The Pain Pathway

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Transduction:

How a mechanical stimulus in the tissues becomes an electrical signal in the nerves.

Transduction occurs when an insult to our tissues, such as a nail in the foot, a surgeon's scalpel, or an infectious process, is converted into an action potential in a primary afferent neuron. When there is potential or actual tissue damage, substances are produced such as prostaglandins. These inflammatory mediators either directly stimulate the nociceptors (pain receptors) or sensitize them to more readily accept a noxious stimulus. Furthermore, when actual tissue damage occurs; potassium, ATP and hydrogen ions from the cells directly stimulate the nociceptors. Nociceptors can be external, found in the skin with varying density based on location (higher concentrations in the fingertips, hands and face for example, and lower concentrations over the torso). They can also be internal within muscles, joints, bones and internal organs. There are specific receptors for different stimuli, such as Piezo receptors for mechanical stimuli, Transient Receptor Potential (TRP) receptors

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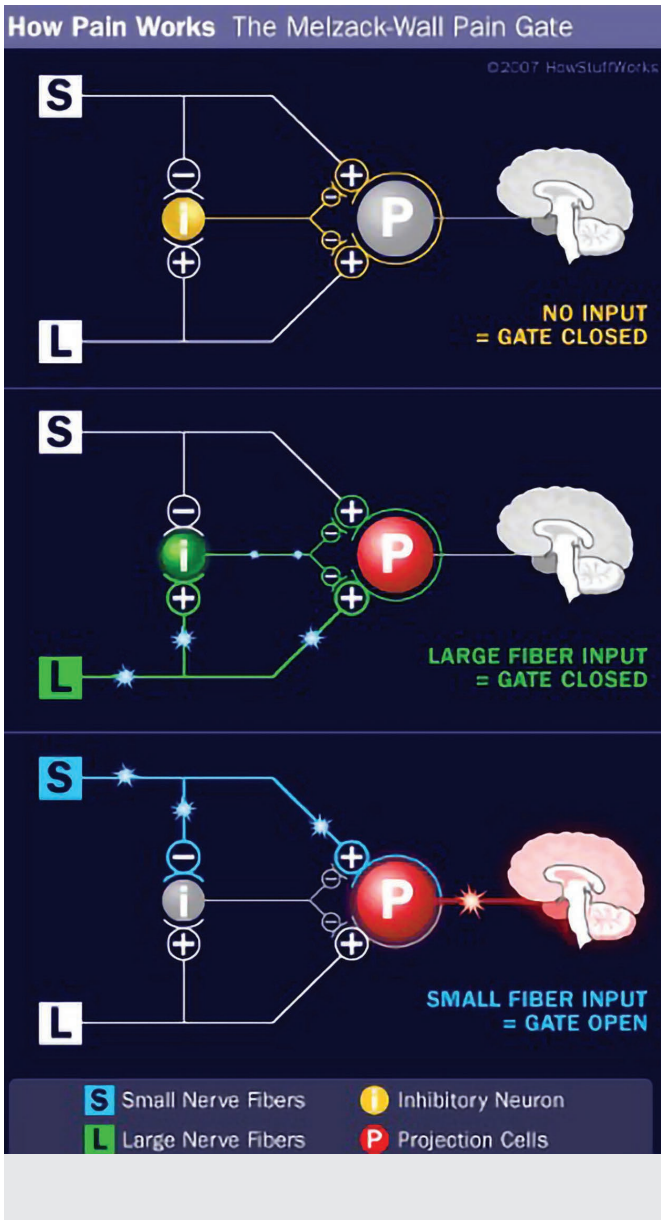
for extremes in temperature, P2X purinergic receptors for ATP, and Acid Sensing Ion Channels (ASICs) for hydrogen ions; or polymodal nociceptors that can be activated by multiple types of stimuli. The primary afferent nerves that contain these nociceptors are either A delta fibers, which are larger and myelinated and responsible for acute sharp pain; or C fibers which are small and unmyelinated and responsible for the slower in onset, dull, lingering, achy pain. Stimulation of the nociceptors open voltage gated ion channels allowing calcium and sodium ions to pass into the cytoplasm raising the resting membrane potential (around -65 mV) downstream within the cytoplasm until the threshold potential (around -40 mV) is achieved leading to action potential formation.

