Behavioral and Neurochemical Evaluation of Phenylpropanolamine[1]

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ABSTRACT

(±)-Phenylpropanolamine (PPA), a widely available anorectic and decongestant, was evaluated in several behavioral paradigms in rhesus monkeys and for central nervous system neurotoxicity in rats. PPA (1–30 mg/kg intragastric) reduced food intake in rhesus monkeys but was not self-administered i.v. (0.3–10 mg/kg/injection) by monkeys experienced in drug self-administration. PPA (30–100 mg/kg intragastric) resulted in amphetamine-like responding in two of four monkeys trained in a drug discrimination paradigm to discriminate *d*-amphetamine from saline. In rats, a 4-day injection regimen of high doses of PPA (200 and 400 mg/kg/day) resulted in approximately a 20% depletion of dopamine in the frontal cortex but failed to deplete dopamine, norepinephrine or serotonin in any other brain region studied. Thus, PPA is an effective anorectic in rhesus monkeys that, based upon drug discrimination results, would be expected to have limited amphetamine-like subjective effects and only at doses well in excess of effective anorectic doses. However, based upon self-administration results, PPA would not be predicted to have amphetamine-like dependence potential. Moreover, repeated administration of PPA did not produce the severe central nervous system neurotoxicity associated with many other amphetamine congeners.

PPA is a phenylethylamine that has been available for over 40 years for use as an anorectic and nasal decongestant (Silverman *et al*, 1980). In spite of its high availability, little is known about the compound behaviorally. In rodents, PPA has been reported to have some effects in common with its close chemical analog *d*-amphetamine, a well-studied psychomotor stimulant. Like *d*-amphetamine, PPA increases locomotor activity (Schulte *et al.*, 1941; Warren and Werner, 1945), induces stereotyped behavior (Davis and Pinkerton, 1972) and reduces food intake (Cairns *et al.*, 1984; Epstein, 1959; Tainter, 1944). However, PPA is substantially less potent than *d*-amphetamine in these effects. The central mechanism(s) involved in these effects is poorly understood. Like *d*-amphetamine, PPA is sympathomimetic and similarities in overt behavioral effects suggest similarities to *d*-amphetamine in central mechanisms of action. Moreover, atropine has been reported to enhance many of the effects of both compounds (Davis and Pinkerton, 1972). On the other hand, other behavioral studies suggest differences between PPA and amphetamine in CNS actions. For instance, PPA and amphetamine have different profiles of effects on electrical stimulation of the brain and on stimulation escape responding (Kornblith and Hoebel, 1976). Thus, the research that has been conducted with rats has found both similarities and differences between PPA and amphetamine.

A limited amount of systematic data are available concerning PPA effects in humans. Fazekas *et al.* (1959) reported that PPA was relatively ineffective as an anorectic when compared to *d*-amphetamine. More recently, however, Hoebel et al. (1975a,b) have reported decreased food intake and body weight loss in humans taking PPA over several days. In addition to therapeutic use, recreational use of PPA has been reported, often in conjunction with caffeine (Mueller, 1983). PPA has also been implicated in the production of psychosis (Kane and Green, 1966), an effect that is well known with amphetamines (Jaffe, 1985) and may be related to their CNS neurotoxicity. Clearly, additional research is needed to elucidate the CNS effects of PPA.

An effective anorectic with no dependence potential, no amphetamine-like subjective effects or neurotoxicity would clearly be preferred to *d*-amphetamine. In the absence of that ideal compound, preferred anorectics should reduce food intake

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ABBREVIATIONS: PPA, (±)-phenylpropanolamine; CNS, central nervous system; i.g., intragastric; DA, dopamine; NE, norepinephrine; 5-HT, serotonin.

at doses well below those necessary to produce other amphetamine-like side effects. The present experiment is part of an ongoing research program designed to assess the anorectic efficacy, dependence potential and CNS toxicity of available anorectics (Schuster and Johanson, 1985). The reinforcing properties of PPA were assessed in rhesus monkeys, a species that has proven quite useful for predicting dependence potential in humans (Johanson and Balster, 1978). To allow systematic potency comparisons, anorectic efficacy and discriminative stimulus properties were determined in this same species. The discriminative stimulus properties of drugs in animals are thought to be a measure of their subjective effects in humans (Woolverton and Schuster, 1983). Neurotoxicity studies were done in rats using procedures similar to studies with other phenylethylamines (Ricaurte *et al.*, 1985; Wagner *et al.*, 1980b). The results suggest that PPA is an effective anorectic with little or no dependence potential and limited amphetamine-like discriminative stimulus properties even at doses 10 to 20 times the effective anorectic dose. Moreover, upon repeated administration PPA does not result in amphetamine-like neurotoxicity in rats.

