

# Neuropeptide Y Receptors

## Key References

- Balasubramaniam, A., Ed. "In: Neuropeptide Y protocols." Humana Press 256 pp (2000).
- Blomquist, A.F., Herzog, H. "Y-receptors subtypes - how many more?" *Trends Neurosci.* **20**, 294-298 (1997).
- Dumont, Y. et al. "Neuropeptide Y, peptide YY and pancreatic polypeptide receptor proteins and mRNAs in mammalian brains." In: *Handbook of Chemical Neuroanatomy*. Chapter IX, Eds. Quirion, R., Bjorklund, A. and Hökfelt, T. Elsevier Science, London, pp 375-475 (2000).
- Fujimiya, A., Inui, A. "Peptidergic regulation of gastrointestinal motility in rodents." *Peptides* **21**, 1565-1582 (2000).
- Gehlert, D.R. "Multiple receptors for the pancreatic polypeptide (PP-fold) family: Physiological implications." *Proc. Soc. Exp. Biol. Med.* **218**, 7-22 (1998).
- Heilig, M., Widerlov, E. "Neurobiology and clinical aspects of neuropeptide Y." *Crit. Rev. Neurobiol.* **9**, 115-136 (1995).
- Inui, A. "Neuropeptide Y feeding receptors: Are multiple subtypes involved?" *Trends Pharmacol. Sci.* **20**, 43-46 (1999).
- Kalra, S.P., Crowley, W.R. "Neuropeptide Y: A novel neuroendocrine peptide in the control of pituitary hormone secretion, and its relation to luteinizing hormone." *Front. Neuroendocrinol.* **13**, 1-46 (1992).
- Larhammar, D. "Structural diversity of receptors for neuropeptide Y, peptide YY and pancreatic polypeptide." *Regul. Pept.* **65**, 165-174 (1996).
- Michel, M.C. et al. "Neuropeptide Y receptor family." in: *The IUPHAR Compendium of Receptor Characterization and Classification, 2nd edition*, pp. 278-289, IUPHAR Media, London, UK (2000).
- Playford, R.J., Cox, H.M. "Peptide YY and neuropeptide Y: Two peptides intimately involved in electrolyte homeostasis." *Trends Pharmacol. Sci.* **17**, 436-438 (1996).
- Vezzani, A. et al. "Neuropeptide Y: Emerging evidence for a functional role in seizure modulation." *Trends Neurosci.* **22**, 25-30 (1999).

## Overview

Neuropeptide Y (NPY) is a 36 amino acid peptide which shares high sequence homology with peptide YY (PYY) and the pancreatic polypeptides (PPs). Additionally, NPY is one of the most abundant peptides found in the mammalian brain. Intracerebroventricular injections of NPY/PYY fragments and analogs, as well as direct administration into specific nuclei, induce several biological responses including increased food intake, modulation of the release of luteinizing hormone releasing hormone (LHRH) and corticotropin releasing factor (CRF), regulation of cardio-respiratory parameters, enhanced cognitive function associated with learning and memory, shifts of circadian rhythms and reduction of anxiety-related behaviors. In peripheral tissues, NPY is one of the most potent neurotransmitters capable of inducing vasoconstriction and has been implicated in several biological responses in the gastrointestinal tract. Furthermore, studies in rodents suggest that NPY and its receptors could have a direct implication in some pathological disorders including obesity, depression and epilepsy.

The various biological effects of NPY and homologs are mediated by the activation of at least five classes of G protein-coupled receptors, designated as Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>4</sub>, Y<sub>5</sub> and y<sub>6</sub>. All these receptor types have been cloned and have been expressed in several species, except for the y<sub>6</sub> which is not expressed in the rat while the monkey and human genome contain a single base pair deletion in the sixth transmembrane domain resulting in a truncated non-functional NPY receptor protein. The pharmacological profile of each of these receptor types has been defined using several analogs and fragments of NPY, PYY and the PPs. NPY, PYY, [Leu<sup>31</sup>, Pro<sup>34</sup>]-NPY/PYY

