and 50.0 mg/kg, PEA induced a behavioral stereotypy syndrome, associated with a depression of horizontal and vertical activities. Relationships between the hypodipsic effect of PEA and its ability to produce psychomotor stimulation at a moderate dose level, and stereotypy at higher dose levels are considered.

β-Phenylethylamine Drinking Water deprivation Locomotor activity Stereotypy

β-PHENYLETHYLAMINE (PEA) is a trace amine which has been identified in human, rat and other mammalian brain tissue [3, 13, 20, 32, 34, 40]. In the rat, highest concentrations have been detected in the hypothalamus [13]. Although PEA is present in tissues in small amounts, there is evidence which indicates that it is metabolically very active. The half-life of PEA in various rat tissues is of the order of several minutes [12,42]. Oxidation by type B monoamine oxidase (MAO) is a major pathway for the inactivation of PEA, and treatment with inhibitors which preferentially inhibit the B form, leads to large increases in brain concentrations of the amine [4, 31, 39]. Recently, specific PEA binding sites in the rat have been described, with the highest specific binding found in hypothalamus and striatum [17].

PEA is structually related to amphetamine, lacking only the amphetamine α-methyl group. It has been suggested that PEA may be a major mediator for the central actions of amphetamine [4]. It is important to note, however, that amphetamine, in contrast to PEA, is resistant to deactivation by MAO and has a considerably longer duration of action. In large doses, PEA produces behavioral stereotypy syndromes in rats and mice which are related to those induced by large doses of d-amphetamine [2, 6, 8, 9, 28, 29, 30]. However, unlike d-amphetamine, PEA (when not given in conjunction with a MAO inhibitor) has not been observed to increase responding for electrical self-stimulation of the brain [19], and does not appear to produce a conditioned taste aversion [16].

Relatively little attention has been paid to the possible effects of PEA on ingestional behavior. PEA has been reported to have potent anorexic effects in rats and dogs, but only after pretreatment with the MAO inhibitor, iproniazid [27]. However, it has been shown that treatment with MAO inhibitors alone is sufficient to produce depressions in food and water intake in rats [18]. Furthermore, the MAO inhibitor treatments also raised brain monoamine levels generally [18]. Hence, is desirable to be able to detect effects of PEA without recourse to MAO inhibitor pretreatments, to avoid confounding effects due to the MAO inhibitors themselves.

The aim of the first experiment was to examine, for the first time, the possibility of a suppressant effect of PEA treatments (3.125–50 mg/kg) on the rat's drinking response which immediately follows water-deprivation. To date there has been a failure to detect any effect of PEA treatments on water intake [1, 7, 10]. This failure poses a problem for the notion that PEA's effects on behavior should bear some relationship to those of d-amphetamine. Several investigations have shown that d-amphetamine will depress water consumption in water-deprived rats and mice [5, 18, 26, 37, 38]. A rebound hyperdipsia occurring 1–4 hr after amphetamine administration has also been described [38]. Owing to PEA's

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short duration of action, however, it seemed particularly important to examine water intake over the first 15 min directly following administration of the drug. This period should provide the strongest test of the hypothesis that PEA, like d-amphetamine, can exert an antidipsogenic action.

EXPERIMENT 1

METHOD

Animals

The subjects were 48 naive adult male Wistar rats, which were obtained from Charles River Canada, Montreal. They were housed individually in metal cages with access to standard lab chow at all times, except during the drinking test. Beginning 7 days before the drinking test, the animals were placed on daily 23 hr water-deprivation schedule. Prior to this, the animals had received experience of handling. They were maintained under a 12 hr light-12 hr dark cycle and the room temperature was maintained at 20±1°C. They weighed between 180–210 g at testing.

Procedure

For the drinking test, which was conducted in the light phase following the preceding period of water deprivation, a weighed bottle containing tap water was returned to each cage. At 15 min intervals during the 1 hr access to water, the bottles were reweighed in order to determine the amount of water consumed (g) during the test period.

The rats were randomly assigned to 6 equal groups, which were allocated to the following injection conditions: 3.125, 6.25, 12.5, 25.0 and 50.0 mg/kg PEA hydrochloride (Sigma) and an isotonic saline vehicle. All injections were administered IP, immediately before the start of the drinking test.

