Pharmacology Biochemistry & Behavior, Vol. 34, pp. 797–803. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Phenylpropanolamine and Amphetamine Disrupt Postprandial Satiety in Rats

MERYL ROSOFSKY AND NORI GEARY[1]

Department of Psychology, Box 28, Schermerhorn Hall
Columbia University, New York, NY 10027

Received 19 December 1988

ROSOFSKY, M. AND N. GEARY. *Phenylpropanolamine and amphetamine disrupt postprandial satiety in rats.* PHARMACOL BIOCHEM BEHAV **34**(4) 797–803, 1989.—Two tests of the behavioral specificity of the anorectic effects of amphetamine (AM) and phenylpropanolamine (PPA) were done. Intraperitoneal injections of each drug reduced the size of condensed milk test meals in 30-min pellet-deprived rats. The dose-response relations in semi-log coordinates were linear and parallel, but AM (ED_{50}, 2.0 ± 0.1 μmol/kg) was about ten times more potent than PPA (ED_{50}, 24.6 ± 0.1 μmol/kg). Periprandial behaviors were observed using a time-sampling technique. Both AM and PPA disrupted the normal behavioral sequence of postprandial satiety throughout their anorectic ranges, but they did so differently. AM increased postprandial exploratory behavior, decreased or eliminated resting, and, at larger doses, elicited stereotypy. In contrast, PPA inhibited both grooming and exploration, and increased resting. The drugs' effects on water intake were tested in 17-hr water-deprived rats. AM's adipsic effect (ED_{50}, 2.3 ± 0.1 μmol/kg) was similar to its anorectic effect. PPA also inhibited drinking, although slightly less potently (ED_{50}, 56.6 ± 0.1 μmol/kg) than it did feeding. Thus, under conditions maximizing the anorectic potencies of systemically administered AM and PPA in rats, both drugs inhibited feeding nonspecifically rather than by eliciting normal postprandial satiety.

Food intake Water intake Phenylethylamines Anorexia

ALTHOUGH the potent anorectic effects of amphetamine (AM) and phenylpropanolamine (PPA) have long been recognized, it remains unclear whether these drugs inhibit feeding by specifically affecting endogenous mechanisms of hunger or satiety. Both drugs, like other phenylethylamines, elicit a wide range of pharmacological effects, including cardiovascular, hyperthermic, rewarding, stimulant, and psychotropic effects [e.g., (3, 6, 16, 22, 29)], which might nonspecifically disrupt feeding. Such effects, however, have sometimes appeared pharmacologically or behaviorally dissociable from their anorectic effects (8, 16, 18, 25). To further investigate whether PPA and AM selectively affect hunger or satiety, we determined whether the drugs disrupted normal postprandial satiety in a behavioral assay for anorexia, and we compared their anorectic and adipsic effects.

The normal behavioral sequence of postprandial satiety is a useful indicator of behavioral specificity of anorexia (14, 15, 20, 27). However, few such microstructural analyses of AM (3, 4, 7) or PPA (30) have been done, especially for the range of small drug doses that have been suggested to elicit specific effects. We observed feeding and periprandial behavior in 30 min food-deprived rats that were offered condensed milk following injection with either AM or PPA. Drinking was tested in water-deprived rats that ingested comparable volumes of fluid. Wellman *et al.* (32) reported that large PPA doses elicit a graded adipsia, but did not directly compare feeding and drinking.

Both of our tests revealed nonspecific effects of modest drug doses. We conclude that systemic administration of neither AM nor PPA selectively elicits postprandial satiety in rats.

METHOD

Feeding

Twenty adult male Sprague-Dawley rats (Charles River Breeding Labs, Wilmington, MA) were individually housed in hanging wire cages and given pelleted chow (5012, Purina, St. Louis, MO) and tap water ad lib. Room temperature was 17–25°C. A 14:10 L:D cycle (lights on at 0600 hr) was automatically maintained. Near the middle of the bright phase, pellets were removed and rats were injected intraperitoneally with 1.0 ml/kg 0.15 M NaCl. Condensed milk (Pet Foods, St. Louis, MO) was presented 30 minutes later in calibrated (±1 ml) drinking tubes. Food intake was measured at 4-minute intervals for 40 minutes. Milk was removed and chow returned after 60 min.

Rats were adapted to this procedure for 5 days/week until, for at least 80% of the rats, the standard deviation of each animal's mean 40-minute milk intake was less than 30% of its running 5-day mean. Experiments were then conducted Tuesday–Friday; the adaptation procedure was repeated each Monday. The effects of PPA and AM were determined in separate experiments. PPA was tested first. Rats' body weight range was 395–486 g during

[1]Requests for reprints should be addressed to N. Geary.

the PPA study and 550–785 g during the AM study.

Drug tests were done with separate crossover designs in order of increasing doses, beginning with doses that were found in pilot experiments to be near threshold for significant inhibition of feeding. Doses were doubled in successive tests until anorexia was maximal. AM doses tested were 0.7 μmol/kg (0.25 mg/kg) to 21.3 μmol/kg (7.85 mg/kg); PPA doses, 2.7 μmol/kg (0.50 mg/kg) to 85.2 μmol/kg (16.00 mg/kg). Drug tests were alternated with saline tests to minimize the possibility of cumulative effects.

