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Enantiomers of Phenylpropanolamine Suppress Food Intake in Hyperphagic Rats

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EISENBERG, M. S. AND T. J. MAHER. *Enantiomers of phenylpropanolamine suppress food intake in hyperphagic rats.* PHARMACOL BIOCHEM BEHAV **35**(4) 865–869, 1990.—Phenylpropanolamine (PPA, d,l-norephedrine), available in many over-the-counter nasal decongestants and appetite suppressants, is a racemic mixture of the enantiomers d- and l-norephedrine. The present study evaluates the effects of the individual PPA enantiomers on a variety of nondrug (food deprivation) and drug-induced hyperphagias (2-deoxyglucose and insulin). Racemic PPA has been shown to significantly suppress food intake in these hyperphagic models. Both l-norephedrine (5–50 mg/kg) and d-norephedrine (5–150 mg/kg), administered intraperitoneally, significantly suppressed feeding after a 4-hr fast during the dark cycle. During the light period, l-norephedrine (7.5, 10, 15 mg/kg) and d-norephedrine (75, 100, 150 mg/kg) significantly reduced food intake at the 1-hr and 3-hr time intervals in the 24-hr food deprivation-, insulin- and 2-deoxyglucose-induced hyperphagic models. Only 7.5 mg/kg l-norephedrine in the insulin-induced hyperphagia at 3 hr failed to significantly suppress feeding. These results indicate that each individual PPA enantiomer possesses the ability to suppress food intake in rats made hyperphagic by various stimuli.

Phenylpropanolamine d,l-Norephedrine d-Norephedrine l-Norephedrine Insulin 2-Deoxyglucose
Food deprivation Hyperphagia Appetite Food intake

PHENYLPROPANOLAMINE (PPA), a racemic mixture of the enantiomers d- and l-norephedrine, has been available in many over-the-counter nasal decongestants and appetite suppressants for over forty years (26). While the mechanism by which PPA suppresses appetite is poorly understood, its ability to reduce food intake and weight gain is well documented. A variety of studies have demonstrated the ability of PPA to reduce weight in rats (28,32), in normal and genetically obese mice (3) and in obese humans (2, 13, 25, 26, 29, 30). Additionally, numerous studies support the ability of PPA to suppress food intake in laboratory animals and man (9, 10, 12, 16, 23, 31, 32). Food intake was significantly reduced by PPA in a dose-related fashion in rats maintained on a 20-hour feeding, 4-hour fasting schedule (9). In other studies feeding was restricted to 1 hour (31), 4 hours (16) or 6 hours (10) of a 24-hour period resulting in dose-related decreases in food intake after PPA. When administered chronically twice a day for twelve days, 20 mg/kg PPA significantly reduced food intake (30). Our laboratory has previously reported the ability of PPA to significantly decrease food intake in a dose-related fashion in rats made hyperphagic by 24-hour food deprivation (FD), or after the administration of 2-deoxyglucose (2-DG) or insulin (23).

Recent reports have attempted to alleviate the confusion between the pharmacological profiles of PPA, its stereoisomer d-norpseudoephedrine (cathine), and its individual enantiomers. While PPA failed to stimulate locomotor activity in rats, d-norpseudoephedrine greatly increased locomotion (9). Zelger and Carlini (34,35), who erroneously identify cathine as PPA, also observed increased locomotion following d-norpseudoephedrine. In addition, a single enantiomer of PPA, l-norephedrine may have been mistaken for PPA in studies reporting severe hypertension from an Australian preparation, Trimolets® (14,15). Moya-Huff and co-workers (22) recently suggested that Trimolets® may have contained the pure l-norephedrine enantiomer, since the package lists the active ingredient as "D-Phenylpropanolamine" (the equivalent of l-norephedrine). Additionally, Moya-Huff *et al.* reported l-norephedrine to be a more potent vasopressor than PPA, while the d-norephedrine enantiomer was relatively inactive when given in large doses intravenously (22).

The purpose of the present experiment was to further characterize the effects of the enantiomers of PPA on food intake. When rats were trained to eat during a three-hour feeding period, l-norephedrine significantly decreased food intake over a one-hour test period (1). Since Wellman and Sellers (32) also reported that both individual enantiomers suppress food intake when administered chronically at 20 mg/kg, and Blosser *et al.* (5) demonstrated that l-norephedrine was nearly five times more potent in reducing food intake than d-norephedrine over a three-hour test period, we initially investigated the dose-dependent effects of d- and l-norephedrine in a food-deprived rat model. In order to further explore the appetite suppressant properties of the PPA enantiomers, we also determined their anorectic activity in rats made hyperphagic (during the light period when they normally do not

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eat) by 24-hour FD, or by the administration of insulin or 2-DG.