Because of PEA's limited duration of action, and also because animals were previously observed to consume most of their water intake within the first 15 min of the test, the data for each animal were divided into the intake during the first 15 min, and the intake during the remaining 45 min. It was anticipated that recovery from an initial depression of drinking might be observed during the latter part of the test. The drinking data were analysed initially using a 2-way analysis of variance (ANOVA), with repeated observations on one measure (time-period: 2 levels). Trend analyses were employed to describe the form of the relationship between the dose of PEA administered and water consumption. Planned group comparisons were carried out using the t-statistic, and unplanned multiple group comparisons using the Newman-Keuls procedure [42].

RESULTS

As expected, there was a highly significant time-period effect, $F(1,42)=54.80$, $p<0.001$. The overall PEA dose main effect was not significant ($F<1.0$), but there was a highly significant interaction between PEA dose and time-period, $F(5,42)=10.14$, $p<0.001$, indicating that the effects of PEA were not the same within the first 15 min of the drinking test, compared to the remaining 45 min. Figure 1 illustrates the nature of the interaction. During the initial 15 min, there was a dose-related *decrease* in water consumption following PEA administration; in contrast, during the final 45 min there was a dose-related increase in water consumption, compared to the control level of intake. The lack of a significant overall PEA dose main effect indicated that the initial depression of water intake tended to be compensated by the later elevation of water consumption.

Analysis of the simple main effect of PEA dose during the first 15 min showed a highly significant effect of PEA to depress drinking, $F(5,42)=7.18$, $p<0.001$. Trend analysis confirmed a highly significant linear effect of PEA dose on the level of water intake, $F(1,42)=27.87$, $p<0.001$, with 77.6% variance which may be accounted for from a linear regression equation. There was a modest quadratic trend which approached significance, $F(1,42)=4.08$, but there was no cubic trend. Comparisons between group means showed that 25 mg/kg PEA produced a significant reduction in water consumption compared with controls, $t(42)=2.02$, $p<0.05$), and 50 mg/kg PEA produced a larger decrement in water intake compared with controls, $t(42)=5.30$, $p<0.01$). Using the Newman-Keuls procedure for unplanned comparisons between group means, the water intake of the 50 mg/kg PEA group was significantly less than the intake of every other group ($p<0.01$, in each case). No other comparison reached a significant difference. Thus, as Fig. 1A indicates, administration of PEA immediately before the drinking test produced a highly significant depression in water intake, an effect which was linearly related to the size of PEA dose.

Analysis of the simple main effect of PEA dose during the latter 45 min of the test revealed a significant effect to enhance water consumption, $F(5,42)=2.62$, $p<0.05$. Trend analysis revealed a significant linear relationship between the level of water intake, $F(1,42)=8.64$, $p<0.01$, but higher-order trends did not reach significance (Fig. 1B). Using the Newman-Keuls procedure, no comparisons between individual group means reached significance.

EXPERIMENT 2

The aim of the second experiment was to examine the effects of PEA (3.125–50.0 mg/kg) on the spontaneous motor activity of water-deprived rats. PEA has been reported to stimulate locomotor activity in mice at dose levels of 50.0 mg/kg and above [8, 9, 21], and at lower doses in mice pretreated with a MAO inhibitor [22, 23, 31]. In the rat, PEA at 40 mg/kg has been reported to increase locomotor activity, as measured in a photocell cage [19]. The second experiment was performed therefore, first, to supplement the meagre information available on the effects of PEA on motor activity in the rat, and, second, to determine whether the depression of drinking observed in the first experiment bore any relationship to its effect on spontaneous motor activity. The effects of PEA were measured both automatically, using equipment which differentiated between vertical activity, ambulation and total horizontal activity, and by observation, to provide ratings of a number of behavioral components.

METHOD

Animals

The subjects were the animals used in Experiment 1. One week was allowed between the two experiments, during which time the animals were maintained on the water-deprivation schedule, and were housed as described previously.