Inhibition of 40-min food intake after drug treatment was expressed as percent of the matched control intake. Statistical analysis was done with ANOVA for repeated measurements followed by bidirectional post hoc *t*-tests of individual differences. Data are reported as mean ± SE. Rats with missing data were dropped from the analysis.

Behavior Observations

Behaviors elicited by each drug in the food intake experiments were observed using a time sampling technique (14, 15, 20). An experimenter blind to the injection protocol observed each rat's behavior once each minute during a tone-signalled 0.6-sec observation period. Behaviors were classified using operational definitions. For example, grooming was defined as biting or licking the coat, paws, genitals, or tail or stroking the head, face or vibrissae with one or both paws. Resting was defined as a stationary position in which the abdomen is on the cage floor and no other behavior is displayed. Stereotypy was defined as an unusual fixed behavior pattern, such as head yawing or chewing motions. Unusually repetitive displays of normal behaviors were also regarded as stereotypic (9). These were differentiated from normal behaviors by a quantitative criterion: if sniffing (or nose twitching) occurred more than four times more frequently after drug administration than after saline, it was rated stereotypic behavior rather than part of the normal exploratory behavior that occurs during the postprandial satiety sequence.

Behavioral observations were grouped into categories of feeding, grooming, exploring (including sniffing, locomoting, rearing on hind legs, and licking cage), resting, stereotypic behaviors, and other behaviors (such as standing in a stationary position with abdomen off the cage floor, urinating, yawning, etc.; this category accounted for only a few percent of total observations). The frequency of observation of behaviors from each category was compiled, and changes in frequencies were analyzed with median and sign tests. Behavioral data are presented as medians ± interquartile ranges.

Water Intake

We tested the effects of AM and PPA on water intake using a separate group of sixteen rats. The design was similar to the feeding tests, except rats were water deprived for 17 hr before tests; water, not milk, was presented; and behavioral observations were not recorded. Pelleted food was available during the water deprivation period, but was removed during the drinking test. This drinking paradigm is comparable to the feeding paradigm in that the motor responses of ingestion are similar and the volume of water ingested in the initial bout of drinking following 17-hr water deprivation approximates the size of control milk meals. Tests of 6 doses of PPA (5.3–170.5 μmol/kg) were done first, then tests of 4 doses of AM (0.7–5.3 μmol/kg). Rats weighed 510–629 g during the PPA tests and 556–729 g during AM tests.

Replications

We performed two tests to check whether tolerance or sensitization of the anorectic effects of PPA or AM had developed during the experiment. First, we repeated the test of 21.3 μmol/kg PPA immediately following the last AM feeding test (i.e., 5 weeks after the original test), then again one week later, and for a third time 15 weeks after the original test. No other drugs were administered after week 5. Second, we conducted a replication testing two doses each of PPA (10.7 and 16.0 μmol/kg) and AM (1.0 and 1.15 μmol/kg) using a third group of 17 rats, body weight 456–620 g, adapted as described above. These four drug tests and two saline control tests were done in orders that were separately randomized for each rat. The inhibitory effects obtained were compared to predictions based on the dose-response relations generated in the first experiment.

TABLE 1

INHIBITORY EFFECTS OF AMPHETAMINE (AM) AND PHENYLPROPANOLAMINE (PPA) ON FOOD AND WATER INTAKES

	AM		PPA	
Dose (μmol/kg)	Food (12)	Water (13)	Food (15)	Water (6)
0.7	13.8 ± 7.6	12.2 ± 5.4		
1.3	36.0 ± 10.9	12.3 ± 6.0		
2.7	48.3 ± 10.9	53.2 ± 5.0	6.0 ± 6.6	
5.3	92.7 ± 4.3	97.1 ± 1.2	8.3 ± 8.6	6.0 ± 8.6
10.7	99.5 ± 0.5		18.8 ± 6.7	14.8 ± 11.4
21.3	93.9 ± 2.3		36.2 ± 6.5	18.2 ± 7.3
42.6			66.5 ± 6.5	37.8 ± 5.3
85.2			94.1 ± 1.5	51.6 ± 11.1
170.5				86.6 ± 4.8

Data are mean (± SE) percent inhibition of 40-min test intakes compared to paired control. Number of rats is given in parentheses. One μmol AM = 0.37 mg; 1 μmol PPA = 0.19 mg.

Control intakes in individual crossover tests were stable in each condition. The ranges of mean control intakes were: AM/feeding, 15.6 ± 1.0–19.2 ± 1.9 ml, $F(5,55) = 1.56$, n.s.; AM/drinking, 17.3 ± 1.1–19.2 ± 1.3 ml, $F(3,36) = 0.98$, n.s.; PPA/feeding, 15.2 ± 1.0–18.8 ± 1.3 ml, $F(5,70) = 2.11$, n.s.; PPA/drinking, 16.7 ± 1.4–19.7 ± 1.6 ml, $F(5,25) = 1.62$, n.s.

Drug effects on percent inhibition of control intake were significant in each condition: AM/feeding, $F(5,55) = 26.87$, $p<0.01$; AM/drinking, $F(3,36) = 113.94$, $p<0.01$; PPA/feeding, $F(5,70) = 30.82$, $p<0.01$; PPA/drinking, $F(5,25) = 14.01$, $p<0.01$.

