Neuropeptide Y (NPY), peptide YY (PYY) and pancreatic polypeptide (PP) belong to a structurally and functionally related family of peptides (NPY peptides), also known as the neuropeptide Y family. Whereas PYY and PP are gut hormones, NPY is one of the most abundant neuropeptides in the brain. The peptides of the neuropeptide Y family mediate their effects through several G-protein-coupled receptors (GPCRs), in case of the NPY system the so-called Y receptors. All three peptide hormones consist of 36 amino acid residues and are C-terminally amidated. In addition to a distinct sequence homology, they share a common hairpin-like three-dimensional structure, known as the pancreatic polypeptide fold (PP-fold). NPY peptides fulfill important physiological functions via their receptors, but are also implicated in a number of disease states. Examples include obesity, cancer, autoimmune-diseases and neurological disorders. Therefore, NPY peptide ligands for the Y receptors are indispensable tools for current research, which we would like to summarize in the following.
**Introduction**

In 1980 Tatemoto and coworkers isolated peptide YY (PYY) during an extensive search for new putative peptide hormones from the porcine intestine. Two years later, they isolated neuropeptide Y (NPY) from extracts of porcine brain. Both peptides belong to the pancreatic polypeptide hormone family, which further includes the gut hormone pancreatic polypeptide (PP). This family of peptides is also known as NPY family, and the corresponding peptides here are referred to as NPY peptides. These hormones exert their effects over certain brain regions, such as the arcuate nucleus (ARC), a brain area which is directly accessible to circulating hormones and responsible for the regulation of food intake.

NPY peptides share a high level of homology and up to 92% conservation in structure between vertebrates and non-vertebrates. NPY itself displays a remarkable degree of sequence conservation: 22 positions out of 36 amino acids are identical in all of the investigated species, and NPY is one of the most evolutionarily conserved peptides known. Furthermore, PYY shares 75% homology with NPY and thus is capable to activate the same receptors (Table 1).

All members of the NPY family exhibit a hairpin-like three-dimensional structure called pancreatic polypeptide-fold (PP-fold). Data obtained by computer modeling based on the crystal structure of avian PP revealed that this tertiary structure consists of an extended type II polyproline helix (residues 1-8), followed by a type II β-turn and an amphipathic α-helix (residues 15-32). The carboxy-terminal residues comprise a flexible turn conformation.

NPY is one of the most abundant neuropeptides in the central and peripheral nervous system. It is present in high concentrations in numerous brain regions including the hypothalamus, amygdala, hippocampus, nucleus of the solitary tract, locus coeruleus, nucleus accumbens and the cerebral cortex. Brain NPY is found colocalized with norepinephrine (NE), γ-aminobutyric acid (GABA) and somatostatin in agouti-related protein containing neurons. In the periphery, NPY is abundantly expressed in the sympathetic nervous system, where it is stored and released along with NE. It is also present in a subpopulation of parasympathetic neurons. Many stress-related functions of NPY are attributed to its function on the peripheral nervous system. Apart from its expression in the nervous system, NPY can also be detected in the adrenal medulla, which represents the primary source of circulating NPY, and furthermore in liver, heart, spleen, and in endothelial cells of blood vessels.

Based on several pharmacological studies a great number of physiological functions for NPY have been revealed. Some of the best studied functions are the control of appetite, body weight and obesity. It became evident that NPY is one of the most potent orexigenic peptides. Apart from its role in feeding control, NPY is involved in the regulation of luteinizing hormone, adrenocorticotropic hormone and insulin secretion, reduction of growth hormone release, anxiolysis, and thermoregulation. NPY causes long-lasting vasoconstriction in skeletal muscle, heart, kidney, and brain.

Pre-junctional, NPY inhibits its own release as well as the release of noradrenaline and ATP, and suppresses synaptic inhibition mediated by GABA receptors. Additionally, NPY enhances memory retention, and is also involved in the modulation of ethanol consumption and resistance.

Several disorders and pathological conditions are associated with altered NPY functions, such as feeding disorders and metabolic diseases, anxiety, seizures, intestinal dysfunction, cardiovascular and respiratory diseases as well as several memory disorders. In line with this, other findings indicate that the orexigenic effect of ghrelin is mediated via central pathways involving, amongst other factors, NPY.