Methods

Self-administration. The animals were two male and two female (4.1–8.2 kg) rhesus monkeys (*Macaca mulatta*). Two monkeys (2035 and 2039) were experimentally naive at the beginning of the experiment. The other two (2029 and 3013) had experience with self-administration of other anorectic compounds (mazindol, 2029; benzphetamine, chlorphentermine and clortermine, 3013). Each monkey was fitted with a stainless-steel restraint harness and spring arm which attached to the rear of the experimental cubicle (70 cm wide × 84 cm deep × 80 cm high) in which the monkey lived for the duration of the experiment. Two response levers (BRS/LVE, PRL-001, Beltsville, MD) were mounted on the inside front of each experimental cubicle 10 cm above the floor and a food dish was mounted between them. Four jewelled stimulus lights, two red and two white, were mounted directly above each lever. In addition, two houselights, one white (34 w) and one red (15 w), were mounted on the ceiling of the cubicle and covered with translucent Plexiglas. Drug injections were delivered by a peristaltic infusion pump (Cole-Parker Co., Chicago, IL). All programming and recording of experimental events were accomplished by solid state equipment located in an adjacent room.

The self-administration procedure has been described in detail previously (Woolverton *et al*, 1984). Briefly, each monkey was prepared surgically with a chronic indwelling venous catheter. Experimental sessions, signalled by the illumination of all white lights, were 2 hr in length and were conducted 7 days a week. During base-line sessions the animals were allowed to press the right lever to receive i.v. injections of cocaine (0.06 mg/kg/injection) under a schedule requiring 10 lever presses per injection (fixed-ratio 10). During injections the white lights were extinguished and the red lights were illuminated. After the establishment of stable rates of responding under these base-line conditions (less than 10% variation in total number of injections per session for at least three consecutive sessions), 0.9% saline was substituted until responding declined to low, stable levels (5–12 sessions). Subsequently, the animal was returned to base-line conditions. When base-line responding was again stable for at least two consecutive sessions that approximated previous levels, a dose of PPA was substituted for the same number of sessions that had been required for responding for saline to decline.

At least four doses of PPA were substituted for cocaine in each monkey in a mixed order using this procedure with base-line conditions reinstated between doses. Doses were tested over a 30-fold range (0.3–10 mg/kg/injection) up to a dose which suppressed lever pressing during the first session of the substitution period. The number of injections over the last three sessions of a PPA substitution period was used in data analysis. These values were compared to the same values for the last three sessions of the corresponding saline substitution period. A dose of PPA was considered to be a positive reinforcer in a particular monkey if the mean number of injections for the last three sessions of a test period exceeded the mean value for saline substitution, and the ranges did not overlap.

Drug discrimination. The animals were four male rhesus monkeys that weighed between 8.0 and 10 kg. All monkeys had participated in studies of i.v. drug self-administration and drug effects on schedule-controlled responding. They were housed individually in stainless-steel cages in which water was available continuously. They were fed 150 to 200 g of monkey chow after each session and were given a chewable vitamin tablet 3 days/week. During experimental sessions the monkeys were seated in a Plas-Lab restraining chair and placed in a wooden cubicle (175 cm high × 85 cm wide × 65 cm deep) containing two response levers mounted 110 cm above the floor. A 34 w white houselight was mounted on the ceiling. A wooden barrier was attached to the chair in such a way as to prevent a monkey from reaching either lever with both hands or both levers simultaneously. The monkey's feet were placed into shoes, the bottoms of which were fitted with brass plates for the delivery of electric shocks.