RESULTS

Food Intake and Water Intake

AM and PPA each elicited graded inhibitions of feeding and drinking, with ingestive behavior almost completely eliminated by large doses of either drug. On a molar basis, however, PPA was much less potent than AM (Table 1).

Except at their extremes, the dose-response relations for mean percent inhibition of food and water ingestion appeared linear in semilogarithmic coordinates. Therefore, we computed linear regressions of group mean inhibition on dose for the relations' middle regions. Doses used for this analysis were those that elicited an inhibition at least 10% greater than the next smaller dose or 10% less than the next larger dose. The regressions are: $\%I = m \log D + c$, where %I is the mean percent inhibition of 40-min intake and D is drug dose in μmol/kg. Figure 1 shows these functions and the data upon which they were based. The

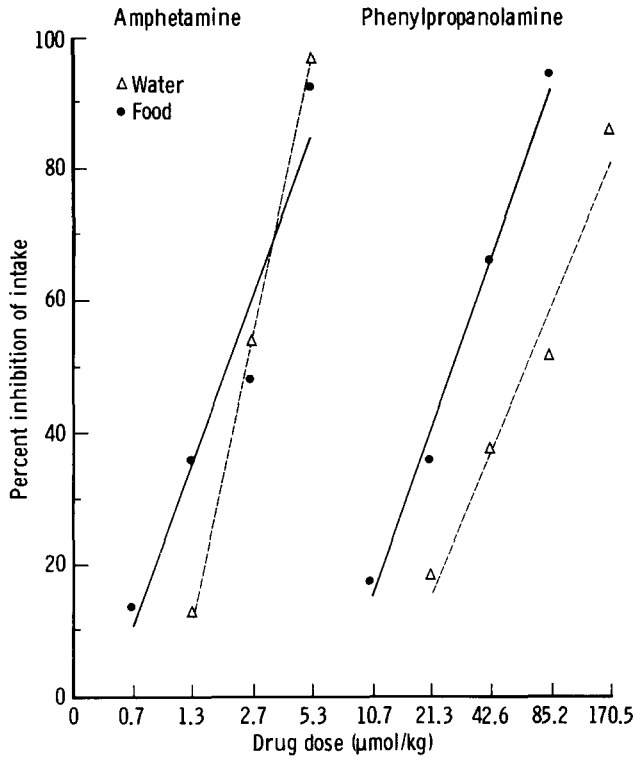

FIG. 1. Mean percent inhibition of 40-min food and water intakes after intraperitoneal injection of AM or PPA, and linear regressions of mean percent inhibition on log drug dose. Milk intake was tested in 1-hr pellet-deprived rats, and water intake in 17-hr water-deprived rats. Only data included in the regression analyses are shown (see text for inclusion criteria).

constants m and c and the goodness of fit coefficient r for the four dose-response relations were, respectively: AM/feeding, 83.7, 23.8, r = .94; AM/drinking, 142.5, −9.4, r = 1.00; PPA/feeding, 87.1, −75.9, r = .99; PPA/drinking, 73.5, −82.9, r = .96.

To permit statistical comparisons of these parameters, we also computed the linear regressions of percent inhibition on drug dose for each animal individually. The slopes of the AM/feeding dose-relation (80 ± 10 %I/log D), the PPA/feeding relation (85 ± 11), and the PPA/drinking relation (77 ± 18) were all similar to one another, but the slope of the AM/drinking relation (144 ± 11) was larger than each of them, $p<0.001$ after ANOVA interaction effect, $F(1,42)=7.53$, $p<0.01$. The ED_{50} of PPA for inhibition of feeding (24.6 ± 0.1 μmol/kg) was about 10 times larger than AM's (2.0 ± 0.1), $p<0.001$ after drug effect, $F(1,42)=441.1$, $p<0.001$. PPA's ED_{50} for inhibition of drinking (56.6 ± 0.1) was about 20 times larger than AM's (2.3 ± 0.1), $p<0.001$. PPA's ED_{50} for inhibition of drinking was also significantly larger than its ED_{50} for feeding, $p<0.001$ after test effect, $F(1,42)=12.3$, $p<0.001$. The ED_{50} of AM for inhibition of drinking, however, was not significantly different from its ED_{50} for feeding.

Behavioral Observations

Following saline injections, rats ate almost continuously for about 10 min, then paused to groom and explore before finally resting. This behavioral sequence characterizes diurnal postprandial satiety in the rat (27). Both AM and PPA disrupted the satiety sequence, but they did so in different ways.

Figure 2 shows the behavioral data for those AM doses included in the analysis of dose-response relations. AM decreased not only feeding, but also resting, which was virtually eliminated by the larger AM doses. The two smaller AM doses also increased exploratory behavior. This pattern contrasts with the increases in resting and stable amount of exploration associated with treatments thought to inhibit feeding by eliciting satiety (14, 15, 20, 27).

