

CATALYTIC RECEPTORS

Natriuretic peptide

Overview: Natriuretic peptide receptors (provisional nomenclature) are homodimeric, catalytic receptors with a single TM domain and guanylyl cyclase (EC 4.6.1.2) activity on the intracellular domain of the protein sequence. Isoforms are activated by the peptide hormones α -atrial natriuretic peptide (ANP, ENSG00000175206), brain natriuretic peptide (BNP, ENSG00000120937) and type C-natriuretic peptide (CNP, ENSG00000163273). Another family member is the receptor for guanylin (ENSG00000113389) and uroguanylin (ENSG00000044012). Family members have conserved catalytic and regulatory domains, but divergent ligand-binding domains. The NPR3 receptor has an extracellular binding domain homologous to that of the NPR1 and 2 receptors, but with a truncated intracellular domain which appears to couple to inhibition of adenylyl cyclase activity (Murthy & Makhlof, 1999).

Nomenclature	NPR1	NPR2	NPR3	STaR
Other names	GC-A, ANP _A receptor, NPR-A	GC-B, ANP _B receptor, NPR-B	ANP _C receptor, NPR-C, clearance receptor	GC-C, guanylin receptor
Ensembl ID	ENSG00000169418	ENSG00000159899	ENSG00000113389	ENSG00000070019
Potency order	ANP ≥ BNP ≥ CNP	CNP ≥ ANP ≥ BNP	ANP > CNP > BNP	Uroguanylin > guanylin
Selective agonists	ANP, sANP (Olson <i>et al.</i> , 1996)	—	C-ANP-(4–23) (Maack <i>et al.</i> , 1987)	<i>E. coli</i> heat-stable enterotoxin (STa)
Selective antagonists	[Asu7,23']- β -ANP-(7–28) (7.5, Kambayashi <i>et al.</i> , 1989)	Monoclonal antibody 3G12 (Drewett <i>et al.</i> , 1995)	—	—
Radioligands	[¹²⁵ I]-ANP	[¹²⁵ I]-CNP	[¹²⁵ I]-ANP	—

Orphan receptors GC-D, GC-E (RetGC-1, ENSG00000132518), GC-F (RetGC-2, ENSG00000101890) and GC-G (ENSG00000080218) have been cloned from various mammals. GC-G exhibits structural similarity to the natriuretic peptide receptors (Schulz *et al.*, 1998).

Abbreviations: [Asu7,23']- β -ANP-(7–28), an antiparallel dimer linked by 7-23' and 7'-23 disulfide bonds (Asu, L- α -aminosuberic acid); C-ANF-(4–23), des[Gln¹⁸,Ser¹⁹,Gly²⁰,Leu²¹,Gly²²]ANP-(4–23)-NH₂; sANP, Thr⁹, Ser¹¹, Arg¹⁶-ANP

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GDNF family

Overview: GDNF family receptors (GFR, provisional nomenclature) are glycosylphosphatidylinositol-linked cell-surface receptors, which, when activated by members of the glial cell-derived neurotrophic factor (GDNF) family, activate a transmembrane tyrosine kinase enzyme, Ret (ENSG00000165731). The endogenous ligands are typically dimeric, linked through disulphide bridges: glial cell line-derived neurotrophic factor (GDNF; 211 aa, ENSG00000168261); neurturin (197 aa, ENSG00000171119); artemin (237 aa, ENSG00000117407) and persephin (156 aa, ENSG00000125650).

Nomenclature	GFR α 1	GFR α 2	GFR α 3	GFR α 4
Other names	GDNF, GDNF family receptor α 1	Neurturin, GDNF family receptor α 2	Artemin, GDNF family receptor α 3	Persephin, GDNF family receptor α 4
Ensembl ID	ENSG00000151892	ENSG00000168546	ENSG00000146013	ENSG00000125861
Potency order	GDNF > neurturin > artemin	Neurturin > GDNF	Artemin	Persephin

Mutations of Ret and GDNF genes may be involved in Hirschsprung's disease, which is characterized by the absence of intramural ganglion cells in the hindgut, often resulting in intestinal obstruction.

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Neurotrophin

Overview: The trk neurotrophin receptors (provisional nomenclature) exhibit a single TM domain, with an intracellular tyrosine kinase catalytic domain (Enzyme Classification 2.7.1.112), although various isoforms exist, including truncated forms of trkB and trkC, which lack catalytic domains. The endogenous ligands are small proteins (ca. 120 aa) and include nerve growth factor (NGF, ENSG00000134259), neurotrophin (NT) 3 (ENSG00000185652), NT4/5 (ENSG00000167744) and brain-derived neurotrophic factor (BDNF, ENSG00000176697). p75, which has homologies with the tumour necrosis factor receptor, lacks a tyrosine kinase domain, but can signal *via* ceramide release and nuclear factor κ B (NF- κ B) activation. trkA and trkB each contain two leucine-rich regions and can exist in monomeric or dimeric forms.

Nomenclature	trkA	trkB	trkC	p75
Other names	gp140 ^{trk} , high-affinity, slow-dissociating NGF receptor	gp145 ^{trkB}	gp145 ^{trkC}	p75 ^{NTR} , low-affinity neurotrophin receptor, NGFR
Ensembl ID	ENSG00000117029	ENSG00000148053	ENSG00000140538	ENSG00000064300
Potency order	NGF > NT3	BDNF, NT4/5 > NT3	NT3	NGF, BDNF, NT3, NT4/5
Radioligands	[¹²⁵ I]-NGF	[¹²⁵ I]-BDNF	—	—

An additional related receptor, termed trk3 (ENSG00000162733), has been identified. The selectivity of small-molecule peptide mimetics of NGF has not been ascertained (Massa *et al.*, 2003). There are, as yet, no selective antagonists, but activation can be blocked using antineurotrophin antisera or selective immunoadhesins that sequester neurotrophins (Shelton *et al.*, 1995). p75 influences the binding of NGF and NT3 to trkA. The ligand selectivity of p75 appears to be dependent on the cell type; for example, in sympathetic neurones, it binds NT3 with comparable affinity to trkC (Dechant *et al.*, 1997).

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