

# Tachykinin Receptors

## Key References

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## Overview

The tachykinins represent a family of structurally related peptides originally isolated and characterized based upon their smooth muscle contractile activity and their ability to induce salivary secretion. The three mammalian peptides include substance P (SP), neurokinin A (NKA) and neurokinin B (NKB). Substance P can be produced from three different forms of precursor protein ( $\alpha$ -,  $\beta$ - and  $\gamma$ -preprotachykinin-A mRNAs) that arise from a single gene by alternative RNA splicing. NKA is also derived from two of these proteins ( $\beta$ - and  $\gamma$ -PPT-A), with the possible generation by differential post-translational processing of the N-terminally extended forms neuropeptide K or neuropeptide  $\gamma$ . Neurokinin B is the only tachykinin peptide that is derived from the separate preprotachykinin-B gene product.

Three receptors for the tachykinin peptides have been pharmacologically and genetically characterized and are named neurokinin-1 (NK<sub>1</sub>), NK<sub>2</sub> and NK<sub>3</sub>. The NK<sub>1</sub> receptor has a natural agonist potency profile of SP>NKA>NKB. The NK<sub>2</sub> receptor agonist potency profile is NKA>NKB>SP, and the NK<sub>3</sub> receptor profile is NKB>NKA>SP. These receptors mediate various biological effects that include smooth muscle contraction, neurotransmission in the CNS and the periphery that is generally excitatory (e.g. pain transmission), involvement in immune and inflammatory responses, hypotensive effects via the peripheral vasculature, and stimulation of endocrine and exocrine gland secretion. The receptors are coupled through G<sub>q</sub> and G<sub>11</sub>, the pertussis toxin insensitive G proteins, to the activation of phospholipase C isoforms. NK<sub>1</sub> receptors are expressed in a wide variety of peripheral

tissues and in the CNS. NK<sub>2</sub> receptors are expressed primarily in the periphery, while NK<sub>3</sub> receptors are primarily expressed in the CNS.

Both peptide and non-peptide antagonists have been developed for each of these receptors. The first generation of peptide antagonists generally had limited utility as pharmacological tools, on account of their low affinity, partial agonist actions, poor pharmacokinetic properties, or toxicity. The introduction of the first non-peptide antagonists in the 1990s transformed the field, beginning with discovery of the 3-aminoquinuclidine CP-96345 by Pfizer. Later piperidine compounds based on this lead from Pfizer (CP-99994, CP-122721), and from Merck (MK-869) and Glaxo (GR 205171) have entered clinical trials initially for pain, migraine or asthma. Important compounds from other chemical classes have been introduced by Rhone-Poulenc Rorer (Aventis) based on the perhydroisoindole RP 67580 lead compound (Dapitant or RPR 100893), and by Eli Lilly (Lanepitant or LY-303870) and Sanofi-Synthelabo (Nolpitanium or SR 140333) among others. To date, the results from clinical studies with various types of pain have been disappointing with all classes of compound, although clinical studies with the NK<sub>1</sub> antagonists are ongoing for emesis and depression, where positive results have been reported.

The first non-peptide antagonist with good affinity and selectivity for the NK<sub>2</sub> receptor SR 48968 (Saredutant), was obtained by Sanofi-Synthelabo from the same screening hit that produced SR 140333. Several other companies have gone on to describe derivatives of SR 48968, including Pfizer, Yamanouchi and Astra-Zeneca. These and

other classes of compound, including cyclic peptides from Menarini (Nepadutant or MEN-11420) are in various stages of development for irritable bowel syndrome, asthma, or micturition disorder. In spite of the paucity of evidence for significant numbers of NK<sub>2</sub> sites in adult brain, there is some interest in the development of NK<sub>2</sub> antagonists for anxiety, based on the initial findings from Glaxo with their compound GR 15897. Several companies have an interest in a mixed NK<sub>1</sub>/NK<sub>2</sub> antagonist for asthma or chronic obstructive pulmonary disease (COPD). Many of these are derived from leads related to SR 48968, including MDL-105212A from Hoechst Marion Roussel, the first compound with high affinity at both sites. The related morpholino-derivative MDL-105172A has high affinity at all three receptor types.

Fewer compounds are available with high affinity and selectivity for the NK<sub>3</sub> receptor, and the specific indications for development of an NK<sub>3</sub> antagonist are less clear. The first compound with high affinity for the NK<sub>3</sub> receptor was SR 142801 (Osanetant), again derived from SR 48968. More selective compounds, though with lower affinity, were obtained from the peptoid series at Parke Davis (PD 161182) or the substituted quinuclidines from SmithKline Beecham (SB-222200, SB-223412). SR 142801 entered clinical trials in France for schizophrenia; SB-223412 (Talnetant) is in Phase I or Phase II trials for COPD and urinary incontinence, and SB-222200 is reported to be under investigation for CNS disorders.

