

Neurotensin Receptors

Key References

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Overview

Neurotensin is a 13 amino acid regulatory peptide found mainly in gut and brain. Intestinal neurotensin is produced by a discrete population of endocrine cells (N cells) scattered throughout the jejuno-ileal mucosa. The peptide is released into the circulation after food ingestion. Its digestive functions include stimulation of pancreatic and biliary secretions, inhibition of gastric acid secretion and motility, stimulation of colon motility and inhibition of jejuno-ileum motility. It also promotes growth of normal gastrointestinal tissues and of cancer cells derived from the colon, pancreas, lung and prostate. In the brain, neurotensin exerts central actions that include hypothermia, analgesia, anorexia, regulation of pituitary hormone secretion and a number of effects that involve the modulation of basal forebrain cholinergic and nigrostriatal/meso-cortico-limbic dopaminergic pathways.

Neurotensin is synthesized as part of a larger precursor peptide that also contains neuromedin N, a six amino acid neurotensin-like peptide which also interacts with neurotensin receptors. Neurotensin and neuromedin N are located in the C-terminal region of the precursor from which they are released upon cleavage at dibasic sites by prohormone convertases (PCs). Pro-neurotensin/neuromedin N is differentially processed in the brain and the gut, giving rise in the former to equimolecular amounts of neurotensin and neuromedin N, and in the latter to neurotensin and a large peptide ending with the neuromedin N sequence at its C-terminal. Recent evidence suggests that PC1 is mainly responsible for the processing pattern observed in the gut, whereas a combination of PC1, PC2 and PC5 generates the pattern found in brain.

Two neurotensin receptors, termed NTS1 and NTS2 (previously referred to as NTRH and NTRL, respectively), have been cloned to date. They share 60% homology and belong to the family of G protein-coupled receptors. The NTS1 receptor has high affinity for neurotensin, whereas the NTS2 receptor has lower affinity for the peptide and is selectively recognized by levocabastine, an H₁ histamine receptor antagonist. In all systems examined, the NTS1 receptor coupled to phospholipase C through G_q. It is also negatively coupled to adenylyl cyclase in the neuroblastoma N1E115 cell line and positively coupled to phospholipase A2 in transfected cell systems through G_{i/o}. Finally, it is positively coupled to adenylyl cyclase in transfected cell systems through G_s.

Recently, a third neurotensin receptor was cloned. It is a 100 kDa protein with a single transmembrane domain that does not belong to the family of G protein-coupled receptors and is identical to a previously cloned protein named sortilin. The status of NTS3/sortilin as a true neurotensin receptor, i.e. as a protein capable of mediating NT responses, remains to be established.

SR 48692, a non-peptide neurotensin receptor antagonist, preferentially binds to the NTS1 receptor and has provided a useful tool with which to define the functions associated with this receptor. In particular, SR 48692 blocks many of the effects attributed to the interaction of neurotensin with mesencephalic dopaminergic neurons. In contrast, it does not antagonize the hypothermic and analgesic responses to neurotensin, suggesting that these effects are not mediated through the NTS1 receptor. *In vivo* blockade of

NTS2 receptor expression using antisense strategies and NTS1 knock-out mice have provided evidence that the NTS2 receptor mediates the analgesic effect of neurotensin. Quite surprisingly, neurotensin is only a weak agonist at the rat NTS2 receptor and an antagonist at the human NTS2 receptor in transfected cell systems, whereas SR 48692 is an efficient agonist on both rat and human NTS2 receptors.

A more recently developed non-peptide neurotensin receptor antagonist, SR 142948A, exhibits higher affinity than SR 48692 for both the NTS1 and the NTS2 receptors but less selectivity for the NTS1 over the NTS2 than SR 48692. In addition to being a potent inhibitor of the neurotensin effects that are blocked by SR 48692, SR 142948A inhibits the analgesic and hypothermic responses induced by neurotensin, albeit with lower potency.

Neurotensin Receptors

CURRENTLY ACCEPTED NAME	NTS1	NTS2
PREVIOUS NAME	NTRH	NTRL
STRUCTURAL INFORMATION	418 aa (human)	410 aa (human)
ENDOGENOUS AGONISTS	Neurotensin (N6383), Neuromedin N	Not known
SELECTIVE AGONISTS	Not known	SR 48692 (rat and human), Neurotensin (rat) (N6383)
SELECTIVE ANTAGONISTS	SR 48692, SR 142948A	Neurotensin (human)
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG), G _{i/o} (decrease cAMP, increase arachidonate), G _s (increase cAMP)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-[Tyr ³]-Neurotensin, [³ H]-SR 48692	[¹²⁵ I]-[Tyr ³]-Neurotensin
TISSUE EXPRESSION	Brain neurons, gut tissues, cancer cells	Brain astrocytes
PHYSIOLOGICAL FUNCTION	Central modulation of dopamine, acetylcholine and pituitary hormones, food intake, modulation of gut motility, secretion and growth	Analgesia
DISEASE RELEVANCE	Schizophrenia, Parkinson's disease, obesity, cancer	Pain suppression

Abbreviations

SR 48692: 2-[1-(7-Chloro-4-quinolinyl)-5-(2-dimethoxyphenyl)pyrazol-3-yl]carbonylamino]tricyclo-(3.3.1.1.3.7)decan-2-carboxylic acid

SR 142948A: 2-[[5-(2,6-Dimethoxyphenyl)-1-(4-(N-(3-dimethylaminopropyl)-N-methylcarbamoyl)-2-isopropylphenyl)-1H-pyrazole-3-carbonyl]-amino]-adamantane-2-carboxylic acid

FOOTNOTES