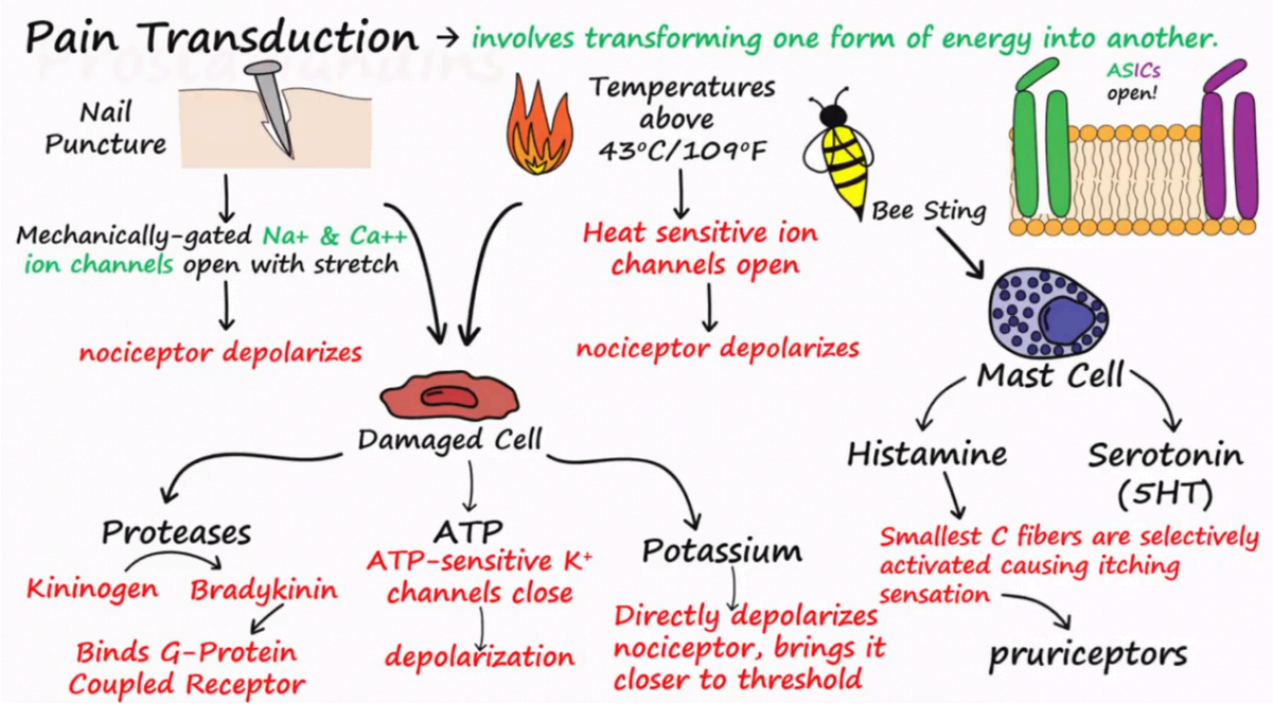
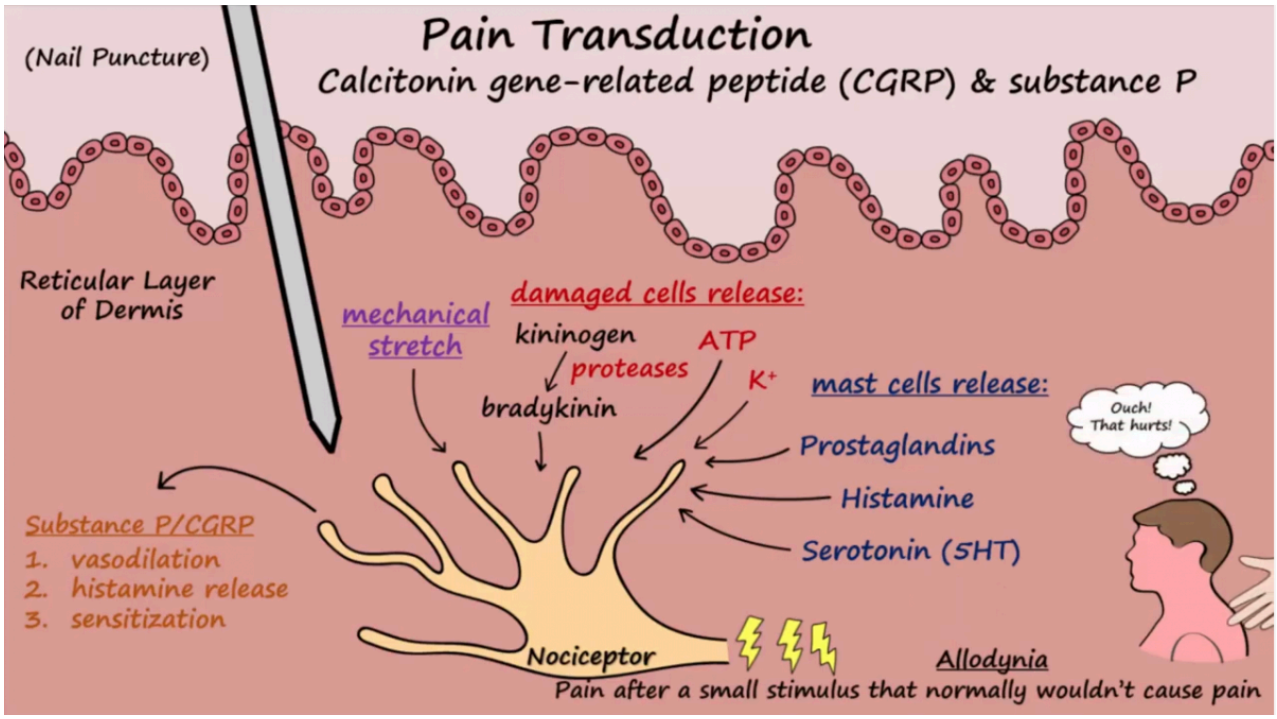
11.1.2

