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Assessment of the Effects of Phenylpropanolamine on Appetite and Food Intake

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CAFFRY, E. W., H. R. KISSILEFF AND J. C. THORNTON. *Assessment of the effects of phenylpropanolamine on appetite and food intake.* PHARMACOL BIOCHEM BEHAV 26(2) 321–325, 1987.—Single 37.5 mg doses of phenylpropanolamine (PPA) were given on each of two separate, nonconsecutive days to each of twelve nonobese women. PPA's effects on reported appetite and food intake were compared to those of a placebo also given on two nonconsecutive days. To control for possible effects on appetitive behavior of knowledge about the drug's putative role as an appetite suppressant, the subjects were told that PPA was a nasal decongestant which was expected to affect their sensitivity to flavors. Hunger rating before eating was significantly lower on trials after PPA than on trials after placebo (carry-over effect), but the direct effect of PPA on hunger was not significant. Although food intake was 26 g less under the PPA condition (407 g) than under placebo (433 g), this difference was not significant. However, because of insufficient power, the null hypothesis could not be accepted. The true effect of PPA on intake remains inconclusive. Either more subjects must be tested at this dose or the effect must be made larger by changing the dose, in order to obtain conclusive results.

Eating Women Obesity

PHENYLPROPANOLAMINE (PPA) is a phenethylamine drug sold over the counter for appetite suppression and nasal decongestion. It has noradrenergic and adrenergic effects on the central nervous system, and it is thought to depress appetite by its action on either of these systems [4].

Although there is extensive literature on the effects of PPA in the treatment of obesity, we are aware of only one published study on PPA's effect on measured food intake in humans [5]. In that study, PPA reduced food intake in an informed group interested in losing weight, but not in a noninformed student group. In our own earlier studies [10], a single 25 mg dose of PPA also failed to reduce food intake significantly in normal weight subjects. Hoebel *et al.* [5] suggested that, in their study, subject awareness of the purpose of the drug and the study could have led to discrepant results, since the subjects in whom the effect was not obtained were given different instructions from those in whom a significant effect was obtained. Other possible reasons for the failure are that the drug level was not sufficiently high, or that repeated administration of the drug is required to obtain an effect on appetite. Even in Hoebel *et al.*'s "successful" study [5], examination of the data reveals only a weak effect. A group of 32 subjects was tested under both placebo and drug conditions in a random order. The mean difference between conditions was only 38 g of a liquid diet, declining from 65 g on the first pair to 9 g on the fifth pair of trials.

There were two reasons for reevaluating the appetite suppressing effect of PPA. First, nonoptimal blood levels of PPA could have resulted in small effects in some groups [5] and none in others [5,10]. These results are not necessarily inconsistent with the occurrence of weight loss attributable to food intake reduction during prolonged administration of PPA [6]. The purported decrease in intake could have been the result of a higher blood level of PPA, since the drug was taken three times a day. As shown by Saltzman *et al.* [16], one dose superimposed on another led to much higher levels after the second or third dose. The second possible reason for Hoebel *et al.*'s failure to obtain large effects on intake is that the test meal used in their study [5] consisted of liquid Metrecal, a formula diet, which may have been marginally palatable. The low palatability of the diet could have depressed intakes under the placebo condition to such a low level that further decreases under the PPA condition would have been difficult to induce.

The present study assessed the effect of single doses of 37.5 mg of PPA in capsular form on the intake of test meals and reported appetite in nonobese women. These subjects were not informed about the purported appetite reducing effect of the drug. In the present study, there were three major differences from that of Hoebel *et al.* [5]: (1) We used a higher dose of PPA (i.e., 37.5 mg compared to 25 mg). (2) We lengthened the interval from administration of the drug to consumption of the test meal to 3 hours, compared to 30 minutes in Hoebel *et al.* (3) We used a palatable, semisolid, warm meal, whereas Hoebel, *et al.* used a cold, liquid, and perhaps marginally palatable formula diet.

