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Characteristics of β-Phenethylamine Self-Administration by Dog[1]

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RISNER, M. E. AND B. E. JONES. *Characteristics of β-phenethylamine self-administration by dog.* PHARMAC. BIOCHEM. BEHAV. 6(6) 689–696, 1977. – Phenethylamine (PEA), a biologically active amine found in the brain, maintained intravenous self-administration behavior by dogs previously trained to respond for amphetamine. Systematic changes in the unit dose of PEA (1.5 to 6.0 mg/kg/infusion) were negatively related to the number of infusions (91.3 to 29.5, respectively) per 4 hr session. The mean intake of PEA was 165 mg/kg/session. Pretreatment with chlorpromazine (0.5 to 2.0 mg/kg, IV, 30 min prior to the session) produced a dose-dependent increase in the number of self-administered PEA infusions. However, there were no changes in responding for PEA following pretreatment with either the dopaminergic antagonist pimozide (5 to 40 μg/kg, IV, 30 min prior to the session) or the adrenergic antagonist phenoxybenzamine (1 to 8 mg/kg, IV, 30 min prior to the session). These data suggest that the reinforcing properties of PEA are not dependent on either a dopaminergic or adrenergic system.

Self-administration β-Phenethylamine Pimozide Phenoxybenzamine Chlorpromazine

β–PHENETHYLAMINE (PEA) is the parent compound from which many sympathomimetic agents are derived. Although PEA has limited therapeutic value, it is biologically active and has a pharmacological profile which resembles that of amphetamine. For example, increased locomotor activity and stereotypy are generally seen in animals given PEA [4, 10, 19], especially following pretreatment with monamine oxidase inhibitors. Electrophysiologically PEA activates the EEG and reduces visual evoked responses recorded from the optic cortex [20].

There is speculation that PEA may be a neurotransmitter or neuromodulator [2,20]. Nakajima, Kakimoto and Sana [13] first reported that PEA was present in rabbit brain. Subsequently, using a variety of more sensitive analytical procedures, other investigators have demonstrated the presence of PEA in several organs of many species, including human brain [3, 6, 18]. The biochemical enzyme systems necessary for the synthesis and metabolism of PEA have also been described [12]. Martin and Eades [11] found that PEA had several actions in the chronic spinal dog which could be distinguished from tryptamine and methoxamine through the use of antagonists, suggesting that there may be a distinct phenethylaminergic receptor system.

EXPERIMENT 1

A large number of psychomotor stimulants can function as reinforcers for nonhuman organisms if infusions are presented on a response-contingent basis [22]. We have shown that several stimulants (including d- and l-amphetamine, phenmetrazine and methylphenidate) are self-administered by dog [14,15]. Since there are structural and pharmacological similarities between amphetamine and PEA, it is possible that the reinforcing properties of amphetamine are related to a phenethylaminergic system in the brain. The purpose of Experiment 1 was to assess the ability of PEA to maintain intravenous self-administration by dog.

METHOD

The animals for Experiment 1 were 2 male and 3 female dogs of the mongrel beagle type weighing between 7.7 and 13.2 kg. They were individually housed in wire mesh cubicles equipped with two response pedals, both affixed to the front of the cage, and two stimulus lights, one each at the top front and rear of the cage. Each dog was fitted with a leather harness and restrained with a steel spring which ran from a feed-through swivel atop the cubicle to the dog's harness. An index of each dog's locomotor activity was obtained by monitoring the number of swivel rotations (see [14]). Other features of the mechanical equipment have been described elsewhere [9].

All of the animals had been previously trained to self-administer several psychomotor stimulants and were

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familiar with the limited-availability response contingencies [15]. Briefly, the training procedure included the following phases: (1) presurgery adapation to the cubicle, harness and spring-swivel attachment, (2) surgery, under sodium pentobarbital anesthesia (30–35 mg/kg administered intravenously), to implant chronic indwelling jugular cannulae, (3) drug self-administration including an initial ad lib acquisition phase followed by limited access conditions. During the acquisition phase, response contingent infusions of either d-amphetamine, methylphenidate, or phenmetrazine were available. Immediately following acquisition of drug-seeking behavior, all of the dogs were placed on a 4 hr limited availability schedule (11:00 a.m. to 3:00 p.m.). The drug access session was signalled by illumination of the rear stimulus light. Throughout the session each response on the reinforced pedal resulted in an infusion of d-amphetamine (0.05 mg/kg/infusion). The front stimulus light was illuminated during each infusion. Responses on the nonreinforced pedal were recorded but had no programmed consequences. Under these limited availability conditions drug intake per session quickly stabilized and remained relatively constant across time.

Substitution of β-Phenethylamine for Amphetamine

When the between-session variation in number of self-administered amphetamine infusions was 15% or less, the amphetamine was replaced with β-phenethylamine sulfate. The PEA was dissolved in physiological saline and given in a volume of 0.1 ml/kg at a rate of 1 ml/min. Three unit doses of PEA were selected for observation: 1.5, 3.0 and 6.0 mg/kg/infusion. The dogs were allowed to self-administer each unit dose for four consecutive daily sessions. The order of unit dose presentation was determined arbitrarily, but was different for each dog. The same five dogs were examined at all three unit doses of PEA.

Substitution of Saline for β-Phenethylamine

Four dogs, with stable rates of responding for PEA, were used to evaluate the rate of saline self-administration immediately following PEA intake. Saline (0.1 mg/kg/infusion) was substituted for PEA for five consecutive daily sessions. All other experimental conditions were unchanged.

