Contemporary Development In NPYY5 Receptor Antagonist
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Citation

Abstract
The prevalence of obesity continues to increase throughout the world and the burden of obesity and related co morbidities is large. Contemporary consideration has focused on physiology of neuropeptide Y and its role in the regulation of energy homeostasis. The data obtained to date with these newly developed tools suggests that neuropeptide Y receptor antagonists, particularly neuropeptide YY5 receptor antagonist, have potentiality to bless the obesity patients worldwide. However, the redundancy of the neurochemical systems regulating energy homeostasis may limit the effect of ablating a single pathway. New leads are under research by major pharmaceutical companies to limit the side effects and explore the area to meet clinical requirement.

INTRODUCTION
Obesity is defined as excess of adiposity for a given body size and results from a chronic imbalance between energy intake and energy expenditure, become the catastrophic illness to increase metabolic complication throughout the world. It increased the risk of diabetes, hypertension, dyslipidemias, cardiovascular disease, gallstone, osteoarthritis, certain forms of cancer and reduce the life expectancy [1] . Neuropeptide Y (NPY) is a neuropeptide made up of 36 amino acids with an amide in carboxy terminal position (pancreatic polypeptide family) originally discovered in extracts of porcine brain [2] . It is found in abundance in the central and peripheral nervous system, whose alterations provoke eating, emotional, cardiovascular, diabetes and other diseases [3] . NPY receptors are a family of seven transmembrane G protein coupled receptors (7t-GPCR), designated collectively as Y receptors that are expressed throughout the central and peripheral nervous systems [4] .

NPY can be found in most brain regions, particularly in the cortex, hippocampus, thalamus, hypothalamus and brainstem [5] . NPY, peptide YY and pancreatic polypeptide elicit their physiological effects by interacting with at least six distinct GPCR designated Y1, Y2, Y3, Y4, Y5 and Y6 [6] . The structural differences among neuropeptide Y receptors is beneficial to drug discovery efforts since compounds with high affinity for a particular neuropeptide Y receptor are less likely to interact with other neuropeptide Y receptors. In addition to having distinct amino acid sequences, each of the neuropeptide Y receptors is characterized by a unique pharmacological profile and distinct tissue localization. The
Y1 receptor was cloned and sequenced in 1992, the Y2 receptor and the Y4/PP1 receptor in 1995, and the Y5 receptor in 1996 [7]. The term dNPY receptors have been retained even though NPY is not the preferred endogenous ligand for all Y receptors [8]. Y1, Y2 and Y5 bind preferentially NPY and PYY, whereas Y4 binds preferentially PP. Y1 and Y5 receptors exhibit similar high affinities for NPY, PYY and [Pro34]-substituted analogs of NPY or PYY (e.g., [Leu31, Pro34] NPY), but can be distinguished by the selective, nonpeptide Y1 antagonist, BIBP 3226 [10]. Thus the efforts have been focused on Y1 or Y5 receptor selective antagonists. They are implicated in several biological roles including vasoconstriction, learning and memory and energy balance [9]. It is highly expressed in several regions of the brain and is released into the circulation from neuronal storages in times of stress. In the CNS, NPY has been implicated in feeding, anxiety and depression, endocrine function, and metabolism [10]. NPY is a powerful stimulant of food intake when administered directly into the hypothalamus.

DEVELOPMENT OF NON-PEPTIDE NYPY5 RECEPTOR ANTAGONISTS

The NPY5Y5 receptor was initially identified by molecular cloning. The NPY5Y5 receptor is pharmacologically distinguished by its high affinity for both N-terminally truncated analogues of NPY and [Pro34] peptide YY. Neuropeptide YY5 receptor mRNA is discretely localized in rat and human brain, primarily in piriform cortex, olfactory tubercle and hypothalamus [11]. NPY5Y5 receptor binding sites have also been detected in these regions, although some groups fail to detect neuropeptide YY5 receptor binding in hypothalamus [12]. The receptor most likely subtypes responsible for centrally mediated NPY induced feeding responses are NPY Y1 and NPY Y5 [13]. There is now a significant body of primary and patent literature describing potent devoted to neuropeptide YY5 receptor antagonists reported. The following discussion focuses on the pharmacology of nonpeptic NPY5Y5 receptor antagonists, with emphasis on reports from the primary literature that attempt to correlate neuropeptide YY5 receptor selective antagonism with effects on food intake and body weight.

