Neuropeptide Y prepares rats for scheduled feeding

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Drazen, Deborah L., Matthew D. Wortman, Randy J. Seeley, and Stephen C. Woods. Neuropeptide Y prepares rats for scheduled feeding. Am J Physiol Regul Integr Comp Physiol 288: R1606–R1611, 2005—When neuropeptide Y (NPY) is administered centrally, meal-anticipatory responses are elicited. If an increase of endogenous NPY is a signal that heralds an imminent large caloric load, timed daily NPY injections may be expected to condition meal-anticipatory responses that facilitate ingestion. Rats received 4 h access to food beginning in the morning and then timed (1600 h), daily third-ventricular injections of NPY or saline for 7 days. On test day (day 8), animals received the conditioning drug (NPY or saline) or the opposite drug. Food was available immediately after injection on test day, and intake was measured. Rats conditioned with NPY and then given saline ate significantly more than rats conditioned with saline and then given saline; they ate the same amount as rats given NPY. Although they ate more, rats trained with NPY did not have changed plasma glucose, insulin, or ghrelin. These data suggest that NPY plays a role in mediating conditionable food-anticipatory responses that help to cope with the effects of large caloric loads.

SEVERAL LINES OF EVIDENCE suggest that consuming large caloric loads poses a metabolic challenge (36, 39). During and after large meals, glucose, fatty acids, and other nutrients flood into the blood from the gut and consequently perturb the rigorously controlled levels of blood nutrients, and insulin and other hormones must be secreted to reduce and hence tolerate the increments. In an endocrine sense, the postprandial elevation of plasma fuels has been considered a stressor in that plasma catecholamines, adrenocorticotropic hormone, glucocorticoids, and β-endorphin are all elevated at that time (10, 21, 25, 36). Although one could argue that individual meal-induced increases in these stress hormones are not major, when hundreds or thousands of meals are considered on a chronic basis, such increases have been implicated in the development of obesity, hypertension, and atherosclerosis (5, 18, 20, 36).

Consistent with this view of meals, animals engage in specific behaviors that help minimize the acute metabolic impact of food. In particular, animals adapt by learning to make anticipatory responses that minimize a meal’s impact, and, if they are unable to reliably anticipate a meal, they eat smaller meals (24). The premeal secretion of insulin is an adaptive response that minimizes prandial increases of blood glucose (3, 35, 36), and it is coincident with a prandial reduction in metabolic rate, a premeal elevation of plasma corticosterone, and a premeal increase in body temperature (11, 14, 23, 25), all of which are initiated well in advance of an anticipated meal. The term “cephalic” describes these anticipatory responses because they are initiated by cues in an individual’s environment that reliably predict meals, cues that can be considered as conditioned stimuli in a learning sense. As an example, animals readily learn to use time of day to entrain their pattern of food intake. Hence, when maintained on a stable light-dark schedule, they consume the largest meals at the most predictable times, i.e., light offset and light onset (19, 32). There is nothing inherent about the changing of the lights, per se, that mandates that an animal eat larger meals at those precise times because rats trained (“meal-fed”) to anticipate food at any arbitrarily selected time during the light-dark cycle eat their largest meal at that time. The point is that the largest meals are eaten at a time that is highly predictable (33).

Neuropeptide Y (NPY) elicits a robust increase in food intake when administered centrally (7, 22, 30). Endogenous NPY levels in the hypothalamus normally peak before the onset of dark and consumption of the largest meal of the day in free-feeding animals (1), and hypothalamic NPY peaks before the time of feeding in meal-fed animals (41, 42). Hence, it is reasonable to speculate that the elevated NPY levels function to facilitate the consumption of a particularly large caloric load. This could occur either because NPY elicits eating per se or because NPY elicits the gamut of anticipatory cephalic responses that secondarily allow a large amount of food to be ingested without eliciting too major a metabolic perturbation.

