Peripheral somatosensory ganglia as a novel target for pain relief

The cell bodies (somata) of primary sensory neurons reside in the peripheral ganglia (e.g. dorsal root ganglia, DRG), and are attached to the conducting axons by relatively short stems. The resulting t-shaped axonal bifurcation (t-junction) is a characteristic of "pseudounipolar" geometry of DRG neurons. Events leading to the sensation of pain (and other somatosensory sensations) normally start from the action potentials (APs) that are generated at the peripheral endings of DRG neurons in response to the appropriate external stimuli. These APs then propagate to the dorsal horn of spinal cord passing through the t-junctions. It has long been recognized that DRG neuron somata are electrically excitable and that propagating APs enter the stem and invade soma. Accumulating evidence suggests that somatic excitation may play a much stronger role in peripheral nociceptive transmission than is generally accepted. We used *in vitro*, *in vivo* and *in silico* approaches to identify axonal t-junction as a critical transmission point at which a peripherally-initiated nociceptive AP can fail. We further demonstrate that somatic membrane potential in nociceptive neurons can control the peripheral nociceptive transmission. Thus, we were able to significantly reduce transmission of nociceptive stimuli in rats *in vivo* by changing somatic/perisomatic membrane potential within the DRG through the pharmacological targeting of various somatic ion channels expressed therein. For instance, somatic hyperpolarization produced by focal application of M-type or K_{ATP} channel enhancers or a cyclic nucleotide-gated channel blocker to L5 DRG *in vivo* significantly alleviated inflammatory pain induced by hind paw injection of bradykinin or formalin. Interestingly, somatic depolarization induced by acute *in vivo* DRG application of GABA also demonstrated strong analgesic efficacy in both inflammatory and neuropathic pain models. Finally, we used computational modelling to demonstrate how either hyperpolarization or depolarization of somatic/perisomatic membrane potential can work in concert with the low-pass filtering properties of the t-junction within the DRG to interfere with action potential propagation from the periphery to the spinal cord. In conclusion, we suggest that sensory ganglia may function as filters and/or integrators of peripheral somatosensory signals and, thus, may represent a novel therapeutic target.