
Neuropeptide Y: History and Overview

K. Tatemoto

Department of Molecular Physiology, Institute for Molecular and Cellular Regulation,
Gunma University, 371-8512 Maebashi, Japan
e-mail: tatekazu@showa.gunma-u.ac.jp

1	Introduction	2
2	Isolation and Primary Structures of NPY	2
2.1	Discovery of NPY	2
2.2	Primary Structure of NPY	3
2.3	NPY mRNA	4
3	Cellular Localization of NPY	4
3.1	NPY in the Peripheral Nervous System	4
3.2	NPY in the Central Nervous System	5
4	Studies on the Receptors and Physiological Functions of NPY (1982–1992)	5
4.1	Peripheral Actions of NPY	5
4.1.1	Cardiovascular Response	5
4.1.2	Hormone Secretion	6
4.2	Central Actions of NPY	6
4.2.1	Cardiovascular Response	6
4.2.2	Circadian Rhythms	6
4.2.3	Food Intake and Energy Expenditure	6
4.2.4	Hormone Secretion and Reproduction	7
4.2.5	Stress, Depression, Anxiety, and Pain	7
4.2.6	Seizures	8
4.3	NPY Receptor Binding and Intracellular Signaling	8
4.4	NPY Receptor Agonists and Antagonists	8
4.5	NPY Receptor Subtypes	8
5	Studies on the Receptors and Physiological Functions of NPY (1992–2002)	9
5.1	Cloning of NPY Receptor Subtypes	9
5.1.1	Y ₁ Receptor	10
5.1.2	Y ₂ Receptor	10
5.1.3	Putative Y ₃ Receptor	10
5.1.4	Y ₄ Receptor	10
5.1.5	Y ₅ Receptor	11
5.1.6	y ₆ Receptor	11
5.2	Selective NPY Receptor Agonists and Antagonists	11
5.3	NPY Receptor Subtypes and Their Physiological Functions	12
5.3.1	Cardiovascular Response	12
5.3.2	Circadian Rhythms	12
5.3.3	Food Intake and Energy Expenditure	12

5.3.4 Hormone Secretion and Reproduction 13

5.3.5 Anxiety, Pain, Stress, and Depression 13

5.3.6 Seizures 14

5.3.7 Ethanol Consumption 14

6 Conclusions and Future Studies 15

References 15

Abstract Neuropeptide Y (NPY) is a 36-amino acid peptide with structural similarities to peptide YY (PYY) and pancreatic polypeptide (PP). NPY, one of the most abundant neuropeptides known, is widely distributed throughout the central and peripheral nervous systems, while PYY and PP are predominantly distributed in the endocrine cells of the intestine and pancreas, respectively. Five NPY receptor subtypes denoted as Y₁, Y₂, Y₄, Y₅, and y₆ mediate the actions of NPY. NPY is involved in the regulation of diverse functions including food intake, blood pressure, circadian rhythms, stress, pain, hormone secretion, reproduction, and alcohol consumption. NPY has also been implicated in the pathophysiology of a number of diseases such as feeding disorders, seizures, hypertension, pain disorders, depression, and anxiety. This review will describe a brief history and an overview of the studies on NPY concerning the isolation, tissue distribution, receptor subtypes, receptor agonists and antagonists, physiological functions, and pharmacological activities.

Keywords Neuropeptide Y · Tissue distribution · Receptor subtype · Receptor antagonist · Review

1
Introduction

In this chapter, a brief history and an overview of the studies on neuropeptide Y (NPY) during the last 20 years are described. The main thrust of this chapter is to critically review the initial findings that have influenced later studies on NPY. Particular attention is focused on the studies concerning the receptors and physiological functions of NPY. The reader is referred to other excellent reviews in this book for more comprehensive discussion.

2
Isolation and Primary Structures of NPY

2.1
Discovery of NPY

In the last century, many neuropeptides and hormonal peptides were identified on the basis of specific biological responses mediated by them. Unlike most oth-

er known neuropeptides, however, NPY was first identified in brain extracts by its C-terminal tyrosine amide structure. In 1978, we developed a novel method for the detection of biologically active peptides based on the C-terminal amide structure that is a unique chemical feature of many peptide hormones and neuropeptides (Tatemoto and Mutt 1978). Since peptides with this structure are likely to be biologically active, the search for unknown peptide amides would result in the finding of novel peptides. We therefore carried out the isolation of previously unknown peptide amides from tissue extracts using a chemical method as the detection device.

In 1980, we isolated two novel peptide amides, which were designated peptide HI (PHI) and peptide YY (PYY) from porcine intestinal extracts (Tatemoto and Mutt 1980). Subsequently, we isolated a peptide with a C-terminal tyrosine amide from porcine brain extracts, which was named neuropeptide Y (Tatemoto et al. 1982). Using a similar approach, we isolated a series of other novel peptides such as galanin (Tatemoto et al. 1983), neuropeptide K (Tatemoto et al. 1985), and pancreastatin (Tatemoto et al. 1986).

2.2

Primary Structure of NPY

NPY is a linear polypeptide with 36 amino acid residues (Tatemoto 1982a). Since NPY contains many tyrosine (Y) residues in its structure, we named this peptide neuropeptide Y to distinguish it from PYY that possesses a very similar structure to NPY (Tatemoto 1982b). A comparison of the primary structures of NPY, PYY and pancreatic polypeptide (PP) reveals a high degree of sequence homology between NPY and PYY, with a lesser degree of homology between NPY and PP, as shown in Fig. 1. It was therefore proposed that NPY, PYY, and PP are members of a previously unrecognized peptide family (Tatemoto 1982a).

Later, human NPY was isolated from adrenal-medullary pheochromocytoma tissue. The primary structure of human NPY differs from that of the porcine peptide in only one position of the 36 residues (Corder et al. 1984). Subsequent studies identified the primary structures of NPY molecules from various animals, birds, frogs, and others (for a review see Larhammar et al. 1993). These

		homology
NPY	<u>Y</u> <u>P</u> <u>S</u> <u>K</u> <u>P</u> <u>D</u> <u>N</u> <u>E</u> <u>G</u> <u>E</u> <u>D</u> <u>A</u> <u>P</u> <u>A</u> <u>E</u> <u>D</u> <u>L</u> <u>A</u> <u>R</u> <u>Y</u> <u>Y</u> <u>S</u> <u>A</u> <u>L</u> <u>R</u> <u>H</u> <u>Y</u> <u>I</u> <u>N</u> <u>L</u> <u>I</u> <u>T</u> <u>R</u> <u>Q</u> <u>R</u> <u>Y</u> *	100%
PYY	<u>Y</u> <u>P</u> <u>A</u> <u>K</u> <u>P</u> <u>E</u> <u>A</u> <u>P</u> <u>G</u> <u>E</u> <u>D</u> <u>A</u> <u>S</u> <u>P</u> <u>E</u> <u>E</u> <u>L</u> <u>S</u> <u>R</u> <u>Y</u> <u>Y</u> <u>A</u> <u>S</u> <u>L</u> <u>R</u> <u>H</u> <u>Y</u> <u>L</u> <u>N</u> <u>L</u> <u>V</u> <u>T</u> <u>R</u> <u>Q</u> <u>R</u> <u>Y</u> *	69%
PP	<u>A</u> <u>P</u> <u>L</u> <u>E</u> <u>P</u> <u>V</u> <u>Y</u> <u>E</u> <u>G</u> <u>D</u> <u>D</u> <u>A</u> <u>T</u> <u>P</u> <u>E</u> <u>Q</u> <u>M</u> <u>A</u> <u>Q</u> <u>Y</u> <u>A</u> <u>A</u> <u>E</u> <u>L</u> <u>R</u> <u>R</u> <u>Y</u> <u>I</u> <u>N</u> <u>M</u> <u>L</u> <u>T</u> <u>R</u> <u>P</u> <u>R</u> <u>Y</u> *	50%

Fig. 1 Comparison of the amino acid sequences of the porcine peptides, neuropeptide Y (NPY), peptide YY (PYY), and pancreatic polypeptide (PP). An asterisk indicates the amidated C-terminus. Identities are underlined

studies revealed that the structure of NPY has been strongly conserved throughout evolution.

