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Effects of Neuropeptide Y on Food-Reinforced Behavior in Satiated Rats

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JEWETT, D. C., J. CLEARY, A. S. LEVINE, D. W. SCHAAL AND T. THOMPSON. *Effects of neuropeptide Y on food-reinforced behavior in satiated rats.* PHARMACOL BIOCHEM BEHAV **42**(2) 207–212, 1992.—The effect of NPY on behavior and food intake of food-satiated rats was examined under three different food availability conditions. Food was available during times when rats normally do not eat under either a fixed-ratio or fixed-interval reinforcement schedule, or it was freely available in the bottom of the cage (FF). Forty responses were required for each 45-mg food pellet under the ratio schedule (FR 40) and for the first response to occur 15 s after the previous reinforcement under the interval schedule (FI 15″). NPY (5 μg) significantly increased food intake under all conditions and increased food-reinforced responses under the FR and FI schedules. NPY's effect on food intake was greatest when food was freely available and least for rats working under the schedule requiring the most effort (FR 40). Food intake peaked after 3 days under repeated daily administration of NPY. Under free food access and under the fixed-interval schedule, eating and/or responding occurred almost immediately following the onset of the initial 4-h session under NPY. However, during the first session following NPY administration under the FR, rats emitted few responses during the first 2 h of the session. The onset of robust responding under the FR schedule began earlier with each successive daily administration of NPY. These data show NPY substantially increases food-maintained behavior and is a potent inducer of food intake even under conditions where considerable effort is required to obtain food. Further, the conditions under which food is made available can dramatically alter NPY's effect on the temporal pattern of food-maintained responding, feeding, and latency to eat.

Neuropeptide Y Food-reinforced behavior Feeding Rats

CENTRAL administration of neuropeptide Y (NPY) produces a large and reliable increase in feeding in several species (3,13,17,21,23,28). The effects of NPY are so strong that feeding occurs when rats ordinarily do not eat, in animals fully satiated by previous feeding, and even when the drug is injected several hours before food is made available (17,22,28). Results such as these suggest NPY might participate in the control of natural feeding and be an important neuroregulator of hunger. In addition to feeding, centrally administered NPY affects several other behavioral phenomena, including sedation (31), sex (4), memory (6), pituitary hormone release (11), autonomic function (9), cardiovascular function (2), and neurotransmitter synthesis and release (24). Information concerning NPY's neurochemical mechanism of action has grown rapidly, with advances in the identification and differentiation of specific receptor types (26,31) and mapping of NPY-active brain areas (18,19).

Most previous studies investigating NPY-induced feeding have used a procedure in which food is freely available, usually placed on the bottom of the cage or in a hopper in generous amounts. This procedure has produced valuable information about NPY-induced feeding, but measurement of the quantity of food eaten does not allow full assessment of the strength of the feeding response, changes in the reinforcing value or efficacy of food, or motivation to eat. Eating patterns and amount eaten can vary dramatically when conditions of access or the size or quality of the food is varied. Effects on the quantity of food eaten due to changes in environmental conditions can be traced to research on the feeding patterns of rats with lesions of the ventromedial hypothalamus (VMH). Although VMH-lesioned rats eat massive quantities of freely available food, their intake decreases disproportionately, relative to unlesioned rats, when quinine is added to their food (29). Further, when food is obtained by lever pressing, VMH-lesioned rats work less for food than unlesioned animals (30). Similar characteristics have been identified in obese humans. In one study, when obese humans were compared to nonobese controls, the obese subjects drank less of a quinine-adulterated milkshake than the nonobese ones, and fewer obese people ate nuts when they had to remove shells, while

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the presence of a shell did not affect eating behavior of nonobese controls (25).

An additional consideration in evaluating NPY's effect on feeding under varying conditions of access is that the food itself may serve several functions in a feeding situation. Food can evoke feeding simply by its presentation, and the sight and smell of food can alter the amount eaten. Food can also reinforce behavior that produces it and thus is affected by operations typically affecting reinforcement, such as conditions of availability (5). Deprivation, that is, the absence of food for a period of time, increases subsequent eating and may be a useful way to increase motivation (10,12). Drugs that increase or reduce feeding could do so by modifying any of these functions. For example, one explanation of NPY's effect on feeding is that it enhances the value of food, or increases the motivation to eat, in a way similar to that produced by changes in the deprivation level. On the other hand, NPY may simply enhance the stimulus properties (sight and smell) associated with the presence of food in the chamber, thus promoting eating. The current study allows an initial quantitative assessment of NPY's effects on both feeding and food-maintained behavior under three conditions of food availability. Parallels between NPY administration and other manipulations that enhance feeding, such as VMH lesions, are also discussed.

