Neuropeptide Y inhibits estrous behavior and stimulates feeding via separate receptors in Syrian hamsters

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Neuropeptide Y inhibits estrous behavior and stimulates feeding via separate receptors in Syrian hamsters. Am J Physiol Regulatory Integrative Comp Physiol 280: R1061–R1068, 2001.—Central injections of neuropeptide Y (NPY) increase food intake in Syrian hamsters; however, the effect of NPY on sexual behavior in hamsters is not known nor are the receptor subtypes involved in feeding and sexual behaviors. We demonstrate that NPY inhibits lordosis duration in a dose-related fashion after lateral ventricular injection in ovariectomized, steroid-primed Syrian hamsters. Under the same conditions, we compared the effect of two receptor-differentiating agonists derived from peptide YY (PYY), PYY-(3–36) and [Leu31,Pro34]PYY, on lordosis duration and food intake. PYY-(3–36) produced a 91% reduction in lordosis duration at 2.4 nmol. [Leu31,Pro34]PYY was less potent, producing a reduction in lordosis duration (66%) only at 2.4 nmol. These results suggest NPY effects on estrous behavior are principally mediated by Y2 receptors. PYY-(3–36) and [Leu31,Pro34]PYY stimulated comparable dose-related increases in total food intake (2 h), suggesting Y5 receptors are involved in feeding. The significance of different NPY receptor subtypes controlling estrous and feeding behavior is highlighted by results on expression of Fos immunoreactivity (Fos-IR) elicited by either PYY-(3–36) or [Leu31,Pro34]PYY at a dose that differentiated between the two behaviors. Some differences were seen in the distribution of Fos-IR produced by the two peptides. Overall, however, the patterns of expression were similar. Our behavioral and anatomic results suggest that NPY-containing pathways controlling estrous and feeding behavior innervate similar nuclei, with the divergence in pathways controlling the separate behaviors characterized by linkage to different NPY receptor subtypes.

LIMITED FOOD AVAILABILITY diminishes fertility in all mammals, particularly female mammals (4). Nutritional infertility is characterized by multiple effects on reproductive physiology and behavior, including suppression of estrous behaviors (for review, see Ref. 46). Female Syrian hamsters provide a useful model for the study of nutritional infertility. Nutritional challenges that put hamsters in a negative energy balance suppress ovulatory cycles and estrous behavior (46). In hamsters and rats, information about nutritional status is communicated to forebrain circuits controlling gonadotropin-releasing hormone (GnRH) and reproductive behaviors via detectors for metabolic fuel availability located in the viscera and caudal hindbrain (26, 32). However, very little is known about the mechanisms by which information regarding energy balance is transmitted from the hindbrain and visceral detectors to the forebrain effector circuits. One possible mediator is neuropeptide Y (NPY).

NPY is a 36-amino acid member of the pancreatic polypeptide (PP), or PP-fold, family of peptides, which includes PYY (42, 43). NPY is highly conserved throughout evolution and found in abundance in the brain of humans and a number of rodent species, including Syrian hamsters (Mesocricetus auratus) (1, 27, 30, 37). Of the six NPY receptor subtypes characterized (31), three subtypes, Y1, Y2, and Y5, are implicated in behavioral function (10, 13, 38), display a distinct pharmacology (2, 47), and have been cloned (13, 24, 36).

Converging evidence suggests NPY may have a functional role in nutritional infertility. Central injections of NPY stimulate robust and long-lasting increases in food intake in rats and hamsters (5, 22, 39) and also suppress reproductive behavior in rats (6, 34). Moreover in rats, NPY synthesis in the hypothalamus appears to be regulated by nutritional status. That is, gene expression and NPY levels increase in response to food restriction or fasting (3, 7). These observations suggest that fluctuations in NPY synthesis and release, controlled by an animal’s energy balance, have a dual effector role in the control of appetite and reproduction. That is, increased NPY synthesis and release at targets in the central nervous system (CNS) result in increased appetite and metabolic efficiency during periods of reduced access to adequate nutrition, whereas at the same time blunting reproductive function, including estrous behavior (21). Thus NPY may be a key neurotransmitter in the neural circuitry involved in nutritional infertility.

