Weight Loss Induced by Chronic Phenylpropanolamine: Anorexia and Brown Adipose Tissue Thermogenesis[1]

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WELLMAN, P J AND T L SELLERS *Weight loss induced by chronic phenylpropanolamine Anorexia and brown adipose tissue thermogenesis* PHARMACOL BIOCHEM BEHAV **24**(3) 605–611, 1986 —The effects of chronic treatment with phenylpropanolamine (PPA) on body weight (BW), food intake (FI), and water intake (WI) and interscapular brown adipose tissue (IBAT) thermogenesis in adult male Sprague-Dawley rats were evaluated in 2 experiments In Experiment 1, rats were treated (IP) twice daily (0900 and 2100 hr) for 12 days with either saline or 5, 10, or 20 mg/kg dl-PPA Rats treated with 20 mg/kg dl-PPA exhibited significant decreases in both FI and BW but not WI Basal IBAT temperature was slightly increased in chronic 20 mg/kg dl-PPA rats and there was no evidence of tolerance to the acute IBAT thermogenic effect of 20 mg/kg dl-PPA In Experiment 2, rats were treated twice daily (0900 and 2100 hr) for 12 days with either saline or 20 mg/kg of either d-PPA or l-PPA There was a 2-fold difference in the potency of these PPA isomers on FI, BW and IBAT thermogenesis Body composition analyses revealed that l-PPA, but not d-PPA, induced a significant loss of carcass lipid without significant changes in carcass ash, water or protein levels These data suggest that the weight-reducing action of PPA may reflect a combined effect of this drug on both food intake and BAT thermogenesis

Phenylpropanolamine Isomers Food intake Body weight Anorexia Brown adipose tissue thermogenesis

PHENYLPROPANOLAMINE (PPA) is a phenethylamine that induces a moderate reduction in body weight [1, 5, 16] Although the weight-reducing action of PPA is well-established, the precise mechanism by which PPA exerts an anti-obesity effect is unclear Hoebel and his coworkers [5,6] have advanced cogent arguments suggesting that the weight loss induced by PPA reflects a suppressive action of this drug on lateral hypothalamic feeding mechanisms More recently, however, Wellman [12] and Wellman and Marmon [14,15] argued that a portion of the weight-reducing activity of PPA may reflect an action of this sympathomimetic compound on peripheral brown adipose tissue (BAT) thermogenesis Rothwell and Stock [10] demonstrated that enhanced heat production from this sympathetic tissue is sufficient to minimize obesity when rats overeat calorically-dense diets In support of a metabolic interpretation of PPA-induced weight loss, Wellman [12] and Wellman and Marmon [14,15] demonstrated that dl-phenylpropanolamine significantly increased interscapular BAT (IBAT) thermogenesis at dose levels that reduce food intake in short-term feeding tests [8,16]

The purpose of the present experiments was to further examine the potential role of BAT thermogenesis in the reduction of body weight induced by phenylpropanolamine Of particular interest was the effect of chronic administration of PPA on food and water intake, body weight and IBAT thermogenesis An examination of the chronic effects of PPA on feeding and body weight was deemed necessary because although the literature has consistently observed reduction in body weight in chronic studies, the effects of PPA on food intake are typically measured using short-term feeding tests Moreover, the tests of IBAT thermogenesis conducted by Wellman [12] and by Wellman and Marmon [14,15] evaluated the acute effects of dl-PPA on IBAT thermogenesis in drug-naive rats Were the IBAT thermogenic effect of dl-PPA to be subject to the rapid development of tolerance, a role for BAT thermogenesis in PPA-induced weight loss would be precluded Experiment 1 therefore evaluated the effect of 5, 10, and 20 mg/kg dl-PPA, given twice a day for 12 days, on food and water intake and on body weight On day 14, rats chronically treated with either saline or 20 mg/kg dl-PPA were treated with either saline or 20 mg/kg dl-PPA to examine the possibility of tachyphylaxis (drug tolerance) for IBAT thermogenesis in rats treated chronically with dl-PPA

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[2]Parts of this manuscript are based on an Honor's Thesis submitted by the second author to the Department of Psychology, Texas A&M University

EXPERIMENT 1

METHOD

Animals

The animals were 28 Sprague-Dawley albino rats (obtained from Timco Inc., Houston, TX) weighing 150–175 grams at the beginning of the experiment. The rats were housed individually in standard wire-mesh cages in a temperature-controlled room (23±1 degrees C) under a 12/12 hr light-dark cycle (lights *on* at 0900 hr). The rats were given continuous access to tap water from calibrated Wahmann drinking tubes attached to each cage front and to standard rat pellets (Purina Rat & Mouse Diet) placed on the cage floor. Bedding (DACB pads covered with several layers of paper towels) beneath each cage was replaced daily.