The drug discrimination procedure has been described in detail previously (de la Garza and Johanson, 1986). Briefly, they were trained in a two lever, trial procedure to avoid electric shock. One hour after an i.g. infusion of *d*-amphetamine (0.56 or 1.0 mg/kg, based upon individual sensitivity) or saline the houselights and lever lights were illuminated (trial) and responding on one lever (the correct lever) avoided electric shock and extinguished the lights. Responding on the incorrect lever started a 2-sec change over delay during which correct lever responding had no consequence. If a correct response was not made within 5 sec of onset of the lights, shock (250 msec duration, 10 mA intensity) was delivered every 2 sec until a correct response was made. After a correct response, there was a 55-sec intertrial interval. The session lasted for 30 trials or 40 min, whichever came first, after which a new trial began. The correct lever was determined by the infusion that was administered before the session. For two monkeys the right lever was correct after *d*-amphetamine infusions and the left lever was correct after saline infusions. This condition was reversed for the other two monkeys.

Monkeys were considered to have acquired the discrimination when more than 90% of the trials were completed on the correct lever for six consecutive sessions. At this point testing was begun with *d*-amphetamine and PPA. A 6-day sequence alternated drug, vehicle and test sessions so that each test session was preceded by two training sessions, one with saline and one with drug pretreatment. In the event that the criterion for stimulus control was not met during the training sessions, the training sequence was continued. During test sessions, both levers were operational. At least four doses of *d*-amphetamine and PPA as well as saline were evaluated under the test conditions for each monkey. The percentage of the total number of trials that were completed on the drug lever is presented for each test session. In addition, the average time between the onset of a trial and a lever press (average latency) was calculated for each test session.

Food intake. The animals were two male and three female rhesus monkeys that weighed between 5.7 and 8.6 kg under free-feeding conditions and were maintained at these weights throughout the experiment. All had previous experience with other drugs under the present feeding conditions. They were housed individually in stainless-steel cages and were trained to enter and sit in a primate restraining chair for i.g. infusion of drugs. Food availability was limited to experimental sessions, but water was available continuously.

To measure food intake, portable pellet-dispensing monitors similar to those used for rats (Balagura and Coscina, 1969) were attached to the front of the home cages. These pellet dispensers were mounted on a piece of aluminum, 35.5 cm square with a square hole cut out near the bottom. A panel consisting of Plexiglas was hung from a hinge at the top of the opening. Pushing the panel open activated a microswitch

and releasing the panel reopened the microswitch, activated a pellet dispenser and delivered a food pellet. Using this system, a pellet was always visible in the food dish. Pellets (1 g, banana flavored, Formula G, 3.7 kcal/g, P. J. Noyes Inc., Lancaster, NH) were delivered by a Gerbrands model A pellet dispenser (Arlington, MA) mounted on the aluminum plate above the food dish. All pellet deliveries were monitored by standard electromechanical equipment located in an adjacent room.

Experimental sessions consisted of 2 hr daily access to banana pellets delivered by the dispenser and were conducted 7 days a week. After stabilization of intake, the effects of various doses of PPA (1, 3, 10 and 30 mg/kg), given 1 hr before the session, were determined in a random order. Doses could be given twice a week (*e.g.*, Tuesday and Friday) if food intake for the preceding two sessions was stable. Results are expressed as percentage of base-line food intake. Base-line intake was calculated separately for each monkey and was based on the intake for the 2 days before each dose. Results were averaged across monkeys and the linear portion of each dose-response function (three or four doses) was analyzed by least-squares linear regression to yield the dose necessary to reduce intake to 50% of base-line levels (ED_{50}) and the 95% confidence intervals.

Neurochemistry. Male Sprague-Dawley rats (Holtzman Co., Madison, WI) weighing between 390 and 590 g were housed individually in stainless-steel cages. Food and water were available continuously. The room was on a 12-hr light, 12-hr dark (6:00 A.M.–6:00 P.M.) cycle and was maintained at approximately 24°C.

After a 10-day period of adaptation to the housing conditions, PPA injections were begun. Twice a day (9:00 A.M. and 7:00 P.M.) each animal was injected s.c. with a 100 ($N = 5$) or 200 ($N = 16$) mg/kg injection of PPA, for 4 consecutive days. Control rats ($N = 10$) were injected with 0.9% saline. Fourteen days after the last injection, the rats were killed by decapitation and the brains were removed and dissected by the method of Heffner *et al.* (1980). Samples were taken of frontal cortex, hippocampus, striatum and hypothalamus. All samples were frozen immediately and stored in liquid nitrogen. Monoamine assays were done by high-performance liquid chromatography coupled with electrochemical detection as described by Kotake *et al.* (1985). Mean monoamine levels and S.E.s were calculated and results were calculated as the percentage of monoamine levels of the control group. Statistical analysis was done by using Student's *t* test after determining overall significance by an analysis of variance.