METHOD

Subjects

Twenty-one male Sprague-Dawley rats (Biolab, St. Paul, MN), 90-days old and 250–275 g at the beginning of the experiment, were housed in individual cages and maintained on a 12 L:12 D cycle (lights on at 1900). Food pellets available in the operant chamber and home cage were of identical composition (#F0021, Bioserv Holton Industries, Frenchtown, NJ). Rat chow was also available in the home cage during some portions of the procedure (Laboratory Rat Chow, Ralston-Purina, St. Louis, MO). Water was available at all times, except during brief periods of lever-press training.

Apparatus

Experimental sessions were conducted in three standard two-lever operant chambers (Model E10-10, Coulbourn Instruments, Inc., Lehigh Valley, PA) equipped with feeders that could deliver 45-mg food pellets and dippers with which 0.8 ml water could be delivered. The chambers were enclosed in sound-attenuating cubicles in a room with white noise present continuously. Electromechanical control and data recording equipment was located in an adjacent room. Home cages were standard stainless steel, equipped with water bottles and spouts.

Surgery

Rats were surgically implanted with cannulae prior to behavioral training. Rats were anesthetized with sodium pentobarbital (40 mg/kg, IP) and fitted with a 20-ga guide cannula terminating in the right lateral ventricle. Stereotaxic coordinates with an incisor bar set 3 mm below the interaural line were 1.5 mm lateral, 1.0 mm posterior, and 3.5 mm below the surface of the skull. Rats were allowed to recover for 7 days before behavioral training began. Coordinates were verified by injection of dye into the cannula and subsequent sectioning through the lateral ventricle.

Drug Preparation and Administration

NPY (Peninsula Laboratories, Belmont, CA) was diluted with 0.9% saline and stored in sealed plastic containers at −20°C. It was thawed and slowly injected, with a microsyringe, into the right lateral ventricle (ICV) at room temperature in 5-μl volumes. The dose of NPY (5.0 μg) has previously been shown to substantially increase feeding [e.g., (3,17)]. Vehicle injections were 5 μl saline, administered ICV.

Procedures

Fixed-ratio schedule of reinforcement. Following the surgery recovery period, body weights of six rats were slowly reduced to 80% of their free-feeding levels. Rats were then trained to press both levers by the method of successive approximations. Responses on the left lever always produced food (45-mg pellet), while responses on the right lever always produced water dipper presentation (0.8 ml). Water-reinforced responding was trained under 22 h water deprivation. Initially, one response on a lever produced reinforcement. This response requirement was slowly increased until 40 responses on the left lever were required to produce a food pellet (FR 40) and 5 responses on the right lever were required to produce water (FR 5). Thus, the terminal schedule for this group was a concurrent fixed-ratio 40 for food, fixed-ratio 5 for water, (con FR 40, FR 5). Session durations were increased from 30 min to 4 h. Availability of water ensured feeding levels would not be unduly influenced by water deprivation during the 4-h session.

After 20–40 sessions of training under these conditions, rats' body weights were returned to their free-feeding levels by providing food and water ad lib in home cages. Under food and water satiation, responding was minimal, and when no obvious trends in lever-pressing were observed, rats were injected ICV with 0.9% saline (5 μl). For the next five daily sessions, rats received ICV injections of 5 μg NPY, in 5 μl solution, 1 h after the light cycle began. Immediately after injection, rats were placed in the operant chamber and the session began. Food- and water-reinforced lever presses were recorded every 30 min for the entire 4-h session. In addition, food and water reinforcers were recorded for the entire session.

Fixed-interval schedule of reinforcement. A second group of rats (n = 5) was housed, maintained, implanted with cannulae, and initially trained to lever press exactly as described above for subjects in the group responding under FR conditions. For these rats, the food reinforcement schedule associated with the left lever was a fixed interval 15 s (FI 15″). This reinforcement schedule allows response rates to vary considerably without substantially affecting the quantity of reinforcers delivered or their temporal distribution within the session. Under this schedule, reinforcers were delivered immediately after the first lever press to occur after 15 s had elapsed since the last reinforcer delivery. Intervals were initially short (e.g., 2 s) and were gradually increased to a terminal value of 15 s. Water reinforcement was available under a FR 5 as described above. Thus, the terminal schedule for this group was concurrent FI 15″, FR 5. Session duration was gradually increased to 4 h.

