Tachykinin

Overview: Tachykinin receptors (provisional nomenclature, see Foord *et al*., 2005) are activated by the endogenous peptides substance P (SP), neurokinin A (NKA; previously known as substance K, neurokinin α, neuromedin L), neurokinin B (NKB; previously known as neurokinin β, neuromedin K), neuropeptide K and neuropeptide γ (*N*-terminally extended forms of neurokinin A). The neurokinins (A and B) are mammalian members of the tachykinin family, which includes peptides of mammalian and non-mammalian origin containing the consensus sequence: Phe-x-Gly-Leu-Met. Marked species differences in pharmacology exist for all three receptors, in particular with non-peptide ligands.

Nomenclature	NK_1	NK_2	NK_3
Other names	Substance P	Substance K	Neurokinin B, neuromedin K
Ensembl ID	ENSG00000115353	ENSG00000075073	ENSG00000169836
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	SP > NKA > NKB	NKA > NKB >> SP	NKB > NKA > SP
Selective agonists	SP methylester, [Sar^9,Met(O$_2$)^{11}]SP, [Pro^9]SP, septide	[β-Ala^8]NKA-(4-10),[Lys^5,Me-Leu^9,Mle^{10}] NKA-(4-10), GR64349	Senktide, [MePhe^7]NKB
Selective antagonists	Aprepitant (10.7; Hale *et al*., 1998), SR140333 (9.5), LY303870 (9.4), CP99994 (9.3), RP67580 (7.6)	GR94800 (9.6), GR159897 (9.5), MEN10627 (9.2), SR48968 (9.0), MEN11420 (8.6; Catalioto *et al*., 1998)	SR142802 (9.2), SB223412 (9.0; Sarau *et al*., 1997), PD157672 (7.8)
Probes	[^{3}H]- or [^{125}I]-SP, [^{3}H]- or [^{125}I]-BH-[Sar^9,Met(O$_2$)^{11}]SP, [^{125}I]-L703606 (0.3 nM), [^{18}F]-SPA-RQ	[^{3}H]-SR48968 (0.5 nM), [^{3}H]-GR100679, [^{125}I]-NKA	[^{3}H]-Senktide, [^{125}I]-[MePhe^7]NKB, [^{3}H]-SR142801 (0.13 nM)

The NK_1 receptor has also been described to couple to other G proteins (Roush and Kwatra, 1998). The hexapeptide agonist septide appears to bind to an overlapping but non-identical site to SP on the NK_1 receptor. There are suggestions for additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK_3 receptor was found to respond to NKB when expressed in *Xenopus* oocytes or Chinese hamster ovary cells (Donaldson *et al*., 1996; Krause *et al*., 1997).

Abbreviations: **[^{18}F]-SPA-RQ**, ([[^{18}F]-2-fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]([2*S*,3*S*]2-phenyl-piperidin-3-yl)-amine; **Aprepitant**, 5-[[(2*R*,3*S*]-2-[(1*R*)-1-[3,5-bis(trifluoromethyl) phenyl]ethoxy]-3-(4-fluorphenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one (also known as Emend); **CP99994**, (+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine; **GR100679**, cyclohexylcarbonyl-Gly-Ala-DTrp-Phe-NMe_2; **GR159897**, (*R*)-1-(2-[5-fluoro-1*H*-indol-3-yl]ethyl)-4-methoxy-4([phenylsulfinyl]methyl)piperidine; **GR64349**, Lys-Asp-Ser-Phe-Val-Gly-(*R*-γ-lactam); **GR94800**, *N*-α-benzoyl-Ala-Ala-DTrp-Phe-DPro-Pro-Nle-NH_2; **L-703606**, *cis*-2(diphenylmethyl)-*N*-([2-iodophenyl] methyl)-1-azabicyclo[2.2.2]octan-3-amide; **L-742694**, 2(*s*)-([3,5-bis{trifluoromethyl}benzyl]-oxy)-3(*S*)-phenyl-4-([3-oxo-1,2,4-triazol-5-yl]methyl)morpholine; **LY303870**, (*R*)-1-(*N*-[2-methoxybenzyl]acetylamino)-3-(1*H*-indol-3yl)-2-(*N*-[2-{4-(piperidin-1-yl)piperidin-1-yl}acetyl] amino)propane; also known as lanepitant; **MEN10627**, *cyc*(2*β*–5*β*)(Met-Asp-Trp-Phe-Dap-Leu); **MEN11420**, *cyc*(2*β*–5*β*)[Asn(2-AcNH-*β*-D-Glc)-Asp-Trp-Phe-Dap-Leu]; also known as nepadutant; **PD157672**, Boc-(*s*)Phe-(*R*)αMePheNH$(CH_2)_7$NHCONH_2; **RP67580**, 3α*R*,7α*R*-(1-imino-2-[2-methoxyphenyl]ethyl)-7,7-diphenyl-4-perhydroisoindolone; **SB223412**, (*s*)-(-)-*N*-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide; **SR140333**, (*s*)-1-(2-[3-{3,4-dichlorophenyl}-1-{3-isopropoxyphenylacetyl}piperidin-3-yl]ethyl)-4-phenyl-1-azoniabicyclo(2.2.2)octane chloride; **SR142801**, (*s*)-(*N*)-(1-[3-{1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl}propyl]-4-phenylpiperidin-4-yl)-*N*-methylacetamide; **SR48968**, (*S*)-*N*-methyl-*N*-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butylbenzamide; also known as saredutant

Further Reading

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