Definition of Pain

Pain: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

Pain is a complex phenomenon resulting from activation of nociceptors (sensory neurons that respond to tissue damage) and transmitted to the brain. The brain interprets the pain signal in the context of the individual’s past experiences, emotional state, and current situation. Pain can be acute, persisting for a short time, or chronic, lasting for months or years. Chronic pain often involves a cycle of pain, disability, and suffering, and can be difficult to manage.

Pain is a protective mechanism that signals tissue damage and prompts the body to take action. However, chronic pain can be debilitating and may lead to a range of physical and psychological problems. Pain management involves a multidisciplinary approach that includes medication, physical therapy, behavioral interventions, and lifestyle changes.
Superficial Pain

Superficial pain is a "call to action." The motor response to superficial pain includes withdrawal from the noxious stimulus, orienting to a potentially noxious stimulus, and escape from the noxious stimulus.

Deep (chronic) pain is inescapable. We respond by becoming immobile, withdrawing from social interaction, and stopping eating. Cardiac output decreases, resources shift to the immune system.

Superficial Pain vs. Deep Pain

<table>
<thead>
<tr>
<th>Superficial Pain</th>
<th>Deep Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>Orientation</td>
</tr>
<tr>
<td>Increase cardiac output</td>
<td>Decrease heart rate</td>
</tr>
<tr>
<td>Withdraw or escape</td>
<td>Decrease blood flow to skeletal muscle</td>
</tr>
<tr>
<td>Increase blood flow to skeletal muscle</td>
<td>Decrease blood flow to digestive tract</td>
</tr>
<tr>
<td>Social withdrawal</td>
<td>Shut down digestion</td>
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</tbody>
</table>

Receptor Types

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Fiber Group</th>
<th>Fiber Type</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptors</td>
<td>Aδ, C</td>
<td>Meissner's</td>
<td>Tactile</td>
</tr>
<tr>
<td>Motor fibers</td>
<td>Aδ, C</td>
<td>Pacinian</td>
<td>Proprioceptive</td>
</tr>
<tr>
<td>Free nerve endings</td>
<td>Aδ, C</td>
<td>Meissner's</td>
<td>Temperature</td>
</tr>
<tr>
<td>Cold receptors</td>
<td>C</td>
<td>Cold receptors</td>
<td>Cold</td>
</tr>
<tr>
<td>Warm receptors</td>
<td>Aδ, C</td>
<td>Warm receptors</td>
<td>Warm</td>
</tr>
<tr>
<td>Touch receptors</td>
<td>Aδ, C</td>
<td>Warm receptors</td>
<td>Mechanical</td>
</tr>
<tr>
<td>Pain receptors</td>
<td>Aδ, C</td>
<td>Warm receptors</td>
<td>Pain</td>
</tr>
<tr>
<td>Free nerve endings</td>
<td>Aδ, C</td>
<td>Warm receptors</td>
<td>Free nerve</td>
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Free Nerve Endings (Pain Receptors)
Nociceptors respond only to noxious, high intensity stimuli. At the peripheral (distal) end of the nociceptor, noxious stimuli generate currents that, above a given threshold, send signals along the nerve fiber to the spinal cord.

- The "specificity" (whether it responds to thermal, chemical or mechanical features of the environment) of a nociceptor is determined by which ion channels it expresses at its peripheral end.
- Dozens of different types of nociceptor ion channels have so far been identified, and their exact nature & functions are still being determined.

