OBJECTIVES

After studying the material of this lecture the student should be familiar with:

1. The relationship between nociception and the experience of pain.
2. The characteristics of fast (epicritic) and slow (protopathic) pain
3. Central mechanisms of pain suppression
4. The Gate Control Theory of Pain
5. Chemical substances that activate or sensitize nociceptors
6. Neuropathic (non-nociceptive) pain
7. Properties of cold and warm fibers

INTRODUCTION

The somatosensory system receives information from mechanoreceptors (touch and position sense), nociceptors (pain), and thermoreceptors (temperature). Pain and temperature information is transmitted centrally by fiber tracts in the spinal cord (lateral spinothalamic tract) which is part of the anterolateral system. The anterolateral system also transmits information perceived as simple (light) touch (anterior spinothalamic tract). The dorsal column system mediates information about the spatial and temporal aspects of touch (tactile discrimination) as well as limb position (proprioception).

Figure 1: The anterolateral system: pathways for non-discriminative touch, temperature and pain
I. PAIN

**Pain** is a subjective experience derived from sensory perceptions and state of mind. It is an unpleasant sensory and emotional experience that is almost always associated with tissue damage and stimulation of nociceptors.

**Nociception** is the sensation experienced following a noxious stimulus (e.g., pin prick, knife cut, burn, crush injury) and is mediated by the activation of specialized receptors called nociceptors that respond to tissue damage.

Pain is highly variable and depends on the mood and circumstances that exist at the time. The stimulation of nociceptors does not always result in “pain”. For example under battlefield conditions soldiers sometimes do not complain of pain from their wounds until they are removed from the battlefield area. Athletes often do not feel pain from their injuries until after the game or event is over. Pain is affected by mood, emotion, and state of mind. Hypnosis for example can reduce or eliminate pain. Placebos can also produce relief from pain.

A. Nociceptors

Nociceptive pain (physiological pain) results when special receptors (nociceptors) are activated by a noxious or harmful stimulus.

There are three main classes of nociceptors:

1. **Thermal nociceptors** - activated by extreme temperatures (>50 degrees C or less than 5 degrees C). These receptors have small diameter axons, are thinly myelinated (A-delta fibers) and conduct action potentials at about 5-30 m/sec.
2. **Mechanical nociceptors** – activated by intense pressure to the skin, have thinly myelinated axons (A-delta fibers) and conduct action potentials at about 5-30 m/sec.
3. **Polymodal nociceptors** – are activated by high intensity mechanical, chemical, or thermal stimuli. Polymodal nociceptors have small diameter axons, are nonmyelinated (C-fibers) and conduct action potentials at velocities less than 1 m/sec.

B. Fast and Slow Pain

The different classes of nociceptors often work together to signal an injury. For example when you hit your thumb with a hammer you first detect a “sharp” pain immediately which is subsequently followed by a longer duration “dull” aching or “throbbing” pain that continues well beyond the initial injury or insult. These two different qualities of pain are called “first” (or “fast”) pain and “second” (or “slow”) pain. They are mediated by two different primary afferent fiber types. The table below summarizes the qualities of pain, and their fiber types.
<table>
<thead>
<tr>
<th></th>
<th>FAST PAIN</th>
<th>SLOW PAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ONSET</strong></td>
<td>rapid (&lt; 100 msec)</td>
<td>delayed (&gt; 1 second)</td>
</tr>
<tr>
<td><strong>QUALITY</strong></td>
<td>sharp, pricking, acute, electric</td>
<td>slow, burning, aching, throbbing, nauseous, chronic</td>
</tr>
<tr>
<td><strong>LOCALIZATION</strong></td>
<td>well localized</td>
<td>poorly localized</td>
</tr>
<tr>
<td><strong>FIBER TYPE</strong></td>
<td>A-delta fibers thinly myelinated (group III)</td>
<td>C fibers unmyelinated (group IV)</td>
</tr>
<tr>
<td><strong>EXAMPLES</strong></td>
<td>knife cut, needle stick,</td>
<td>crush injury, burn</td>
</tr>
</tbody>
</table>

Fibers of different diameters can be blocked selectively. A pressure block to a peripheral nerve will block transmission in large fibers first and then smaller diameter fibers. Loss of sensations begins with light touch, then pressure, then epicritic (fast) pain and finally protopathic (slow) pain. Local anesthetics work in the reverse order beginning with the smallest C fibers and then larger fibers. Local anesthetics block pain before touch and proprioception.

