

# Tachykinin Receptors

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## Overview

The tachykinins represent a large family of peptides whose common structural feature is the C-terminal amino acid sequence Phe-X-Gly-Leu-Met.NH<sub>2</sub>. Substance P (SP), neurokinin A (NKA), neurokinin B (NKB), hemokinin-1, endokinin A and endokinin B are the major tachykinins found in mammals. They are encoded by three genes named *TAC1*, *TAC3* and *TAC4* by the Human Genome Organization Nomenclature Committee, whereas the gene for chromosome 14 tachykinin-like peptide-1 awaits to be identified. SP and NKA are derived from the *TAC1* (preprotachykinin-A or *PPT-A*) gene. Alternative splicing of the *TAC1* transcript generates four different precursor proteins ( $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -*TAC1*) all of which can produce SP, while NKA and its N-terminally extended forms neuropeptide K and neuropeptide  $\gamma$  arise from  $\beta$ - and  $\gamma$ -*TAC1* only. NKB is the only tachykinin derived from the *TAC3* (*PPT-B*) gene. The human *TAC4* (*PPT-C*) gene can yield several precursor proteins ( $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -*TAC4*) which give rise to the tachykinins hemokinin-1, hemokinin-1(4-11), endokinin A and endokinin B and the tachykinin-like peptides endokinin C and endokinin D. While SP, NKA and NKB are conserved across mammalian species, the amino acid sequence of *TAC4* gene-derived tachykinins differs considerably between humans and rodents.

The biological actions of tachykinins are brought about by three types of tachykinin receptor. Encoded by the genes *TAC1*, *TAC2* and *TAC3*, they are currently named by the acronyms NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub>. These receptors are coupled through G<sub>q</sub> and G<sub>11</sub> to phospholipase C. The agonist potency profile at the NK<sub>1</sub> receptor is SP>NKA>NKB, at the NK<sub>2</sub> receptor NKA>NKB>SP, and at the NK<sub>3</sub> receptor NKB>NKA>SP. Human hemokinin-1 and its N-terminally extended forms endokinin A and B act preferentially at NK<sub>1</sub> receptors. Agonists with high selec-

tivity for only one tachykinin receptor have been obtained by synthetic modification of the natural tachykinins. There are small species differences in the amino acid sequence of the tachykinin receptors, which has little impact on agonist activity, but entails that the affinity of many nonpeptide tachykinin receptor antagonists differs profoundly between humans and rodents.

Tachykinins are known to mediate excitatory neurotransmission in the CNS and periphery, cause arteriolar dilatation, hypotension and contraction of nonvascular smooth muscle, increase venular permeability, participate in immune and inflammatory responses and stimulate endocrine and exocrine gland secretion. NK<sub>1</sub> receptors are widely expressed in peripheral tissues and the CNS. NK<sub>2</sub> receptors predominate in the periphery, while NK<sub>3</sub> receptors prevail in the CNS. The functional roles attributed to tachykinins in health and disease indicate that tachykinin receptors are important targets for novel medicines. This has led to the development of peptide-based and nonpeptide antagonists that are highly potent and selective for either the NK<sub>1</sub>, NK<sub>2</sub> or NK<sub>3</sub> receptor.

The quinuclidine CP-96345 was the first nonpeptide NK<sub>1</sub> receptor antagonist reported by Pfizer in 1991, although its utility was limited by toxicity due to nonselective ion channel blockade. Subsequently, many other NK<sub>1</sub> receptor antagonists based on piperidine, perhydroisoindole and related structures were developed, including CP-99994, CP-122721, CJ-11974/ezlopitant (Pfizer), MK-869/aprepitant, L-754,274 (Merck), GR-203040, GR-205171/vofopitant (Glaxo), SR-140333/Nolpitantium (Sanofi), RP-67580, RPR-100893/dapitant (Rhone-Poulenc) and LY-303870/lanepitant (Eli Lilly). In 2003, aprepitant was approved for the combination treatment of chemotherapy-

induced emesis, whereas clinical studies addressing pain, migraine, inflammation and chronic obstructive pulmonary disease (COPD) have been disappointing. Although aprepitant reduced anxiety and depression in Phase II trials, its development for this condition was discontinued following negative Phase III studies. Other possible indications of NK<sub>1</sub> receptor antagonists include skin disorders, inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS).