METHOD

Animals

Male Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, MA) obtained at 125–150 grams were individually housed in suspended wire mesh cages with food and tap water available ad lib. The animals were acclimated to our climate-controlled animal facility for at least one week prior to experimentation. Animals were retired from the study when reaching 300 grams.

Food Intake During Dark Cycle

Upon arrival, animals were maintained on a reversed lighting schedule (dark cycle 1100 to 2300 hr) and given access to a prepared diet composed of 50% ground rat chow (Ralston Purina Rodent Laboratory Chow No. 5001-meal form) and 50% of a 4% nutrient agar (Teklad Diets) solution (weight/volume). The agar-based chow ensured greater accuracy for the measurement of the amount of food consumed during the dark period and was sufficient for maintaining normal growth and health of the rats as compared to standard pellet chow (9).

On the day of the experiment, rats were fasted for 4 hr at the onset of the dark cycle. After the 4-hr fasting period groups of at least 5 rats were injected intraperitoneally (IP) with saline (control), d-norephedrine HCl 5–150 mg/kg (Aldrich) or l-norephedrine HCl 5–50 mg/kg (Roehr). Each group received only one dose of a particular drug in a volume of 1 ml/kg body weight. Thirty minutes later, animals were allowed free access to preweighed dishes of the prepared diet. The amount of food eaten in one hour was determined to the nearest 0.01 gram and any spillage was caught on clean paper and returned to the feeding dish prior to weighing. A dull 25-watt red light allowed the investigators to see in the dark. Rats were allowed free access to the prepared diet and water for 4 days prior to subsequent experimentation.

The data are presented as food intake expressed in grams vs. the dose. Regression lines were calculated by the method of least squares and AD_{50} (anorectic dose required to suppress food intake by 50%) values compared by the testing of overlap of 95% confidence limits (27). All data were analyzed by a one-way ANOVA and a Newman-Keuls test for the comparison of drug dosage groups to saline controls. The minimum significance level was set at $p<0.05$.

Daytime Feeding After Hyperphagic Stimuli

Upon arrival, rats had free access to water and food (Ralston Purina Laboratory Chow No. 5001-pellet form placed in a cup on the cage floor) and were maintained on 12-hr light/12-hr dark cycle (lights on from 0700 to 1900 hr). Animals were handled and injected IP with saline for three days to habituate them to the experimental procedure.

Food intake was stimulated 3 hr after the beginning of the light period by the subcutaneous (SC) injection of 2-DG (800 mg/kg, Sigma Chemical Company) or insulin (100 U/kg, Eli Lilly and Company Regular Iletin I®), or by 24-hr FD in groups of at least 5 rats. Immediately after injection preweighed dishes of food were placed on the cage floor and food intake was measured to the nearest 0.01 gram at 1 hr and 3 hr after food presentation. Any spillage was caught on clean paper and replaced in the dishes prior to weighing. Saline, d-norephedrine (75, 100, 150 mg/kg) or l-norephedrine (7.5, 10, 15 mg/kg) were injected IP 30 minutes prior to the hyperphagic stimuli. All injections were given in a volume of 1 ml/kg and each group was compared to the 0 mg/kg group which received saline. Control animals were classified as those animals which were not fasted and/or had received the appropriate vehicle.

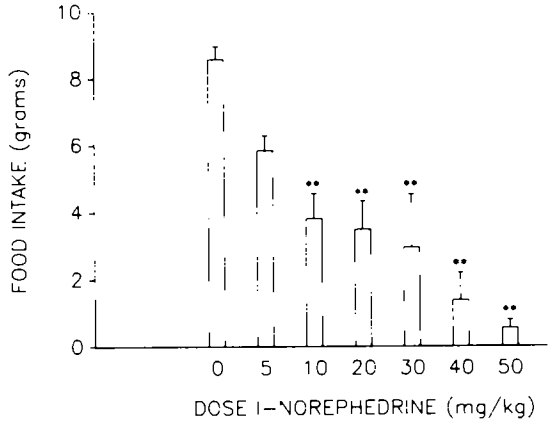

FIG. 1. Effect of l-norephedrine on food intake in rats food-deprived for four hours at the beginning of the dark cycle. Groups of at least 5 male Sprague-Dawley rats were administered saline (0 mg/kg) or l-norephedrine (5–50 mg/kg) IP following a four-hour fast. Thirty minutes later food intake was measured during the following hour to the nearest 0.01 gram and expressed as the mean ± SEM. **Significantly different from controls ($p<0.01$) by a one-way ANOVA and Newman-Keuls test.