The identification of the Y5 receptor as a potential feeding receptor subtype has stimulated a number of investigations in this area. In light of this conflicting evidence, the evaluation of structurally diverse compound classes remains important in order to better understand the role of the Y5 receptor in the control of appetite, and hence the potential utility of these compounds for the treatment of obesity. The initial evidence supporting the role of Y5 as an important regulator of feeding behavior include the positive correlation between the binding affinity of Y5 peptide agonists in vitro and there in vivo potency as orexigenic agents in animal feeding models [14]. For example, Novartis and Synaptic were the first to report a series of 2, 4-diaminoquinazolines and aryl sulfonamides as potent Y5 receptor antagonists [15]. Subsequently, a number of patents have also claimed a variety of compound classes that act at the Y5 receptor.

Youngman and co-workers from synaptic have described the results of their structure-activity investigations of a series of L-aralkylaminotetralin sulfonamides (1) targeted to the Y5 receptor antagonism. Further development leads to compound (2 & 3) shows effective binding with NPY5Y5 antagonism (21 nM & 1.0 nM respectively). Compound shows no significant affinity for human neuropeptide YY1 and Y2 receptors, as well as for over 30 GPCRs and ion channels [16]. Amgen scientists have also work on the same chemical skeleton and developed compound (4) but the datas were not disclosed officially [17]. Benzoxazinone derivative (5) is a good lead with specific binding with NPY5Y5 receptor specifically at 7.6 nM and antagonism confirmed by filter binding assay in forskolin-induced cyclic AMP test using PYY [18]. Aminoquinazoline derivative CGP 71683A (6) reported in 1998 by a group from Novartis and Synaptic [19]. A novel series of NPY5Y5 receptor antagonists based on an alpha-aminotetralin scaffold has been reported by a group at R.W. Johnson [20]. Potent analogues such as 1 and 2 were identified through optimization of a micro molar screening lead. The latter compound contains the bis-(amino methyl) cyclohexyl linker present in CGP71683A. Starting from a lead with weak affinity for neuropeptide YY1 and Y5 receptors, CGP 71683A was discovered through a process of combinatorial chemistry and traditional medicinal chemistry. Structure–activity relationship studies suggest that important pharmacophore elements of CGP71683A are the hydrogen bond donor–acceptor properties of the amino quinazoline ring and the hydrogen bond accepting sulfonamide separated by an appropriate distance by the hydrophobic spacer [21]. CGP 71683A has high affinity for the rat and human neuropeptide YY5 receptors (rat Y5 IC50=1.4 nM; human Y5 IC50=2.9 nM) and low affinity for human neuropeptide Y Y1, Y2 and Y4 receptors (IC50>1000 nM). The compound was an antagonist of the rat neuropeptide Y Y5 receptor, selectively inhibiting neuropeptide Y-induced intracellular Ca2+ transients in cells expressing neuropeptide YY5 receptors. Intraperitoneal
injection of CGP 71683A to satiated lean rats at a dose of 10 mg/kg inhibited neuropeptide Y-induced food intake by 50% and attenuated feeding after food deprivation, but had little effect on food intake in free-feeding rats. Rats that were chronically dosed with CGP 71683A showed reduced food intake and body weight gain over the first few days of treatment, but food intake and body weight gain subsequently approached control levels. A combination of intraperitoneal administered CGP 71683A and the neuropeptide YY1 receptor antagonist BIBO3304 was recently reported to produce anorectic effects in lean rats, Zucker rats, and ob/ob mice at doses where either agent alone was ineffective. CGP 71683A has recently been reported to have potent affinity for the 5-hydroxytryptamine (5-HT) reuptake recognition site and muscarinic receptors, so the possibility that CGP 71683A produces anorectic effects through mechanisms other than neuropeptide YY5 receptor blockade cannot be ruled out. Indeed, it was recently reported that the anorectic effects of CGP 71683A are identical in wild type and Y5 receptor-deficient mice, thus indicating that the anorectic effects of the compound are non-specific. The utility of this compound is questioned in a report that shows that it interacts with a number of non-NPY receptors. It recently has been reported that CGP 71683A and another Y5 antagonist (JCF 104) of undisclosed