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Inhibition of Feeding and Hoarding Behaviors by Phenylpropanolamine in the Adult Rat

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WELLMAN, P. J. AND A. LEVY. *Inhibition of feeding and hoarding behaviors by phenylpropanolamine in the adult rat.* PHARMACOL BIOCHEM BEHAV **29**(1) 79–81, 1988.—The mechanism by which phenylpropanolamine (PPA) reduces feeding and body lipid is unknown. To determine if malaise associated with PPA treatment mediates its anorexic action, the present study compared the actions of PPA on feeding and hoarding behavior with that of lithium chloride at dose levels that induce comparable conditioned taste aversions. Adult male rats were injected (IP) 30 minutes prior to a test of feeding and hoarding behavior with either 0.9% saline, 32 mg/kg lithium chloride or with 10 mg/kg, 20 mg/kg or 40 mg/kg PPA. Although 32 mg/kg lithium chloride was without effect on either feeding or hoarding behaviors, PPA significantly suppressed both behaviors. These results do not support the notion that malaise is a critical aspect of the anorexic property of PPA and that hoarding behavior may represent a sensitive index of anorexic drug potency.

Phenylpropanolamine (PPA) Lithium chloride Feeding Hoarding Malaise

CHRONIC treatment with phenylpropanolamine (PPA), a phenethylamine, induces anorexia [6,9] and weight loss [14], yet the mechanism of action of this drug remains undisclosed [8]. A variety of mechanisms have been advanced to account for the anorexic action of PPA. These include an action of PPA on a hypothalamic satiety mechanism [5], an action on gastric emptying [12] and finally, a non-specific malaise action of PPA [13]. The latter mechanism was proposed to account for the observations that PPA induces conditioned saccharin aversion and suppresses drinking. Yet, the mere demonstration that a substance will serve as an unconditioned stimulus in the taste aversion paradigm is not conclusive evidence for an aversive action of that substance. Amphetamine, for example, will produce a conditioned saccharin aversion yet amphetamine is readily self-administered. The latter reinforcing effect of amphetamine is inconsistent with its effects on conditioned saccharin aversion [4].

Schallert, Pendergrass and Farrar [11] suggested that a comparison of drug effects on feeding and "hoarding-like" behavior (the accumulation of pellets by rats) might offer a means to dissociate illness effects from satiety effects. Briefly, this report noted that lithium chloride, at doses that suppressed feeding also suppressed hoarding-like behavior, whereas cholecystokinin suppressed feeding but not hoarding-like behavior. Presumably, a suppression of both feeding as well as hoarding would indicate an illness-mediated basis for drug-induced anorexia. To determine if a similar dissociation would be obtained for phenylpropanolamine, the present study examined the action of various doses of PPA (10, 20 and 40 mg/kg) on hoarding behavior and feeding, using the procedures of Blundell [1]. Moreover, an additional group treated with 32 mg/kg lithium chloride was included so as to compare the actions of various doses of PPA on hoarding and feeding with that of a dose of lithium chloride that induces conditioned taste aversion [2,7]. Were an aversive drug action, as assessed by the conditioned taste aversion paradigm, to be an important factor in PPA-induced anorexia, then comparable changes in feeding and hoarding behaviors ought to be observed in the lithium chloride and 40 mg/kg PPA groups of the present study.

METHOD

Animals

The animals were 40 male Sprague-Dawley albino rats (obtained from Timco Farms, Houston, TX) weighing between 250–297 grams at the beginning of the experiment. The rats were housed individually in plastic rodent cages in a colony room maintained at a constant temperature (23±1 degrees C) under a 12 hr/12 hr light/dark illumination schedule (lights *on* at 0800 hours). Each rat cage was equipped with a removable wire floor positioned over a paper pad. The rats were given access to Teklad Rat & Mouse Diet and tap water as described in the schedules below.

Drugs

Phenylpropanolamine solutions (10, 20 and 40 mg/ml) were prepared prior to injection by dissolving phenylpropanolamine hydrochloride (d, l-norephedrine: H. Reisman Corporation, Lot Number 3E37) into sterile distilled water. A lithium chloride solution (32 mg/ml) was similarly

prepared using lithium chloride (Fischer Chemicals). All solutions were prepared as the weight of base and salt per volume.

Procedure

The rats were deprived of food for 15 hours prior to each of 6 daily test sessions. Each session began at 1100 hr and consisted of a measurement of hoarding behavior at 30 minutes and feeding behavior at 60 minutes. A cardboard insert positioned parallel to the cage front served to separate the front and rear halves of each test cage. A 3 inch × 4 inch opening in each insert formed a doorway through which a rat could enter and exit the front of the test cage. At the start of each test session, 20 pellets (of a known weight) were placed on the wire floor in the front of each test cage. Hoarding scores were computed, at 30 minutes after the start of the test session, by noting the number of pellets (range=0 to 20) moved by each rat to the rear of the test cage. Food pellets (as well as spillage collected on a pad beneath the wire floor of each cage) were removed from each cage at 60 minutes after the start of the session. Food intakes were recorded to the nearest 0.1 gram. A handful of pellets was then placed into each cage for 8 hours after the end of the feeding test. Food was then removed from each cage at 2000 hr. Water was continuously available throughout the study.

On Day 7, the procedures were as above except that separate groups of rats, matched on the basis of feeding and hoarding scores, were treated (IP) with either 0.9% saline, 32 mg/kg lithium chloride or with either 10 mg/kg, 20 mg/kg or 40 mg/kg PPA 30 minutes prior to the start of the hoarding test.

