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 - being pain linked to normal tissue function or damage
  - Non-maladaptive Pain
  - Adaptive

Bad Pain

- Neuropathic Pain: Non-purposeful Pain
  - Maldynia - pain linked to disorder, illness or damage
  - Le 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
Inflammatory pain
Neuropathic pain
Functional pain

Nociceptive vs Neuropathic Pain

Pain Pathway Steps
### Molecular Elements: Peripheral - Central

<table>
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<th>Transduction</th>
<th>Synaptic Transmission</th>
<th>Peripheral sensitization</th>
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<th>Gene expression</th>
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<tr>
<td>TRPV1, TRPV2, TRPV3, TRPM8, ASIC, TREK-1, BK, SK, PKA, PKC isoforms, CaMK IV, Erk ½, p38, JNK</td>
<td>Adenosine-R, mGlu-R</td>
<td>NGF, TrkA, TRPV1, Nav 1.8, Nav 1.9, K⁺ channel</td>
<td>GABA, GABA-A-R, GABA-B-R, Glycine-R, NE, 5-HT, Opioid receptors</td>
<td>PAM, P2X receptors</td>
<td>c-fos, c-jun, CREB, DREAM</td>
</tr>
</tbody>
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### How is Pain Transduced?

- **Nociception**
  - Mechanical
  - Thermal
  - Chemical

- **Mediators**
  - Prostaglandins
  - Substance P
  - Histamine
  - Bradykinin
  - Serotonin
  - Hydroxyacids
  - Reactive oxygen species
  - Inflammatory cytokines and chemokines

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**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
- Triggers
  - receptors activated directly by stimuli
  - injury/inflammatory response
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.

References:
How is Pain Conducted and Transmitted?

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

- Inhibitory Transmitters (Descending inhibitory pathways)
  - GABA
  - Glycine
  - Somatostatin
  - α2 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
    - Prolongs short-term and permanent changes
  - Pivotal to the development of hyperalgesia 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 receptors 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

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

- 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-methyle 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; CGRP = Calcitonin gene related peptide
Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing

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

Adapted from:

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 affecting glutamate/NMDA receptors activity
  - Reduced threshold for activation
  - Increased availability of glutamate
  - Increased influx of Na+/Ca2+ (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

- Prefrontal cortex: Motor planning, context/situation of pain
- Anterior cingulate cortex: Pain judged to the degree and where pain is imagined
- Insular cortex: Pain
- Amygdala: Emotional aspect
- Thalamus: Localization
- Somatosensory cortex: Localization

Analgesics That Modify Pain Processes

- Transduction:
  - NSAIDs
  - Antihistamines
  - Membrane-stabilizing agents
  - Local anesthetics
  - Opioids
- Transmission/Modulation:
  - Spinal opioids
  - NMDA receptor antagonists
  - NK-1 antagonists
  - K+ channel openers
- Conduction:
  - Local anesthetics
  - Preparations such as regional block

- Pain and emotion
- Pain only
- Prefrontal cortex: Motor planning
- Anterior cingulate cortex: Context/situation of pain
- Insular cortex: Pain judged to the degree and where pain is imagined
- Amygdala: Emotional aspect
- Thalamus: Localization
- Somatosensory cortex: Localization
Pharmacological Targets in Pain

The Chronic Pain Armamentarium

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

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Nonopioids: NSAIDs

**Examples**
- Acetylated (aspirin); nonacetylated (dilugen); acetic acid (diclofenac); propionic acid (naproxen); fenamic acid (mefenamic acid); enolic acids (piroxicam); nonacidic (naproxen); 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

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Opioids

**Examples**
- Morphine, hydromorphone, fentanyl, oxycodone, oxymorphone, meperidine, codeine, methadone, tramide

**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
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)

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
  - 5-HT1a (Blood Vessels/CNS)
    - Addiction
    - Aggression
    - Anxiety
    - Appetite
    - BP
    - Cardiovascular function
    - Emesis
    - Heart Rate
    - Impulsivity
    - Memory
    - Mood
    - Nausea
    - Nociception
    - Penile Erection
    - Pupil Dilatation
    - Respiration
    - Sexual Behavior
    - Sleep
    - Sociality
    - Thermoregulation
    - Sexual Function
    - Sleep
    - Anxiety
    - Cognition
    - Learning
    - Memory
    - Mood
    - Nociception

- Serotonin/5-HT Receptors
  - 5-HT6 (Blood Vessels/CNS)
    - Addiction
    - Aggression
    - Anxiety
    - Appetite
    - BP
    - Cardiovascular function
    - Emesis
    - Heart Rate
    - Impulsivity
    - Memory
    - Mood
    - Nausea
    - Nociception
    - Penile Erection
    - Pupil Dilatation
    - Respiration
    - Sexual Behavior
    - Sleep
    - Sociality
    - Thermoregulation

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
Adjuvant Analgesics: Antiepileptics

**Examples**
- Gabapentin, pregabalin*, carbamazepine, phenytoin, divalproex sodium, 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
  - Blocks the α2δ subunit of voltage gated Ca+ channels, inhibits NT release

Adjuvant Analgesics: Topicals

**Examples**
- Lidocaine Patch 5%, eutectic, mixture of lidocaine and prilocaine
- Capsaicin cream/patch
- Diclofenac (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, carisoprodol, tizanidine (α-2 agonist), tizanidine (GABA agonist), oxybutynin (benzodiazepine)
- Common adverse effects
  - sedation, lethargy, or confusional (cyclobenzaprine), dependence (carisoprodol)

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
  - Clozapine
  - 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
  - Many therapeutic options are available
    - (non-pharmacological)
  - Tailoring treatment based on the individual patient and pain type can improve outcomes
  - Understanding how treatments affect functional clinical presentation and function
  - Do not forget to look for the spear