C. **Primary Afferents and Layers of the Spinal Cord Dorsal Horn**

Primary pain afferents enter the spinal cord and synapse onto cells in the dorsal horn. The A-delta fibers signal nociceptor stimuli and terminate on cells in lamina I and V. The small diameter C fibers terminate in laminae I and II. The major pain transmission cells that convey pain information to higher levels of the CNS are located in both laminae I and V. Cells in lamina I are called **nociceptive specific** (NS) neurons and respond only to noxious (painful) stimuli. The cells in lamina V respond to touch, pressure, and painful stimuli and are called **Wide Dynamic Range** (WDR) neurons. These neurons use a frequency code to signal the stimulus. Light touch produces low frequency discharges, pressure produces higher frequencies, and pain even higher frequency discharge rates.

![Figure 2: Nociceptor afferents and pain transmission neurons in the dorsal horn.](image-url)
D. Central Mechanisms Controlling Pain

1. Gate Control Theory of Pain

The Gate Control Theory of Pain proposes that there is a “gate” in the dorsal horn of the spinal cord that controls the output of pain transmission neurons (PTNs). The gate is opened or closed by differences in the amount of afferent input received from small and large diameter fibers. Increased activity in the large diameter (A-beta) fibers closes the gate, activity in the small diameter (C) fibers opens the gate. Inhibitory interneurons located in the substantia gelatinosa (SG) control the gate by a mechanism called presynaptic inhibition. When activated by large diameter fibers the SG neurons inhibit the input to the pain transmission neurons (decreases pain transmission). Activity in the small diameter fibers inhibits SG cells therefore removing the presynaptic inhibition and opening the gate (increases pain transmission). The Gate Control Theory of Pain provides an explanation for why rubbing the site of an injury (stimulation of large diameter touch fibers) often helps to reduce pain. The clinical use of transcutaneous electrical neural stimulation (TENS) to reduce pain is also based in part on the Gate Control Theory of Pain. Electrodes are placed on the skin over a peripheral nerve and selective stimulation of the large diameter fibers (using low threshold voltages) is used to inhibit nociceptor neuron transmission and reduce pain. This non invasive procedure has been successfully used in some cases of intractable pain.

![Figure 3: Gate Control Theory of Pain](image)

2. Descending Inhibitory Pathways

Stimulation of neurons in the periaqueductal gray area (PAG) surrounding the midbrain cerebral aqueduct produces a profound reduction in pain (analgesia).
This selective inhibition of pain is mediated by descending pathways that terminate onto cells in the dorsal horn.

Cells in the PAG make excitatory connections with serotonergic neurons in the medulla (nucleus raphe magnus) and with noradrenergic neurons in the pons (locus ceruleus). These neurons in turn have a direct and indirect inhibitory effect on pain transmission neurons in laminae I and V of the spinal cord. The net result is a descending inhibitory (anti-nociceptive) effect on pain.

3. **Opiate Receptors**

Opiates such as morphine and codeine have a powerful inhibitory effect on pain (are potent analgesic agents). Three classes of endogenous opioid peptides have been identified (enkephalins, beta-endorphins, and dynorphins). Both enkephalins and dynorphins are found in the periaqueductal gray area, the medulla, and the dorsal horn of the spinal cord. Beta-endorphins are primarily found in the hypothalamus. Direct injection of morphine into the brainstem causes inhibition of pain transmission cells in the spinal cord by activating the descending raphespinal serotonergic pathways from the NRM (n. raphe magnus). This response can be blocked by the opiate
antagonist naloxone. Opiate induced analgesia uses the same central descending inhibitory pathways discussed above.