Consistent with the latter possibility, the administration of exogenous NPY into the brain does not always elicit eating. Eating can be partitioned into the appetitive phase, which refers to the finding and acquisition of food, and the consummatory phase, which consists of eating per se (chewing, swallowing) (8). In models that dissociate the consummatory and appetitive phases of food intake, such as when liquid food is provided freely to rats through an intraoral catheter, NPY given into the brain does not increase the consummatory act of food intake but does cause the same rats to initiate anticipatory, appetitive responses such as approaching and licking the liquid food (2, 27). These data have two important implications. First, at least when we use the above-mentioned model and rats need not make anticipatory responses to get food, NPY has no effect on food intake. Second, these data suggest that once anticipatory behaviors have been elicited by NPY and food is available, intake is excessive.

In support of the hypothesis that NPY functions to mediate food-anticipatory responses, when NPY is administered centrally, responses are elicited that resemble those made when consuming food is anticipated, including insulin and corticosterone secretion (26), increased corticotropin-releasing hormone (CRH) mRNA and CRH-immunoreactivity in the hypothalamus (15, 34), and increased locomotor activity (29).

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Collectively, these data lead to the hypothesis that hypothalamic NPY, rather than functioning to increase food intake per se, mediates food-anticipatory responses that help to lessen the metabolic impact of a large caloric load.

If NPY is a signal that heralds the opportunity to consume an imminent large caloric load, we reasoned that receiving third-ventricular (i3vt) injection NPY at the same time each day for several days should prepare animals to ingest a large quantity of food at that time; that is, daily injections of NPY at a specific time should condition meal-anticipatory physiological and behavioral responses that facilitate ingesting a large meal at that specific time, and NPY-conditioned animals should consequently be better prepared for consuming a caloric load at that time than control animals injected at the same time of day with i3vt saline. We assessed this hypothesis in several experiments.

MATERIALS AND METHODS

Animals

For all experiments, male Long-Evans rats (300–350 g, Harlan, Indianapolis, IN) were housed in individual tub cages with ad libitum access to pelleted rat chow (Teklad, Harlan, Madison, WI) and water in a temperature-controlled vivarium (22°C) on a 12:12-h light-dark schedule, with lights on at 0800 unless otherwise noted. Research was conducted in AAALAC-approved facilities that conformed to National Institutes of Health and U.S. Department of Agriculture regulations; research was approved by the University of Cincinnati Internal Animal Care and Use Committee.

Third-Ventricular Cannulation

All animals were surgically implanted with a 22-gauge cannula (Plastics One, Roanoke, VA) aimed at the third cerebral ventricle as described previously (6). For surgery, rats were anesthetized with intraperitoneal ketamine (86 mg/kg)-xylazine (12.9 mg/kg) and allowed to recover until they reached presurgical body weight (~1 wk). Verification of cannula placement was accomplished by i3vt injection of 10 ng of angiotensin II in 1 μl of 0.9% saline. Animals that did not drink 5 ml of water within 60 min after this treatment were not included in the experiments.

Experimental Procedures

Experiment 1. The goal of experiment 1 was to assess the longevity of NPY’s orexigenic action when food is not immediately provided to the animal, i.e., to determine how much time must elapse with no food available before animals no longer overeat once food is presented after they receive i3vt NPY. This was necessary to ensure that the daily injections of NPY in subsequent experiments did not elicit any change in food intake, so that the influence of NPY conditioning could be assessed independent of altering food intake or body weight. It was also necessary to demonstrate that there were no lingering effects of NPY that would have any effect on behavior on subsequent days.

Values for food intake (g) are means ± SE. Food was made available to animals either immediately after injection, 4 h after injection, or 18 h after injection. i3vt, Third-ventricular injection; NPY, neuropeptide Y. *Significantly different from saline-injected group at the same time of food return (P < 0.05).

Table 1. One-hour food intake of rats that received i3vt saline or NPY

<table>
<thead>
<tr>
<th>Drug</th>
<th>Immediate Return</th>
<th>4-h Delay</th>
<th>18-h Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>0.4 ± 0.9</td>
<td>0.7 ± 0.8</td>
<td>8.5 ± 0.9</td>
</tr>
<tr>
<td>NPY</td>
<td>9.7 ± 0.8*</td>
<td>5.2 ± 0.8*</td>
<td>7.5 ± 0.9</td>
</tr>
</tbody>
</table>

Food was removed from all rat cages at 0900 h. Rats (n = 60) were divided into two i3vt groups: those receiving a single injection of NPY (9.5 μg, American Peptide, Sunnyvale, CA) in 2 μl of saline and those receiving a single injection of saline (2 μl) at 1000 h. This dose was chosen based on previous i3vt NPY dose-response studies (e.g., Ref. 4). The animals were further subdivided into groups that received their food immediately after the injection or 4 or 18 h after the injection. In each of these conditions, food intake was recorded 1 h after food return. Water was available at all times for all groups.

