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 certain pharmacotherapies
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
  - ie, 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

Nociceptive pain

Noxious stimuli
- Heat
- Cold
- Technical force
- Chemical irritants

Spinal cord

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

Injury
Stroke

Maladaptive, low-threshold pain
Disease state of nervous system

Functional pain

Dysfunctional pain

Normal peripheral tissue and nerves

Nociceptive vs Neuropathic Pain

Nociceptive Pain
Caused by activity in neural pathways in response to potentially tissue-damaging stimuli

Mixed Type
Caused by a combination of both primary injury and secondary effects

Neuropathic Pain
Initiated or caused by primary lesion or dysfunction in the nervous system

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
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

**Transduction**
Peripheral nociceptor converts input to electric charge

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

PAG = periaqueductal grey
RVM = rostral ventromedial medulla
Molecular Elements: Peripheral - Central

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

**Peripheral sensitization**
NGF, TrkA
TRPV1
Naᵥ 1.8
PKA, PKC isoforms, CaMK IV
Erk ½, p38, JNK
IL-1B, cPLA₂, COX2, EP1, EP3, EP4
TNFα

**Membrane excitability of peripheral afferents**
Naᵥ 1.8, Naᵥ 1.9
K⁺ channel

**Synaptic Transmission**

**Presynaptic**
VGCC
Adenosine-R
(mGlu-R)

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

**Central Inhibition**
GABA, GABAₐ-R, GABAₜ-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 in Peripheral Pain Transmission


IL-6, IL1β = interleukin 6, 1beta; MOR = μ opioid receptor; COX2 = cyclooxygenase; PKC, PKA = protein kinases C, A; TrkA = tyrosine kinase A receptor; Erk1/2 = extracellular signal-regulated kinases; TNFα = tumor necrosis factor alpha; TRPV1 = Transient receptor potential vanilloid 1; BK = bradykinin; AA = arachidonic acid; PGE2 = prostaglandin E2
Peripheral Sensitization

Sensitizing agent
(BK, H+, epi, lipoxygenase products, histamine, PGE2, NGF)

Mechanical

Chemical

Thermal

PLC

B1, ASIC, EP, TrkA receptors

IP3

DAG

PKC active

PKC

PKA

PKC

AC

ATP

cAMP

Ion channel phosphorylation

Ion influx

Generator potential (membrane depolarization)

Reach voltage sensitive channel threshold

Action potential

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

Afferent first order neuron

Dorsal horn neuron

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

Adapted from Schlotz 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 (5HT)

• Mu opioid receptor

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; CRGP = Calcitonin gene related peptide

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Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing 1,2

Neuroplasticity: Neural Reorganization

CTB = cholera toxin B

Modulation

Axotomy

C fibre terminals in laminae I/II
Aβ fibre terminals in laminae III-VI
CTB label in laminae I/II

Photo courtesy of Professor S.B. McMahon
Neuroplasticity: Cross Talk

CTB = cholera toxin B
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

**Pain and emotion**

**Pain only**

Analgesics That Modify Pain Processes

- **Perception**
  - parenteral opioids
  - $\alpha_2$ agonists
  - General anesthetics

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

- **Transmission/Modulation**
  - Spinal opioids
  - $\alpha_2$ agonists
  - NMDA receptor antagonists
  - NSAIDs
  - NO inhibitors
  - K+ channel openers

- **Transduction**
  - NSAIDs
  - Antihistamines
  - Membrane stabilizing agents
  - Local anesthetic cream
  - Opioids
  - Bradykinin & serotonin antagonists
Pharmacological Targets in Pain

Ectopic Activity
- Na+ channel blockers
- Ca+2 channel blockers
- GABAergic enhancement
- Glutaminergic inhibition

Peripheral Sensitization
- NSAIDS
- Vanilloids
- TCAs
- Anticonvulsants
- Local Anesthetics
- Opioids

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

CNS

Central Sensitization
- Opioids/Tramadol
- Central α-agonists
- NMDA antagonists
- Anticonvulsants

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
Common Pharmacologic Therapies

- Acetaminophen
- NSAIDS
- Antiepileptics
- TCAs
- SNRIs
- Topicals
- Muscle Relaxants
- Opioids
Site of Action—Antiepileptics
TCAs and SNRIs Pharmacological Properties

- Serotonin-norepinephrine reuptake inhibitors
  - Mechanism of action
    - Inhibition of 5-HT (serotonin) and norepinephrine (noradrenaline) reuptake
      - Treatment of neuropathic pain
      - Treatment of depressive disorders
  - Receptor blockade
    - Muscarinic receptors
      - Blurred vision, xerostomia, urinary retention, constipation, narrow angle glaucoma
    - Histamine H1 receptors
      - Sedation
    - Alpha adrenergic receptors
      - Orthostatic hypotension, dizziness, reflex tachycardia

Tricyclic antidepressants

http://pharmacologycorner.com
Modulation of Central Sensitization by 5-HT & NE Descending Pathways

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—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), baclofen (GABA agonist), orphenadrine (benzodiazepine)
- Common adverse effects
  - Sedation, lethargy & confusion (cyclobenzaprine), dependence (carisoprodol)
Overview of Descending Pain Inhibitory Pathways and Modulation of Pain Response


ACC = Anterior cingulate cortex; AMYG = Amygdala; PAG = periaqueductal gray; RVM = rostral ventromedial medulla;
DLPT = dorsolateral pontine tegmentum; Glu = glutamate; GABA = Gamma-aminobutyric acid
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
- 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