Freely available food. Rats in this group (n = 6) were implanted with cannula in the right lateral ventricle as described above. Following recovery, rats initially received 0.9% saline (5 μl) ICV for two sessions. For the next five sessions, rats received 5 μg of NPY in 5 μl of solution each day. Injections occurred immediately before the 4-h session and no more than

2 h after the onset of the light portion of the 12 L:12 D cycle. After injection, all rats were returned to their home cages and given free access to 1-g food pellets, identical in composition to those used as reinforcers under the schedules described above. Water was available ad lib. The amount of food consumed was recorded each 30 min for 4 h by weighing the remaining food and spillage.

Statistics

Means for responses per session, reinforcers per session, and total grams consumed were compared across drug condition or across days of successive injection of NPY using the nonparametric Wilcoxon sign-rank test. All significant mean differences are identified in the figures and in the figure captions.

RESULTS

Initial NPY administration produced large increases in food pellets consumed, compared to saline administration,

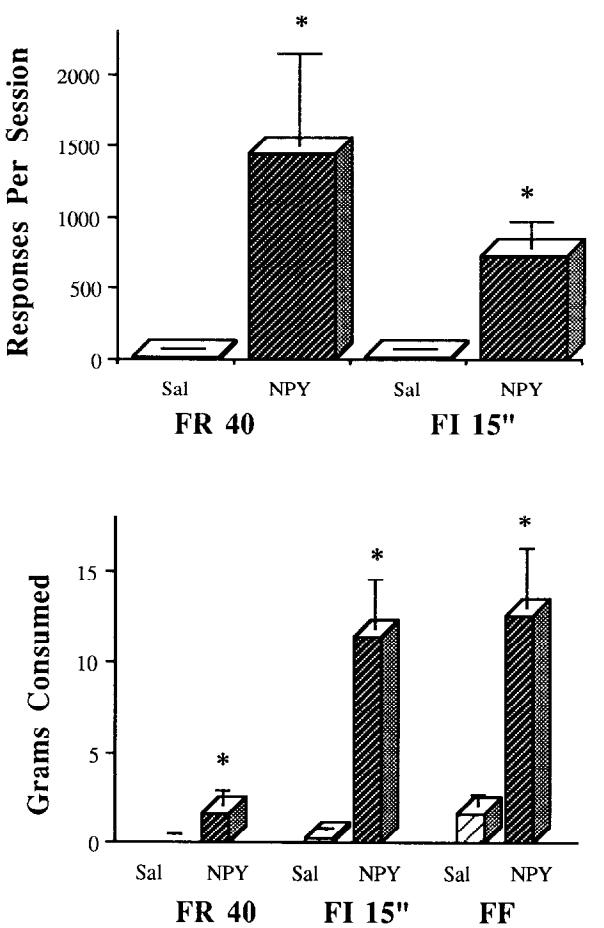

FIG. 1. *Top panel:* Mean responses per session under saline and initial NPY administration (0.5 μg/μl) for rats responding under either a FR 40 or FI 15″ schedule of reinforcement. *Bottom panel:* Grams of food consumed per session under saline and initial NPY administration for rats responding under either a FR 40 or FI 15″ schedule of reinforcement or when food was freely available (FF). *NPY significantly increased food-reinforced responses relative to saline (Wilcoxon signed-rank, $p < 0.05$). Brackets represent +1 SEM.