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In the study reported here, we found that central administration of NPY reduced estrous behavior, as measured by lordosis duration, in ovariectomized (OVX), steroid-primed female Syrian hamsters. In addition, we determined the effect of two NPY receptor agonists, [Leu$^{31}$,Pro$^{34}$]$\text{PYY}$ and PYY-(3–36), on lordosis duration and food intake. Agonists were chosen based on their differential interaction with NPY receptor subtypes (9) and because they are known to have powerful effects on behavior in other rodent species (13). PYY-(3–36) binds with high affinity to both Y2 and Y5 receptors, but exhibits intermediate to low affinity for Y1 receptors (2, 13, 17). [Leu$^{31}$,Pro$^{34}$]PYY, in contrast, binds with high affinity to Y1 as well as Y5 receptors but is highly selective against Y2 receptors (9). In addition to behavioral studies, to assess differences between neural pathways involved in estrous and feeding behavior, we also examined the effect of [Leu$^{31}$,Pro$^{34}$]PYY and PYY-(3–36) on expression of the c-Fos-IR in forebrain loci that contain estrogen receptors and are implicated in control of reproductive function or food intake.

**MATERIALS AND METHODS**

**Animals and Housing Conditions**

Female Lak:LVG Syrian hamsters (Charles River Breeding Laboratories, Wilmington, MA), weighing between 110 and 154 g at the time of testing, were singly housed in stainless-steel, wire-bottom cages on a 14:10-h light-dark cycle (lights on at 6:00 AM). Ambient temperature was maintained at 22 ± 2°C. Purina laboratory rodent chow (5001) was available ad libitum, except where indicated. Water was available at all times.

**Surgery**

After acclimation to the laboratory for 1 wk, hamsters were bilaterally OVX under pentobarbital sodium anesthesia (80 mg/kg ip). One week after OVX, each hamster was reanesthetized and stereotaxically implanted with a 22-gauge, stainless-steel guide cannula (Plastics One, Roanoke, VA) aimed at the lateral ventricle (1.1 mm posterior to bregma, lateral 1.7 mm, and subdural 2.2 mm). Guide cannulas were held in place with dental acrylic bonded to stainless steel screws anchored to the skull. An obturator was inserted into each guide cannula and remained in place, flush with the tip of the guide cannula, except during injections. Animals were given at least 1 wk to recover from stereotaxic surgery before the start of behavioral testing. During that time they were handled and mock injected to facilitate adaptation to the intracerebroventricular injection procedure.

**Behavioral Experiments**

Forty-eight hours before each behavioral test, hamsters were injected subcutaneously with 5.0 μg of estradiol benzoate (EB) followed 44 h later with 500 μg of progesterone (P). Intracerebroventricular injections were made 20–50 min before the start of lordosis testing. Briefly, this procedure involved intracerebroventricular injections made by replacing the obturator with an injector that extended 1.0 mm beyond the tip of the guide cannula. Each injector was connected by saline-filled PE tubing to a microliter syringe controlled by an infusion pump (Stoetling model 53220, Wood Dale, IL). A small air bubble separated saline in the PE tubing from intracerebroventricular solutions. The volume of all intracerebroventricular infusions was 5 μl, delivered over a 1-min period. Testing of lordosis duration was initiated 6 h after injection of P by placing each hamster in a Plexiglas arena in the presence of a male hamster. The total number of seconds spent by the female in the lordosis posture during a 3-min test was recorded. To elicit lordosis, a consistent level of stimulation was applied to each female’s flank region throughout the test period using strokes of a soft 1-cm artist’s paintbrush (45).

In experiment 1 ($n = 16$), the effect of NPY on duration of lordosis was tested using two doses of NPY, administered intracerebroventricularly, each dose given in crossover design with vehicle. To verify cannula placement, hamsters were deeply anesthetized at the end of the experiment and given an intracerebroventricular injection of India ink using infusion conditions identical to those used in peptide tests. Animals were immediately killed, and brains were removed and sectioned to analyze the distribution of ink.

In experiment 2 ($n = 8$), the dose effect of two receptor differentiating NPY agonist analogs PYY-(3–36) and [Leu$^{31}$,Pro$^{34}$]PYY, on lordosis duration and food intake was examined and compared using a two-group design, one peptide per group, with dose as a repeated variable in each group. Half the hamsters in each group received doses in an ascending order, starting with vehicle, half in descending order, ending with vehicle. Food intake was measured in addition to estrous behavior by removing food at the time of the intracerebroventricular injections and placing a preweighed pellet of chow in each cage. Intake, corrected for spillage, was measured 1 and 2 h after the infusion. Cheek pouches were checked at the beginning of the experiment and at each time point. Pouching was rare and treated as spillage. Hamsters were removed from their home cages for ~8 min for testing of estrous behavior; hence, during this period in the first hour after intracerebroventricular injection they did not have access to the food pellet.