At doses of 2.7 μmol/kg or more AM, enhanced exploratory behavior was replaced by stereotypy, especially continuous stereotypic sniffing (Fig. 3, upper panel). Interestingly, increasingly complex stereotypical patterns appeared after larger AM doses. Several rats displayed continuous sniffing in a stationary position after 2.7 and 5.3 μmol/kg AM, and sniffing while moving the head in a circular pattern or while rearing uninterruptedly after 10.7 or 21.3 μmol/kg AM.

The larger AM doses also appeared to produce carry-over effects. For example, there was a reduction in resting behavior in the saline test paired with the 5.3 μmol/kg AM dose compared to the three other saline tests (Fig. 2). Retrospective analysis showed that this decrease was accounted for solely by the half of the rats that received saline *after* AM in this crossover test. Those rats rested less during the saline test following the test of 5.3 μmol/kg AM (10 ± 5.2 occurrences) than they did on their previous saline test [19 ± 3.9, Wilcoxon test, $t(7)=3$, $p<0.05$], whereas the rats tested with saline *prior* to 5.3 μmol/kg AM did not rest less than during their previous saline test [19 ± 3.9, Wilcoxon text, $t(7)=3$, $p<0.05$], whereas the rats tested with saline *prior* to 5.3 μmol/kg AM did not rest less than during their previous saline test [21 ± 5.9 vs. 25.7 ± 3.3, $t(5)=12$, n.s.]. The difference between the frequencies of resting in these subgroups during the saline test paired with 5.3 μmol/kg AM was also significant, Mann-Whitney test, $t(5,7)=43.5$, $p<0.05$. Doses of 10.7 and 21.3 μmol/kg AM elicited similar carry-over effects. Interestingly, this carry-over reduction of resting behavior did not affect food intake. The meal size of rats administered saline after 5.3 μmol/kg AM was 18.4 ± 1.6 ml vs. 15.4 ± 1.7 ml in rats tested with saline before AM, $t(10)=1.29$, n.s.

A different behavioral profile accompanied PPA anorexia. The incidence of grooming was markedly reduced by all doses of PPA that inhibited feeding (Fig. 2). All but the smallest PPA dose also decreased exploring and increased resting, that is, had the opposite effect as AM. The larger PPA doses also tended to elicit anomalous behaviors, such as lying stationary with the limbs extended, and stereotypy (Fig. 3, lower panel). Stereotypy occurred in fewer rats after PPA than after AM, and stereotypical behaviors after PPA occurred less frequently and were of a different topography. The predominant stereotypical behaviors elicited by PPA were repetitive chewing motions and continuous nose twitches.

Replication

The inhibition of food intake produced by 21.3 μmol/kg PPA did not vary significantly during tests done over a 15-week period, whether other drug tests intervened (weeks 1–5) or not (weeks 5–15) (Table 2). Further, replicated tests of two moderate doses each of PPA and AM in naive rats also produced inhibitions in good agreement with the dose-response relations determined in the first experiments (Table 3). Thus, probably neither tolerance nor sensitization to PPA's anorectic effect developed during the course of the original study. Tolerance to the anorectic effect of repeated AM injections occurs frequently (10, 16, 26), although Wellman