PYY is predominantly expressed in endocrine cells of the upper and lower gastrointestinal tract, but can also be found in endocrine cells of the adrenal gland, respiratory tract and pituitary. In addition, PYY exists in neurons, which discriminates it from the other members of the family: These are expressed either

<table>
<thead>
<tr>
<th>Nervous system</th>
<th>Receptor Y₁</th>
<th>Receptor Y₂</th>
<th>Receptor Y₄</th>
<th>Receptor Y₅</th>
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<tbody>
<tr>
<td>Preferred ligand</td>
<td>NPY (Pro³⁴)-NPY (Leu⁴¹, Pro³⁴)-NPY PYY (Pro³⁴)-PYY (Leu⁴¹, Pro³⁴)-PYY</td>
<td>NPY NPY (3-36) PYY PYY (3-36)</td>
<td>PP</td>
<td>NPY NPY (3-36) (Ala⁴¹, Aib⁴²)-NPY PYY PYY (3-36)</td>
</tr>
<tr>
<td>Expression</td>
<td>Central</td>
<td>Cerebral cortex, brainstem and thalamus</td>
<td>Hippocampus, brainstem and hypothalamus</td>
<td>Paraventricular nucleus and hypothalamus</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Smooth muscle of blood vessels, immune cells, osteoblasts</td>
<td>Autonomic nerves, gastrointestinal tract, endothelial cells, adipocytes</td>
<td>Colon, small intestine and prostate</td>
<td></td>
</tr>
<tr>
<td>Tissue with highest expression</td>
<td>Smooth muscle of vessels innervated by the sympathetic nervous system</td>
<td>Central and peripheral neurons</td>
<td>Gut</td>
<td></td>
</tr>
<tr>
<td>Physiological function</td>
<td>Central</td>
<td>Regulation of food intake, anxiolytic</td>
<td>Inhibition of neurotransmitter release (glutamate). Improved learning and memory</td>
<td>Luteinizing hormone secretion?</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Vasoconstriction, regulation of neurotransmitter release</td>
<td>Inhibition of NE release (pre-junctional); angiogenesis, adipogenesis (post-junctional)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

in endocrine cells (PP) or in neurons (NPY), but not in both. The highest concentration of PYY can be found in the rectum.

PYY is involved in a number of physiological actions, which are associated with the regulation of the digestive organs, such as inhibition of gastric acid secretion, pancreatic exocrine secretion, intestinal secretion, and gastrointestinal motility. With respect to the clinical pattern of obesity, researchers found that the hormones ghrelin and PYY are linked to short-term feeding behavior, whereas leptin, and to a lesser extent insulin, are associated with the long-term regulation of weight.

**Processing**

Peptides of the NPY family are expressed as precursor peptides (prepro-NPY, -PYY and -PP) and directed to the endoplasmatic re-
ticulum by amino-terminal signal sequences. After cleavage of the signal sequence, the resulting pro-peptides are translocated via the Golgi apparatus and the trans-Golgi network (TGN) towards the secretory pathway for exocytosis. Thereby, the peptides can be stored in vesicles of the TGN until they are needed. During their intracellular travel the precursor peptides undergo several steps of posttranslational modification.

Recently, first three-dimensional structural data of folded prepro-NPY have been obtained by cryo-electron microscopy and single particle analysis. These studies aimed to reveal the quaternary arrangement of the alpha-helices with the lipid membrane, but more data is required. Comparatively well described is the proteolytic processing and the modification of NPY, leading in several steps to the biologically active NPY, or to one of the truncated forms NPY (2-36) and NPY (3-36), respectively (Figure 1).

The carboxy-terminal amidation is a characteristic feature of many biologically active peptides, since it protects against the attack of carboxypeptidases. Amidation of Tyr\(^{36}\) in NPY in addition is crucial for binding of the latter to the \(Y_1\) receptor.

Posttranslational processing of PYY can lead to PYY (1-36) or the truncated form PYY (3-36). The latter lacks the amino-terminal dipeptide Tyr-Pro, which is removed by the action of the enzyme dipeptidyl peptidase-IV (DPP-IV). PYY (1-36) and PYY (3-36) are bioactive, but differ in their selectivity for the various receptor subtypes.