2.3

NPY mRNA

Dixon and coworkers were the first to identify the sequence of a human cDNA encoding NPY from human pheochromocytoma cells. The 97-amino acid precursor has at least two processing sites, which would generate three peptides of 28 (signal peptide), 36 (NPY), and 30 (COOH-terminal peptide) amino acid residues (Minth et al. 1984). Subsequently, the structure of a human NPY gene identified from a human genomic DNA library was reported. The DNA sequences located within 530 bases of the start of transcription were found to be sufficient for transient expression in the two cell lines examined (Minth et al. 1986).

3

Cellular Localization of NPY

Since NPY was discovered by its chemical nature, no biological activity of the peptide was known when it was isolated. Therefore, we prepared a large quantity of natural NPY from more than 1,000 kg of porcine brains, and the natural NPY preparations thus obtained were sent to a number of laboratories in Europe and the USA to examine the biological activities of the peptide and to generate specific antisera against NPY for immunohistochemistry and radioimmunoassay studies. Between 1982 and 1985, the natural NPY preparations were used for many studies on the biological activity and localization of NPY, until synthetic NPY preparations became commercially available.

3.1

NPY in the Peripheral Nervous System

Lundberg et al. (1982) were the first to demonstrate NPY-like immunoreactivity in many peripheral neurons with a distribution mostly paralleling that of tyrosine hydroxylase (TH) and dopamine-beta-hydroxylase (DBH) containing neurons. Very high levels of NPY-like immunoreactivity were found in sympathetic ganglia and in tissues receiving a dense sympathetic innervation, such as the vas deferens, heart atrium, blood vessels, and spleen. NPY- and DBH-nerves had a roughly parallel occurrence in the heart, spleen, kidney, respiratory and urogenital tracts, around blood vessels, and within visceral smooth muscle. NPY thus seems to be a major peptide in the sympathetic nervous system (Lundberg et al. 1983). The presence of NPY-like immunoreactivity was also demonstrated in the neuronal elements of the gut and pancreas (Sundler et al. 1983). NPY has generally been found in the sympathetic neurons, costored and

coreleased with catecholamines, although NPY is also present in peripheral non-sympathetic neurons (for a review see MacDonald 1988).

3.2

NPY in the Central Nervous System

Bloom and his colleagues have shown that NPY-like immunoreactivity is widely and unevenly distributed in rat and human brains, and it is the most abundant neuropeptide known (Allen et al. 1983; Adrian et al. 1983). The highest concentrations of NPY were found in the paraventricular hypothalamic nucleus, hypothalamic arcuate nucleus, suprachiasmatic nucleus, median eminence, dorsomedial hypothalamic nucleus, and paraventricular thalamic nucleus (Chronwall et al. 1985). The extremely high concentrations and widespread distribution indicate important roles of NPY in many brain functions. Hokfelt and coworkers (1983) reported the coexistence of NPY-like immunoreactivity in catecholamine neurons in the medulla oblongata. During subsequent years, a number of in vitro studies have shown the coexistence of NPY not only with catecholamines but also with a variety of other neurotransmitters or neuropeptides (for a review see Everitt and Hokfelt 1989). It is suggested that the physiological roles of NPY in the central nervous system are very complex because of the interactions of NPY with other effector systems. More recently, localization of NPY mRNA by means of in situ hybridization was found to be comparable to that of NPY-immunoreactivity (Terenghi et al. 1987; Gehlert et al. 1987).

4

Studies on the Receptors and Physiological Functions of NPY (1982–1992)

During the first 10 years of NPY research, a number of important biological activities of NPY in both the central and peripheral nervous systems were discovered, and the presence of NPY receptor subtypes, Y_1 and Y_2 , was demonstrated using specific NPY receptor agonists.

4.1

Peripheral Actions of NPY

4.1.1

Cardiovascular Response

Lundberg and Tatemoto (1982) were the first to find a biological activity of NPY, demonstrating that NPY induced potent vasoconstriction, more potent than noradrenaline, which was resistant to alpha-adrenoceptor blockade. It was also shown that NPY caused strong contractions of cerebral arteries (Edvinsson et al. 1983), and that NPY produced an inhibition of colonic motility and a vasoconstriction of long duration (Hellstrom et al. 1985). NPY induced renal vasoconstriction and inhibited renin release by inhibiting adenylate cyclase in the

vascular smooth muscle and renin-producing cells (Hackenthal et al. 1987). NPY produced potent pressor responses (Allen et al. 1984; Petty et al. 1984), while NPY (18–36), a C-terminal NPY fragment, exhibited substantial hypotensive action (Boublik et al. 1989).

Interestingly, NPY was found to prevent the blood pressure fall induced by endotoxin in conscious rats with adrenal medullectomy (Evequoz et al. 1988), and plasma levels of NPY were found to markedly increase in patients with septic shock (Watson et al. 1988). These data suggest that NPY plays a role in maintaining blood pressure during endotoxic shock.

4.1.2

Hormone Secretion

Allan et al. (1982) found that NPY inhibited the contraction of electrically stimulated mouse vas deferens, suggesting inhibitory actions of NPY on noradrenaline release at a pre-synaptic level. Subsequently, NPY was shown to depress the secretion of ^3H -noradrenaline and the contractile response evoked by field stimulation in the vas deferens (Lundberg and Stjarne 1984).

4.2

Central Actions of NPY

4.2.1

Cardiovascular Response

Fuxe et al. (1983) first demonstrated an effect of central administration of NPY. They found that NPY induced hypotension and bradypnea in the rat, suggesting the involvement of NPY in the cardiovascular and respiratory controls of the central nervous system.

4.2.2

Circadian Rhythms

Albers and Ferris (1984) found that microinjection of NPY into the suprachiasmatic region of the hypothalamus (SCN) phase-shifted the circadian rhythm of hamsters housed in constant light. It is suggested that NPY functions as a chemical messenger that is important for the light–dark cycle entrainment of circadian rhythms.

4.2.3

Food Intake and Energy Expenditure

In 1984, NPY was found, for the first time, to stimulate feeding behavior in rats (Clark et al. 1984; Levine and Morley 1984; Stanley and Leibowitz 1984). Since then, a number of studies have shown that NPY is the most potent orexigenic

peptide identified to date. Later, cerebrospinal fluid NPY concentrations were found to be significantly elevated in anorectic and bulimic patients. These levels normalized in long-term weight-restored anorectic patients who had a return of normal menstrual cycles (Kaye et al. 1990). This suggests that NPY plays a role in eating disorders. It was also reported that NPY decreased rectal temperature after intracerebroventricular administration (Morioka et al. 1986). These observations suggest that NPY is involved in the regulation of food intake and energy expenditure.

4.2.4

Hormone Secretion and Reproduction

Kalra and Crowley (1984) found that central administration of NPY suppressed luteinizing hormone (LH) release in ovariectomized rats, while it stimulated LH release in ovariectomized rats pretreated with estrogen and progesterone. Kalra and coworkers found that NPY not only stimulated food intake but also inhibited sexual behavior in rats (Clark et al. 1985). NPY inhibited excitatory synaptic transmission in the hippocampus by acting directly at the terminal to reduce a calcium influx (Colmers et al. 1988). These observations suggest that NPY is involved in the central control of hormone and neurotransmitter release.

4.2.5

Stress, Depression, Anxiety, and Pain

Fuxe et al. (1983) demonstrated that central administration of NPY induced EEG synchronization. It is therefore suggested that NPY produces behavioral signs of sedation. Subsequently, Heilig and Murison (1987) found that intracerebroventricular administration of NPY protected against stress-induced gastric erosion in the rat. Stress-induced erosion was reduced by approximately 50% by NPY, suggesting the anti-stress action of NPY as a manifestation of its sedative properties. In addition, it was reported that the administration of NPY into the third ventricle of the brain enhanced memory retention. It is suggested that NPY modulates memory processes (Flood et al. 1987).

