11.1.5

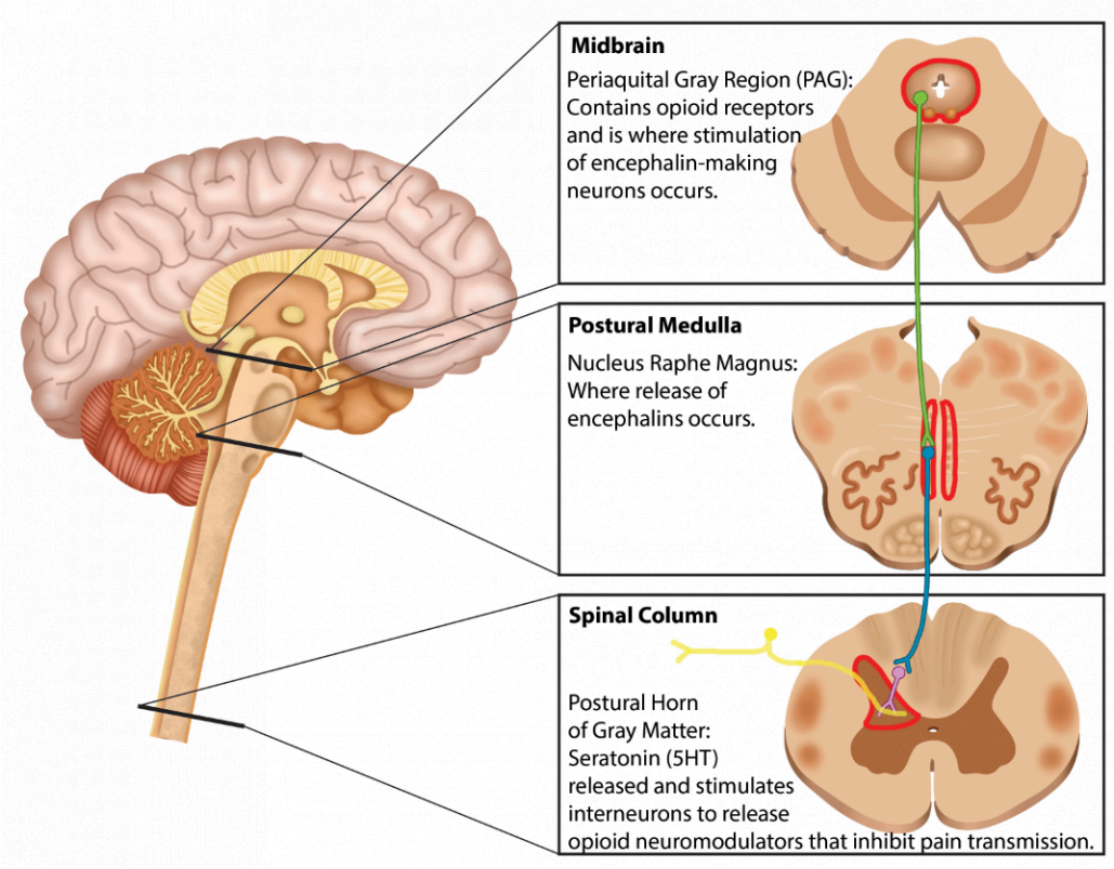
Pain Modulation

Watch this video on Opioid Mechanism of Action

Pain is modulated by central descending pathways. Most of the pathways originate in the midbrain and brainstem, especially the ventromedial medulla and **periaqueductal gray region** or **PAG** (gray matter surrounding the cerebral aqueduct in the midbrain). When these brain areas are stimulated by afferent pathways, they send efferent signals down the dorsal horn of the spinal cord to inhibit or sometimes facilitate incoming pain signals. These modulating descending pathways contribute to the pain-relieving actions of acupuncture, anesthesia, hypnosis, and the placebo effect. They also play a role in the little-to-no pain reported by people injured in intense situations like newly wounded soldiers on the battlefield.