Figure 1.
Synthesis and processing of NPY. The figure shows a schematic outline of the human NPY gene, mRNA and protein precursor. In the gene, filled boxes show the coding parts and open boxes show non-coding parts. GKR constitutes the proteolytic processing site in the peptide precursor. Please, note that the gene and mRNA are not drawn to scale (bp: base pairs; mRNA: messenger ribonucleic acid; nt: nucleotides; UTR: untranslated regions; CPON: C-flanking peptide of NPY). Modified after J.M. Cerdá-Reverter and D. Larhammar, Biochem. Cell Biol. 78, 371-392 (2000)
NPY Peptides

**Y receptors**

NPY peptides mediate their biological effects through several Y receptors that belong to the family of G-protein-coupled receptors (GPCRs). GPCRs are characterized by seven transmembrane α-helices that interact with a family of heterotrimeric GTP-binding proteins, referred to as G-proteins. GPCRs are found in a wide range of organisms, and many kinds of chemical messengers act through them.

Five subtypes of Y receptors (Y₁, Y₂, Y₃, Y₄, Y₅, and Y₆) could be identified in mammals. In humans, only Y₁, Y₂, Y₄, and Y₅ are functionally expressed. The members of the Y receptor family show comparatively low sequence identity and different affinities for their endogenous ligands. All Y receptors are mainly distributed in hypothalamic brain regions, but can also be found in many peripheral tissues, where they mediate diverging effects.

Amino acid Asp 6.59 in the extracellular loop three, which is the only fully conserved residue of all so far investigated Y receptors, is crucial for the binding of NPY and PP to all Y receptors. It has been postulated that high affinity interactions with Asp 6.59 are established via the conserved residues Arg 33 and Arg 35 at the carboxy-termini of NPY and PP. The same studies suggest that binding of ligands to the receptors Y₁ and Y₅ involves different molecular mechanisms, than binding to Y₂ and Y₆.

Binding of NPY to the Y₁-receptor is largely impaired when the N-terminal part of the peptide is removed. Truncations of NPY leading to NPY (2-36), NPY (3-36) or NPY (13-36) result in a marked loss of their affinity and biological activity, which strongly suggests that the Y₁-receptor interacts with the N-terminal part of the ligand. Peptides with structural modifications at the C-terminal end, such as (Pro₃⁴)-NPY and (Leu₃¹,Pro₃⁴)-NPY retain full activity for the Y₁-receptor, and lose their affinity for the Y₅-receptor. This further indicates that the N-terminal part of the peptide determines its binding to and activity at the Y₁-receptor.

The Y₁ receptor, also known as PP-prefering receptor, differs substantially from other Y receptors and shares only 30% primary sequence identity with them. Y₁ binds PP with affinities in a picomolar range, while it can only be moderately activated by NPY and PYY. Noteworthy, the relative binding affinities differ between species, and diverging specificities for NPY and PYY for example can be found in rodents. Histochemical studies indicate that Y₁ is distributed in the whole body including the brain. It is expressed in the hypothalamus, hippocampus, skeletal muscle, heart, adrenal medulla and cortex, thyroid gland, prostate, small intestine, colon and pancreas. Low expression levels can also be detected in the cerebellum, medulla, and spinal cord of the central nervous system (CNS).

Receptor Y₄, also referred to as feeding receptor, is strongly expressed in the hypothalamus, where it stimulates appetite. In the periphery, it seems mainly expressed in the testis. Y₅ binds the Y₁ agonist (Leu₃¹,Pro₃⁴)-NPY, but also has affinity for Y₂ agonists such as NPY (2-36), NPY (3-36) and PP. The modified variant (D-Trp₃²)-NPY appears to act as a partial agonist of Y₅. The NPY analog (Ala₃¹,Aib₃₂)-NPY was described as a selective agonist of Y₅. This substituted peptide was even more potent than NPY in its capacity to stimulate food intake.

**Medical Applications and Outlook**

The functions of the NPY peptides have been implicated in a number of serious disease states.

One of the preeminent is obesity. Today, obesity is a concerning health problem in the industrialized countries. According to estimations by the World Health Organization (WHO), about 1.7 billion adults are overweight and 400 million obese, and these numbers are expected to increase. Thereby, also 10% of the world’s children’s under the age of 15 years might be affected by obesity in future.

Obesity itself is a major risk factor for a number of severe diseases and health problems like metabolic disorders, orthopedic problems and cancer. For a long time, obesity had been considered to be a behavioral disorder. Nowadays it is clear that besides environ-
mental conditions the origins of obesity are of physiological and genetic nature.

Due to the physiological functions triggered by the Y receptors, ligands acting on them including the NPY peptides are of greatest interest for the development of drugs against obesity. In the focus are basically all four Y receptors: Y1 as a modulator of food intake, Y2, which has potential to induce satiety, Y4 due to its potential role in regulation of food intake and because of its potential to suppress orexigenic and to stimulate anorexigenic signaling pathways as well as Y5, since it is postulated to stimulate food intake.

