Pain Pathophysiology Unraveled

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Disclosures

- Nothing to disclose
Learning Objectives

- Differentiate between nociceptive and neuropathic pain
- Describe the process of pain transmission
- Identify the specific pain pathways that can be acted upon by common pharmacotherapy classes

Classification of Pain

- Good pain vs bad pain
Good Pain

- **Nociceptive pain**: purposeful pain
  - **Eudynia**: being in pain linked to normal tissue function or damage
  - Non-maldynic pain
  - Adaptive

Bad Pain

- **Neuropathic pain**: non-purposeful pain
  - **Maldynia**: pain linked to disorder, illness, or damage
  - i.e. may be abnormal, unfamiliar pain, assumed to be caused by dysfunction in PNS or CNS
Pain Mechanisms

General Anatomy of Pain

Cortex and subcortical regions: Perception, sensory, & affective pain components

Brainstem: Descending modulation

Spinal cord: Synaptic transmission, modulation & central sensitization

Periphery: Transmission & peripheral sensitization


Pain Roadmap:
Peripheral and Central Nervous System Landmarks

- Physiologic process involving multiple areas of the nervous system
- Bidirectional
- Involves normal as well as pathological processes
- A sensory experience associated with affective and cognitive responses
- Dynamic (i.e. occurring in real time)
- Adapts or changes in response to function—“neuroplasticity”

Common Types of Pain

<table>
<thead>
<tr>
<th>Nociceptive pain</th>
<th>Noxious stimuli</th>
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<tbody>
<tr>
<td></td>
<td>Heat, Cold, mechanical force, chemical irritants</td>
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<thead>
<tr>
<th>Inflammatory pain</th>
<th>Macrophage, Mast cell, Neutrophil, Granulocyte, Tissue Damage</th>
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<tr>
<th>Neuropathic pain</th>
<th>Neural lesion, Positive and negative symptoms</th>
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<tr>
<th>Functional pain</th>
<th>Dysfunctional pain</th>
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**Nociceptive vs Neuropathic Pain**


**Pain Pathway Steps**

- **Perception**
  - Cortex and subcortical regions: sensory, and affective pain components
  - Behavioral/Limbic

- **Transmission**
  - Spinal Cord/Ascending Spinal Pathways

- **Conduction**
  - Peripheral nerve synapsing in the dorsal horn

Adapted from Schott J, Woolf CJ. *Nat Neuroscience*, 2002;5:1062-1067.
### Molecular Elements: Peripheral—Central

**Transduction**
- TRPV1, TRPV2, TRPV3, TRPM8
- ASIC, DRASIC
- MDEG, TREK-1
- BK₁, BK₂
- P2X₃

**Membrane excitability of peripheral afferents**
- Na₁, 1.8, Na₁, 3.2
- K⁺ channel

**Peripheral sensitization**
- NGF, TrkA
- TRPV1
- Na₁, 1.8
- PKA, PKC isoforms, CaMK IV
- Erk ½, p38, JNK
- IL-1β, cPLA₂, COX2, EP1, EP3, EP4
- c-fos

**Central Inhibition**
- GABA, GABAₐ-R, GABAₜ-R
- Glycine-R
- NE, 5-HT
- Opioid receptors
- CB₁

**Synaptic Transmission**

**Presynaptic**
- VGCC
- Adenosine-R
  (mGlu-R)

**Postsynaptic**
- AMPA/kainate-R, NMDA-R, mGlu-R
- NK₁
- Na₁, 3.2
- K⁺ channel

**Signal transduction**
- PKA, PKC isoforms
- ERK, p38, JNK

**Gene expression**
- c-fos, c-jun, CREB, DREAM

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### Transduction:
Processing at Peripheral Nerve Endings

- Conversion of mechanical, thermal or chemical stimuli into an electric charge
- Involves
  - Receptors activated directly by stimuli
  - Injury/inflammatory response

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Adapted from Scholz J, Woolf CJ. Nature Neuroscience supplement Vol 5, 2002

How is Pain Transduced?

