Neurokinin Receptor Antagonists
Therapeutic Potential in the Treatment of Pain Syndromes

Tsukasa Sakurada,1 Chikai Sakurada,1 Koichi Tan-No2 and Kensuke Kisara2

1 Department of Biochemistry, Daiichi College of Pharmaceutical Sciences, Fukuoka, Japan
2 Department of Pharmacology, Tohoku College of Pharmacy, Sendai, Japan

Summary

The involvement of tachykinin neuropeptides, such as substance P and the neurokinins, in pain transmission is supported by a wealth of evidence. At present, the therapeutic potential of manipulating tachykinin-mediated effects is being investigated and has been assisted by the discovery of several non-peptide, metabolically stable compounds that are antagonists at neurokinin (NK) receptors. Since multiple neurotransmitters or neuromodulators are involved in nociception in primary afferents, drugs that are antagonists at both tachykinin NK1 and NK2 receptors could be clinically more useful than receptor-selective drugs in the treatment of pain syndromes. NK1 receptor antagonists that are also opioid receptor agonists or the combination of neurokinin receptor antagonists with opioids may also be promising approaches to treating pain.

The tachykinins are a group of structurally related peptides that have been identified in the mammalian CNS, including the spinal cord, as well as in various peripheral tissues.1-4 The tachykinin family of peptides share the common carboxyl terminal sequence, Phe-X-Gly-Leu-Met-NH2 (see table I). Substance P was the first of the family to be identified in the mammalian CNS. Other tachykinins subsequently identified in the CNS were neurokinin A (NK A) and neurokinin B (NK B).5-7 These peptides mediate a variety of biological effects including neuronal excitation, bronchoconstriction, vasodilation, salivary secretion, neurogenic inflammation and activation of the immune system.2,3 Additional mammalian tachykinins, such as the N-terminally extended forms of neuropeptide K and neuropeptide y, have been proposed to play a role as neurotransmitters.8 The tachykinin family also includes the amphibian skin peptides physalaemin and kassinin, and the molluscan salivary gland peptide, eledoisin (table I).

The existence of at least 3 major types of receptor for tachykinins (NK1, NK2 and NK3) is now well established.3,9-13 Substance P binds most potently to NK1 receptors, whereas NK A and NK B preferentially bind to NK2 and NK3 receptors, respectively. Subsequently, the characterisation of NK1, NK2 and NK3 receptors as distinct sites was confirmed with the cloning and sequencing of separate cDNAs encoding each of the receptors.14-17 However, complete characterisation of tachykinin receptors has been hampered by the poor receptor selectivity of the endogenous peptides, which can activate more than one receptor type under physiological conditions. Some of the more recent investigations dealing with receptors, antagonists and neurotransmitter functions of tachykinins have been reviewed elsewhere.14,18-23
1. Role of Tachykinins in Nociceptive Transmission

The pain perception generated by high intensity stimulation and inflammation involves synaptic transmission from the periphery to the cortex. Nociceptive information integrated in the dorsal horn of the spinal cord and corresponding structures of trigeminal nucleus is relayed and further processed in the brain stem and in thalamic structures before it reaches somatosensory regions of the cerebral cortex.\[24\]

1.1 Substance P

Among mammalian tachykinins, substance P has been suggested to be a transmitter candidate, or nociceptive, in primary afferent neurons.\[25-27\] Substance P is localised in small diameter primary afferent fibres\[28,29\] that presumably carry nociceptive inputs. Substance P-like immunoreactivity has been identified in the dorsal horn,\[29,30\] especially in areas where small diameter afferents terminate.\[31,32\] Fine afferent C and Aδ nociceptive nerves are activated by noxious cutaneous stimuli.\[33\] Stimulation that is strong enough to excite unmyelinated C-fibres and thinly myelinated Aδ-fibres elicits pain in humans and results in aversive behaviours in animals.\[33\] The activation of afferent nerves induces the release of substance P in the spinal cord.\[34-37\]

Capsaicin (8-methyl-N-vanillyl-6-noneamide), the principal pungent constituent of hot peppers, has been shown to selectively activate a subset of primary afferent neurons involved in nociception.\[38\] Capsaicin excites polymodal nociceptive neurons with conduction velocities in the ranges of both C- and Aδ-fibres.\[39\] Capsaicin directly administered into the spinal cord in vivo and in vitro can cause the release of substance P and calcitonin gene-related peptide (CGRP), which co-exist in many sensory neurons.\[38\] In addition to this afferent function, these peptides are released from peripheral nerve endings and control a variety of local tissue processes.\[33,40\] Dorsal rhizotomy has been shown to decrease the level of substance P in the dorsal horn\[41,42\] and increase its binding,\[43\] suggesting a predominant origin of this peptide in primary afferents.

Functional studies indicate that intrathecal injection of tachykinins in conscious mice induces an irritant behavioural response, consisting of caudally directed biting, licking and scratching. The spinally mediated behavioural response occurs mainly through the NK1 receptor, as evidenced by the rank order of potency of mammalian and non-mammalian tachykinins in inducing the behaviour.\[44\] This characteristic behaviour is a useful model for evaluating the effects of tachykinin receptor antagonists injected intrathecally into the spinal cord.\[44,45\] Intrathecal administration of substance P reduces the nociceptive threshold to both thermal and mechanical stimuli, as assayed by the tail-flick and tail-pressure test in rats, and represents another model of tachykinin-mediated effects.\[46,47\]