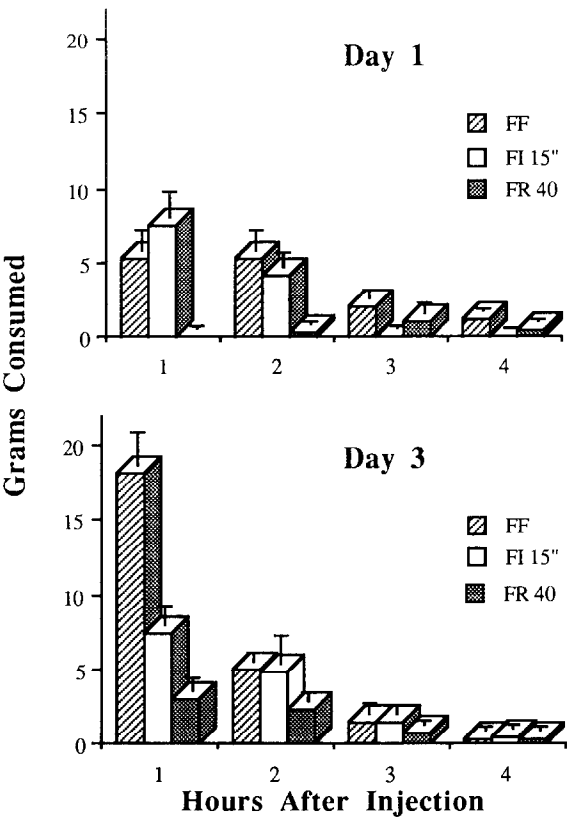

FIG. 2. *Top panel:* Grams of food consumed during each hour following the initial NPY administration (0.5 μg/μl) under all conditions of food availability. *Bottom panel:* Grams of food consumed during each hour following the third NPY administration (0.5 μg/μl). Brackets represent +1 SEM.

under all three conditions of food availability (Fig. 1, bottom panel). Animals provided food freely (FF) consumed the largest amount of food and did not consume significantly more than the group responding under the FI 15″ schedule of reinforcement. Both groups with relatively easy access to food (FF and FI) ate significantly more than the group required to emit 40 responses for each pellet. Rats trained to lever press under FR 40 or FI 15″ schedules when food-deprived responded very little under saline administration when food-satiated. NPY increased mean responses/session significantly more under the FR 40 schedule than under the FI 15″ (Fig. 1, top panel). Mean responses per session were 1442 under FR 40 and 729 under FI 15″. Although significantly more lever presses were emitted under the ratio than the interval schedule, the amount of food consumed was significantly greater under the interval schedule.

The conditions of access to food also influenced food intake patterns across the 4-h session. Figure 2 shows the amount of food consumed under each condition of access during each hour after the initial NPY administration (top panel) and after several successive days of NPY (bottom panel). Although food consumption after the first NPY injection increased during the first hour for rats lever-pressing under the FI schedule and for rats with free access to food, levels of consumption for rats lever-pressing under the FR schedule did not increase until late in the session, and then only by an insignificant amount (Fig. 2, top panel). This early-session

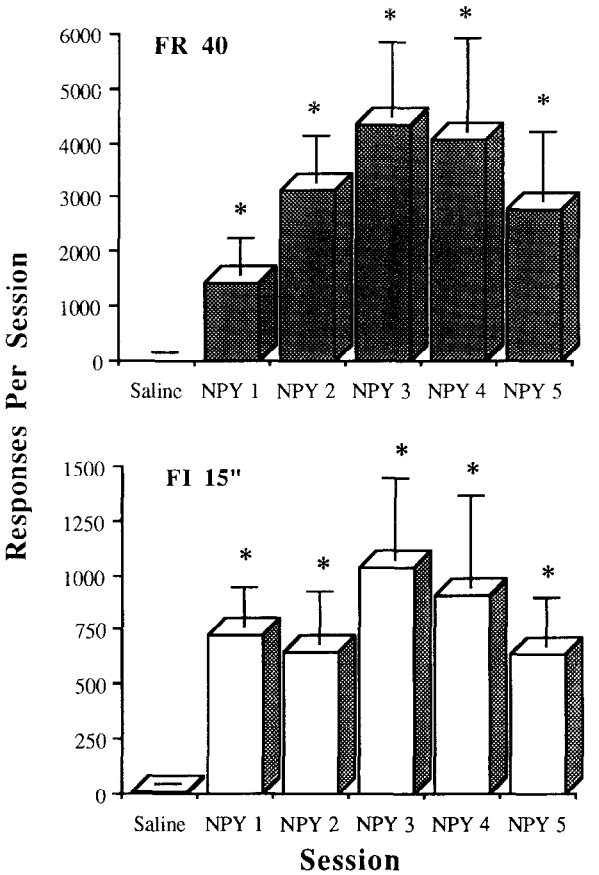

FIG. 3. Mean food-reinforced responses during each 4-h session under chronic daily NPY administration (0.5 μg/day). *NPY significantly increased response rate relative to saline (Wilcoxon signed-rank, $p < 0.05$). Brackets represent +1 SEM.

