

Neuropeptide Y Receptors

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Overview

Neuropeptide Y (NPY), a 36 amino acid peptide and one of the most abundant peptides found in the mammalian brain, shares high sequence homology with peptide YY (PYY) and the pancreatic polypeptides (PPs). Intracerebroventricular injections of NPY/PYY fragments and analogs, as well as direct administration into specific brain 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, reduction of anxiety-related behaviors and alcohol consumption. 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 may be implicated in several pathological disorders including obesity, depression and epilepsy.

The various biological effects of NPY and homologs are mediated through the activation of at least five classes of G protein-coupled receptors, designated as Y₁, Y₂, Y₄, Y₅ and Y₆. All these receptor types have been cloned and have been shown to be expressed in several species, except for the Y₆ 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, [Leu³¹, Pro³⁴]-NPY/PYY and [Pro³⁴]-NPY/PYY are highly potent

agonists, while short and long C-terminal fragments of NPY and PYY and the PPs are active only in the micromolar range at the Y₁ receptor type. On the other hand, the Y₂ receptor type is activated by NPY, PYY and their short and long C-terminal fragments whereas the [Leu³¹, Pro³⁴]-substituted analogs and the PPs demonstrate much lower affinity. The major characteristics of the Y₄ 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 [Leu³¹, Pro³⁴]-PYY. The Y₅ receptor type has high affinity for human PP, NPY, PYY, [Leu³¹, Pro³⁴]-NPY, [Leu³¹, Pro³⁴]-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 Y₆ receptor is somewhat controversial with different laboratories having obtained inconsistent results. In addition, another receptor type called Y₃, has been proposed, which is activated by NPY and its derivatives, but not by PYY.

The recent development of several non-peptide NPY receptor antagonists, such as BIBP 3226 (Y₁), BIBO 3304 (Y₁), BIIE 0246 (Y₂) and CGP71683A (Y₅) as well as a Y₁ dipeptide antagonist, 1229U91, also named GW1229 or GR 231118, has helped in understanding the role of NPY receptor types in mediating the effects of NPY. BIBP 3226 (Y₁), BIBO3304 (Y₁) and BIIE 0246 (Y₂) have been shown to behave as a competitive, selective and specific Y₁ or Y₂ 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 Y₁ peptide antagonist, GR 231118 has been shown to possess rather high affinity and partial agonist activity at the Y₄ receptor type

and neuropeptide FF receptor, while the Y₅ antagonist, CGP71683A possesses high affinity for muscarinic and adrenoceptors in addition to serotonin transporters. Other antagonists have also been reported, including SR 120819 (Y₁), LY-357897 (Y₁), GI 264879 (Y₁), J-104870 (Y₁), J-115814 (Y₁), JNJ-5207787 (Y₂), JCF109 (Y₅), NPY5RA (Y₅), GW438014 A (Y₅) and L-152,804 (Y₅). The specificity and selectivity of these non-peptide NPY receptor antagonists remains to be fully elucidated.