Apparatus

Testing was conducted in 4 individual Plexiglas cages (40 cm square, 23 cm high) positioned in automatic activity recording devices (Opto-Varimex Minor, Columbus Instru-

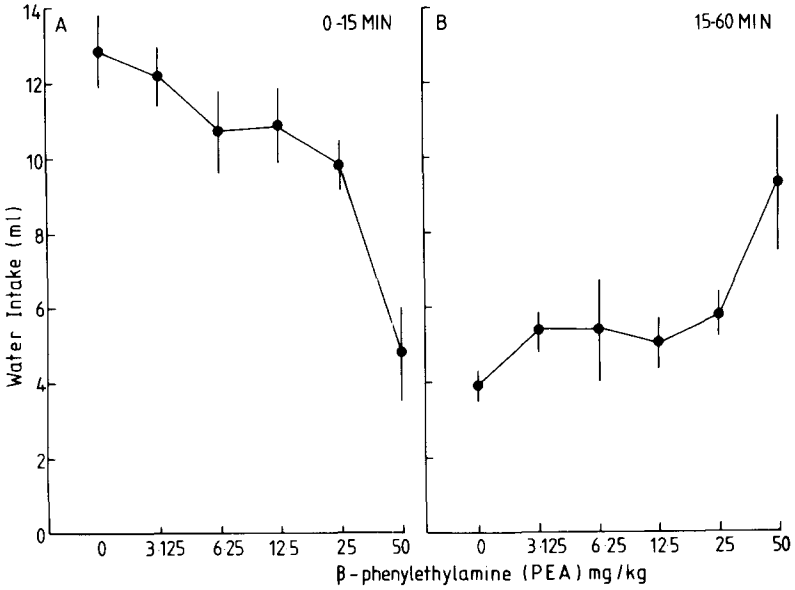

FIG. 1. Effects of β-phenylethylamine (PEA) on water consumption (ml) in the water-deprived rat. A: Initial depression of water intake in the first 15 min following PEA administration (3.125–50.0 mg/kg). The degree of depression had a highly significant linear relation to dose. B: Recovery of drinking in the following 45 min period. For the total 60 min intake, there was not a significant PEA effect, indicating that the subsequent recovery tended to compensate for the initial drug-induced depression in drinking. See text for full statistical description. Each point represents the mean result for 8 animals; vertical lines indicate the S.E.M. The vertical scale is the same for both panels.

ments, Columbus, OH). A logic circuit in these devices enabled a distinction to be made between whole-body ambulatory movements and photobeam interruptions due to other movements made by the animals. Total horizontal activity (including grooming, scratching, stereotypy, head swaying, tail movements, etc.) was determined by the interruption of any one of 12×12 infrared photobeams (3 cm apart), in any order. Ambulatory activity (locomotion), on the other hand, was determined by the interruption of consecutive photobeams. Vertical activity (rearing and jumping) was recorded by units equipped with a series of 12 photobeams (3 cm apart) (Opto Vertimex, Columbus Instruments) which were suspended (15 cm above the cage base) from the walls of the cages. Interruption of any photobeam produced a 1 msec pulse which was counted by a microprocessor/Apple II plus microcomputer system (see reference [11], for full apparatus details). A program written in Apple Pascal enabled the experimenter to control the microprocessor and to display the data collected either continuously, or at pre-selected intervals, in the form of tables or histograms. The data could be stored on disc file, or recorded directly on a silent type printer.

Procedure

As in Experiment 1, the rats were assigned to 6 equal groups which consisted of the injection conditions of 3.125, 6.25, 12.5, 25.0 and 50.0 mg/kg PEA hydrochloride and an isotonic saline vehicle. Injections were administered IP immediately before the test. Since PEA has an extremely short duration of action we employed a 15 min test. Scores for total horizontal activity, ambulation and vertical activity were recorded automatically by the microprocessor/microcomputer system. In addition, at 5 min intervals 2 observers (who were not blind to the injection conditions) recorded the presence and intensity of various behaviors on a 5 point scale (the legend to Fig. 3 provides details of the scale). The response categories rated were those employed in our previous studies on PEA and are most descriptive of PEA's elicited behavioral effects at higher doses. They comprised headmovements, forepaw padding, splayed hindlimbs, hyperreactivity and grooming (see Table 1 for brief descriptions).

