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Researchers identify innate channel that protects against pain

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Scientists have identified a channel present in many pain detecting sensory neurons that acts as a 'brake', limiting spontaneous pain. It is hoped that the new research, published today [22 January] in the *Journal of Neuroscience*, will ultimately contribute to new pain relief treatments.

Spontaneous pain is ongoing pathological pain that occurs constantly (slow burning pain) or intermittently (sharp shooting pain) without any obvious immediate cause or trigger. The slow burning pain is the cause of much suffering and debilitation. Because the mechanisms underlying this type of slow burning pain are poorly understood, it remains very difficult to treat effectively.

Spontaneous pain of peripheral origin is pathological, and is associated with many types of disease, inflammation or damage of tissues, organs or nerves (neuropathic pain). Examples of neuropathic pain are nerve injury/crush, post-operative pain, and painful diabetic neuropathy.

Previous research has shown that this spontaneous burning pain is caused by continuous activity in small sensory nerve fibers, known as C-fiber nociceptors (pain neurons). Greater activity translates into greater pain, but what causes or limits this activity remained poorly understood.

Now, new research from the University of Bristol, has identified a particular ion channel present exclusively in these C-fiber nociceptors This ion channel, known as TREK2, is present in the membranes of these neurons, and the researchers showed that it provides a natural

innate protection against this pain.

Ion channels are specialised proteins that are selectively permeable to particular ions. They form pores through the neuronal membrane. Leak potassium channels are unusual, in that they are open most of the time allowing positive potassium ions (K+) to leak out of the cell. This K+ leakage is the main cause of the negative membrane potentials in all neurons. TREK2 is one of these leak potassium channels. Importantly, the C-nociceptors that express TREK2 have much more negative membrane potentials than those that do not.

Researchers showed that when TREK2 was removed from the proximity of the cell membrane, the potential in those neurons became less negative. In addition, when the neuron was prevented from synthesizing the TREK2, the membrane potential also became less negative.

They also found that spontaneous pain associated with skin inflammation, was increased by reducing the levels of synthesis of TREK2 in these C-fiber neurons.

They concluded that in these C-fiber nociceptors the TREK2 keeps membrane potentials more negative, stabilizing their membrane potential, reducing firing and thus limiting the amount of spontaneous burning pain.

Professor Sally Lawson, from the School of Physiology and Pharmacology at Bristol University, explained: "It became evident that TREK2 kept the C-fiber nociceptor membrane at a more negative potential. Despite the difficulties inherent in the study of spontaneous pain, and the lack of any drugs that can selectively block or activate TREK2, we demonstrated that TREK2 in C-fiber nociceptors is important for stabilizing their membrane potential and decreasing the likelihood of firing. It became apparent that TREK2 was thus likely to

act as a natural innate protection against pain. Our data supported this, indicating that in chronic pain states, TREK2 is acting as a brake on the level of spontaneous pain."

Dr Cristian Acosta, the first author on the paper and now working at the Institute of Histology and Embriology of Mendoza in Argentina, said "Given the role of TREK2 in protecting against spontaneous pain, it is important to advance our understanding of the regulatory mechanisms controlling its expression and trafficking in these C-fiber nociceptors. We hope that this research will enable development of methods of enhancing the actions of TREK2 that could potentially some years hence provide relief for sufferers of ongoing spontaneous burning pain."

The research, funded by the Wellcome Trust, was carried out in the School of Physiology and Pharmacology at the University of Bristol.

More information: 'TREK2 Expressed Selectively in IB4-Binding C-Fiber Nociceptors Hyperpolarizes Their Membrane Potentials and Limits Spontaneous Pain' by Cristian Acosta, Laiche Djouhri, Roger Watkins, Carol Berry, Kirsty Bromage and Sally Lawson in the *Journal of Neuroscience*.

Provided by University of Bristol