Selective Antagonism of the NPY Y5 Receptor Does Not Have a Major Effect on Feeding in Rats

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Neuropeptide Y (NPY) is thought to play a key role in stimulating feeding, thus making NPY receptors attractive appetite suppressant drug targets for treating obesity. Because the orexigenic effects of NPY have been ascribed to actions at the NPY Y5 receptor, we have determined the role of this receptor in feeding in rats, using a small molecule antagonist of this receptor. NPY5RA-972 is a selective and potent (<10 nmol/l) NPY Y5 receptor antagonist. This compound is central nervous system (CNS) penetrant, and an oral dose of 10 mg/kg NPY5RA-972 to rats produced concentrations in cerebrospinal fluid that greatly exceeded the in vitro IC50 (inhibitory concentration 50%). Indeed, at doses to rats as low as 1 mg/kg, NPY5RA-972 inhibited feeding induced by intracerebroventricular (ICV) administration of a selective NPY Y5 agonist ([cPP1–7,NPY19–23,Ala31,Aib32,Gln34]-hPP). However, in the dose range 1–10 mg/kg, NPY5RA-972 had no significant effect on food intake in Wistar rats induced to feed by either ICV NPY or 24 h fasting or in free-feeding Wistar or obese Zucker rats. Chronic administration of NPY5RA-972 (10 mg/kg twice daily) had no effect on food intake or body weight in either free-feeding Wistar rats or dietary obese rats. These data indicate that NPY5RA-972 is a potent, selective, orally active, and CNS-penetrant antagonist of the NPY Y5 receptor that prevents feeding driven by activation of this receptor. The data obtained with this antagonist indicate that the NPY Y5 receptor is not a major regulator of feeding in the rat. Diabetes 51: 2441–2449, 2002

Research into appetite control during the past decade has been ignited by the discovery of leptin and fueled by the recognition of obesity as a widespread and rapidly growing disease (1). Leptin is a fat-derived hormone that signals energy (fat) storage levels to the hypothalamus. A number of previously identified (e.g., neuropeptide Y [NPY], melanin-storing levels to the hypothalamus. A number of previous studies have implicated NPY in the regulation of feeding. NPY is a 36–amino acid peptide that is probably the most studied putative neuropeptide regulator of appetite. In rodents, NPY is expressed in regions of the hypothalamus thought to be important in the regulation of feeding. Its level of expression is sensitive to energy status, and its administration stimulates feeding and reduces energy expenditure; immunoneutralization of endogenous NPY inhibits feeding (reviewed in 12,13). Collectively, these types of data have resulted in the recognition of NPY as a key regulator of appetite even though targeted gene deletion of NPY provides only limited evidence to support this concept (14,15).

The effects of NPY are mediated by distinct receptor subtypes; NPY Y1 and NPY Y5 have become recognized as the most likely candidates for the mediation of the effects of NPY on food intake (12,13,16). In particular, the importance of NPY Y5 has been suggested by the parallel pharmacology of the receptor in vitro and feeding in rodents (17–24), and the inhibitory effects of NPY Y5 receptor antisense oligonucleotides (25–28), NPY Y5 deficiency (29), and an NPY Y5 antagonist (30) on NPY-induced feeding in rodents. We investigated the role the NPY Y5 receptor in feeding in the rat using a previously described peptidic NPY Y5 selective agonist [cPP1–7,NPY19–23,Ala31,Aib32,Gln34]-hPP (20) and a novel, small molecular weight, potent, and selective NPY Y5 antagonist (9-isopropyl-4-methyl-3-(4-morpholinocarbonyl- amino)-9H-carbazole, termed NPY5RA-972) (31). The data described herein argue that, contrary to many previous data, NPY Y5 is not a significant regulator of feeding behavior in the rat.
**ROLE OF NPY Y5 IN RAT FEEDING**

**RESEARCH DESIGN AND METHODS**

**Peptides**

Ala31,Aib32,Gln34-hPP, and sibutramine were purchased from Bachem (Saffron Walden, Essex, U.K.), Sigma Aldrich, Tocris Cookson (Bristol, U.K.), and St. Andrews ChemTech (Fife, U.K.). Specifically, NPY5RA-972 (31) was synthesized within the Medicinal Chemistry Laboratory at AstraZeneca (Alderley Park, U.K.).