The genes encoding the different classes of opiate receptors have been cloned and are members of the G protein-coupled class of receptors. Some opiate receptors are located in regions of the nervous system not associated with pain and account for some of the side effects associated with the administration of drugs such as morphine and other narcotics. For example constipation is a common side effect due to opiate receptors in the muscles of the bowel and anal sphincter. Receptors located in the brain stem (e.g., nucleus of the solitary tract) account for respiratory depression and cardiovascular changes. To minimize side effects of systemic injections of morphine it is now administered locally into the spinal cord. Intrathecal or epidural injections of morphine into the CSF of the spinal cord produces profound and prolonged analgesia. They are often used to manage post operative caesarean section pain and cancer pain.

E. Peripheral Mechanisms

1. Agents That Activate or Sensitize Nociceptors

![Image: Peripheral mechanism of nociception following tissue damage.](from Kandel,Schwartz, and Jessell, 2000.)

After injury or inflammation a variety of chemical substances are released by the damaged cells and tissue. These chemicals can decrease the threshold of nociceptors (sensitization) or in some cases cause direct activation of the nociceptor afferents.
<table>
<thead>
<tr>
<th>SOURCE</th>
<th>CHEMICAL</th>
<th>EFFECT ON NOCICEPTOR FIBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damaged cells</td>
<td>Potassium</td>
<td>Direct activation</td>
</tr>
<tr>
<td>Damaged cells</td>
<td>Prostaglandins</td>
<td>Sensitization</td>
</tr>
<tr>
<td>Damaged cells</td>
<td>Leukotrienes</td>
<td>Sensitization</td>
</tr>
<tr>
<td>Plasma</td>
<td>Bradykinin</td>
<td>Direct activation</td>
</tr>
<tr>
<td>Platelets</td>
<td>Serotonin</td>
<td>Direct activation</td>
</tr>
<tr>
<td>Nerve terminals</td>
<td>Substance P</td>
<td>Sensitization</td>
</tr>
<tr>
<td>Nerve terminals</td>
<td>CGRP*</td>
<td>Sensitization</td>
</tr>
<tr>
<td>Mast cells</td>
<td>Histamine</td>
<td>Direct activation</td>
</tr>
</tbody>
</table>

The classic signs of local inflammation are 1.) heat, 2.) redness, and 3.) swelling. Heat and redness are produced by dilation of the peripheral blood vessels. The swelling is due to a leaking of plasma and proteins from the capillaries which is accompanied by an increase in extracellular fluid.

**Substance P** can produce all these symptoms. By acting directly on venules substance P and the calcitonin gene-related protein (CGRP) produce vasodialation and edema. They also cause mast cells to release histamine which decreases the threshold for activation of nociceptor. Antagonists of substance P can be used clinically to block the neurogenic inflammatory response.

**Bradykinin** is a very potent pain producing agent. It has a dual action. It can activate both A-delta and C nociceptor fibers directly and it increases the synthesis and release of prostaglandins by nearby cells.

**Prostaglandin** is a metabolite of arachidonic acid and is generated by the enzyme cyclooxygenase released by damaged cells. Aspirin and other nonsteroidal anti-inflammatory agents are effective in reducing pain because they block cyclooxygenase and the production of prostaglandins.

2. **Hyperalgesia**

Hyperalgesia is an increase in the sensitivity of pain pathways that occurs following injury. For example, it is possible for non painful mechanical stimuli (light touch) to produce pain when applied to an area where there is tissue damage (Primary hyperalgesia). Areas surrounding the area of tissue damage may also become hypersensitive to non-noxious stimuli and produce pain sensations (secondary hyperalgesia). Repetitive stimulation from nociceptor C fibers can also produce hyperexcitability in dorsal horn neurons and result in a central based hyperalgesia.