The first potent nonpeptide antagonist selective for NK<sub>2</sub> receptors was SR-48968/saredutant (Sanofi). This compound has since been joined by many other nonpeptide compounds such as SR-144190 (Sanofi), GR-159897 (Glaxo), YM-38336 (Yamanouchi) and SB-414240 (SmithKlineBeecham) and by cyclic peptide-based compounds such as MEN-11420/nepadutant (Menarini). Although several of these compounds are in development for IBS, COPD, anxiety and depression, data on their therapeutic utility are not yet available.

The development of selective NK<sub>3</sub> receptor antagonists began in 1993, when SR-142801/osanetant was discovered by Sanofi to be a high affinity nonpeptide antagonist at NK<sub>3</sub> receptors. More selective than osanetant, though with lower affinity, are peptoids such as PD-161182 (Parke-Davis) or substituted quinuclidines such as SB-222200 and SB-223412/talnetant (SmithKlineBeecham). Clinical trials of osanetant in schizophrenia, of talnetant in COPD, and of SB-222200 in CNS disorders have been carried out. Other possible indications of NK<sub>3</sub> receptor antagonists include somatic and visceral pain.

# Tachykinin Receptors

<b>CURRENTLY ACCEPTED NAME</b>	NK <sub>1</sub>	NK <sub>2</sub> ( <b>T180</b> )	NK <sub>3</sub>
<b>STRUCTURAL INFORMATION</b>	407 aa (human)	398 aa (human)	465 aa (human)
<b>PREFERRED ENDOGENOUS PEPTIDE</b>	Substance P ( <b>S6883</b> )	Neurokinin A ( <b>N4267</b> )	Neurokinin B ( <b>N4143</b> )
<b>SUBTYPE SELECTIVE AGONISTS</b>	Substance P methyl ester ( <b>S2011</b> ), [Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]-Substance P ( <b>S3672</b> )	[β-Ala <sup>8</sup> ]-Neurokinin A(4-10) ( <b>N147</b> ), GR-64349 ( <b>G113</b> )	Senktide ( <b>S6772</b> ), [MePhe <sup>7</sup> ]-Neurokinin B
<b>SUBTYPE SELECTIVE PEPTIDE ANTAGONISTS</b>	GR-82334 ( <b>G115</b> ), GR-71251 ( <b>S2421</b> ), L-668,169 ( <b>L116</b> ) <sup>a</sup>	L-659,877 ( <b>L117</b> ), L-659,874, MEN-11420 (Nepadutant)	R820, R486
<b>SUBTYPE SELECTIVE NON-PEPTIDE ANTAGONISTS</b>	L-703,606 ( <b>L119</b> ), L-733,060 ( <b>L137</b> ), CP-99994, <sup>a</sup> CP-122721, CJ-11974, FK888, GR-203040, GR-205171, NKP608, RP-67580, <sup>a</sup> RPR 100893, SR-140333 (Nolpitantium), PD-154075, <sup>a</sup> LY-303870 (Lanepitant), <sup>a</sup> MK-869 (Aprepitant) <sup>a</sup>	SR-48968 (Saredutant), GR-159897 ( <b>G7543</b> ), SR-144190, SB-414240 <sup>a</sup>	SR-142801 (Osanetant), <sup>a</sup> SB-223412 (Talnetant), SB-222200, PD-161182 <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
<b>TISSUE EXPRESSION</b>	CNS (e.g., hippocampus, amygdala, hypothalamus, striatum, brainstem, dorsal horn of spinal cord), vascular endothelial cells, inflammatory cells, skin cells, bronchial and intestinal smooth muscle, enteric neurons	Some neurons in CNS, inflammatory cells, bronchial, gastrointestinal and urinary smooth muscle	CNS (e.g., hippocampus, hypothalamus, substantia nigra, brainstem, dorsal horn of spinal cord), enteric neurons
<b>PHYSIOLOGICAL FUNCTION</b>	Central stress reactions, mood control, afferent neuron transmission, pain, airway and lung function, control of vascular diameter and permeability (neurogenic inflammation), immune modulation, control of intestinal secretion and motility	Mood control, afferent nerve traffic, airway and lung function, gastrointestinal contraction	CNS functions, afferent neuron transmission, control of intestinal motility and secretion
<b>DISEASE RELEVANCE</b>	Anxiety and depression, nausea and emesis, inflammatory hyperalgesia, inflammation, skin diseases, COPD, IBS, bladder hyperreflexia	Anxiety and depression, COPD, visceral hyperalgesia, IBS, urinary incontinence	Psychoses, schizophrenia, somatic and visceral hyperalgesia, COPD, IBS

