THE KAVLI PRIZE

NEUROSCIENCE PRIZE 2020 EXPLANATORY NOTES

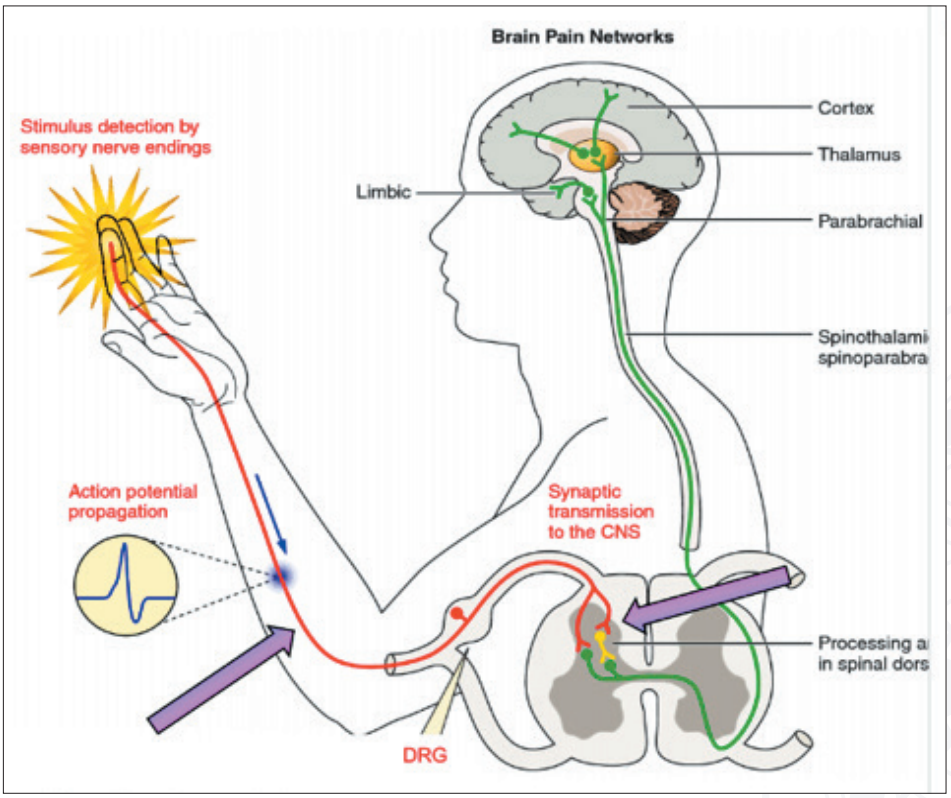
Ouch! When heat and pressure become painful

Picture standing on a beach – warm sunshine, a sea breeze caressing your cheeks, and rough sand between your toes. These are familiar but quite different sensations, yet they all depend on our sense of touch. Whether something feels hot, cold, hard, soft or painful, it is our tactile sensitivity that helps us discriminate between these stimuli. They are all part of our sense of touch, which has been the least well understood of the five senses (compared to seeing, hearing, smell, and taste), until the work of the 2020 Kavli Prize in Neuroscience winners, David Julius and Ardem Patapoutian.

Over the past two decades, they have independently described the molecular mechanisms that underpin our sensitivity to temperature, pressure and pain, and provided new insights into human physiology and disease.

Julius was originally fascinated by how natural products such as hallucinogens used in folk medicine could be used to explore the nervous system. His postdoctoral research focused on receptors for the neurotransmitter serotonin, and drew his attention to sensory neurons that relay sensations to the brain.

Later, as an independent investigator, he came across the work of Hungarian scientists and others showing that a subset of sensory neurons became active in the presence of both heat and capsaicin, the 'hot' ingredient of chili peppers. There was controversy, however, about what the mechanism might be and its significance to pain sensation. It remained a niche area until 1997, when Julius identified the receptor molecule TRPV1 on pain-sensing neurons, and showed that it was activated by both heat and capsaicin, and thus represented a point of convergence for the two stimuli.

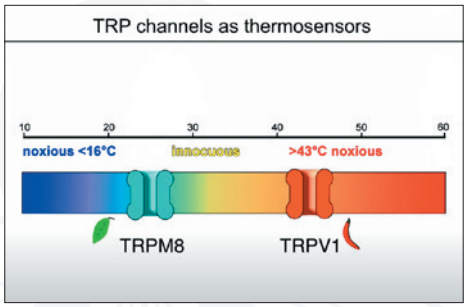


External environmental stimuli such as heat and pressure activate ion channel receptors in the membranes of sensory nerves, resulting in electrical impulses which travel via the dorsal root ganglia (DRG) to sensory regions of the brain. [Illustration adapted from Bourinet et al. 2014]

TRPV1 belongs to a family of ion channels, which sit in the cell membrane and upon activation, open a pore to allow the flow of charged ions (such as sodium and calcium) into the cell. Better understood in fruit flies, this was the first TRP channel to be assigned a physiological role in vertebrates.