and [Pro<sup>34</sup>]-NPY/PYY are highly potent, while short and long C-terminal fragments of NPY and PYY and the PPs are active only in the micromolar range at the Y<sub>1</sub> receptor type. On the other hand, the Y<sub>2</sub> receptor type is activated by NPY, PYY and their short and long C-terminal fragments whereas the [Leu<sup>31</sup>, Pro<sup>34</sup>]-substituted analogs and the PPs demonstrate much lower affinity. The major characteristics of the Y<sub>4</sub> receptor type are its very high affinity for PP-related peptides, such as human PP, bovine PP, porcine PP, and its high affinity for rat PP and [Leu<sup>31</sup>, Pro<sup>34</sup>]-PYY. The Y<sub>5</sub> receptor type has high affinity for human PP, NPY, PYY, [Leu<sup>31</sup>, Pro<sup>34</sup>]-NPY, [Leu<sup>31</sup>, Pro<sup>34</sup>]-PYY and PYY(3-36), but low affinity for short C-terminal fragments such as NPY(13-36) and PYY(13-36) as well as rat PP. The pharmacological profile of the y<sub>6</sub> receptor is somewhat controversial with different laboratories having obtained inconsistent results regarding this receptor type. In addition, another receptor type called Y<sub>3</sub>, has been proposed, which is activated by NPY and its derivatives, but not by PYY.

The recent development of non-peptide NPY receptor antagonists, such as BIBP 3226 (Y<sub>1</sub>), BIBO 3304 (Y<sub>1</sub>), BIIE 0246 (Y<sub>2</sub>) and CGP71683A (Y<sub>5</sub>) as well as a Y<sub>1</sub> peptidergic antagonist, 1229U91, also named GW1229 or GR 231118, has helped in our understanding of the role of NPY receptor types in mediating the effects of NPY. BIBP 3226 (Y<sub>1</sub>), BIBO3304 (Y<sub>1</sub>) and BIIE 0246 (Y<sub>2</sub>) have been shown to behave as a competitive, selective and specific Y<sub>1</sub> or Y<sub>2</sub> receptor antagonists in various binding assays and *in vitro* and *in vivo* bioassays, without exhibiting any significant affinity for other NPY receptor types. The

purported Y<sub>1</sub> peptide antagonist, GR 231118 has been shown to possess rather high affinity and agonist activity at the Y<sub>4</sub> receptor type and neuropeptide FF receptor, while the Y<sub>5</sub> antagonist, CGP71683A possesses high affinity for muscarinic and adrenergic receptors in addition to serotonin transporters. Other antagonists have also been reported, including SR 120819 (Y<sub>1</sub>), LY-357897 (Y<sub>1</sub>), GI 264879 (Y<sub>1</sub>) and L-152,804 (Y<sub>5</sub>). The specificity and selectivity of these non-peptide NPY receptor antagonists remains to be fully demonstrated.

