The Pathophysiology of Nociception and Pain

Objectives:
1. Understand the different classes of nociceptors and their association with slow and fast pain.
2. Describe the different peripheral mechanisms that activate nociceptors and the pathological changes that occur during inflammation.
3. Understand sensitization, the mechanisms that produce it and its significance for patients.
4. Understand the physiological and pharmacological mechanisms that modulate transmission of pain signals involving descending pathways from the brainstem.

I. Overview:
1. Pain receptor types are simple. However, peripheral mechanisms for initiation of pain are diverse and extremely important in understanding pain. This requires an understanding of the pathology of the inflammatory response. How many ways can you hurt!!
2. Pain activity follows parallel pathways to the cortex that differ in speed (slow vs fast), mechanism of activation, and destination.
3. Unlike touch, built-in anatomical, physiological and pharmacological mechanisms can shut-off/decrease pain sensation. This involves cortical, brainstem, and spinal cord levels.

II. First Order Neurons for Pain (nociceptors)
• The peripheral receptors for pain are naked nerve endings of the 1° neuron.
• Nociceptors contain specialized ion channels that are activated by noxious stimuli. These fall into 3 categories based on stimuli:
  • Mechanical – excess deformation
  • Thermal – temperature > 45°C or < 5°C activate TRPV1, TRPV2 channels; some also activated by capsaicin (the chemical in hot peppers that makes them burn).
  • Polymodal – noxious mechanical, thermal stimuli, and chemicals; also activated by capsaicin.

• Similar transduction events occur in nociceptors as for tactile receptors. Ion channel opening in nociceptor terminals causes depolarization (graded generator potential) that evokes action potentials if the depolarization reaches threshold. Also, noxious stimulus information is encoded by action potential frequency for stimulus intensity and duration of activity for period of stimulation on the body.
• Receptive Fields of nociceptors, as well as 2° and 3 neurons, are larger (more convergence!) than those for tactile receptors. Apparently, it is more important to know that a stimulus has caused pain than to precisely localize it!
• What activates nociceptors?
A diversity of peripheral mechanisms activate nociceptors (how many ways can you hurt):

1. Noxious stimuli directly activate specific ion channels on nociceptor terminals
   - Noxious mechanical, thermal, and chemical stimuli activate specific ion channels on nociceptor terminals in the skin.

2. Damaged tissue releases inflammatory molecules that activate nociceptor terminals
   - Some molecules such as K⁺, ATP, H⁺ are released from damaged cells into the extracellular environment. Some molecules such as serotonin, histamine, NGF are secreted by cells upon stimulation. Some molecules such as bradykinin and prostaglandins (PGE₂, PGD₂) are enzymatic byproducts or receptor-stimulated products.

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Sources</th>
<th>Effects</th>
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<tr>
<td>K⁺, ATP, H⁺</td>
<td>Damaged cells</td>
<td>Vasodilation, increased vascular permeability, pain (increased nociceptor excitability)</td>
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<tr>
<td>Serotonin, Histamine</td>
<td>Platelets, mast cell</td>
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<tr>
<td>NGF</td>
<td>Mast cells, Fibroblasts</td>
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<td>Bradykinin</td>
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<td>Prostaglandins</td>
<td>Mast cells</td>
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<td>Substance P, Calcitonin gene-related peptide (CGRP)</td>
<td>Nerve terminals</td>
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- Nociceptor terminals contain receptors for H⁺, ATP, serotonin, histamine, bradykinin, prostaglandin, NGF, and other molecules. These molecules have 2 effects:
  1. They depolarize nociceptor terminals by directly activating ion channels/receptors (histamine, serotonin, bradykinin, ATP, H⁺, K⁺).
2. They lower the threshold for nociceptor action potentials by phosphorylating ion channels in the terminal (serotonin, bradykinin, prostaglandin, NGF).

- These signals influence polymodal nociceptors of C fibers.
- Bradykinin is produced by enzymatic cleavage of HMW kininogen in plasma.
- Prostaglandin synthesis is initiated by the binding of molecules such as bradykinin to membrane receptors. This activates phospholipases that cleave phospholipids to produce arachidonic acid, which is enzymatically modified to prostaglandins in mast cells. An important enzyme in this sequence is cyclooxygenase.