RESULTS

Total Horizontal Activity

The effects of PEA (3.125–50.0 mg/kg) on total horizontal activity in the water-deprived rats are shown in Fig. 2A. There was a significant difference between the PEA treatment groups, and trend analysis showed significant quadratic and cubic trends in the data (Table 2). A Newman-Keuls test on all possible comparisons between the group means confirmed a significantly greater effect at 12.5 mg/kg PEA compared with every other group ($p<0.01$ in each case). No other comparison reached significance. Hence, at a moderate dose of 12.5 mg/kg, PEA significantly stimulated total horizontal activity over a 15 min period in water-deprived rats. Higher or lower doses did not significantly modify the activity.

TABLE 1
DEFINITION OF BEHAVIORAL COMPONENTS SCORED IN THE OBSERVATIONAL ANALYSIS

Behavioral Component	Description
Head-movements	Repetitive side-to-side (head-weaving), or up-and-down (head-bobbing) movements of the head, often in one location in the cage.
Forepaw padding	Repetitive placing movements of the forepaws.
Splayed hindlimbs	A dramatic extension of the hindlimbs causing a flattening of the body posture.
Hyperreactivity	Startle response to a pencil tap on the cage top.
Grooming	Purposeful licking and cleaning of the body

Ambulatory Activity

Figure 2B shows the effects of PEA treatments on ambulatory activity. There was a significant difference between the groups, and trend analysis showed a significant quadratic and cubic trends in the results (Table 2). Tests using the Newman-Keuls procedure indicated that ambulatory activity at 50 mg/kg was significantly less than all other groups ($p<0.05$ in each case), with the exception of the group tested at 3.125 mg/kg. In addition, the activity of the 3.125 mg/kg PEA group was depressed, and was significantly less than the activity of the animals tested at 12.5 mg/kg ($p<0.05$).

Vertical Activity

The effects of PEA on vertical activity (rearing) are depicted in Fig. 2C. There was a significant difference between the groups, and trend analysis showed significant linear, quadratic and cubic trends (Table 2). Comparisons amongst all treatment means indicated that vertical activity at 50 mg/kg was significantly less than all other groups ($p<0.01$in each case), with the exception of the 25 mg/kg group; vertical activity at 25 mg/kg was significantly less than groups tested at lower PEA doses and the control group ($p<0.05$ in each case). Reflecting the slight stimulant action at 12.5 mg/kg PEA, the mean for this group was significantly greater than the mean for the 3.125 mg/kg group ($p<0.05$).

Observational Data

In confirmation of earlier findings, PEA at the two highest doses, 25.0 and 50.0 mg/kg, induced some behavioral changes which are thought to be indicative of stereotyped behavior (Fig. 3). Compared with control animals, rats treated with 25.0 and 50.0 mg/kg PEA displayed significantly greater hyperreactivity, and showed drug-induced stereotyped head-movements. At 50.0 mg/kg PEA, grooming behavior was completely absent, in contrast to the consistent grooming observed in the control animals; both forepaw-padding and splayed-hindlimbs were in evidence.

DISCUSSION

The data of the first experiment provided a strong indication that PEA administration (3.125–50 mg/kg) produced a transient depression of the water intake of water-deprived rats, an effect which showed a marked linear relationship to the size of the drug dose. PEA is a rapidly-metabolized compound [12,42], and therefore would be expected to produce only a short-lived reduction in drinking. Our results indicate that the transient hypodipsic effect of PEA was followed by a rapid recovery of drinking, so that by the end of the one hour test, the overall water consumption was not significantly different across the treatment groups. In this behavioral test, the effects of PEA were closely reminiscent of those of amphetamine. Amphetamine-induced hypodipsia has been documented by several investigators [5, 18, 26, 37, 38] and it is followed by a secondary hyperdipsia 1–4 hr after administration [38]. The PEA effect was considerably abbreviated, however, as compared with that of amphetamine, which was

TABLE 2
SUMMARY OF THE SIGNIFICANCE LEVELS FROM THE ANALYSIS OF TREND COMPONENTS IN THE DOSE-RESPONSE RELATIONSHIPS FOR ACTIVITY MEASURES FOLLOWING PEA (3.125–50 mg/kg) ADMINISTRATION IN WATER-DEPRIVED RATS

		Trend		
Activity Measure*	Dose Effect†	Linear	Quadratic	Cubic
Total horizontal activity	$p<0.001$	n.s.	$p<0.005$	$p<0.05$
Ambulatory activity	$p<0.001$	n.s.	$p<0.05$	$p<0.005$
Vertical activity	$p<0.001$	$p<0.001$	$p<0.005$	$p<0.05$

*Activity scores were recorded automatically by a microprocessor/microcomputer system.
†Significance of the F ratio from a one-way ANOVA.