RESULTS

The results of substituting PEA for amphetamine are shown in Fig. 1. PEA maintained responding at significantly higher levels than saline at all three unit doses. As depicted in the upper right quadrant of Fig. 1, there was a negative relationship between unit dose and number of self-administered infusions. The mean number of infusions per 4 hr session was 91.3 at the lowest unit dose of PEA (1.5 mg/kg/infusion) and 29.5 at the highest unit dose (6.0 mg/kg/infusion). Mean drug intake per session ranged from 137 to 177 mg/kg; these differences were not statistically significant ($F<1$). The mean activity index per session is plotted as a function of PEA unit dose in the lower right quadrant of Fig. 1. Although there was a tendency for activity to increase with unit dose, the regression was not significant ($p>0.05$). As shown in Fig. 1, the mean activity level during saline baseline was 1888. In addition to increased locomotor activity, the dogs receiving PEA displayed stereotyped behavior such as head-bobbing and repetitious motor patterns like circling about the cage.

For comparative purposes the quantitative aspects of d-amphetamine self-administration are also depicted in Fig. 1. (Portions of these data have been previously reported [15].) There was an inverse relationship between unit dose of d-amphetamine and number of infusions self-administered per session. At unit doses of 0.025, 0.05 and 0.10 mg/kg/infusion the dogs responded for an average of 47.9, 29 and 15.8 infusions, respectively. Total drug intake per session increased from 1.2 to 1.58 mg/kg. Note that the mean activity index during amphetamine self-administration was similar to values seen when dogs responded for PEA.

The frequency distribution of infusions/hr during the drug session is shown in Fig. 2. At all three unit doses of PEA approximately 25% of the total number of infusions/session were self-administered each hour. This is in contrast to the frequency distribution when each response produced an infusion of amphetamine [15]. A large portion (62.4 to 79.5%) of the amphetamine infusions were self-administered during the first hour of the session and relatively few infusions occurred during the remainder of the session; however, the amphetamine infusions self-administered during the last three hr tended to be evenly distributed across each hour period.

Representative event recordings depicting the response patterns of PEA self-administration for one dog are shown in the upper portion of Fig. 3. There was a tendency for the inter-infusion intervals to be shorter at the beginning of the PEA self-administration sessions, particularly at the lower unit doses. These short bursts of responding seen at the session onset probably represent a drug accumulation phase during which the dog is rapidly increasing drug levels until a criterion amount is reached. The marked regularity of PEA self-administration is in contrast to the response behavior seen when amphetamine is the reinforcer [15]. As seen in the lower portion of Fig. 3, the initial burst of responding for amphetamine lasted from 20 to 50 min; the remaining infusions were irregularly spaced.

The results of substituting saline for PEA are shown in Table 1. There was a significant ($p<0.01$) increase in the number of self-administered infusions during the first saline session as compared with the preceding PEA baseline sessions. On the second through the fifth day of saline substitution the response rate was extremely variable and the dogs exhibited several periods of response bursts interspersed with periods of minimal responding. By the fifth day of saline substitution all but one of the dogs had returned to response rates similar to those seen prior to PEA self-administration.

EXPERIMENT 2

In the second experiment an attempt was made to modify the patterns of PEA self-administration by pretreating the dogs with other pharmacologic agents. The results of such manipulations may help identify the neurochemical substrates of PEA self-administration. We have previously shown that pretreatment with the dopaminergic antagonist pimozide produced a dose-dependent increase in subsequent responding for amphetamine, thus suggesting that an intact dopaminergic system is critical for amphetamine self-administration [16]. The selective adrenergic antagonist phenoxybenzamine did not