Drugs

A drug vehicle (0.9% saline) solution was prepared by dissolving 0.9% sodium chloride into sterile distilled water. Phenylpropanolamine solutions were prepared just prior to injection by dissolving either 5, 10, or 20 mg of dl-PPA (Lot #3E7, obtained from the H. Reisman Company) into sterile distilled water. A urethane solution consisted of 1.2 g/10 ml urethane (Sigma Chemical) dissolved in sterile distilled water. All solutions were calculated as the weight of salt and base per unit volume of the drug vehicle [11].

Procedure

The rats were housed in the colony room for a 9 day acclimation period with free access to food and water. The rats were weighed (to the nearest gram) at 0900 hr daily to accustom them to handling. During Days 1–3 following the acclimation period, baseline food and water intakes were recorded for each rat. During this period, the rats were weighed at 0900 hr, injected with 1 ml/kg saline vehicle and then offered a weighed amount of food pellets. At 2100 hr, a second daily saline vehicle injection was given. Food intakes, corrected for spillage collected on paper towels placed beneath the floor of each cage, were recorded for each rat on the following morning at 0900 hr. In addition, water intake over 24 hours was recorded for each rat. To compensate for spillage associated with cage movement, an extra bottle was placed on an empty cage, the difference in volume (typically 1–2 mls) for this bottle between successive morning readings served to adjust the daily water intake of each rat for fluid spillage.

At the end of the 3 day baseline period, 4 groups (n=7 each) were formed on the basis of comparable average group food intake, water intake and body weight and then randomly assigned to drug treatment conditions. The chronic drug treatment was carried out on Days 1–12 following baseline measurements. Each rat was injected twice (0900 and 2100 hr) daily with either saline or with 5, 10, or 20 mg/kg dl-PPA. Body weights, food intakes and water intakes were measured daily at 0900 hr as during the baseline period.

A test of the effect of dl-PPA on IBAT thermogenesis was carried out on Day 14. To provide an estimate of the potential tachyphylaxis associated with 24 injections of dl-PPA uncomplicated by cumulative drug injections, no drug injections were given on Day 13. Surgery and temperature measurements were made under anesthesia induced by injection (IP) of urethane (Sigma Chemical 1.2 grams/10 ml/kg). For each rat, the skin over the shoulders was shaved and a 3 cm

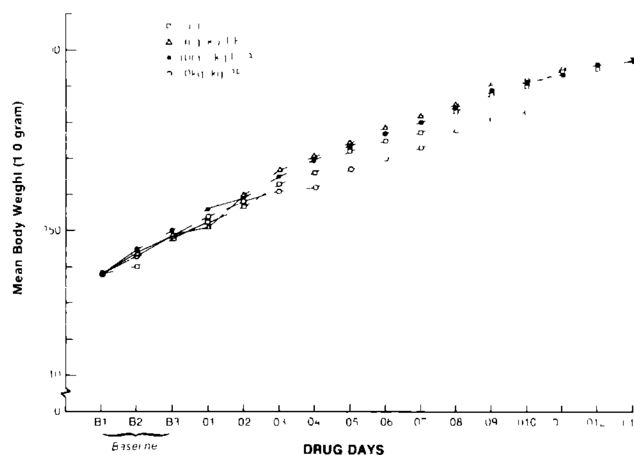

FIG. 1. Mean group body weight (g) in rats prior to and during 12 days treatment (2× daily) with either saline or 5, 10, or 20 mg/kg dl-PPA.

longitudinal incision made over the interscapular region. After placement of the rat on a foam-insulated plastic base, a thermoprobe insulated with silicone (Strawberry Tree, 3 mm in length and 2 mm in diameter) was positioned between the major lobes of IBAT and the skin over IBAT closed around the thermoprobe cable using hemostatic forceps. The tip of a second thermoprobe was positioned 4 cm into the rectum to record core temperature. IBAT and rectal temperatures were recorded every minute to the nearest 0.1 degree Centigrade using a microcomputer (Apple-IIE) outfitted with a dual thermometer card (Strawberry Tree Computers, Inc.).