Results are expressed as food intake (grams) ± S.E.M. for each hyperphagic stimulus. All data were analyzed by a one-way ANOVA and Newman-Keuls test for comparing differences between each dosage group and the appropriate control. The minimum significance level was set at $p<0.05$.

RESULTS

Food Intake During Dark Cycle

l-Norephedrine produced a dose-dependent suppression of food intake (Fig. 1), while d-norephedrine was less potent over a wider dosage range (Fig. 2). Significant ($p<0.01$) inhibition of food intake was evident with all doses of l-norephedrine tested except the lowest dose of 5 mg/kg. d-Norephedrine significantly ($p<0.05$) inhibited feeding at 15 and 25 mg/kg and produced a highly significant ($p<0.01$) reduction in food intake at all other doses tested. Only 5 mg/kg d-norephedrine failed to produce a statistically significant suppression of food intake. l-Norephedrine was significantly ($p<0.05$) more potent than d-norephedrine producing AD_{50} values of 10.1 ± 1.7 mg/kg ($\pm$95% confidence limit) and 58.7 ± 2.0 mg/kg, respectively.

Daytime Feeding After Hyperphagic Stimuli

Twenty-four hours of FD and the SC injection of 2-DG or insulin significantly (at least $p<0.05$) increased food intake 1 and 3 hr after food presentation. At the 1-hr time interval, there was a significant ($p<0.01$) 1734% and 726% increase and a significant ($p<0.05$) 184% increase in food intake for 24-hr FD, 2-DG and insulin, respectively, when compared to control animals (Figs. 3 and 5). There was also a significant ($p<0.01$) increase in food intake of 1100%, 333% and 580% for 24-hr FD, 2-DG and insulin, respectively, when compared to control animals 3 hr after food presentation (Figs. 4 and 6).

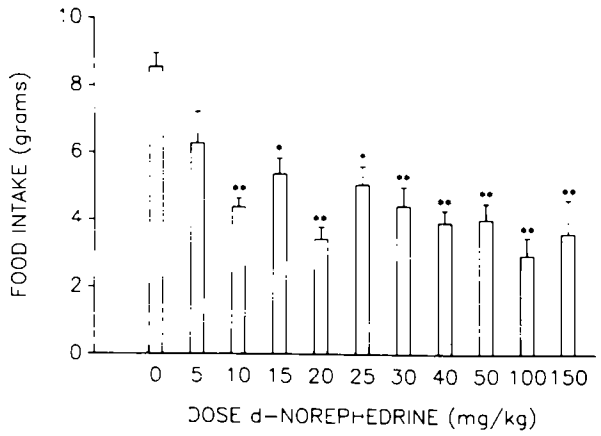

FIG. 2. Effect of d-norephedrine on food intake in rats food-deprived for four hours at the beginning of the dark cycle. Groups of at least 5 male Sprague-Dawley rats were administered saline (0 mg/kg) or d-norephedrine (5–150 mg/kg) IP following a four-hour fast. Thirty minutes later food intake was measured during the following hour to the nearest 0.01 gram and expressed as the mean ± SEM. *Significantly different from controls ($p<0.05$); **Significantly different from controls ($p<0.01$) by a one-way ANOVA and Newman-Keuls test.

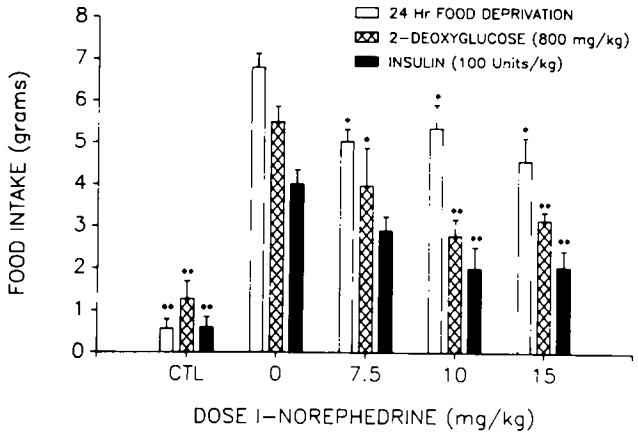

FIG. 4. Three-hour determination of the effect of l-norephedrine on 24-hour food deprivation-, 2-deoxyglucose- and insulin-induced eating. Rats were administered l-norephedrine (7.5, 10 and 15 mg/kg) 30 minutes prior to the above hyperphagic stimuli. Control (CTL) animals received the appropriate vehicle only by the appropriate route of administration. Food intake was then determined 3 hr later and expressed as grams eaten ± SEM. *$p<0.05$, **$p<0.01$, significantly different than the respective 0 mg/kg l-norephedrine group by a one-way ANOVA and Newman-Keuls test.