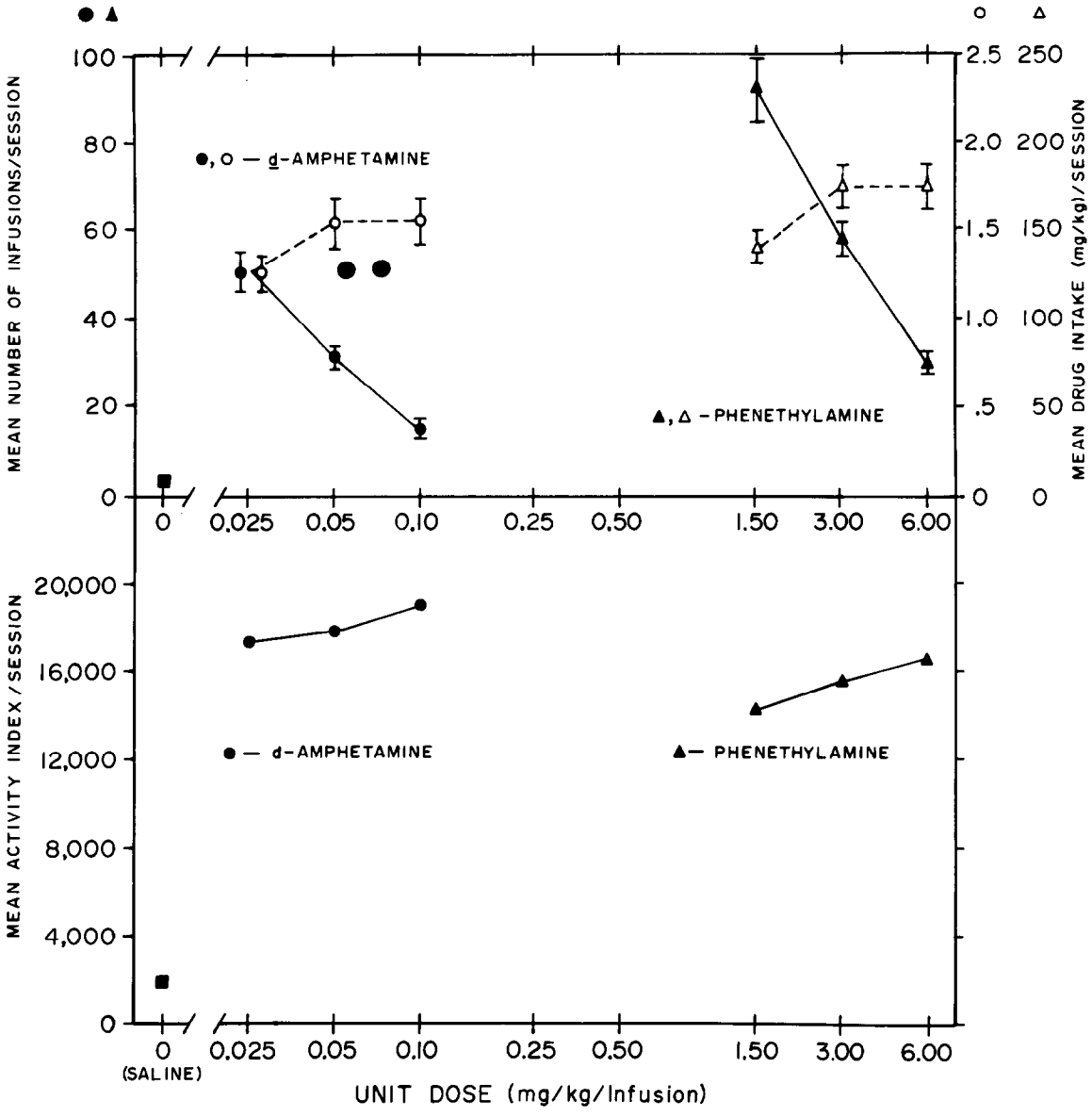

FIG. 1. The mean number of amphetamine (●) or phenethylamine (▲) infusions self-administered per 4-hr session and the mean amphetamine (○) or phenethylamine (△) intake are plotted in the upper panel of Fig. 1. The mean activity index per session, as a function of d-amphetamine or phenethylamine, is shown in the lower panel. The mean number of saline infusions (■) self-administered per 4-hr saline predrug session and the associated activity index (■) are shown in the upper and lower panels of Fig. 1, respectively. Each data point represents the mean of data obtained from 5 dogs. Vertical lines depict standard errors of the means (N = 5). No standard errors are shown for the activity data since the between-animal variability was quite large. (Portions of the amphetamine data have been published elsewhere [15].)

alter amphetamine self-administration, thus indicating that adrenergic processes do not appear to be important in amphetamine reinforcement.

METHOD

The animals for Experiment 2 were the same 5 dogs used in Experiment 1 plus an additional 3 dogs (1 male and 2 female mongrel beagle dogs, weighing between 7.7 and 11.8 kg, all with past histories of drug self-administration). Using the procedures described in Experiment 1, all 8 dogs were trained to self-administer PEA (6.0 mg/kg/infusion) during daily 4 hr sessions. As previously described, under these limited access conditions drug intake (mg/kg/session) becomes stable over time and the variation in the number of infusions/session decreases to 15% or less.

Following acquisition of stable baseline responding the dogs were treated with one of three drugs: phenoxybenzamine HCl (1, 2, 4, or 8 mg/kg), pimozide HCl (5, 10, 20 or 40 μg/kg), or chlorpromazine HCl (0.25, 0.50, 1.0 or 2.0 mg/kg). All of the pretreatment agents were administered through the intravenous jugular catheters 30 min

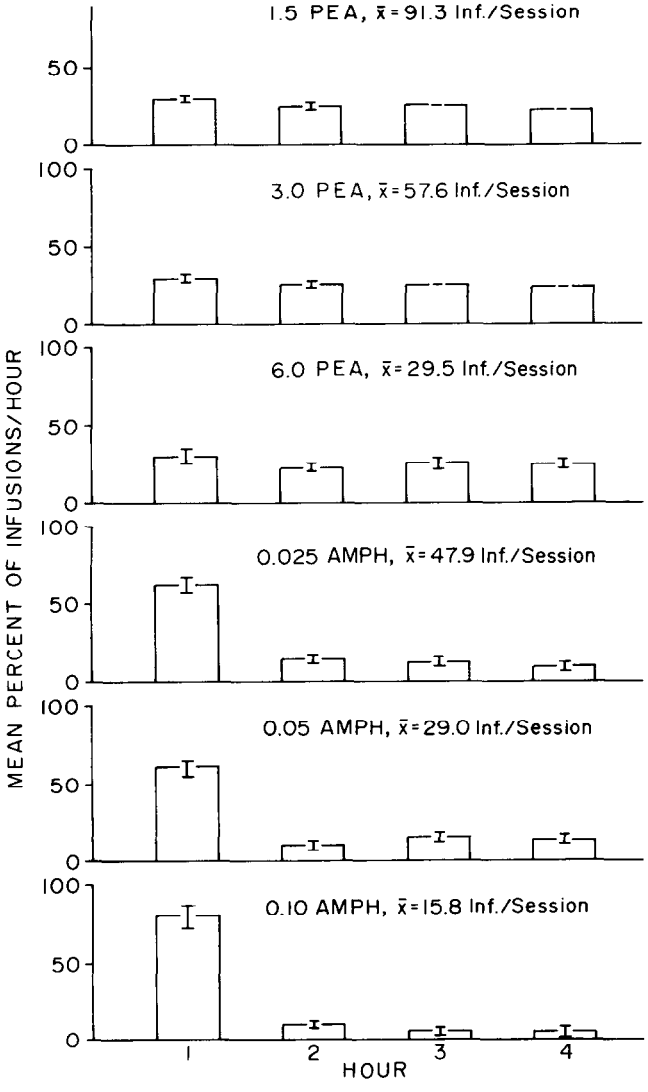

FIG. 2. The mean percent of phenethylamine (either 1.5, 3.0 or 6.0 mg/kg/infusion) or d-amphetamine (either 0.025, 0.05 or 0.10 mg/kg/infusion) infusions self-administered during each 1-hr segment of a 4-hr session. Each percent was based on the mean of data obtained from 4 or more dogs. The mean number of infusions received each session is also presented. Vertical brackets at the top of each bar represent standard errors of the means. (The standard errors are based on the number of dogs × 1 mean for each dog).