- Nociception
  - Mechanical
  - Thermal
  - Chemical

- Mediators
  - Prostaglandins
  - Leukotrienes
  - Substance P
  - Histamine
  - Bradykinin
  - Serotonin
  - Hydroxyacids
  - Reactive oxygen species
  - Inflammatory cytokines and chemokines

Conduction

- Conduction impulses from primary nociceptors to the spinal cord (dorsal horn) along the peripheral nerve
**Primary Nociception**

- **A-delta fibers**
  - Small receptive fields
  - Thermal & mechanical
  - Myelinated
  - Rapidly conducting
    - 10-30 m/sec
  - Large diameter

- **C-fibers**
  - Broad receptive fields
  - Polymodal
  - Unmyelinated
  - Slower conducting
    - .5-2.0 m/sec
  - Cross sensitized
  - Small diameter

**Peripheral Pain Nociceptors**

- Aβ - muscle spindle secondary endings, touch, and kinesthesia.
- Aδ - pain, temperature, crude touch, and pressure.

Transmission & Modulation

Ascending nociceptive pathways
Transmitting nociceptive impulses from the dorsal horn to supraspinal targets
- **Fast** (green) Neospinalthalamic
- **Slow** (yellow) Paleospinalthalamic

Descending inhibitory tracts
- (blue)
  Increase or decrease volume control of incoming nociceptive signals reaching the brain
- 5-HT - Serotonin
- NE - Norepinepherine

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How is Pain Conducted and Transmitted?

- **Excitatory Transmitters**
  - Substance P
  - Calcitonin gene related peptide
  - Aspartate, Glutamate

- **Inhibitory Transmitters**
  (descending inhibitory pathways)
  - GABA
  - Glycine
  - Somatostatin
  - a2 agonists
Role of Neuronal Plasticity in Pain

- Nervous system changes in
  - Neuronal structure
  - Connections between neurons
  - Quantity/properties of neurotransmitters, receptors, ion channels
- Decreases body’s pain inhibitory systems (increased pain)
- Injury, inflammation, and disease are culprits
- Produces short-term and permanent changes
- Pivotal to the development of hypersensitivity of inflammatory pain

- Enables NS to modify its function according to different conditions or demands placed upon it

How Acute Pain Becomes Chronic

- Peripheral sensitization
  - Tissue damage releases sensitizing “soup” of cytokines and neurotransmitters
  - COX-mediated PGE2 release
  - Sensitized nociceptors exhibiting a decreased threshold for activation and increased rate of firing
- Central sensitization—Resulting from noxious input to the spinal cord
  - Resulting in hyperalgesia and allodynia
Definitions

- **Hyperalgesia**
  - Lowered threshold to different types of noxious stimuli

- **Allodynia**
  - Painful response to what should normally be non-painful stimuli

Neuroplasticity in Pain Processing

![Graph showing pain intensity vs. stimulus intensity]

Neuroplasticity in Peripheral Pain Transmission

Peripheral Sensitization
How Acute Pain Becomes Chronic

- Central sensitization
  - Activation
    - “Wind up” of dorsal horn nociceptors
  - Modulation
    - Excitatory/Inhibitory neurotransmitters
  - Decreased central inhibition of pain transmission
  - Prime role in chronic pain, particularly neuropathic pain

Definitions

- Wind Up
  - Causes long-term changes in nociceptive neurons, which become hyperexcitable such that they respond to lower stimuli
    - NMDA-type glutamate receptors play an important role in this process\(^1,2,3,4\)
  - Prolonged opening of the ion channels enables greater influx of calcium and sodium across the post-synaptic membrane and greater excitation of nociceptive neurons\(^2,3\)