Drugs. Cocaine HCl and *d*-amphetamine sulfate were provided by the National Institute on Drug Abuse (Rockville, MD) for use in these experiments. PPA was purchased commercially (Sigma Chemical Co., St. Louis, MO). Each was dissolved in 0.9% saline and doses are expressed as the salt.

Results

All monkeys self-administered cocaine under base-line conditions (table 1). Average intake of cocaine (0.06 mg/kg/injection) ranged between 36 (2035) and 119 (3013) injections per session (2.2–7.4 mg/kg session). Although there was considerable variability between subjects in base-line drug intake, within-subject intake was comparatively stable over the course of the experiment. When saline was substituted, responding declined to less than 20 injections per session over a period of 5 to 12 sessions.

PPA failed to maintain self-administration rate above the range of saline rates at any dose in any monkey (table 1). For the group, the mean number of saline injections taken in the last three sessions ranged between 3 and 15 whereas the mean number of PPA injections across doses ranged between 3 and 13. In addition, the pattern of responding during a session was similar to that seen with saline, with the largest proportion of injections taken in the early segments of the session. When saline was available an average of 68% of the injections were taken in the first half of the session whereas the mean across doses of PPA ranged between 68 and 76% in the first half. However, it was clear that doses of PPA high enough to have CNS effects were tested. After the first session of a substitution period with a higher dose of PPA (3.0 or 10 mg/kg/injection) total drug intake was high (30–300 mg/kg) and animals generally refused a food biscuit offered after the session. Furthermore, fewer injections were taken during these sessions than in the first session of saline substitution, suggesting response suppression by a behaviorally active dose of PPA. During subsequent sessions of a substitution period, responding declined to low levels comparable to saline.

In the monkeys trained to discriminate *d*-amphetamine from saline, the percentage of trials that were completed on the drug-appropriate lever after various doses of *d*-amphetamine ranged from 0% at 0.03 mg/kg to over 90% at 0.3 mg/kg (fig. 1). When PPA was administered before test sessions, results differed between monkeys. Monkeys 7039 and 5127 completed 100% of the trials on the drug-appropriate lever at 30 and 100 mg/kg, respectively, whereas lower doses engendered only saline lever responses. PPA was 1/200 to 1/300 as potent as *d*-amphetamine in these monkeys. Monkey 7037 was tested twice and the results differed between tests. During the initial dose-response determination, 33% of the trials were completed on the drug-appropriate lever at the dose of 30 mg/kg but, at 100 mg/kg, only 3% of the trials were completed on the drug-appropriate lever. However, during the second determination, 100% of the trials were completed on the drug-appropriate lever when 100 mg/kg of PPA was given whereas at the lower doses only saline lever responses occurred. Monkey 8002 responded exclusively on the saline-appropriate lever across a dose range of 3 to 100 mg/kg. PPA did not affect average latency in any monkey at any dose tested.

d-Amphetamine (0.12–0.5 mg/kg i.g.) reduced food intake in a dose-related manner (fig. 2). The calculated ED_{50} was 0.22 mg/kg. Similarly, PPA reduced food intake over a dose range of 1 to 30 mg/kg. The dose calculated to reduce intake by 50%

TABLE 1

Self-administration results with PPA in four rhesus monkeys

Values for PPA are the mean (range) of the number of injections self-administered in the last three sessions of availability of each dose. For cocaine, values are the mean (range) of 12 sessions, the last three preceding substitution of each of 4 doses of PPA.

Monkey	Cocaine	Saline	PPA			
	mg/kg/injection		*mg/kg/injection*			
	0.06		0.3	1.0	3.0	10
2029	48 (40–66)	10 (5–20)	11 (5–14)	12 (8–18)	3 (0–8)	
2035	36 (31–47)	3 (2–6)	7 (5–8)	5 (1–8)	2 (1–3)	1 (0–1)
2039	68 (54–86)	15 (7–26)	12 (13–19)	3 (3–4)	5 (2–6)	6 (2–13)
3013	119 (105–152)	15 (15–16)	13 (9–17)	9 (3–17)	3 (2–6)	1 (0–2)