before the PEA self-administration session. The order of each drug series and doses within each series was determined arbitrarily and was different for each dog. Five or more days intervened between successive pretreatments. At least 4 dogs were used for each pretreatment condition. The phenoxybenzamine was dissolved in either normal saline following heat and agitation or saline adjusted to pH 1.9; pimozide was dissolved in 0.5% tartaric acid solution; the vehicle for chlorpromazine was normal saline. Appropriate vehicle controls were included in the series of pretreatment conditions.

RESULTS

The effects of phenoxybenzamine on subsequent self-administration of PEA are depicted in Fig. 4. There were no significant changes in PEA intake at any of the phenoxybenzamine doses used in the present study. Likewise, none of the other behavioral actions of PEA appeared to be altered by phenoxybenzamine. As previously reported [16], phenoxybenzamine, dissolved in normal saline following heat and agitation, also failed to alter amphetamine self-administration. These latter data are also shown in Fig. 4. (We have subsequently found that phenoxybenzamine solubilized in acidified saline does not change responding for amphetamine.)

There were no changes in PEA self-administration following pretreatment with pimozide (Fig. 5). Neither PEA intake nor PEA-induced locomotor activity were affected by pimozide. It is of special interest to note that, as previously reported [16], amphetamine self-administration was increased markedly following pretreatment with pimozide (see Fig. 5).

There was a significant, dose-dependent change in the number of PEA infusions (Fig. 6) following pretreatment with chlorpromazine. At doses of 0.25, 0.50 and 1.0 mg/kg responding for PEA was increased 13%, 33% and 46%, respectively. Although the increased responding for PEA following 2.0 mg/kg chlorpromazine was less than that seen at the 1.0 mg/kg dose, the curvilinear expression was not significant. The results of chlorpromazine pretreatment on responding for amphetamine, as reported earlier [16], are also plotted in Fig. 6. Note the qualitative similarity in chlorpromazine's effects on PEA and amphetamine self-administration.

TABLE 1

NUMBER OF INFUSIONS SELF-ADMINISTERED DURING 3 SUCCESSIVE PHENETHYLAMINE (6.0 MG/KG/INFUSION) SESSIONS AND THE 5 SALINE (0.1 ML/KG/INFUSION) EXTINCTION SESSIONS IMMEDIATELY FOLLOWING

	PHENETHYLAMINE DAYS			SALINE DAYS				
	1	2	3	1	2	3	4	5
DOG 2091	26	24	23	39	9	20	5	1
1681	24	25	27	88	17	24	5	0
2194	35	21	33	50	12	50	75	7
1498	23	24	25	52	2	24	16	19
$\bar{X}$ =	27	23.5	27	57.3	10	29.5	25.3	6.8
SEM =	2.7	0.9	2.2	10.6	3.1	6.9	16.8	4.4

DISCUSSION

The results of the experiments and observations described above suggest that β-phenethylamine can serve as a reinforcer. (1) Response-contingent infusions of PEA maintained regular, sustained responding on the reinforced pedal; whereas, the response rate on the non-reinforced pedal was near-zero or did not vary systematically with PEA intake. (2) Variations in the unit dose of PEA were inversely related to the rate of responding for PEA infusions. (3) When the PEA was replaced with saline there was an initial increase in responding followed by a gradual decrease with sporadic periods of response bursts. Before exposure to PEA the dogs responded for few, if any, saline

