Pain... We’ve All Felt It

Pain, a problem faced by most humans, can be felt in two different ways: acute pain, which is the sharp pain usually brought about by injury, and chronic pain, which is pain that persists for three or more months. Chronic neuropathic pain affects 3-4% of people worldwide. Treating pain that lasts this long is costly. Annual treatment for chronic pain costs roughly $560-$635 billion in the U.S. alone. This is partly due to ineffective treatments that are currently available. Opioids, used effectively to treat acute pain, are highly addictive and lose efficacy when used as a treatment for chronic pain. Pregabalin is a promising non-opioid drug option, but one study showed it only works in 26.1% of patients. Researching pain is difficult because of differences in people’s genetics and pain thresholds.

Perception of Pain

Pain is sensed by sensory neurons in our skin and other tissues (see figure 3). These neurons can be activated by mechanical, chemical or thermal stimuli. The neurons have specific receptors designed to pick up on the stimuli (see figure 1). The stimuli open the ion channels and allow positive ions in, which cause depolarizations that make the neuron’s interior less negative. When enough stimuli are received and the threshold of the neuron is reached, that neuron produces an action potential of its own (see figure 2). An action potential is a very quick influx of sodium ions and efflux of potassium ions through voltage-gated channels. This generates an electric current in a wave down the axon. This impulse travels to the spinal cord and when it reaches the end of the neuron, a chemical neurotransmitter is released into the synaptic cleft, stimulating the next neuron. This second neuron sends the impulse to the brain so the pain sensation can be interpreted.

TRPA1 Makes You Feel the PA1N

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The Story of TRPA1

The transient receptor potential cation channel, subfamily A, member 1 (TRPA1) is one of the many receptors that allow us to feel pain (see figure 7). TRPA1 can be triggered either mechanically, chemically or thermally. TRPA1 is an ion channel located in the free nerve endings in your skin. Several agonists that chemically trigger TRPA1 include: mustard oil, tear gas, hydrogen peroxide, nicotine, and wasabi (see figure 4). When the skin is stretched, the ion channel is opened. Researchers speculate that the ankyrin repeats are the mechanism that allow the channel to mechanically open. Positive amino acid residues in the coiled coil may assist ion passage by attracting polyphosphates (see figure 6) which help to open the channel. Some amino acids make the channel so narrow that most ions are restricted from passing through. Ca++ and Na+ are able to pass through the channel depolarizing the neuron, which may result in an impulse sent to our brain. Researchers know that TRPA1 is involved in mechanical pain because when they remove the genes for TRPA1 in mice, they are less sensitive to pain. These “knock out” animals can be poked on a sensitive paw and they don’t elicit a withdrawal response. (See “Evidence that TRPA1 works for more detail.”) TRPA1 is also responsible for pain sensation in humans. A study was performed on a family who had a NBSS5 mutation in the 54 region of TRPA1. This mutation is an autosomal dominant disease carried on chromosome 8. With normal突觸, the mutant channel created five times as many depolarizations which caused pain in these patients. Debilitating upper body pain is brought on by fasting, illness, cold, or fatigue in this example of pain sensed by TRPA1 receptors.

Involvement of TRPA1 in Pain

To show how TRPA1 facilitates pain sensation, an experiment was performed on mice with a control group and a group with the TRPA1 gene knocked out (see figure 8). Without a functioning TRPA1 gene, knock out mice respond to pain less often.

In another experiment, the paws of mice were sensitized with Complete Freund’s Adjuvant (CFA), a compound that induces inflammation (see figure 9). When the paw is touched, fewer actions potentials are sent in mice lacking TRPA1 receptors. Therefore, mice responded less often (see figure 10).

Summary: Why Study TRPA1?

By studying TRPA1, researchers hope to find more effective pharmaceuticals or alternative treatments to alleviate the pain in individuals suffering from chronic pain. Research hopes to decrease the health care costs of pain treatment, as well as the lost productivity of people out of the workforce. By mitigating chronic pain, people will be able to live a quality pain-free life. If restored to health, people will have the ability to work, enjoy recreational activities and everyday life without pain.

References