3, 4. Peripheral nociceptor terminals release inflammatory molecules that affect blood vessels and mast cells (*neurogenic inflammation* – also Dr Heffner; Dr Sheehan-Asthma)

- Yes, dendrites can release molecules in addition to receiving signals! Electrical activity in one branch of a peripheral nociceptor terminal evokes release of molecules (Substance P, CGRP (tachykinins), ATP) from other branches as depolarization spreads electrotonically. Thus, nociceptor terminals are both sensory/receptive and secretory. This is called the *axon reflex*.
  - This is mediated by C fiber nociceptors.
  - Substance P and CGRP are neuropeptides, but here they have potent effects on blood vessels and mast cells.

- Steps 3, 4, and 2 contribute to the *inflammatory response* of damaged tissue. The initial release of Substance P and CGRP causes release of bradykinin, serotonin and histamine from blood vessels, platelets, and mast cells in the region. These molecules have 3 important effects:
  1. vasodilation ➔ redness
  2. increased vascular permeability ➔ swelling
  3. pain – due to increased nociceptor excitability

### III. Inflammatory Response leads to Sensitization

- The inflammatory response involving vasodilation, increased vascular permeability and pain are part of the healing process. The goal is to increase blood flow to the injured area and to prevent further damage by making the area painful to ensure its protection. The inflammation that occurs contributes directly to increased sensitivity to stimuli (*Sensitization*) that indicates the complexity of pain and its treatment. *This is really important for understanding clinical pain syndromes.*
- **Sensitization** is characterized by:
  - generation of pain by stimuli that previously were not painful—*allodynia*. For example, a light touch to sunburned skin evokes pain. Typically, the sensitive area extends beyond the injured tissue.
  - Patients perceive an increased sensitivity to pain; noxious stimuli evoke significantly more intense pain than normal – *hyperalgesia*.
- Sensitization has both peripheral and central causes
  - Generally, sensitization is due to increased excitability of nociceptors, but the specific reasons that cause it are different in the periphery vs CNS.
• **Peripheral Sensitization**
  - This is due to changes at nociceptor terminals in the skin, which become more sensitive as a result of the inflammatory response.
  - The molecules released into the injured area can:
    1. cause depolarization by binding to receptors on nociceptor terminals (e.g., histamine, bradykinin, ATP, H+)
    2. cause receptor-mediated changes in nociceptor channel phosphorylation that facilitate channel activity (e.g., serotonin, bradykinin, prostaglandin, NGF)
  - These changes make nociceptors more sensitive and responsive by decreasing the threshold for evoking action potentials, increasing the frequency of action potential activity in response to noxious stimuli, or inducing spontaneous activity in nociceptors, which normally are quiescent.
  - Peripheral sensitization can be reduced by application of COX inhibitors, which reduce prostaglandin synthesis and thus their effects on blood vessels and channel phosphorylation.

• **Central Sensitization**
  - Stimuli that were normally subthreshold in the spinal cord/CNS will evoke activity after central sensitization. It is caused by increased excitability of 2° neurons and interneurons in the dorsal horn.
  - Physiological causes:
    - enhanced efficacy of postsynaptic potentials in dorsal horn neurons
    - decreased threshold for evoking action potentials in dorsal horn neurons
  - The reason for these physiological changes is not fully understood. However, they involve the repeated or sustained activity of 1° nociceptors, which induces changes at their synapses in the dorsal horn. Nociceptors release both Substance P and Glutamate simultaneously from their central terminals. Substance P has long-lasting excitatory effects on activity of postsynaptic neurons. Glutamate and Substance P released together produce an increased depolarization (via Substance P receptors) that activates NMDA receptors on spinothalamic neurons to cause Ca\(^{2+}\) influx. The increased Ca\(^{2+}\) activates numerous molecules including phospholipase A\(_2\), which can lead to prostaglandin synthesis with subsequent effects on channel activity and synaptic efficacy.
Nociceptor ending in body

1. molecules bind to their receptors causing depolarization
2. molecules bind to other receptors and modulate their activity
3/4. bradykinin, prostaglandin, histamine binding causes phosphorylation of channels and receptors
5. secreted molecules bind to receptors, become internalized, are transported to nucleus where they affect gene expression (⇑ expression of Na channels).