TABLE 1

SUMMARY OF DIRECT AND CARRY-OVER EFFECTS OF TREATMENT*

Variable	Mean		Direct Effect			Carry-Over Effect		
	Active	Placebo	Estimate	SEE	p-Value	Estimate	SEE	p-Value
Intake (g)	407.1	433.2	−26.1	25.5	0.31	−55.1	30.7	0.08
Duration (min)	6.78	6.93	−0.15	0.37	0.69	0.09	0.44	0.84
Diet Rating	5.79	5.87	−0.08	0.23	0.72	0.24	0.28	0.39
Hunger†	7.93	8.78	−0.85	0.51	0.10	−1.25	0.62	0.05
Satiety	4.66	4.05	0.61	0.64	0.35	0.97	0.77	0.22
Sickness‡	1.00	1.17	−0.17	0.10	0.11	−0.09	0.12	0.46
Content	3.29	3.04	0.25	0.23	0.28	−0.18	0.27	0.51
Depressed	1.29	1.33	−0.04	0.14	0.77	−0.20	0.17	0.25
Irritable	1.33	1.37	−0.04	0.16	0.80	−0.14	0.20	0.49
Good Mood	3.04	2.66	0.38	0.17	0.04	0.20	0.21	0.36
Boredom	1.13	1.13	0.00	0.13	1.00	0.00	0.16	1.00
Elated	2.04	1.79	0.25	0.22	0.27	0.09	0.27	0.74
Bad Mood	1.08	1.08	0.00	0.08	1.00	−0.03	0.10	0.76
Lin§ (g/min)	78.43	77.45	1.31	6.43	0.84	−13.12	7.88	0.11
Quad§ (g/min)	−2.85	−1.88	−1.20	0.92	0.20	−0.12	1.13	0.91

*Each of these effects is expressed as a difference between treatment means with the standard error of the estimate (SEE) showing reliability. Except for intake and duration, all of the responses reported are taken from questionaires administered before the subjects' test meals.

†These hunger and satiety ratings were assessed before the meal. Subjects placed marks on separate 15 cm lines. The maximum was 15 (hungriest or most satiated I can imagine being), and the minimum was 0 (not hungry or satiated at all).

‡The sickness and mood variables below it were measured on 5-point category scales, where 1 was 'not at all,' 2 was 'slightly,' 3 was 'moderately,' 4 was 'very' and 5 was 'extremely.'

§Lin is the linear coefficient of the cumulative intake curve [11] and represents the initial rate of eating. Quad is the quadratic coefficient of the cumulative intake curve [11] and represents half the rate of deceleration. The computation of the direct effect is biased because of a missing value; consequently, the difference between active and placebo is not equal to the direct effect.

METHOD

Overall Procedure

The following protocol was approved by the Institutional Reveiw Board of St. Luke's-Roosevelt Hospital. Twelve nonobese women participated in the study (see the Subject Selection section for details). Each subject was subsequently tested on four nonconsecutive days. On each test day the subject reported for a standardized breakfast between 8:30 and 11:00 a.m. Blood pressure measurements taken before each meal were within normal limits for all subjects. Meal time was approximately the same for any given subject. Immediately following breakfast, each subject received, along with water, either a single capsule containing PPA or an identical placebo capsule without the drug. Each subject returned for lunch 2¾ hours later and was first given a questionnaire which included queries about the subject's hunger, satiety and bodily sensations [12]. A macaroni and beef luncheon was served about 15 minutes later so that the interval between taking the capsule and eating lunch remained constant at three hours. In order to minimize visual cues about the amount of food consumed, an excess amount of macaroni and beef was put in a bowl and placed on an eating monitor [8]. Each subject was instructed by tape recording to eat until she "felt she had enough." Five minutes after the subject stopped eating, she was asked to complete a second questionnaire, identical to the first but with additional queries regarding the palatability, texture and temperature ratings of the meal. Intake was measured by a computerized eating monitor while the subject ate, and by separate weighing of the bowl before and after the meal. Following the last test meal, but on a separate day, the subjects were interviewed and paid $125. During this interview, the subjects were asked to rate and rank the importance they attached to several variables measured in the study.

Subject Selection

Twelve nonsmoking women within 10% of desirable weight [3] were studied. They were selected from a population of 38 qualified women by means of procedures and criteria previously employed in our laboratory [8,9]. In order to be included, subjects had to range in age from 18 to 25 years, rate the macaroni and beef test meal at least 6 on a 9-point scale of liking [14] either at a brief exposure taste test or after having eaten it as a meal, and eat between 250 and 700 g of the macaroni and beef test luncheon. In addition, subjects had to be in good health and have no medical problems as determined by an oral medical history questionnaire administered by the experimenter on the screening day. Subjects' blood pressure readings (taken in duplicate while sitting) were not to exceed 140/90. In order to exclude pregnant women, each received an in-office pregnancy test (EPT, Warner Lambert Co., Morris Plains, NJ) on the day she was screened.