Experiment 2. The goal of experiment 2 was to determine whether cues predictive of NPY are sufficient to allow animals to ingest a large caloric load. To test this, we conditioned animals by administering NPY at the same time each day. On a subsequent test day, the critical group did not receive NPY, allowing us to determine whether the responses to anticipated NPY are sufficient to cause an individual to eat. The nominal conditioned stimulus in this experiment consisted of the time of day and the injection procedure, and the unconditioned stimulus consisted of responses elicited by central NPY that facilitate eating.

Based on the results of experiment 1, a novel cohort of rats (n = 30; maintained as in experiment 1) had access to chow plus water from 1000 to 1400 h daily and had only water available the remainder of the day. Food intake was monitored daily to determine when it reached a plateau, after which the experimental protocol began; i.e., after 12 days.
days, these meal-fed rats were consuming close to their normal (i.e., premeal-feeding) daily caloric load during the 4-h access period. The same meal-feeding schedule was maintained throughout the experiment.

After 12 days of meal feeding, rats were assigned to one of two i3vt groups with equal body weight: one group received NPY (9.5 μg in 2 μl; n = 15) and the other received vehicle, physiological saline (2 μl; n = 15). The injections were administered for 7 consecutive days (days 1–7), a protocol that we used previously for drug conditioning (38) at precisely 1600 h. Food intake and body weight were recorded each day. On day 8, the test day, animals were fed as on the previous 7 days, from 1000 to 1400. On the test day, animals were further subdivided, with approximately half of each group (NPY or saline on days 1–7) receiving i3vt saline and the other half receiving i3vt NPY (9.5 μg) at 1600 h (throughout the 7 days of training, 4 animals, 2 from each group, became ill and were not included in the rest of the experiment). Thus there were four groups: Sal/Sal (n = 6), Sal/NPY (n = 7), NPY/Sal (n = 7), and NPY/NPY (n = 6). On test day (day 8), immediately after the injection, food was given to each animal (a novel time for food access in all groups), and intake was measured after 1, 2, 4, and 20 h.

Experiment 3. At the conclusion of experiment 2, the same rats were returned to the meal-feeding schedule (food available only from 1000 to 1400) for the next 3 consecutive days (days 10–12; food was removed at 1400 on day 9 to reestablish the conditioned responses (37). Each rat was injected with i3vt NPY or i3vt saline at 1600 h on these days, receiving the same drug as on days 1–7. On day 13, rats received their food from 1000 to 1400 (consuming 18.6 ± 0.6 g, similar to what it had been in experiment 2), but no injection was given; instead, all animals were killed at 1600, and trunk blood and brains were harvested. Blood was centrifuged at 4°C for 15 min at 4,000 rpm. Plasma aliquots were aspirated and stored in sealable polypropylene microcentrifuge tubes at −80°C until used for hormone assays. Brains were immediately immersed in 20 ml of RNA later (Ambion, Austin, TX). Plasma insulin, glucose, and ghrelin were assessed to determine whether NPY conditioning altered hormonal cephalic responses. Hypothalamic NPY gene expression was measured to determine whether endogenous NPY mRNA was influenced by the daily administration of NPY to the brain.

Plasma Glucose, Insulin, and Ghrelin

We measured glucose using a glucose oxidase method. Insulin was determined by a previously described RIA (12). We determined ghrelin values using a commercially available RIA kit (Phoenix Pharmaceuticals, Belmont, CA). The lowest detection limit was 20–30 pg/ml, the intra-assay variation was 5.0%, and the linear range was from 40 to 1,280 pg/ml.