## FOOTNOTES

## Tachykinin Receptors

### Abbreviations

**CJ-11974:** ((2*S*,3*S*-*cis*)-2-Diphenylmethyl)-*N*-1-azabicyclo-[2.2.2]octan-3-amine  
**COPD:** Chronic obstructive pulmonary disease  
**CP-99994:** (+)-(2*S*-3*S*)-3-(2-Methoxybenzylamino)-2-phenylpiperidine  
**CP-122721:** (+)-2*S*,3*S*-(3-(2-Methoxy-5-trifluoromethoxybenzyl)amino)-2-phenylpiperidine  
**FK888:** (4*R*)-4-Hydroxy-1-[(1-methyl-1*H*-indol-3-yl)carbonyl]-*L*-prolyl-*N*-benzyl-*N*-methyl-3-(2-naphthyl)-*L*-alaninamide  
**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-1*H*-indol-3-yl)ethyl]-4-methoxy-4[(phenylsulfinyl)-methyl]piperidine  
**GR-203040:** (2*S*, 3*S*)-2-Methoxy-5-tetrazol-1-yl-benzyl-(2-phenyl-piperidin-3-yl)-amine  
**GR-205171:** 3(*S*)-(2-Methoxy-5(5-trifluoromethyltetrazol-1-yl)-phenylmethylamino)-2(*S*)-phenylpiperidine  
**IBS:** Irritable bowel syndrome  
**L-659874:** *N*-Acetyl-*L*-leucyl-*L*-methionyl-*L*-glutamyl-*L*-tryptophyl-*L*-phenylalanyl-glycinamide  
**L-659877:** Cyclo(Gln-Trp-Phe-Gly-Leu-Met)  
**L-703606:** *cis*-2-(Diphenylmethyl)-*N*-([2-iodophenyl]methyl)-1-azabicyclo(2.2.2)octan-3-amine  
**L-733060:** (2*S*,3*S*)3-([3,5-bis(Trifluoromethyl)phenyl]methoxy)-2-phenylpiperidine  
**L-668169:** Cyclo(Gln-D-Trp(NMe)-Phe(R)Gly(ANC-2)Leu-Met)<sub>2</sub>  
**LY-303870:** (R)-1-[*N*-(2-Methoxybenzyl)acetyl]amino-3-(1*H*-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  
**NKP-608:** Quinoline-4-carboxylic acid [trans-(2*R*,4*S*)-1-(3,5-bis-trifluoromethyl-benzoyl)-2-(4-chloro-benzyl)-piperidin-4-yl]-amide  
**PD-154075:** [(2-Benzofuran)-CH<sub>2</sub>OOC]-(*R*)-α-MeTrp-(*S*)-NHCH(CH<sub>3</sub>)Ph  
**PD-161182:** [(1*R*)-2-[[7-[(Aminocarbonyl)amino]heptyl]amino]-1-[(2,3-difluorophenyl)methyl]-1-methyl-2-oxoethyl]-carbamic acid (1*S*)-2-methyl-1-phenylpropyl ester  
**R486:** H-Asp-Ser-Phe-Trp-β-Ala-Leu-Met-NH<sub>2</sub>  
**R820:** (4*R*)-4-Hydroxy-1-(1*H*-indol-3-ylcarbonyl)-*L*-prolyl-*N*-methyl-2-phenyl-*N*-(phenylmethyl-(2*S*)-glycinamide  
**RP-67580:** 2-[1-Imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4-perhydroisoindolone-(3*aR*,7*aR*)  
**RPR-100893:** (3*aS*,4*S*,7*aS*)-7,7-Diphenyl-4-(2-methoxyphenyl)-2[5-2-(2-methoxyphenyl)propionyl]perhydroisoindol-4-ol  
**SB-223412:** (*S*)-*N*-(1-Phenylpropyl)-3-hydroxy-2-phenylquinoline-4-carboxamide  
**SB-222200:** (*S*)-(-)-α-Ethylbenzyl)-3-methyl-2-phenylquinoline-4-carboxamide  
**SB-414240:** (*S*)-(+)-*N*-(1,2,2-Trimethylpropyl)-3-[(4-piperidin-1-yl)piperidin-1-yl]methyl-2-phenylquinoline-4-carboxamide  
**SR-48968:** (*S*)-*N*-Methyl-*N*[4-(4-acetyl-amino-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  
**SR-144190:** (R)-3-[1-[2-(4-Benzoyl-2-(3,4-difluorophenyl)-morpholin-2-yl)-ethyl]-4-phenylpiperidin-4-yl]-1-dimethylurea

### FOOTNOTES

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