Particularly interesting in the context of obesity is peptide PYY (3-36), which has been demonstrated to be a specific agonist of Y2 receptors in the ARC. PYY (3-36) has potential to act as an “appetite regulator”, and to serve for a long-term regulation of food intake.

Although a number of peptidic and non-peptidic Y receptor agonists and antagonists with potent anti-obesity effects had been developed, they had not yet been converted into clinical tools, referring for instance to a study of Yulyaningsih et al. (2011). Major obstacles remain a lack of selectivity, low oral bioavailability, poor brain penetrability or interaction with other receptors, toxicity or lack of long-term effects. Another problem is posed by the redundancy of the system, which controls feeding. The latter potentially compromises the success in long-term treatments, since the human body is basically capable of circumventing the effect of anti-obesity drugs.

Co-therapies with two or more drugs at once, for example administration of Y5 receptor agonist in combination with a Y1 receptor antagonist, Y1 receptor antagonists or oral anorexiants like sibutramine, have potential to improve the anti-obesity effect. Furthermore, the emerging role of the NPY system for controlling the energy homeostasis besides food intake can provide new opportunities to target the Y receptors. The same applies for the regulation of lipid metabolism by peripheral Y receptors, which could be a target for new medications.

Specific roles of the NPY system in aspects of tumor progression and cancer are proposed on basis of the high abundancies of several Y receptors, found in some tumor cell lines. For example, Y1 receptors are overexpressed on breast cancer cells, in primary human sarcomas, cortical adenomas, prostate cancer and ovarian cancer (in concert with Y2 receptors). Remarkable high expression levels of Y4 were additionally identified in human brain tumors, such as neuroblastomas and glioblastomas. Overall, Y receptors belong to the most promising targets for cancer therapy, although they found so far more application in tumor diagnosis, than in therapy.

In cancer treatment, the natural internalization of Y receptors, decorated with ligands carrying diagnostics or potent anti-cancer drugs, presumably will play a central role. Some time ago, the first positive results could be obtained, when breast cancer cells in patients could selectively be labeled via Y1 specific NPY analogs. As another medical application, the suitability of NPY peptides and their receptors as tumor markers in certain tissues is discussed.

The finding that Y receptors, especially Y1, Y2 and Y4, are expressed at high levels in developing and adult hippocampal regions, is an indication that NPY is associated with diseases and repair processes of the CNS. In addition, NPY acts as a neuromodulator and affects the release of several neurotransmitters such as dopamine and glutamate, which bears potential for the treatment of some chronic disorders of the CNS.

However, only limited data so far is available for the role of the NPY system in neurodegenerative conditions like Alzheimer’s disease, Parkinson’s disease, Huntington’s disease and amyotrophic lateral sclerosis. In contrast, a pro-epileptic effect of the activation of Y1 as well as an anti-epileptic effect of the activation of Y2 and Y4 are meanwhile scientifically well established.

Abnormal levels of all NPY peptides have been found with patients and in animal models of human inflammatory bowel disease (IBD), an autoimmune disorder of the digestive tract. The interaction of NPY with immune
cells during the inflammatory process could play a main role in IBD. Current treatments of IBD are not completely satisfactory, but NPY antagonists could have potential for ameliorating the inflammation. 

Despite of substantial progresses achieved in the understanding of the multiple roles of NPY peptides and their receptors and despite of the advances obtained in respect to some diagnostic applications, therapeutic agents are still lacking. Therefore, existing or new Y receptor ligands are crucially required as tools to explore novel medication strategies. This is where our broad offering of NPY research peptides can substantially contribute to the progress in your research.