\( \text{TNF} \)

\( \text{NGF} \)

\( \text{PDE} \)

\( \text{ATP} \)

\( \text{Bradykinin} \)

\( \text{Histamine} \)

\( \text{5-HT} \)

\( \text{H}^+ \)

\( \text{microtubules} \)

\( \text{Na}^+ \)

\( \text{Na}^+ \)

\( \text{P} \)

\( \text{P} \)

\( \text{P~} \)

\( \text{P~} \)

\( \text{1} \)

\( \text{2} \)

\( \text{3} \)

\( \text{4} \)

\( \text{5} \)

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\( \text{= ionotropic receptor/ channel} \)

\( \text{= metabotropic receptor} \)

\( \text{~P = phosphorylation} \)
• Clinical conditions caused by central sensitization:
  • Windup – An acute condition in which repeated nociceptor activation causes a progressive increase in action potential frequency of spinothalamic neurons. A constant intensity stimulus is perceived as more intense because of this effect.
  • Allodynia – Light touch to an inflamed area of the skin causes pain. Why? Due to some convergence in pathways, tactile mechanoreceptor (1°) axons make synaptic connections with spinothalamic neurons in the dorsal horn. Normally, these connections are not sufficient to evoke action potentials in the spinothalamic neurons. However, after central sensitization, which lowers the threshold for activity, tactile stimuli can evoke action potentials in the pain fibers.

• Clinical Implications of Sensitization
  • Sensitization usually declines as tissue heals. However, with nerve injury (trauma, diabetes, AIDS, shingles, MS, stroke), sensitization is often sustained, resulting in neuropathic pain. Pain arises without nociceptor activity or from mild (non-noxious) stimuli.
  • Neuropathic pain caused by nerve injury involves central sensitization, a prolonged increase in excitability of central neurons. It includes features of allodynia and hyperalgesia and it cannot be reduced by decreasing activity in 1° nociceptors.
  • Growth factors like NGF released during inflammation are transported to the DRG cell bodies where they cause long term changes in gene expression that alter levels of neuropeptides, ion channels, and receptors. This results in long-lasting pain syndromes.
  • Postsurgical pain is the single most common reason for patient readmission following outpatient surgery. It is now recognized that much of this pain is due to sensitization. Current strategies to decrease sensitization involve the use of local anesthetics (in addition to sedation) during surgery to prevent the increased activity in nociceptors that would induce synaptic changes in the dorsal horn. In addition, NSAIDs appear to block both peripheral and central components of sensitization by inhibiting prostaglandin production in peripheral tissues and in the dorsal horn. (reading accompanying article)

IV. Intrinsic Circuits Modulate Pain
  • Clinical evidence initially indicated that pain could be modulated by stimulation of certain brainstem regions and by drugs such as morphine. We now know these effects are due to intrinsic CNS pathways that modulate ALS activity.
  • Where are these regions:
    • Three locations in the brainstem reticular formation act as relays that ultimately influence the transmission of nociceptive signals in the spinal cord:
      1. Midbrain – Periaqueductal grey
      2. Dorsal lateral Pons – locus ceruleus
      3. Medulla – raphe and other nuclei of the reticular formation

![Diagram of intrinsic circuits modulating pain](image)
• **How do these regions influence pain**
  - These brainstem regions send axons (direct and indirect routes) to the spinal cord where they modulate the transmission of nociceptive signals from 1° to 2° nociceptive neurons.
  - Two important neurotransmitters used by the descending brainstem axons are serotonin from raphe nuclei in the medulla and norepinephrine from locus ceruleus neurons in pons. These transmitters excite opiate interneurons in the spinal cord to inhibit nociceptive signals. Opiate interneurons 1) presynaptically inhibit neurotransmitter release from 1° nociceptors and to 2) postsynaptically inhibit spinothalamic neurons.
  - The CNS naturally uses these pathways to modulate pain. The PAG is activated by the hypothalamus and cortex in response to stressful and emotional situations.
• Pain modulation is even more complicated!
  • The above information is an example of one type of interaction for pain modulation.
  • An appreciation for the complexity of interactions in the dorsal horn is important for an understanding of how pain is treated pharmacologically.
  • Descending brainstem axons have both inhibitory and excitatory effects on nociceptive signals. This influences how nociceptive signals are transmitted (increased or decreased sensitivity) in relation to different behavioral states and timing of injury.
  • These axons and axons of interneurons use a large variety of neurotransmitters. In addition, dorsal horn neurons use a variety of neurotransmitter receptor types, including multiple members within each family. This determine the physiological effects of each transmitter at each synapse.
  • In the dorsal horn, descending brainstem axons synapse on interneurons, terminals of 1° neurons and dendrites of 2° neurons.
  • These different possibilities make it very difficult to understand and develop pharmacological strategies to treat pain.