Because of equipment limitations, the effects of saline or 20 mg/kg dl-PPA treatment was assessed only in the saline and the 20 mg/kg dl-PPA groups. The 5 and 10 mg/kg groups were not tested because it was reasoned that were tolerance to develop to the thermic action of dl-PPA within IBAT, such a tolerance effect ought to be most easily detected in the 20 mg/kg dl-PPA group. Baseline temperatures were recorded for a 10 minute period prior to drug or saline injection (IP) in a room maintained at 24.0 (±0.5) degrees C. Rectal temperature, at this room temperature, was stable (mean of approximately 36.3 degrees C) during the 10 minute period prior to injection. Thus, an external heat source was not required in the present experiment. Both IBAT and rectal temperatures were recorded for a 30 minute period following injection.

Statistical Analyses

The data of this experiment were analyzed using split-plot factorial analyses of variance (ANOVA). Body weight, food intake and water intake data were analyzed separately for baseline (Days 1–3) and drug treatment phases (Days 1–12) using Dose (0, 5, 10, and 20 mg/kg dl-PPA) as the between-group factor and Days as the within-group factor. The IBAT and rectal temperature data were also analyzed separately using Chronic Drug (SAL or PPA) and Acute Drug (SAL or PPA) as the between-group factors and Time (after injection −10, −5, 0, 5, 10, 15, 20, 25, and 30 minutes) as the within-group factor. Between- and within-group comparisons were made using a priori two-tailed *t* tests [7] after separate ANOVA's of the data.

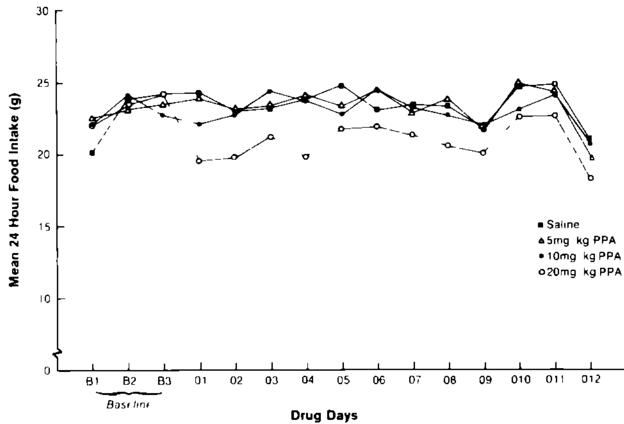

FIG 2 Mean group daily food intake (g) in rats prior to (Baseline days 1–3) and during 12 days treatment (2× daily) with either saline or 5, 10, or 20 mg/kg dl-PPA

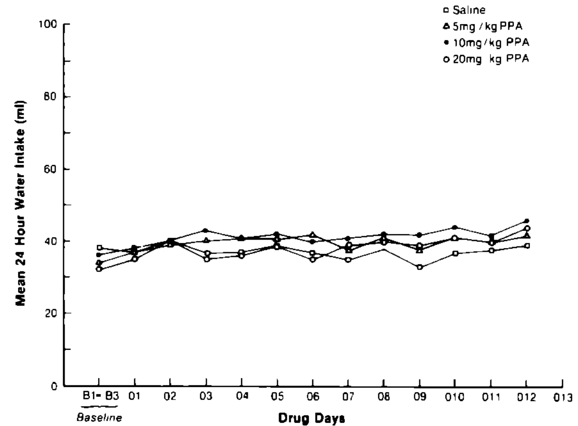

FIG 3 Mean group daily water intake (ml) in rats prior to (average of Baseline Days 1–3) and during 12 days treatment (2× daily) with either 5, 10, or 20 mg/kg dl-PPA

RESULTS

Body Weight

The influence of dl-PPA on mean group body weight is depicted in Fig 1 There were no significant differences between the drug groups on baseline Days 1–3, F(3,24)=0 1, *p*<0 98 Normal growth was observed in rats treated twice daily with either saline or 5 or 10 mg/kg dl-PPA as evidenced by comparable increases in body weight in these groups during Days 1–12 In contrast, rats treated with 20 mg/kg dl-PPA exhibited reduced body weight gain Analyses of variance revealed a significant drug × day interaction, F(36,288)=1 91, *p*<0 002, but no significant effect of drug, F(3,24)=0 34, *p*<0 79 Subsequent comparisons between group means revealed no significant differences between the control and 20 mg/kg dl-PPA groups either in terminal body weight or in change in body weight over the 12 day treatment period