Central Sensitization

Afferent first order neuron
Dorsal horn neuron

NK-1 = Neurokinin 1 receptor; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartate; VGCC = voltage gated sodium channel; TrkB = tropomyosin receptor kinase B; BDNF = Brain derived neurotrophic factor; SP = substance P

Adapted from Schlotz J, Woolf CJ. Nat Neuroscience. 2002;5:1062-1067

Central Sensitization (cont’d)

Key Influences upon signal propagation

- Excitatory neurotransmitters
  - Substance P, CGRP, glutamate
- NMDA channel activity
  - Glutamate binding
  - Altering channel activity
- Descending inhibitory tracts
  - NE/serotonin (5HT)
- Mu opioid receptor

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Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing$^{1,2}$

Spinal cord glial cell

A$\delta$

C Fiber

Descending inhibitory axon

Second-order projection neuron (to brain)

GABA-ergic inhibitory interneuron


Neuroplasticity: Neural Reorganization
Neuroplasticity: Cross Talk

Central Sensitization:
Neuroplasticity in Spinal Cord Processing

- Definition: Altered function of neurons or synaptic activity
- Mechanisms of central sensitization may include:
  - Changes effecting glutamate/NMDA receptors activity
    - Reduced threshold for activation
    - Increased availability of glutamate
    - Increased influx of Na+/Ca+ (receptor open longer)
  - Modulation—excitatory/Inhibitory neurotransmitters
  - Decreased tone—descending inhibitory pathways\(^2\)
  - Activation/migration of glial cells into the spinal cord\(^3\)
  - Changes in the thalamus and primary somatosensory cortex\(^4\)

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Brain Regions Involved in Pain Processing

- Somatosensory cortex
  - Localization
- Thalamus
  - Routing
- Hippocampus
  - Pain memory/Learning
- Amygdala
  - Emotional Aspect

Pain and emotion
- Prefrontal cortex
  - Motor planning
- Anterior cingulate cortex
  - Context/situation of pain
- Insular cortex
  - Pain judged to the degree and where pain is imagined

Analgesics That Modify Pain Processes

- Transduction
  - NSAIDs
  - Antihistamines
  - Membrane stabilizing agents
  - Local anesthetic cream
  - Opioids
  - Bradykinin & Serotonin antagonists
- Transmission/Modulation
  - Spinal opioids
  - α₂ agonists
  - NMDA receptor antagonists
  - NSAIDs
  - NO inhibitors
  - K+ channel openers
- Conduction
  - Local anesthetics
    - Peripheral nerve, plexus, epidural block
- Perception
  - Parenteral opioids
  - α₂ agonists
  - General anesthetics

Pharmacological Targets in Pain

Peripheral Sensitization

Ectopic Activity
- Non-Native Modulators
- Cation Channel Blockers
- NMDA Receptor Antagonists
- Enzyme Inhibitors

Descending Modulation
- Central Inhibitors
- 5-HT3
- GABA Agonists
- Neuropeptide Antagonists

Central Sensitization
- Enzyme Inhibitors
- Anticonvulsants
- NMDA Antagonists
- Neuropeptide Antagonists

The Chronic Pain Armamentarium

**Nonopioids**
- Acetaminophen
- NSAIDs
- COX-2 inhibitors

**Opioids**
- Mu-opioid agonists
- Mixed agonist-antagonists

**Adjuvant analgesics**
- Antidepressants
- Anticonvulsants
- Topical agents/local anesthetics
VA DoD Stepped Pain Care Model

Common Pharmacologic Therapies

- Acetaminophen
- NSAIDS
- Antiepileptics
- TCAs
- SNRIs
- Topicals
- Muscle relaxants
- Opioids
Nonopioids: Acetaminophen

Example
– Acetaminophen

Mechanism of action
– Inhibits prostaglandin production in CNS; antipyretic activity
– No effect on blocking peripheral prostaglandin production; no anti-inflammatory or antirheumatic activity

FDA Warning
– Potential severe liver damage if over-used
– Stevens-Johnson Syndrome and toxic epidermal necrolysis

