Pain Pathways Made Simple

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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** - being 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
  - 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

Functional pain
- Non-Nociceptive
- Non-Inflammatory
- Dysfunctional pain

Nociceptive vs Neuropathic Pain

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

- **Mixed**
  - Facial neuralgia
  - Herpes zoster
  - Low back pain
  - Mononeuropathic pain syndrome
  - Dental/venous pain

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


Pain Pathway Steps

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

- **Transduction**
  - Peripheral receptor converts input to an electric charge

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

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

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

![Dorsal Root Ganglion (DRG)](image)

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

![Painweek Logo](image)
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 - Norepineherine

How is Pain Conducted and Transmitted?

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

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

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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 & 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 in Peripheral Pain Transmission
Peripheral Sensitization

Central Sensitization

- Activation
  - "Wind up" of dorsal horn nociceptors
- Modulation
  - Excitatory/Inhibitory neurotransmitters
- Decreased central inhibition of pain transmission
  - NE/5HT

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

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**Central Sensitization**

![Diagram of afferent first order neuron and dorsal horn neuron]

NIK-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; TNF = Tumor necrosis factor; BDNF = Brain derived neurotrophic factor; SP = substance P

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

Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing

Spinal cord glial cell
Second-order projection neuron (to brain)
A6
C Fiber
Descending inhibitory axon
GABA-ergic inhibitory interneuron

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

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 pathways²
  - Activation/migration of glial cells into the spinal cord³
  - Changes in the thalamus and primary somatosensory cortex⁴

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Brain Regions Involved in Pain Processing

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Function Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatosensory cortex</td>
<td>Localization</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Routing</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Pain memory/learning</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Emotional Aspect</td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td>Motor planning</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>Context/Situation of pain</td>
</tr>
<tr>
<td>Insular cortex</td>
<td>Pain judged to the degree and where pain is imagined</td>
</tr>
</tbody>
</table>

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Analgesics That Modify Pain Processes

- **Perception**
  - Parenteral opioids
  - α₂ agonists
  - General anesthetics

- **Conduction**
  - Local anesthetics
    - Peripheral nerve, plexus, epidural block

- **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

Pharmacological Targets in Pain

- Ectopic Activity
- Descending Modulation
- Peripheral Sensitization

Woolf C, Max M Anesthesiology 2001
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 & toxic epidermal necrolysis
Nonopioids: NSAIDs

**Examples**

- Acetylated (aspirin); nonacetylated (difulunisal); 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**

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

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)
**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>Gαi/Gi-protein coupled.</td>
<td>Decreasing cellular levels of cAMP.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5-HT2</td>
<td>Gαq/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>Gα-protein coupled.</td>
<td>Increasing cellular levels of cAMP.</td>
<td>Excitatory</td>
</tr>
<tr>
<td>5-HT6</td>
<td>Gα-protein coupled.</td>
<td>Decreasing cellular levels of cAMP.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5-HT7</td>
<td>Gα-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

**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 Dorsal Horn and Spinal Cord Glial Cell with neurotransmitter pathways and inhibitory axons](image-url)
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 (diphenhydramine)
- 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
    - Methocarbamol
    - 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