RNA Isolation and cDNA Synthesis

Whole brains were rapidly removed from anesthetized animals and placed in 20 ml of RNA later (Ambion). After equilibration for 4 h at 4°C, hypothalami were dissected and placed in RNA later (1.5 ml) and held at −80°C until use. TRI reagent (MRC, Cincinnati, OH) was used to isolate RNA from individual hypothalami according to manufacturer’s recommendations. A ratio of 50 mg of tissue per milliliter of TRI reagent was maintained for each sample, and bromochloro-propane was used in place of chloroform. The Superscript first-strand synthesis system (Invitrogen, Carlsbad, CA) was used to synthesize cDNA from 5 μg of total RNA.

Semi-Quantitative PCR

Semi-quantitative PCR was performed on a Bio-Rad (Hercules, CA) Icycler using Bio-Rad iQ SYBR green supermix. We performed RT-PCR using Superscript II according to the manufacturer’s protocol (Invitrogen). Cycling conditions were initial denaturing step at 95.0°C for 3 min followed by 40 × 2-step cycles at 95.0°C for 10 s and 60.0°C for 30 s. Primers for rat NPY were designed with MGB Eclipse design software (version 3.0, http://www.epochbio.com). The sequence of the forward primer was CTCTGGCATCACTACATCAA, and the reverse primer was GG*GGCATTTTCTGTGCTTT (asterisk denotes that prior nucleotide is chemically modified, see above website for details). PCR efficiency was 101.6%, and the correlation coefficient over five orders of magnitude spanning test concentrations was 0.996. Gel and melt-curve analyses demonstrated no competing products. Samples were run in triplicate and normalized to the constitutively expressed ribosomal protein L32, which has identical reaction characteristics.

Statistical Analyses

For experiment 2, meal-feeding data were analyzed with a t-test; all other data were analyzed with a one-way between-subjects ANOVA. All pairwise comparisons of mean differences were conducted with Tukey’s honestly significant difference comparisons. Differences between group means were considered statistically significant if P < 0.05.

RESULTS

Experiment 1

As revealed by one-way ANOVA, there was a main effect of the time of food return after injection on food intake (P < 0.05). NPY significantly increased 1-h food intake when food was returned immediately after injection, as well as when food

<table>
<thead>
<tr>
<th>Drift</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>351.5 ± 6.8</td>
<td>348.8 ± 7.3</td>
<td>337.6 ± 8.7</td>
<td>328.9 ± 6.7</td>
<td>331.5 ± 6.8</td>
<td>329.8 ± 7.1</td>
<td>327.5 ± 6.4</td>
</tr>
<tr>
<td>NPY</td>
<td>350.8 ± 4.7</td>
<td>345.5 ± 6.9</td>
<td>334.1 ± 8.4</td>
<td>332.2 ± 7.2</td>
<td>336.6 ± 8.3</td>
<td>330.5 ± 6.7</td>
<td>329.5 ± 5.7</td>
</tr>
</tbody>
</table>

Values for body weight (g) are means ± SE. Body weight did not differ statistically between the 2 groups on any day.
was returned 4 h after injection, compared with saline ($P < 0.05$ in both cases). The increase in intake elicited by NPY relative to saline was greater in the group receiving food immediately compared with the animals whose food return was delayed by 4 h ($P < 0.05$ in all cases; Table 1). There was no difference in 1-h food intake after NPY compared with saline when food was returned 18 h after injection ($P > 0.05$ in all cases; Table 1). NPY significantly increased food intake when food was returned immediately or 4 h after injection ($P < 0.05$) but not when food was returned 18 h after injection ($P > 0.05$). Hence, having received NPY 18 h earlier had no discernable effect on food intake. We therefore incorporated an 18-h delay after NPY in experiment 2.

**Experiment 2**

The relative timing of the 4 h of food availability and the i3vt injections in experiment 2 were determined based on the findings of experiment 1. That is, the food was made available beginning 18 h after the daily injections, a time when the NPY was no longer effective at increasing food intake, so that NPY-conditioned and saline-conditioned animals would have similar behavioral profiles before test day.