Subjects were told that the purpose of the study was to determine their reactions to foods and internal sensations after taking a capsule of PPA, a nasal decongestant, which was expected to affect their sensitivity to flavors. Other details of the experimental procedures were similar to those published in Kissileff *et al.* [8].

In order to complete the screening procedures, the subjects came to the laboratory after an overnight fast, participated in the taste test, had their height and weight measured in the laboratory, ate the standardized breakfast and returned 2½ to 3 hours later for lunch. Of the 38 subjects, 26 were called, 18 were actually screened, and 13 were selected to participate. One subject was dismissed because she spooned the test meal into a container instead of eating it. The characteristics of the subjects selected were (mean±SD): weight, 56.1±6.6 kg; height, 162.4±7.7 cm; age, 21.7±3.1 years; percentage of average desirable weight, 102.5±5.5%; and taste test rating of the test meal, 7.5±1.0

Foods

The standardized pretest meal consisted of a white, toasted Thomas' English muffin with 1.5 pats of butter (6 g) and 249 g (8 fl. oz) Red Cheek apple juice (total of 300 kcal). The test meal was four 326 g packets of Stouffer's macaroni and beef with tomatoes served hot (54°C). The test meal was served in a 1.9 l, white Corningware bowl and provided an estimated 1.16 kcal/g.

Medications and Treatment Units

The active agent was a No. 1 white capsule containing 37.5 mg phenylpropanolamine, USP, while the placebo was an identical capsule containing only excipient (pregelatinized starch, NF). Immediately following breakfast on the day of screening, each subject received 100 g Deer Park spring water only. On the four subsequent test days, subjects received either the active or placebo agent along with 100 g of water. The order of treatments was administered in a double-blind fashion according to a scheme previously employed in our laboratory [9]. Each participant received one of the following treatment sequences: AABB, ABBA, BBAA or BAAB, with A being active and B being placebo. The treatment sequences were then randomly assigned so that each sequence was included once in each block of four subjects.

Universal Eating Monitor (UEM) and Physical Setting

Details of the UEM and physical setting are described fully by Kissileff, *et al.* [8]. Briefly, the test meal was served on a table containing a concealed balance that continuously registered and recorded the weight of the food removed from it. The monitor was used to determine the amount of food eaten and to generate a cumulative intake curve for the test meal. The subject was instructed to place her spoon on a special holder when she had eaten as much as she wanted of the test meal. The interval from the start of the meal to the placement of the spoon on the holder was timed by the experimenter and recorded as meal duration.

Design and Statistical Analysis

Meal variables were analyzed using the GLM procedure in the SAS statistical package [17]. A linear model was used to characterize the response:

$$D = \mu + S + I(seq) + P + T + C + E,$$

where D is the dependent variable and μ is the population mean. The effects included in the model were sequence (S) (i.e., one of the four treatment sequences AABB, etc.), subject nested within the sequence (I), trial (P), treatment (T), first order carry-over (C) [2], and the error term (E). The direct treatment effect in this design was orthogonal to (i.e., statistically independent of) the carry-over effect. The treatment effect was determined by an F-test with MS treatment in the numerator and MS error in the denominator.

This procedure was performed on the following variables: Food intake, rating of the diet on a 9-point scale of liking [14], hunger and satiety ratings [19], responses to eight questions about bodily sensations and moods [12], including feeling of sickness, and the coefficients of the cumulative intake curve [11].

RESULTS

Intake under the PPA condition (407.1 g) was 26.1 g (30.3 kcal) less than under the placebo condition (433.2 g). This difference was not statistically significant ($p=0.39$). The ratio of the effect to its standard error was equal to 1. Standard tables for the power of a test [13] indicate that 64 subjects would have been required to provide a power of 0.5 with $\alpha=0.05$ for the mean and standard deviation of this study. A 55.5 g difference in intake between active and placebo would have been required to obtain a significant effect of the drug given the standard error in this experiment. Because of the low power, it is not possible to state with confidence that a single dose of PPA is ineffective in reducing food intake in a single test meal. The carry-over effect (difference between active and placebo on the next trial regardless of what was given that trial) was larger (55.1 g) than the direct effect but was still not significant ($p=0.11$). The direct effect of treatment and first-order carry-over effect and error are given in Table 1. Two of the measures (i.e., carry-over effect on hunger and direct effect on good mood) reached statistical significance.