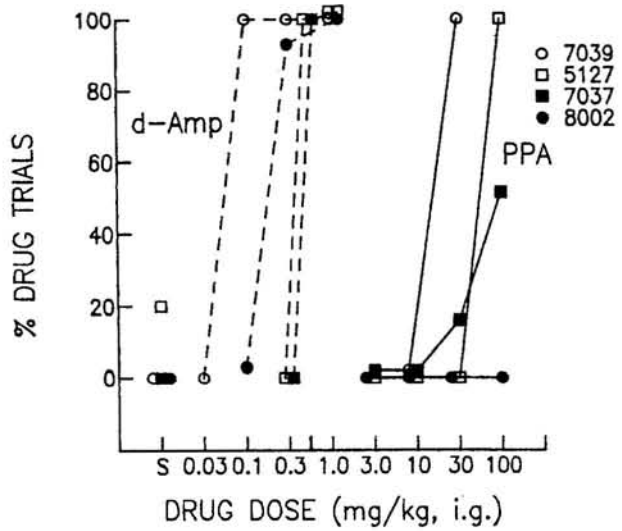

Fig. 1. Dose-response relationships for PPA (i.g.) in rhesus monkeys trained to discriminate *d*-amphetamine (d-Amp) (i.g.) from saline (S). Unit doses of PPA are on the abscissa. Percentage of trials of the total completed on the drug lever are on the ordinate. Each point represents the results of one or two determinations of the effects of each dose in individual animals.

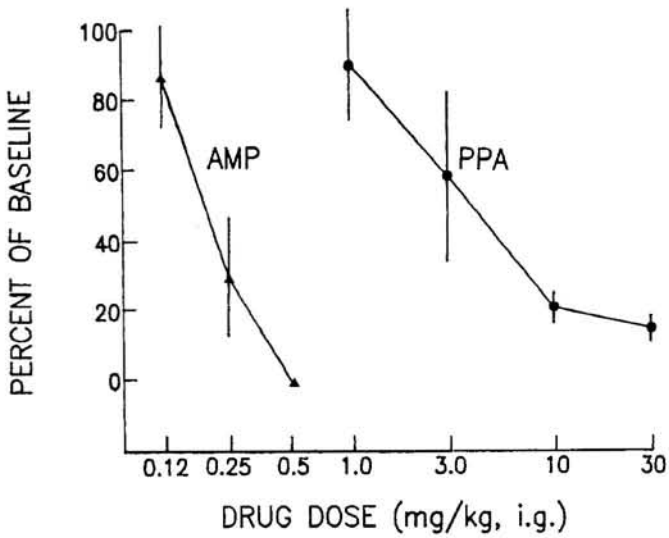

Fig. 2. Effects of PPA and *d*-amphetamine (AMP) (i.g.) on food intake in rhesus monkeys. Each point represents the mean intake of five monkeys and vertical lines are the S.E.s. Base-line values ranged between 115 and 200 g/2-hr session.

was 4.4 mg/kg, 20 times larger than a comparably effective dose of *d*-amphetamine in this paradigm. Therefore, the dose of PPA necessary to produce greater than 90% drug lever responses was 7 to 23 times greater than the ED_{50} for reducing food intake. For *d*-amphetamine, this ratio was approximately 2.

Monoamine levels in various brain regions of control rats are presented in table 2. PPA did not change levels of DA, NE or 5-HT in striatum, hippocampus or hypothalamus. In frontal cortex, DA was reduced to 71% of control levels 2 weeks after the last injection of 200 mg/kg of PPA ($N = 8$). In a replication of this experiment, this effect was again found but was somewhat smaller (to 83% of control levels; $N = 8$). Although the effect was small, it was statistically significant ($P < .05$) in both cases. Grossly observable behavioral effects included mild stereotyped behavior and a reduction in food intake. Both

TABLE 2

Levels of monoamines in various brain regions of saline-treated rats

Values are expressed as the mean (S.E.M.) nanograms of monoamine per milligram of tissue for 10 rats. n.m., not measured.