Pain Transduction

Watch this video: Pain Transduction

Take notes as needed to interpret, explain, and even reproduce your own drawings that will explain all the information in the pictures below:





Images by Lanning Baker BYU-Idaho F19

Stimuli that are capable of activating nociceptors are stimuli that may cause tissue damage like chemical exposure, temperature extremes, mechanical stimulation due to trauma, and oxygen deprivation that can result in ischemia. These stimuli result in the opening of ion channels in nociceptors so Na^+ and Ca^{2+} can enter and cause the nociceptor to reach threshold, thus converting the initial stimulus into an action potential.

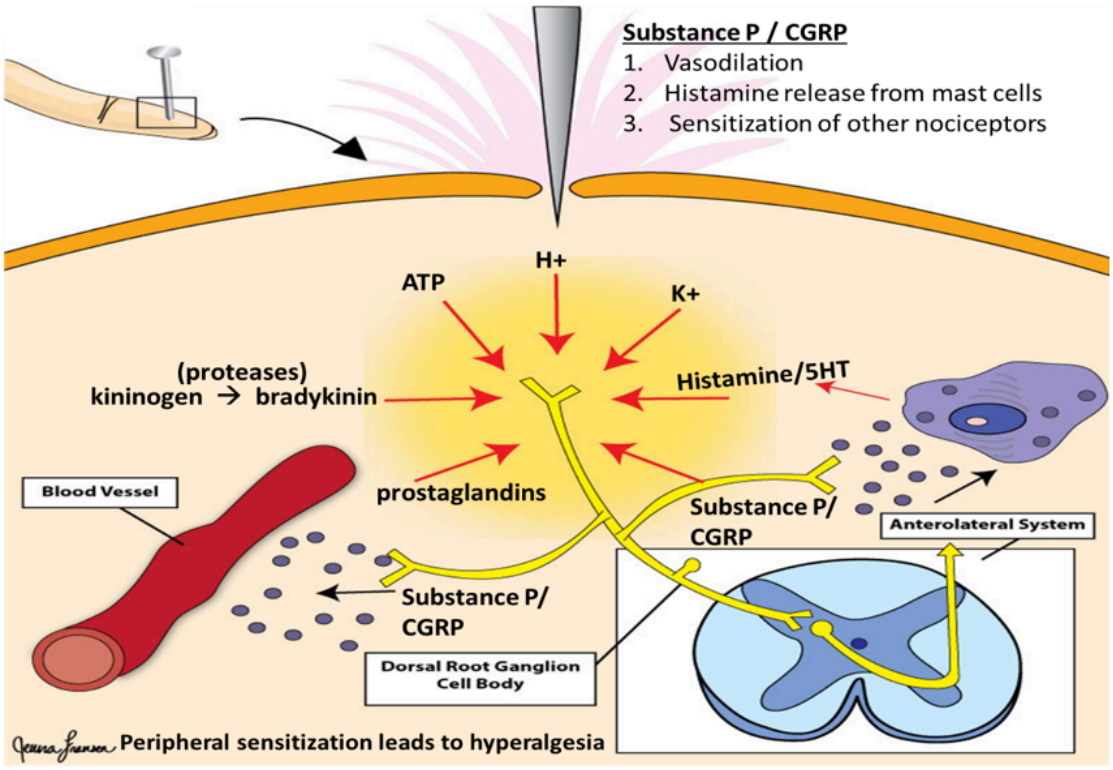
When a cell is damaged and releases its intracellular contents into the **extracellular fluid (ECF)**, certain components can also induce, or contribute to the depolarization of nociceptors:

- Proteases released due to cellular damage will break down the extracellular peptide kininogen into **bradykinin**. Bradykinin then binds to a specific receptor on nociceptors and causes their depolarization.
- ATP also causes depolarization of nociceptors when it is released from damaged cells and binds directly to ATP-sensitive K^+ ion channels, thus decreasing their permeability.
- Elevated extracellular K^+ from damaged cells increases the resting membrane potential (RMP) of nociceptors, bringing them closer to threshold and therefore action potential formation.

Factors such as heat, H^+, histamine, serotonin, and prostaglandins will also activate or sensitize nociceptors.

- Heat-sensitive ion channels in nociceptor membranes open at temperatures above 43 degrees C (or 109 degrees F) and cause depolarization.
- H^+ levels build up in the ECF around cells that are undergoing anaerobic metabolism (for example high intensity contracting muscle, or ischemic tissue). This acid can activate **acid-sensitive ion channels (ASICs)** in nociceptors and result in depolarization. The opening of ASICs produces the agonizing dull ache associated with intense exercise.
- Venom from stinging insects can cause the release of histamine from mast cells. Histamine binds to its receptor on nociceptors and contributes to their depolarization. The perception of itch comes from the smallest C fibers responding to histamine.
- Serotonin (5HT) is also released from inflammatory cells including mast cells and contributes to pain transduction similar to histamine.
- Prostaglandins are released from resident immune cells in response to painful stimuli and bind to G-protein coupled receptors expressed on nociceptors. This binding leads to increased cAMP levels that facilitate depolarization. Prostaglandins also reduce the threshold potential required for generating action potentials via phosphorylation of a specific class of TTX-resistant sodium channels.

Other contributors to transduction in nociceptors include the peptides and neurotransmitters known as **calcitonin gene related peptide (CGRP)** and **substance P**. An increase in nociceptor membrane potential induces the release of substance P and CGRP. These substances contribute to neurogenic inflammation and heightened sensitivity to pain. Substance P and CGRP cause vasodilation, release of histamine from mast cells, and increased sensitization of neighboring nociceptors.



Activation of Nociceptors *Image by BYU-I student F18*

It is important to understand the meaning of the terms peripheral sensitization, hyperalgesia, and allodynia. **Peripheral sensitization** is an increased sensitivity to an afferent nerve stimulus. Peripheral sensitization results from the interaction of nociceptors with the "inflammatory soup" of substances released with tissue damage. These substances