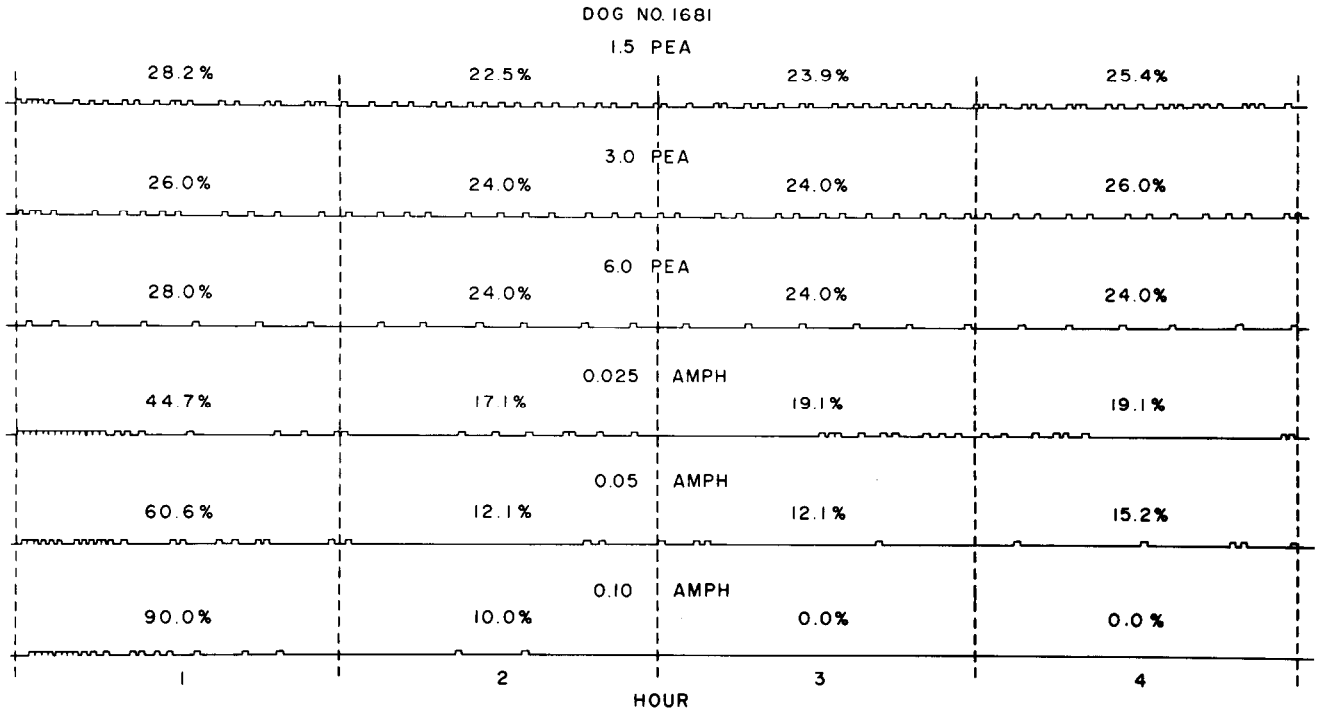

FIG. 3. Representative event recordings, for one dog, depicting the distribution of self-administered phenethylamine (either 1.5, 3.0 or 6.0 mg/kg/infusion) or d-amphetamine (either 0.025, 0.05 or 0.10 mg/kg/infusion) infusions during the 4-hr drug session. The percent of infusions received in each 1-hr block of the session is presented above each event tracing.

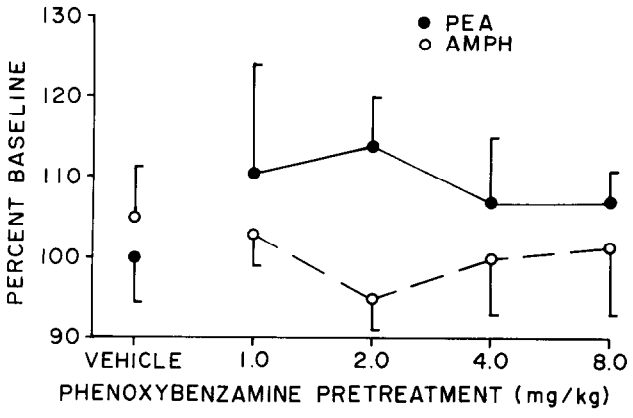

FIG. 4. The effects of phenoxybenzamine pretreatment on responding for phenethylamine (●, 6.0 mg/kg/infusion) or d-amphetamine (○, 0.05 mg/kg/infusion). The data are plotted as the percent of the number of infusions self-administered during baseline sessions. Each data point depicts the mean of data obtained from at least 4 dogs. Vertical lines represent standard errors of means. (The standard errors are based on the number of dogs × 1 mean for each dog. The data describing the effects of phenoxybenzamine on amphetamine self-administration were presented earlier [16].)

infusions. The saline extinction function seen following PEA self-administration is an indication of drug-seeking behavior. (4) When the pedal contingencies were reversed there was a reversal in the response rate on each pedal; responding on the previously reinforced pedal decreased to baseline values and responding on the previously nonreinforced pedal increased so that PEA self-administration was resumed. The results of one such reversal in pedal contingencies are shown in Fig. 7. In this example, the contingencies were reversed during a PEA self-administration session. We have previously shown that dogs self-administering other psychomotor stimulants reverse their pedal preference if the contingencies are switched [17]. Taken together, the experiments and observations summarized above indicate that PEA, a trace amine found in the CNS, can function as a reinforcer. Thus, the endogenous amine PEA can be added to the list of compounds that will be self-administered by non-human organisms.

There were marked increases in locomotion and stereotypy during the drug self-administration period. The stereotypy was characterized by repetitious motor behavior such as circling about the cage, head movements including lateral and vertical components, and other complex sequences. Although qualitatively similar behavior patterns are produced by many psychomotor stimulants [15], the intensity of the PEA-induced changes in locomotor activity and stereotypy appeared to be appreciably greater.

Since PEA is an excellent substrate for degradation by monoamine oxidase, most of its pharmacological actions are observable for only 10 min or less [13]. Indeed, the half-life of PEA in the central nervous system is approximately 4 min [26]. Consequently, most researchers elect to pretreat the animals with monamine oxidase inhibitors to prolong the effects of PEA. However, since monamine oxidase inhibitors may produce behavioral depression and other actions, none of the dogs studied in the experiments

