Substance P: an odd player in a painful game

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Neuropeptide substance P (SP) is both produced and released by a subset of peripheral nociceptive sensory fibers; some of these fibers also express SP receptors (neurokinin receptors 1-3, NK1-3). SP exerts excitatory effects in CNS and attempts have been made to develop novel analgesics based on NK1 antagonists; these attempts were hitherto unsuccessful. Here we show that SP paradoxically inhibits excitability of small-diameter dorsal root ganglion (DRG) neurons *in vitro* and produces a peripheral analgesic effect *in vivo*. This effect can be attributed to the acute modulation of two ion channels that control sensory neuron excitability: potentiation of M-type K^+ channels and inhibition of T-type voltage-gated Ca^{2+} channels. Fluorescent imaging utilizing superoxide-sensitive fluorescent protein mt-cpYFP revealed that SP induced mitochondrial release of superoxide radical in DRG neurons, an effect that may explain the modulation of both channel types as both are redox-sensitive (although in opposite directions). In addition, SP effects on both channel types were prevented or reversed by the reducing agent dithiothreitol and mimicked by exogenous or endogenous delivery of reactive oxygen species (ROS). Focusing on the T-type channels, we further demonstrate that the SP-induced and redox-mediated T-type channel inhibition operated through the modulation of Cav3.2 channel sensitivity to ambient zinc as it was prevented or reversed by zinc chelation and mimicked by exogenous zinc. Moreover, elimination of the zinc binding site in Cav3.2 rendered the channel insensitive to SP-mediated inhibition. Using behavioural tests we demonstrate that peripheral injections of SP into rat hind paw produced no nocifensive behaviour but pre-injection of SP significantly attenuated nocifensive behaviour produced by injection of inflammatory mediator bradykinin. This effect of SP was attenuated by the knock-down of Cav3.2 in DRG *in vivo* and mimicked by the peripheral injections M channel opener retigabine or by T-type channel inhibitor Z944. In summary, our studies established a convergent mechanism by which SP exerts a paradoxical peripheral analgesic effect by simultaneous inhibition of pro-algesic T-type Ca^{2+} current and enhancement of anti-algesic M-type K^+ current. These findings will help us to better understand the the complex role of SP in pain pathways.

Key words: M-type K^+ channels/ T-type Ca^{2+} channel/ Substance P/ redox mechanisms/ sensory neuron/ nociception/ inflammatory pain.