Receptor Types

Pathways of Nociception

- The spinal tracts: A. The peripheral processes of dorsal root ganglion cells end as receptors sensing pain, temperature, and complex (chemical) sensations.
- B. The central processes of these dorsal root ganglion cells synapse with the neurons of the spinal cord's propriospinal pathway.
- C. The propriospinal pathway crosses the spinal cord's midline, making the contralateral white matter a site of normal sensory integration.
- D. The axons of third-order neurons project to the primary somatosensory cortex (S1).
Nociceptive Input

STT

Return to Objectives

Dorsal Column & Spinothalamic Tracts

(Dorsal Columns)

STT

f. gracilis

f. cuneatus

Nociceptive input

dorsal spinocerebellar tract

ventral spinocerebellar tract

spinothalamic tract

Primary differences between DC and ALS pathways:

1. ALS cells are post-synaptic (synapsed in nucleus proprius)
2. ALS axons cross spinal cord BEFORE ascending
3. DC projects to Thalamus only, while ALS projects to Brainstem, Thalamus, Reticular formation, PAG and Hypothalamus
4. Both project to contralateral cortex, but ALS has ipsilateral connections as well.
• Peptidergic C fibers & Aδ fibers terminate superficially; synapse on large projecting neurons in lamina I & interneurons in outer lamina II (express TrkA receptors)
• Non-peptidergic C fibers terminate in the inner part of lamina II (express c-RET neurotrophin receptors)
• Innocuous Aβ fibers terminate on PKCγ-expressing interneurons in the ventral half of lamina II
• Projection neurons in lamina V receive direct input from both Aδ and Aβ fibers, indirect from C fibers (induced pain vs. innocuous pain).


Not all C fibers are nociceptors...

Merkel cells
Pacinian corpuscles
Hair follicles

Stratification of Afferent Subtypes in the Dorsal Horn

1st order fibers from pseudounipolar cells transmit pain sensations via the DRG to the Nucleus Proprius.
2nd Order fibers cross the cord at the anterior commissure and “pile up” in the lateral portion of the anterior funiculus.
These 2nd order fibers ascend, and synapse in the VPL of the thalamus.
3rd Order fibers from the thalamus ascend through the internal capsule and synapse in the somatosensory area of the cortex, specifically area 3,1,2.

An identical arrangement exists for pain sensations from the face, using the trigeminal tract (1st order), trigeminal nucleus and dorsal trigeminothalamic tract (2nd order) to the VPM, and the internal capsule to the area 3,1,2 (3rd order).

Pathways of Nociception

PAIN - the perception of aversive sensations originating from a specific area of the body.

NOCICEPTION - the transduction and conveyance of signals from specialized sensory receptors concerning tissue damage.

Nociceptors are the LEAST specialized of sensory receptors. They are free nerve endings with little or no specialized structures.

• Thermal or Mechanical - small diameter, thinly myelinated fibers (Aδ or moderate, slow conduction velocities: 5-30m/s); convey sharp pain.
• Polymodal - respond to a variety of stimuli (temperature, chemical, mechanical); small diameter, Unmyelinated axons (C); slowest conduction velocities (0.5-2m/s); convey dull or diffuse pain.
• Silent – receptors found in viscera which are unresponsive to normal stimuli; respond only to inflammatory stimuli (sensitized); alter both peripheral & central pathways.

Both Aδ and C fibers are distributed in skin & deep tissues.
First and Second Pain

First pain causes a fast, sharp, well-localized sensation (Aδ).
Second pain causes a less well-defined aching, or burning (C).

Nociceptors are the common entry point for pain pathways, but they subsequently diverge.

Hyperalgesia

"An increased response to a stimulus which is normally painful.

Due to the lowering of the nociceptor’s threshold by either peripheral (primary) or central (secondary) mechanisms, resulting in an increase in the number of action potentials sent to the CNS.

Primary Hyperalgesia – "This occurs at the site of the lesion when the nociceptive fiber is sensitized or directly activated by chemical agents released by the damaged tissue, nearby cells, or the neuron itself."

Injury can rallies a host of mediators, such as bradykinin, serotonin, prostaglandin, etc., which sensitizes the primary afferent fiber of substance P, which in turn interact with many sites. (Aspirin is now known to specifically interact with an enzyme which makes prostaglandins, and therefore can reduce inflammation & algiesa).