Food Intake

Figure 2 depicts mean group food intake over successive 24 hour intervals prior to and during daily treatments with dl-PPA There were no significant differences between the drug groups during the baseline period, F(3,24)=0 03, *p*<0 99 Analyses of variance of changes in food intake during Days 1–12 revealed significant effects of drug, F(3,24)=6 8, *p*<0 002, and of day, F(12,276)=12 5, *p*<0 0001, but the interaction of drug and day was not statistically significant Comparison of mean group food intake (collapsed across the day factor) revealed that the food intake of rats treated with 20 mg/kg dl-PPA was significantly lower than that of the saline control group, *t*(24)=3 9, *p*<0 001 There were no significant differences in food intake between the saline group and either the 5 mg/kg or 10 mg/kg dl-PPA groups

Water Intake

The influence of dl-PPA on 24 hour water intake is depicted in Fig 3 There were no significant differences between the groups in water intake during baseline Days 1–3, F(3,24)=1 8, *p*<0 17 Analyses of variance of water intake during chronic drug treatment revealed a significant interaction between the factors of drug and day, F(36,288)=2 3, *p*<0 0001, whereas the effect of drug was not statistically significant, F(3,24)=1 2, *p*<0 33 On Day 1 of drug treatment, there was a trend for the 10 and 20 mg/kg dl-PPA groups to consume less water than control rats but these differences were not statistically significant The basis for the significant interaction between drug and day was the result of the increase in water intake exhibited by the 10 mg/kg dl-PPA group A comparison of water intake on Day 12 revealed a significant increase in water intake by the 10 mg/kg dl-PPA group relative to the saline control group, *t*(24)=2 56, *p*<0 02, but comparisons between the saline groups and the other drug groups were not significant

Temperature

Figure 4 depicts the influence of chronic PPA treatment on basal IBAT temperature and of acute PPA on IBAT temperature Rats treated with 20 mg/kg dl-PPA (groups PPA-SAL and PPA-PPA) during Days 1–12 exhibited a slight but non-significant increase in basal IBAT temperature during the 10 minute baseline recording period on Day 14 relative to the respective chronic saline-treated groups (SAL-SAL and SAL-PPA), F(1,11)=3 4, *p*<0 09 There was stability in the IBAT temperature exhibited by the acute saline-treated groups (SAL-SAL and PPA-SAL) during the 30 minute post-injection period In contrast, rats treated with 20 mg/kg dl-PPA exhibited marked increases in IBAT temperature, F(8,72)=126 2, *p*<0 0001 There were no differences between the SAL-PPA and PPA-PPA groups in terms of the absolute change in IBAT temperature induced by 20 mg/kg dl-PPA, F(8,72)=2 0, *p*<0 07 It should be noted that there was a trend toward a larger change in IBAT temperature in the PPA-PPA group relative to that of the SAL-PPA group but this difference was not statistically significant

There were no differences between the groups in rectal temperature (not depicted) prior to drug treatment at Time 0 Analyses of variance revealed significant effects of 20 mg/kg

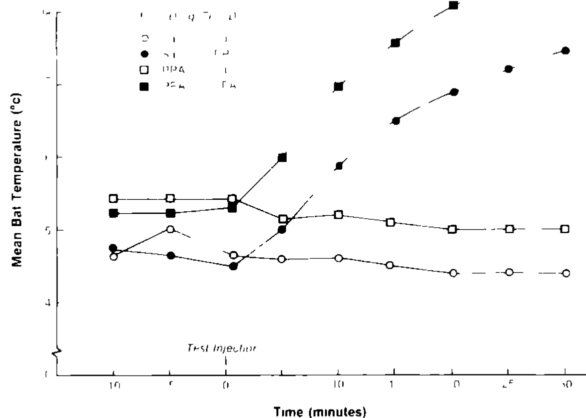

FIG 4 Mean group changes in interscapular brown adipose tissue temperature (degrees C) over a 30 minute period in rats chronically treated (prior treatment) with either saline or 20 mg/kg dl-PPA and then treated (at Time 0 of figure) with either saline or 20 mg/kg dl-PPA

