An Antinociceptive Role for Substance P in Acid-induced Chronic Muscle Pain


Chronic pain is a major medical problem. However, current analgesics are not effective in many types of chronic pain. Here we discovered a novel antinociceptive mechanism against acid-induced chronic muscle pain. This finding is essentially opposite to the role that substance P (SP) has been proposed to play over many years—SP signaling promotes pain.

SP is an undecapeptide belonging to the tachykinin small peptide family. SP is an excitatory neurotransmitter that helps to excite and transmit pain signals. SP signaling is excitatory in almost all neuronal cells, including neurons in spinal dorsal horn, brain stem, hippocampus, and dorsal root ganglia, etc. Substances that inhibit SP signaling pathways generally show antinociceptive effects in animal models. However, though high levels of SP in muscle tissues and spinal fluid are frequently associated with chronic muscle pain, such as myofascial pain syndrome and fibromyalgia, researchers do not fully understand the role of SP in muscle pain.

We have used mouse models to test how SP contributes to muscle pain sensitivity. In contrast to SP’s usually excitatory role, mice lacking SP signaling showed increased pain sensitivity after intramuscular acid injections, compared with mice with normal SP signaling. Both mice with null mutation of SP gene and those administrated with SP receptor antagonists showed similar increased sensitivity to muscle pain. We further used electrophysiological approach to identify an inhibitory signal pathway of SP that was found exclusively in muscle nociceptors expressing acid-sensing ion channel 3, where SP enhances M-type potassium channels through the NK1 receptor in a G protein-independent but tyrosine kinase-dependent manner. Furthermore, the SP signaling could increase action potential thresholds and reduce the expression of TTX-resistant sodium currents in muscle nociceptors. Thus, the intramuscular SP mediates an unconventional NK1 receptor signaling to inhibit acid-induced chronic muscle pain.

The finding suggests that SP may inhibit pain sensitization in muscle nociceptors and increased SP in patients with chronic muscle pain may be present as part of an inhibitory feedback loop. This study opens up a new direction for pain research and also partially annotates the failure of clinical trials for analgesic drugs based on SP antagonism. The research team is now working on analgesic drug development against chronic muscle pain, such as fibromyalgia.

Schematic model of substance P (SP)-mediated inhibition of ASIC3 signaling. When tissue acidosis occurs in muscles, protons depolarize the muscle nociceptors by activating ASIC3 channels, and cause the firing of action potentials, which can release SP in the nerve terminals. SP then acts on NK1 receptors in the local nerve terminals. The NK1 receptors on muscle nociceptors are coupled with a G-protein-independent signal pathway by activating tyrosine kinase and M channels to inhibit the ASIC3-mediated neural firing.