Region	DA	NE	5-HT
Striatum	8.27 (0.77)	n.m.	0.3 (0.03)
Frontal cortex	0.14 (0.006)	0.19 (0.01)	0.14 (0.01)
Hippocampus	n.m.	0.32 (0.02)	0.36 (0.01)
Hypothalamus	0.33 (0.03)	1.14 (0.09)	0.70 (0.01)

groups of PPA rats lost weight during the daily injection regimen but 2 weeks after the regimen body weights of the PPA and the control group were comparable. In pilot studies, 400 and 800 mg/kg of PPA usually were lethal making it impossible to evaluate the effects of higher doses in this paradigm.

Discussion

d-Amphetamine, the prototypical anorectic, has dependence potential and is neurotoxic upon repeated administration (Schuster and Johanson, 1985; Wagner *et al.*, 1980a). Clearly, an anorectic with little or no potential for abuse or the induction of toxicity would be preferred to *d*-amphetamine. PPA, based on the results of the present experiment, appears to fulfill some of these criteria. PPA given i.g. reduced food intake in rhesus monkeys effectively. Doses of PPA that were effective in reducing food intake were not self-administered by rhesus monkeys in a substitution procedure that reliably predicts dependence potential (Johanson and Balster, 1978). Similar anorectic efficacy and self-administration results have been reported previously with PPA using baboons as experimental subjects (Griffiths *et al.*, 1978). In this regard, PPA differs from several other compounds marketed as anorectics including *d*-amphetamine, diethylpropion, mazindol, phenmetrazine and benzphetamine all of which are self-administered under conditions similar to those used in the present experiment (Balster and Schuster, 1973; Johanson and Schuster, 1977; Griffiths *et al.*, 1979; Schuster and Johanson, 1985; Woolverton *et al.*, 1986). Regarding central mechanisms of action of PPA, these results suggest that PPA does not have a strong dopaminergic action inasmuch as this effect has been implicated in the reinforcing action of anorectics that are psychomotor stimulants (Woolverton *et al.*, 1984).

PPA also differs from *d*-amphetamine in terms of its discriminative stimulus properties. In rhesus monkeys trained to discriminate *d*-amphetamine from saline, PPA resulted in principally saline lever responding in two of four monkeys tested. Individual differences between animals were observed in this effect and may reflect differences between the two drugs and/or attention to different components of the *d*-amphetamine or PPA discriminative stimulus by different animals. Nevertheless, these mixed results are clearly different from those with most other marketed anorectics which engendered *d*-amphetamine-like responding in monkeys and pigeons (Schuster and Johanson, 1985). Moreover, even in those animals in which PPA was like *d*-amphetamine, the dose was at least 7-fold higher than the ED_{50} for reducing food intake compared to a 2-fold difference for *d*-amphetamine. To the extent that similar discriminative stimulus properties indicate similar subjective effects, these results suggest that therapeutically effective doses of PPA have few if any amphetamine-like subjective effects.

The development of neurotoxicity with repeated administration has been recognized as an important issue not only for anorectics but also for phenylethylamines in general. It has been demonstrated repeatedly that *d*-amphetamine, methamphetamine and fenfluramine can produce long-lasting depletions in central monoamines and evidence of neuronal degeneration when administered to rats repeatedly (Harvey, 1978; Schuster and Johanson, 1985; Wagner *et al.*, 1980a). For instance, when 50 mg/kg/day of methamphetamine was given to rats for 4 days, caudate DA was reduced to 60% of control levels (Wagner *et al.*, 1980b). Lower doses of methamphetamine had no significant effect. In the present experiment, 400 mg/kg/day of PPA produced a small depletion of DA in frontal cortex and no evidence of depletion of NE or 5-HT when administered under similar conditions. The ED_{50} for methamphetamine for reducing food intake in rats is 1.8 mg/kg (Cox and Maickel, 1972) whereas the ED_{50} for PPA is approximately 30 mg/kg (Hoak *et al.*, 1984). Thus, under these conditions the ratio of minimal neurotoxic dose to the anorectic ED_{50} for methamphetamine can be estimated to be approximately 28 and for PPA to be approximately 13. Clearly, the DA depletions with methamphetamine were more substantial than those with PPA making precise quantification of this ratio difficult. Nevertheless, in this rough comparison there is a larger margin between the neurotoxic and the anorectic dose for methamphetamine than for PPA. It should be noted that the short-term, high-dose injection regimen used here is probably unlike a therapeutic exposure to PPA. The possibility that a longer exposure to PPA may produce more neurotoxicity should be evaluated. In addition, route of administration may play an important role in these results. Tissue necrosis was noted at the site of injection of PPA suggestive of a local vasoconstriction that may have interfered with drug absorption. Nevertheless, our initial results suggest significant differences between PPA and other anorectic phenylethylamines in this neurotoxic effect.