F. **Neuropathic Pain**

Neuropathic pain (sometimes called intractable pain) occurs when there is injury to the nervous system resulting in a permanent change to CNS connections.
Unlike nociceptive pain where the activity of specialized pain receptors signal the presence of a noxious stimulus (to protect against further injury), neuropathic pain appears to have no useful function (is maladaptive). When afferent pain fibers are injured, the nervous systems tries to repair itself thought regeneration of axon processes. Large diameter fibers (A-beta fibers) are more likely to survive injury than small diameter fibers (e.g., C fibers). During the recovery process the surviving large diameter fibers sprout and take over pain circuits that previously received input from the small diameter nociceptor fibers. When these large diameter fibers are stimulated they activate pain transmission neurons and produce pain (normally they would signal innocuous mechanoreceptor stimuli).

**Phantom pain** is a type of neuropathic pain associated with amputation of an extremity. The patient often reports they feel painful sensations localized to part of the missing extremity.

**Entrapment lesions** such as Carpal Tunnel Syndrome can also cause neuropathic pain. This pain is due to the irritation or inflammation of a nerve due to constant pressure or irritation. In carpal tunnel syndrome the median nerve is frequently injured by compression at the flexor retinaculum. Pain or discomfort is often felt not only in the hand but can extend to the wrist and extend up the arm.

**Thalamic Pain Syndrome** is another example of neuropathic pain resulting from a central lesion involving the thalamus (VPL). These lesions are typically caused by a vascular insult such as a stroke. Patients with thalamic pain report the sensation of pain as unlike and more excruciating than anything they have ever experienced before.

**G. Brain Centers**

Different centers in the brain contribute to the composite perception of pain. The somatosensory cortex (post central gyrus) for example plays a role in the **localization of pain**. Lesions or damage in this region of the brain can eliminate the ability to localize pain. Both discriminative and non-discriminative touch pathways project to the somatosensory cortex. Lesions in the hypothalamus and limbic system have been shown to alter the **affective component of pain**. The suffering component of pain is associated with these structures.

**H. Referred Pain**

**Referred pain** is a phenomenon in which the stimulation of visceral pain fibers is interpreted by the central nervous system as coming from the body surface. This occurs because pain afferents from the viscera project onto the same transmission pathways that somatic pain afferents use. During development some of the visceral organs migrate from their embryonic origin and therefore referred pain from a visceral organ is often perceived on a remote location on the surface of the body. For example damage to the heart (heart attack) results in pain localized to
the arm and shoulder. Abdominal bleeding can irritate the diaphragm and cause pain localized to the scapular area not the abdomen. This is because the diaphragm originates from the same cervical dermatome during development.

II. THERMORECEPTORS

There are two types of thermoreceptors: (cold and warm receptors). Both are sensitive to changes in skin temperature.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Fiber type</th>
<th>Temperature range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold receptors</td>
<td>A-delta fibers</td>
<td>5-40 degrees C</td>
</tr>
<tr>
<td>Warm receptors</td>
<td>C fibers</td>
<td>30-47 degrees C</td>
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</tbody>
</table>

At 37 degrees C both cold and warm fibers have a low level of spontaneously active. Cold fibers increase their firing rate as the skin temperature decreases (max firing at about 27 degrees), warm fibers increase their firing rate as the skin temperature increases (max firing at about 46 degrees). When the skin temperature begins to increase cold fibers become inactive, when the temperature decreases, warm fibers become inactive. Warm fibers stop firing above 47 degrees. Warm fibers do not signal the heat from high temperatures where tissue damage begins to occur. Nociceptors signal extreme skin temperatures and burns. Temperatures below freezing also activate nociceptors.

![Figure 6: Response properties of temperature sensitive fibers](From Byrne and Levy 1998)

ADDITIONAL REFERENCES