Interestingly, NPY-like immunoreactivity was found to be significantly lower in cerebrospinal fluid from patients with a major depressive disorder compared with healthy controls (Widerlov et al. 1988). It was also found that antidepressant drugs increased the concentrations of NPY-like immunoreactivity in the brain (Heilig et al. 1988). These observations support the hypothesis that NPY is involved in the pathophysiology of depressive illness.

Furthermore, Heilig et al. (1989) found that centrally administered NPY produced anxiolytic-like effects that were mediated through interactions with noradrenergic systems in animal anxiety models. In a hot plate test, spinally administered NPY produced a dose-dependent elevation in the nociceptive threshold in rats, suggesting the involvement of NPY in the mechanism of pain control (Hua et al. 1991).

4.2.6

Seizures

Marksteiner and Sperk (1988) observed significantly increased levels of NPY-like immunoreactivity in the frontal cortex of rats that had undergone strong limbic seizures induced by kainic acid. The increase could be prevented by early injection of an anticonvulsant (Marksteiner et al. 1990). These observations suggest that NPY is involved in the control of seizures.

4.3

NPY Receptor Binding and Intracellular Signaling

The specific binding of the iodinated NPY to membranes from the cerebral cortex was demonstrated. The binding of iodinated NPY was characterized by a K_d value of 0.38 nM (Uden et al. 1984). A study on autoradiographic localization of NPY receptors indicated that the receptors were discretely distributed in the rat brain with high densities found in areas such as the olfactory bulb, superficial layers of the cortex, ventral hippocampus, and area postrema (Martel et al. 1986).

NPY was found to be a potent inhibitor of cyclic AMP accumulation in feline cerebral blood vessels (Fredholm et al. 1985). NPY was shown to inhibit adenylate cyclase through a pertussis toxin-sensitive G protein (Kassis et al. 1987). In addition to inhibiting adenylate cyclase, NPY was found to elevate intracellular calcium (Motulsky and Michel 1988). It was also shown that guanine nucleotide-binding protein G_o mediated the inhibitory effects of NPY on dorsal root ganglion calcium channels (Ewald et al. 1988).

4.4

NPY Receptor Agonists and Antagonists

Centrally truncated synthetic NPY agonists were synthesized and shown to be biologically active (Beck et al. 1989; Krstenansky et al. 1989). Fuhlendorff et al. (1990) reported that [Leu³¹, Pro³⁴] NPY was a specific Y1 receptor agonist that could be useful in delineating the physiological importance of Y1 receptors. About the same time, the first NPY receptor antagonists, Ac-[3-(2,6-dichlorobenzyl)Tyr²⁷, D-Thr³²] NPY(27–36) and Ac-[3-(2,6-dichlorobenzyl) Tyr^{27,36}, D-Thr³²] NPY(27–36), designated PYX-1 and PYX-2, respectively, were synthesized based on the C-terminal structure of the NPY molecule (Tatemoto 1990). PYX-2 was found to block the stimulatory action of NPY on carbohydrate ingestion (Leibowitz et al. 1992).

4.5

NPY Receptor Subtypes

Wahlestedt et al. (1986) first suggested the presence of two receptor subtypes for NPY and its related peptides. They studied the effects of NPY, PYY, and the

C-terminal fragments of NPY or PYY on different smooth muscle preparations *in vitro*, and found that PYY(13–36) reproduced the NPY- and PYY-induced suppression of noradrenaline release. Thus, the C-terminal portion seems to be sufficient for exerting pre-junctional effects of NPY and PYY, while the whole sequence seems to be required for post-junctional effects. Later, Schwartz and coworkers showed that two subtypes of NPY/PYY-binding sites occurred in different cells, supporting the hypothesis of NPY receptor subtypes (Sheikh et al. 1989).

Since 1989, a number of the studies on NPY receptor subtypes have been published. Using selective receptor agonists, it was shown that Y_1 and Y_2 receptors were independently expressed in the brain and the majority of NPY receptors in the brain were of the Y_2 type (Aicher et al. 1991). It was found that the hypothalamic Y_1 receptors mediated the stimulatory effect of NPY on carbohydrate intake and meal size, while the Y_2 receptors had the opposite effect of suppressing carbohydrate intake (Leibowitz and Alexander 1991). Presynaptic inhibition by NPY observed in rat hippocampal slice was shown to be mediated by a Y_2 receptor (Colmers et al. 1991). Involvement of Y_1 receptor subtype in the regulation of LH secretion was demonstrated by using NPY, NPY(2–36), [Leu³¹, Pro³⁴] NPY, NPY(13–36) and other NPY fragments (Kalra et al. 1992).

5

Studies on the Receptors and Physiological Functions of NPY (1992–2002)

The main topics for the last 10 years have been the cloning of NPY receptor subtypes, Y_1 , Y_2 , Y_4 , Y_5 , and y_6 , and subsequent studies on the biological functions of these receptor subtypes. Thus, in addition to studies on NPY-transgenic and deficient animals, a number of animals lacking specific NPY receptor subtypes were generated and the physiological functions of these animals were studied. Moreover, specific receptor agonists and antagonists for each NPY receptor subtype were developed and their physiological and pharmacological properties were evaluated. The synthesis of selective and potent receptor agonists and antagonists has provided useful tools to study the physiological functions of NPY receptor subtypes and to develop novel pharmacological treatments.

5.1

Cloning of NPY Receptor Subtypes

Recent advances in molecular biology have resulted in the identification of five NPY receptor subtypes, Y_1 , Y_2 , Y_4 , Y_5 , and y_6 receptors (for a review see Michel et al. 1998). These receptor subtypes were found to share only modest sequence homologies (30–50%). Moreover, each of the receptor subtypes seems to be characterized by a distinct tissue localization and unique pharmacological profile. The next section describes a brief history of the cloning of NPY receptor subtypes.

5.1.1

Y₁ Receptor

In 1992, the primary structures of rat and human Y₁ receptors were identified (Krause et al. 1992; Herzog et al. 1992; Larhammar et al. 1992). The Y₁ receptor, the first NPY receptor to be cloned, was found to be a 384-amino acid protein belonging to a G protein-coupled receptor family. The functionality of the expressed NPY receptor was demonstrated by inhibition of adenylate cyclase and mobilization of intracellular calcium, both being characteristic of an NPY receptor. The distribution of Y₁ receptor expression correlated with that of NPY-immunoreactive nerves and the apparent actions of NPY in the intestine, kidney, and heart (Wharton et al. 1993).

5.1.2

Y₂ Receptor

The cloned Y₂ receptor consists of 381 amino acids, and has only 31% identity to the structure of the Y₁ receptor (Rose et al. 1995; Gerald et al. 1995, Gehlert et al. 1996; Rimland et al. 1996). The Y₂ receptor expressing cells have high affinity binding sites for NPY, PYY, and NPY(13–36), whereas [Leu³¹, Pro³⁴] NPY binds with lower affinity. The Y₂ receptor is localized on a number of NPY-containing neurons in the brain, suggesting that this receptor has a characteristic of an autoreceptor (Caberlotto et al. 2000).

5.1.3

Putative Y₃ Receptor

The Y₃ receptor is distinguished from the other NPY receptors by its high affinity for NPY but relatively low affinity for PYY. However, evidence for the existence of such a subtype is not clear as the clone initially reported as a Y₃ receptor (Rimland et al. 1991) failed to confer NPY binding sites (Herzog et al. 1993; Jazin et al. 1993). Therefore, the evidence is not sufficient to grant the presence of a Y₃ receptor (Michel et al. 1998).