**c-Fos Immunocytochemistry**

In experiment 3, forebrains of hamsters that were used in experiment 2 ($n = 19$) were analyzed for Fos-IR 2 wk after completion of behavioral testing. Hamsters were steroid primed, as in experiments 1 and 2, and randomly assigned to receive intracerebroventricular administration of either 0.72 nmol PYY-(3–36), 0.72 nmol [Leu$^{31}$,Pro$^{34}$]PYY, or vehicle. Loci chosen for analysis have been shown to be rich in estrogen receptors and express Fos-IR when animals were made sexually receptive by treatment with EB and P (12, 33). Some of these regions are also NPY sensitive and implicated in control of food intake (25). Fos-IR cell counts were made in the anterior parvocellular paraventricular nucleus of the hypothalamus (apPVN), the suprachiasmatic nucleus (SCN), medial preoptic area (mPOA), ventral lateral septum, including the ventrolateral hypothalamic nucleus (VLH), ventromedial hypothalamic nucleus including the ventrolateral portion (VMH), arcuate nucleus (Arc), the dorsoposterior principal nucleus of the bed nucleus of the stria terminalis (BNST), and dorsomedial amygdala (mAMy).

For both peptides, a dose 0.72 nmol was given because this dose was optimal for eliciting the differential behavioral effects produced by the two peptides. That is, 0.72 nmol of [Leu$^{31}$,Pro$^{34}$]PYY was effective in stimulating food intake but did not affect lordosis, whereas 0.72 nmol PYY-(3–36) completely inhibited lordosis but had no significant effect on 1- or 2-h food intake. Hamsters were randomly assigned to...
receive either vehicle or the peptide that they received in experiment 2. Food was removed at the time of the intracerebroventricular injection. One hour after intracerebroventricular injection, hamsters were deeply anesthetized with pentobarbital sodium, injected with 5,000 U heparin, and perfused intracardially with 0.9% saline for 30 s followed by 2% acrolein infusion for 15 min. Brains were removed, blocked, and immersed overnight in phosphate-buffered 20% sucrose. The following morning, coronal 40-μm sections were cut on a freezing rotary microtome, beginning in the medial preoptic area and extending to the caudal ventromedial nucleus of the hypothalamus. Cut sections were stored in cryoprotectant until the start of the Fos immunostaining procedure.

After removal from cryoprotectant, every fourth section was taken in series, rinsed thoroughly in 0.05 M Tris-buffered saline (TBS; pH 7.6), and processed in 1% sodium borohydride for 10 min followed by thorough rinsing in 0.05 M TBS. To reduce nonspecific staining, tissue was incubated for 10 min in 20% goat antirabbit serum, Ab-5 (1:100,000; Oncogene Research Products, Cambridge, MA), in 1% goat serum and 0.05 M TBS (including 0.52% Triton X-100, 1.0% gelatin, and 0.02% sodium azide) for 72 h at 4°C. After incubation, sections were rinsed in 0.05 M TBS buffer (pH 7.6; including 0.02% Triton X-100, 1.0% gelatin, and 0.02% sodium azide) followed by a 90-min incubation in 3 μg/ml biotinylated goat antirabbit IgG (Vector, Burlingame, CA). After two 5-min rinses in 0.05 TBS (with 0.02 Triton X-100, 1.0% gelatin and 0.02% sodium azide) and a single 5-min rinse in 0.05 M TBS, sections were incubated in 1:100 dilution of Vector ABC Elite Kit (Burlingame, CA). Sections were then rinsed in three 5-min rinses of 0.05M TBS. Finally, sections were placed in 0.05% diaminobenzidine tetrahydrochloride (DAB) in 0.05 M TBS, including 0.05% hydrogen peroxide for, ~5 min and then rinsed three times in 0.05% TBS.

Loci targeted for analysis were matched for each animal. Fos-IR was visualized using a light microscope and digitized using image analysis software (National Institutes of Health Image 1.61). Cell counting was done using the same software. Threshold parameters for target size and density were derived using the program, and criteria were consistently applied to all sections in each locus measured. Experimenters who were blind to treatment conditions carried out matching and measurements.

