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PAIN

Feeling the heat (and cold)

The precise role of somatosensory dorsal root ganglion (DRG) neurons that express calcitonin gene-related peptide (CGRP) in nociception is unknown. A new study reveals that these neurons not only sense numerous stimuli including noxious heat but also indirectly regulate cold sensitivity and core body temperature.

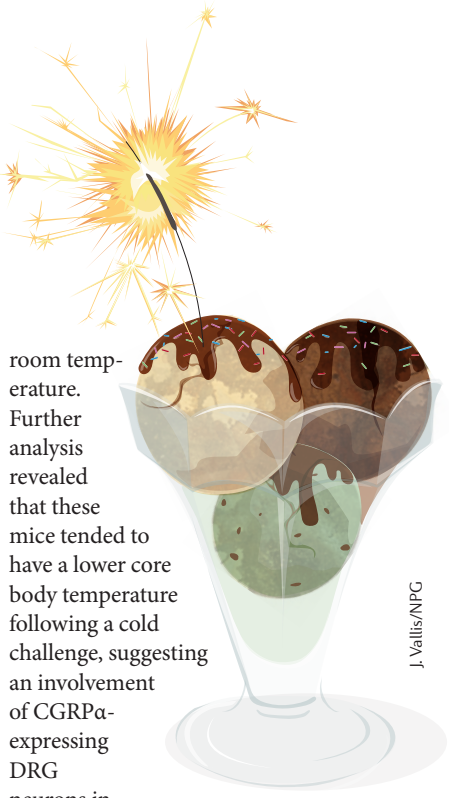
Peptidergic DRG sensory neurons signal to postsynaptic neurons in the spinal cord. Using a Cre–*loxP* system to selectively ablate the DRG neurons that express the CGRPα form of CGRP (which predominates in DRG neurons), the authors were able to perform physiological and behavioural tests to elucidate their function.

Isolated peripheral nerves from animals with ablated CGRPα-expressing neurons exhibited a notable reduction in responsiveness to heat applied to the skin, but their cold-responsiveness was unaffected. In line with the heat-responsiveness finding, CGRPα-ablated animals showed a marked reduction in noxious heat sensitivity in behavioural assays (such as the tail flick assay) and reduced sensitivity to capsaicin, which activates transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors on CGRPα-expressing neurons. However, these mice exhibited a marked increase in sensitivity to cold temperatures, suggesting that CGRPα-expressing neuron ablation might be affecting temperature processing downstream of the peripheral sensory nerves, such as in the postsynaptic neurons in the spinal cord.

> “heat-sensing CGRPα-expressing neurons mediate responses to sensory stimuli such as noxious heat and capsaicin but also cross-inhibit cold-sensing neurons in the spinal cord”

The authors measured the frequency of the excitatory postsynaptic current (EPSC) in spinal cord slices from CGRPα-ablated mice that had been treated with either capsaicin (which activates TRPV1-expressing, heat-sensing afferents) or icilin (which activates TRPM8-expressing, cold-sensing afferents). EPSC frequency was decreased by capsaicin as expected, but was markedly increased by icilin. Overall, these findings reveal a mechanism whereby heat-sensing, CGRPα-expressing neurons mediate responses to sensory stimuli such as noxious heat and capsaicin but also cross-inhibit cold-sensing neurons in the spinal cord. Ablation of CGRPα-expressing neurons thus leads to disinhibition and an enhanced responsiveness to cold stimuli.

Last, the authors noticed that, unlike controls, CGRPα-ablated mice appeared to be piloerected at room temperature. Further analysis revealed that these mice tended to have a lower core body temperature following a cold challenge, suggesting an involvement of CGRPα-expressing DRG neurons in thermoregulation.



J. Vallis/NPG

Given that cold hypersensitivity is associated with neuropathic pain, targeting CGRPα-expressing neurons could be a therapeutic option for pain management.

Sian Lewis

ORIGINAL RESEARCH PAPER McCoy , E. S. *et al.* Peptidergic CGRPα primary sensory neurons encode heat and itch and tonically suppress sensitivity to cold. *Neuron* **78**, 138–151 (2013)