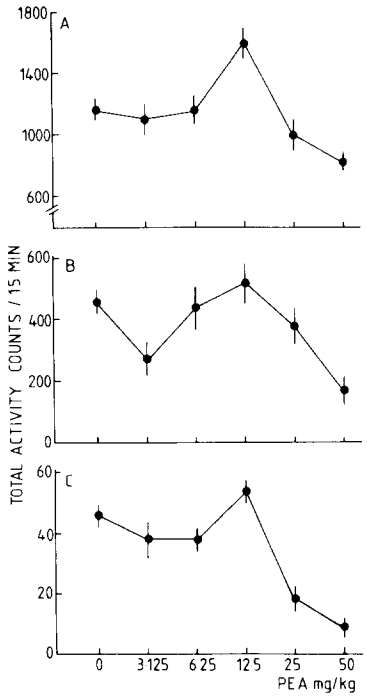

FIG. 2 Effects of PEA (3.125–50.0 mg/kg) on automated measures of spontaneous motor activity in the water-deprived rat. A: Total scores over 15 min period immediately after PEA administration for total horizontal activity. B: Total scores for forward ambulation. C: Total scores for vertical activity. Analysis of trends showed significant effects which differed amongst the three measures. See text for full statistical description. Each point represents the mean result for 8 animals; vertical lines indicate the S.E.M. Note the scale differences in the three panels.

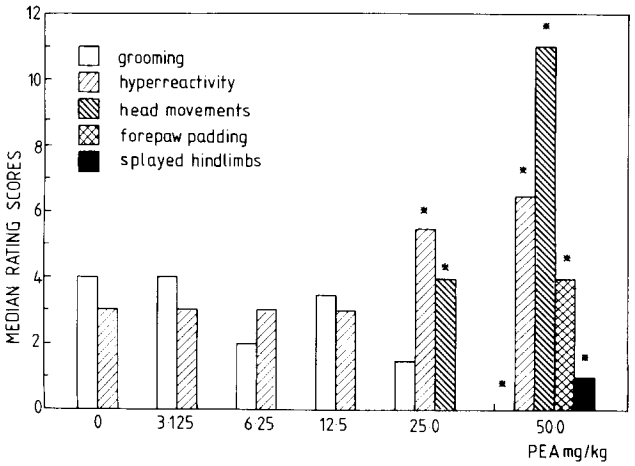

FIG. 3. Induction of a behavioral stereotypy syndrome at higher doses of PEA (25.0 and 50.0 mg/kg). The syndrome was characterised by a loss of grooming activity, increased hyperreactivity and the induction of head-movements, forepaw padding and splayed hindlimbs. Rats were rated over 3 consecutive 5-min periods for the presence of these 5 behavioral components on a 5-point scale (0 absent; 1 mild intensity; 2 moderate intensity; 3 high intensity; 4 severe). For each rat, its scores on each of the 5-min periods were added together (i.e., maximum possible score was 12). For each group (corresponding to an individual PEA dose condition), the median total score was then determined. A Kruskal-Wallis one-way ANOVA was used to determine the presence of a drug effect, and the Mann-Whitney U test was used to detect significant departures from control scores for individual drug groups. *Indicates the presence of a significant drug effect compared with the corresponding control score ($p<0.05$).

therefore consistent with the biochemical evidence for a short duration of action of PEA.