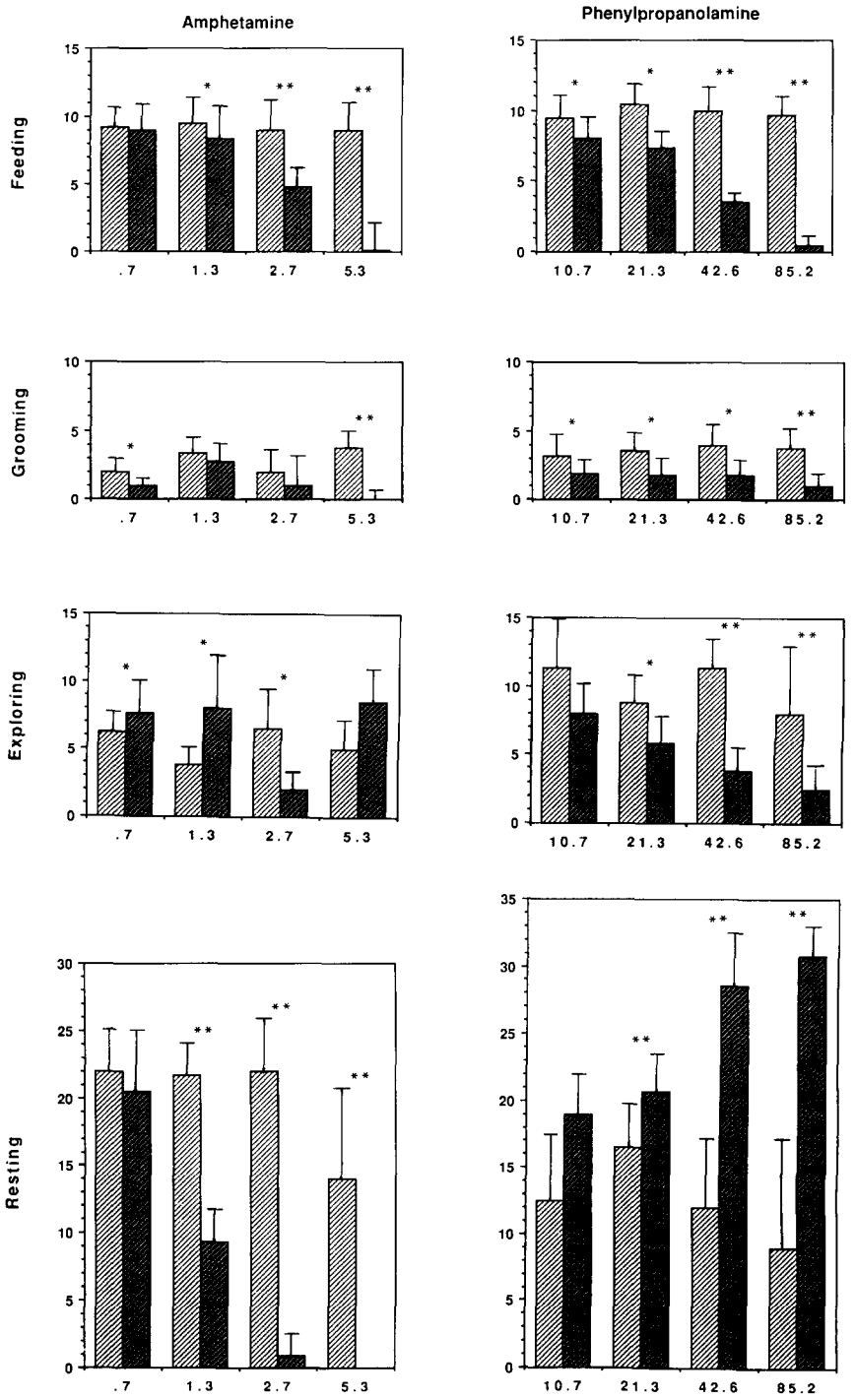

FIG. 2. Frequencies of observation of feeding, grooming, exploratory behavior, and resting after intraperitoneal injection of AM (left panels) or PPA (right panels) during 40 min of observation, 1 observation per min; median ± semi-interquartile range. Lighter bars show frequencies after saline injections; darker bars, after paired drug tests. Drug doses are μmol/kg. *Different than saline, $p<0.05$, sign test after overall median test showed significant drug effects; **$p<0.01$.

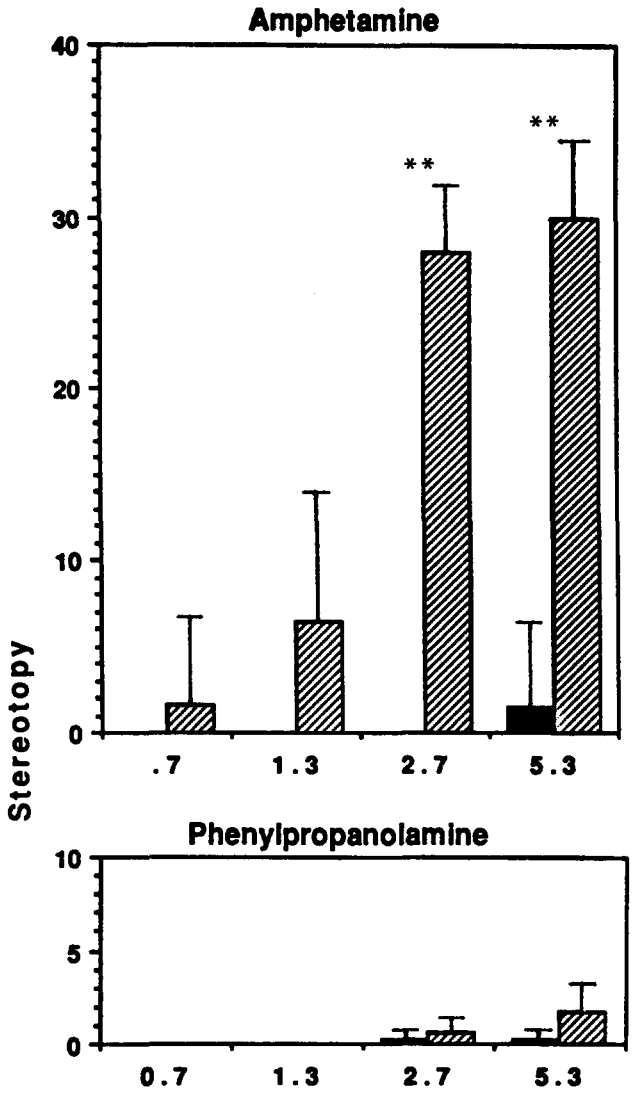

FIG. 3. Frequencies of stereotypy after intraperitoneal injections of AM (upper panel) or PPA (lower panel) during 40 min of observation, 1 observation per min; median ± semi-interquartile range. Lighter bars show frequencies after saline injections; darker bars, after paired drug tests. Drug doses are μmol/kg. **Different than saline, $p<0.05$, sign test after significant overall median test AM effect, $\chi^2(4)=41.89$, $p<0.01$; PPA effect was not significant.

and Sellars (34) failed to see tolerance when 20 mg/kg PPA was injected twice daily for 12 days.