Neuropeptide Y Receptors

CURRENTLY ACCEPTED NAME	Y ₁ (N186)	Y ₂ (N4036)	Y ₄	Y ₅	Y ₆ ^a
PREVIOUSLY NAMED	Not known	Not known	PP ₁	Atypical Y ₁	Y ₅ , PP2 and Y2B
STRUCTURAL INFORMATION	384 aa (human)	381 aa (human)	375 aa (human)	445 aa (human)	Truncated 290 aa (human)
ENDOGENOUS PEPTIDES	NPY (N5017 (h), N3266 (p)), PYY (P1306)	NPY (N5017 (h), N3266 (p)), PYY (P1306), NPY(3-36) (N9407 (h), N4279 (p)), PYY(3-36) (P220)	PP (P9903 (h), P6410 (r))	NPY (N5017 (h), N3266 (p)), NPY(3-36) (N9407 (h), N4279 (p))	NPY (N5017 (h), N3266 (p)), PYY (P1306), PP (P9903 (h), P6410 (r))
AGONISTS	NPY (N5017 (h), N3266 (p)), PYY (P1306), [Pro ³⁴]-NPY, [Pro ³⁴]-PYY (P3982), [Leu ³¹ ,Pro ³⁴]-NPY (N6146), [Leu ³¹ ,Pro ³⁴]-PYY (P4107)	NPY (N5017 (h), N3266 (p)), PYY (P1306), NPY(3-36) (N9407 (h), N4279 (p)), PYY(3-36) (P220), NPY(13-36) (N6521), PYY(13-36), NPY(1-4)-Ahx-NPY(25-36)	PP (P9903 (h), P6410 (r)), PYY (P1306), [Leu ³¹ ,Pro ³⁴]-PYY (P4107), GR 231118 (N8648)	NPY (N5017 (h), N3266 (p)), PYY (P1306), [Pro ³⁴]-NPY, [Pro ³⁴]-PYY (P3982), [Leu ³¹ ,Pro ³⁴]-NPY (N6146), [Leu ³¹ ,Pro ³⁴]-PYY (P4107), NPY(3-36) (P9407), PYY(3-36) (P220), human PP (P9903), [cPP1-7,NPY ¹⁹⁻²³ ,Ala ³¹ ,Aib ³² ,Gln ³⁴]human PP	Pharmacological profile not well defined
ANTAGONISTS	BIBP 3226 (B174), ^b BIBO 3304, GR 231118 (N8648), ^c J-104870, J-115814, LY357897, H409/22	BIIE 0246, JNJ-5207787	Not known	NPY5RA, L-152,804, JCF109	Not known
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation)	G _i (cAMP modulation)	G _i (cAMP modulation)	G _i (cAMP modulation)	G _i (cAMP modulation)
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-PYY, [¹²⁵ I]-[Leu ³¹ ,Pro ³⁴]-PYY, [¹²⁵ I]-GR 231118	[¹²⁵ I]-PYY, [¹²⁵ I]-PYY(3-36)	[¹²⁵ I]-PPs, [¹²⁵ I]-[Leu ³¹ ,Pro ³⁴]-PYY	[¹²⁵ I]-PYY, [¹²⁵ I]-[Leu ³¹ ,Pro ³⁴]-PYY	[¹²⁵ I]-PYY
TISSUE EXPRESSION	Cerebral cortex, thalamus, blood vessels, gastrointestinal tract	Hippocampus, brain stem nuclei, hypothalamus, gastrointestinal tract	Gastrointestinal tract, interpeduncular nuclei	Hippocampus, brain stem nuclei, hypothalamus	Not known
PHYSIOLOGICAL FUNCTION	Vasoconstriction, food intake, anxiolytic, nociception, alcohol consumption, neurogenesis	Inhibition of neurotransmitter release, food intake	Gastrointestinal modulation	Food intake	Not known
DISEASE RELEVANCE	Depression and anxiety, alcoholism, feeding disorders	Epilepsy, cognitive decline	Not known	Feeding disorders	Not known

Abbreviations

BIBP 3226: R-N2-(Diphenylacetyl)-N-(4-hydroxyphenyl)-methyl argininamide
BIBO 3304: N-[4-(Aminocarbonylaminoethyl)-phenyl]methyl-N2-(diphenylacetyl)-argininamide trifluoroacetate
BIIE 0246: (S)-N2[[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
GI264879A: 1-Substituted-4-methylbenzimidazole (413), N-α-[3,3-bis(1-naphthyl)propionyl]-D-arginine N-[(S)-1-benzyl-2-methoxyethyl] amide
GW438014A: 3-[2-[6-(2-tert-Butoxyethoxy)pyridin-3-yl]-1H-imidazol-4-yl]benzimidazole hydrochloride salt

GR 231118 (also known as GW1229 and 1229U91): Homodimeric Ile-Glu-Pro-Dpr-Tyr-Arg-Leu-Arg-Tyr-CONH₂
H409/22: (2R)-5-[(Amino(imino)methyl)amino]-2-[(2,2-diphenylacetyl)amino]-N-[(1R)-1-(4-hydroxyphenyl)ethyl]-pentanamide
J-104870: 2-[[4-Chlorophenoxy)methyl]benzimidazoles (411), 6-(5-ethyl-1,3-thiazol-2-ylthiomethyl)-2-[3-methoxy-5-(2-propenylloxycarbonylamino)benzylamino]-4-morpholinopyridine
J-115814: (2)-2-[1-(3-Chloro-5-isopropylloxycarbonylamino)phenyl]ethylamino]-6-[2-(5-ethyl-4-methyl-1,3-thiazol-2-yl)ethyl]-4-morpholinopyridine
JCF109: [(Naphthalen-2-ylmethyl)-amino]-methyl-2-nitro-benze-nesulphonamide
JNJ-5207787: (N-(α-Acetyl-2,3-dihydro-1H-indol-6-yl)-3-(3-cyano-phenyl)-N-[1-(2-

cyclopentyl-ethyl)-piperidin-4yl]-acrylamide)
L-152,804: 2-(3,3-Dimethyl-1-oxo-4H-1H-xanthen-9-yl)-5,5-dimethyl-cyclohexane-1,3-dione
LY357897: 1-((1-[3-((3S)-Piperidyl)]propyl)-2-[(4-chlorophenoxy)-methyl]indol-3-yl)-2-(4-piperidyl)piperidyl)ethan-1-one, code name
NPY5RA-972: 9-Isopropyl-4-methyl-3-(4-morpholinecarbonylamino)-9H-carbazole
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.

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