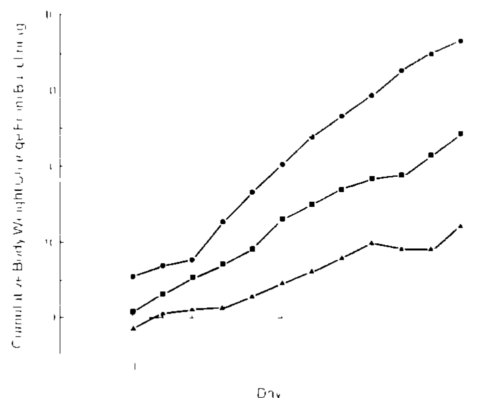

FIG 5 Mean group cumulative changes in body weight (g) in rats treated (2× daily) over a 12 day period with either saline or 20 mg/kg d-PPA or 20 mg/kg l-PPA

dl-PPA on rectal temperature, $F(8,72)=3.4$, $p<0.05$, but there was no interaction between the pretreatment and treatment factors in that PPA induced comparable acute increases in rectal temperature in rats chronically treated with either saline or 20 mg/kg dl-PPA

DISCUSSION

The results of Experiment 1 indicate that dl-PPA has significant effects on body weight, food and water intake and on IBAT thermogenesis and that chronic treatment with PPA does not result in tolerance to the thermogenic action of PPA within BAT The experiment did not, however, reveal whether BAT thermogenesis plays a significant role, if any, in the weight loss induced by PPA In addition to the racemic mixture, PPA exists as d- and l-isomers Wellman and Marmon [15] noted that l-PPA induces twice as much temperature change within IBAT as does d-PPA The purpose of Experiment 2 was to compare the potency of d-PPA and l-PPA on food intake, water intake, body weight and IBAT thermogenesis using the procedures of Experiment 1 with the hope of dissociating the effect of PPA on food intake from that of PPA on IBAT thermogenesis Such an evaluation would identify the relative contribution, if any, of these factors to the weight loss induced by PPA

EXPERIMENT 2

METHOD

Animals

The animals were 28 male Sprague-Dawley rats (Timco, Inc , Houston, TX) weighing 175–200 grams at the beginning of the experiment The rats were maintained as in Experiment 1 except that a different colony room was employed owing to a malfunction of heating/air conditioning equipment in the colony used in Experiment 1 The average ambient temperature of this colony room was slightly lower (approximately 22±1 degrees C) than that used in Experiment 1 In addition, a Teklad chow diet was used in the present experiment This diet was identical in nutritional composition to the Purina diet but was slightly different in pellet size and texture

Procedures

The procedures of this experiment were similar to those of Experiment 1 with the following exceptions In this experiment, the rats were randomly assigned to one of three groups control (n=12), d-PPA (n=8) and l-PPA (n=8) These groups were comparable in terms of mean group body weight, food intake and water intake during the baseline period Because of time and equipment constraints for the final thermogenesis test on Day 14, the rats of this experiment were run in two squads, each offset by one day The rats were randomly assigned to each squad with the provision that half of each drug group be assigned to a squad During Days 1–12, the rats were injected, using the procedures of Experiment 1, with either saline, 20 mg/kg d-PPA or 20 mg/kg l-PPA The 20 mg/kg value was chosen to provide a comparison with the data of Experiment 1

No drug injections were given on Day 13 and the IBAT thermogenesis tests were carried out on Day 14 using the procedures of Experiment 1 In this phase of the experiment, the rats in the chronic saline group were treated with either saline (group SAL-SAL), 20 mg/kg d-PPA (SAL-D) or 20 mg/kg l-PPA (SAL-L) (n=4 per group) at Time 0 In contrast, the rats in the chronic d-PPA group were treated with saline (D-SAL) or 20 mg/kg d-PPA (D-D) whereas the rats chronically treated with l-PPA were treated with either saline (L-SAL) or l-PPA (L-L) (n=4 per group)

Following the thermogenesis tests, it was decided to determine the effect of PPA isomer treatment on body composition Each rat was shaved using electric clippers while under deep anesthesia induced by a second injection of urethane Each carcass was then decapitated and the intestinal tract discarded Each carcass was further cleaned of hair using a cream depilatory agent (Nair), scrubbed and then washed Each carcass was then blotted dry, weighed and frozen (at −20 degrees C) until analyses of carcass composition could be performed