DISCUSSION

A drug inhibits feeding specifically if it excites endogenous mechanisms of postprandial satiety (or inhibits endogenous mechanisms of hunger) without recruiting anomalous behaviors that might competitively antagonize ingestion. To determine whether systemic administration of AM or PPA specifically inhibits feeding in rats, we tested two predictions that follow from this definition. First, a drug eliciting a specific satiety effect should not disrupt the normal behavioral pattern that characterizes postprandial satiety. We monitored periprandial behaviors closely to test this prediction. Second, a drug with a specific satiety effect should not inhibit behaviors other than feeding. Therefore, we tested water drinking, a behavior that required a similar response topography and occurred in similar amounts.

TABLE 2

STABILITY OF INHIBITORY EFFECT ON FEEDING OF 42.6 μmol/kg PPA

	Week of Test			
	1	5	6	15
Percent Inhibition	40.6 ±5.8	35.5 ±6.6	32.3 ±8.7	33.8 ±5.2

Data are mean ± SE for 14 rats completing this test. Tests of AM were done in weeks 2–4; no other drug tests were done after week 5.
Inhibitions did not vary, $F(3,33)=0.24$, n.s.

The results were clear. Both AM and PPA disrupted the behavioral sequence of satiety throughout the range of doses that inhibited feeding. PPA decreased grooming and exploring, increased resting, and, at the largest doses, sometimes elicited anomalous or stereotypical behaviors. AM increased exploring at small doses, inhibited resting at all doses, and inhibited exploring and elicited stereotypy at larger doses. The behavioral satiety sequence is an unambiguous marker of biological meals under similar test conditions (15,27). If, as here, it is absent or disrupted, it is unlikely that normal satiety has occurred. Drinking was also inhibited by all but the smallest doses of each drug. Thus, AM and PPA either did not excite endogenous mechanisms of satiety and inhibited feeding only by stimulating competing behaviors, or AM and PPA simultaneously excited both satiety and other behaviors. In the absence of any other reason to believe that these drugs inhibit feeding by stimulating normal satiety mechanisms, we conclude that they do not.

Wolgin and his colleagues (26,35) have attempted to determine whether interference from competing behaviors causes AM anorexia. When sweetened milk was delivered through intraoral cannulas to avoid nonspecific effects on preconsummatory appetitive behaviors, 0.7–2.7 μmol/kg AM did not reduce intake at all, and the effect of 5.3–10.7 μmol/kg AM was greatly attenuated. Thus, nonspecific behavioral effects of the type we report here may indeed be the cause of AM anorexia.

Our conclusion that AM and PPA inhibit feeding nonspecifically contrasts with suggestions that there is a range of doses in which both drugs elicit specific satiety effects (3, 6, 12, 16).

TABLE 3

REPLICABILITY OF THE INHIBITORY EFFECTS ON FEEDING OF AM AND PPA

	Dose (μmol/kg)	Observed Inhibition	Predicted Inhibition	*t*-Value
AM	1.02	35.3 ± 5.2	24.5	2.08, n.s.
	1.15	31.9 ± 6.4	28.9	0.47, n.s.
PPA	10.7	12.5 ± 4.1	12.5	0.27, n.s.
	16.0	27.6 ± 5.1	28.9	0.25, n.s.

Data are mean (± SE) percent inhibitions of 40-min test intakes compared to paired control. Predicted values are derived from dose-response relations of Fig. 1. Observed and predicted values were compared with *t*-tests, 16 *df*.

Procedural differences, in particular our use of minimally deprived rats and our attention to the microstructure of meals, very probably account for these different findings. Fine-grained behavioral analyses remain relatively rare in the study of feeding, but have already proven fruitful. For example, both PPA and AM appear to increase the latency to eat and to alter the intrameal eating rate (4,30). In contrast, such agents as cholecystokinin, glucagon, and bombesin produce substantial inhibitions of feeding in the absence of such behavioral signs of nonspecificity (14, 15, 20, 27). These data demonstrate the usefulness of detailed behavioral analyses in differentiating normal satiety mechanisms from nonspecific anorexia.

We wished to test fairly small drug doses in order to increase the likelihood of eliciting specific satiety effects. Therefore, we attempted to maximize the drugs' anorectic potencies by depriving rats of their maintenance diet for only 30 min before offering them unsweetened condensed milk. This strategy appeared successful. The observed ED_{50} of AM was 2.0 μmol/kg, or 0.74 mg/kg, in comparison to typical ED_{50} values of about 1–2 mg/kg in overnight food-deprived rats offered pellets or palatable food (3, 6, 8, 13, 33). [The AM ED_{50} also appeared similar to ours in nondeprived rats tested at the onset of the dark phase (28), but was increased to 1.6 mg/kg in rats food deprived only 4 hr before testing in the middle of the dark phase (11).] The ED_{50} of PPA here, 24.6 μmol/kg or 4.62 mg/kg, was also modest in comparison to the values of about 10–20 mg/kg found after deprivation (11, 19, 24, 31). Thus, the nonspecific effects of AM and PPA that we observed occurred in a situation which, in comparison to previous research, should have maximized any specific satiety effects. Interestingly, though, the relative difference of roughly one log unit between AM's and PPA's potency appears similar in both the short- and the long-deprivation paradigms. The same difference also occurred in a drug discrimination test of the similarity of the stimulus properties of intraperitoneal AM and PPA (21). A simple comparison of AM's and PPA's anorectic potencies is not always appropriate, however, because the two drugs do not always produce parallel dose response relations (11). Further, the difference in anorectic potency of AM and PPA does not appear to result from a similar difference in affinity for the hypothalamic AM binding site (2,25).