l-Norephedrine, 7.5, 10 and 15 mg/kg significantly ($p<0.05$) inhibited feeding induced by insulin, by 83%, 90% and 95%, respectively, when compared to the 0 mg/kg saline-treated group 1 hr after food presentation (Fig. 3). At the 3-hr time interval (Fig. 4), the 10 and 15 mg/kg doses of l-norephedrine significantly ($p<0.01$) inhibited food intake by 50% and 49%, respectively, while 7.5 mg/kg failed to significantly reduce feeding. 2-Deoxyglucose-induced eating was significantly ($p<0.01$) inhibited at the 1-hr measurement by 84%, 90% and 90% by pretreatment with 7.5, 10 and 15 mg/kg l-norephedrine, respectively (Fig. 3). The 7.5 mg/kg dose of l-norephedrine significantly ($p<0.05$) inhibited

FIG. 3. One-hour determination of the effect of l-norephedrine on 24-hour food deprivation-, 2-deoxyglucose- and insulin-induced eating. Rats were administered l-norephedrine (7.5, 10 and 15 mg/kg) 30 minutes prior to the above hyperphagic stimuli. Control (CTL) animals received the appropriate vehicle only by the appropriate route of administration. Food intake was then determined 1 hr later and expressed as grams eaten ± SEM. *$p<0.05$, **$p<0.01$, significantly different than the respective 0 mg/kg l-norephedrine group by a one-way ANOVA and Newman-Keuls test.

feeding induced by 2-DG at 3 hr by 27%, while the 10 and 15 mg/kg doses significantly ($p<0.01$) decreased food intake by 49% and 43%, respectively (Fig. 4). Eating induced by 24-hr FD was significantly ($p<0.05$) decreased at 1 hr by 34% from 7.5 mg/kg l-norephedrine and significantly ($p<0.01$) reduced by 54% and 48% with the 10 and 15 mg/kg doses, respectively (Fig. 3). l-Norephedrine also significantly ($p<0.05$) suppressed 24-hr FD-induced feeding at the 3-hr time interval by 26%, 21% and 33% for the 7.5, 10 and 15 mg/kg doses, respectively.

The 75, 100 and 150 mg/kg doses of d-norephedrine significantly ($p<0.01$) inhibited 24-hr FD-induced feeding at the 1-hr measurement by 69%, 67% and 95%, respectively (Fig. 5), and by 34%, 45% and 78%, respectively, at the 3-hr time interval (Fig. 6). 2-Deoxyglucose-induced eating was also significantly ($p<0.01$) reduced by the 75, 100, and 150 mg/kg doses of d-norephedrine at 1 hr by 73%, 73% and 96%, respectively (Fig. 5), and by 79%, 83% and 94% respectively, at the 3-hr measurement (Fig. 6). A significant ($p<0.05$) inhibition of insulin-induced feeding was observed at 1 hr for the 75, 100 and 150 mg/kg doses of d-norephedrine (84%, 95% and 96%, respectively) as shown in Fig. 5. At the 3-hr food intake measurement the 75, 100 and 150 mg/kg doses of d-norephedrine significantly ($p<0.01$) inhibited insulin-induced feeding by 52%, 76% and 86%, respectively (Fig. 6).

DISCUSSION

The hyperphagic treatments employed in this study are believed to induce eating by a variety of mechanisms. Insulin-induced hyperphagias have been reported to be associated with striatal dopamine activity (19,21). 2-Deoxyglucose- and FD-induced hyperphagias have been shown to be sensitive to both opioid and dopaminergic blockade (6, 7, 11, 17, 18, 20, 24), while insulin-induced eating may be less sensitive to opioid receptor blockade (17,24). Phenylpropanolamine has been previously reported to inhibit these types of hyperphagias, however, its exact mechanism(s) of appetite suppression remains unclear (23).