**Peptides, Drugs, and Reagents**

Human/rat NPY, human [Leu31,Pro34]PYY, and human des(Tyr-Pro)PYY [PYY-(3–36)] were purchased from Peninsula Laboratories. Peptides were dissolved in a vehicle of artificial cerebrospinal fluid (aCSF) from Harvard Apparatus (Holliston, MA), which served as the control injection. EB and P were dissolved in a vehicle of sesame oil. Steroids, peptides were dissolved in a vehicle of sesame oil, and all other reagents were purchased from Sigma Chemical.

**Statistical Analysis**

Peptide effects on lordosis duration for the first test were compared using two-way ANOVA. Because baseline food intake for the two peptide treatment groups differed significantly (Student’s t-test, P < 0.01), a two-way ANOVA was used to compare peptide effects on 2-h food intake with food intake after vehicle treatment subtracted for each animal. Dose response analyses were performed using 1-way ANOVA, with dose as the repeated measure. Significant ANOVA results at α = 0.05 were followed by pairwise comparisons using Dunnett’s multiple comparisons test or Student-Newman-Keuls test. Paired t-tests were used where indicated.

**RESULTS**

**Experiment 1**

**Effect of NPY on lordosis duration.** NPY produced significant 33 and 67% reductions in lordosis duration at 0.24 and 2.4 nmol, respectively (Fig. 1). Analysis of India ink distribution revealed widespread distribution in the lateral ventricle injection site, third ventricle, contralateral lateral ventricle, and cerebral aqueduct in all hamsters.

**Experiment 2**

**Effect of PYY-(3–36) and [Leu31,Pro34]PYY on lordosis duration.** PYY-(3–36) was significantly more effective than [Leu31,Pro34]PYY in suppressing lordosis [Fig. 2; treatment × dose interaction, F(3,54) = 15.97, P < 0.0001]. PYY-(3–36) suppressed lordosis at all doses in the first hour after intracerebroventricular injection [F(3,24) = 36.5, P < 0.0001]. On the other hand, [Leu31,Pro34]PYY suppressed lordosis [F(3,30) = 10.18, P < 0.0001], but only at the highest dose tested, 2.4 nmol (Fig. 2).

The effect of PYY-(3–36) on lordosis appeared to be reversible but long lasting (Fig. 3). PYY-(3–36) continued to suppress lordosis 4 h after the initial test [F(3,24) = 3.98, P < 0.02], with significant suppression produced by 0.72 and 2.4 nmol doses. Partial recovery of lordosis was apparent 8 h after the initial test, as indicated by failure of all three doses to significantly suppress lordosis. For [Leu31,Pro34]PYY, full recovery of lordosis was evident by 4 h after the initial test.

![Fig. 1. Effect of intracerebroventricular neuropeptide Y (NPY; n = 16) on lordosis duration (means ± SE) in 3-min tests in ovariectomized (O VX) hamsters pretreated with estradiol benzoate (EB) and progesterone (P). Each dose of NPY (closed bars) was tested in a crossover design with artificial cerebrospinal fluid (aCSF) vehicle (0.00, open bars). Paired t-test: *P < 0.01 vs. 0.00.](http://ajpregu.physiology.org/)
Effect of PYY-(3–36) and [Leu 31,Pro34]PYY on food intake. [Leu31,Pro34]PYY and PYY-(3–36) produced dose-related stimulations of food intake 1 (analysis not shown) and 2 after intracerebroventricular injection \( F(3,30) = 514.14, P < 0.0001 \) and \( F(3,24) = 9.84, P = 0.002 \), respectively (Fig. 4). The two peptides did not differ in their capacity to stimulate food intake at either time point.

Experiment 3

Effect of PYY-(3–36) and [Leu31,Pro34]PYY on expression of c-Fos-IR. Fos-IR expression was significantly affected by peptide treatments in four of eight loci examined (Fig. 5). In aPVN, both peptides induced large increases in the number of Fos-IR cells \( F(2,18) = 22.2, P < 0.0001 \), and PYY-(3–36) was significantly more effective than [Leu31,Pro34]PYY. In SCN, PYY-(3–36) reduced the number of Fos-IR cells \( F(2,18) = 7.19, P = 0.0059 \), but [Leu31,Pro34]PYY produced a nonsignificant reduction that did not differ from vehicle or PYY-(3–36). In mPOA, both peptides produced equivalent inhibition of Fos-IR cell number \( F(2,18) = 7.56, P = 0.0049 \). The distribution of Fos-IR in representative sections containing aPVN, SCN, and mPOA is shown in Fig. 6. In the VLS, [Leu31,Pro34]PYY reduced the number of Fos-IR cells \( F(2,18) = 4.91, P = 0.02 \), but PYY-(3–36) did not. Neither peptide affected the number of Fos-IR cells in VMH, Arc, BNST, and mAMY.