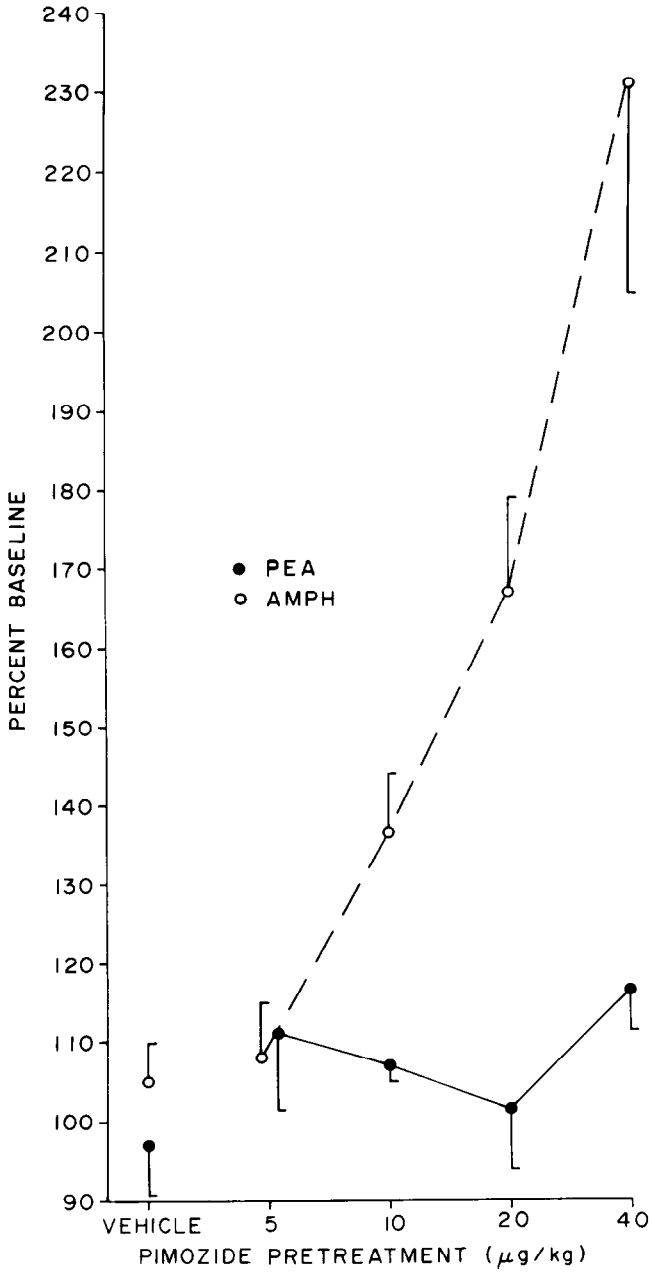

FIG. 5. The effects of pimozide pretreatment on responding for phenethylamine (●, 6.0 mg/kg/infusions) or d-amphetamine (○, 0.05 mg/kg/infusion). The data are plotted as the percent of the number of infusions self-administered during baseline sessions. Each data point depicts the mean of data obtained from at least 4 dogs. Vertical lines represent standard errors of the means. (The standard errors are based on the number of dogs × 1 mean for each dog. The data describing the effects of pimozide on amphetamine self-administration were presented earlier [16].)

described above was given monamine oxidase inhibitors. Jackson [7,8] has also characterized the actions of PEA on spontaneous motor activity in animals which had not been treated with monamine oxidase inhibitors and clearly demonstrated hyperactivity and other stimulant effects.

When the unit dose of PEA was varied from 1.5 to 6.0

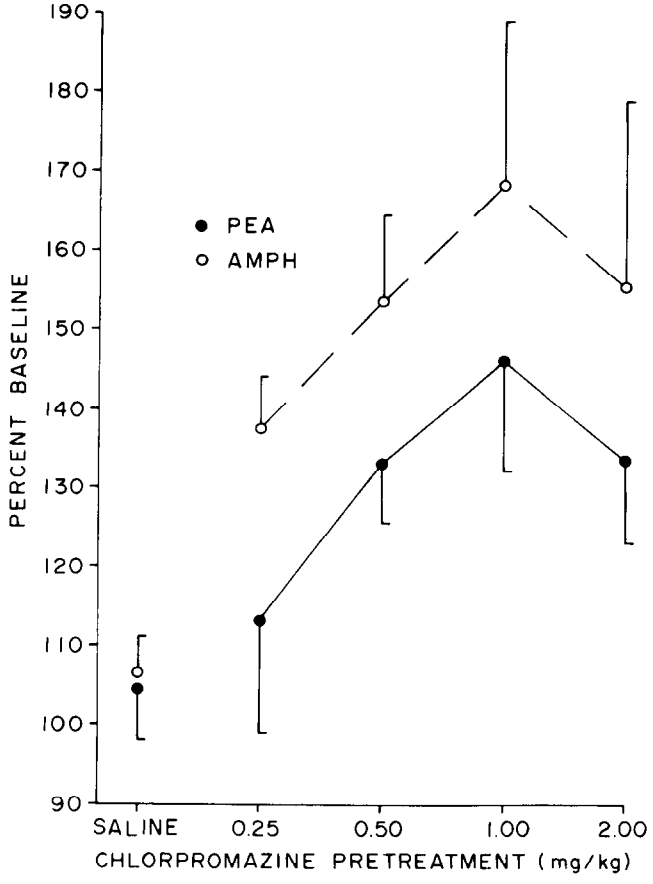

FIG. 6. The effects of chlorpromazine pretreatment on responding for phenethylamine (●, 6.0 mg/kg/infusion) or d-amphetamine (○, 0.05 mg/kg/infusion). The data are plotted as the percent of the number of infusions self-administered during baseline sessions. Each data point depicts the mean of data obtained from at least 4 dogs. Vertical lines represent standard errors of the means. (The standard errors are based on the number of dogs × 1 mean for each dog. The data describing the effects of chlorpromazine on amphetamine self-administration were presented earlier [16].)

mg/kg/infusion, the dogs adjusted their response rate so that total drug intake per 4 hr session remained relatively constant. The inverse relationship between unit dose and number of infusions self-administered per session is a typical finding when access to psychomotor stimulants is limited to one session each day (e.g., [24]). The dogs may have varied their response rate at each unit dose to maintain a particular level of PEA at critical receptor sites. Using a modified vision of a procedure described by Wagner [23], the average whole-body concentration of PEA was found to range from 2.4 to 3.2 mg/kg throughout the 4 hr self-administration session (E. J. Cone and M. E. Risner, manuscript in preparation). Additionally, the plasma levels of PEA had declined below 0.2 μg/ml whenever the dog responded for PEA infusions. These data support the notion that response rate per session varies as a function of unit dose so the dog can maintain a desired amount of PEA in the body. As indicated earlier, there was a marked regularity of responding throughout the self-administration session. With the exception of some short bursts of