Primary Hyperalgesia

When tissue damage occurs, the damaged cells release chemical agents which depolarize the pain fiber, which send APs into the CNS AND get conducted (retrogradely) through each branch point. When the AP reaches the nerve ending, peptides (SubP, CGRP, NkA) are released.

CGRP causes vasoconstriction (flare).
SubP & NkA render vessels more permeable (edema).
SubP stimulates mast cells to degranulate (histamine), stimulates leukocytes into area (cytokines, prostaglandins, NO, leukotrienes).
In addition to the TRP family of channels, other receptors and ion channels participate in the transduction of stimuli expressed by nociceptors. These include a class of Na+ channels (Nav1.7), purinergic receptors (PTX3) activated by ATP, and Mas-related G protein-coupled receptors (Mrg).

* Individuals lacking the Nav1.7 receptor (due to a gene mutation which inactivates the channel) are completely insensitive to pain. All other sensations, however, are normal. Other mutations can make the channel hypersensitive.
Transient Receptor Potential channels (tetrameric non-selective cation channels)

- **Subtype**
  - **Threshold (°C)**
  - **Chemical Stimuli**
  - **Selectivity (PCa/PNa)**
  - **Fiber Expression**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Threshold</th>
<th>Chemical Stimuli</th>
<th>Selectivity</th>
<th>Fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRPV1</td>
<td>&gt;43</td>
<td>Capsaicin, anandamide, PIP2, extracellular H⁺, 2‐APB</td>
<td>10 A⁻</td>
<td>Fibers</td>
</tr>
<tr>
<td>TRPV2</td>
<td>52</td>
<td>2‐APB</td>
<td>CNS</td>
<td></td>
</tr>
<tr>
<td>TRPV3</td>
<td>31</td>
<td>IGF‐1, 2‐APB</td>
<td>keratinocytes</td>
<td></td>
</tr>
<tr>
<td>TRPV4</td>
<td>&gt;27</td>
<td>Hypotonicity, phorbol esters, anandamide</td>
<td>6</td>
<td>Keratinocytes, muscle, kidney, CNS</td>
</tr>
<tr>
<td>TRM8</td>
<td>8</td>
<td>Menthol, icilin</td>
<td>1</td>
<td>3D R G</td>
</tr>
<tr>
<td>TRPA1</td>
<td>&lt;18</td>
<td>Icilin, isothiocyanate (wasabi, mustard); thiosullfinates (garlic, onions); acrolein (smoke)</td>
<td>1.4</td>
<td>DRG, fibroblasts</td>
</tr>
</tbody>
</table>

**H1**: itch

**P2Y2**: Kinins

**P2X3**: Bladder

**TrkA**: Degenerin / Epithelial Na⁺ (DEG/ENaC) channels (tetrameric non-selective cation channels)

- Gated by mechanical tension
- DEG channels are tethered to ECM and anchored intracellularly to microtubule network

Homologous with Acid Sensing Ion Channels (ASIC) & Amiloride-sensitive Sodium Channels

- ASIC2 & ASIC3 involved in mechanosensation, but controversial; others, or TREK-1 (K⁺ channel)

Many receptors are polymodal, activated by thermal, mechanical, and chemical stimuli.

Secondary Hyperalgesia

- "This occurs during severe or persistent injury, where the nociceptors fire repeatedly, thereby increasing the firing of neurons in the dorsal horn (called "wind-up"), which results in long-term changes to the excitability of these cells, at the target neurons (post-synaptic neurons)."

The resulting long-term changes in excitability/sensitivity of these dorsal horn neurons are termed **Central Sensitization**. These long-term changes in the excitability of the dorsal horn neurons and their terminals have been attributed to the induction of immediate early genes, resulting in changes in the expression of neuropeptides (NAPs), neurotransmitters, and corresponding receptor populations. In essence, the dorsal horn neurons have a "stored memory" for the pain and its temporal and spatial features, leading to an increased excitability of these neurons. This leads directly to an overall increase in the number and severity of pain perceived."
Effects of primary and secondary hyperalgesia following an injury:

Before the injury (mild burn), the thresholds of all neurons were quite high (>12mV). After the injury, you would expect the threshold to be lower at the site of the injury where tissue damage occurred (B) and in adjacent tissues where the chemical agents could have easily diffused to (A & D; primary hyperalgesia).