DISCUSSION

Our results show that NPY inhibits estrous behavior in hamsters after its administration into the lateral ventricle. On the basis of analysis of india ink distribution in experiment 1, the lateral ventricular route allows injected substances access to a large number of potential targets in the forebrain. In the direct comparison of [Leu31,Pro34]PYY and PYY-(3–36), the most potent and effective agonist in inhibiting estrous behavior was PYY-(3–36), a form of PYY that binds preferentially to Y2- and Y5-NPY receptor subtypes.
and exhibits low to intermediate affinity for Y1 receptors (2, 13, 17, 47). PYY-(3–36) acted with 10-fold greater potency, based on the lowest dose eliciting a threshold effect, was more efficacious in the dose range tested, and had a longer duration of action than [Leu\textsuperscript{31},Pro\textsuperscript{34}]PYY, an agonist that binds preferentially to Y1 and Y5 receptors but is inactive on Y2 receptors (2, 13, 24). Because [Leu\textsuperscript{31},Pro\textsuperscript{34}]PYY and PYY-(3–36) exhibit comparable affinity for Y5 receptors (13), the relative differences in potency and efficacy between these two agonists favor the hypothesis that estrous behavior is principally inhibited through activation of Y2 receptors in Syrian hamsters. [Leu\textsuperscript{31},Pro\textsuperscript{34}]PYY does not bind to Y2 receptors (11, 14, 16); therefore, the modest inhibition of estrous behavior produced by the highest dose of [Leu\textsuperscript{31},Pro\textsuperscript{34}]PYY suggests that another NPY receptor subtype, perhaps Y1, may also link to neural pathways that inhibit estrous behavior.

Conclusions regarding receptor subtype involvement are made cautiously given that only two receptor-differentiating ligands were tested, and both are agonists at more than one NPY receptor subtype. Moreover, although NPY binding sites are abundant in Syrian hamster brain (29), the pharmacology of NPY receptor binding sites in this species has not been explored. In this regard it is noteworthy, however, that Y1, Y2, and Y5 receptor mRNAs are present in hamster brain (S. Chua, personal communication).

The large difference in potency and efficacy between [Leu\textsuperscript{31},Pro\textsuperscript{34}]PYY and PYY-(3–36) in the inhibition estrous behavior was not characteristic of their effects on food intake. The two peptides produced compar-

Fig. 5. Fos immunoreactive (IR) cell numbers (means ± SE) in 8 loci of hamsters treated either with vehicle (n = 6), 0.72 nmol PYY-(3–36) (n = 6) or 0.72 nmol LP PYY (n = 7). Treatment effects in each locus were analyzed by 1-way ANOVA with post hoc comparisons by Student-Newman-Keuls method. Different letters denote significant differences at P < 0.05 level of confidence. PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; mPOA, median preoptic area; VLS, ventral lateral septum; VMH, ventromedial hypothalamus; ARC, arcuate nucleus; BNST, bed nucleus of the stria terminalis; mAMY, dorsomedial amygdala.
able dose-related increases in food intake, with [Leu$^{31}$, Pro$^{34}$]PYY slightly more potent than PYY-(3–36) based on the lowest dose required for a significant effect. It was previously demonstrated that NPY stimulates food intake in Syrian hamsters (22). The relative potency of [Leu$^{31}$, Pro$^{34}$]PYY and PYY-(3–36) in stimulating food intake in the current experiment is a very close match to their relative potency to activate Y5 receptors in biochemical experiments (13). Our results, therefore, favor the hypothesis that the effect of NPY on feeding in Syrian hamsters is mediated by Y5 receptors. As is the case with estrous behavior, other alternatives are possible, including an action at multiple or novel receptors. Our results are comparable to those obtained in rats using similar agonists (13, 40).

A dual behavioral effect of NPY, inhibition of estrous behavior, and stimulation of feeding was first demonstrated in female rats (6). The present results, taken together with previous reports (22), argue that NPY has a similar function in Syrian hamsters. Moreover, the current results suggest that NPY’s effects on feeding and estrous behavior are mediated by separate and independent receptors.