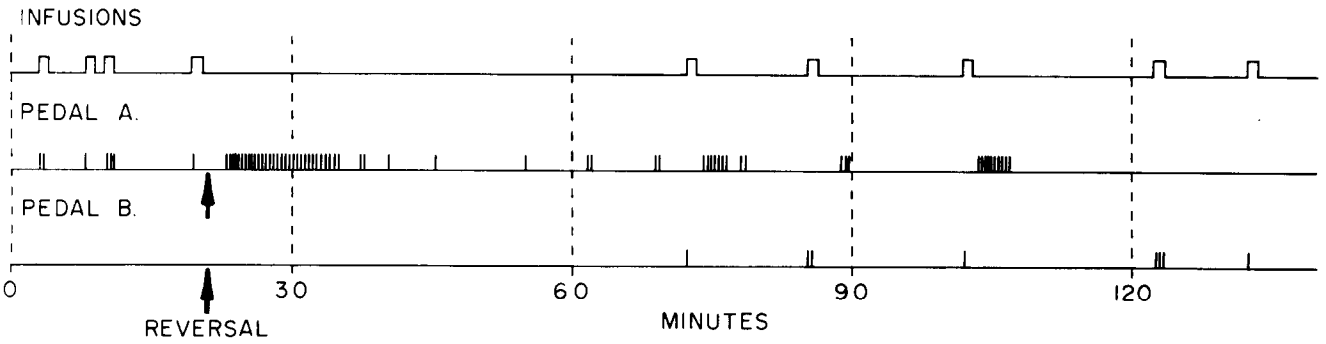

FIG. 7. An event recording depicting the distribution of self-administered PEA infusions (6.0 mg/kg/infusion) during a 150-min portion of a 4-hr session. During the first 20-min segment of the recording each response on Pedal A resulted in one PEA infusion. Responses on Pedal B had no programmed consequences. These contingencies had been in effect for several preceding sessions. The response rate on Pedal B had been zero throughout these preceding periods. At the point indicated Reversal the pedal contingencies were reversed; thus, responses on Pedal A no longer produced PEA infusions, but responding on Pedal B was effective.

responding at the beginning of the session, the inter-infusion intervals tended to be consistent for the remainder of the session. This phenomenon may be due to the short duration of action of PEA. The plasma half-life of intravenously administered PEA was found to range from 1.8 to 3.0 min in dog (E. J. Cone and M. E. Risner, manuscript in preparation). This finding is consistent with previous reports indicating that PEA is metabolized rapidly by monamine oxidase. The observation that PEA is metabolized quickly, coupled with our finding that the plasma level had decreased below a relatively consistent value each time the dog responded for another drug infusion, may explain why PEA was self-administered at short, regular intervals.

The results of the pretreatment studies described in Experiment 2 suggest that the reinforcing properties of PEA are not mediated exclusively by either a noradrenergic or a dopaminergic transmitter system. Responding for PEA was not altered when the dogs were pretreated with the noradrenergic antagonist phenoxybenzamine. These data are consistent with previous studies which demonstrated that: (1) phenoxybenzamine did not antagonize the effects of PEA on the flexor reflex, pupillary diameter, skin twitch reflex, and nictitating membrane of the chronic spinal dog [11], and (2) PEA-induced increases in mouse locomotor activity were not significantly antagonized by phenoxybenzamine [8]. Since there is evidence that phenoxybenzamine crosses the blood-brain barrier and blocks central noradrenergic mechanisms (see [16] for discussion), the failure of phenoxybenzamine to alter responding for PEA indicates that the reinforcing properties of PEA are not based on NE neurotransmission. It has already been shown that the self-administration of amphetamine is likewise not dependent on an intact NE system [16,27].

When the dogs were pretreated with the dopaminergic antagonist pimozide over a broad dose range, there were no significant changes in responding for PEA. This was an unexpected result since there are several lines of evidence suggesting a relationship between PEA and dopamine. For example, PEA has been shown to deplete the dopamine content of dopamine-containing nerve terminals [4], and pretreatment with either pimozide or haloperidol blocked PEA-induced locomotion in mice [8]. Since the half-life of pimozide is approximately 10 hr [1], it would appear there was effective antagonism of dopaminergic receptors during the entire 4 hr self-administration session. The failure of pimozide to change responding for PEA, whereas amphetamine self-administration is markedly altered by pimozide, may be an indication that stimulant self-administration is subserved by pharmacologically redundant systems, specifically phenethylaminergic and dopaminergic pathways. An antagonist which specifically blocks the actions of PEA would be useful in examining such a possibility.

In the third pretreatment study we found that chlorpromazine administered over an eight-fold dose range produced an increase in responding for PEA infusions. Increased responding for drug infusions is presumably an attempt to compensate for the pharmacological attenuation of the neurochemical mechanisms responsible for PEA self-administration. Since chlorpromazine has several actions including an ability to block a variety of putative neurotransmitters, it is difficult to know which of the properties of chlorpromazine produced the observed changes in responding for PEA. Martin and Eades [11] also found that chlorpromazine antagonized several effects of PEA in the chronic spinal dog. It is of special interest to note that the effects of chlorpromazine on PEA self-administration were qualitatively similar to those of chlorpromazine on amphetamine-reinforced responding by dog [16] or by monkey [25]. However, equal doses of chlorpromazine produced greater changes in responding for amphetamine than PEA.