include prostaglandins, extracellular protons (i.e. lactic acid buildup), arachidonic acid, bradykinin, histamine, serotonin, nucleotides, and NGF (nerve growth factor). All of these substances can interact with receptors or ion channels of nociceptive fibers to augment their response. **Hyperalgesia** is an abnormally heightened sensitivity to pain. Peripheral sensitization leads to hyperalgesia. It is easier to transmit an action potential for pain if the cells proximal to the nociceptor are damaged. Similar to hyperalgesia is **allodynia**, which is pain due to a stimulus that does not normally provoke pain. To understand the difference between hyperalgesia and allodynia, consider a sunburn. If you pour water on sunburned skin or touch it or even have a rush of air blow across it, you might feel some level of pain that you normally wouldn't have felt. This is allodynia. Hyperalgesia would be if someone slapped the sunburn. The slap might have normally caused some mild pain, but with a sunburn the pain is more exaggerated.

Normally, nociceptors are activated only when a stimulus is strong enough to cause tissue or cell damage. Skin, muscles, and joints that have already been damaged bring about changes in neighboring nociceptors that make them extra sensitive and much easier to activate. This helps protect already damaged tissues from being damaged further. However, chronic pain can become a debilitating issue when allodynia and hyperalgesia continue long after the damaged cells have healed.

Postherpetic neuralgia is an example of peripheral sensitization leading to an exaggerated pain response. The pain occurs because of damage to neurons caused by the herpes zoster virus (chicken pox and shingles virus) and persists even after the rash and blisters are healed. The pain is described as a burning sensation with episodes of shooting or "electric-like" pain. This type of pain is called neuropathic pain. Allodynia and hyperalgesia occur with these damaged neurons as well.