In the present study, the PPA enantiomers were both found to

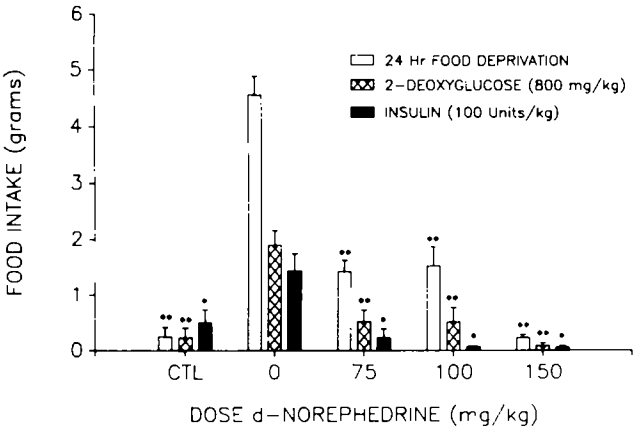

FIG. 5. One-hour determination of the effect of d-norephedrine on 24-hour food deprivation-, 2-deoxyglucose- and insulin-induced eating. Rats were administered d-norephedrine (75, 100 and 150 mg/kg) 30 minutes prior to the above hyperphagic stimuli. Control (CTL) animals received the appropriate vehicle only by the appropriate route of administration. Food intake was then determined 1 hr later and expressed as grams eaten ± SEM. $*p<0.05$, $**p<0.01$, significantly different than the respective 0 mg/kg d-norephedrine group by a one-way ANOVA and Newman-Keuls test.

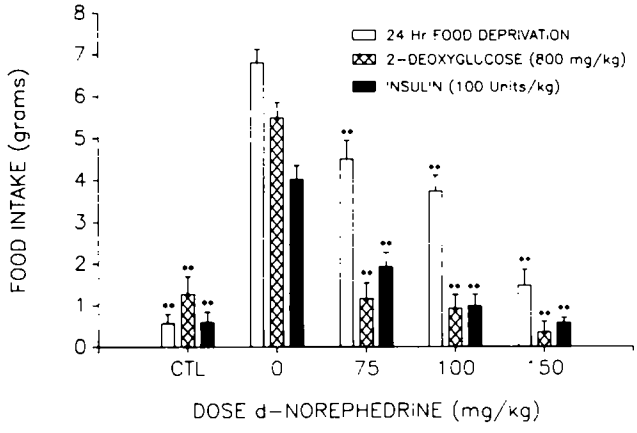

FIG. 6. Three-hour determination of the effect of d-norephedrine on 24-hour food deprivation-, 2-deoxyglucose- and insulin-induced eating. Rats were administered d-norephedrine (75, 100 and 150 mg/kg) 30 minutes prior to the above hyperphagic stimuli. Control (CTL) animals received the appropriate vehicle only by the appropriate route of administration. Food intake was then determined 3 hr later and expressed as grams eaten ± SEM. $**p<0.01$, significantly different than the respective 0 mg/kg d-norephedrine group by a one-way ANOVA and Newman-Keuls test.

possess the ability to suppress food intake in rats made hyperphagic during the daytime, a time when rats normally do not eat. Both enantiomers effectively reduced 2-DG-, 24-hour FD- and insulin-induced eating at 1 and 3 hours after application of the hyperphagic stimuli. These results suggest that the individual PPA enantiomers, like PPA itself, may suppress appetite by a variety of neurochemical mechanisms. In addition, l-norephedrine was nine times more potent than d-norephedrine at the 1-hour time interval and five times more potent at the 3-hour measurement (based on the entire average of the dosage range of each enantiomer in combination with all four hyperphagic treatments studied), indicating that d-norephedrine produced a longer lasting inhibition of experimentally induced feeding. This difference in potency and duration of action may possibly be attributable to differences in the pharmacodynamic activities and/or pharmacokinetic profiles of the individual PPA enantiomers. Moya-Huff *et al.* (22) have previously demonstrated the pharmacodynamic differences between these enantiomers in the cardiovascular system of the rat. Although no studies to date exist which have characterized differences between the pharmacokinetic profiles of these enantiomers, numerous studies exist which document significant pharmacokinetic differences between enantiomeric compounds (4, 8, 33).

Both enantiomers are capable of inhibiting food intake during the dark period. When comparing the AD_{50} value for racemic PPA, previously reported to be 18 mg/kg (9), to its individual enantiomers, PPA is 4.5 times more potent than d-norephedrine ($AD_{50} = 58.7$ mg/kg), while l-norephedrine ($AD_{50} = 10.1$ mg/kg) is almost twice as potent as PPA. These results demonstrate that the individual PPA enantiomers are capable of suppressing both nighttime and daytime food intake in rats, as well as confirming the potency series previously found by Moya-Huff and co-workers (22) regarding the cardiovascular profiles of PPA and its enantiomers.

The effectiveness of racemic PPA as an appetite suppressant may result from an action of both component enantiomers. While l-norephedrine may be more potent and possibly act to initiate the anorexic activity, d-norephedrine may be more responsible for the favorable duration of action observed with racemic PPA. Further study of the time-course of the pharmacodynamic activities and pharmacokinetic profiles of these individual enantiomers will be required to better understand PPA's anorectic activity.

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