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NPY PEPTIDES
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<td><strong>NPY, ANALOGS AND FRAGMENTS</strong></td>
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<tr>
<td>BIBP3226</td>
<td>(Leu&lt;sup&gt;31&lt;/sup&gt;,Pro&lt;sup&gt;34&lt;/sup&gt;)-Neuropeptide Y (porcine)</td>
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H-3318
PAEDMARYYSALRHYINLITRPRY-NH₂
Neuropeptide Y (13-36) (porcine)
H-9300
PAELARYYSALRHYINLITRQRY-NH₂
Neuropeptide Y (18-36)
H-3296
ARYYSALRHYINLITRQRY-NH₂
Pancreatic Polypeptide
(1-17)-(Ala³¹,Aib³²)-Neuropeptide Y (18-36) (human)
H-5086
APLEPVYPGDATPEQMARYYSALRHYIN-LA-Aib-RQRY-NH₂
Neuropeptide Y (22-36)
H-9305
SALRHYINLITRQRY-NH₂
Acetyl-(Leu²⁸³¹)-Neuropeptide Y (24-36)
H-6182
Ac-LRHYLNLLTRQRY-NH₂
Galalin (1-13)-Neuropeptide Y (25-36) amide
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YKGR-c(EYIK)-LITRPRY-NH₂
(D-Tyr²⁷³⁶,D-Thr²²)-Neuropeptide Y (27-36)
H-3328
yiNLitRQRY-NH₂
((Cys³¹,Nva³⁴)-Neuropeptide Y (27-36))₂
H-3704
(YINLCTR-Nva-RY-NH₂)₂
(Disulfide bond)
(Pro³⁰,Tyr³²,Leu³⁴)-Neuropeptide Y (28-36)
H-3546
INPIYRLRY-NH₂
(His³²,Leu³⁴)-Neuropeptide Y (32-36)
H-3544
HRLRY-NH₂
PYX-1
H-5786
Ac-Y(3-(2,6-dichloro-Bzl))INLItRQRY-NH₂
PEPTIDE YY AND RELATED PRODUCTS

Peptide YY (human)
H-9180
YPIKEAPGEDASPEELNRYASL-RHYLNVTQRY-NH₂

(Leu¹¹,Pro²⁸)-Peptide YY (human)
H-2812
YPIKEAPGEDASPEELNRYASL-RHYLNVTQRY-NH₂

(Pro²⁴)-Peptide YY (human)
H-2808
YPIKEAPGEDASPEELNRYASL-RHYLNVTQRY-NH₂

Peptide YY (canine, mouse, porcine, rat)
H-4505
YPAKEAPGEDASPEELNRYASL-RHYLNVTQRY-NH₂

Peptide YY (3-36) (human)
H-8585
IKPEAPGEDASPEELNRYASL-RHYLNVTQRY-NH₂

Peptide YY (3-36) (canine, mouse, porcine, rat)
H-6042
AKPEAPGEDASPEELNRYASL-RHYLNVTQRY-NH₂

Pancreatic Polypeptide (human)
H-1610
APLEPVYPGDNATPEQMAQYAADLRRY-INMLTRQRY-NH₂

Biotinyl-Pancreatic Polypeptide (human)
H-7622
BIOTINYL-APLEPVYPGDNATPEQMAQYAADLRRY-INMLTRQRY-NH₂

(Gly¹,Ser²²,Gln³⁴,Thr⁴,Arg¹⁹,Tyr²¹, Ala²³,3¹,Aib³²)-Pancreatic Polypeptide (human)
H-5088
GPSQPTYPGDNATPEQMARYSLRRY-INMA-Aib-RQRY-NH₂

Pancreatic Polypeptide (1-17)-(Ala³¹,Aib³²)-Neuropeptide Y (18-36) (human)
H-5086
APLEPVYPGDNATPEQMARYSLRHYINLA-Aib-RQRY-NH₂

Pancreatic Polypeptide (bovine)
H-6610
APLEPVYPGDNATPEQMARYSLRHYINLA-Aib-RQRY-NH₂

Pancreatic Polypeptide (rat)
H-6890
APLEPVYPGDYATHEQRAYETQRLRRY-INMLTRQRY-NH₂

Peptide YY (3-36) (canine, mouse, porcine, rat)
H-9185
SPEELNRYASLRHYLNVTQRY-NH₂

Peptide YY (human)
H-9180
YPIKPEAPGEDASPEELNRYASL-RHYLNVTQRY-NH₂

(Leu¹¹,Pro²⁸)-Peptide YY (human)
H-2812
YPIKPEAPGEDASPEELNRYASL-RHYLNVTQRY-NH₂

Pancreatic Polypeptide (canine, mouse, porcine, rat)
H-4505
YPAKPEAPGEDASPEELNRYASL-RHYLNVTQRY-NH₂
Molecular model of PYY (3-36), a part of peptide YY (PYY), which helps to regulate appetite. It is released by parts of the gastrointestinal tract, in levels proportional to the calorific content of the food. Atoms are represented as balls, and are colour-coded: carbon, light blue; nitrogen, dark blue; oxygen, red; and hydrogen, yellow. The yellow strip shows the structure of the protein, which includes an alpha helix.

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