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

Nociceptive pain
- Noxious stimuli
  - Heat
  - Cold
  - Mechanical force
  - Chemical irritants
- Peripheral nerve damage
- Adapted, high-threshold pain
  - Early warning system (protective)

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

Neuropathic pain
- Neural lesion
  - Positive and negative symptoms
- Peripheral nerve damage

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

Transduction
Peripheral nociceptor converts input to electric charge

Transmission
Spinal Cord/Ascending Spinal Pathways

Conduction
Peripheral nerve synapsing in the dorsal horn

PAG = periaqueductal grey
RVM = rostral ventromedial medullar

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

Pain Pathway Steps
Molecular Elements: Peripheral—Central

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

Membrane excitability of peripheral afferents
Na+, 1.8, Na+, 3, K+ channel

Peripheral sensitization
NGF, TrkA, TRPV1, Na+, 1.8, PKA, PKC isoforms, CaMK IV, Erk Ḵ, p38, JNK, IL-1β, cPLA2, COX2, EP1, EP3, EP4, TNFα

Synaptic Transmission
Presynaptic
VGCC
Adenosine-R (mGlu-R)

Postsynaptic
AMPA/kainite-R, NMDA-R, mGlu-R, NK1, Na+, 1.3, K+ channel

Central Inhibition
GABA, GABAα-R, GABAβ-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

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

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

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**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 - Norepinephrine

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

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
  - Prolonged opening of the ion channels enables greater influx of calcium and sodium across the post-synaptic membrane and greater excitation of nociceptive neurons

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-aspartic acid; VGCC = voltage gated sodium channel; TrkB = tropomyosin receptor kinase B; BDNF = Brain derived neurotrophic factor; SP = substance P

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\textsuperscript{1,2}

Spinal cord glial cell

Second-order projection neuron (to brain)

A\textdelta

C Fiber

Descending inhibitory axon

GABA-ergic inhibitory interneuron

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Neuroplasticity: Neural Reorganization

Receptor fields

Modulation

Axotomy

C fiber terminals in lamina III
A\textdelta fiber terminals in lamina II-IV

CTB = cholera toxin B

Photo courtesy of Professor S.B. McMahon
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 affecting 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
  - Activation/migration of glial cells into the spinal cord
  - Changes in the thalamus and primary somatosensory cortex

Brain Regions Involved in Pain Processing

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

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

Peripheral Sensitization
- NSAIDs
- Vanilloids

Ectopic Activity
- Na+ channel blockers
- Ca2+ channel blockers
- GABAergic enhancement
- Glutaminergic inhibition

CNS

Descending Modulation
- Central α-agonists
- TCAs
- SNRIs
- Opioids/Tramadol

Central Sensitization
- Opioids/Tramadol
- Central cannabinoids
- NMDA antagonists
- Anticonvulsants

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

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

Adapted from Woolf C, Max M Anesthesiology 2001

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

[Diagram showing the pharmacological properties of TCAs and SNRIs]

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!*

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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>Gα/Gβ protein coupled.</td>
<td>Decreasing cellular levels of cAMP.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5-HT2</td>
<td>Gq/G11 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/G11 protein coupled [4]</td>
<td>Decreasing cellular levels of cAMP.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5-HT6</td>
<td>Gq 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>

- **5-HT1a (Blood Vessels/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

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**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**

[Diagram showing modulation of central sensitization by 5-HT and 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