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

Clinical Pearl
Good Pain

- **Nociceptive pain**: purposeful pain
  - **Eudynia**—pain linked to normal tissue function or damage
  - **Nonmaldynic pain**
  - **Adaptive**

Bad Pain

- **Neuropathic Pain**: Nonpurposeful 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 (ie, occurring in real time)
- Adapts or changes in response to function—“Neuroplasticity”

Common Types of Pain

Nociceptive pain
- Noxious stimuli: Heat, Cold, Mechanical force, Chemical irritants
- Spinal cord
- Nociceptor sensory neuron
- Adaptive, high-threshold pain
- Early warning system (protective)

Inflammatory pain
- Macrophage, Mast cell, Neutrophil, Granulocyte
- Tissue Damage
- Adaptive, low-threshold pain
- Promotes repair (protective)

Neuropathic pain
- Neural lesion
- Positive and negative symptoms
- Peripheral nerve damage
- Maladaptive, low-threshold pain
- Disease state of nervous system

Functional pain
- Non-Neuropathic, Non-inflammatory
- Dysfunctional pain
- Normal peripheral tissue and nerves

Nociceptive vs Neuropathic Pain


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 Scholz J, Woolf CJ. J Neurosci. 2002;S183:S187

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

Transduction
Peripheral nociceptor converts input to electric charge

Transmission
Spinal Cord/Ascending Spinal Pathways

Conduction
Peripheral nerve synapsing in the dorsal horn

Adapted from Scholz J, Woolf CJ. J Neurosci. 2002;S183:S187

PAG = periaqueductal grey
RVM = rostral ventromedial medulla
## Molecular Elements: Peripheral - Central

### Transduction
- TRPV1, TRPV2, TRPV3, TRPM8
- ASIC, DRASIC
- MDEG, TREK-1
- BK<sub>1</sub>, BK<sub>2</sub>
- P2X<sub>3</sub>

### Membrane excitability of peripheral afferents
- Na<sub>1</sub>, Na<sub>1.8</sub>, Na<sub>1.9</sub>
- K<sup>+</sup> channel

### Peripheral sensitization
- NGF, TrkA
- TRPV1
- Na<sub>1</sub>, Na<sub>1.8</sub>
- PKA, PKC isoforms, CaMK IV
- Erk ½, p38, JNK
- IL-1β, cPLA<sub>2</sub>, COX2, EP1, EP3, EP4
- TNFα

### Synaptic Transmission

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

#### Postsynaptic
- AMPA/kainite-R, NMDA-R, mGlu-R
- NK1
- Na<sub>1.3</sub>
- K<sup>+</sup> channel

### Central Inhibition
- GABA, GABA<sub>A</sub>-R, GABA<sub>B</sub>-R
- Glycine-R
- NE, 5-HT
- Opioid receptors
- CB1

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

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

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

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### Transduction: Processing at Peripheral Nerve Endings

- Conversion of mechanical or chemical stimuli into an electric charge
- Involves
  - receptors activated directly by stimuli
  - injury/inflammatory response

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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
    - 0.5-2.0 m/sec
  - Cross sensitized
  - Small diameter

**Peripheral Pain Nociceptors**

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

How is Pain Conducted and Transmitted?

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

- **Inhibitory Transmitters** *(Descending Inhibitory Pathways)*
  - GABA
  - Glycine
  - Somatostatin
  - $\alpha_2$ agonists

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 - Norepinephrine

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

How Acute Pain Becomes Chronic

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

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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

Key Influences upon signal propagation

- Excitatory Neurotransmitters
  - Substance P, CGRP, Glutamate
- NMDA Channel Activity
  - Glutamate binding
  - Altering channel activity
- Descending inhibitory tracts
  - NE/Serotonin (SHT)
- Mu opioid receptor

Adapted from Schlotz J, Woolf CJ. Nat Neuroscience. 2002;5:1062-1067
Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing

Spinal cord glial cell

Aδ

C Fiber

Descending inhibitory axon

Second-order projection neuron (to brain)

GABA-ergic inhibitory interneuron


Neuroplasticity: Neural Reorganization

CTB = cholera toxin B
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 pathways²
  - Activation/migration of glial cells into the spinal cord³
  - Changes in the thalamus and primary somatosensory cortex⁴

