Pathophysiology of Pain

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Learning Objectives

- Anatomic pathway of nociception
- Discuss the multiple target sites of pharmacological agents
- Learn risk factors for the development of chronic pain
- Utilize information to treat pain at multiple target sites
What is pain?

"an unpleasant sensory and emotional experience associated with actual or potential tissue damage"
Anatomy of the Pain Pathway

**Transduction:** Conversion of a noxious stimuli (chemical, mechanical, or thermal) into electrical energy

**Transmission:** Electrical stimulus is sent to the dorsal horn of the spinal cord and synapse at the 2nd order neuron

**Modulation:** Inhibition vs amplification of signal (facilitated by EAA)

**Perception:** Conscious awareness of pain as a culmination of previous processes in the context of the individuals experiences.
A closer look

Transduction: Primary afferents

<table>
<thead>
<tr>
<th>Nerve Fiber</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-beta</td>
<td>low threshold mechanoreceptors</td>
</tr>
<tr>
<td>A-delta</td>
<td>low threshold mechano and thermoreceptors</td>
</tr>
<tr>
<td>C</td>
<td>high threshold thermal, mechano, and chemical receptors</td>
</tr>
</tbody>
</table>
Transduction: Primary afferents

**Inflammatory Soup**

- Mast cells and Neutrophils: ATP, bradykinin, PGE2, Na+, H+, serotonin
- COX-2 activation
- Macrophage: NGF, IL-6, TNFα
- C-fibers: CGRP, Substance P, neurokinin
Transduction: Primary afferents

- Up-regulation of substance P
- Enzyme activation
- TRPV activation
- Increased excitability of nociceptors
- Activation of silent nociceptors
Transduction: Primary afferents

Naked mole rat: Inability to convert capsaicin and acid stimulus to electrical signal
NGF/TRKA Pathway: Activates TRPV1 ion channel allows depolarization and activation of voltage gated Na+ channels
Transmission: Electrical stimulus is sent to the dorsal horn of the spinal cord and synapse at the 2nd order neuron.
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Transmission: C fiber activity increases Wide Dynamic Range Neurons firing
Modulation: Inhibition vs amplification of signal.

- **Excitatory:**
  - EAA
  - Ach
  - Glycine
  - sP
  - Oxytocin
  - CRH

- **Inhibitory:**
  - Serotonin
  - NE
  - GABA
Perception: Conscious Awareness of Pain

Cortical:
Somatosensory cortex, insula, and anterior cingulate cortex

Subcortical:
hypothalamus, Thalamus, amygdala, hippocampus
When the norm diverges...
When acute pain turns to chronic...

- **Acute Pain**: Begins suddenly and is usually sharp. Serves as warning of disease or injury. Generally disappears when underlying cause is treated.

- **Subacute Pain**: Last from 6-12 weeks. Usually improves with nonsurgical treatment.

- **Chronic Pain**: More difficult to treat. Can persist for months or years. May cause depression, anxiety, and sleep problems.
Surgical procedures and prevalence rates of developing postsurgical pain syndrome

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Surgery</td>
<td>22-35%</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>11-52%</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>21%</td>
</tr>
<tr>
<td>Limb Amputation</td>
<td>5-50%</td>
</tr>
<tr>
<td>Hip</td>
<td>7-13%</td>
</tr>
<tr>
<td>Laparoscopic Hernia Repair</td>
<td>15% at nine months</td>
</tr>
</tbody>
</table>
From: Severing the Link between Acute and Chronic Pain: The Anesthesiologist's Role in Preventive Medicine

Table 1. Numbers of Procedures for Specific International Disease Classification (ICD-9) Procedure Codes, Rate of Complex Regional Pain Syndrome (CRPS) for Specific Procedures, and Corresponding Numbers of Cases of CRPS Associated with Common Orthopedic Surgical Procedures

<table>
<thead>
<tr>
<th>Procedure (ICD-9 Code)</th>
<th>N† (in thousands/yr)</th>
<th>Rate‡ (%)</th>
<th>CRPS (in thousands/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthroscopic knee surgery (80.26)</td>
<td>657</td>
<td>2.3–4.0</td>
<td>15.1–26.3</td>
</tr>
<tr>
<td>Carpal tunnel surgery (04.43)</td>
<td>366</td>
<td>2.1–5.0</td>
<td>7.7–18.3</td>
</tr>
<tr>
<td>Ankle fractures (79.”6 and 79.”7)</td>
<td>257</td>
<td>13.6</td>
<td>35.0</td>
</tr>
<tr>
<td>Total knee arthroplasty (81.54)</td>
<td>247</td>
<td>0.8–13.0</td>
<td>2.0–32.1</td>
</tr>
<tr>
<td>Wrist fractures (79.”2 and 79.”3)</td>
<td>194</td>
<td>7.0–37.0</td>
<td>13.6–71.8</td>
</tr>
<tr>
<td>Fasciectomy for Dupuytren’s Contracture (82.35)</td>
<td>20</td>
<td>4.5–40</td>
<td>0.9–8.0</td>
</tr>
<tr>
<td>Total</td>
<td>1741</td>
<td>4.3–11.0</td>
<td>74.3–191.5</td>
</tr>
</tbody>
</table>

