TREKing noxious thermosensation

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The ability to sense environmental temperature as pleasant or unpleasant is associated with the activity of thermo-sensitive neurons in the peripheral nervous system. Differential sensation of pleasant environmental temperatures (warm and cool) versus unpleasant and noxious (cold and hot) temperatures requires the definition of thresholds and temperature ranges for activating thermoreceptors. In this issue of *The EMBO Journal*, a study by Noël *et al.* (2009) entitled 'The mechano-activated K^+ channels TRAAK and TREK-1 control both warm and cold perception' shows that the potassium leak channels TREK-1 and TRAAK have an important regulatory role in noxious thermoreceptors to ensure a high-enough activation threshold that does not interfere with the sensing of innocuous (warm and cool) temperature, but low enough in order to avoid tissue damage.

Of the five senses—sight, hearing, smell, taste, and touch—touch is perhaps the most varied. Touch describes the ability to sense chemical stimuli, mechanical forces, and temperature. Temperature sensing comes essentially in two flavours: pleasant (innocuous) and unpleasant (noxious). In the peripheral nervous systems, at the level of the skin two basic classes of innocuous- and noxious-temperature-sensing neurons have been recognized: myelinated A δ -fibres responsible for the first sharp pain, and C-fibres responsible for the slow, longer-lasting nociception of noxious temperature (Kandel *et al.*, 2000).

A major breakthrough in the identification of molecules involved in temperature sensing was the discovery of temperature-activated transient receptor potential (TRP) ion channels that were directly gated by a change in temperature. Four heat-activated TRP ion channels (TRPV1–4) and two cold-sensitive TRP ion channels (TRPM8 and TRPA1) were identified. Recently, two studies (Brauchi *et al.*, 2004; Voets *et al.*, 2004) convincingly have argued that the temperature-sensing properties of TRPM8 and TRPV1 channels arise directly from intrinsic thermodynamic channel properties. Whether this also applies to the other TRP channels is still a matter of debate (Dhaka *et al.*, 2006). Importantly, TRPM8 and TRPV1 are voltage activated and temperature shifts the voltage-dependent activation of the channels to more physiological ranges. The implication of this observation is that membrane potential plays an important role in the

temperature-sensing activity of the TRP channels. Given the sophistication of thermo-sensitivity, it most likely involves complex interactions of ion channels, receptors, and proteins

Figure 1 Temperature sensing at peripheral terminals of unmyelinated C-fibres (thin axons) and myelinated A δ -fibres (thick axons) is transmitted to the spinal cord, and from there onwards to the cortex via central pathways. The diagram illustrates schematically ion channel populations in four subgroups of sensory neurons investigated in the study of Noël *et al.* (2009). One group represented capsaicin-insensitive, heat-sensitive C-fibres, probably expressing TRPV3 and TRPV4 channels, which responded to temperature increases between 30 and ~48°C (coloured in yellow). The population of these neurons was markedly increased in the TREK-1 $^{-/-}$, TRAAK $^{-/-}$ double knockout mice. A second group corresponded to heat-sensitive, capsaicin-sensitive, TRPV1-expressing A δ neurons (coloured in red), which are normally in charge of signalling high temperature ($\geq 50^\circ\text{C}$)-induced pain, but were activated within a significantly lower temperature range. On the cold side, a small population of neurons (lightly blue coloured, A δ fibres?) sensitive to menthol, allyl-isothiocyanate (AI) and cold is increased. However, the major effect concerns the population of menthol- and AI-insensitive and cold-sensitive C-fibre neurons (coloured in blue) that are normally active only at temperatures below 12°C. The question mark indicates that the nature of the cold-sensing excitatory ion channel is unclear. In the double knockout mice the population of these sensory neurons is significantly increased and their response activity is shifted to temperatures between 30 and 12°C.

in addition to TRP channel activation. A report in this issue of *The EMBO Journal* by Noël *et al* (2009) has well characterized one important player in this complex game. Investigating thermosensitivity in TREK-1/TRAAK double knock-out mice, it was observed that both K^+ channels control the response of sensory neurons to hot and cold.

TREK-1 and TRAAK are dimeric, two-pore domain potassium (K_{2P}) channels belonging to the TWIK-channel family (TWIK—tandem of P domains in a weak inwardly-rectifying K^+ channel) (Talley *et al*, 2003). K_{2P} channels are leak channels that are open at all membrane voltages and, therefore, are involved in controlling the resting membrane potential. Importantly, the two K_{2P} channels are activated by certain anaesthetics, membrane stretching, intracellular acidosis, and by heat (Maingret *et al*, 1999a,b, 2000; Patel *et al*, 1999). Loss of TREK-1 and TRAAK channel activity in the TREK-1, TRAAK double knockout mouse apparently has two important consequences. Firstly, the firing threshold of thermosensitive neurons is lowered, resulting in an increased

firing activity in response to a change in temperature. Secondly, the population of sensory neurons is increased, which respond to relatively mild changes in temperature. These two effects highlight the important interplay of depolarizing TRP and repolarizing K_{2P} channel activity to control the threshold for sensory neuron activation. In detail, the measured cell-physiological and phenotypical effects could be divided into several informative subgroups (see Figure 1). The results shed light on the mystery behind how sensory neurons set the alarm off when noxious cold or hot temperatures are encountered. Also, the data concur with the notion that nociceptive thresholds are not fixed and can be lowered or elevated to modulate the responsiveness of the sensory neurons. Changes in threshold are associated with clinical pain syndromes (Scholz and Woolf, 2002). It will be interesting to see how this type of neural plasticity relates to altered K_{2P} channel activity. Possibly, the new data on the role of K_{2P} channels in nociception open new avenues for more effective therapies in pain treatment.

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