## Tachykinin Receptors

<b>CURRENTLY ACCEPTED NAME</b>	NK <sub>1</sub>	NK <sub>2</sub> ( <a href="#">T-180</a> )	NK <sub>3</sub>
<b>STRUCTURAL INFORMATION</b>	407 aa (human)	398 aa (human)	465 aa (human)
<b>PREFERRED ENDOGENOUS PEPTIDE</b>	Substance P ( <a href="#">S 6883</a> )	Neurokinin A ( <a href="#">N 4267</a> )	Neurokinin B ( <a href="#">N 4143</a> )
<b>SUBTYPE SELECTIVE AGONISTS</b>	Substance P methyl ester ( <a href="#">S 2011</a> ) [Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]-Substance P ( <a href="#">S 3672</a> )	[β-Ala <sup>8</sup> ]-Neurokinin A(4-10) ( <a href="#">N-147</a> ) GR 64349 ( <a href="#">G-113</a> )	Senktide ( <a href="#">S 6772</a> ) [MePhe <sup>7</sup> ]-Neurokinin B
<b>SUBTYPE SELECTIVE PEPTIDE ANTAGONISTS</b>	GR 82334 ( <a href="#">G-115</a> ) GR 71251 ( <a href="#">S 2421</a> ) L-668,169 ( <a href="#">L-116</a> )	L-659,877 ( <a href="#">L-117</a> ) L-659,874 MEN 11420	R820 R486
<b>SUBTYPE SELECTIVE NON-PEPTIDE ANTAGONISTS</b>	L-703,606 ( <a href="#">L-119</a> ) L-733,060 ( <a href="#">L-137</a> ) CP-99,994 <sup>a</sup> RP 67580 <sup>a</sup> SR 140333 PD 154,075 LY-303870 MK-869	SR 48968 GR 159897	SR 142801 <sup>a</sup> SB-223412 SB-222,200 PD 161,182 <sup>a</sup>
<b>SIGNAL TRANSDUCTION MECHANISMS</b>	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)
<b>RADIOLIGANDS OF CHOICE</b>	[ <sup>3</sup> H]-Substance P [ <sup>125</sup> I]-L-703,776	[ <sup>125</sup> I]-Neurokinin A [ <sup>3</sup> H]-SR 48968	[ <sup>125</sup> I]-[MePhe <sup>7</sup> ]-Neurokinin B [ <sup>3</sup> H]-SR 142801

### Abbreviations

**CP-99,994:** (+)-(2S-3S)-3-(2-Methoxybenzylamino)-2-phenylpiperidine

**GR 64349:** Lys-Asp-Ser-Phe-Val-Gly-R-γ-lactam-Leu-Met-NH<sub>2</sub>

**GR 82334:** pGlu-Ala-Asp-Pro-Asn-Lys-Phe-Tyr-Pro spiro-γ-lactam-Leu-Trp-NH<sub>2</sub>

**GR 71251:** [D-Pro<sup>9</sup>,[spiro-γ-lactam]Leu<sup>10</sup>,Trp<sup>11</sup>]substance P

**GR 159897:** (R)-1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-methoxy-4[(phenylsulfanyl)-methyl]piperidine

**L-659,874:** N-Acetyl-L-leucyl-L-methionyl-L-glutamyl-L-tryptophyl-L-phenylalanyl-glycinamide

**L-659,877:** Cyclo(Gln-Trp-Phe-Gly-Leu-Met)

**L-703,606:** *cis*-2-(Diphenylmethyl)-N-(2-iodophenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine

**L-733,060:** (2S,3S)-3-([3,5-bis(trifluoromethyl)phenyl]methoxy)-2-phenylpiperidine

**L-668,169:** Cyclo(Gln-D-Trp(NMe)-Phe(R)Gly[ANC-2]Leu-Met)<sub>2</sub>

**LY-303870:** (R)-1-[N-(2-Methoxybenzyl)acetylamino]-3-(1H-indol-3-yl)-2-[N-(2-(4-(piperidin-1-yl)acetyl)amino)propane

**MK-869:** 2-(R)-1-(R)-3,5-Bis(trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine

**PD 154,075:** [(2-Benzofuran)-CH<sub>2</sub>OCO]-R-α-MeTrp-(S)-NHCH(CH<sub>3</sub>) Ph

**PD 161,182:** [(1R)-2-[[7-[(Aminocarbonyl)amino]heptyl]amino]-1-[(2,3-difluorophenyl)methyl]-1-methyl-2-oxoethyl]-carbamic acid (1S)-2-methyl-1-phenylpropyl ester

**R486:** H-Asp-Ser-Phe-Trp-β-Ala-Leu-Met-NH<sub>2</sub>

**R820:** (4R)-4-Hydroxy-1-(1H-indol-3-ylcarbonyl)-L-prolyl-N-methyl-2-phenyl-N-(phenylmethyl-(2S)-glycinamide

**RP 67580:** 2-[1-Imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4-perhydroisoindolone-(3aR,7aR)

**SB-223412:** (S)-N-(1-Phenylpropyl)-3-hydroxy-2-phenylquinoline-4-carboxamide

**SB-222200:** (S)-(-)-(α-Ethylbenzyl)-3-methyl-2-phenylquinoline-4-carboxamide

**SR 48968:** (S)-N-Methyl-N[4-(4-acetylamino-4-[phenylpiperidino]-2-(3,4-dichlorophenyl)-butyl]benzamide

**SR 140333:** (S)-1-(2-[3,4-Dichlorophenyl]-1-(3-isopropoxyphenylacetyl)piperidin-3-yl)ethyl)-4-phenyl-1-azoniabicyclo[2.2.2]octane chloride

**SR 142801:** (S)-(N)-(1-(3-(1-Benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl)propyl)-4-phenylpiperidin-4-yl)-N-methylacetamide

### FOOTNOTES

<sup>a</sup> Note that significant species differences exist.