5.1.4

Y₄ Receptor

A unique feature of the Y₄ receptor is a high affinity for PP. Therefore, the Y₄ receptor is probably a PP receptor. The cloned human Y₄ receptor has 43% sequence homology with the human Y₁ receptor (Lundell et al. 1995; Bard et al. 1995; Yan et al. 1996). Both NPY and PYY have low affinities for this receptor. Y₄ receptor is present in the intestine, prostate, and pancreas (Lundell et al. 1995). The Y₄ receptor mRNA is sparsely expressed in the brain, except in the brainstem (Parker and Herzog 1999).

5.1.5

Y₅ Receptor

The cloning of a novel NPY receptor designated Y₅ receptor was reported (Gerald et al. 1996; Hu et al. 1996). The complementary DNA encoded a 456-amino-acid protein with less than 35% overall identity to the other known NPY receptors. [D-Trp³²] NPY had a high affinity for the Y₅ receptor, while it had low affinities for the other known NPY receptors. The Y₅ receptor, originally cloned as the 'feeding' receptor in the hypothalamus, was also found in the peripheral nervous system such as the testis, spleen, and pancreas (Statnick et al. 1998).

5.1.6

y₆ Receptor

The cloning of a novel NPY receptor proposed to be a Y₅ receptor was reported (Weinberg et al. 1996). However, other researchers reported the same clone as a PP receptor or Y_{2b} receptor (Gregor et al. 1996; Matsumoto et al. 1996). To avoid confusion, it was renamed the y₆ receptor. The y₆ receptor gene is present in chicken, rabbit, cow, dog, mouse, and human, but it is completely absent in rat (Burkhoff et al. 1998). Sequence data revealed the y₆ gene to be the orthologue of the mouse Y₅ gene. Rabbits encode functional y₆ receptor, but the y₆ receptors in primates are functionally inactive due to a frameshift mutation occurring during early primate evolution (Matsumoto et al. 1996).

5.2

Selective NPY Receptor Agonists and Antagonists

Based on the C-terminal structure of the NPY molecule, the first nonpeptide Y₁ receptor antagonist BIBP 3226 was designed and synthesized (Rudolf et al. 1994), demonstrating that such a nonpeptide compound could be a useful tool for studying physiological functions and exploring therapeutic relevance.

Furthermore, synthesis of both peptide and nonpeptide Y₁ receptor antagonists such as [D-Tyr^{27,36}, D-Thr³²] NPY(27–36), SR120819A, 1229U91, BIBO3304, LY-357897, J-115814, and CP-617,906 have been reported. More recently, T4-[NPY(33–36)]4 and BIIE0246 have been described as selective Y₂ receptor antagonists. After the cloning of the Y₅ receptor, a number of Y₅ receptor antagonists including CGP71683A and L-152,804, and Y₅ receptor agonists such as [D-Trp³⁴] NPY and [Ala³¹, Aib³²] NPY were synthesized (for reviews see Balasubramaniam 1997; Pheng and Regoli 2000; Parker et al. 2002). The Y₁ receptor antagonist 1229U91 has been shown to exhibit an agonist activity for the Y₄ receptor (Parker et al. 1998). However, no selective antagonist for the Y₄ receptor has yet been reported.

5.3

NPY Receptor Subtypes and Their Physiological Functions

The cloning of NPY receptor subtypes has made it possible to generate specific receptor subtype-deficient animals. The generation of such animals has provided unique models to examine the physiological functions of NPY. The next section focuses on the physiological functions of NPY and its receptor subtypes revealed by the use of receptor agonists and antagonists and genetically modified animals.

5.3.1

Cardiovascular Response

BIBP3226 antagonized vasoconstriction induced by NPY. This suggests that endogenous NPY acting on the Y_1 receptor is likely to account for the long-lasting component of sympathetic vasoconstriction in response to high-frequency stimulation (Malmstrom and Lundberg 1995). It was reported that the incubation of the subcutaneous arteries with Y_1 receptor antisense oligodeoxynucleotides attenuated NPY-induced vasoconstriction (Sun et al. 1996). Furthermore, Y_1 receptor-deficient mice showed a complete absence of blood pressure responses to NPY, suggesting the importance of Y_1 receptors in the NPY-mediated cardiovascular response (Pedrazzini et al. 1998).

However, it was also reported that the depressor effect of intrathecal NPY injection was primarily mediated by a Y_2 receptor (Chen and Westfall 1993). Furthermore, a Y_2 receptor agonist evoked vasoconstriction in the spleen, while a Y_2 receptor antagonist BIIE0246 antagonized the response. These suggest that the Y_2 receptor is also involved in NPY/PYY-evoked vasoconstriction (Malmstrom 2001).

5.3.2

Circadian Rhythms

NPY has been implicated in the phase shifting of circadian rhythms. Microinjection of a Y_2 receptor agonist produced phase advances that were significantly greater than those produced by the injection of a Y_1 receptor agonist. This suggests that NPY phase shifts circadian rhythms via the Y_2 receptor (Huhman et al. 1996; Golombek 1996). There is, however, some evidence that the Y_1/Y_5 receptors, in addition to the Y_2 receptor, may also be involved in the mechanism of NPY action by altering the levels of circadian clock-related genes (Fukuhara et al. 2001).

5.3.3

Food Intake and Energy Expenditure

NPY has been implicated to be a central stimulator of feeding behavior by interacting with a number of other hormones and neuroregulators that play roles in

the regulation of body weight. A novel obese gene product, leptin, was found to regulate food intake by inhibiting the synthesis and release of NPY in the central nervous system (Stephens et al. 1995). It was reported that the mild obesity found in Y_1 receptor-deficient mice was caused by impaired insulin secretion and low energy expenditure (Kushi et al. 1998). Furthermore, NPY-induced food intake was remarkably reduced in Y_1 -deficient mice (Kanatani et al. 2000). These results suggest the importance of Y_1 receptors in the regulation of food intake and body weight through the central control of energy expenditure.

It was found that the Y_5 receptor was also involved in NPY-induced food intake (Gerald et al. 1996). The Y_5 receptor-deficient mice responded significantly less to NPY-induced food intake than wild-type mice (Marsh et al. 1998). On the other hand, the results obtained using Y_2 receptor-deficient mice indicated an inhibitory role for the Y_2 receptor in the central regulation of body weight and food intake (Naveilhan et al. 1999). Hypothalamus-specific Y_2 receptor-deleted mice showed a significant decrease in body weight and a significant increase in food intake, suggesting an important role of hypothalamic Y_2 receptors in body weight regulation (Sainsbury et al. 2002). In addition, it was reported that peripheral injection of PYY(3–36) in rats inhibited food intake and reduced weight gain. PYY(3–36) also inhibited food intake in mice, but not in Y_2 receptor-deficient mice. This suggests that the anorectic effect requires the Y_2 receptor (Batterham et al. 2002).

5.3.4

Hormone Secretion and Reproduction

NPY has been known to be a putative neuroregulator of the reproductive axis in the central nervous system. A selective Y_5 agonist inhibited LH secretion, while the inhibitory action was fully prevented by Y_5 receptor antagonists (Raposo et al. 1999). It was also shown that Y_5 receptor activation suppressed the reproductive axis in both virgin and lactating rats (Toufexis et al. 2002). These results suggest that the actions of NPY on the reproductive axis are predominantly mediated by the Y_5 receptor. On the other hand, using Y_1 receptor-deficient mice, crucial roles for the Y_1 receptor in controlling food intake, the onset of puberty, and the maintenance of reproductive functions were demonstrated (Pralong et al. 2002).

5.3.5

Anxiety, Pain, Stress, and Depression

It has been shown that NPY exhibits anxiolytic, antinociceptive, anti-stress, and anti-depressive actions. Involvement of the Y_1 receptor in the anxiolytic-like action of NPY was demonstrated (Wahlestedt et al. 1993; Heilig et al. 1993). NPY may produce not only an anxiolytic effect via the Y_1 receptor, but also an anxiogenic effect via the Y_2 receptor (Nakajima et al. 1998). It was reported that NPY transgenic mice displayed anxiolytic behaviors (Inui et al. 1998). Moreover,

transgenic rats with hippocampal NPY overexpression were insensitive to restraint stress, had no fear suppression behavior, and displayed impaired spatial learning (Thorsell et al. 2000). It was also reported that Y_1 receptor-deficient mice developed hyperalgesia to acute pain, and showed a complete absence of the pharmacological analgesic effects of NPY (Naveilhan et al. 2001). These data suggest that NPY and its receptors are involved in the mechanisms of anxiety, stress, learning, and nociception.