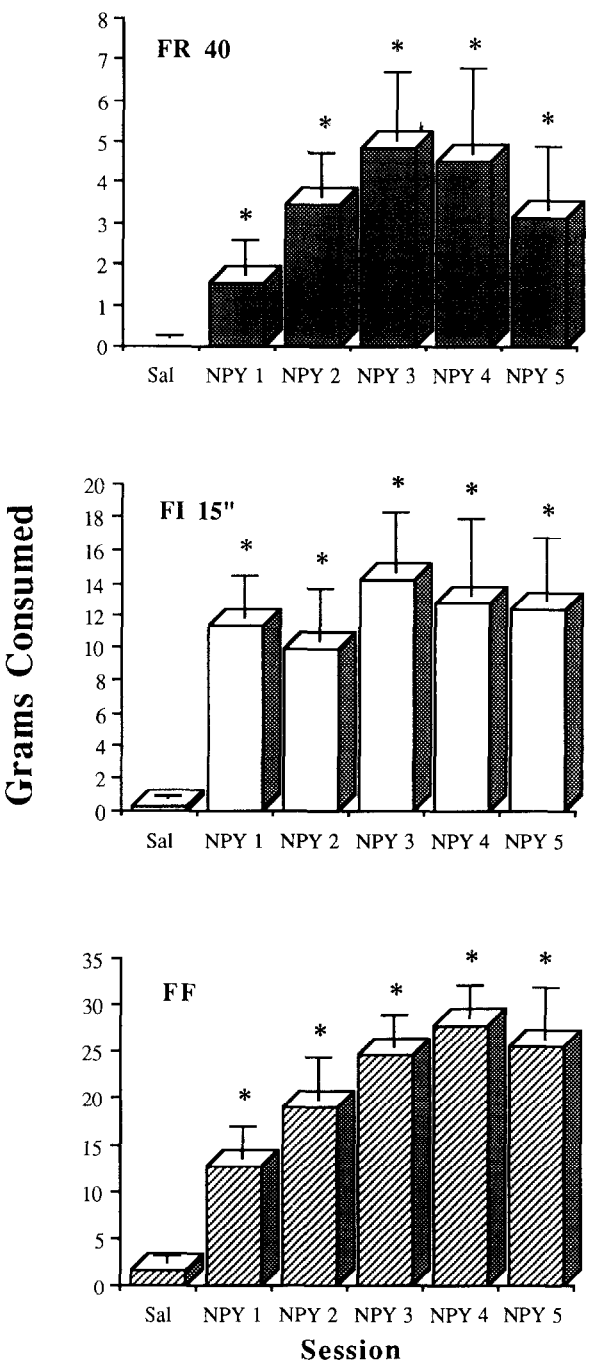

FIG. 4. Mean grams of food consumed during each 4-h session under chronic daily administration of NPY (0.5 μg/day). *NPY significantly increased food intake relative to saline (Wilcoxon signed-rank, $p < 0.05$). Brackets represent +1 SEM.

pattern of NPY-induced eating under conditions of low effort (FF and FI) did not emerge under the FR schedule until 3 days of daily NPY administration (Fig. 2, bottom panel). Eating patterns under all three schedules were similar and consistent after the third consecutive day of NPY.

NPY significantly increased responding under both the FI and the FR reinforcement schedules on all 5 days of repeated daily administration (Fig. 3). Reinforcers delivered were also significantly increased by daily administration of NPY. Across successive days of NPY, responding under the two reinforcement schedules was markedly different. Under the low-response requirements of the FI (Fig. 3, bottom panel), total responses were not significantly different across the 5 days of NPY. However, under the FR schedule of reinforcement (top panel), responding on day 1 was significantly lower than on the maximal day (day 3). This emergence of robust responding after repeated exposure to NPY, under the FR schedule, parallels the delayed emergence of a characteristic and stable pattern of within-session responding (Fig. 2).

Figure 4 depicts effects of NPY on the total amount of food consumed by rats lever-pressing under the FR 40 (top panel) and FI 15″ schedule of reinforcement (middle panel), as well as under free access to food (lower panel). Overall levels of food consumption depended on the conditions of access. Rats with free access to food ate considerably more than rats responding under the FR 40 schedule, and eventually ate more than rats responding on the FI 15″ schedule. Successive NPY administration increased the amount of food consumed under FR and FF, reaching a maximum after 3 or 4 days. Amount of food consumed under the FI schedule did not change significantly across days of NPY.