The present data do not conflict with the results of earlier studies, which reported negative findings with regard to a PEA effect on water intake. Failures to detect an effect of PEA on 24 hr water intake [1, 7, 10], or on water intake in food-deprived rats treated with PEA doses of 16 mg/kg or less [1], can be explained by the present results which demonstrate that PEA's effects on drinking are short-lived, reversible and dose-related. The PEA-induced hypodipsia could have been due to a specific reduction in thirst. Alternatively it may have occurred secondary to some other behavioral action(s). The hypodipsia was probably not due to a drug-induced aversive condition, since recent results demonstrated that PEA doses in the range 12.5–100 mg/kg failed to induce a conditioned taste aversion in water-deprived rats [16]. Evidence which may help account for the hypodipsic effect of PEA comes from the results of the second experiment.

The effects of PEA on spontaneous motor activity were varied, and complex in nature. At the two highest doses, 25.0 and 50.0 mg/kg, PEA induced characteristic behavioral stereotypy (Fig. 3). Previous studies using the rat have shown that PEA treatments at high dose levels produce a behavioral syndrome (consisting of forepaw-padding, head-movements, splayed hindlimbs, hyperreactivity, disruption of co-ordinated ambulatory and vertical activity), which may be mediated by 5-hydroxytryptamine mechanisms [6,36]. It is parsimonious to suggest that due to the induction of stereotyped behavior, drinking was inhibited at these higher doses. It is interesting to note that PEA (40–60 mg/kg) has also been shown to depress operant responding in the rat [15]. Hence, the induction of stereotypy by PEA may be incompatible with the execution of both instrumental and consummatory responses (cf [25]).

The second experiment provided evidence for the stimulation of activity at the moderately low dose of 12.5 mg/kg PEA, in the absence of induced stereotyped behavior. To the best of our knowledge, this is the first reported instance of a PEA-induced stimulation of behavior, in rats not previously treated with a MAO inhibitor, and occurring at a moderate dose level. The behavioral stimulation was clearly demonstrated for the measure of total horizontal activity (Fig. 2A), but may also have contributed to the significant departures from linear dose-related trends in the cases of ambulatory and vertical activity. The stimulant effect was clearly behaviorally-specific, since there was no indication of an enhancement of drinking at this dose (Experiment 1).

It is interesting that the PEA-induced stimulation of spontaneous motor activity at 12.5 mg/kg was not simply a consequence of an interaction of the PEA treatment with the deprivation state of the animals. Testing the animals in a

water-deprived state in the apparatus certainly produced high baseline levels of activity. In subsequent work, we have examined the effects of PEA (6.25, 12.5 and 25 mg/kg) in non-deprived rats of the same strain, and have discovered significant peaks in horizontal and vertical activities, at the 12.5 mg/kg dose level (Dourish and Cooper, unpublished data). Hence, in animals with lower baseline levels of activity, the psychomotor stimulant effect of PEA was more clearly discernible. The behavioral stimulation which we observe in both water-deprived and non-deprived animals may represent either a generalised behavioral stimulation or a more selective increase in exploratory and searching behaviors. We tend to favor the latter explanation at present, although clearly additional work has to be done to throw light on this particular question.

At present, we have no information concerning the neurochemical bases of the lower-dose behavioral stimulation produced by PEA, and therefore it is not yet known to what extent it can be clearly distinguished from the neurochemical mechanisms which mediate the behavioral stereotypy elicited by higher dose treatments. The result may be compared however with the possibility that PEA possesses an antidepressant action in humans. It has been proposed that PEA deficiency in the brain may be linked to endogenous depression [34,36], and more recently, fluctuating levels of PEA have been reported in manic-depressive patients [24]. If there is a link between PEA activity in the brain and depressive illness, it would clearly be of particular interest to establish the neurochemical bases of the PEA stimulant effect.

In summary, Experiment 1 confirmed that PEA shares its antidipsogenic property with d-amphetamine. Other data from our laboratory rule out the possibility that the suppression of drinking was due in any measure to a drug-induced aversive state, since PEA does not generate a conditioned taste aversion. Instead, we looked in Experiment 2 for evidence that the hypodipsic effect may have been related to drug-induced changes in spontaneous activity. At 25 and 50 mg/kg, PEA produced a characteristic behavioral stereotypy syndrome which has been described previously.

The induced repetitive behavior may have precluded drinking behavior. Most interesting of all, however, was the new observation of a significant stimulant action of PEA at 12.5 mg/kg, which occurred in the absence of any behavioral stereotypy. The behavioral and neurochemical bases of this reaction remain to be elucidated.

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