Transmission:

The propagation of the electrical signal from the nerves to the brain.

The signal as an action potential travels up the primary afferent axon as it is propagated by the continued reaching of threshold potential due to the opening of voltage gated Na+ channels upstream (saltatory conduction). The primary afferent neurons have their cell bodies in the dorsal root ganglion. The primary afferent neurons synapse with secondary efferent neurons in the dorsal horn of the spinal cord (Rexed Laminae I, II, or V). The action potential generated in the secondary afferent neuron then crosses over to the other side of the spinal cord (decussation) within a few levels of the stimulus and ascends within the spinothalamic tract primarily. The secondary afferent neurons synapse with tertiary afferent neurons in the thalamus (the relay station between the brain and the rest of the nervous system), and the action potential generated in the tertiary afferent neuron then travels to the somatosensory cortex primarily. Other cortical areas receiving input include the anterior cingulate cortex, the insular cortex, the ventrolateral orbital cortex and the motor cortex. Together, they localize the pain; and orchestrate an emotional, autonomic and motor response. The neurotransmitters commonly involved with the ascending pathway are glutamate (primary) and substance P (secondary) within the spinal cord and others including GABA, norepinephrine, serotonin, dopamine and endogenous opioids within the cortexes. Within the dorsal horn, primary afferent neurons from the viscera (heart, etc.) synapse with the secondary afferent neurons as well. Since the visceral primary afferents are usually "silent," their action potentials are frequently interpreted by the cortexes as signals coming from other "commonly" active primary afferent neurons within the same part of the body. This leads to "referred pain."



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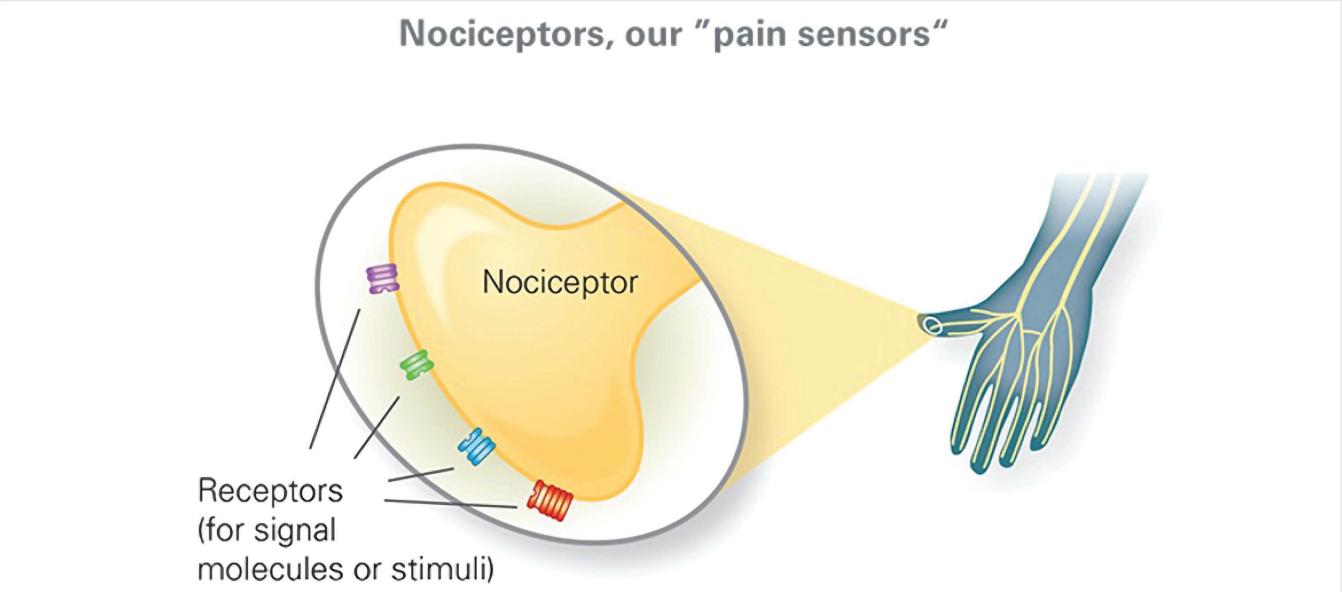

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Modulation:

Altering or blocking the pain signal as it travels through the spinal cord, medulla, pons and midbrain to the cerebral cortex.