Due to central sensitization (secondary hyperalgesia), site C also shows a decreased threshold to pain. This is due to the sensory afferents ascending & descending in the tract of Lissauer before synapsing at the spinal cord & modifying interneurons.

In addition, the test subject may also be experiencing allodynia at all 3 sites.

Short-term effects of painful stimuli:

Nociceptive fibers enter the dorsal horn and activate both second order pathways (3) and many other interneurons projecting to pain control interneurons (1 & 2), other projection neurons, sympathetic interneurons, and interneurons leading to the spinal cord (4). Due to descending control, most of these interneurons have only sub-threshold responses and do not contribute to central sensitization.

Long-term effects of painful stimuli:

During prolonged or persistent activation, the nociceptive and interneurons become sensitized, resulting in long-term changes in the excitability of these neurons and leading to spontaneous activity, increased irritability, and altered release of neurotransmitters. This can result in hyperalgesia and allodynia, which is sometimes referred to as a "memory" for this type of pain.
Long-term effects of painful stimuli:

The initial response of interneurons and 2° neurons in the spinal cord may include activation of 2nd messenger systems, resulting in the formation/increase of second messengers (cAMP), thereby releasing/increasing protein kinase activity (PKA) and the activation or inactivation of various ion channels, thus temporarily altering the excitability of these neurons.

Continuous or tonic stimulation can also result in protein kinases crossing the nuclear envelope, interacting with regulatory proteins (Enhancer) and immediate early genes (IEGs) to stimulate the formation of new/additional channels. These new channels, then inserted into the membrane, permanently alter the excitability properties of interneurons and 2° neurons, resulting in a "memory" for pain long after the initial injury has healed.

Neurotrophins are Pain Mediators

Brain-derived neurotrophic factor (BDNF) further increases excitability and facilitates the activation of dorsal horn neurons. BDNF is released from the presynaptic terminals of sensory neurons and binds to its receptor on the postsynaptic membrane of spinal cord neurons, leading to an increase in intracellular calcium and the activation of protein kinase C (PKC), which in turn phosphorylates the neuronal voltage-gated sodium channel, increasing its sensitivity to activation by depolarization. This leads to an increased firing rate of the neuron, contributing to pain sensation.

Spinal Cord Synapses

Neurotrophins, such as BDNF, play a crucial role in the modulation of pain. They promote the survival and differentiation of dorsal horn neurons, enhancing their excitability and facilitating the activation of pain-related circuits. This process is essential for the proper processing and transmission of nociceptive signals, ensuring an adequate response to injury or tissue damage.
Spinal Afferents

- Aδ and C fibers enter dorsal horn at equal 1 or 2 levels in the tract of Lissauer and penetrate:
  - 2° projection neurons to the CNS (ALS).
  - Local excitatory interneurons (direct & indirect) to the α MN's (for local reflexes) and other ascending tracts.
  - Local inhibitory interneurons which regulate pain perceptions and set the overall level of responsiveness of the nociceptive system.
  - Sympathetic motorneurons located in the IML.
  - Long and short propriospinal interneurons (control posture & voluntary movements).

Spinal Cord Synapses

Reflected Pain

"Reflected Pain" is due to convergence of somatic sensory afferents and visceral afferents from pain & stretch receptors onto the same interneurons and 2° neurons. The cortex typically interprets the pain coming from somatic sources rather than visceral.
Sites for Referred Pain for Various Organs

Analysis - the modulation or reduction of pain:

Pain perception can be modified at the first synapse in the spinal cord by Aβ and other afferents, as well as descending projections from higher centers in the CNS.