Nonopioids: NSAIDs

Examples
– Acetylated (aspirin); nonacetylated (diflunisal); acetic acid (diclofenac); propionic acid (naproxen); fenamic acid (mefenamic acid); enolic acids (piroxicam); nonacidic (nabumetone); ibuprofen, selective COX-2s (celecoxib)

Mechanism of action
– Exhibit both peripheral and central effects; antiinflammatory and analgesic effects
– Inhibition of cyclooxygenase and prostaglandin production
– Inhibition of leukotriene B4 production
– Lipoxins (signaling resolution of inflammation)
Opioids

**Examples**
- Morphine, hydromorphone, fentanyl, oxycodone, oxymorphone, meperidine, codeine, methadone, tramadol

**Mechanism of action**
- Bind to opioid receptors in the central nervous system (CNS) to inhibit transmission of nociceptive input from periphery to spinal cord
- Activate descending pathways that modulate transmission in spinal cord
- Alter limbic system activity; modify sensory and affective pain aspects

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**Overview of Descending Pain Inhibitory Pathways and Modulation of Pain Response**

[Diagram of brain pathways involving opioid receptors and modulation of pain response]

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Note: The diagram includes labels for different brain regions and pathways, such as ACC (Anterior cingulate cortex), VGic (Ventral posterolateral thalamus), and NRM (Nucleus raphe magnus), with corresponding neurotransmitters and receptor types indicated.
Modulation of Central Sensitization by 5-HT & NE Descending Pathways

Mechanism of Action: Opioids
Adjuvant Analgesics: Tricyclic Antidepressants

**Examples**
- Amitriptyline, desipramine, doxepin, imipramine, nortriptyline

**Mechanism of action**
- Reduction in action potential firing of sodium channel activity
- Inhibition of reuptake of NE and 5-HT
- Analgesia is independent of antidepressant function
- High side effect profile (tolerability)
  - cardiotoxic (overdose)

TCAs and SNRIs Pharmacological Properties

http://pharmacologycorner.com
SSRIs (Selective Serotonin Reuptake Inhibitors)

Examples
– Citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline

Mechanism of action
– Selectively inhibit 5-HT reuptake without affecting NE

Therefore, no pain relief expected!

Serotonin

- International Union of Pure and Applied Chemistry nomenclature
  – 5-Hydroxytryptamine (5-HT)
  – Monoamine neurotransmitter, biochemically derived from tryptophan
  – Receptors are a group of G protein-coupled receptors (GPCRs) and ligand-gated ion channels (LGICs) found in the central and peripheral nervous systems
Serotonin/5-HT Receptors

<table>
<thead>
<tr>
<th>Family</th>
<th>Type</th>
<th>Mechanism</th>
<th>Potential</th>
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<tbody>
<tr>
<td>5-HT1</td>
<td>G(_a)/G(_i) protein coupled.</td>
<td>Decreasing cellular levels of cAMP.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5-HT2</td>
<td>G(_a)/G(_i) protein coupled.</td>
<td>Increasing cellular levels of IP(_3) and DAG.</td>
<td>Excitatory</td>
</tr>
<tr>
<td>5-HT3</td>
<td>Ligand-gated Na(^+) and K(^+) channel</td>
<td>Depolarizing plasma membrane.</td>
<td>Excitatory</td>
</tr>
<tr>
<td>5-HT4</td>
<td>G(_a) protein coupled.</td>
<td>Increasing cellular levels of cAMP.</td>
<td>Excitatory</td>
</tr>
<tr>
<td>5-HT6</td>
<td>G(_a)/G(_i) protein coupled.</td>
<td>Decreasing cellular levels of cAMP.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5-HT7</td>
<td>G(_a) protein coupled.</td>
<td>Increasing cellular levels of cAMP.</td>
<td>Excitatory</td>
</tr>
</tbody>
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Serotonin/5-HT Receptors (cont’d)