Modulation is the way the brain (descending pathway) alters the intensity of the signal traveling up the ascending pathway depending on the circumstance surrounding the initiation of the nociceptive signal. For example, if you sprain your ankle while running from a lion, it would be best to be able to ignore the pain and keep running. How does this occur? Signals originating in the cerebral cortex as well as the spinothalamic tract pass through the periaqueductal grey matter in the midbrain. A signal as an action potential is generated there which then travels to the pons (locus coeruleus) and medulla (locus raphe magnus). From there, another action potential is generated that travels down the spinal cord through the dorsolateral tract and terminates upon an interneuron near the synapse between the primary and secondary afferent neurons. At that level, inhibitory signals are sent by the interneuron which alter or inhibit (modulate) the pain signals traveling to the brain by decreasing the release of glutamate and substance P from the presynaptic terminals of the primary afferent axons and reducing the postsynaptic excitatory signals originating in the postsynaptic terminal of the secondary afferent axons. Many neurotransmitters are involved here as well such as norepinephrine, serotonin, and primarily endogenous opioids (enkephalins).

This is part of the "Gate Theory of Melzack and Wall". This theory also helps to explain why TENS units work, or rubbing the painful area soothes the pain. By providing other non-painful signals via non-nociceptive afferent neurons (the much larger, myelinated A beta fibers), the site of the synapse between the primary and secondary afferent neurons become "busy" with incoming signals which create a "traffic jam," slowing or blocking the action potential triggered by the activation of the nociceptors at the site of injury.

Perception:

How the brain interprets the signal and produces "pain"

Perception occurs when the nociceptive signal is received by the involved cortexes within the brain. The individual becomes aware of the insult, and an emotional and motor response is initiated. It has reached consciousness and now moves from nociception to pain.

Inflammation / Inflammatory Pain

When tissues are damaged, inflammatory mediators are released causing arteriole dilation which then causes the area to become red and hot (rubor and calor). Furthermore, the endothelium of capillaries and venioles contract opening spaces for fluid and cells to escape into the "inflamed" area causing swelling (tumor). These same mediators then cause pain (dolor). The nociceptors can eventually become "sensitized" to the signals they receive causing allodynia (pain from non-painful stimuli), and hyperalgesia (exaggerated pain from a painful stimulus).

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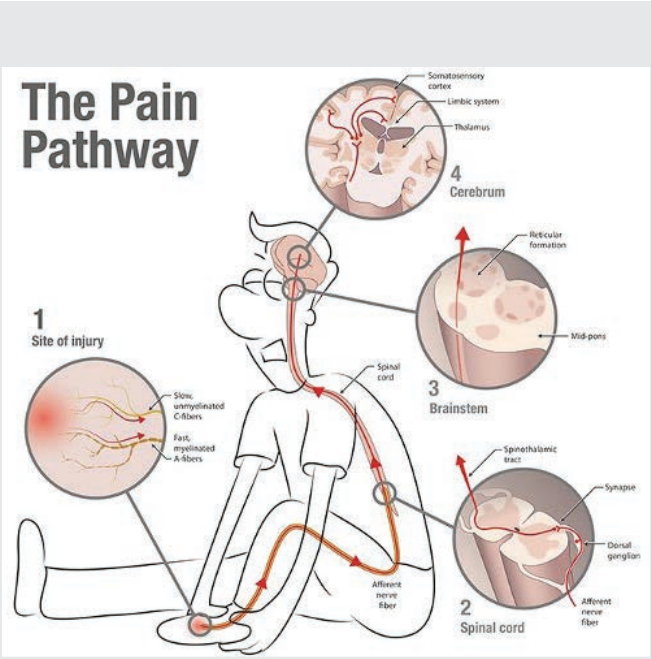

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Arachidonic acid is freed from intracellular phospholipids when tissues are damaged or there is a threat of tissue damage. Other substances are then formed from arachidonic acid, most notably, prostaglandins which are produced from its breakdown by cyclooxygenase 2 (COX 2), which is produced in high concentrations during inflammation. The prostaglandins are important to perpetuate the inflammatory process (PGI2 or prostacyclin), and trigger and sensitize nociceptors (PGE2).

