**Objectives**
- 1. Recognize the pain pathways from peripheral stimulus to supraspinal processing.
- 2. Understand the differences between pain fibers.
- 3. Discuss pain modulation from supraspinal processing to substantia gelatinosa.
- 4. Explain the physiology of nociception.

**PAIN PATHWAYS**

1. Peripheral stimulus
2. Receptor (transduction)
3. Peripheral transmission
4. Spinal transmission
5. Ascending tracts
6. Supraspinal processing

Pain is conducted along three neuron pathways (first, second and third order neurons) that transmit noxious stimuli from the periphery to the cerebral cortex.

Primary afferent neurons are located in the dorsal root ganglion which lie in the vertebral foramina at each spinal cord level. Each neuron has a single axon that bifurcates, sending one end to the peripheral tissues it innervates and the other into the dorsal horn of the spinal cord.

**PAIN PATHWAYS**

- First order neurons
  - The majority enter the dorsal spinal root at each cervical, thoracic, lumbar, and sacral level
  - Pain fibers originating in the head are carried by the trigeminal (V), facial (VII), glossopharyngeal (IX), and vagal (X)
  - Each have specific ganglion which hold cell bodies of these nerves. The first order neurons in the ganglia (head) reach the brainstem and synapse with the second order neuron

**PAIN PATHWAYS**

- Second order neurons
  - Spinal cord gray matter is divided by Rexed into 10 lamina
  - First six makeup the dorsal horn, receive all afferent neural activity, represent the principle site for modulation of pain
  - Second order neurons are either nociceptive-specific or wide dynamic range (WDR)
**PAIN PATHWAYS**

- Lamina I responds to nociceptive stimuli from cutaneous and deep somatic tissues
- Lamina II (substantia gelatinosa), contains many interneurons responsible for processing and modulating nociceptive input from cutaneous tissue. Major site of action for opioids
- Lamina VII contains preganglionic sympathetic neurons
- Lamina V and I contains visceral afferents
- Lamina V responds to both noxious and non noxious stimuli and receives both somatic and visceral inputs
- Thus referred pain

- Spinothalamic tract
  - Cross the midline to the level of origin to the contralateral side of the spinal cord
  - Divided into lateral and medial
  - Lateral spinothalamic tract projects—location, density, duration of pain in the ventral posterior lateral nucleus of the thalamus
  - Medial spinothalamic tract projects—unpleasant emotional perception of pain in the medial thalamus

- Spinal reticular pain pathway- arousal and autonomic responses to pain
- Spinalmesencephalic--anti-nociceptive descending pathways because of its projections in the periductal gray area

**THIRD ORDER NEURONS**

- Located in the thalamus
- Send fibers to the somatosensory areas I and II in the post central gyrus of the parietal cortex and superior wall of the sylvian fissure

**AFFERENT NERVE FIBERS**

- A and B fibers are myelinated
- A delta fibers are fast, sharp well-localized sensation
- A are further defined as alpha, beta, gamma, and delta
- C fibers are nonmyelinated
- C fibers slow poorly localized
- The classification of these fibers are based on diameter and velocity of conduction
- Each innervation provides a specific function

<table>
<thead>
<tr>
<th>Fiber Group</th>
<th>Innervation</th>
<th>Mean Diameter µm</th>
<th>Mean Velocity m/sec</th>
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</thead>
<tbody>
<tr>
<td>A alpha</td>
<td>Muscle spindle motor to skeletal</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>B beta</td>
<td>Touch &amp; pressure afferents</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>C gamma</td>
<td>Motor to muscle spindle</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>D delta</td>
<td>Mechanoreceptors, nociceptors</td>
<td>&lt;3</td>
<td>15</td>
</tr>
<tr>
<td>B sympathetic preganglionic</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>C sympathetic post ganglionic</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
PHYSIOLOGY OF NOCICEPTION

Free nerve endings sense heat, mechanical, and chemical damage

Mechanonociceptors—respond to pinch and pinprick

Silent nociceptors—respond to inflammation

Ploymodal mechoheat nociceptors—respond to heat and pressure

ALOGENS—include bradykinin, histamine, serotonin, 5-HT, histmine, serotonin, H\textsubscript{+}, K\textsuperscript{+}, some prostaglandins, and possibly ATP

