Pain Pathophysiology Unraveled
David M Glick, DC, DAAPM, CPE

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heat</td>
</tr>
<tr>
<td></td>
<td>Cold</td>
</tr>
<tr>
<td></td>
<td>Mechanical force</td>
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<tr>
<td></td>
<td>Chemical irritants</td>
</tr>
</tbody>
</table>

Adaptive, high-threshold pain
Early warning system (protective)

Adaptive, low-threshold pain
Promotes repair (protective)

Inflammatory pain
Macrophage
Mast cell
Neutrophil
Granulocyte
Tissue Damage

Neuropathic pain
Neural lesion
Positive and negative symptoms

Maladaptive, low-threshold pain
Disease state of nervous system

Functional pain
Non-Neuropathic
Non-inflammatory

Dysfunctional pain

Nociceptive vs Neuropathic Pain

**Nociceptive**
- Arthritis
- Mechanical low back pain
- Post-operative pain
- Sickle cell crisis
- Sports/Exercise injury

**Mixed**
- Fibromyalgia
- Headache
- Low back pain
- Myofascial pain syndrome
- Skeletal muscle pain

**Neuropathic**
- Neuropathic low-back pain
- Polyneuropathy (diabetic, HIV)
- Postherpetic neuralgia
- Trigeminal neuralgia

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**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

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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
- BK<sub>1</sub>, BK<sub>2</sub>
- P2X<sub>3</sub>

#### Membrane excitability of peripheral afferents
- Na<sub>1.8</sub>, Na<sub>1.3</sub>
- K<sup>+</sup> channel

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

#### Synaptic Transmission

<table>
<thead>
<tr>
<th>Presynaptic</th>
<th>Postsynaptic</th>
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</thead>
<tbody>
<tr>
<td>VGCC</td>
<td>AMPA/kainite-R, NMDA-R, mGlu-R</td>
</tr>
<tr>
<td>Adenosine-R</td>
<td>Na&lt;sub&gt;1.3&lt;/sub&gt;, K&lt;sup&gt;+&lt;/sup&gt; channel</td>
</tr>
<tr>
<td>(mGlu-R)</td>
<td></td>
</tr>
</tbody>
</table>

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

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
- \( \alpha_2 \) 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

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

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\textsuperscript{1,2}

Adapted from:

Neuroplasticity: Neural Reorganization

CTB = cholera toxin B

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 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

- 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

- Perception
  - Parenteral opioids
  - $\alpha_2$ agonists
  - General anesthetics
- Conduction
  - Local anesthetics
    - Peripheral nerve, plexus, epidural block

Pharmacological Targets in Pain

Peripheral Sensitization
- NSAIDs
- Venoms

Descending Modulation
- TCA
- EPB
- Opioid/Translators

Central Sensitization
- Antidepressants
- Local Anesthetics
- Opioids

Ectopic Activity
- Non-ion channel Modulators
- P2X Channel Modifiers
- NMDA/AMPA antagonists
- Glutamate 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

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
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 mechanisms and properties of tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (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-HT1a</td>
<td>G/Gq protein coupled</td>
<td>Decreasing cellular levels of cAMP</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5-HT2</td>
<td>G protein coupled</td>
<td>Increasing cellular levels of IPs 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>G protein coupled</td>
<td>Increasing cellular levels of cAMP</td>
<td>Excitatory</td>
</tr>
<tr>
<td>5-HT6</td>
<td>G protein coupled</td>
<td>Decreasing cellular levels of cAMP</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5-HT7</td>
<td>G protein coupled</td>
<td>Increasing cellular levels of cAMP</td>
<td>Excitatory</td>
</tr>
</tbody>
</table>

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

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

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

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 (carisopradol)
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