Mean water-reinforced responses under FR 40 were signifi-

cantly increased from 13.0 responses per session under saline to 188.4 responses per session under NPY (Wilcoxon sign-rank, $p < 0.05$). Under the FI 15″ reinforcement schedule, mean water-reinforced responding was 104.5 under saline and 119.5 under NPY (Wilcoxon sign-rank, $p > 0.05$). However, under conditions employed in the current experiment, effects on responding for water due to NPY cannot be separated from drinking induced by increased dry food intake or by the schedule of food presentation (i.e., schedule-induced polydipsia). As mentioned above, availability of water in the experimental chamber ensured feeding levels would not be unduly influenced by water deprivation during the 4-h sessions.

DISCUSSION

Rats ate large amounts of freely available food following ICV injection of 5 μg NPY, a finding consistent with other reports (3,17,28). NPY also increased feeding when food presentation was contingent upon lever-pressing under two different reinforcement schedules. Rats lever-pressed for food under conditions where 40 presses were required per food pellet (FR 40) and under conditions in which a single response could produce food every 15 s (FI 15″). Overall amount of food consumed was highest when rats had free access to food and lowest for rats responding under the FR 40 reinforcement schedule. Even though amount of food consumed increased most under the low-effort free-feeding and FI 15″ conditions, responding for food increased most dramatically under the FR schedule of reinforcement, a condition where rats were required to expend substantial effort to obtain relatively small amounts of food.

The temporal pattern of within-session eating after initial NPY was similar under free-feeding and fixed-interval conditions. Rats ate the most food early in the session and reduced their intake (and responding) late in the session. The pattern of lever-pressing and eating under the FR 40 reinforcement schedule was quite different. Under FR 40, eating and responding were greatest during the third hour after initial NPY injection and a substantial proportion of eating occurred during the final hour of the session. However, with each successive injection of NPY, rats ate earlier in the session, until, by the third session, their pattern of within-session eating resembled the pattern in the FF and FI 15″ groups. Previous experiments under free-access conditions [e.g., (27)], and under all conditions in the current study, have also shown increases in the amounts of food consumed with repeated NPY injections. Amount of food consumed did not increase under the FI 15″ schedule with repeated NPY administration, but initial response rates and grams consumed under NPY and this schedule were equal to levels obtained under conditions of 80% free-feeding weight imposed during training. The emergent pattern of eating and responding after repeated administration of NPY could be due to any of several effects of NPY. For example, some adverse effect of NPY may be tolerated with repeated administration, allowing more lever-pressing and feeding to occur on subsequent days. Another possibility is that some other NPY-induced behavior, such as increased general activity (16), initially competes with eating and with behavior that produces food.

The relatively large amount of work expended for food under NPY and FR 40 contrasts with reports of feeding in rats lesioned in the VMH. Typically, lesioned rats eat large amounts of palatable food when response requirements are minimal. When food is slightly adulterated or when substantial effort is required to obtain food, VMH-lesioned rats will reduce their intake disproportionately compared to unlesioned rats (30). VMH lesions affect eating due to collateral damage to neurons connecting the paraventricular nucleus of the hypothalamus (PVN) with the brain stem (7,8). Destruction of the PVN itself also causes overeating (14). Basically, damage to the VMH or PVN, or injection of norepinephrine into the PVN, produces excessive eating associated with increased insulin levels and reduced glucagon levels. Although NPY clearly acts in association with norepinephrine in the PVN, the mechanism of NPY's feeding induction is still speculative. Multiple potential subnuclei may be the specific site(s) of action, and NPY's effect on insulin levels is still unclear (1,20). In spite of the similarities of norepinephrine involvement, anatomical location, and effect on free-feeding, the present data suggest a functional assessment of food-maintained behavior may expose different effects of NPY compared to those produced by lesions of the VMH or PVN.

For studies involving operations intended to affect feeding, such as NPY administration, simply measuring the amount of food eaten may not be a fully adequate measure of the strength of the feeding behavior or a good indication of the changes in the value of food. By the assessment techniques used in the current study, NPY proves to be a strong and reliable food-inducing agent even when substantial effort is required to obtain relatively small amounts of food. Some feeding-induction operations, such as VMH lesions, produce substantial eating only if food is available with little effort. These differences may be particularly important in fully understanding operations that affect human eating behavior, in that eating is known to be affected by a great many stimuli and conditions (15).

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