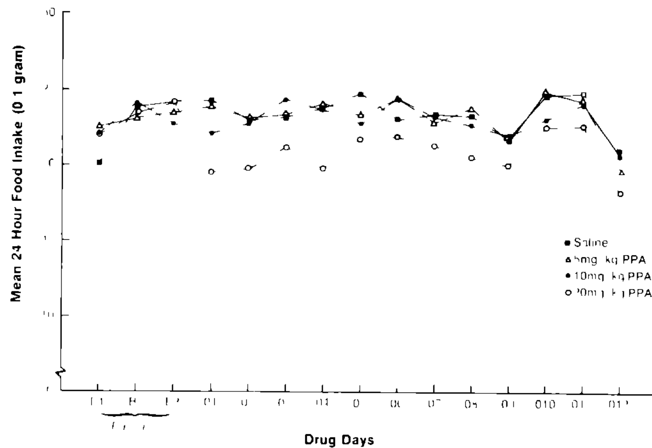

FIG 6 Mean group daily food intake (g) in rats treated (2× daily) over a 12 day period with either saline or 20 mg/kg d-PPA or 20 mg/kg l-PPA

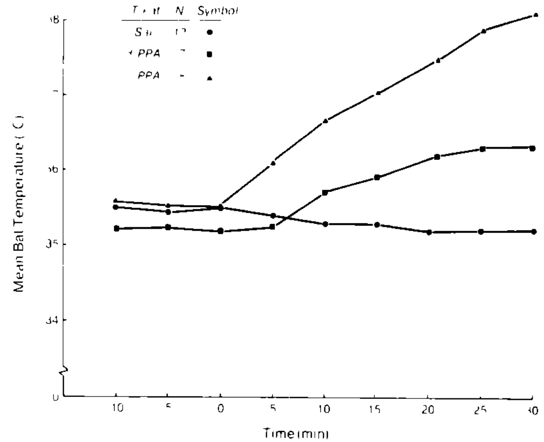

FIG 7 Mean group temperature changes (difference between baseline and 30 minutes after injection in degrees C) within interscapular brown adipose tissue for rats chronically treated with either saline or 20 mg/kg l-PPA or d-PPA and then treated (at Time 0) with either saline or 20 mg/kg d-PPA or l-PPA

Each carcass was analyzed for ash, water, fat (lipid) and protein content using slight modifications of the procedures of Leshner, Littvin and Squibb [9] Each carcass was frozen in liquid nitrogen and then blended to a fine powder All tests of this homogenous powder were run in duplicate for each rat

RESULTS

Body Weight

The influence of chronic d-PPA and l-PPA on body weight, here given as cumulative changes in body weight, is expressed in Fig 5 There were no significant differences between the groups during the baseline period Rats treated with d-PPA or l-PPA gained less body weight than saline-treated rats over the 12-day period Rats treated with saline over the 12-day period exhibited an average gain in body weight of 38 grams (3 2 grams/day) In contrast, rats treated with 20 mg/kg d-PPA exhibited a reduced average weight gain of 26 grams (2 2 grams/day) whereas 20 mg/kg l-PPA reduced average weight gain to 13 8 grams (1 2 grams/day) These values were 68% and 36% respectively of the weight gains exhibited by the saline group Analyses of variance of the changes in body weight revealed a significant effect of drug, $F(2,25)=26$ 2, $p<0$ 0001, and a significant interaction between the factors of drug and day, $F(22,275)=12$ 6, $p<0$ 0001 Comparison of final weight changes on Day 12 revealed that each group was significantly different from each other group, $t(25)$ at least 4 4, $p<0$ 001

