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ANALGESIA

Anti-itch and anti-ouch antibody

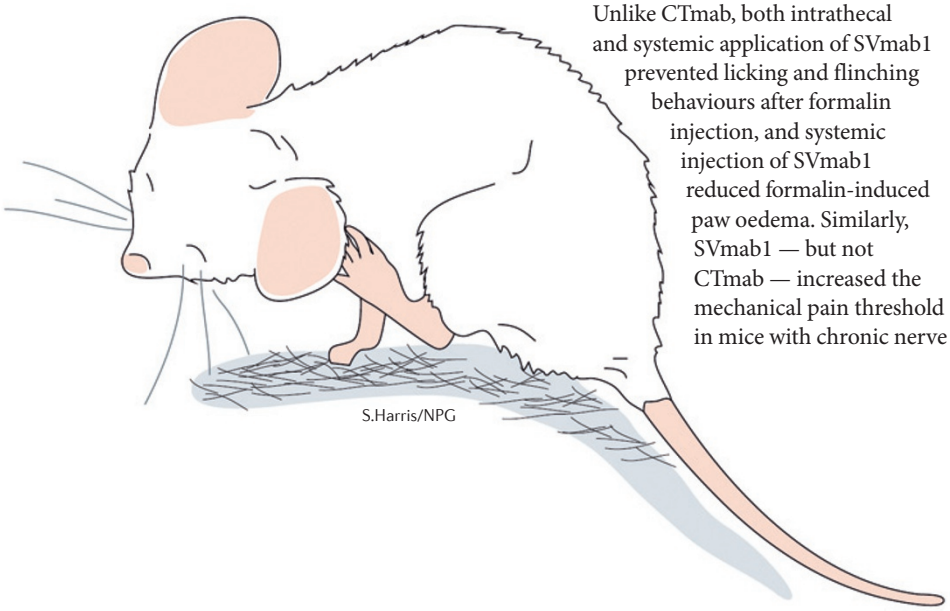
> SVmab1 reduces excitatory transmission in pain-sensitive neurons

The voltage-gated sodium channel Nav1.7 plays a key part in the sensation of pain, but past efforts to develop analgesics that target this channel have often not achieved high enough Nav subtype selectivity to avoid adverse off-target effects. In a recent paper in *Cell*, Lee *et al.* developed a Nav1.7-specific antibody called SVmab1, which not only reduces inflammatory and neuropathic pain in mouse models but also reveals a role of Nav1.7 in itch.

The authors produced a monoclonal antibody against the voltage-sensor paddle of human Nav1.7 — a region that modulates channel gating and shows high variation among Nav subtypes. Patch-clamp experiments showed that, unlike a control antibody (CTmab) against a Nav1.7 region not involved in gating, SVmab1 reduced the size of sodium currents through cell-line-expressed Nav1.7 channels by ~87%, with a half-maximal inhibitory concentration of 30 nM. Moreover, these effects were specific to Nav1.7 over other Nav subtypes; besides Nav1.7, SVmab1 only partially inhibited Nav1.6.

Voltage-clamp recordings from mouse dorsal root ganglion neurons revealed that the inhibitory effects of SVmab1 on sodium currents were specific to small-sized nociceptive neurons. In spinal cord slices, the frequency of excitatory postsynaptic currents (EPSCs) in interneurons that receive input from nociceptive neurons was markedly reduced by SVmab1. Furthermore, in slices taken from mice 4 days after sciatic nerve ligation, EPSC frequency was increased, but reduced to normal levels by SVmab1; thus, SVmab1 reduces excitatory transmission in pain-sensitive neurons.

The authors tested the analgesic properties of SVmab1 in mouse models of inflammatory and neuropathic pain. Intraplantar injection of formalin induces paw inflammation and pain-associated behaviour. Unlike CTmab, both intrathecal and systemic application of SVmab1 prevented licking and flinching behaviours after formalin injection, and systemic injection of SVmab1 reduced formalin-induced paw oedema. Similarly, SVmab1 — but not CTmab — increased the mechanical pain threshold in mice with chronic nerve constriction injury, with analgesia lasting ~24 hours after SVmab1 injection.



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Finally, the authors investigated the role of Nav1.7 in the sensation of itch. Compared with CTmab-treated animals, mice treated with intrathecal SVmab1 exhibited less scratching behaviour after intradermal injection of itch-inducing agents and after spinal injection of gastrin-releasing peptide, which evokes itch sensation via spinal cord neurons. Likewise, scratching behaviour in chronic itch models of dry skin and allergic contact dermatitis was reduced by intrathecal or intravenous application of SVmab1. Compared with healthy controls, spinal cord neurons from mice with dry itchy skin exhibited higher-frequency EPSCs that were suppressed by SVmab1, implying that itch increases Nav1.7-mediated excitatory activity in the spinal cord.

This study indicates that specific inhibition of peripheral and central Nav1.7 channels may be a viable strategy for treating inflammatory or neuropathic pain, as well as itch-related disorders. The authors' approach for developing a channel-specific antibody might also be applicable to other voltage-gated cation channels of therapeutic interest.

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ORIGINAL RESEARCH PAPER Lee, J.-H. *et al.* A monoclonal antibody that targets a $Na_v1.7$ channel voltage sensor for pain and itch relief. *Cell* **157**, 1393–1404 (2014)