Somatic nociceptors included muscle tendon, fascia, bone

Cornea and tooth pulp and innervated by A delta and C fibers

Visceral organs—silent nociceptors

Nociceptive C fibers travel from the esophagus, larynx, and trachea with the vagus nerve to enter the nucleus solitarius in the brainstem

CHEMICAL MEDIATORS OF PAIN

1. Substance P—released by first order neurons both peripherally and in the dorsal horn

Facilitates transmission in pain pathways via NK-1 receptor activation

Sends collaterals to blood vessels, sweat glands, hair, mast cells in the dermis

Degranulates histamine and serotonin from platelets, is a vasoconstrictor, chemoreactor for leukocytes

Nervates the viscera—post ganglionic sympathetic discharge

PERIPHERAL MODULATION OF PAIN

Release of alogens from damage tissues

Histamine from mast cells, basophils, platelets

Serotonin from mast cells, platelets

Factor XII allows the release of bradykinin

Phospholipase A\textsubscript{2} on phospholipids produce prostaglandins and form arachidonic acid and the cascade begins
PERIPHERAL MODULATION OF PAIN

- Cyclooxygenase converts arachidonic acid to prostacyclin and PGE2
- This potentiates the edema from bradykinin
- Lipooxygenase pathway converts AA into leukotrienes
- ASA and NSAID inhibit cyclooxygenase
- Corticosteriods inhibit prostaglandin production through blockage of phospholipase A2 activation

CENTRAL MODULATION

1. Wind up and sensitization of second order neurons— increase frequency of repetitive prolong discharge even after C fibers input has stopped
2. Receptor field expansion—Dorsal horn neurons increase their receptive fields to become more responsive to stimuli (noxious or not)
3. Hyperexcitability of flexion reflexes.

NEUROCHEMICAL MEDIATORS

- Glutamine and asparate wind-up activation of NMDA and non-NMDA receptors— this increases intracellular calcium in spinal neurons and activates phospholipase A2
- Then to arachidonic acid and the cascade begins

MODULATION OF PAIN

- Impulses arising in the periventricular/periaqueductal gray matter of the brainstem are transmitted through the raphe magnus to the substantia gelatinosa by way of the descending dorsolateral funiculus.
- Action potentials arriving at the substantia gelatinosa activate enkephalin neurons. The release of enkephalin decreases the release of substance P, thereby reducing the number of pain impulses ascending in the lateral spinothalamic tract. Also, action potentials descending in the dorsolateral funiculus hyperpolarize cell bodies of the second neurons in the pain pathway, thereby decreasing the number of action potentials in the ascending lateral spinothalamic tract. The descending dorsolateral modulates pain.
Intravenous opioids produce analgesia in part by initiating action potentials in the descending dorsolateral funiculus.

Spinal analgesia, mediated by mu-2 receptors, occurs when the number of pain impulses passing through the substantia gelatinosa is decreased.

Intravenous opioids act in other sites in the brain (limbic system, hypothalamus, and thalamus) produce supraspinal analgesia is mediated primarily by mu-1 receptors.

Opioids act in a complex fashion to decrease the perception of pain and decrease the response to pain.

**PREEMPTIVE ANALGESIA**

- Induces an effective analgesic state prior to surgical trauma.
- By: infiltration of site with local anesthetic, central neural blockade, administration of effective opioids, NSAIDs, or ketamine.
- This attenuates peripheral and central sensitization to pain.
- The use of preemptive analgesia may reduce the postoperative analgesic requirements.