Using an animal model of depression, alterations in the NPY levels and Y_1 receptor mRNA were observed after treatment with an anti-depressant drug (Caberlotto et al. 1998). When compared with healthy controls, the levels of NPY appeared to be low in patients who had recently attempted suicide. Patients who had repeatedly attempted suicide were found to have the lowest NPY levels (Westrin et al. 1999). These data suggest the possible involvement of NPY and Y_1 receptors in depression.

5.3.6

Seizures

NPY has been implicated to function as an endogenous anticonvulsant. It was reported that NPY-deficient mice were susceptible to seizures induced by a GABA antagonist (Erickson et al. 1996). Kainic acid-induced limbic seizures in NPY-deficient mice progressed uncontrollably and ultimately produced death in 93% of the mice, whereas intracerebroventricular NPY infusion could prevent such death (Baraban et al. 1997). Furthermore, the transgenic rats with NPY overexpression showed a significant reduction in the number and duration of kainic acid-induced seizures (Vezzani et al. 2002).

It was found that NPY, acting predominantly via Y_2 receptors, could dramatically inhibit epileptiform activity in vitro models of epilepsy (Klapstein and Colmers 1997). NPY was also found to potently inhibit seizures induced by kainic acid via Y_5 receptor (Woldbye et al. 1997). Moreover, mice lacking the Y_5 receptor were more sensitive to kainic acid-induced seizures (Marsh et al. 1999). In human epilepsy it is suggested that abundant sprouting of NPY fibers, concomitant upregulation of Y_2 receptors, and downregulation of Y_1 receptors in the hippocampus of patients with Ammon's horn sclerosis is involved in the anticonvulsant mechanism by the NPY system (Furtinger et al. 2001).

5.3.7

Ethanol Consumption

Thiele et al. (1998) first reported that NPY-deficient mice showed increased ethanol consumption, while transgenic mice with NPY overexpression had a lower preference for ethanol. These data suggest that alcohol consumption and resistance are inversely related to the NPY levels in the brain. Recently, it was reported that knockout mice lacking the Y_1 receptor showed increased ethanol consumption. It is suggested that the Y_1 receptor regulates voluntary ethanol con-

sumption and some of the intoxicating effects caused by administration of ethanol (Thiele et al. 2002).

It was shown that blockade of central Y_2 receptors by a Y_2 receptor antagonist, BIIIE0246, reduced ethanol self-administration in rats. It is therefore suggested that the Y_2 receptor is a candidate target for developing novel pharmacological treatments for alcoholism (Thorsell et al. 2002).

6 Conclusions and Future Studies

NPY has been shown to be involved in the regulation of diverse physiological functions and has been implicated in a variety of disorders such as anxiety, depression, obesity, epilepsy, and alcohol dependence. Thus, the NPY system has emerged as a potential drug target for a number of disorders.

During the last decade, the cloning of NPY receptor subtypes has made it possible to clarify the functional importance of the subtypes and to discover novel compounds with selective affinity to individual receptor subtypes. Indeed, a number of impressive advances have been made in the development of non-peptide antagonists to NPY receptor subtypes. However, further studies are needed to clarify the potential of these compounds as useful drugs. In contrast, synthesis of nonpeptide NPY receptor agonists has not yet been successful, thereby hampering the development of drugs for the treatment of disorders such as anxiety, depression, pain disorders, and epilepsy. In addition, such an agonist may be of clinical importance for modulating the circadian-clock responses to light.

Advances in the development of orally-active nonpeptide NPY receptor agonists and antagonists that are capable of crossing the blood-brain barrier will facilitate our understanding of the physiological roles of NPY and will undoubtedly underscore the importance of NPY in the fields of pharmacology and clinical medicine.

References

- Adrian TE, Allen JM, Bloom SR et al. (1983) Neuropeptide Y distribution in human brain. *Nature* 306:584–586
- Aicher SA, Springston M, Berger SB et al. (1991) Receptor-selective analogs demonstrate NPY/PYY receptor heterogeneity in rat brain. *Neurosci Lett* 130:32–36
- Albers HE, Ferris CF (1984) Neuropeptide Y: role in light-dark cycle entrainment of hamster circadian rhythms. *Neurosci Lett* 50:163–168
- Allen JM, Adrian TE, Tatemoto K et al. (1982) Two novel related peptides, neuropeptide Y (NPY) and peptide YY (PYY) inhibit the contraction of the electrically stimulated mouse vas deferens. *Neuropeptides* 3:71–77
- Allen JM, Rodrigo J, Yeats JC et al. (1984) Vascular distribution of neuropeptide Y (NPY) and effect on blood pressure. *Clin Exp Hypertens A* 6:1879–1882
- Allen YS, Adrian TE, Allen JM et al. (1983) Neuropeptide Y distribution in the rat brain. *Science* 221:877–879

- Balasubramaniam AA (1997) Neuropeptide Y family of hormones: receptor subtypes and antagonists. *Peptides* 18:445–457
- Baraban SC, Hollopeter G, Erickson JC et al. (1997) Knock-out mice reveal a critical anti-epileptic role for neuropeptide Y. *J Neurosci* 17:8927–8936
- Bard JA, Walker MW, Branchek TA, Weinshank RL (1995) Cloning and functional expression of a human Y4 subtype receptor for pancreatic polypeptide, neuropeptide Y, and peptide YY. *J Biol Chem* 270:26762–26765
- Batterham RL, Cowley MA, Small CJ et al. (2002) Gut hormone PYY(3–36) physiologically inhibits food intake. *Nature* 418:650–654
- Beck A, Jung G, Gaida W et al. (1989) Highly potent and small neuropeptide Y agonist obtained by linking NPY 1–4 via spacer to alpha-helical NPY 25–36. *FEBS Lett* 244:119–122
- Boublik J, Scott N, Taulane J et al. (1989) Neuropeptide Y and neuropeptide Y18–36. Structural and biological characterization. *Int J Pept Protein Res* 33:11–15
- Burkhoff A, Linemeyer DL, Salon JA (1998) Distribution of a novel hypothalamic neuropeptide Y receptor gene and its absence in rat. *Brain Res Mol Brain Res* 53:311–316
- Caberlotto L, Fuxe K, Overstreet DH et al. (1998) Alterations in neuropeptide Y and Y1 receptor mRNA expression in brains from an animal model of depression: region specific adaptation after fluoxetine treatment. *Brain Res Mol Brain Res* 59:58–65
- Caberlotto L, Fuxe K, Hurd YL (2000) Characterization of NPY mRNA-expressing cells in the human brain: co-localization with Y2 but not Y1 mRNA in the cerebral cortex, hippocampus, amygdala, and striatum. *J Chem Neuroanat* 20:327–337
- Chen X, Westfall TC (1993) Depressor effect of intrathecal neuropeptide Y (NPY) is mediated by Y2 subtype of NPY receptors. *J Cardiovasc Pharmacol* 21:720–724
- Chronwall BN, DiMaggio, DA, Massari VJ et al. (1985) The anatomy of neuropeptide Y-containing neurons in rat brain. *Neuroscience* 15:1159–1181
- Clark JT, Kalra PS, Crowley WR, Kalra SP (1984) Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. *Endocrinology* 115:427–429
- Clark JT, Kalra PS, Kalra SP (1985) Neuropeptide Y stimulates feeding but inhibits sexual behavior in rats. *Endocrinology* 117:2435–2442
- Colmers WF, Lukowiak K, Pittman Q (1988) Neuropeptide Y action in the rat hippocampal slice: site and mechanism of presynaptic inhibition. *J Neurosci* 8:3827–337
- Colmers WF, Klapstein GJ, Fournier A et al. (1991) Presynaptic inhibition by neuropeptide Y in rat hippocampal slice in vitro is mediated by a Y2 receptor. *Br J Pharmacol* 102:41–44
- Corder R, Emson PC, Lowry PJ (1984) Purification and characterization of human neuropeptide Y from adrenal-medullary pheochromocytoma tissue. *Biochem J* 219:699–706
- Edvinsson L, Emson P, McCulloch J et al. (1983) Neuropeptide Y: cerebrovascular innervation and vasomotor effects in the cat. *Neurosci Lett* 43:79–84
- Erickson JC, Clegg KE, Palmiter RD (1996) Sensitivity to leptin and susceptibility to seizures of mice lacking neuropeptide Y. *Nature* 381:415–421
- Evequoz D, Waeber B, Aubert JF et al. (1988) Neuropeptide Y prevents the blood pressure fall induced by endotoxin in conscious rats with adrenal medullectomy. *Circ Res* 62:25–30
- Everitt BJ, Hokfelt T (1989) The existence of neuropeptide Y with other peptides and amines in the central nervous system. In: Mutt V et al. (eds) *Neuropeptide Y*. Raven Press, New York, pp 61–71
- Ewald DA, Sternweis PC, Miller RJ (1988) Guanine nucleotide-binding protein Go-induced coupling of neuropeptide Y receptors to Ca²⁺ channels in sensory neurons. *Proc Natl Acad Sci USA* 85:3633–3637
- Flood JF, Hernandez EN, Morley JE (1987) Modulation of memory processing by neuropeptide Y. *Brain Res* 421:280–290