Food Intake

Figure 6 depicts the effects of the PPA isomers on mean 24 hour food intake There were no differences between the groups in food intake during the baseline period, $F(2,25)=0$ 6, $p<0$ 60 Commencing with the first day of chronic treatment, food intake was moderately suppressed in the isomer groups Saline-treated rats consumed an average of 23 grams/day whereas the d-PPA and l-PPA groups consumed an average of 20 and 18 grams/day, respectively These food intake values were 87% and 78% of the saline values Analyses of variance of the food intake data revealed a significant effect of drug, $F(2,25)=20$ 3, $p<0$ 0001, and a significant interaction between the factors of drug and day, $F(22,275)=1.6$, $p<0$ 05 An estimate of feeding efficiency (milligram body weight gained/cumulative food intake, gram) was calculated for control rats in Experiment 2 This was approximately 11 94 mg body weight per gram of chow consumed We then extrapolated the predicted weight gain for the d-PPA and l-PPA groups given their mean group cumulative food intakes during drug treatment These values were 10 7 mg/g and 9 69 mg/g, respectively Although the value predicted for the d-PPA group (10 7 mg/g) was remarkably close to their actual food efficiency (10 4 mg/g), the estimated weight gain for the l-PPA group (9 69 mg/g) was 45% larger than that actually observed (6 9 mg/g) Analyses of variance of the feeding efficiency ratios revealed a significant effect of group, $F(2,25)=9$ 9, $p<0$ 0006 Subsequent comparisons indicated that the feeding efficiency of the l-PPA group, but not of the d-PPA group, was significantly different from that of the saline group, $t(25)=4$ 34 and 1 2, $p<0$ 001 and 0 30, respectively

Water Intake

The rats consumed an average of 30 ml of water per day (not depicted) during the baseline period with no differences between the groups, $F(2,25)=0$ 4, $p<0$ 66 Rats treated with saline or 20 mg/kg d-PPA slightly increased their daily water intake (35 8 and 33 7 ml, respectively) during Days 1–12 whereas rats treated with l-PPA exhibited even greater water intake (41 7 ml) Analysis of variance of water intake during Days 1–12 revealed a significant effect of drug, $F(2,25)=9$ 0, $p<0$ 0011 There were no significant differences between the intakes of saline and 20 mg/kg d-PPA groups whereas the intake of water by the l-PPA group significantly exceeded that of the saline group, $t(25)=3$ 3, $p<0$ 01

Temperature

The effects of acute treatment of saline, 20 mg/kg d-PPA

TABLE 1

INFLUENCE OF d-PPA AND l-PPA ON BODY COMPOSITION IN RATS

Group	N	% Ash*	% Water*	% Lipid†	% Protein‡
Saline	11	3.6 ± 0.3	67.4 ± 0.4	22.5 ± 0.7	18.3 ± 0.5
d-PPA	8	3.2 ± 0.4	67.1 ± 0.4	22.8 ± 1.2	19.1 ± 0.6
l-PPA	8	4.1 ± 0.8	65.9 ± 1.5	17.8 ± 1.2§	18.6 ± 0.5

*Based on percent wet sample weight
†Based on percent lipid extraction from dried tissue sample
‡Based on percent nitrogen content
§Refers to a significant difference between drug and control group, $p<0.05$
Each value represents the mean ± SEM

or 20 mg/kg l-PPA on brown adipose tissue thermogenesis is depicted in Fig. 7. Rats treated with saline on Day 14 exhibited a slight decrease in IBAT temperature over the 30 minute post-injection period (Fig. 7). There was no effect of the chronic drug treatment on basal temperature in the groups treated with saline. There also was no evidence of tolerance. d-PPA induced similar changes in IBAT temperature in rats treated chronically with saline or 20 mg/kg d-PPA. Similarly, l-PPA induced comparable acute changes in IBAT temperature in chronic saline or 20 mg/kg l-PPA treated rats. Because there were no pre-treatment differences, the data were combined across pretreatment conditions (data not presented). There were clear differences between the PPA isomers, l-PPA induced approximately twice as much thermogenesis as d-PPA, $F(10,100)=27.1$, $p<0.0001$.

Rectal temperature data (not depicted) indicated significant overall effect of PPA on rectal temperatures, $F(2,23)=4.9$, $p<0.01$. Moreover, there was a significant interaction between the factors of drug and time, $F(10,115)=35.2$, $p<0.0001$, after the test injection. Rats treated with saline exhibited a constant rectal temperature whereas the d-PPA and l-PPA groups exhibited changes in rectal temperature of 0.4 and 1.2 degrees C, respectively. Thus, the interaction was produced by the large effect induced by l-PPA and the relative lack of effect of d-PPA.