**Membrane binding assays.** H15 insect cells transiently (48 h) transfected (baculovirus-infected) with either rat or human NPY Y5 receptor were used for preparation of NPY Y5 membranes. Human Y1, Y2, and NPY Y4 membranes were prepared from SK-N-MC, KANT-TS, and stable NPY Y4 expressing CHO cells, respectively. Membranes were prepared by sonication (3 × 15 s) in ice-cold hypotonic buffer (12.5 mmol/l Tris, 1.25 mmol/l EDTA, 2.5% sucrose [pH 7.4]) containing complete protease inhibitor tablets (1/100 ml; Roche Molecular Biochemicals). The lysate was layered onto a 41% sucrose cushion and centrifuged at 100,000 g for 1 h. The membrane layer was harvested and stored (in 50 mmol/l Tris, 5 mmol/l EDTA, 10% sucrose [pH 7.4]) at −80°C until use.

**Binding assays.** Were performed in presiliconized, round-bottomed, polypropylene 96-well plates (Corning Costar). Compounds were dissolved in DMSO and diluted (20-fold) in binding buffer (50 mmol/l HEPES, 2.5 mmol/l CaCl2, 1 mmol/l MgCl2, 0.5% BSA [pH 7.4]). Each incubate had 100 μl of membranes (sufficient to give a specific binding of 1,500 cpm) and 10 μl of compound solution. After a 2-h incubation at room temperature, incubates were filtered (Whatman GF/C) using well-filter plates (Packard Instruments) pretreated with 0.5% polyethyleneimine using a Brandel harvester.

**NPY5RA-972 concentrations in plasma** were determined by high-performance liquid chromatography–ultraviolet (285 nm) analysis. In separate experiments, male Wistar rats (350–400 g) were dosed with NPY5RA-972 (10–80 mg/kg p.o.). One hour later, they were terminally anesthetized with sagatal (pentobarbitone, 60 mg/ml, 0.6 ml/rat) and mounted in a stereotaxic apparatus, and a cerebrospinal fluid sample (~100 μl) was collected using a 25-G butterfly needle inserted through the muscles of the neck and piercing the dura overlying the cisterna magna. Cerebrospinal fluid (CSF) samples that showed any discoloration were discarded; only clear samples were subject to analysis. CSF and plasma samples collected terminaly were processed for subsequent analysis of compound concentrations.

**Effects of NPY** or [cPP-7, NPY-19-23]Ala31,Ala-29,Glut34-hPP on food intake. Either NPY or [cPP-7, NPY-19-23]Ala31,Ala-29,Glut34-hPP was injected intracerebroventricularly into male Wistar rats (n = 5–7) in the free-feeding state during the early light phase (commencing 08:00–10:00 h). Animals were returned to their home cage that contained a preweighed amount of food, and food that remained at 2, 4, and 6 h was determined on a Mettler Toledo PG2002-S balance (Fischer Scientific, Leicester, U.K.), corrected for spillage, and recorded to the nearest 0.1 g.

**Effects of NPY5RA-972 on food intake induced by NPY or [cPP-7, NPY-19-23]Ala31,Ala-29,Glut34-hPP.** NPY5RA-972 (1–10 mg/kg) or vehicle was dosed (p.o.) to male Wistar rats (n = 4–7) in the free-feeding state during the early light phase (commencing 08:00–10:00 h). One hour later, these rats received an ICV injection of either [cPP-7, NPY-19-23]Ala31,Ala-29,Glut34-hPP (0.2 or 0.6 mmol/rat) or NPY (0.2 or 2.0 mmol/rat). Cumulative food intake was measured as described.