The drinking tests revealed additional differences between the behavioral actions of PPA and AM. In contrast to AM, PPA inhibited food intake slightly more potently than water intake at every dose tested. This is consistent with the possibility that PPA affects neural networks mediating feeding more potently than it does those mediating drinking and, therefore, that PPA indeed has a degree of specificity for anorexia relative to adipsia. Alternatively, PPA may have only a single neural effect, and the behavioral differences may be due simply to a greater sensitivity of our feeding test than our drinking test. That is, perhaps PPA does inhibit feeding and drinking nonspecifically, but this effect was less evident in the water intake test merely because the rats were thirstier. PPA, however, has also inhibited food intake more potently than water intake under conditions in which hunger and thirst were probably more similar in intensity: Twice daily injection of 105 μmol/kg PPA decreased 24-hr food intake, but not 24-hr water intake (34), and 79–158 μmol/kg PPA inhibited feeding, but not drinking, elicited by electric stimulation of the lateral hypothalamus (17). Nevertheless, in the present experiment, only the smallest AM dose and the two smallest PPA doses appeared to inhibit feeding without affecting drinking. Thus, our data support at best the contention that AM and PPA possess only modest, relative behavioral specificities.

The various qualitative differences in the actions of PPA and AM here presumably reflect the fact that phenylethylamines differentially affect multiple neuroendocrine mechanisms (2, 8, 16, 25, 29). For example, at doses equipotent for anorexia, AM increased activity and decreased resting, whereas PPA decreased activity and increased resting. Similar distinctions between AM's and PPA's effects on open-field motor activity have been reported in both mice (5) and rats (11). AM and PPA also elicited different patterns of stereotypical behavior in our tests. Interestingly, although AM elicited stereotypy much more frequently, PPA more often elicited oral stereotypies, which are usually considered the more intense form (9). Additionally, PPA, but not AM, inhibited feeding more than drinking at all doses. Further differences in the drugs' actions have also been reported (16, 17, 24, 36). What remains unclear is whether phenylethylamine anorexia ever occurs independently of other, nonspecific effects. Are there, for example, brain loci where local phenylethylamine application selectively elicits satiety? Direct intracerebral phenylethylamine administration has been shown to inhibit feeding (1, 16, 22), but analysis of the behavioral specificity of these effects has just begun (23).

ACKNOWLEDGEMENTS

This research was supported by N.I.H. Research Grant DK 32448 to N. Geary. We thank Jennifer Granger, Veronica Hinton and Steve Trevor for help with the experiments, and Anthony Skorupski, Jennifer Fudge, Unkyung Noh and Deborah Rosenzweig for help with the data analysis. A preliminary report of these data was given at the 57th Annual Meeting of Eastern Psychological Association, Proc. EPA 57:57; 1986.

REFERENCES

1. Angel, I.; Stivers, J. A.; Paul, S. M.; Crawley, J. N. Site of action of anorectic drugs: Glucoprivic- versus food deprivation-induced feeding. Pharmacol. Biochem. Behav. 27:291–297; 1987.
2. Blosser, J. C.; Barrantes, M.; Parker, R. B. Correlation between anorectic potency and affinity for hypothalamic (+)-amphetamine binding sites of phenylethylamines. Eur. J. Pharmacol. 134:97–103; 1987.
3. Blundell, J. E. Psychopharmacology of centrally acting anorectic agents. In: Sandler, M.; Silverstone, T., eds. Psychopharmacology and food. Oxford: Oxford University Press; 1985:71–109.
4. Blundell, J. A.; Latham, C. J. Characterisation of adjustments to the structure of feeding behaviour following pharmacological treatment: Effects of amphetamine and fenfluramine and the antagonism produced by pimozide and methergoline. Pharmacol. Biochem. Behav. 12:717–722; 1980.
5. Cairns, M. J.; Foldys, J. E.; 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.
6. Carruba, M. O.; Mantegazza, P. Drugs with effects on food intake and energy expenditure. In: Cioffi, L. A., *et al.* The body weight regulatory system: Normal and disturbed mechanisms. New York: Raven Press; 1981:279–287.
7. Cole, S. O. Interaction of arena size with different measures of amphetamine anorexia. Pharmacol. Biochem. Behav. 7:181–184; 1977.
8. Cox, R. H.; Maickel, R. P. Comparison of anorexigenic and behavioral potency of phenylethylamines. J. Pharmacol. Exp. Ther. 81:1–9; 1972.
9. Creese, I.; Iversen, S. D. The role of forebrain dopamine systems in amphetamine induced stereotyped behavior in the rat. Psychopharmacologia 39:345–357; 1974.
10. Demellweek, C.; Goudie, A. J. Behavioural tolerance to amphetamine and other psychostimulants: The case for considering behavioural mechanisms. Psychopharmacology (Berlin) 80:287–307; 1983.
11. Eisenberg, M. S.; Maher, T. J.; Silverman, H. I. A comparison of the