structure and selectivity reduce feeding induced by high doses of NPY after the main initial feeding response. Mcnally and his coworkers developed Wo9955667 (7) by keeping the cyclohexyl sulphonamide common shows good binding with NPYY5 receptor in 1 nM concentration range. Synaptic scientist have further explored the series and developed compound 8 which can reduce the 80 % food intake in rats with concentration of 9.8 nM. Compound 8 shows poor affinity towards Y1, Y2 and Y4 receptor. The initial exploration of different substitution patterns within this framework quickly revealed that electron withdrawing groups (e.g. CF3 or CN) at the 3-position of the 4-aryl ring produced exceptionally potent compounds. The series was generally plagued by poor oral bioavailability in rats. For example, an early analogue of interest, 4-(4-chlorophenyl)-2-(4-fluorophenyl) imidazole, demonstrated an oral bioavailability in rats of only 3%. Structure activity relationship study of the series of diarylimidazole series shows that replacement of the 2 aryl ring with a saturated ring system produced compounds with only a modest loss of activity at the Y5 receptor and Placement of a nitrogen atom into the cyclohexyl ring generate the corresponding piperidine analogues that maximize potency and solubility with slightly decreased potency level. Patent literature also found the same basic cyclohexyl sulphonamide utilized by Neurogen (10), shionogi (11), synaptic (12 & 13) based nucleus in compound showing good binding potency with NPYY5. Scientist from Bayer has developed piperidine acetamide derivative 14 with 160 nM level binding affinity for the NPYY5 receptor in 2001. Further improvement of the compound by replacement of tetrazole with benzimidazole (15) fraction leads to increase the specificity very high (4 nM). Elliot and his coworkers have explored the importance of imidazole nucleus with synthesizing compound 16 which require 1.2 nM concentration of drug to antagonise the NPYY5 receptor. A group from Pfizer and Neurogen has recently reported extensive pharmacological evaluation of a more potent, orally bioavailable, brain penetrant NPYY5 receptor antagonist, and the 2, 4-diarylimidazole 16, in models of feeding and energy expenditure. The in vitro and in vivo characterization of 3-[2-6-(2-tert-butoxyethoxy) - pyridin-3-yl]-1H-imidazol-4-yl]-benzonitrile, (I), a potent and selective NPY-Y5 antagonist. Compound 16 showed high affinity for human neuropeptide YY5 receptors (IC50=1.2 nM), and inhibited neuropeptide Y-induced Ca2+ mobilization in Bowes melanoma cells expressing the neuropeptide YY5 receptor (IC50=0.4 nM). The compound did not have significant affinity for human neuropeptide YY1 or Y2 receptors (IC50>1000 nM), or for over 50 other receptors. Food intake elicited by bovine pancreatic polypeptide was inhibited by 56% after oral administration of compound 16 (30 mg/kg). Brain and CSF levels were found to be 4 and 0.2 AM, respectively, 0.5 h after dosing. These data demonstrate that compound achieves excellent CNS exposure and can block a neuropeptide YY5 receptor-specific effect in vivo. However, compound 16 at a dose of 40 mg/kg orally failed to inhibit feeding following food deprivation in rats, and had no effect on spontaneous feeding at a dose of 30 mg/kg orally. Thermogenic effects were not evident with compound 16, as it did not cause significant changes in oxygen consumption or respiratory quotient when dosed at 30 mg/kg orally. There was no effect of the compound on spontaneous locomotor activity, consistent with a lack of overt behavioral effects. These data indicate that while activation of the neuropeptide YY5 receptor with an exogenous ligand can promote food intake, it does not play a significant role in regulation of food intake and energy expenditure in lean rats under physiological conditions. Modification in compound 16 lead to the generation of compound 17, which is less