**Acute effects of NPY5RA-972 on food intake in fasted, free-feeding, and obese Zucker rats.** Male Wistar rats (219–267 g, n = 8–12) were fasted from 10:00 h and 23 h later dosed (p.o.) with either vehicle or NPY5RA-972 (1–10 mg/kg). One hour later, preweighed food hoppers were returned to the animals, and cumulative food intake was measured 1, 2, 4, and 6 h later. Male-free-feeding male Wistar rats (240–306 g, n = 8 per group) or male obese Zucker rats (472–492 g, n = 7–12) were dosed (p.o. or vehicle) with either NPY5RA-972 (1–10 mg/kg) 1 h before the onset of the dark-phase (18:00 h) and cumulative food intake measured from 18:00 h for either 2, 4, 15, and 24 h or 6, 14, and 24 h, respectively.

**Chronic effects of NPY5RA-972 and sibutramine on food intake and body weight in diet-induced obese Zucker rats.** To ascertain a suitable twice-daily dosing regimen for chronic studies that provided 24-h blockade of NPY Y5 receptors in brain, we determined the effects of 12-h predosing of NPY5RA-972 on food intake induced by [cPP-7, NPY-19-23]Ala31,Ala-29,Glut34-hPP. Male Wistar rats (n = 6/group) were dosed with NPY5RA-972 (1–10 mg/kg) at 21:00 h and received an ICV injection of [cPP-7, NPY-19-23]Ala31,Ala-29,Glut34-hPP (0.6 mmol/rat) 12 h later. Food intake for the 2 h after [cPP-7, NPY-19-23]Ala31,Ala-29,Glut34-hPP injection was determined as described above. As a positive control, an additional group of rats were administered NPY5RA-972 (3 mg/kg p.o., n = 5) 1 h before [cPP-7, NPY-19-23]Ala31,Ala-29,Glut34-hPP.

**In chronic studies that used previously unmanipulated Wistar rats, NPY5RA-972 (10 mg/kg, n = 7) or vehicle (n = 6) was dosed (p.o.) twice daily (at 06:00 h and 16:00 h). For 3 days before commencement of dosing with compound, rats were accustomed to handling and dosing with vehicle only. Food intake and body weight were measured daily. A positive control group (n = 7) receiving sibutramine was included in the chronic studies. Sibutramine is marketed appetite-suppressant drug that acts principally by inhibiting the reuptake of serotonin and norepinephrine (33). Sibutramine was dosed at 3 mg/kg once daily (at 16:00 h), a dose that was previously proved to be effective in our and others’ hands (34), and is the maximum dose we have found that avoids marked behavioral disruption. Sibutramine-treated rats also received a dose of vehicle (at 06:00 h) to maintain consistency of procedures across all groups.

**Data presentation and statistical analysis.** Unless otherwise stated, results are presented as mean ± SE. In vitro dose-response curves were
NPY5RA-972 bound with high affinity to both the human and the rat Y5 receptor (half-maximal inhibitory concentration (IC50), 3.1 ± 1.0 nmol/l and 9.3 ± 1.2 nmol/l, respectively; Table 1). In contrast, 10 μmol/l NPY5RA-972 displayed no binding to human NPY Y1, NPY Y2, or NPY Y4 receptors and showed at least 1,000-fold selectivity for NPY Y5 in a commercially available panel (MDS Pharma Services) of 129 different bindings assays (including assays for NPY, muscarinic, serotonergic opioid, melanocortin, galanin, cholecystokinin, cannabinoid, neurotensin, glucagon-like peptide receptors, and serotonin transporter).