As mentioned, the periaqueductal gray region is in the midbrain. It expresses a lot of opiate receptors which can be triggered by **exogenous opioid pain medications** or **endogenous opioids** synthesized naturally by the body. The three families of endogenous opioid peptides that have been identified are **enkephalins**, **endorphins**, and **dynorphins**. Enkephalins are the most prevalent of the natural opioids while endorphins are the most studied. These endogenous opioids can be released as neurotransmitters, neuromodulators, or neurohormones. They bind to mu, delta, and kappa opioid receptors.

Neurons from many areas of the brain send efferent signals to the PAG and can release opiate-like neurotransmitters that bind to the opiate receptors of efferent neurons in the PAG. Opiates excite these neurons which then leave the PAG to synapse in the **nucleus raphe magnus** of the medulla. The nucleus raphe magnus neurons project to the dorsal horn of the spinal cord where they synapse with an interneuron releasing the stimulatory neurotransmitter serotonin (or 5HT). When stimulated, the interneurons release opioid neuromodulators onto the terminal ends of primary order nociceptors entering the dorsal horn of the spinal cord gray matter inducing an inhibitory postsynaptic potential. This causes inhibition of nociceptive pain transmission onto second order neurons. Understanding the important role of serotonin in the interneurons of the dorsal spinal cord can help us interpret why serotonin reuptake inhibitors can sometimes help some individuals with chronic pain.



Pain Modulation by Central Descending Pathway *Image by Becky T. BYU-Idaho W20*

The images below is another depiction of the pain modulation mechanism. When interneurons in the dorsal horn receive excitatory signals (serotonin) from efferent neurons of the medulla, they release enkephalins or endorphins onto the axon terminal of the primary nociceptive afferent neurons. Endogenous opioids like enkephalin or exogenous opioids such as morphine bind to G-protein opioid receptors (e.g., mu receptors) expressed on these axon terminals and cause closure of voltage-gated calcium channels and thus reduced intracellular Ca^{2+} at the axon terminal. Since Ca^{2+} is required for exocytosis, this reduction results in decreased release of substance P, glutamate, and norepinephrine, all of which are excitatory to second order neurons. Consequently, there is decreased action potential frequency in secondary neurons and decreased pain signals sent to the brain. Opioids also bind to mu receptors expressed on secondary neurons and open K^+ channels which then cause hyperpolarization. This also decreases pain transmission to higher brain areas.