Body Composition

The influence of d-PPA and l-PPA on body composition is depicted in Table 1. Data were not analyzed from one rat for the body composition analyses (this rat exhibited values that were >2 standard deviations from the control mean). Neither d-PPA nor l-PPA induced a pronounced or reliable effect on either ash content, $F(2,23)=2.1$, $p<0.15$, water content, $F(2,23)=1.0$, $p<0.38$, or protein content, $F(2,23)=0.4$, $p<0.66$. The l-isomer of PPA produced a significant reduction in carcass fat content, $F(2,23)=7.7$, $p<0.004$, but the d-isomer did not. The body composition data demonstrate that although the l-PPA isomer induced greater water intake over the course of the 12 day treatment period, body water was normal. Moreover, the composition data demonstrate that l-PPA induces weight loss via loss of lipid. These data confirm the observations of Arch *et al.* [2] who noted that mice treated over a 28 day period with dl-PPA exhibited significant reductions in carcass lipid. These data, however, demonstrate that l-PPA is the active isomer with regard to reduction of carcass lipid.

DISCUSSION

Wellman, Malpas and Wikler [13] demonstrated that rats treated with either 10, 20, or 40 mg/kg dl-PPA exhibited conditioned taste aversion and unconditioned suppression of water intake, outcomes that suggested that PPA reduced food intake and therefore body weight via some unspecified malaise mechanism. Their conclusions, derived from short-term consummatory tests, were not supported by the present experiments. Rats treated with 5, 10 or 20 mg/kg dl-PPA (twice daily) or with 20 mg/kg d-PPA or l-PPA exhibited either no change in feeding or a significant decline in feeding but either an increase or no change in water intake. This outcome parallels the dissociation between the effect of PPA feeding and drinking elicited by electrical stimulation of the lateral hypothalamus [6]. That the effect of PPA on feeding can be dissociated from that of PPA on water intake suggests that malaise is unlikely to explain PPA-induced anorexia and weight loss. Moreover, the difference in outcomes points to the importance of using chronic drug tests rather than more convenient short-term (e.g., 30 minute duration) consummatory tests.

The present study represents an addition to a large literature that documents the anorexic property of PPA [5]. Although as little as 5 mg/kg dl-PPA induces a reduction in feeding in short-term tests [8], the present data suggest that significant reductions in chronic feeding require at least 20 mg/kg (given twice per day) of dl-PPA. Moreover, the present study is the first to examine the relative potency of the PPA isomers on daily feeding. Rats treated (twice daily) with 20 mg/kg l-PPA exhibited a reduction in food intake two-fold greater than that induced by 20 mg/kg d-PPA. Over the counter (OTC) weight loss formulations presently contain the racemic mixture of PPA. Although it is tenuous to extrapolate from rat data to the human condition, it seems likely that a similar potency difference in the effect of the PPA isomers on human feeding and weight gain might be observed.

The primary purpose of the present experiment was to evaluate the working hypothesis that drug-induced BAT thermogenesis may play a role in the control of body weight. This hypothesis assumes that a drug such as PPA might reduce body weight, in part, by increasing energy expenditure via increasing BAT heat production and that this effect may be dissociable from the effect of PPA on feeding [12]. The outcomes of Experiment 2 illustrate the difficulty of evaluating this working hypothesis. Here, d-PPA and l-PPA induced com-

parable differential effects on feeding, IBAT thermogenesis and body weight gain Two-fold differences in isomer potency (l>d) were noted for each effect of PPA Considering just the contribution of feeding to weight gain, calculation of feeding efficiency ratios (cumulative weight gain/cumulative food intake) suggested that anorexia *per se* could account for the moderate weight loss exhibited by the 20 mg/kg d-PPA group but not for the weight loss exhibited by the l-PPA group That anorexia *per se* underestimated the predicted weight loss of the l-PPA group suggests that another factor contributed to the weight loss exhibited by this group The reduced feeding efficiency of the l-PPA group is compatible with the working hypothesis advanced above It is important to note that Experiment 2 also demonstrated that chronic d-PPA or l-PPA treatment does not result in tolerance to the acute effect of either isomer of PPA on IBAT thermogenesis Thus, BAT thermogenesis, although not directly implicated by these data, was not excluded as a potential factor Whether these factors are dissociable is unclear from the present data Reductions in carcass lipid and in body weight were clearly observed only in rats exhibiting both marked reductions in feeding *and* marked increases in IBAT thermogenesis To isolate the factors of BAT thermogenesis and anorexia requires studies in which PPA-induced weight loss is evaluated in rats (a) whose food intake is "clamped" at control levels using yoked intragastric food infusions, and (b) chronically treated with a beta-adrenergic antagonist that precludes induction of BAT thermogenesis by PPA

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