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Tachykinins

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Definition

Tachykinins are short-chain amino acid neuromodulators found from invertebrates to mammals sharing the common C-terminal amino-acid sequence: Gly-Leu-Met-NH₂. The name Tachykinin suggests the ability of these molecules to induce rapidly (tachys, swift) a contraction of smooth muscles (kineo, to move).

Pharmacological Properties

History

In 1931, Euler and Gaddum characterized an unidentified substance able to induce rapidly contraction of intestinal tissue. They named it ► **substance P** (SP) because it was stable in a dry powder form. Substance P remained the unique mammalian member of the tachykinin family until identification of ► **neurokinin A** (NKA) in 1983. Other mammalian tachykinins have been isolated since: neuropeptide K (NPK), neuropeptide γ (NP γ), ► **neurokinin B** (NKB), endokinins, and hemokinins. Studies of the distribution pattern of tachykinins showed a widespread expression in peripheral tissues where they have various effects such as inducing vasodilatation, hypotension, or contraction of smooth muscle. In the central nervous system, the three prominent mammalian tachykinins SP, NKA, and NKB are widely distributed with different distribution patterns. Maximal NKB concentrations are found in the cortex, whereas SP and NKA share a more similar distribution with a strong expression in the spinal cord and in the nuclei implicated in emotional process (e.g., nucleus accumbens, septum, amygdala). At a cellular level, SP and NKA are mostly co-localized in neurons and interneurons with glutamate, GABA, monoamines or acetylcholine. One or several tachykinins can be expressed within the same neurons and be co-released

with classical neurotransmitters or neuromodulators (Beaujouan et al. 2004). The co-expression of SP and NKA is not surprising since there are three genes that encode for all known mammalian tachykinins. SP, NKA, NPK and NP γ mRNA are generated by alternative splicing of a unique preprotachykinin-A (PPT-A) gene. NKB is derived from a second gene, the preprotachykinin-B (PPT-B) gene. A third gene, the more recently cloned preprotachykinin-C, is coding for hemokinins and endokinins that are primarily expressed in non-neuronal cells.

In parallel with the discovery of new peptides from the mammalian tachykinin family, three types of receptors have been identified. They belong to the ► **G-protein coupled receptors** (GPCR) superfamily containing seven transmembrane domains. The activation of tachykinin receptors leads to a transduction cascade, which in turn activates, among others, phospholipase C, the release of intracellular Ca²⁺ and the stimulation of neurotransmitter release (Chahl 2006). However, tachykinins are neuromodulators, preferentially released when neurons are strongly activated (or under pathological conditions). Consequently, blockade of their receptors by ► **antagonists** may result in effects only when the system is stimulated (Hökfelt et al. 2000). This is of great relevance as it may provide pharmacological targets for therapeutic applications with potentially less pronounced side effects than drugs acting on tonically active modulators such as ► **monoamines**. Tachykinin receptors termed NK1, NK2 and NK3 bind with a high affinity respectively, SP, NKA, and NKB. Antagonists for these receptors have been suggested to have therapeutic value in a variety of areas, including inflammation, emesis, ► **anxiety** and ► **depression**. However, the development of highly selective antagonists was hampered by findings from pharmacological and molecular studies that showed the existence of NK1 receptor isoforms with different affinities for tachykinins and a tissue specific expression. Furthermore, it was observed that several NK1 receptor antagonists have a greater affinity for the guinea-pig and human receptor than for the rat and mouse receptor (Beaujouan et al. 2004). This species heterogeneity, evidenced for NK1 and NK3, but not for NK2 receptors, had a major impact in the development of specific antagonists for these receptors as it

required the development of suitable behavioral models in atypical species such as guinea pigs and gerbils to characterize their psychopharmacological properties.

NK1 Receptor Antagonists

The development of highly selective NK1 receptor antagonists was initiated after the discovery of the role of substance P as a key mediator of pain processes. NK1 antagonists were used as tools to specify the topological and functional features of NK1 receptors leading to the idea that SP could be used for the treatment of other pathologies such as emesis, ► **Parkinson's disease**, anxiety or depression. Thus, the use of these antagonists in experimental research on depression and anxiety was based, for instance, on findings showing (1) an expression of SP and NK1 receptor in fear and depression-associated pathways; (2) fear-related behaviors after intracerebroventricular injection of SP and reduced fear following the peripheral administration of NK1 receptor antagonists; (3) that binding sites for SP are co-localized with those of monoamine transmitters in the human brain.

The antidepressant- and anxiolytic-like effects of MK-0869 (aprepitant), the first NK1 receptor antagonist tested in human, were initially demonstrated in a range of animal models. The further development of NK1 and SP receptor knock-out mice confirmed these results as mutant animals displayed an anxiolytic- and antidepressant-like phenotype.

Several randomized, ► **placebo-controlled**, ► **double-blind**, clinical studies were carried out to measure the safety and efficacy of aprepitant. In an initial clinical phase II trial, aprepitant was shown to display significant antidepressant activity. It was well tolerated, and had fewer side effects than the selective serotonin reuptake inhibitor, ► **paroxetine**, which was used as a positive control in this study. Unfortunately, this result was never replicated in phase III clinical trials, thereby questioning the idea that NK1 receptor antagonists may be effective antidepressants (Rost et al. 2006).

