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New insight on inflammatory regulation could inform future pain drug development

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A novel way in which the inflammatory response to pain is regulated has been described in the open-access journal *eLife*.

The results add to our understanding of the mechanisms that cause increased sensitivity to pain in response to injury and inflammation, and could pave the way for more effective therapies.

Inflammatory hyperalgesia, the hypersensitivity to thermal and chemical stimuli, can be divided into two phases—acute and chronic. As part of this condition, inflammatory mediators, including growth factors, stimulate and sensitise pain receptors. A protein that also plays a key role here is Transient Receptor Potential Vanilloid Subtype 1 (TRPV1).

Nerve growth factor (NGF) is also involved in inflammatory hyperalgesia and, in chronic pain, produces changes in the protein expression of TRPV1. "It has been known for over a decade that NGF sensitises pain-receptor neurons through increased trafficking of TRPV1 channels to the cell surface, and that this sensitisation requires the activation of an enzyme called phosphoinositide 3-kinase, or PI3K," explains first author Anastasiia Stratiievska, Ph.D. candidate in the Department of Physiology and Biophysics at the University of Washington, Seattle, US. "But the mechanism by which this occurs was still unknown, and we wanted to gather more insights into the process."

To do this, Stratiievska and her team used an imaging technique called two-colour total internal reflection fluorescence microscopy to study

TRPV1-expressing cells. Their analysis revealed that TRPV1 increased PI3K activity. Although TRPV1 is a large, multi-domain protein embedded in the cell surface, a small fragment of the protein called the ARD was enough to cause this increase in activity.

"Because the ARD is structurally conserved among TRPV channels, we tested whether other channels besides TRPV1 could increase NGF-induced PI3K activity," says senior author Sharona Gordon, Professor of Physiology and Biophysics at the University of Washington, Seattle. "We saw that this was indeed also true for TRPV2 and TRPV4."

"Together, our findings reveal a previously unknown reciprocal regulation among multiple TRPV channels and PI3K," Stratiievska concludes. "The next steps will be to identify ARD mutations that prevent this regulation. It would also be interesting to determine the exact role that reciprocal regulation plays in sensitisation to painful stimuli within model organisms, as this could help with the development of more effective painkillers further down the line."

More information: Anastasiia Stratiievska et al, Reciprocal regulation among TRPV1 channels and phosphoinositide 3-kinase in response to nerve growth factor, *eLife* (2018). DOI: 10.7554/eLife.38869

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