specific to the receptor than parent compound but can inhibit spontaneous and fast induce food intake in rats [3a]. GW 59884A (18), a bis-heteroaryl guanidine, is a selective NPYY5 receptor antagonist that was under development with GlaxoSmithKline as a potential antiobesity agent. GW 59884A was undergoing preclinical evaluation in the USA; however no further development has been reported [35]. 1-((1R,2R)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(4-phenoxophenyl) urea was identified as a hit from the screening of the NPYY5 receptor. This lead was optimized for in vitro potency by changing the stereochemistry, the phenyl ethyl segment, the urea portion, and the 4-phenoxophenyl group on the molecule. The most potent compounds in this class have IC50s less than 0.1 nM at the NPY5 receptor 19. The compound is specific to NPYY5 binding as it did not effectively bind with NPYY1 and NPYY2 receptor and its antagonistic property was confirmed by forskolin induced cyclic AMP accumulation assay in 293 cells [31]. Among the published thioether amides (20) series of Y5 antagonists are reported by Bayer, of which 1 (Table 1) is a representative example. Thioether linkage is not essential for Y5 binding, replaced with bioisoster carbon analogue 2 having equivalent activity. This compound represented an interesting starting point but suffered from poor oral bioavailability and real concerns about potential toxicity as a consequence of the N-ethyl aminocarbazole fragment, which is a known animal carcinogen [36]. Scientists from Banyu have developed NPYY5 antagonist imidazole derivative compound 21 (23 nM) and further development not disclosed [36]. The R.W. Johnson group has also described a structurally distinct pyrazole series represented by 22 and 23 [37]. Compounds 22 and 23 were reported to show IC50s of 15 and 80 nM, respectively, against the human neuropeptide YY5 receptor, and did not bind significantly to human neuropeptide YY1 or YY2 receptors. No data confirming the antagonistic properties of these compounds at neuropeptide YY5 receptors was reported. At a dose of 30 mg/kg administered intraperitoneally to rats, 22 decreased fasting-induced feeding by 43% in the period 2–6 h after administration. Compound 22 was said to be well tolerated. However, in the absence of data to support neuropeptide YY5 receptor specificity, the mechanism of the anorectic effects of 22, must be considered circumstantial and open to question. Fukami and his coworkers have developed dianinopyridine derivative (24) which is specific to NPYY5 receptor (4.1 nM) [38]. Bayer scientists reported the indanyl derivative (25) which is specific to NPYY5 receptor in 99 and further development is not disclosed [3a]. Norman et al., 1999 developed the pyrrolo pyrimidine derivative (26) which shows their activities below 0.1 nM range [39]. Scientist of Bayer has developed the heterocyclic benzimidazole derivative (27) which shows specific NPYY5 binding affinity (25 nM) compare to other receptor [40]. Daniel has reported Benz- imidazol Benzamide derivative (28) GW438014A which can decreased weight gain and fat mass in Zucker rats after 4 days of Intraperitoneal injection [41]. Another heterocyclic nucleus quinidine derivative (29) was reported by Hoffmann- LA- Roche with good binding affinity for NPYY5 (9.9 nM) [42]. More specific quinazoline 2, 4 – diamine derivative (30) was reported by Novartis in 1997, but the compound dropped for further development is suspended due to some undisclosed reasons [43]. In 1996 synaptic scientist were working on naphthalene derivative (31) for NPYY5 receptor antagonism but the project dropped [44]. L-152,804(32) is an orally bioavailable, brain-penetrant NPYY5 receptor antagonist that has reasonable affinity for human and rat neuropeptide YY5 receptors (human Y5 Ki=26 nM; rat Y5 Ki=31 nM) and low affinity for human neuropeptide YY1, Y2, and Y4 receptors (Ki>10,000 nM) [45]. The antagonist activity of L-152,804 was confirmed in cells expressing the human neuropeptide YY5 receptor, in which L-152,804 inhibited the neuropeptide Y-induced increase in intracellular Ca2+ levels (IC50=210 nM). When administered intracerebroventricularly to satiated rats, L-152,804 inhibited food intake elicited by the neuropeptide YY4/Y5 receptor-selective agonist, bovine pancreatic polypeptide. Administration of L-152,804 alone had no effect on food intake, and was reported not to induce overt behavioral changes, indicating that the anorectic effect of the compound is neuropeptide YY5 receptor-specific. When administered orally to rats, L-152,804 (10 mg/kg) also inhibited food intake elicited by intracerebroventricular bovine pancreatic polypeptide. However, L-152,804 administered intracerebroventricularly or orally failed to inhibit neuropeptide Y-stimulated food intake, despite brain levels of 2.9 AM 2 h after oral administration. Based on these observations, it was concluded that activation of the neuropeptide Y5 receptor does not substantially contribute to food intake in rodents. Banuy has reported tricyclic imidazolyl derivative compound 33 which was tested in rat and found effective with concentration 2.3 nM [46]. Carbazole anilide is an interesting starting points but suffering from poor bioavailability and concerns about potential toxicity as a consequence of the embedded aminocarbazole fragment, skeleton remarkably increase in
