A Is For . . .

Neurokinin

neurokinin *One of a group of peptide neurotransmitters, also known as tachykinins, involved in sensory pathways.*

Substance P was first described in 1931 as a factor present in brain and gut that stimulated smooth muscle and lowered blood pressure. Its designation came from the fact that it retained activity when it was evaporated to a powder. In the 1950s, substance P was found to be most highly concentrated in the dorsal root of the spinal cord, suggesting it was involved in the perception of pain.

After substance P was characterized as a peptide of 11 amino acids, two other peptides with similar carboxy-terminal ends were described in mammals and named neurokinins A and B, and more examples were found in various species.

Three mammalian neurokinin receptors have been cloned and designated NK-1, 2, and 3. Each has a preferred neurokinin ligand: substance P for NK-1, neurokinin A for NK-2, and neurokinin B for NK-3. However, all three peptides can bind to any of the receptors, depending on peptide concentration and receptor availability.

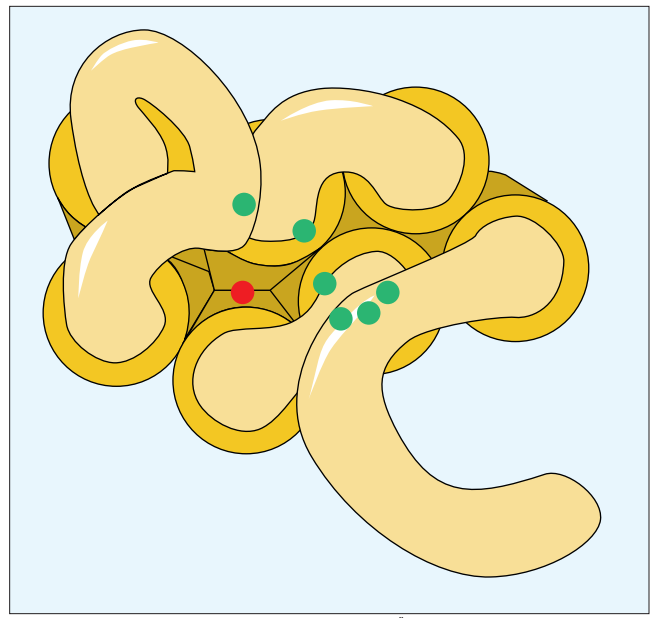
Understanding neurokinin function requires the design of receptor antagonists, of which about 20 are in use by different laboratories, mostly within pharmaceutical companies. Most published work is on release of substance P from peripheral endings of primary sensory neurons and its binding to NK-1 receptors on effector cells. An extensive literature deals mainly with three effects:

(1) When the effector cells are vascular endothelial cells, the effect is termed neurogenic inflammation. Specifically, gaps appear between vascular endothelial cells, allowing plasma leakage. Accompanying increased blood flow results in arteriolar dilatation, plasma protein extravasation in venules, and leukocyte adhesion to endothelial cells. Other effects in different tissues include bronchoconstriction and smooth muscle contraction.

(2) In the gut, substance P and neurokinin A are expressed in different neural pathways, and the three receptors are found on neurons, muscle, epithelium, vascular endothelium, and immune cells in a cell-specific distribution. The most important effect of neurokinins is on motility, which can be stimulated or inhibited depending on which receptors are activated. In stimulating circular smooth muscle, neurokinins act together with acetylcholine.

Another effect is on secretory activity. In animal experiments, some inflammatory conditions are associated with up-regulation of NK-1 and an apparent shift away from cholinergic to neurokininergic regulation.

(3) NK-1 is the most common neurokinin receptor in brain areas that govern mood and stress responses, and in animals, substance P magnifies the agitation that is a measure of the stress response. If an NK-1 antagonist could inhibit that response in animals and was not toxic, it might be tried to treat depression without the side effects of the serotonin-enhancing drugs. Trials of one of them have been reported.



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On the NK1 receptor, binding sites for substance P (*green*) occur on the extracellular transmembrane loops, and that for the nonpeptide antagonist (*red*) is located in a deep pocket between the loops. This principle of interaction, where the peptide ligand and nonpeptide antagonist bind to different parts of the receptor, each inducing a conformational change, was described first for substance P and its receptor and since found to be generally true for neuropeptide receptors.

Work also continues on clarifying the involvement of substance P in pain perception. Dorsal root ganglion neurons are stimulated to release substance P by many excitatory factors, among them heat and tissue injury. Within the spinal cord, NK-1 receptors have been found on neurons in different dorsal laminae, and here, the response to substance P applied experimentally is the same slow and prolonged excitation of relay neurons that constitutes their response to peripheral noxious stimuli.

Substance P is only one of many messengers in the dorsal root ganglion, so pain perception likely involves a number of transmitters and modulators. It is also known that the sensitivity of the system is adjusted up or down by regulating synthesis of both transmitters and receptors. The consensus now is that no single factor ordinarily dominates, but that there may be clinical conditions in which regulation fails. If so, then one transmitter, perhaps substance P, could become dominant, so that an NK-1 antagonist would be an effective analgesic.

Selena Harrison and Pierangelo Geppetti: Substance P. *International Journal of Biochemistry & Cell Biology* 33:555-576, June 2001.