V. Clinical Treatment of Pain – Alternatives
• Most strategies seek to reduce pain by stopping the transmission of nociceptive signals in the spinal cord. What procedures can accomplish this:
  A. Electrical stimulation:
    i. Stimulation of descending brainstem axons arising in the PAG causes a long lasting reduction in pain.
    ii. 1° tactile axons make inhibitory connections onto spinothalamic neurons!
      • (A) Stimulation of the dorsal column axons sends action potentials back into the dorsal horn to inhibit nociceptors.
      • (B) Transcutaneous Electrical Nerve Stimulation (TENS) – a patch electrode is placed on the skin over a peripheral nerve associated with an injured area. The stimulus is adjusted to excite large diameter (tactile) 1° axons, which will inhibit nociceptive transmission in the spinal cord. Similarly, rubbing a nearby area of skin soon after a wound or sting can reduce the pain for the same reason.
      • this mechanism partially explains how acupuncture reduces pain.
B. Pharmacological treatments – multifaceted approach

i. Decrease inflammation to reduce peripheral sensitization – NSAIDS

ii. Increase inhibition of the pain pathway:

• **Opiates** – All brainstem and dorsal horn areas involved in the modulation of pain utilize opiate neuropeptides. Opiates have long-lasting inhibitory effects on pain transmission.

• **Norepinephrine** – Descending NA axons arise from pontine locus ceruleus. These axons inhibit 1° nociceptive terminals in spinal cord via α2-ARs and excite inhibitory interneurons via α1-ARs. Thus, α2 agonists and α1 agonists both can reduce pain.

• **Antidepressants** – 5-HT and NE reuptake inhibitors potentiate the effects of serotonin, a pain modulator in the spinal cord.

• **Antiseizure drugs** – increase GABA activity; (they also decrease Na channel activity)

iii. **Glutamate** antagonists – Glutamate is a transmitter for 1° pain fibers. Excessive stimulation activates NMDA receptors, leading to central sensitization. However, NMDAR antagonists cannot be used because they would cause severe cognitive deficits.

iv. **Capsaicin** creams – Capsaicin binds to 1° peripheral terminals of heat and polymodal nociceptors. Continued presence of capsaicin can desensitize these receptors to prevent their activation by inflammatory molecules in the injured area.

C. Surgical Treatment

• Tractomy or Chordotomy – the lateral location of the ALS in the spinal cord makes it possible to sever these axons without damaging deeper areas. This results in immediate cessation of pain. However, this is transient and pain often returns after several months probably for several reasons involving sensitization at higher levels induced by the injury.

D. Alternative Med – Acupuncture can be an effective treatment to reduce pain. Imaging studies have shown that it can reduce activity of areas such as anterior cingulate gyrus involved in the emotional component of pain.

E. Placebo effect – If you think it, you just might feel it! The psychological expectation of an effect is enough stimulus to activate pain modulatory pathways. (see articles on website)

VI. Molecular/Genetic Aspects of Pain

• Channelopathies are mutations in ion channels that result in neurological syndromes. Mutations can result in Loss of Function (LOF) or Gain of Function (GOF) disorders. A specific isoform of Na channels is used by nociceptors (Aδ, C fibers) to conduct action potentials. In LOF disorders, this Na channel isoform cannot be activated (nonfunctional) and causes inability to feel pain. In GOF disorders, this Na channel isoform is easier to activate (lower threshold). In these patients, warm stimuli cause burning pain. In other GOF mutations, Na inactivation is decreased, causing a paroxysmal pain disorder.

• A recent Nature publication showed that in one family of Pakastani street performers there was a LOF mutation in the nociceptor Na channel, preventing the perception of painful stimuli.
Synthetic Pathways Reminder

- **Bradykinin**
  - Synthesized in plasma from enzymatic cleavage of HMW Kininogen

- **Prostaglandins**
  - Receptor-mediated synthesis involving cleavage of membrane phospholipid