* Refers to any number 0–9. † See reference 7. ‡ See reference 4.
Abnormal Transmission of Pain

Gottschalk et al. 2001
Changes to the pain pathway in chronic pain

**Transduction**
- Sustained increase in nociceptors.
- Activation of TRPV1-R
- Increase in sP and CGRP

**Transmission**
- NMDA-R activation
- Wind-up
- WDR-Neurons sprout abnormal connections
- Activation of glial cells
- Central sensitization

**Modulation**
- Decreased inhibition vs increased amplification
- Loss of pain filtering
- Increased release of pain transmitters

**Perception**
- Gray matter decrease (reversible)
- Increased connections: Medial Prefrontal Cortex (mPFC) and Nucleus Accumbens
Risk Factors for acute pain to become chronic...

Higher preop and postop pain scores, increases risk for CPSP
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- Extensive surgery, long surgical time, radiation and chemotherapy.
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- Perioperative anxiety, pain catastrophizing, excessive empathy from family.
Risk Factors for acute pain to become chronic...

Higher preop and postop pain scores, increases risk for CPSP

Surgical Procedure | Nerve Injured
--- | ---
Mastectomy | Lateral pectoral, medial pectoral, intercostal
Thoracotomy | Intercostal
Cesarean section | Ilioinguinal, iliohypogastric
Herniorrhaphy | Ilioinguinal

Extensive surgery, long surgical time, radiation and chemotherapy.

Perioperative anxiety, pain catastrophizing, excessive empathy from family.
Risk Factors for acute pain to become chronic...

Higher preop and postop pain scores, increases risk for CPSP

May explain ~70% of pain variability

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Cesarean section | Ilioinguinal, iliohypogastric
Herniorrhaphy | Ilioinguinal
Genetic polymorphisms result in altered nociception

Genetics may explain 70% of variability in experiencing pain

SCN9A Gene: Nav1.7

“Man on Fire Syndrome”

“Normal Pain Perception”

“No pain”
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein affected</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased Pain Sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCNS1</td>
<td>Voltage gated potassium ion channel</td>
<td>Increase sciatica pain and phantom limb pain</td>
</tr>
<tr>
<td>SCN9A</td>
<td>Voltage gated sodium ion channel</td>
<td>Chronic burning pain, phantom limb pain</td>
</tr>
<tr>
<td>ADRB2</td>
<td>Beta-2-adrenergic receptor</td>
<td>Risk for widespread body pain</td>
</tr>
<tr>
<td>IL6</td>
<td>Interleukin 6</td>
<td>Pain from endometriosis</td>
</tr>
<tr>
<td>CACNG2</td>
<td>Voltage-gated calcium ion channel</td>
<td>Post mastectomy pain</td>
</tr>
<tr>
<td>HTR2A</td>
<td>Serotonin receptor</td>
<td>Increased post-surgical pain</td>
</tr>
<tr>
<td><strong>Decreased Pain Sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
<td>Decreased or increased pain perception</td>
</tr>
<tr>
<td>OPRM1</td>
<td>OPRM1: opioid receptor mu 1</td>
<td>Decreased pain perception</td>
</tr>
<tr>
<td>TRPV1</td>
<td>Transient receptor potential vanilloid 1</td>
<td>Decreased thermal pain sensitivity</td>
</tr>
<tr>
<td>MC1R</td>
<td>Melanocortin 1 receptor</td>
<td>Decreased pain perception</td>
</tr>
<tr>
<td>GCH1</td>
<td>GTP cyclohydrolase</td>
<td>Decreased post-surgical pain</td>
</tr>
<tr>
<td>CACNA2D3</td>
<td>Voltage-gated calcium ion channel</td>
<td>Decreased thermal pain sensitivity</td>
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Summary

Normal Pain Signaling
Transduction
Transmission
Modulation
Perception

When acute becomes chronic pain
Rates of chronic pain
Abnormal changes in the pain pathway
RF for acute to chronic pain
Genetics in pain pathway
Thank you for your attention!