NK2 Receptor Antagonists

The identification of NK2 receptors in a number of peripheral tissues such as the smooth muscles of the gastrointestinal tract, the respiratory and the urinary tracts, along with studies using selective NK2 receptor antagonists has led to the idea that this receptor may represent a potential therapeutic target for a wide-range of disorders, including irritable bowel syndrome, pulmonary and urinary tract disorders. The demonstration of the existence of NK2 receptors in the brain has been made much later.

Data obtained from adult brain were not convincing due to non-specific binding and poor selectivity of ligands, and weak expression of the NK2 receptor. In 2001, the demonstration of the existence of central NK2 receptors was made using radiolabelled endogenous NKA in the presence of NK1 and NK3 receptor antagonists to avoid labeling of other tachykinin binding sites. These results were strengthened by detection of NK2 receptor mRNA in human and rat in brain structures affected in mood disorders, such as the ► **prefrontal cortex** and the ► **hippocampus**. Moreover neurochemical studies have identified a central regulatory role of NK2 receptors on monoaminergic and cholinergic neurotransmission. For instance, in anesthetized rats, the peripheral administration of the NK2 receptor antagonist, saredutant, has no effects on basal ► **norepinephrine** levels in the prefrontal cortex but reduces its release elicited by tail pinch. In addition, in non-anesthetized rats, local infusion of saredutant in the septum blocks stress-induced increase of hippocampal acetylcholine release but has no effect on basal conditions (Desvignes et al. 2003). These results underline the ability of NK2 receptor antagonists to regulate neurotransmission only when systems are activated (Steinberg et al. 2001).

Furthermore, recent data suggest an interaction between the tachykinin system and ► **corticotropin-releasing factor** (CRF). CRF is a neurohormone known to be involved in the regulation of the stress axis and in the etiology of mood disorders. The injection of saredutant was found to block CRF-induced increase in acetylcholine and norepinephrine release, suggesting that NK2 receptor antagonists counteract, at least in part, the effects of stress on neurotransmission.

At a behavioral level, the activation of central NK2 receptors by intracerebroventricular administration of NKA produces ► **anxiogenic**-like effects. Moreover several NK2 receptor antagonists have been shown to produce ► **anxiolytic**-like activity in animal studies. For example, GR159897 and saredutant exhibited anxiolytic-like effects in exploration-based procedures such as the light/dark and the ► **elevated plus-maze** tests. It is noteworthy that the anxiolytic-like properties of saredutant were observed across species as evidenced in the mouse defense test battery, the marmoset human intruder test and the social interaction test in gerbils and rats. In addition, saredutant also exhibited antidepressant-like properties in the rat forced swim test. Moreover, the drug attenuated physical degradation in the mouse ► **chronic mild stress test** (Griebel et al. 2001; Louis et al. 2008). In addition to the neurochemical and behavioral effects of NK2 receptor antagonists, molecular and cellular studies showed that

chronic treatment with saredutant upregulates cAMP response element binding protein (CREB) and promotes ► [neurogenesis](#) in ► [hippocampus](#) after chronic stress exposure in mice. Similar effects are observed with classical antidepressant treatment such as ► [fluoxetine](#). Together, these results suggested that selective NK2 receptor antagonists could have therapeutic utility for the pharmacological treatment of ► [mood disorders](#) and anxiety. Unfortunately, the low efficacy and poor brain penetration of the NK2 receptor antagonist tested in recent clinical trials did not allow a definitive conclusion on the pertinence of the target.

NK3 Receptor Antagonists

The NK3 receptor has been the least studied of the NK receptor family. The first paper on a selective NK3 receptor antagonist, published in 1995, was the starting point of numerous studies which explored the pharmacology of the NK3 receptor (Edmond-Alt et al. 1995).

In peripheral tissues, similar to other tachykinin receptors, it was found that the NK3 receptor plays a role in smooth muscle contraction. However, NK3 receptors are mostly expressed in the central nervous system with a wide distribution throughout the spinal cord and brain, in particular in limbic areas, well known to play a crucial role in psychiatric disorders. Importantly, the activation of NK3 receptors expressed on dopaminergic neurons by the highly selective agonist senktide leads to an increased dopamine release in the striatum and the prefrontal cortex. This excitatory activity, as well as the stimulation of serotonergic and noradrenergic systems, is blocked by the selective NK3 receptor antagonist osanetant, but not by NK1 or NK2 antagonists (Spooren et al. 2005). Decreasing the dopaminergic activity may be of interest for the treatment of the positive symptoms of ► [schizophrenia](#) since all currently approved antipsychotics share this feature.

Cross-References

- [Chronic Mild Stress](#)
- [Distress Vocalizations](#)
- [Elevated Plus Maze](#)
- [G-Protein Coupled Receptors](#)
- [Isoforms](#)
- [Selective Serotonin Reuptake Inhibitors](#)
- [Social Interaction Test](#)

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Tachyphylaxis

Definition

Tachyphylaxis is the rapid development of tolerance to the effect of a drug. That is, the response to a drug rapidly decreases after a few initial doses. In the case of hallucinogens, the process is thought to be a result of rapid desensitization and internalization of serotonin 5-HT_{2A} receptor.

Tacrine

- [Acetylcholinesterase and Cognitive Enhancement](#)

Tail Suspension Test

- [Behavioral Despair](#)