Potency the potency of the compound. Component aniline is carrying a risk of mutagenic activity. A series of carbazole amides and ureas have been identified as highly potent and selective Y5 antagonists with the demonstrated potential for good drug metabolism and pharmacokinetic (DMPK) properties. Parallel structure-activity studies looking at the effects of ring substitution have proved that it is possible by incorporation of a 4-methyl substituent to produce carbazole ureas with potent Y5 activity, comprised of carbazole anilines that in themselves are devoid of activity in the Ames test. NPY5RA-972 (34) is a highly potent Y5 antagonist (hY5 IC50 = 3 nM) in vivo but does not block neuropeptide Y-induced feeding nor does it reduce feeding in rats, suggesting that the Y5 receptor alone has no significant role in feeding in these models. In Vivo Properties of NPY5RA-972 was not only bound very potently to the Y5 receptor (hY5 IC50 = 3nM, rY5 IC50 = 3nM) and had excellent selectivity with respect to other NPY receptors (IC50 > 10 nM) and to a large and diverse selection of unrelated receptors, enzymes, and transporters. The only other activity observed was a degree of binding to the 5HT2b receptor and partial inhibition of adenosine transport, both determined at 10 μM. Compound 34 has a low level of metabolism in vitro (Rat S9) and displays an excellent PK profile in rats including low clearance, good oral bioavailability, and an iv half-life of 3.7 h. Robust levels of 34 are seen in the CSF (153 nM at 1 h after 10.5 mg/kg oral dose), and face little barrier to penetration to the CNS [54]. Compound 35 & 36 are also the derivative of carbazole nucleus and found to be effective analogue to file for patent [50, 51]. Compound (37) FMS586 developed by Kakui and his coworkers by further optimization of carbazole nucleus which was found to be effective (4.3 nM) NPYY5 inhibitor. Compound is not working through noradrenaline, galanine or GABA receptor antagonist [52]. 9H-fluoren-9-one amide derivative (38), a very specific NPYY5 receptor antagonist (IC50 = 0.47 nM) and shows no significant affinity at NPY1, NPY2, and NPY4 receptors (IC50 values > 5 μM) [53]. Compound 39 is a -6-oxo-5, 6-dihydrophenanthridin-9-y1 derivative and very effective in antagonizing the NPYY5 receptor at 12 nM concentration. The compound antagonizing property was confirmed by PYY binding assay of human NPY receptors expressed in Sf9 cells [54]. Compound 40 was generated by Novartis scientist from the lead developed by fused tetrahydro-5H-benzo annulene to thiazole ring is an effective NPYY5 antagonist at 5.8 nM concentrations. Again the compound was found not significant in binding with Y1, Y2 and Y4 Ki > 10000 nM [55, 56]. Scientist from Fujisawa have changed the thiazole fraction with imidazole and developed compound 41 which was found to require 24 nM concentration of the compound and selectively inhibit the NPYY5 receptor and file patent in European patent office [57]. Collaborating project of Merck and Banyu have reported compound 42 which was generated by preparation of spiro[indoline-3, 4'-piperidine] and it was effective at 1 – 30 mg/Kg p.o. dose to inhibit the NPY feeding activity through NPYY5 receptor [58]. Further Banyu have elaborated the project to develop 1'H-spiro[cyclohexane-1, 3'-fluro [3, 4-c] pyridine]-1'-one, a spironolactone derivative compound 43 which selectively inhibit the NPYY5 receptor at dose 1.3 nM [59]. Spironolactone ring was modified to 3'H-spiro[cyclohexane-1, 1'-isobenzofuran]-3'-one and linked it to benzimidazoline fraction, but the reported compound 44 was not effective (7.2 nM) as parent compound [60].
Table 1: Neuropeptide YY5 receptor antagonist
Evidence from rodent studies suggests a potential therapeutic role for Y5 receptor antagonism in the treatment of human obesity and a number of good tool molecules with structurally diversity are available. However, the exact therapeutic potential associated to this biological target in obesity has still to be clarified. The therapeutic potency of Y5 receptor antagonism in human might be smaller than other antiobesity drugs [63].

