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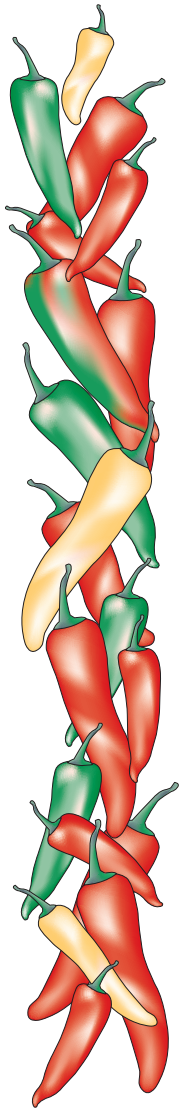

ION CHANNELS

Spicing up local anaesthetics

Whenever we visit the dentist we have good reason to be grateful for over a century of developments in anaesthesia. Local anaesthetics can now provide long-lasting relief from pain without loss of consciousness. However, one problem remains: most local anaesthetics block sodium channels in all types of neurons and so can also cause loss of non-painful sensations and muscle paralysis. A study by Binshtok *et al.* outlines a new approach for the development of anaesthetics that numb pain without affecting other types of neurons.

To develop their strategy, the authors took advantage of two key observations. The first was that most nociceptors (the neurons that are responsible for detecting painful stimuli) uniquely express transient receptor potential vanilloid 1 (TRPV1) channels. These channels are sensitive to both noxious heat and capsaicin, the ingredient that puts the 'heat' in chilli peppers. When activated, TRPV1 channels open a pore that appears to be capable of passing relatively large positively charged molecules across the cell membrane. The second key to the strategy was the realization that a derivative of lidocaine, QX-314, is a positively charged molecule that does not permeate the cell membrane but which can block sodium channels if present inside a neuron. The authors hoped to use the TRPV1 channel pore to allow QX-314 to gain selective entry to nociceptors.

They tested the idea by carrying out whole-cell voltage-clamp recordings in cultured rat dorsal-root-ganglion (DRG) neurons, using the response to capsaicin to identify nociceptors. They found that when QX-314 was applied at the same time as capsaicin, the sodium current and action potentials normally elicited by a depolarizing pulse were abolished. The effect was restricted to small-diameter DRG neurons that expressed TRPV1 channels, suggesting that it was likely to be nociceptor-specific.

Next, the authors tested the effects of the combination of QX-314 and capsaicin on pain transmission *in vivo* in adult rats. They examined the rats' sensitivity to a noxious mechanical stimulus using Von Frey's hairs — thin fibres that are used to exert a gradually increasing mechanical pressure on the rat's hindpaw. They found that, 60 minutes after the injection of the compounds into the hindpaw, the level of mechanical pressure that the rats were able to endure before withdrawing the hindpaw was increased. Similarly, the latency before paw withdrawal from a noxious heat source was also increased. A delay of 10 minutes between the injections of QX-314 and capsaicin produced anaesthesia that developed over 15–30 minutes and lasted for several hours. The authors did not observe any motor deficits, suggesting that the effects were restricted to nociceptors.

Further work is needed to evaluate the likelihood of efficacy in a clinical setting. Nevertheless, such pain-specific anaesthesia could have advantages in a number of situations, not least the treatment of chronic pain conditions. Furthermore, the study highlights a new strategy for the delivery of therapeutic compounds to specific subsets of neurons.

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ORIGINAL RESEARCH PAPER Binshtok, A. M., Bean, B. P. & Woolf, C. J. Inhibition of nociceptors by TRPV1-mediated entry of impermeant sodium channel blockers. *Nature* **449** 607–610 (2007)