- Fredholm BB, Jansen I, Edvinsson L (1985) Neuropeptide Y is a potent inhibitor of cyclic AMP accumulation in feline cerebral blood vessels. *Acta Physiol Scand* 124:467–469
- Fuhlendorff J, Gether U, Aakerlund L et al. (1990) [Leu31, Pro34] neuropeptide Y: a specific Y1 receptor agonist. *Proc Natl Acad Sci USA* 87:182–186
- Fukuhara C, Brewer JM, Dirden JC et al. (2001) Neuropeptide Y rapidly reduces Period 1 and Period 2 mRNA levels in the hamster suprachiasmatic nucleus. *Neurosci Lett* 314:119–122
- Furtinger S, Pirker S, Czech T et al. (2001) Plasticity of Y1 and Y2 receptors and neuropeptide Y fibers in patients with temporal lobe epilepsy. *J Neurosci* 21:5804–5812
- Fuxe K, Agnati LF, Harfstrand A et al. (1983) Central administration of neuropeptide Y induces hypotension bradypnea and EEG synchronization in the rat. *Acta Physiol Scand* 118:189–192
- Gehlert DR, Chronwall BM, Schafer MP, O'Donohue TL (1987) Localization of neuropeptide Y messenger ribonucleic acid in rat and mouse brain by in situ hybridization. *Synapse* 1:25–31
- Gehlert DR, Beavers LS, Johnson D et al. (1996) Expression cloning of a human brain neuropeptide Y Y2 receptor. *Mol Pharmacol* 49:224–228
- Gerald C, Walker MW, Vaysse PJ et al. (1995) Expression cloning and pharmacological characterization of a human hippocampal neuropeptide Y/peptide YY Y2 receptor subtype. *J Biol Chem* 270:26758–26761
- Gerald C, Walker MW, Criscione L et al. (1996) A receptor subtype involved in neuropeptide-Y-induced food intake. *Nature* 382:168–171
- Golombek DA, Biello SM, Rendon RA, Harrington ME (1996) Neuropeptide Y phase shifts the circadian clock in vitro via a Y2 receptor. *Neuroreport* 7:1315–1319
- Gregor P, Millham ML, Feng Y et al. (1996) Cloning and characterization of a novel receptor to pancreatic polypeptide, a member of the neuropeptide Y receptor family. *FEBS Lett* 381:58–62
- Hackenthal E, Aktories K, Jakobs KH, Lang RE (1987) Neuropeptide Y inhibits renin release by a pertussis toxin-sensitive mechanism. *Am J Physiol* 252:F543–F550
- Heilig M, Murison R (1987) Intracerebroventricular neuropeptide Y protects against stress-induced gastric erosion in the rat. *Eur J Pharmacol* 137:127–129
- Heilig M, Wahlestedt C, Ekman R, Widerlov E (1988) Antidepressant drugs increase the concentration of neuropeptide Y (NPY)-like immunoreactivity in the rat brain. *Eur J Pharmacol* 147:465–467
- Heilig M, Soderpalm B, Engel JA, Widerlov E (1989) Centrally administered neuropeptide Y (NPY) produces anxiolytic-like effects in animal anxiety models. *Psychopharmacology (Berlin)* 98:524–529
- Heilig M, McLeod S, Brot M et al. (1993) Anxiolytic-like action of neuropeptide Y: mediation by Y1 receptors in amygdala, and dissociation from food intake effects. *Neuropsychopharmacology* 8:357–363
- Hellstrom PM, Olerup O, Tatemoto K (1985) Neuropeptide Y may mediate effects of sympathetic nerve stimulations on colonic motility and blood flow in the cat. *Acta Physiol Scand* 124:613–624
- Herzog H, Hort YJ, Ball H et al. (1992) Cloned human neuropeptide Y receptor couples to two different second messenger systems. *Proc Natl Acad Sci USA* 89:5794–5798
- Herzog H, Hort YJ, Shine J, Selbie LA (1993) Molecular cloning, characterization, and localization of the human homolog to the reported bovine NPY Y3 receptor: lack of NPY binding and activation. *DNA Cell Biol* 12:465–471
- Hokfelt T, Lundberg JM, Lagercrantz H et al. (1983) Occurrence of neuropeptide Y (NPY)-like immunoreactivity in catecholamine neurons in the human medulla oblongata. *Neurosci Lett* 36:217–222
- Hu Y, Bloomquist BT, Cornfield LJ et al. (1996) Identification of a novel hypothalamic neuropeptide Y receptor associated with feeding behavior. *J Biol Chem* 271:26315–26319