In a functional reporter assay for NPY Y5 antagonism, NPY5RA-972 completely reversed the suppressive effect of 10 nmol/l NPY on 1 μmol/l forskolin-stimulated HEK 293 cells stably expressing the rat Y5 receptor (Table 1). NPY5RA-972 displayed no agonist activity as indicated by a lack of effect of 10 μmol/l of the compound in the absence of NPY in this reporter assay (data not shown).

NPY5RA-972 (10 mg/kg p.o.) inhibited food intake in rats induced by [cPP1–7, NPY19–23, Ala31, Aib32, Gln34]-hPP (ICV). NPY5RA-972 (10 mg/kg) inhibited food intake in rats induced by either submaximum (0.2 nmol) or maximum (0.6 nmol) doses of the NPY Y5 selective agonist, NPY5RA-972 (p.o.) massively exceeded the IC50 of NPY5RA-972 (153 ± 35 nmol/l) after a dose of 10 mg/kg (p.o.) massively exceeded the IC50 of NPY5RA-972 (by 16- to 50-fold; Tables 1 and 2), with higher doses producing even greater CF concentrations.

NPY5RA-972 completely reversed the suppressive effect of [cPP1–7, NPY19–23, Ala31, Aib32, Gln34]-hPP injected intracerebroventricularly produced a marked and dose-dependent increase in food intake (Fig. 1A). The maximum dose of this NPY Y5 selective agonist seemed slightly lower (0.6 nmol) than that for NPY (2.0 nmol; Fig. 1A and B). The time course of effect of these two peptides seemed slightly different, with the NPY Y5 selective agonist having a less pronounced initial but more sustained effect (Fig. 1C), a profile identical to what we have observed with the less selective NPY Y5 agonist hPP (data not shown).

NPY5RA-972 on food intake induced by NPY or [cPP1–7, NPY19–23, Ala31, Aib32, Gln34]-hPP. NPY5RA-972 (p.o.) inhibited food intake in rats induced by either submaximum (0.2 nmol) or maximum (0.6 nmol) doses of the NPY Y5 agonist (Fig. 2A). Even at doses as low as 1 mg/kg, NPY5RA-972 produced a marked and significant inhibition of the feeding response to NPY Y5 agonist (Fig. 2B).

In contrast to the abolition of the feeding response to a maximum dose of NPY Y5 selective agonist, NPY5RA-972 (3 mg/kg p.o.) had no effect on food intake induced by a maximum dose (2.0 nmol) of NPY infused 1 h later (Fig. 2A).

### Table 1

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<thead>
<tr>
<th>Binding (IC50, nmol/l)</th>
<th>cAMP reporter response (EC50, nmol/l)</th>
<th>cAMP reporter response (IC50, nmol/l)</th>
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<tr>
<td>hNPY Y5</td>
<td>rNPY Y5</td>
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<tr>
<td>hNPY Y1</td>
<td>0.11</td>
<td>0.07</td>
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<td>hNPY Y2</td>
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<td>14</td>
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<td>hNPY Y4</td>
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<td>36</td>
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<td>rNPY Y5</td>
<td>0.47</td>
<td>0.22</td>
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<td>3.1</td>
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IC50 values at the human NPY Y1, Y2, Y4 and NPY Y5 and rat NPY Y5 were determined using membrane binding assays described in RESEARCH DESIGN AND METHODS. Functional activities were determined in cAMP reporter assays using HEK293 cells stably expressing the rat NPY Y5 receptor and a reporter cassette consisting of a cAMP-driven β-galactosidase gene.

In separate dose-response studies (10–80 mg/kg p.o.), total plasma concentrations of NPY5RA-972 at 1 h increased with dose but did not scale linearly. CSF concentrations of NPY5RA-972 (153 ± 35 nmol/l) after a dose of 10 mg/kg (p.o.) massively exceeded the IC50 of NPY5RA-972 (by 16- to 50-fold; Tables 1 and 2), with higher doses producing even greater CSF concentrations.