**CHALLENGES IN DEVELOPMENT**

Antagonism of NPY remains a tantalizing target, but it appears difficult to find a developable compound with a suitable pharmacology, and it has yet to be demonstrated that such a compound can reduce obesity in animals, let alone humans. A particular challenge will be to demonstrate anti-obesity activity in situations where leptin levels are high and NPY release is low [66].

Most of the evidence in support of the Y5 hypothesis has been generated in rodents, but recently, there have been reports suggesting that Y5 antagonists have little or no effect in rodent feeding models [63]. NPY induced feeding was reduced in Y1 deficient mice while it was not significantly influenced in the Y5. The strongest support for the study in rhesus monkeys showing that icv administration of Y5 antagonist attenuates NPY mediated feeding [66].

**POTENTIAL SIDE EFFECTS OF NPY RECEPTOR ANTAGONISTS**

Because NPY is involved in a wide variety of physiological processes, many of which are mediated via NPY5 receptors, it is possible that NPY5 receptor antagonists developed for the treatment of obesity will be associated with specific mechanism-based side effects. The latter effect presumably reflects effects of the neuropeptide YY1 receptor antagonist on pituitary gonadotropin secretion. All studies reported to date used i.c.v., administration of neuropeptide YY5 receptor antagonists and additional studies with newer, orally active, brain penetrant compounds would be more informative. Similarly, neuropeptide YY5 receptor activation has been associated with anti-epileptic effects, attenuation of opiate withdrawal, modulation of circadian rhythms, regulation of pituitary hormone secretion, natriuresis and decreases in plasma glucose [62]. Unfortunately, the effect of neuropeptide YY5 receptor antagonists on these processes has not been reported.

**SUMMARY AND PERSPECTIVE**

Much of the data published on small non peptide molecule of various chemical classes, selective Y5 antagonists to date has been compiled using compounds that suffer from a variety of pharmacokinetic issues such as poor brain penetration, or short in vivo half-lives which prevent definitive interpretation of the results [69].

The role of the NPY5 receptor in energy homeostasis is less clear, however. Mice lacking the NPY5 receptor do not differ from wild type mice in paradigms that assess food intake and body weight under a variety of conditions. Furthermore, the reported effects of NPY5 receptor antagonists on food intake and body weight are conflicting. Although administration of some NPY5 receptor antagonists is associated with reduced food intake and body weight gain, evidence for the specificity of these effects is lacking. The lack of any consistent effect of NPY5 receptor deficiency and NPY5 receptor antagonists on energy homeostasis suggest that the role of neuropeptide Y in the regulation of body weight is more complicated than previously envisioned. Overall, these results may indicate that the high level of redundancy in the regulation of body weight insures that mice can substantially compensate for the loss of a single neuropeptide or neuropeptide receptor under normal conditions. However, the data obtained to date suggests that NPYY plays a critical role in energy homeostasis under very specific physiological conditions, particularly conditions of real or apparent deprivation. These data indicate that NPYY receptor antagonists may be most useful in human conditions where appetite is increased and energy expenditure is decreased due to activation of the starvation response. Such conditions include obese patients who are dieting, formerly obese patients who have lost substantial weight, and patients with complete or partial leptin deficiency. Significant progress has been made in the identification of structurally diverse, orally bioavailable NPY5 receptor antagonists that can cross the blood brain barrier. However, there is a clear need for further studies with both NPY5 receptor antagonists in order to clarify their potential as anti-obesity agents. Most studies have been performed in lean rodents or in genetically obese rodents that do not mimic common obesity in the human population. It would be desirable to evaluate the effects of compounds in diet-induced obese rodents and non-rodents as disease models that more closely mimic human obesity. Other critical issues in the development of NPY receptor antagonists as effective agents for obesity management are the need to overcome counter balancing effects of the multiple complementary mechanisms involved in energy homeostasis that tend to oppose any changes in body weight.
and the identification of patient subclasses most likely to benefit from treatment. In summary, numerous investigations to date suggest that NPY is implicated in the pathophysiology of a number of diseases including feeding and metabolic disorders, anxiety, seizures, memory, circadian rhythm, drug addiction, pain, cardiovascular diseases, rhinitis, and endothelial cell dysfunctions. Thus, the design of selective antagonists of NPYY5 receptors could be useful compounds for the treatment of metabolic diseases like obesity. But large tissue distribution of NPY receptors and their stimulation or blockade could produce untoward effects which must be overcome to produce effective and safe drug.

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