PPA has been used as an anorectic for over 40 years (Silverman *et al.*, 1980) and has generally been found to be free of overt amphetamine-like behavioral effects. The recent increase in interest in PPA because of its use as an amphetamine "look-alike" (Mueller, 1983) led us to evaluate the compound in procedures designed specifically to detect amphetamine-like dependence potential and neurotoxicity. Our results generally confirm that, except for reduction in food intake, PPA is unlike amphetamine.

References

BALAGURA, S. AND COSCINA, D. V.: Influence of gastrointestinal loads on meal-eating pattern. J. Comp. Physiol. Psychol. **69:** 101–106, 1969.

BALSTER, R. L. AND SCHUSTER, C. R.: A comparison of *d*-amphetamine, *l*-amphetamine and methamphetamine self-administration in rhesus monkeys. Pharmacol. Biochem. Behav. **1:** 67–71, 1973.

CAIRNS, M. J., FOLDYS, J. E. AND REES, J. M. H.: The effects of phenylpropanolamine and other sympathomimetics on food consumption and motor activity in mice. J. Pharm. Pharmacol. **36:** 704–706, 1984.

COX, R. H. AND MAICKEL, R. P.: Comparison of anorexigenic and behavioral potency of phenylethylamines. J. Pharmacol. Exp. Ther. **181:** 1–9, 1972.

DAVIS, W. M. AND PINKERTON, J. T. III: Synergism by atropine of central stimulant properties of phenylpropanolamine. Toxicol. Appl. Pharmacol. **22:** 138–145, 1972.

DE LA GARZA, R. AND JOHANSON, C. E.: The discriminative stimulus properties of cocaine and *d*-amphetamine: The effects of three routes of administration. Pharmacol. Biochem. Behav. **24:** 765–768, 1986.

EPSTEIN, A. N.: Suppression of eating and drinking by amphetamine and other drugs in normal and hyperphagic rats. J. Comp. Physiol. Psychol. **52:** 37–45, 1959.

FAZEKAS, J. F., EHRMANTRAUT, W. R., CAMPBELL, K. D. AND NEGRON, M. C.: Comparative effectiveness of phenylpropanolamine and dextro amphetamine on weight reduction. J. Am. Med. Assoc. **170:** 1018–1021, 1959.

GRIFFITHS, R. R., BRADY, J. V. AND BRADFORD, L. D.: Predicting the abuse liability of drugs with animal drug self-administration procedures: Psychomotor stimulants and hallucinogens. *In* Advances in Behavioral Pharmacology, volume 2, ed. by T. Thompson and P. B. Dews, pp. 164–208, Academic Press, New York, 1979.

GRIFFITHS, R. R., BRADY, J. V. AND SNELL, J. D.: Relationship between anorectic and reinforcing properties of appetite suppressant drugs: Implications for assessment of abuse liability. Biol. Psychiatry **13:** 282–290, 1978.

HARVEY, J. A.: Neurotoxicity of halogenated amphetamines. Ann. N.Y. Acad. Sci. **35:** 289–304, 1978.

HEFFNER, T. G., HARTMAN, J. A. AND SEIDEN, L. S.: A rapid method for the regional dissection of the rat brain. Pharmacol. Biochem. Behav. **13:** 453–456, 1980.

HOAK, D. A., SCHLEMMER, R. F., KATZ, N. L. AND DAVIS, J. M.: Failure of caffeine to potentiate phenylpropanolamine-induced suppression of food intake in rats. Pharmacologist **26:** 223, 1984.

HOEBEL, B. G., COOPER, J., KAMIN, M. C. AND WILLARD, D.: Appetite suppression by phenylpropanolamine in humans. Obesity/Bariatric Med. **4:** 192–197, 1975a.

HOEBEL, B. G., KRAUSS, I. K., COOPER, J. AND WILLARD, D.: Body weight decreased in humans by phenylpropanolamine taken before meals. Obesity/Bariatric Med. **4:** 200–206, 1975b.