"The cloning of the capsaicin receptor was a bit of a landmark moment in terms of understanding a molecular basis for touch and pain sensation... in particular a mechanism by which a physical force can activate these neurons." says Julius. A role for TRP channels in temperature sensation was further confirmed when Julius and Patapoutian independently identified TRPM8 as a receptor responding to menthol and cold.

Capsaicin, the 'hot' ingredient of chili peppers, stimulates the same sensory nerves as heat via the receptor TRPV1. [credit: Marat Musabirov]



Caption: TRP ion channels respond to changes in temperature by opening pores that allow positively charged sodium and calcium ions to flow through the membranes of nerve cells, triggering a change in voltage across the membrane.

Julius also revealed that TRPV1 was sensitive to chemicals produced during inflammation and mediates inflammatory-related pain hypersensitivity, opening up new potential avenues for the treatment of cancer pain and other conditions.

Julius, Patapoutian, and others have since identified other ion channels that are important to touch and pain. The 'wasabi receptor' TRPA1, for example, responded to wasabi, mustard oil, garlic and a variety of chemical irritants, making this an important receptor for detecting noxious environmental toxins. But its activation by a chemical produced in osteoarthritis signifies a dual role in pain sensation.

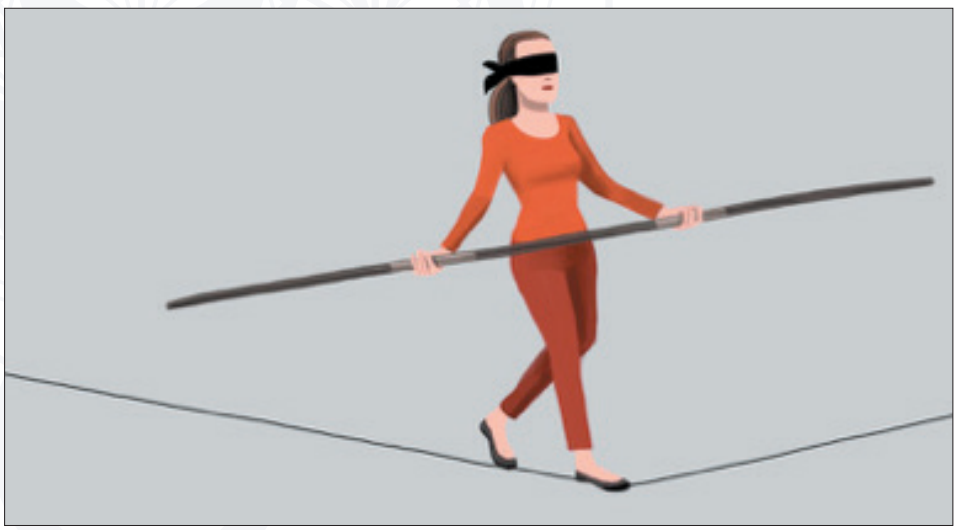
Patapoutian's research took a different direction, however, when he started questioning how we sense pressure. In 2010, his team discovered two new ion channels that were activated by mechanical pressure (a gentle poke with a fine rod), to produce electrical activity. They cloned and named the ion channels PIEZO1 and PIEZO2 (from the Greek piezi meaning pressure).

PIEZO1 and PIEZO2 were found on sensory neurons and other cell types, leading to an explosion of research on the role of these ion channels in pressure sensation for touch, pain, blood pressure regulation, lung inflation, and proprioception.

Proprioception refers to our ability to sense where our body is in space. It normally enables us to stand and walk, even with our eyes closed or blindfolded, and depends on neurons that signal muscle stretch to the brain. Patapoutian's team and others have shown that PIEZO2 is the key receptor involved, with reports that humans with a rare deficiency in PIEZO2 have difficulty standing and walking in the dark. They also do not experience pain hypersensitivity.

Patapoutian's more recent research in human genetics and mouse models has demonstrated a role for PIEZO1 in controlling red blood cell volume. He found a PIEZO1 gene variant that appears to protect against infection by the malaria parasite, and is carried by one in three people of African descent.

"It's been a very fascinating journey following where PIEZOs take us, from one biology and pathophysiology to another," says Patapoutian.



Caption: Proprioception – which enables us to balance and walk blindfolded - depends on PIEZO receptors expressed in 'stretch receptor' neurons. Illustration: Jorge Colombo