Immunocytochemical detection of the protein product of the immediate early gene c-fos has served as a marker of neural activation in a number of studies examining effects of either NPY or steroid hormones (12, 23, 25, 33, 48). To illuminate the neural circuitry controlling inhibition of estrous behavior and stimulation of feeding, we compared Fos-IR expression after administration of an intermediate dose of each peptide. PYY-(3–36) was tested at a dose that almost totally suppressed estrous behavior but did not significantly increase food intake, whereas [Leu$^{31}$, Pro$^{34}$]PYY was tested at a dose that stimulated food intake at 1 and 2 h but did not inhibit estrous behavior.

We observed widespread distribution of Fos-IR expression in O VX hamsters primed with EB and P. Peptide treatments influenced Fos-IR in four of eight loci examined, and in three of those four loci, PYY-(3–36) or [Leu$^{31}$, Pro$^{34}$]PYY, or both, reduced the number of cells expressing Fos-IR. In one locus, the aPVN, both peptides stimulated large increases in Fos-IR expression, suggesting that neural circuitry controlling both food intake and estrous behavior may include the aPVN. It is noteworthy that PYY-(3–36) was significantly more potent than [Leu$^{31}$, Pro$^{34}$]PYY in stimulating Fos-IR in aPVN, suggesting the possibility that PYY-(3–36) activated a pathway insensitive to [Leu$^{31}$, Pro$^{34}$]PYY. In the VLS, on the other hand, [Leu$^{31}$, Pro$^{34}$]PYY inhibited Fos-IR, whereas PYY-(3–36) was without effect. Despite these differences, the distributions of Fos-IR elicited by the two agonists were strikingly similar. Assuming that PYY-(3–36) and [Leu$^{31}$, Pro$^{34}$]PYY affect behaviors through signaling pathways that activate Fos-IR, our results are consistent with the notion that NPY control of estrous and feeding behavior involves neural circuits that innervate several of the same nuclei including the aPVN, mPOA, and SCN. Whether these pathways overlap at any level remains to be determined. Of course, other interpretations of the data are plausible.

It should be noted that peptide effects on Fos-IR might be unrelated to the function of these peptides in feeding or estrous behavior. In fact, NPY and its analogs are known to affect neuroendocrine functions, including timing of the circadian clock in the SCN (15, 18) and GnRH activity in the mPOA (20, 35, 44).

Our results are consistent with previous studies showing that NPY potently induces Fos-IR in the PVN of rats (23, 25, 48). Changes in Fos-IR, however, were not seen in all regions important in feeding (3, 41) or neuroendocrine function (12, 33). Neither peptide affected Fos-IR expression in the BNST and mAMY, nor in the Arc or VMH, where NPY has been shown to stimulate moderate increases in Fos-IR in rats (25).

Support for NPY’s physiological role in the control of feeding and reproductive behavior remains to be established in hamsters. Pharmacological evidence from rats, however, argues persuasively that NPY plays a physiological role in these behaviors. Central administration of NPY antibodies, for example, suppresses 24-h food intake (8) and attenuates 2-deoxy-D-glucose-induced hyperphagia (19) in rats. NPY antibody influ-
sion also increases sexual receptivity and reduces food intake and body weight gain in genetically obese and infertile Zucker rats (28).

Perspectives

Limited food availability increases hunger and diminishes fertility in mammals (4). Little is known about the neurotransmitters controlling nutritional infertility; however, the close relationship between fertility and nutrient status suggests neurotransmitters important in control of feeding may also be involved in the control of reproductive function. NPY fits this model. It has been proposed that NPY plays a dual role in motivation, decreasing sexual drive while increasing drive to secure adequate nutrient energy (21). The brain is enriched in NPY afferents to sites such as the aPVN, which has a well-characterized role as a target of NPY in the control of food intake (39). The large effect of PYY-(3–36) on stimulation of Fos-IR expression in the aPVN and inhibition of lordosis raises the suggestion that NPY may act on targets in the aPVN to control reproductive behavior. When access to adequate nutrition is restricted, activity may increase in NPY pathways integrating nutritional status. The present results suggest that divergence between the neural circuits controlling feeding and reproduction may be through pathways expressing differing NPY receptor subtypes, Y2 for estrous behavior, and Y5 for feeding behavior.

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