effects of phenylpropanolamine, d-amphetamine and d-norpseudoephedrine on open-field locomotion and food intake in the rat. Appetite 9:31–37; 1987.
12. 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.
13. Foltin, R. W.; Woolverton, W. L.; Schuster, C. R. The effect of d-amphetamine and haloperidol alone and in combination on milk drinking in rats. Psychopharmacology (Berlin) 80:342–344; 1983.
14. Geary, N.; Smith, G. P. Pancreatic glucagon and postprandial satiety in the rat. Physiol. Behav. 28:313–322; 1982.
15. Hinton, V.; Esguerra, M.; Farhoody, N.; Granger, J.; Geary, N. Epinephrine inhibits feeding nonspecifically in the rat. Physiol. Behav. 40:109–115; 1987.
16. Hoebel, B. G. The psychopharmacology of feeding. In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., eds. Handbook of psychopharmacology, vol. 8, Drugs, neurotransmitters, and behavior. New York: Plenum Press; 1977:55–129.
17. Hoebel, B. G.; Hernandez, L.; Thompson, R. D. Phenylpropanolamine inhibits feeding, but not drinking induced by hypothalamic stimulation. J. Comp. Physiol. Psychol. 89:1046–1052; 1975.
18. Joyce, E. M.; Iversen, S. D. Dissociable effects of 6-OHDA-induced lesions of neostriatum on anorexia, locomotor activity and stereotypy. Psychopharmacology (Berlin) 83:363–366; 1984.
19. Kornblith, C. L.; 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.
20. Kulklowsky, P.; Gibbs, J.; Smith, G. P. Behavioral effects of bombesin administration in rats. Physiol. Behav. 28:505–512; 1982.
21. Lee, F.; Stafford, I.; Hoebel, B. G. Similarities between the stimulus properties of phenylpropanolamine and amphetamine. Psychopharmacology (Berlin) 97:410–412; 1989.
22. Leibowitz, S. F. Identification of catecholamine receptor mechanisms in the perifornical lateral hypothalamus and their role in mediating amphetamine and L-DOPA anorexia. In: Garattini, S.; Samanin, R., eds. Central mechanisms of anorectic drugs. New York: Raven Press; 1978:39–81.
23. Leibowitz, S. F.; Shor-Posner, G.; Maclow, C.; Grinker, J. A. Amphetamine: Effects on meal patterns and macronutrient selection. Brain Res. Bull. 17:681–689; 1986.
24. Moya-Huff, F. A.; Maher, T. J. Phenylpropanolamine decreases food intake in rats made hyperphagic by various stimuli. Pharmacol. Biochem. Behav. 28:71–74; 1987.
25. Paul, S. M.; Hulihan-Giblin, B.; Skolnick, P. (+)-Amphetamine binding to rat hypothalamus: relation to anorexic potency of phenylethylamines. Science 218:487–490; 1982.
26. Salisbury, J. J.; Wolgin, D. L. Role of anorexia and behavioral activation in amphetamine-induced suppression of feeding: implications for understanding tolerance. Behav. Neurosci. 99:1153–1161; 1985.
27. Smith, G. P.; Gibbs, J. Postprandial satiety. In: Sprague, J.; Epstein, A., eds. Progress in psychobiology and physiological psychology, vol. 8. New York: Academic; 1979:179–242.
28. Tordoff, M. G.; Hopfenbeck, J.; Butcher, L. L.; Novin, D. A peripheral locus for amphetamine anorexia. Nature 297:148–150; 1982.
29. Weiner, N. Norepinephrine, epinephrine, and the sympathomimetic amines. In: Goodman Gilman, A.; Goodman, L. S.; Rall, T. W.; Murad, F., eds. Goodman and Gilman's the pharmacological basis of therapeutics, 7th ed. New York: Macmillan Publishing Company; 1985:145–180.
30. Wellman, P. J.; Cockroft, R. Effects of amphetamine and phenylpropanolamine on latency to feed and cumulative liquid diet intake in rats. Pharmacol. Biochem. Behav. 32:147–150; 1989.
31. Wellman, P. J.; Levy, A. Inhibition of feeding and hoarding behaviors by phenylpropanolamine in the adult rat. Pharmacol. Biochem. Behav. 29:79–81; 1988.
32. Wellman, P. J.; Malpas, P. B.; Wikler, K. C. Conditioned taste aversion and unconditioned suppression of water intake induced by phenylpropanolamine in rats. Physiol. Psychol. 9:203–207; 1981.
33. Wellman, P. J.; Pittenger, D. J.; Wikler, K. C. Diet palatability and amphetamine-induced anorexia. Physiol. Psychol. 10:117–121; 1982.
34. Wellman, P. J.; Sellers, T. L. Weight loss induced by chronic phenylpropanolamine: Anorexia and brown adipose tissue thermogenesis. Pharmacol. Biochem. Behav. 24:605–611; 1986.
35. Wolgin, D. L.; Oslan, I. A.; Thompson, G. B. Effects of "anorexia" on appetitive and consummatory behavior. Behav. Neurosci. 102: 312–318; 1988.
36. Woolverton, W. L.; Johanson, C. E.; de la Garza, R.; Ellis, S.; Seiden, L. S.; Schuster, C. R. Behavioral and neurochemical evaluation of phenylpropanolamine. J. Pharmacol. Exp. Ther. 237:926–930; 1986.