- Hua XY, Boublik JH, Spicer MA et al. (1991) The antinociceptive effects of spinally administered neuropeptide Y in the rat: systematic studies on structure-activity relationship. *J Pharmacol Exp Ther* 258:243–248
- Huhman KL, Gillespie CF, Marvel CL, Albers HE (1996) Neuropeptide Y phase shifts circadian rhythms in vivo via a Y2 receptor. *Neuroreport* 7:1249–1252
- Inui A, Okita M, Nakajima M et al. (1998) Anxiety-like behavior in transgenic mice with brain expression of neuropeptide Y. *Proc Assoc Am Physicians* 110:171–182
- Jazin EE, Yoo H, Blomqvist AG et al. (1993) A proposed bovine neuropeptide Y (NPY) receptor cDNA clone, or its human homologue, confers neither NPY binding sites nor NPY responsiveness on transfected cells. *Regul Pept* 47:247–258
- Kalra SP, Crowley WR (1984) Norepinephrine-like effects of neuropeptide Y on LH release in the rat. *Life Sci* 35:1173–1176
- Kalra SP, Fuentes M, Fournier A et al. (1992) Involvement of the Y-1 receptor subtype in the regulation of luteinizing hormone secretion by neuropeptide Y in rats. *Endocrinology* 130:3323–3330
- Kanatani A, Mashiko S, Murai N et al. (2000) Role of the Y1 receptor in the regulation of neuropeptide Y-mediated feeding: comparison of wild-type, Y1 receptor-deficient, and Y5 receptor-deficient mice. *Endocrinology* 141:1011–1016
- Kassiss S, Olasmaa M, Terenius L, Fishman PH (1987) Neuropeptide Y inhibits cardiac adenylate cyclase through a pertussis toxin-sensitive G protein. *J Biol Chem* 262:3429–3431
- Kaye WH, Berrettini W, Gwirtsman H, George DT (1990) Altered cerebrospinal fluid neuropeptide Y and peptide YY immunoreactivity in anorexia and bulimia nervosa. *Arch Gen Psychiatry* 47:548–556
- Klapstein GJ, Colmers WF (1997) Neuropeptide Y suppresses epileptiform activity in rat hippocampus in vitro. *J Neurophysiol* 78:1651–1661
- Krause J, Eva C, Seeburg PH, Sprengel R (1992) Neuropeptide Y1 subtype pharmacology of a recombinantly expressed neuropeptide receptor. *Mol Pharmacol* 41:817–821
- Krstenansky JL, Owen TJ, Buck SH et al. (1989) Centrally truncated and stabilized porcine neuropeptide Y analogs: design, synthesis, and mouse brain receptor binding. *Proc Natl Acad Sci USA* 86:4377–4381
- Kushi A, Sasai H, Koizumi H et al. (1998) Obesity and mild hyperinsulinemia found in neuropeptide Y-Y1 receptor-deficient mice. *Proc Natl Acad Sci USA* 95:15659–15664
- Larhammar D, Blomqvist AG, Yee F et al. (1992) Cloning and functional expression of a human neuropeptide Y/peptide YY receptor of the Y1 type. *J Biol Chem* 267:10935–10938
- Larhammar D, Blomqvist AG, Soderberg C (1993) Evolution of neuropeptide Y and its related peptides. *Comp Biochem Physiol* 106 C:743–752
- Leibowitz SF, Alexander JT (1991) Analysis of neuropeptide Y-induced feeding: dissociation of Y1 and Y2 receptor effects on natural meal patterns. *Peptides* 12:1251–1260
- Leibowitz SF, Xuereb M, Kim T (1992) Blockade of natural and neuropeptide Y-induced carbohydrate feeding by a receptor antagonist PYX-2. *Neuroreport* 3:1023–1026
- Levine AS, Morley JE (1984) Neuropeptide Y: a potent inducer of consummatory behavior in rats. *Peptides* 5:1025–1029
- Lundberg JM, Tatemoto K (1982) Pancreatic polypeptide family (APP, BPP, NPY and PYY) in relation to sympathetic vasoconstriction resistant to alpha-adrenoceptor blockade. *Acta Physiol Scand* 116:393–402
- Lundberg JM, Terenius L, Hokfelt T et al. (1982) Neuropeptide Y (NPY)-like immunoreactivity in peripheral noradrenergic neurons and effects of NPY on sympathetic function. *Acta Physiol Scand* 116:477–480
- Lundberg JM, Terenius L, Hokfelt T, Goldstein M (1983) High levels of neuropeptide Y in peripheral noradrenergic neurons in various mammals including man. *Neurosci Lett* 42:167–172

- Lundberg JM, Stjarne L (1984) Neuropeptide Y (NPY) depresses the secretion of ^3H -noradrenaline and the contractile response evoked by field stimulation, in rat vas deferens. *Acta Physiol Scand* 120:477–479
- Lundell I, Blomqvist AG, Berglund MM et al. (1995) Cloning of a human receptor of the NPY receptor family with high affinity for pancreatic polypeptide and peptide YY. *J Biol Chem* 270:29123–29128
- MacDonald JK (1988) NPY and related substances. *Crit Rev Neurobiol* 4:97–135
- Malmstrom RE (2001) Vascular pharmacology of BIE0246, the first selective non-peptide neuropeptide Y Y(2) receptor antagonist, in vivo. *Br J Pharmacol* 133:1073–1080
- Malmstrom RE, Lundberg JM (1995) Neuropeptide Y accounts for sympathetic vasoconstriction in guinea-pig vena cava: evidence using BIBP 3226 and 3435. *Eur J Pharmacol* 294:661–668
- Marksteiner J, Sperk G (1988) Concomitant increase of somatostatin, neuropeptide Y and glutamate decarboxylase in the frontal cortex of rats with decreased seizure threshold. *Neuroscience* 26:379–385
- Marksteiner J, Prommegger R, Sperk G (1990) Effect of anticonvulsant treatment on kainic acid-induced increases in peptide levels. *Eur J Pharmacol* 81:241–246
- Marsh DJ, Hollopeter G, Kafer KE, Palmiter RD (1998) Role of the Y5 neuropeptide Y receptor in feeding and obesity. *Nature Med* 4:718–721
- Marsh DJ, Baraban SC, Hollopeter G, Palmiter RD (1999) Role of the Y5 neuropeptide Y receptor in limbic seizures. *Proc Natl Acad Sci USA* 96:13518–13523
- Martel JC, St-Pierre S, Quirion R (1986) Neuropeptide Y receptors in rat brain: autoradiographic localization. *Peptides* 7:55–60
- Matsumoto M, Nomura T, Momose K et al. (1996) Inactivation of a novel neuropeptide Y/peptide YY receptor gene in primate species. *J Biol Chem* 271:27217–27220
- Michel MC, Beck-Sickinger A, Cox H et al. (1998) XVI International union of pharmacology recommendations for the nomenclature of neuropeptide Y, peptide YY, and pancreatic polypeptide receptors. *Pharmacol Rev* 50:143–150
- Minth CD, Bloom SR, Polak JM, Dixon JE (1984) Cloning, characterization, and DNA sequence of a human cDNA encoding neuropeptide tyrosine. *Proc Natl Acad Sci USA* 81:4577–4581
- Minth CD, Andrews PC, Dixon JE (1986) Characterization, sequence, and expression of the cloned human neuropeptide Y gene. *J Biol Chem* 261:11974–11979
- Morioka H, Inui A, Inoue T et al. (1986) Neuropeptide Y decreases rectal temperature after intracerebroventricular administration in conscious dogs. *Kobe J Med Sci* 32:45–57
- Motulsky HJ, Michel MC (1988) Neuropeptide Y mobilizes Ca^{2+} and inhibits adenylate cyclase in human erythroleukemia cells. *Am J Physiol* 255:E880–885
- Nakajima M, Inui A, Asakawa A et al. (1998) Neuropeptide Y produces anxiety via Y2-type receptors. *Peptides* 19:359–363
- Naveilhan P, Hassani H, Canals JM et al. (1999) Normal feeding behavior, body weight and leptin response require the neuropeptide Y Y2 receptor. *Nature Med* 5:1188–1193
- Naveilhan P, Hassani H, Lucas G et al. (2001) Reduced antinociception and plasma extravasation in mice lacking a neuropeptide Y receptor. *Nature* 409:513–517
- Parker RM, Herzog H. (1999) Regional distribution of Y-receptor subtype mRNAs in rat brain. *Eur J Neurosci* 11:1431–1448
- Parker EM, Babij CK, Balasubramaniam A et al. (1998) GR231118 (1229U91) and other analogues of the C-terminus of neuropeptide Y are potent neuropeptide Y Y1 receptor antagonists and neuropeptide Y Y4 receptor agonists. *Eur J Pharmacol* 349:97–105
- Parker E, Van Heek M, Stamford A (2002) Neuropeptide Y receptors as targets for anti-obesity drug development: perspective and current status. *Eur J Pharmacol* 440:173–187

