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

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

<table>
<thead>
<tr>
<th>Nociceptive pain</th>
<th>Noxious stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heat, Cold, Mechanical force, Chemical irritants</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Inflammatory pain</th>
<th>Macrophage, Mast cell, Neutrophil, Granulocyte, Tissue Damage</th>
</tr>
</thead>
</table>

- Adaptive, low-threshold pain: Promotes repair (protective)

<table>
<thead>
<tr>
<th>Neuropathic pain</th>
<th>Neural lesion, Positive and negative symptoms</th>
</tr>
</thead>
</table>

- Maladaptive, low-threshold pain: Disease state of nervous system

<table>
<thead>
<tr>
<th>Functional pain</th>
<th>Dysfunctional pain</th>
</tr>
</thead>
</table>

- Normal peripheral tissue and nerves

**Nociceptive vs Neuropathic Pain**


---

**Pain Pathway Steps**

### Molecular Elements: Peripheral - Central

<table>
<thead>
<tr>
<th>Transduction</th>
<th>Peripheral sensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRPV1, TRPV2, TRPV3, TRPM8</td>
<td>NGF, TrkA</td>
</tr>
<tr>
<td>ASIC, DRASIC</td>
<td>TRPV1</td>
</tr>
<tr>
<td>MDEG, TREK-1</td>
<td>Na+, 1.8, Na+, 1.3</td>
</tr>
<tr>
<td>BKp, BKs</td>
<td>PKA, PKC isoforms, CaMK IV</td>
</tr>
<tr>
<td>P2X3</td>
<td>IL-1β, cPLA2, COX2, EP1, EP3, EP4</td>
</tr>
<tr>
<td></td>
<td>TNFα</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Membrane excitability of peripheral afferents</th>
<th>Synaptic Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+, 1.8, Na+, 1.3</td>
<td>Presynaptic</td>
</tr>
<tr>
<td></td>
<td>VGCC</td>
</tr>
<tr>
<td></td>
<td>Adenosine-R</td>
</tr>
<tr>
<td></td>
<td>(mGlu-R)</td>
</tr>
</tbody>
</table>

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

| | Central Inhibition |
| | GABA, GABA_A-R, GABA_B-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 |

---

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

**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

---

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.

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

![Neuroplasticity Diagram](image)

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 (5HT)
- **Mu opioid receptor**

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

NK-1 = Neurokinin 1 receptor; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolopropanoic 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; CRGP = Calcitonin gene related peptide
Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing 1,2

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

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
- 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
- Ectopic Activity
- Non-channels Models
- Fast Channel Blockers
- M2/M3 receptor antagonists
- Eledenizine inhibition

Descending Modulation
- Central sensitization
- CNS
- Pain Amplification
- PNS
- Pain Transmission
- Local Anesthetics
- Opioids

Central Sensitization
- Peripheral sensitization
- CNS
- Pain Amplification
- Pain Transmission
- Local Anesthetics
- Antidepressants

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

WHO
- Pain
- Non-opioid analgesics
- Opioid or non-opioid plus a second analgesic
- Opioid, if not contraindicated
- Opioid, if not contraindicated
- Opioid, if not contraindicated
- Opioid, if not contraindicated
- Opioid, if not contraindicated
- Opioid, if not contraindicated
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 (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

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

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>Gq/Gi 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>Gq protein coupled.</td>
<td>Increasing cellular levels of cAMP.</td>
<td>Excitatory</td>
</tr>
<tr>
<td>5-HT6</td>
<td>Gi/Gq protein coupled.</td>
<td>Decreasing cellular levels of cAMP.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5-HT7</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>

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

**Site of Action - Antiepileptics**
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 ($\alpha$-2 agonist), baclofen (GABA agonist), orphenadrine (benzodiazepine)
- 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