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In broad agreement with Cabrele et al. (20), we found that [cPP1–7, NPY19–23, Ala31, Aib32, Gln34]-hPP binds with high affinity to rat NPY Y5, but in contrast to what we have observed with the less selective NPY Y5 agonist hPP (data not shown).

### Table 2

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<th>Plasma and CSF concentrations of NPY5RA-972</th>
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<td>Oral dose</td>
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<tr>
<td>Total plasma (μmol/l)</td>
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<td>CSF (μmol/l)</td>
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Compound concentrations in plasma and CSF were determined by high-performance liquid chromatography–ultraviolet (285 nm) analysis.
Furthermore, even at higher doses of NPY5RA-972 (10 mg/kg), this antagonist had no effect on feeding induced by a submaximum dose (0.2 nmol) of NPY (Fig. 3A). Acute effects of NPY5RA-972 on food intake in fasted, free-feeding, and obese Zucker rats. NPY5RA-972 (1–10 mg/kg p.o.) dosed 1 h before presentation of food had no significant effect on food intake for the ensuing 6 h (Fig. 4A). NPY5RA-972 (1–10 mg/kg) also failed to affect the fast-induced feeding response in another strain of rat (Sprague-Dawley, data not shown). Similarly, in free-feeding Wistar rats (Fig. 4B) or obese Zucker rats (Fig. 4C) dosed 1 h before the onset of the dark cycle (main feeding phase), NPY5RA-972 had no significant effect on food intake.

Chronic effects of NPY5RA-972 and sibutramine on food intake and body weight in normal and dietary obese rats. At a dose of 10 mg/kg, NPY5RA-972 (but not lower doses) 12 h predosing markedly inhibited food intake induced by the NPY Y5 selective agonist for 2 h (Fig. 5), indicating that this dose is sufficient to antagonize NPY Y5 receptors in the brain for at least 12–14 h. Therefore, a dosing regimen of 10 mg/kg twice daily was selected for chronic studies.
In normal Wistar rats, 3 mg/kg sibutramine produced a marked (30%) inhibition of food intake on the first day of dosing (Fig. 6A). Consistent with published data, the effects of sibutramine on food intake diminished with time (34,37), although cumulative food intake over the 9-day study was significantly (P < 0.001) lower in sibutramine-treated (213.3 ± 5.7 g) than in vehicle-treated (260.2 ± 3.0 g) rats. Sibutramine also significantly reduced overall body weight gain (vehicle 30 ± 2 g, sibutramine 14 ± 3 g; P < 0.001; Fig. 6B). However, chronic antagonism of NPY Y5 with NPY5RA-972 produced no significant effect on either food intake (cumulative food intake 252.3 ± 6.3 g; Fig. 6A) or body weight gain (27 ± 1g; Fig. 6B) compared with vehicle-treated controls.

Five-week-old Wistar rats were placed on a highly palatable high-energy diet or maintained on normal rat diet for a period of 12 weeks. After 10 weeks on the high-energy diet, only rats that exhibited clear hyperphagia and obesity compared with rats fed a normal diet were selected. Indeed, the calorie intakes (107 ± 4 vs. 72 ± 3 kcal/d) and body weights (596 ± 8g vs. 478 ± 18 g) were markedly higher in this selected obese cohort compared with the age-matched controls that were fed the regular

![Image](image1.png)

**FIG. 3.** Effect of NPY Y5 selective antagonist NPY5RA-972 on food intake induced by NPY or the NPY Y5 selective agonist [cPP1-7, NPY18-23,Ala31,Aib32,Gln34]-hPP. A: Vehicle or NPY5RA-972 (3 mg/kg) was dosed by oral gavage (p.o.) 1 h before administration of NPY Y5 agonist (0.6 nmol) or NPY (2.0 nmol) into the third cerebroventricle of male rats during the light cycle. Control animals received vehicle (HPMC/Tween, p.o.) followed 1 h later by ICV vehicle (sterile water). ANOVA indicated significant intergroup differences at all time points. *P < 0.05, **P < 0.001 versus 0.6 nmol NPY Y5 agonist, not significant (ns) versus 2.0 nmol NPY (n = 5–6).

