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PAIN

Turning down the heat in pain

The heat-activated transient receptor potential cation channel TRPV1, which is expressed by sensory nociceptors, is implicated in several pain disorders; however, efforts to alleviate pain by blocking TRPV1 currents have been hampered by the fact that TRPV1 also has an important role in thermoregulation. TRPV1 is sensitized by inflammatory mediators: thus, identifying and targeting the mechanisms underlying this sensitization may be an effective approach to treat chronic pain. In a new paper in *Cell*, Siemens and colleagues reveal that the GABA receptor subunit $GABA_{B1}$ inhibits TRPV1 sensitization through a non-canonical signalling mechanism.

To identify possible modulators of TRPV1 sensitization, the authors purified TRPV1-containing complexes from mouse dorsal root ganglion (DRG) neurons. Mass spectrometry showed that $GABA_{B1}$ was present in many of these TRPV1-containing complexes, suggesting that it can interact with TRPV1 channels.

Capsaicin (the 'hot' chemical component of chillies) elicits TRPV1-mediated currents in cultured mouse DRG neurons. When administered alone, the $GABA_{B1}$-specific agonist baclofen did not affect these currents, but it did inhibit the sensitization of TRPV1 currents by nerve growth factor (NGF), serotonin, bradykinin or a protein kinase C activator. By contrast, TRPV1 sensitization was not inhibited by baclofen in DRG neurons from mice in which $GABA_{B1}$ was conditionally knocked out from TRPV1-expressing cells. Together, these results show that $GABA_{B1}$ activity prevents sensitization of TRPV1.

Next, the authors began to explore the pathways downstream of $GABA_{B1}$ that might mediate its effects on TRPV1 sensitization. They showed that baclofen-induced inhibition of TRPV1 sensitization was unaffected by pertussis toxin — which inactivates $G_{i/o}$ proteins — indicating that the effects of $GABA_{B1}$ on TRPV1 are independent of canonical $GABA_B$–$G_{i/o}$ signalling.

$GABA_{B1}$ is expressed by nociceptors and by neurons in central pain pathways. To determine where it has its effects of TRPV1 sensitization, the authors used a mouse model of heat hyperalgesia. Mice were given intraplantar injections of NGF into each hind paw and an injection of baclofen into only one of these paws before exposure to a hot stimulus. The authors found that heat hyperalgesia (indicated by rapid paw withdrawal) was attenuated only in the hind paw co-injected with baclofen, implying that $GABA_{B1}$ activity counteracts TRPV1 sensitization locally in the periphery, rather than via central mechanisms. Moreover, in the heat hyperalgesia model and in a model of inflammatory pain, hyperalgesia was reduced by baclofen even when the drug was administered after pain had been established, implying $GABA_{B1}$ activity can reverse as well as prevent such hyperalgesia.

Intriguingly, the authors detected GABA in blister fluid taken from humans, suggesting that GABA might be released from peripheral terminals and thus activate $GABA_{B1}$ to suppress TRPV1 activity. Indeed, GABA and GABAergic vesicles were observed in nociceptor terminals of mouse corneas. Strikingly, the GABA content of TRPV1-expressing terminals was reduced by stimulation with capsaicin, suggesting that TRPV1 activity might trigger the release of GABA from peripheral nerve endings.

Altogether, this study identifies a new mechanism of peripheral nociceptive modulation, whereby $GABA_{B1}$ inhibits the sensitization of TRPV1 by inflammatory mediators, independently of the canonical $GABA_B$ signalling pathway. $GABA_{B1}$ agonism may therefore represent a possible strategy for treating pain disorders associated with upregulated TRPV1 activity.

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> “$GABA_{B1}$ activity counteracts TRPV1 sensitization locally in the periphery, rather than via central mechanisms”

ORIGINAL RESEARCH PAPER Hanack, C. *et al.* GABA blocks pathological but not acute TRPV1 pain signals. *Cell* **160**, 759–770 (2015)
FURTHER READING Vriens, J., Nilius, B. & Voets, T. Peripheral thermosensation in mammals. *Nature Rev. Neurosci.* **15**, 573–589 (2014)

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