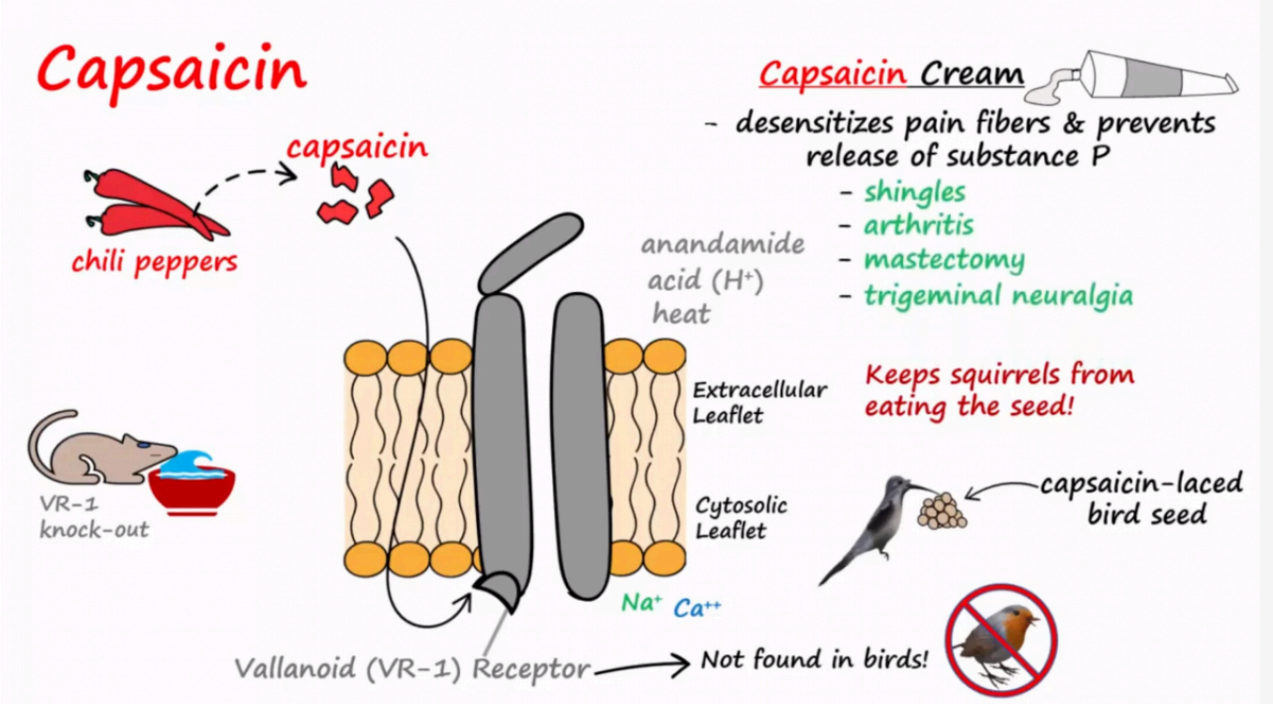
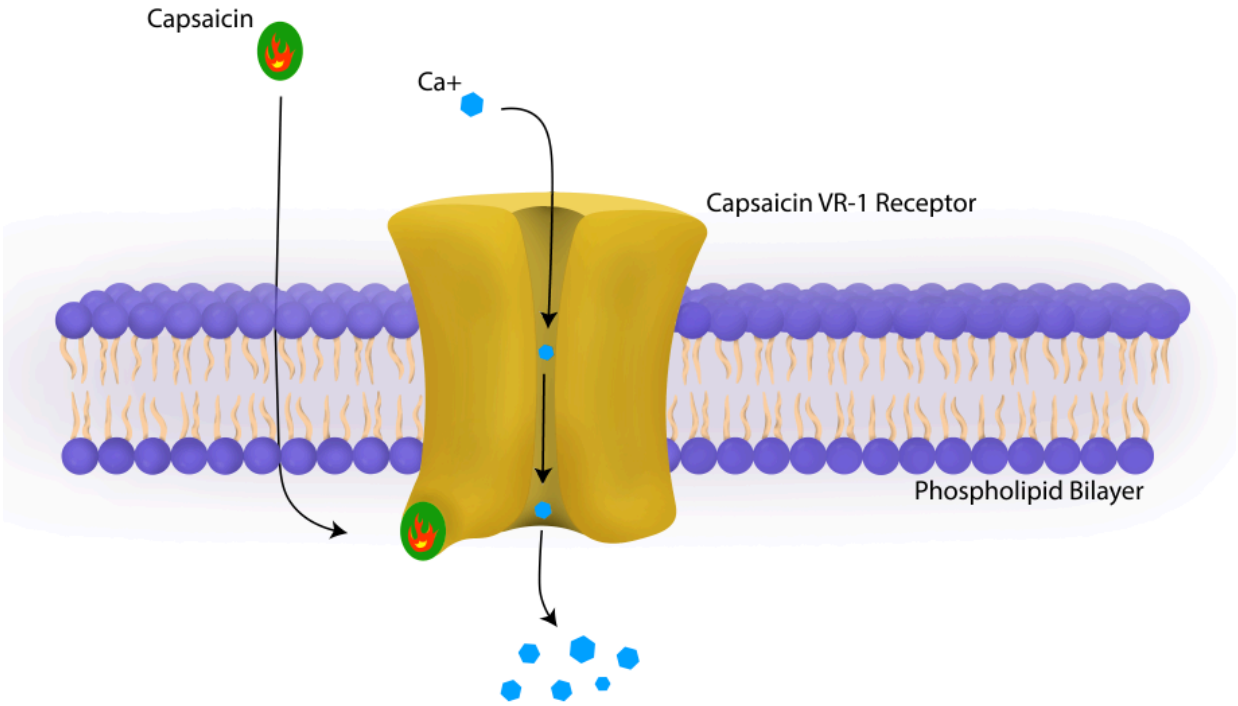


Image by Lanning Baker BYU-Idaho F19

The substance in peppers that gives them their spiciness is known as **capsaicin**. Capsaicin binds to and activates ligand-gated Ca^{2+} and Na^{+} channels known as **vallanoid (VR-1)** receptors. Heat and acid will also open these channels. Interestingly, mice who have had their VR-1 receptors knocked out are able to drink capsaicin solutions. VR-1 receptors have not been found in birds. This finding led to the idea to produce capsaicin-laced bird seed to keep the squirrels from eating the seed. It was also found that repeated application of capsaicin desensitizes pain fibers and prevents substance P from being released from peripheral and central nerves. For this reason, a capsaicin cream (0.075%) has been developed and is used to treat painful conditions such as shingles, arthritis, mastectomy, and neuralgias.



Capsaicin Acting on Receptor *Image by Becky T. BYU-I F19*