RESULTS

Figure 1 depicts changes in mean group hoarding behavior and feeding behavior induced by the various treatments of this experiment. Rats treated with saline hoarded an average of 15 pellets during the 30 minute hoarding test interval and consumed an average of 10 grams of pellets during the 60 minute feeding test interval. Treatment with lithium chloride at 32 mg/kg did not significantly reduce either hoarding behavior or feeding behavior, $t(14)=0.47$ and 1.8, $p<0.99$ and 0.18, respectively) relative to the saline treatment control group. In contrast, separate analyses of variance revealed that PPA significantly reduced both hoarding behavior and feeding behavior, $F(3,28)=13.4$ and 26.8, respectively, $p<0.001$. Subsequent *a posteriori* between-group *t*-tests using Tukey's multiple comparison procedure revealed that PPA dose levels of 20 mg/kg and 40 mg/kg significantly reduced hoarding behavior relative to the saline control group ($p<0.01$) whereas 10 mg/kg PPA was without significant effect on hoarding behavior. There were no significant differences between 20 mg/kg and 40 mg/kg PPA dose levels on hoarding behavior. Subsequent *a posteriori* comparisons of feeding behavior revealed a significant dose-dependent suppression of feeding behavior by PPA. All comparisons between each drug group and the saline group were significant ($p<0.01$) except that between the 20 mg/kg PPA and 40 mg/kg PPA groups.

DISCUSSION

Phenylpropanolamine, at dose levels ranging from 10 to 40 mg/kg, significantly reduced food intake induced by moderate food deprivation in rats. Moreover, hoarding behavior was significantly reduced by the 20 mg/kg and 40 mg/kg dose

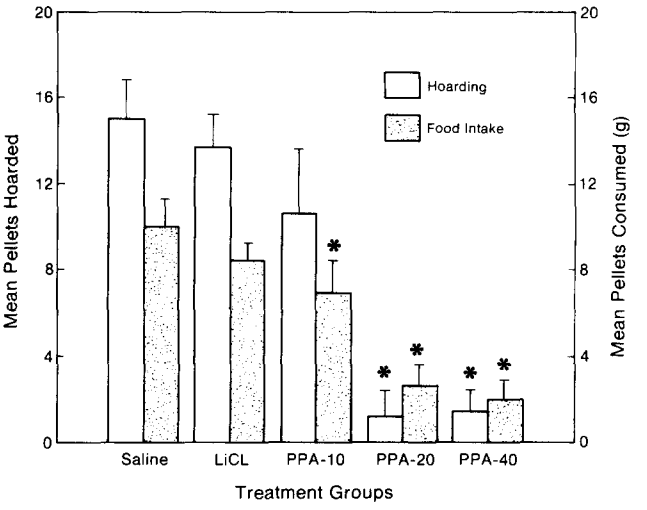

FIG. 1. Mean group hoarding behavior (left panel: open bars) and mean group hoarding scores (right panel closed bars) for rats treated on Day 7 with either saline (s), 32 mg/kg lithium chloride (LiCl), 10 mg/kg, 20 mg/kg or 40 mg/kg PPA. The vertical bar above each bar represents the S.E.M. for each group. Each asterisk (*) represents a significant comparison between a drug group and the saline group ($p<0.01$).

levels of PPA. Although the 10 mg/kg PPA dose level did not significantly reduce hoarding behavior, this dose did significantly reduce feeding behavior during a 60 minute test session. The reasons for the lack of correspondence between the action of 10 mg/kg PPA on feeding and hoarding behavior may relate to different thresholds of drug action for the two behaviors as well as to the different intervals of measurement used in the present experiment for these two dependent variables. Whereas hoarding was assessed during a 30 minute period, the test interval for feeding behavior was 60 minutes in length. Nonetheless, PPA clearly suppressed both feeding and hoarding behaviors at above threshold dose levels.

Unexpectedly, lithium chloride, at a dose of 32 mg/kg (0.75 meq/kg) was without effect on either feeding or hoarding behavior in the present study. Our interest in this lithium chloride dose stemmed from the observation that 32 mg/kg lithium chloride would support a conditioned taste aversion comparable in magnitude to that produced by 40 mg/kg PPA (compare [2,7] with [13]). If an aversive drug effect was the factor that produced the suppression of feeding noted in rats after PPA treatment, then lithium chloride would be expected to produce a reduction in hoarding behavior and feeding comparable to that observed in a group of rats treated with 40 mg/kg PPA. Yet, no reduction in either hoarding behavior or feeding after lithium chloride treatment at 32 mg/kg was observed in the present study. It is likely, however, that higher doses of lithium chloride would suppress feeding behavior and perhaps hoarding behavior. Domjan [3], for example, noted that lithium chloride at a dose of 127.2 mg/kg (3.0 meq/kg) suppressed intake of novel solutions (e.g., saccharin, casein) but that even this dose of lithium chloride was without effect on intake of familiar test solutions. In the present study, a familiar pellet diet was offered to the rats during hoarding and feeding tests; thus lithium chloride doses greater than 3.0 meq/kg might be required to suppress feeding. The present data again make it

clear that the ability of a compound to produce conditioned taste aversion does not warrant the assumption that the compound will produce anorexia. Moreover, as Gamzu *et al.* [4] note, the benzodiazepines produce conditioned taste aversion yet the benzodiazepines increase rather than decrease feeding.

In contrast to the expectation that suppression of feeding and hoarding behavior might be useful as an index of aversive drug actions, the present study suggests that hoarding behavior may be a useful index of anorexic potency. Indeed, a survey of the literature suggests that a variety of drugs, including amphetamine and fenfluramine, reduce hoarding behavior at dose levels that induce anorexia [1,10]. The present study demonstrates a similar correspondence for the anorexigen phenylpropanolamine and suggests that the latter drug suppresses feeding and hoarding behavior via a non-aversive mechanism unrelated to malaise or illness.

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