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Specific activation of nociceptor subgroups by slowly depolarising electrical stimuli

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Slow depolarising stimuli represent a more suitable type of electrical stimulation to activate unmyelinated C-fibres, excluding myelinated A-fibre responses, and preferential activation of C-nociceptors provides a useful tool for clinical trials involving chronic pain patients. In this study we applied slow depolarising stimuli, as well as the traditional rectangular stimuli for comparison, to record compound action potentials and responsiveness of characterized single nerve fibres in presence of specific voltage-gated sodium channel blockers.

Our results indicate a higher sensitivity of low threshold mechanosensitive (LT) fibres and polymodal (HT) nociceptors to sine wave 4Hz and half-sine wave 500ms stimuli compared to mechano-insensitive (CMi) "*silent*" and cold sensing (CN) nociceptors. This sensitivity was attributed to the presence of tetrodotoxin-sensitive (TTX-S) Na^+ channels. The data also suggests that the presence of TTX-S, specifically $Na_V1.7$, is especially relevant in the response to high intensity and high frequency types of electrical stimulus. The TTX-induced blockade of $Na_V1.7$ and $Na_V1.6$ separately shows that $Na_V1.7$ alone determines a slowing in conduction velocity without affecting the time needed to generate a C-fibre response to slow depolarising stimulus. LT fibres and HT nociceptors still responded after TTX albeit at about ten-fold higher current intensities. Thus, either the $Na_V1.8$ component in LT and HT fibres can carry a depolarisation upon long duration depolarising stimulations or current spread to a more proximal non-blocked area of the axon initiates the action potential. Moreover, it cannot be ruled out that the contribution of other voltage gated channels, such as K^+, Ca^+ and Ca^+ dependent Cl^- channels for instance, as well as the biophysical properties of the neuronal membrane, influenced the response of C-afferents to slow depolarising electrical stimulation.

The participation of K^+ channels in the response of C-fibres to slow depolarising stimulus, rendering the nociceptors particularly sensitive to this type of stimulus at colder temperatures, provided further evidence for the relevance in studying these channels, but also shed some light on the mechanisms leading to spontaneous activity and cold hypersensitivity in neuropathic pain patients.

The development of more specific $Na_V1.8$ blockers as well as studying other neuronal membrane channels will be crucial to clarify why unmyelinated axons seem to be particularly prone to respond to slow depolarising stimulus. The knowledge about the mechanisms of peripheral activation can possibly contribute to the understanding of the pathophysiology of cold allodynia in neuropathic pain patients, providing more accurate targets for the treatment of painful neuropathy in the future.