B: Vehicle or NPY5RA-972 (10 mg/kg) was dosed by oral gavage (p.o.) 1 h before administration of NPY Y5 agonist (0.6 nmol) or NPY (0.2 nmol) into the third cerebroventricle of male rats during the light cycle. ANOVA indicated significant intergroup differences at all time points. *P < 0.05, **P < 0.001 versus 0.6 nmol NPY Y5 agonist, not significant (ns) versus 0.2 nmol NPY (n = 6–7).

![Image](image2.png)

**FIG. 4.** Effect of NPY Y5 selective antagonist NPY5RA-972 on food intake in male Wistar rats induced to feed by previous fasting for 24 h (n = 8–12; A), free-feeding male Wistar rats (n = 8 per group; B), and free-feeding male obese Zucker rats (n = 7–12; C). In each experiment, NPY5RA-972 (1–10 mg/kg) was dosed by oral gavage (p.o.) 1 h before commencement of food intake measurements. In fasted rats, this meant that rats were dosed 1 h before presentation of food. ANOVA indicated no significant intergroup differences at any time point in any of the three experiments.
diet. This diet-induced obese (DIO) cohort was randomly divided into three groups that were dosed (p.o.) with vehicle (twice daily), sibutramine (3 mg/kg, once daily) or NPY5RA-972 (10 mg/kg, twice daily). As in the previous experiment, sibutramine produced a significant ($P < 0.001$) inhibition of energy intake (cumulative energy intake $791 \pm 26$ kcal) compared with vehicle-treated (1,227 \pm 55 kcal) rats, although its effects in DIO animals seemed far greater (Fig. 7A) than in Wistar rats that were fed a regular diet (Fig. 6A). Indeed, sibutramine not only slowed weight gain but also caused significant ($P < 0.001$) weight loss in DIO rats over the 12-day study period (vehicle 14.0 \pm 6.1 g, sibutramine 37.0 \pm 7.8 g; Fig. 7B).

In contrast, NPY5RA-972 had no significant effect on either calorie intake (cumulative intake 1,199 \pm 87 kcal) or body weight (12 \pm 9 g; Fig. 7).

**DISCUSSION**

A number of lines of evidence have suggested that NPY Y5 is a major receptor subtype that mediates the effects of NPY on feeding and has attracted much academic and industrial interest as a possible appetite suppression approach to the treatment of obesity (12,30,38). Notably, the majority of these data have been generated in rodents. Supportive data in humans has been restricted to a neuroanatomical distribution similar to rodents (39,40) and to preliminary human genetic evidence in a very specific cohort (41). Indeed, other human genetic studies have resulted in negative findings (42,43). The data reported herein identify NPY5RA-972 as a potent and selective NPY Y5 receptor antagonist with good systemic and CNS exposure after oral dosing in rats, suggesting that it is a useful tool with which to explore the role(s) of NPY Y5 in physiological processes. Coadministration studies indicated that NPY5RA-972 prevented feeding induced by the NPY Y5 selective agonist [cPP$_{1-7}$,NPY$_{19-23}$, Ala$_{31}$,Alb$_{32}$,Gln$_{34}$]-hPP. The most obvious conclusion of these experiments is that NPY5RA-972 after oral dosing occupies sufficient NPY Y5 receptors in the brain to prevent NPY Y5 agonist–induced feeding. The possibility that this apparent agonism-antagonism reflects activities at alternative, non–NPY Y5 feeding-related targets cannot be totally disproved. However, 1) [cPP$_{1-7}$,NPY$_{19-23}$, Ala$_{31}$,Alb$_{32}$,Gln$_{34}$]-hPP is highly selective for NPY Y5 compared with other known NPY receptors (20 and present study); 2) NPY5RA-972 shows at least 1,000-fold selectivity against a panel of 129 receptors, enzymes, and transporters that included a number of receptors relevant to feeding; and 3) [cPP$_{1-7}$,NPY$_{19-23}$,Ala$_{31}$,Alb$_{32}$,Gln$_{34}$]-hPP and NPY5RA-972 are of different structural classes (peptidic versus nonpeptidic), optimized for NPY Y5 potency and selectivity by two different groups using completely different chemical strategies, making it highly unlikely that both were unwittingly optimized for activity at alternative identical targets. It seems much more likely that their activities in co-administration experiments reflect agonism and antagonism at the NPY Y5 receptor, leading us to conclude that at the doses used in this study, NPY5RA-972 is an ideal tool to test hypotheses regarding the role of the NPY Y5 receptor in the rat.