**Table 4. Cumulative food intake of rats that received i3vt saline or NPY on 7 consecutive days and then received i3vt saline or NPY on the test day**

<table>
<thead>
<tr>
<th>Time</th>
<th>Sal/Sal</th>
<th>Sal/NPY</th>
<th>NPY/Sal</th>
<th>NPY/NPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-h Intake</td>
<td>5.4±0.5</td>
<td>12.1±1.6*</td>
<td>10.9±1.4*</td>
<td>13.8±0.6*</td>
</tr>
<tr>
<td>4-h Intake</td>
<td>6.1±0.8</td>
<td>13.7±1.8*</td>
<td>13.1±2.2*</td>
<td>14.5±0.4*</td>
</tr>
</tbody>
</table>

Values for cumulative food intake (g) are means ± SE. Food was presented on test day. Sal, saline. *Significantly different from Sal/Sal group ($P < 0.05$).

All animals significantly increased their food intake over the course of 12 days of 4-h daily meal feeding, as revealed by a t-test that compared food consumed on day 1 (6.47 ± 0.31 g) of meal feeding with that consumed on day 12 (19.47 ± 0.71 g) of meal feeding ($t(28) = -15.17, P < 0.05$). Importantly, as revealed by one-way ANOVAs, there was no difference in cumulative food intake between the NPY-conditioned and the saline-conditioned groups over the course of the seven daily i3vt injections ($F(1, 28) = 0.136$, not significant) (Fig. 1A and see Table 2 for average daily intakes) or in body weight between the NPY-trained and the saline-trained groups just before test day ($F(1, 28) = 0.32$, not significant) (Fig. 1B and see Table 3 for average daily body weights).

A one-way ANOVA indicated a main effect of the conditioning group on food intake on the test day, at 1 [$F(3, 22) = 7.75$, 2 [$F(3, 22) = 8.26$, and 4 [$F(3, 22) = 5.59$] h ($P < 0.1$ in all cases). Post hoc analysis revealed that at 1, 2, and 4 h, food intake was significantly greater in the Sal/NPY, NPY/Sal, and NPY/NPY groups than in the Sal/Sal group ($P < 0.05$ in all cases). Figure 2A depicts the 1-h data, and Table 4 lists the other time points. By 20 h, as revealed by one-way ANOVA, food intake was no longer significantly different among any of the groups [$F(3, 22) = 0.31$, not significant] (Fig. 2B).

**Experiment 3**

One-way ANOVAs yielded no significant differences in plasma insulin, glucose, or ghrelin at the time of death between NPY- and saline-trained groups ($P > 0.05$ in all cases, Table 5). There was also no difference in hypothalamic NPY mRNA between the NPY- and saline-trained groups ($P > 0.05$) (Table 5).

**DISCUSSION**

These experiments sought to assess the ability of animals trained to anticipate i3vt NPY to cope with unanticipated food, to test the hypothesis that NPY, rather than functioning to increase food intake per se, mediates food-anticipatory responses that help to cope with a large caloric load. To accomplish this, we first determined the duration of central NPY’s

**Table 5. Plasma values and NPY mRNA in rats that were retrained with 3 consecutive days of i3vt saline or NPY**

<table>
<thead>
<tr>
<th>Group</th>
<th>Insulin, pm</th>
<th>Glucose, mg/dl</th>
<th>Ghrelin, ng/dl</th>
<th>NPY mRNA (relative to L32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>436.5±57.1</td>
<td>156.8±3.4</td>
<td>820.4±64.9</td>
<td>40.0±2.7</td>
</tr>
<tr>
<td>NPY</td>
<td>408.8±68.9</td>
<td>152.5±4.1</td>
<td>928.0±87.9</td>
<td>37.3±3.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. Constitutively expressed ribosomal protein L32 was used to obtain relative quantification of NPY mRNA. Levels in the NPY and saline groups did not differ statistically.
effects on food intake when food is not available and its return delayed. Previous studies demonstrated that NPY increases food intake even after a 2-h delay in access (22). Therefore, we needed to ensure that the daily NPY injections would have no effect on food intake during the 4-h access period. In experiment 2, we therefore administered NPY (or saline) 18 h before food access. Consistent with the findings of experiment 1, rats receiving NPY ate the same amount of food and weighed the same as rats receiving saline over the seven daily training sessions in experiment 2.