Gate Control Theory:

A “balance” exists between unmyelinated and myelinated fibers in the dorsal horn. There are four primary classes of spinal neurons which can interact to modulate pain:

1. Unmyelinated nociceptive afferents (pain fibers).
3. Projection neurons to the CNS (2° via ALS).
4. Spontaneously active inhibitory interneurons (the “gate”).

* Normally, the spontaneously active inhibitory interneurons limit the output of the projection neurons to the CNS, thereby setting the threshold for pain.

Analgesia - the modulation or reduction of pain:

If you stimulate the pain pathway, this results in inhibition of the inhibitory interneuron and excitation of the projection neurons, resulting in the perception of pain.

By stimulating the non-nociceptive Aβ fibers of the somatosensory system (i.e. touch, temperature, proprioceptive fibers), you can reduce the output of the projection neurons and a decrease in the pain. This is known as “shaking it out” and reducing the amount of perceived pain.
This type of regulation is only effective in mildly painful stimuli, and cannot overcome the pain associated with severe injuries. Remember, this is a "balance" that is being moved back and forth between the nociceptive and non-nociceptive fibers. This balance is achieved together determining the final end set point for the perception of pain.

Pain synapses can also be modified by descending pathways in the CNS. Direct stimulation of the PeriVentricular and PeriAqueductal Gray (PVG & PAG) results in excitation of the rostroventral medulla, which then stimulates cells in the dorsal horn of the spinal cord that terminate in the spinal cord and do not suppress the nociceptive inputs.

The PVG and PAG are extremely sensitive to morphine, and are therefore the primary site of action of morphine and morphine-like drugs (opiates). Endogenous opioids (enkephalins, leptin, and proopiomelanocortins) are released in the PeriVentricular gray matter and therefore stimulate the PVG and PAG. Other descending pathways, such as the locus ceruleus and the raphe nuclei (raphe magnus) also terminate in the dorsal horn and suppress nociceptive inputs.
The descending inputs to the dorsal horn result in the modulation of the primary pain afferent onto the projection neurons either directly (via an inhibitory connection) or indirectly (via stimulation of enkephalin interneurons) by two possible mechanisms.

**CNS Modulation of Pain: Presynaptic Inhibition**

Presynaptic inhibition (indirect; extrinsic form of synaptic plasticity) of the pain fibers in the dorsal horn via opiate receptors on the presynaptic cell, which results in an increased K⁺ conductance and hyperpolarization of the presynaptic terminal. This hyperpolarization of the presynaptic terminal results in a decrease in the duration of the AP, decreased Ca²⁺ influx and a decrease in the amount of neurotransmitter released onto the post-synaptic cell (projection neuron).

**CNS Modulation of Pain: Postsynaptic Inhibition**

Postsynaptic (direct) modification of the EPSP via hyperpolarization of the postsynaptic membrane via opiate receptors on the postsynaptic cell (intrinsic method of synaptic plasticity – hyperpolarizes the resting membrane potential of the postsynaptic neuron, taking it farther from threshold).

The net result is a significant (albeit temporary) reduction in output from the 2nd order neuron into the CNS, and a reduction in perceived pain.

*Remember that there is a limited supply of endogenous opioids and enkephalins in the spinal cord!*
Terminology / Definitions

Please look over the “Pain Terminology” handout related to this lecture and familiarize yourself with the following definitions.

Be able to differentiate between the various types of pain described.

- Allodynia
- Analgesia
- Causalgia
- Central Pain
- CRPS Type I & II
- Hyperalgesia (Primary & Secondary)
- Hyperpathia
- Hypoalgesia
- Neuralgia

Neurogenic Pain (Deafferentation & Sympathetically Maintained)

Neuropathic Pain

Neuropathy

Nociceptive Pain (Nociceptor)

Pain

Pain Threshold

Paresthesia & Dysesthesia

Sensitization

And finally...