Although low doses (1–10 mg/kg p.o.) of NPY5RA-972 inhibited food intake elicited by a selective NPY Y5 receptor agonist, it had no effect on feeding as a result of NPY (ICV), fasting, free-feeding in normal, genetically obese, or dietary obese rats. These findings strongly sug-
inhibiting food intake in NPY Y5 antagonists (47,48) reported to produce marked hypophagic effects in rodents is unknown, but notably no data have been presented to indicate that antagonism of NPY Y5 is their primary mode of action. We believe that the present data show convincingly that NPY5RA-972 potently antagonizes NPY Y5 receptors in the brain but fails to affect feeding in a variety of rat feeding models. Emerging preliminary data with a range of other small molecular weight NPY Y5 antagonists (38,49–52) are consistent with our findings.

It seems pertinent to revisit the evidence supporting a role for Y5 in feeding in rodents. This primarily consisted of data showing similarities of the pharmacology of NPY Y5 receptors in vitro and the pharmacology of NPY-related peptides on feeding in vivo (17–19,23). Although this conclusion has been disputed (53,54), it is now clear that selective activation of NPY Y5 stimulates feeding in rats (20–22). The present study therefore argues that the hyperphagic effect of selective receptor activation is not necessarily a good predictor of the importance of that receptor in feeding under more physiological circumstances. Studies using antisense oligonucleotides to down-regulate NPY Y5 expression have also supported the hypothesis that full expression of this receptor is required to elicit the full hyperphagic effects of NPY and that NPY Y5 is important in the regulation of feeding in normal rats (25–28). The explanation for the differences in findings with antisense and the effects of an antagonist are unknown, but this discrepancy serves to indicate that such antisense studies are not always predictive of the effects of pharmacological manipulation.

The lack of a hypophagic phenotype of NPY Y5–deficient mice clearly is not supportive of a major role for NPY Y5 in regulating feeding in mice (29). Furthermore, studies indicating that NPY Y5–deficient mice have a reduced hyperphagic response to ICV NPY (29) have now been contradicted (55), and such knockout studies equally indicate that NPY Y1 (or other NPY receptor) is a likely receptor subtype mediating the effects of NPY on food intake. Indeed, a recent study of the effects of a selective NPY Y1 antagonist in NPY-treated wild-type, NPY Y1–deficient, and NPY Y5–deficient mice provides compelling evidence for the involvement of NPY Y1 in NPY-induced feeding (55). A number of other groups have shown that selective NPY Y1 antagonism inhibits NPY-induced feeding in rats (12,13,38,48).

Little is known about the function of NPY Y5 in rodent brain other than its putative role in feeding and its possible mediation of the antiseizure activity of NPY (56). The development of highly potent and selective agonists and antagonists for NPY Y5 should now permit a more detailed investigation of the biology of this receptor.

ACKNOWLEDGMENTS

The technical assistance of Gunn-Britt Forsberg, Britt-Marie Fihn, and Bill Brown and critical evaluation of the manuscript by Drs. David Morgan, David Smith, Lynn
Pritchard, and Carl Montague are gratefully acknowledged.

REFERENCES