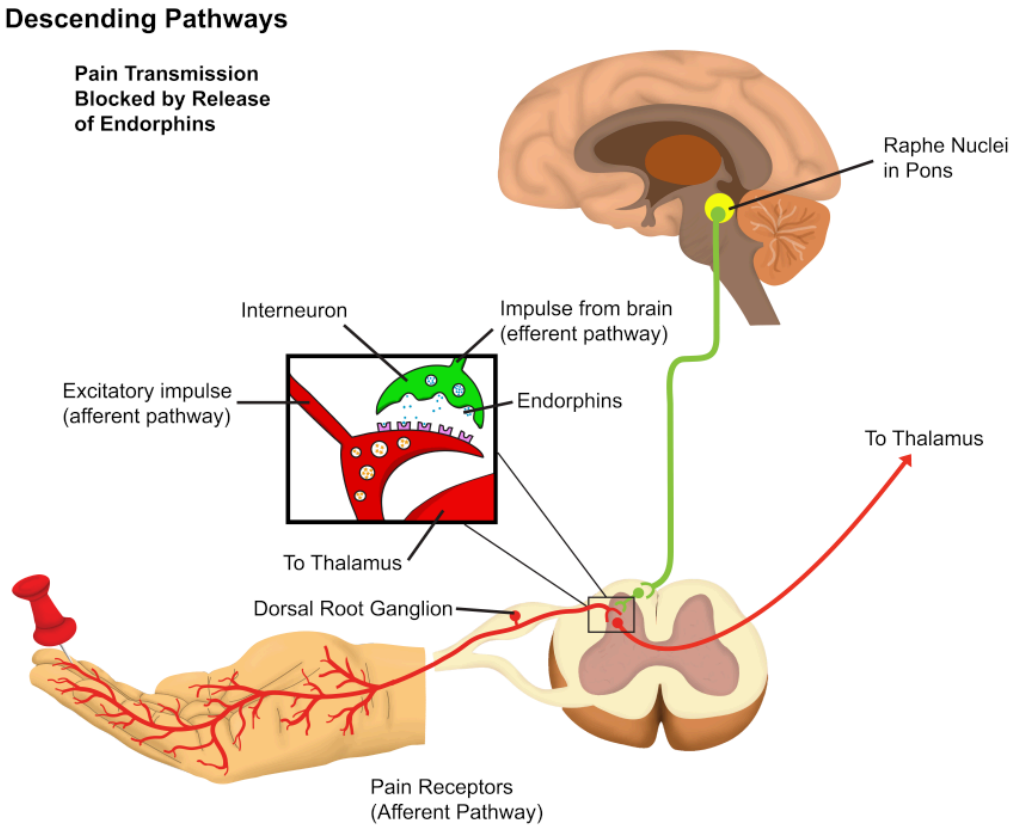
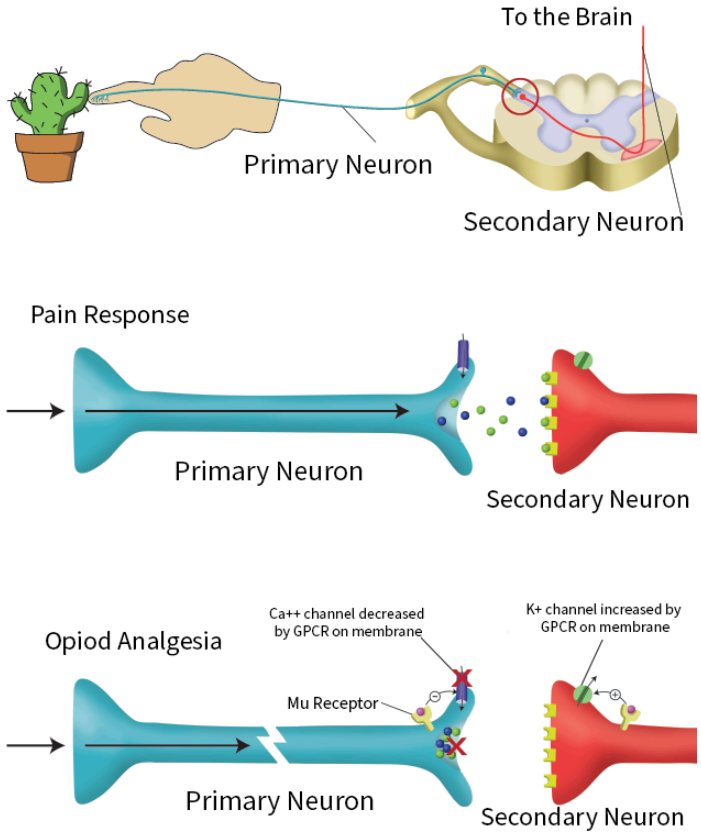


Image by Becky T. BYU-Idaho W20



Uninhibited Pain Response vs Modified Pain Response *Image by Becky T. BYU-Idaho W20*

There is also a modulatory pathway called the **diffuse noxious inhibitory controls (DNIC)** that describes how afferent pain signals coming from different areas of the body can be inhibited by one another. For example, if you have both chronic hip and chronic knee pain usually one will predominate at any given time in what is known as perceptual dominance. DNIC also describes how stimuli like pressure, heat, and electrical stimulation can reduce pain. DNIC is believed to originate when pain is being interpreted in the higher cortical centers of the brain. The brain then uses the PAG and nucleus raphe magnus of the central nervous system to selectively inhibit ascending pain signals from the spinal cord.