JAFFE, J.: Drug addiction and drug abuse. *In* The Pharmacological Basis of Therapeutics, 7th ed., ed. by A. G. Gilman, L. S. Goodman, T. W. Rall and F. Murad, pp. 532–581, MacMillan Publishing Co., New York, 1985.

JOHANSON, C. E. AND BALSTER, R. L.: A summary of the results of a drug self-administration study using substitution procedures in rhesus monkeys. Bull. Narc. **30:** 43–54, 1978.

JOHANSON, C. E. AND SCHUSTER, C. R.: A comparison of cocaine and diethylpropion under two different schedules of drug presentation. *In* Cocaine and Other Stimulants, ed. by E. H. Ellinwood and M. M. Kilbey, pp. 545–570, Plenum Press, New York, 1977.

KANE, F. J. AND GREEN, B. Q.: Psychotic episodes associated with the use of common proprietary decongestants. Am. J. Psychiatry **123:** 484–487, 1966.

KORNBLITH, C. L. AND HOEBEL, B. G.: A dose-response study of anorectic drug effects on food intake, self-stimulation and stimulation-escape. Pharmacol. Biochem. Behav. **5:** 215–218, 1976.

KOTAKE, C. HEFFNER, T. G., VOSMER, G. AND SEIDEN, L. S.: Determination of dopamine, norepinephrine, serotonin and their major metabolic products in rat brain by reverse-phase ion-pair high performance liquid chromatography with electrochemical detection. Pharmacol. Biochem. Behav. **22:** 85–89, 1985.

MUELLER, S. M.: Neurologic complications of phenylpropanolamine use. Neurology **33:** 650–652, 1983.

RICAURTE, G., BRYAN, G., STRAUSS, L., SEIDEN, L. S., AND SCHUSTER, C. R.: Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals: Neurochemical and anatomical evidence. Science (Wash. DC) **229:** 986–988, 1985.

SCHULTE, J. W., REIF, E. C., BACHER, J. A., LAWRENCE, W. S. AND TAINTER, M. L.: Further study of central stimulation from sympathomimetic amines. J. Pharmacol. Exp Ther. **71:** 62–74, 1941.

SCHUSTER, C. R. AND JOHANSON, C. E.: Efficacy, dependence potential and neurotoxicity of anorectic drugs. *In* Behavioral Pharmacology: The Current Status, ed. by L.S. Seiden and R.L. Balster, pp. 263–279, Alan R. Liss, Inc., New York, 1985.

SILVERMAN, H. I., KREGER, B. E., LEWIS, G. P., KARABELAS, A., PAONE, R. AND FOLEY, M.: Lack of side effects from orally administered phenylpropanolamine with caffeine: A controlled three-phase study. Curr. Ther. Res. **28:** 185–194, 1980.

TAINTER, M. L.: Actions of benzadrine and propadrine in the control of obesity. J. Nutr. **27:** 89–105, 1944.

WAGNER, G. C., RICAURTE, G. A., JOHANSON, C. E., SCHUSTER, C. R. AND SEIDEN, L. S.: Amphetamine induces depletion of dopamine and loss of dopamine uptake sites in caudate. Neurology **30:** 547–550, 1980a.

WAGNER, G. C., RICAURTE, G. A., SEIDEN, L. S., SCHUSTER, C. R., MILLER, R. J. AND WESTLEY, J.: Long-lasting depletions of striatal dopamine and loss of dopamine uptake sites following repeated administration of methamphetamine. Brain Res. **181:** 151–160, 1980b.

WARREN, M. R. AND WERNER, H. W.: The central stimulant action of some vasopressor amines. J. Pharmacol. Exp. Ther. **85:** 119–121, 1945.

WOOLVERTON, W. L., DE LA GARZA, R., JOHANSON, C. E. AND SCHUSTER, C. R.: Reinforcing and discriminative stimulus properties of anorectics in rhesus monkeys. *In* Problems of Drug Dependence, 1985, N.I.D.A. Research Monograph, ed. by L. S. Harris, in press, 1986.

WOOLVERTON, W. L., GOLDBERG, L. I. AND GINOS, J. Z.: Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. J. Pharmacol. Exp. Ther. **230:** 678–683, 1984.

WOOLVERTON, W. L. AND SCHUSTER, C. R.: Behavioral and pharmacological aspects of opioid dependence: Mixed agonist-antagonists. Pharmacol. Rev. **35:** 33–52, 1983.

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