How do the inflammatory mediators sensitize the nociceptors?

By mediators such as PGE2 binding to the nociceptors on A delta and C fibers (creating cyclic AMP from ATP), and by altering voltage gated sodium channels, the depolarization threshold is lowered, therefore, non-painful stimuli cause a nociceptive action potential to be produced (allodynia) and painful stimuli trigger more action potentials (hyperalgesia). Furthermore, other receptors such as TRPV1 which is sensitive to high temperatures, will be altered to fire at lower temperature levels, therefore, creating temperature dependent allodynia. The C fiber nociceptors can be altered to the point that the threshold potential is at resting potential, therefore, action potentials are continuously produced creating ongoing unrelenting pain during inflammation (tonic firing).

How is bradykinin formed during inflammation?

Hageman factor (factor XII), high molecular weight (HMW) kininogen and prekallikrein are produced in the liver and released into the bloodstream. When they pass into the inflammatory exudate, factor XII is converted to activated factor XII (factor XII A) when it interacts with substances such as collagen. Factor XII A converts prekallikrein to kallikrein. Kallikrein in turn converts HMW (high molecular weight) kininogen to bradykinin. Bradykinin, like PGE2, is important in the inflammatory process because it too directly stimulates and sensitizes peripheral nociceptors. Furthermore, as with PGE2, it sensitizes the TRPV1 receptor creating thermal allodynia and hyperalgesia.

Neuropathic Pain Mechanism

Neuropathic pain is distinguished from nociceptive pain where the pain begins with signaling from nonneural tissues. Neuropathic pain originates from a lesion within the nervous system. The nerve injury leading to the pain directly involves the nociceptive pathways and alters the way pain is processed. This usually causes increased pain signal transmission, to the extent that innocuous stimuli may cause a sensation of pain. The mechanisms that lead to the development of neuropathic pain are more complex than nociceptive pain. Psychological processes are also commonly involved with neuropathic pain. Factors including stress, fear and anxiety commonly play a large part in neuropathic pain.

Conclusion

As we strive to utilize a diverse group of pharmacologic and non-pharmacologic pain management modalities with multiple mechanisms of action, a better understanding of the nociceptive process and the actual mechanisms of action of the modalities employed is warranted to tailor a regimen for each patient and situation, therefore maximizing effect and minimizing complications.

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Continuing Education Quiz

To test your knowledge on this issue's article, provide correct answers to the following questions on the form below. Follow the instructions carefully.

1. Which is not part of the pain pathway?
a) Transmission
b) Transduction
c) Termination
d) Modulation

2. Which does not cause stimulation of a nociceptor?
a) Extreme heat
b) Nitrogen
c) Potassium
d) ATP

3. The resting membrane potential inside a neuron is positive.
a) True
b) False

4. Neurotransmitters involved with pain include:
a) Oxygen
b) Bradykinin
c) PGE2
d) Glutamate

5. Visceral afferents are usually silent.
a) True
b) False

6. Modulation involves all but which one?
a) Pons
b) Spinal cord
c) Peripheral nerve
d) Spinal cord

7. Which is the correct order?
a) Hageman factor, factor XII A, prekallikrein, kallikrein, HMW kininogen, bradykinin
b) Hageman factor, factor XII A, prekallikrein, bradykinin, kallikrein, HMW kininogen
c) Factor XII A, Hageman factor, prekallikrein, bradykinin, kallikrein, HMW kininogen
d) Hageman factor, factor XII A, HMW kininogen, prekallikrein, bradykinin, kallikrein

8. The sensation of pain occurs at the site of injury.
a) True
b) False

9. Neuropathic pain originates where?
a) Site of injury
b) Neuron involved in the pain pathway
c) Neuron outside the pain pathway
d) None of the above

10. Only an opioid agonist can treat pain.
a) True
b) False

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Quiz 1 of 2

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