The final interview questionnaires revealed that although the subjects were not told the purpose of the study, they nevertheless believed that hunger ratings and amount consumed were slightly more important than ratings of sensory quality.

DISCUSSION

The principal finding in this study was that single 37.5 mg doses of PPA given 3 hours before single-course meals did not significantly reduce food intake of those meals. There are several factors that may be responsible for this result. One possibility is that the experimental techniques failed to assess adequately the drug's effectiveness. Previous studies done in our laboratory, however, have demonstrated that our method for studying food intake is sensitive to several variables, although we have not tested any other anorectic drugs. For example, test meal intakes of normal weight females were smaller after they received a large, rather than a small, preload of soup [7]. Lean and obese men ate significantly less food after receiving cholecystokinin intravenous infusions than after receiving saline [9,15]. In another study the satiating effects of a fiber-containing bar and a control food combination, at high and low calorie levels, were compared to the satiating effects of a 25 mg capsule containing either PPA or a placebo of magnesium oxide. Intakes were lower after both of the high-calorie preloads than either of the capsule conditions, and there was no appetite or intake

suppressing effect of PPA [10]. All these studies show that our procedure is sensitive enough to demonstrate significant reductions in food intake.

Another possible reason for our negative findings may be the inability of a brief administration of the drug to elicit a reduction in food intake. Also, it may be necessary to alter the drug-meal interval or the form of presentation of the drug. In a previous study, (Phyllis Schumann, Ciba Consumer Pharmaceuticals, personal communication) the time course of PPA levels in the bloodstream following a single 37.5 mg dose showed a peak level of 110 ng/ml at 2 hours, and the PPA level dropped to 95 ng/ml in 3 hours and 80 ng/ml in 4 hours. Although there was only a small decrease in plasma concentration from 2 to 3 hours, a shorter interval might be more effective in determining the drug's efficacy. The possibility that slow dissolution of the capsule would cause sub-optimal PPA levels was negated by subsequent studies showing that 97% of the PPA was released within 20 minutes (Phyllis Schumann, Ciba Consumer Pharmaceuticals, personal communication).

It is also possible that subjects may require a prolonged exposure to PPA prior to testing in order to establish and sustain an effective level of the drug in the bloodstream, or to induce neural changes which require time for synthesis of new transmitters or hormones. It may be that appetite suppression, a pharmacodynamic effect, lags behind the plasma concentration, a pharmacokinetic effect. Prolonged exposure to PPA could be achieved by administering PPA for several successive days before measuring food intake in the laboratory at the end of the period. Reduction in food intake has already been suggested as a possible cause of weight loss in a study in which a prolonged administration for two weeks at a dose of 25 mg three times a day did reduce body weight [6]. It is uncertain, however, whether a particular level of drug must simply be reached or whether a person must be exposed to that level over a period of time.

In spite of the previously demonstrated effects of PPA on weight loss, it is conceivable that PPA does not actually have a strong effect on acutely measured food intake, either in obese or nonobese individuals. Perhaps success in weight loss with PPA has been the result of effects on the central nervous system that heightened arousal [18] and thereby served to reinforce the subjects' motivation to lose weight. Taking PPA might have reminded them to restrict food intake in a variety of temporal patterns (e.g., by omitting snacks or skipping meals, etc.) whose effects might not appear in a single test meal situation. The heightened arousal effects in weight-conscious individuals could account for Hoebel *et al.* [5] findings of the appetite reducing effect of PPA in an informed sample interested in weight loss but not in a group that thought PPA was only a nasal decongestant.

Finally, another possible reason for the differential effects of PPA between obese and nonobese individuals is that obese individuals may be more susceptible to food intake reducing effects in general, because their excess fat stores may provide a negative feedback signal [20] to the central nervous system either directly or indirectly. However, it is also possible that PPA can cause weight loss by increasing thermogenesis as suggested by animal studies [1,21], and that appetite may be unaffected.

In conclusion, the experiment failed to detect a significant effect on food intake by single doses of 37.5 mg of phenylpropanolamine hydrochloride administered to twleve nonobese women three hours before standard test meals. However, because of insufficient power, the difference was not small enough to accept the null hypothesis nor large enough to reject it, and therefore the results are inconclusive. Either more subjects must be tested at the present dosage to accept the null hypothesis, or a more effective dosage must be administered to demonstrate efficacy on food intake. The cognitive effects suggest that drug did have effects but they were too small to affect intake.

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