In experiment 2, the key group of animals was trained to anticipate receiving i3vt NPY at precisely 1600 h. When they subsequently received a saline injection on day 8 at 1600 (NPY/Sal group on the test day), they behaved as if they had actually received NPY on that day, consuming as much food as the NPY/NPY animals. Importantly, both of these groups (NPY/Sal and NPY/NPY) ate the same amount of food on day 8 as rats that received NPY for the first time (Sal/NPY), and all three groups ate more food than the control rats (Sal/Sal). This effect persisted throughout 4 h but was gone by 20 h. These data have several implications. First, they suggest that repeated administration of NPY at the same time each day may initiate a sequence of endogenous events that normally allows an animal to anticipate and eat a large quantity of food. The results further imply that, whether the sequence of large meal-enabling events is elicited by exogenous NPY itself (i.e., Sal/NPY or NPY/NPY group) or by a stimulus that predicts NPY administration (i.e., injection procedure and time of day, NPY/Sal group), the effect is the same in that the rats eat more food than they otherwise would at that time. Finally, the results imply that the conditioned, NPY-anticipatory response (NPY/Sal group) is not enhanced by injection of exogenous NPY (NPY/NPY group); however, this assertion this requires further testing because only one dose of NPY was used in the present set of experiments.

Experiment 3 was an initial attempt to determine the mechanisms by which NPY may mediate meal-preparatory responses. It is well known that plasma insulin and ghrelin both rise in a predictable manner before an anticipated meal (9, 31). It is conceivable, therefore, that if the primary function of NPY is to mediate meal-anticipatory responses, training animals to anticipate NPY would condition them to make comparable anticipatory responses. The data, however, did not reveal any changes in these hormones. It should be emphasized, however, that only one time point was assessed and that, importantly, no injection was given on the day blood was collected. An injection per se has been found to be a critical part of the conditioned stimulus in drug-conditioning experiments when time of day is not precise and behavior is assessed (16), whereas time of day has been sufficient in other experiments, especially those assessing plasma levels of hormones (40). However, experiment 2 included both time of day and injections, whereas experiment 3 relied solely on the time of day cue. It is also possible that changes in these parameters took place at points earlier in the sequence leading up to the expectation of the NPY injection since cephalic insulin and ghrelin changes occurred before an anticipated meal (9, 31). Alternatively, it is possible that these hormones were not influenced at any time by the NPY conditioning. Plasma values of insulin, glucose, and ghrelin were all consistent with post-prandial values, as they were measured at injection time, which was only 2 h after the 4-h meal-feeding period. Other important meal-anticipatory factors such as plasma corticosterone, body temperature, and locomotor activity need to be assessed with NPY conditioning in future studies.

Regardless of the mechanisms by which the daily NPY injections lead to an increase in feeding in the NPY/Sal group, it is important that the feeding effect and the hormonal responses were dissociated. Despite no differences in plasma ghrelin, insulin, or glucose, there was a large effect on behavior, suggesting that simultaneous changes in these hormones may not be necessary to initiate an increase in food intake. Although it is tempting to speculate that NPY may be able to override these hormonal signals in preparing an animal to ingest a large calorific load, the different procedures undertaken for experiments 2 and 3 make it difficult to draw such a conclusion.

Traditionally, it has been accepted that NPY functions to stimulate food intake. However, there is compelling evidence that, as an orexigenic peptide, NPY is important as a meal-anticipatory hormone that prepares animals for meal consumption. Consistent with this, when rats are on a strict meal-feeding schedule, they develop a reliable rise in extracellular NPY in the paraventricular nucleus 2 h before the scheduled meal (42). An analogous rise in arcuate nucleus NPY mRNA is also observed before dark onset, the time of the largest meal, in freely feeding rats (1). Further supporting this concept, mice that do not synthesize NPY (i.e., NPY−/− mice) have normal daily 24-h food intake and normal body weight (13), indicating that NPY is not necessary for animals to elicit meals. However, NPY−/− mice cannot anticipate meals properly, eating relatively small meals after being fasted (28). In addition, NPY−/− mice have an increased latency to eat after fasting, further implicating NPY in meal anticipation (28). The present data are consistent with these other data in that they support the hypothesis that NPY is involved in meal anticipation and does not function simply to stimulate food intake.

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GRANTS

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NPY CONDITIONS FOOD INTAKE