- Pedrazzini, Seydoux, Kunstner et al. (1998) Cardiovascular response, feeding behavior and locomotor activity in mice lacking the NPY Y1 receptor. *Nature Med* 4:722–726
- Petty MA, Dietrich R, Lang RE (1984) The cardiovascular effects of neuropeptide Y (NPY). *Clin Exp Hypertens A* 6:1889–1892
- Pheng LH, Regoli D (2000) Receptors for NPY in peripheral tissues bioassays. *Life Sci* 67:847–862
- Pralong FP, Gonzales C, Voirol MJ et al. (2002) The neuropeptide Y Y1 receptor regulates leptin-mediated control of energy homeostasis and reproductive functions. *FASEB J* 16:712–714
- Raposo PD, Broqua P, Pierroz DD et al. (1999) Evidence that the inhibition of luteinizing hormone secretion exerted by central administration of neuropeptide Y (NPY) in the rat is predominantly mediated by the NPY-Y5 receptor subtype. *Endocrinology* 140:4046–4055
- Rimland J, Xin W, Sweetnam P et al. (1991) Sequence and expression of a neuropeptide Y receptor cDNA. *Mol Pharmacol* 40:869–875
- Rimland JM, Seward EP, Humbert Y et al. (1996) Coexpression with potassium channel subunits used to clone the Y2 receptor for neuropeptide Y. *Mol Pharmacol* 49:387–390
- Rose PM, Fernandes P, Lynch JS et al. (1995) Cloning and functional expression of a cDNA encoding a human type 2 neuropeptide Y receptor. *J Biol Chem* 270:22661–22664
- Rudolf K, Eberlein W, Engel W et al. (1994) The first highly potent and selective non-peptide neuropeptide Y Y1 receptor antagonist: BIBP3226. *Eur J Pharmacol* 271:R11–13
- Sainsbury A, Schwarzer C, Couzens M et al. (2002) Important role of hypothalamic Y2 receptors in body weight regulation revealed in conditional knockout mice. *Proc Natl Acad Sci USA* 99:8938–8943
- Sheikh SP, O'Hare MM, Tortora O, Schwartz TW (1989) Binding of monoiodinated neuropeptide Y to hippocampal membranes and human neuroblastoma cell lines. *J Biol Chem* 264:6648–6654
- Stanley BG, Leibowitz SF (1984) Neuropeptide Y: stimulation of feeding and drinking by injection into the paraventricular nucleus. *Life Sci* 35:2635–2642
- Statnick MA, Schober DA, Gackenhimer S et al. (1998) Characterization of the neuropeptide Y5 receptor in the human hypothalamus: a lack of correlation between Y5 mRNA levels and binding sites. *Brain Res* 810:16–26
- Stephens TW, Basinski M, Bristow PK et al. (1995) The role of neuropeptide Y in the anti-obesity action of the obese gene product. *Nature* 377:530–532
- Sun XY, Zhao XH, Erlinge D et al. (1996) Effects of phosphorothioated neuropeptide Y Y1-receptor antisense oligodeoxynucleotide in conscious rats and in human vessels. *Br J Pharmacol* 118:131–136
- Sundler F, Moghimi-zadeh E, Hakanson R et al. (1983) Nerve fibers in the gut and pancreas of the rat displaying neuropeptide-Y immunoreactivity. Intrinsic and extrinsic origin. *Cell Tissue Res* 230:487–493
- Tatemoto K (1982a) Neuropeptide Y: complete amino acid sequence of the brain peptide. *Proc Natl Acad Sci USA* 79:5485–5489
- Tatemoto K (1982b) Isolation and characterization of peptide YY (PYY), a candidate gut hormone that inhibits pancreatic exocrine secretion. *Proc Natl Acad Sci USA* 79:2514–2518
- Tatemoto K (1990) Neuropeptide Y and its receptor antagonist. *Ann New York Acad Sci* 611:1–6
- Tatemoto K, Mutt V (1978) Chemical determination of polypeptide hormones. *Proc Natl Acad Sci USA* 75:4115–4119
- Tatemoto K, Mutt V (1980) Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides. *Nature* 285:417–418

- Tatemoto K, Carlquist M, Mutt V (1982) Neuropeptide Y—a novel brain peptide with structural similarities to peptide YY and pancreatic polypeptide. *Nature* 296:659–660
- Tatemoto K, Rokaeus A, Jornvall H et al. (1983) Galanin—a novel biologically active peptide from porcine intestine. *FEBS Lett* 164:124–128
- Tatemoto K, Lundberg JM, Jornvall H, Mutt V (1985) Neuropeptide K: Isolation, structure and biological activities of a novel brain tachykinin. *Biochem Biophys Res Commun* 128:947–953
- Tatemoto K, Efendic S, Mutt V et al. (1986) Pancreastatin, a novel pancreatic peptide that inhibits insulin secretion. *Nature* 324:476–478
- Terenghi G, Polak JM, Hamid Q et al. (1987) Localization of neuropeptide Y mRNA in neurons of human cerebral cortex by means of in situ hybridization with a complementary RNA probe. *Proc Natl Acad Sci USA* 84:7315–7318
- Thiele TE, Marsh DJ, Ste Marie L et al. (1998) Ethanol consumption and resistance are inversely related to NPY levels. *Nature* 396:366–369
- Thiele TE, Koh MT, Pedrazzini T (2002) Voluntary alcohol consumption is controlled via the neuropeptide Y Y1 receptor. *J Neurosci* 22:RC208:1–6
- Thorsell A, Michalkiewicz M, Dumont Y et al. (2000) Behavioral insensitivity to restraint stress, absent fear suppression of behavior and impaired spatial learning in transgenic rats with hippocampal neuropeptide Y overexpression. *Proc Natl Acad Sci USA* 97:12852–12857
- Thorsell A, Rimondini R, Heilig M. (2002) Blockade of central neuropeptide Y (NPY) Y2 receptors reduces ethanol self-administration in rats. *Neurosci Lett* 332:1–4
- Toufexis DJ, Kyriazis D, Woodside B (2002) Chronic neuropeptide Y Y5 receptor stimulation suppresses reproduction in virgin female and lactating rats. *J Neuroendocrinol* 14:492–497
- Uden A, Tatemoto K, Mutt V, Bartfai T (1984) Neuropeptide Y receptor in the rat brain. *Eur J Biochem* 145:525–530
- Vezzani A, Michalkiewicz M, Michalkiewicz T et al. (2002) Seizure susceptibility and epileptogenesis are decreased in transgenic rats overexpressing neuropeptide Y. *Neuroscience* 110:237–243
- Wahlestedt C, Yanaihara N, Hakanson R (1986) Evidence for different pre- and post-junctional receptors for neuropeptide Y and related peptides. *Regul Pept* 13:307–318
- Wahlestedt C, Pich EM, Koob GF, Yee F, Heilig M (1993) Modulation of anxiety and neuropeptide Y-Y1 receptors by antisense oligodeoxynucleotides. *Science* 259:528–531
- Watson JD, Sury MR, Corder R et al. (1988) Plasma levels of neuropeptide tyrosine Y (NPY) are increased in human sepsis but are unchanged during canine endotoxin shock despite raised catecholamine concentrations. *J Endocrinol* 116:421–426
- Weinberg DH, Sirinathsinghi DJ, Tan CP et al. (1996) Cloning and expression of a novel neuropeptide Y receptor. *J Biol Chem* 271:16435–16438
- Westrin A, Ekman R, Traskman-Bendz L (1999) Alterations of corticotropin releasing hormone (CRH) and neuropeptide Y (NPY) plasma levels in mood disorder patients with a recent suicide attempt. *Eur Neuropsychopharmacol* 9:205–211
- Wharton J, Gordon L, Byrne J et al. (1993) Expression of the human neuropeptide tyrosine Y1 receptor. *Proc Natl Acad Sci USA* 90:687–691
- Widerlov E, Lindstrom LH, Wahlestedt C, Ekman R (1988) Neuropeptide Y and peptide YY as possible cerebrospinal fluid markers for major depression and schizophrenia, respectively. *J Psychiatr Res* 22:69–79
- Woldbye DP, Larsen PJ, Mikkelsen JD et al. (1997) Powerful inhibition of kainic acid seizures by neuropeptide Y via Y5-like receptors. *Nature Med* 3:761–764
- Yan H, Yang J, Marasco J et al. (1996) Cloning and functional expression of cDNAs encoding human and rat pancreatic polypeptide receptors. *Proc Natl Acad Sci USA* 93:4661–4665



<http://www.springer.com/978-3-540-40581-8>

Neuropeptide Y and Related Peptides

Michel, M.C. (Ed.)

2004, X, 555 p., Hardcover

ISBN: 978-3-540-40581-8