Brain Regions Involved in Pain Processing

- Somatosensory cortex
- Localization
- Thalamus
- Routing
- 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
  - $\alpha_2$ agonists
  - NMDA receptor antagonists
  - NSAIDs
  - NO inhibitors
  - K$^+$ channel openers
- Conduction
  - Local anesthetics
    - Peripheral nerve, plexus, epidural block
- Perfusion
  - Parenteral opioids
  - $\alpha_2$ agonists
  - General anesthetics

Pharmacological Targets in Pain

Peripheral Sensitization
- Acetaminophen
- NSAIDs
- COX-2 inhibitors

Opioids
- Mu-opioid agonists
- Mixed Agonist-antagonists

Adjuvant analgesics
- Antidepressants
- Anticonvulsants
- Topical agents/local anesthetics

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
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 & toxic epidermal necrolysis
**Nonopioids: NSAIDs**

**Examples**
- Acetylated (aspirin); nonacetylated (dilunisol); 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

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

Modulation of Central Sensitization by 5-HT & NE Descending Pathways
Mechanism of Action - Opioids

- Cortex and subcortical regions: Perception, sensory, and affective pain components
- Thalamus
- Brainstem: Descending modulation
- Spinal cord: Synaptic transmission, modulation and central sensitization
- Periphery: Transmission and peripheral sensitization

Adapted from Woolf C, Max M Anesthesiology 2001

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

Adjuvant Analgesics: 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>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT₁</td>
<td>Gq/Gi protein coupled.</td>
<td>Decreasing cellular levels of cAMP.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5-HT₂</td>
<td>Gi/Gi protein coupled.</td>
<td>Increasing cellular levels of IP₃ and DAG.</td>
<td>Excitatory</td>
</tr>
<tr>
<td>5-HT₃</td>
<td>Ligand-gated Na⁺ and K⁺ cation channel</td>
<td>Depolarizing plasma membrane.</td>
<td>Excitatory</td>
</tr>
<tr>
<td>5-HT₄</td>
<td>Gq protein coupled.</td>
<td>Increasing cellular levels of cAMP.</td>
<td>Excitatory</td>
</tr>
<tr>
<td>5-HT₅</td>
<td>Gq/Gi protein coupled.</td>
<td>Decreasing cellular levels of cAMP.</td>
<td>Inhibitory</td>
</tr>
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<td>5-HT₆</td>
<td>Gq/Gi protein coupled.</td>
<td>Increasing cellular levels of cAMP.</td>
<td>Excitatory</td>
</tr>
<tr>
<td>5-HT₇</td>
<td>Gq protein coupled.</td>
<td>Increasing cellular levels of cAMP.</td>
<td>Excitatory</td>
</tr>
</tbody>
</table>

Serotonin/5-HT Receptors

- 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

http://en.wikipedia.org/wiki/5-HT_receptor

Adjuvant Analgesics: 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)
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

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**Site of Action - Antiepileptics**

![Diagram of site of action for antiepileptic drugs]
Adjuvant Analgesics: Topicals

**Examples**
- Lidocaine Patch 5%, eutectic, mixture of lidocaine and prilocaine
- Capsaicin cream/patch
- Dicofenac (cream/liquid/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, carisopradol, tizanadine (α-2 agonist), baclofen (GABA agonist), orphenadrine (benzodiazipine)
- Common adverse effects
  - sedation, lethargy & confusion (cyclobenzaprine), dependence (carisopradol)

Case Study

- 54 year-old with three 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
- Enhances use of non-pharmacologic treatments
- Improve overall patient care and outcome

Summary

- Today’s clinicians must possess a working knowledge of the etiology and mechanisms of pain syndromes
  - Understanding pain mechanisms/pathophysiology is key to successful pain control
    - Reduce the number of medications and incidence of drug-related adverse events
      - (rationale polypharmacy)
    - Many therapeutic options are available
      - (non-pharmacological)
  - Tailoring treatment based on the individual patient and pain type can improve outcomes
  - Understanding how treatments effect function clinical presentation and function
  - Do not forget to look for the spear