It has been shown that the microiontophoretic application of PEA on single optic cortex neurons of the rabbit produced different effects than norepinephrine [5], suggesting that the effects of PEA are not mediated through the release of norepinephrine or activation of norepinephrine receptors. Additionally, the tryptaminergic antagonist cyproheptadine did not alter PEA's actions in the chronic spinal dog [11]. Coupled with the results of the three pretreatment studies described in the present report, it appears that many of the central actions of PEA are not mediated by noradrenergic, dopaminergic, or tryptaminergic systems. Thus, there may be a separate phenethylaminergic system.

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REFERENCES

1. Ahlenius, S. and J. Engel. On the interaction between pimozide and α-methyltyrosine. *J. Pharm. Pharmac.* **25:** 172–174, 1973.
2. Fischer, E., R. I. Ludmer and H. C. Sabelli. The antagonism of phenylethylamine to catecholamines on mouse motor activity. *Acta physiol. latinoam.* **17:** 15–21, 1967.
3. Fischer, E., H. Spatz, B. Heller and H. Reggiani. Phenethylamine content of human urine and rat brain, its alteration in pathological conditions and after drug administration. *Experientia* **28:** 307–308, 1972.
4. Fuxe, K., H. Grobecker and J. Jonsson. The effect of β-phenylethylamine on central and peripheral monoamine-containing neurons. *Eur. J. Pharmac.* **2:** 202–207, 1967.
5. Giardina, W. J., W. Pedemonte and H. C. Sabelli. Iontophoretic study of the effects of norepinephrine and 2-phenylethylamine on single cortical neurons. *Life Sci.* **12:** 153–161, 1973.
6. Inwang, E. E., A. D. Mosnaim and H. C. Sabelli. Isolation and characterization of phenylethylamine and phenylethanolamine from human brain. *J. Neurochem.* **20:** 1469–1473, 1973.
7. Jackson, D. M. The effect of β-phenethylamine upon spontaneous motor activity in mice: A dual effect on locomotor behavior. *J. Pharm. Pharmac.* **24:** 383–389, 1972.
8. Jackson, D. M. β-Phenethylamine and locomotor activity in mice. *Arzneimitte Forsh.* **25:** 622–626, 1975.
9. Jones, B. E. and J. A. Prada. Relapse to morphine use in the dog. *Psychopharmacologia* **30:** 1–12, 1973.
10. Mantegazza, P. and M. Riva. Amphetamine like activity of β-phenylethylamine. *J. Pharmac.* **15:** 472–478, 1963.
11. Martin, W. R. and C. G. Eades. Effects of phenethylamine (PEA) in the chronic spinal dog. *Pharmacologist* **16:** 205, 1974.
12. Mosnaim, A., E. Inwang, J. Sugerman, W. De Martini and H. C. Sabelli. Ultra-violet spectrophotometric determination of 2-phenylethylamine in biological samples and its possible correlation with depression. *Biol. Psychiat.* **6:** 235–256, 1973.
13. Nakajima, T., Y. Kakimoto and I. Sana. Formation of β-phenylethylamine in mammalian tissue and its effect on motor activity in the mouse. *J. Pharmac. exp. Ther.* **143:** 319–325, 1964.
14. Risner, M. E. Intravenous self-administration of d- and l-amphetamine by dog. *Eur. J. Pharmac.* **32:** 344–348, 1975.
15. Risner, M. E. and B. E. Jones. Self-administration of CNS stimulants by dog. *Psychopharmacologia* **43:** 207–213, 1975.
16. Risner, M. E. and B. E. Jones. The role of noradrenergic and dopaminergic processes in amphetamine self-administration. *Pharmac. Biochem. Behav.* **5:** 477–482, 1976.
17. Risner, M. E. and B. E. Jones. Characteristics of unlimited access to self-administered stimulant infusions in dogs. *Biol. Psychiat.* **11:** 625–634, 1976.
18. Saavedra, J. M. Enzymatic isotopic assay for and presence of β-phenethylamine in brain. *J. Neurochem.* **22:** 211–216, 1974.
19. Sabelli, H. C., W. J. Giardina, A. D. Mosnaim and N. H. Sabelli. A comparison of the functional uses of norepinephrine, dopamine, and phenylethylamine in the central nervous system. *Acta physiol. pol.* **24:** 33–40, 1973.
20. Sabelli, H. C., A. D. Mosnaim and A. J. Vazquez. Phenylethylamine: Possible role in depression and antidepressive drug action. In: *Neurochemical Coding of Brain Function,* edited by R. D. Myers and R. R. Drucker-Colin. New York: Plenum Publishing, 1974, pp. 331–357.
21. Sabelli, H. C., A. J. Vazquez and D. Flavin. Behavioral and electrophysiological effects of phenylethanolamine and 2-phenylethylamine. *Psychopharmacologia* **42:** 117–125, 1975.
22. Thompson, T. and R. Pickens. *Stimulus Properties of Drugs.* New York: Appleton-Century-Crofts, 1971.
23. Wagner, J. R. *Fundamentals of Clinical Pharmacokinetics.* Hamilton: Drug Intelligence Publications, 1975.
24. Wilson, M. C., M. Hitomi and C. R. Schuster. Psychomotor stimulant self-administration as a function of dosage per injection in the rhesus monkey. *Psychopharmacologia* **22:** 271–281, 1971.
25. Wilson, M. C. and C. R. Schuster. The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. *Psychopharmacologia* **26:** 115–126, 1972.
26. Wu, P. H. and A. A. Boulton. Metabolism, distribution and disappearance of injected β-phenylethylamine in the rat. *Can J. Biochem.* **53:** 42–50, 1975.
27. Yokel, R. A. and R. Wise. Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. *Science* **187:** 547–549, 1975.