- 5-HT1a (Blood Ves/CNS)
  - Addiction
  - Aggression
  - Anxiety
  - Appetite
  - BP
  - Cardiovascular function
  - Emesis
  - Heart rate
  - Impulsivity
  - Memory
  - Mood
  - Nausea
  - Nociception
  - Penile erection
  - Pupil dilatation

- 5-HT1a (cont)
  - Respiration
  - Sexual behavior
  - Sleep
  - Sociability
  - Thermoregulation

- 5-HT5a & 5-HT6 (CNS)
  - Locomotion
  - Sleep
  - Anxiety
  - Cognition
  - Learning
  - Memory
  - Mood
**SNRIs** (Serotonin/Noradrenaline Reuptake Inhibitors)

**Examples**
- Duloxetine, milnacipran, and venlafaxine

**Mechanism of action**
- Block reuptake of 5-HT and NA
  - Better tolerated, lower tendency for drug-drug interactions, better overdose safety

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**Modulation of Central Sensitization by 5-HT & NE Descending Pathways**
Site of Action: SNRIs

Adapted from Woolf C, Max M Anesthesiology 2001

Adjuvant Analgesics: Antiepileptics

**Examples**
- Gabapentin, pregabalin*, carbamazepine, phenytoin, divalproex sodium, clonazepam, levetiracetam, topiramate, lamotrigine

**Mechanism of action**
- Suppress neuronal hyperexcitability via
  - Reducing neuronal influx of sodium (Na+) and calcium (Ca+ +)
  - Direct/indirect enhancement of GABA inhibitory effects
  - Reduce activity of glutamate and/or blocking NMDA receptors
  - Binds the α2δ subunit of voltage gated Ca+ channels, inhibit NT release
Site of Action: Antiepileptics

Adjuvant Analgesics: Topicals

**Examples**
- Lidocaine patch 5%, eutectic, mixture of lidocaine and prilocaine
- Capsaicin cream/patch
- Diclofenac (cream/liquid/gel/patch)

**Mechanism of action**
- Block sodium channels and inhibit generation of abnormal impulses by damaged nerves
- Depletion of peripheral small fibers and therefore Substance P release from sensory nerve endings
- Target local inflammatory response
**Muscle Relaxants**

- Decrease tone of skeletal muscles
- Subclasses
  - Neuromuscular blockers
    - Act at the neuromuscular junction
    - Often used in surgery to cause temporary paralysis
  - Spasmolytics
    - Centrally acting

**Muscle Relaxants: Spasmolytics**

- Enhancing the level of inhibition
  - Mimicking or enhancing the actions of endogenous inhibitory substances, such as GABA
- Reducing the level of excitation
- Common examples
  - Cyclobenzaprine (TCA) methocarbamol, carisoprodol, tizanadine (α-2 agonist), baclofen (GABA agonist), orphenadrine (benzodiazepine)
- Common adverse effects
  - Sedation, lethargy & confusion (cyclobenzaprine), dependence (carisoprodol)
Case Study

- 54-year-old with 3 year history of neck, shoulder, and upper extremity pain following a lifting injury
  - Current medications
    - Fluoxetine
    - Milnacipran
    - Gabapentin
    - Clonazepam
    - Alprazolam
    - Robaxin
    - Tapentadol
    - Acetaminophen and propoxyphene
    - Zolpidem
    - Diclofenac topical
    - Acetaminophen

Importance for Understanding Pain Mechanisms

- Allow for rational rather than empirical approach to pain control
- Foster the development of diagnostic tools to identify specific pain mechanisms
- Facilitate pharmacotherapies that act on specific pain pathways and mechanisms
- Reduce the number of pharmacotherapies and incidence of drug-related adverse events (rationale polypharmacy)
- Enhances use of non-pharmacologic treatments
- Improve overall patient care and outcome
  - Tailoring treatment based on the individual patient and pain type
- Do not forget to look for the spear