**ACUTE PAIN**

- Defined as that which is caused by noxious stimulation due to injury, a disease process, or abnormal function of muscle or viscera. It is nearly always nociceptive.
- Two types of acute pain: somatic and visceral.
**ACUTE PAIN: SOMATIC**

- **Superficial somatic** - skin, subcutaneous, mucous membranes
- Well localized - sharp, pricking, throbbing, burning
- **Deep somatic** - muscles, tendons, joints, bones
- Less well localized, dull, aching

**ACUTE PAIN: VISCERAL**

- Disease process or abnormal function of an internal organ or its covering (e.g., parietal pleura, pericardium, or peritoneum).
- Four types: true localized visceral, true localized parietal, referred visceral, referred parietal
  - True visceral is dull, diffuse, midline and is associated with abnormal sympathetic or parasympathetic activity (N/V, sweating, changes in BP and HR)
  - True parietal is sharp and localized
  - Referred - disease process involving the peritoneum or pleura over the central diaphragm is referred to the neck and shoulder whereas disease affecting the parietal surfaces of the peripheral diaphragm is referred to the chest or upper abdominal wall

**ACUTE PAIN: SYSTEMIC RESPONSE**

**CARDIOVASCULAR**: hypertension, tachycardia, enhanced myocardial irritability, increased SVR
- Increased CO, may be decrease with patients who have compromised ventricular function
- Increased myocardial oxygen demand, therefore, pain can aggravate or precipitate myocardial ischemia

**GASTROINTESTINAL & URINARY**: Enhanced sympathetic tone increases sphincter tone and decreases intestinal and urinary motility, promoting ileus and urinary retention
- Hyper-secretion of gastric acid promotes stress ulceration, together with decreased motility, predisposes the patients to severe aspiration pneumonitis

**RESPIRATORY**: Increase in total body O₂ consumption and CO₂ production increases minute ventilation
ACUTE PAIN: SYSTEMIC RESPONSE
- **Endocrine**: increase in catabolic hormones (catecholamines, cortisol, and glucagon) and decrease in anabolic hormones (insulin and testosterone)
- Develops a negative nitrogen balance, carbohydrate intolerance and increased lipolysis
- Increase in cortisol with increase in renin, aldosterone, angiotensin, and antidiuretic hormone results in NA retention and water retention

ACUTE PAIN: SYSTEMIC RESPONSE
- **IMMUNE**: Produces leukocytosis with lymphopenia, predisposes patients to infection
- **HEMATOLOGIC**: Increases in platelet adhesiveness, reduced fibrinolysis, and hypercoagulability
- **PERCEPTION**: Anxiety, sleep disturbance—if duration of pain is prolonged depression and anger

ACUTE PAIN: SYSTEMIC RESPONSE
- **MODERATE TO SEVERE ACUTE PAIN, REGARDLESS OF SITE, CAN AFFECT NEARLY EVERY ORGAN FUNCTION AND MAY ADVERSELY INFLUENCE POSTOPERATIVE MORBIDITY AND MORTALITY**

CHRONIC PAIN
- Chronic pain is defined as that which persists beyond the usual course of an acute disease or after a reasonable time for healing to occur.
- This period varies between 1-6 months
- Chronic pain may be nociceptive, neuropathic, or a combination of both

CHRONIC PAIN
- Patients with chronic pain often have an attenuated or absent neuroendocrine response
- Psychological mechanisms, sleep and affective disturbances
- Neuropathic pain classically spontaneous, has a burning sensation, and is associated with hyperpathia
CHRONIC PAIN

- **COMMON FORMS**: Musculoskeletal disorders, chronic visceral disorders, lesions of the peripheral nerves, nerve roots, dorsal root ganglia, phantom limb pain, lesions of the central nervous system (stroke, spinal cord injury, multiple sclerosis) and cancers invading the nervous system.

- Peripheral-central and central mechanisms for chronic pain:
  1. Spontaneous self-sustaining neuronal activity in the primary afferent neuron (neuroma)
  2. Marked mechanosensitivity associated with chronic nerve compression
  3. Short circuits between pain fibers, following demyelination, activating nociceptors by nonnoxious stimuli
  4. Reorganization of receptor fields in the dorsal horn neurons

- Treatment includes a wide variety of blocks, COX inhibitors, opioids, antidepressants, neuroleptic agents, anticonvulsants, corticosteroids and systemic local anesthetics.
- [http://www.youtube.com/watch?v=n2Jzt3zd8vQ](http://www.youtube.com/watch?v=n2Jzt3zd8vQ)

**References**

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