# Neuropeptide Y Receptors

CURRENTLY ACCEPTED NAME	Y <sub>1</sub> (N-186)	Y <sub>2</sub>	Y <sub>4</sub>	Y <sub>5</sub>	Y <sub>6</sub> <sup>a</sup>
PREVIOUSLY NAMED			PP <sub>1</sub>	Atypical Y <sub>1</sub>	Y <sub>5</sub> , PP <sub>2</sub> and Y <sub>2B</sub>
STRUCTURAL INFORMATION	384 aa (human)	381 aa (human)	375 aa (human)	445 aa (human)	Truncated 290 aa (human)
ENDOGENOUS PEPTIDES	NPY (N 5017 (h), N 3266 (p)) PYY (P 1306)	NPY (N 5017 (h), N 3266 (p)) PYY (P 1306) NPY(3-36) (N 9407 (h), N 4279 (p)) PYY(3-36) (P-220)	PP (P 9903 (h), P 6410 (r))	NPY (N 5017 (h), N 3266 (p)) NPY(3-36) (N 9407 (h), N 4279 (p))	NPY (N 5017 (h), N 3266 (p)) PYY (P 1306) PP
AGONISTS	NPY (N 5017 (h), N 3266 (p)) PYY (P 1306) [Pro <sup>34</sup> ]-NPY [Pro <sup>34</sup> ]-PYY (P 3982) [Leu <sup>31</sup> ,Pro <sup>34</sup> ]-NPY (N 6146) [Leu <sup>31</sup> ,Pro <sup>34</sup> ]-PYY (P 4107)	NPY (N 5017 (h), N 3266 (p)) PYY (P 1306) NPY(3-36) (N 9407 (h), N 4279 (p)) PYY(3-36) (P-220) NPY(13-36) (N 6521) PYY(13-36) NPY(1-4)-Ahx-NPY(25-36)	PP (P 9903 (h), P 6410 (r)) PYY (P 1306) [Leu <sup>31</sup> ,Pro <sup>34</sup> ]-PYY (P 4107) GR 231118	NPY (N 5017 (h), N 3266 (p)) PYY (P 1306) [Pro <sup>34</sup> ]-NPY [Pro <sup>34</sup> ]-PYY (P 3982) [Leu <sup>31</sup> ,Pro <sup>34</sup> ]-NPY (N 6146) [Leu <sup>31</sup> ,Pro <sup>34</sup> ]-PYY (P 4107) NPY(3-36) (P 9407) PYY(3-36) (P-220) human PP (P 9903) [cPP <sup>1-7</sup> ,NPY <sup>19-23</sup> ,Ala <sup>31</sup> , Aib <sup>32</sup> , Gln <sup>34</sup> ]human PP	Pharmacological profile not well defined
ANTAGONISTS	BIBP 3226 (B-174) <sup>b</sup> BIBO 3304 GR 231118 <sup>c</sup>	BIIE 0246	None	None	None
SIGNAL TRANSDUCTION MECHANISMS	G <sub>i</sub> (cAMP modulation)	G <sub>i</sub> (cAMP modulation)	G <sub>i</sub> (cAMP modulation)	G <sub>i</sub> (cAMP modulation)	G <sub>i</sub> (cAMP modulation)
RADIOLIGANDS OF CHOICE	[ <sup>125</sup> I]-PYY [ <sup>125</sup> I]-[Leu <sup>31</sup> ,Pro <sup>34</sup> ]-PYY [ <sup>125</sup> I]-GR 231118	[ <sup>125</sup> I]-PYY [ <sup>125</sup> I]-PYY(3-36)	[ <sup>125</sup> I]-PPs [ <sup>125</sup> I]-[Leu <sup>31</sup> ,Pro <sup>34</sup> ]-PYY	[ <sup>125</sup> I]-PYY [ <sup>125</sup> I]-[Leu <sup>31</sup> ,Pro <sup>34</sup> ]-PYY	[ <sup>125</sup> I]-PYY

## ABBREVIATIONS

**BIBP 3226:** R-N<sup>2</sup>-(Diphenylacetyl)-N-(4-hydroxyphenyl)-methyl argininamide

**BIBO 3304:** N-[[4-(Aminocarbonylaminoethyl)-phenyl]methyl]-N<sup>2</sup>-(diphenylacetyl)-argininamide trifluoroacetate

**BIIE 0246:** (S)-N<sup>2</sup>[[1-[2-[4-[(R,S)-5,11-dihydro-6(6h)-oxodibenz[b,e]azepin-11-yl]-1-piperazinyl]-2-oxoethyl] cyclopentyl]acetyl]-N-[2-[1,2-dihydro-3,5 (4H)-dioxo-1,2-diphenyl-3H-1,2,4-triazol-4-yl]ethyl]-argininamid

**GR 231118** (also known as GW1229 and 1229U91): Homodimeric Ile-Glu-Pro-Dpr-Tyr-Arg-Leu-Arg-Tyr-CONH<sub>2</sub>

**NPY:** Neuropeptide Y

**NPY1-4-Ahx-NPY25-36:** NPY(1-4)-6-aminohexanoic acid-NPY(25-36)

**PP:** Pancreatic polypeptide

**PYY:** Peptide YY

**h:** human

**p:** porcine

**r:** rat

## FOOTNOTES

**a** The use of lower case denotes the identification of a gene product only; the endogenous receptor has yet to be characterized.

**b** BIBP 3226 has affinity of 100 nM at Neuropeptide FF receptors.

**c** GR 231118 has affinity of 50 nM at Neuropeptide FF receptors.