Pain Pathophysiology and Pathways: a foundation

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Disclosures:

No disclosures to report
“That really hurts”

http://youtube.com/watch?v=_OBlgSz8sSM
Pre-Test Questions

1. Which proteins activate primary afferent nociceptor (PAN) nerve endings?
   A. Bradykinins
   B. Histamines
   C. Prostaglandins
   D. Serotonin
   E. Substance P
   F. All of the above
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TRUE
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3. The development of pathologic pain states causing hyperalgesia and allodynia involves which of the following theorized processes?
A. Spinal sensitization
B. Loss of inhibitory interneurons from excitotoxicity
C. Perpetuation of the inflammatory response/peripheral nociception cascade
D. Activation of “silent nociceptors”
E. Deficits in the “inflammatory reflex” including the cholinergic anti-inflammatory pathway
F. All of the above
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Objectives

- Review key neurotransmitters and neuroanatomical structures involved in peripheral pain
- Discuss proposed hypotheses of pain mechanisms including the Inflammatory Cascade, Dorsal Root Reflexes, Gate Control Theory, and Spinal Facilitation
- Briefly review treatment approaches designed to modify what we understand of these “Ascending” and “Descending” pathways
Outline

- Review nomenclature
- Peripheral pain
  - pathways and pathophysiology
- Spinal cord facilitation
  - gate theory, wind-up, and plasticity
- Central pain pathways
  - ascending and descending modulators
- Treatment strategies
What is Nociception?

- Nociception is a mechanical or chemical event, originating in peripheral tissues.
  - This includes bone, intervertebral discs, muscles, vasculature, and viscera as well as cutaneous tissue.

- Nociception is (arguably) consistent between individuals.
What is Pain?

- The International Association for the Study of Pain Subcommittee on Taxonomy defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” (Merskey & Bogduk 1994)

- Pain is a perception of the activity of nociception in the spinal cord, brainstem, and cortex.

- Pain varies with cognitive and emotional states.

- Perception of pain can be modulated.
Types of Pain

- **Acute pain** is a normal condition in which “pain is a symptom of tissue injury.” (Bloodworth et al in Braddom 2004)
- Purpose: Activates the arousal system to form a protective action or response (ex. wound healing) to nociceptive event
- Result: Changes in the body
  - Muscle stiffening and altered ROM
  - Vasodynamic changes, shifting of circulatory compartments
  - Local release of pro-inflammatory compounds
  - Metabolic alterations favoring glucose production
- New adaptive state, “ALLOSTASIS”
  - the maintenance of stability through change
Types of Pain

- **Chronic pain** is “an abnormal condition…in which pain and pain behavior become the primary disease processes.” (Bloodworth et al in Braddom 2004)
- Failure to re-establish homeostasis
- Consequences:
  - repetitive nociceptive input on plastic neurons → neuromodulation/spinal facilitation → hyperalgesia (↑gain), allodynia (↓threshold), analgesia (↓output)
  - sustained allostasis → slow, progressive organ system damage
Types of Pain

- **Allodynia** refers to pain evoked by a non-painful stimuli (ie. touch)
  - As acute pain processes progress, “a threshold...is lowered to the extent that body temperature and the pressure of edema are adequate stimuli to result in spontaneous pain.” (Sorkin 1999)

- **Hyperalgesia** refers to an increased pain or heightened response evoked by a painful stimuli (out-of-proportion)
Peripheral Pathway

Small Caliber (pain/PT)
- virtually unmyelinated
- naked endings
- high threshold AP
- diffuse projections
- rapidly sensitize to repetitive stimulation
- synapse in laminas I-III
  = warning system
  = protection via nociception

Large Caliber (touch/2PV)
- myelinated
- encapsulated endings
- low threshold AP
- precise projections
- adapt to repetitive stimulation
- synapse in laminas IV-VII
  = decrease excitability of small caliber fibers
  = localization
Peripheral Nociception

- Primary Afferent Nociceptors (PANs): pain fibers
  - FAST Aδ-fibers (warning)
    - Mechanoreceptors and chemoreceptors
  - SLOW C-fibers (protection)
    - Chemoreceptors

- 30% Aδ, 40% C-fibers = “silent nociceptors”
  - become active only with tissue damage or inflammation
Peripheral Nociception

- Noxious stimuli or tissue damage causes release of proteins which irritate and activate PANs

- PAN Activators: induction of metabolic cascades
  - *Neuropeptides (PANs): substance P, calcitonin gene-related polypeptide (CGRP), and somatostatin
  - Bradykinins (from tissue)
  - Histamines (mast cells)
  - Prostaglandins (cell membrane)-increases pain in the PNS, decreases pain in CNS
  - ATP (damaged muscles): activate receptors on PAN membrane
  - H+ (tissue)
  - Chemokines (immune and nervous system cells)
  - Serotonin (platelets)
Peripheral Sensitization

- **“TRIAD” setup:** juxtaposed bare PANs, vessels, and mast cells

- Tissue Injury: vasodilation $\rightarrow$ swelling/edema $\rightarrow$ activation of stretch receptors and immunocyte migration to the region $\rightarrow$ cytokine release (IL, IF, TNF)

- Irritation of distal PAN ending $\rightarrow$ proximal relay to Dorsal Root Ganglia

- **Dorsal Root Reflexes** $\rightarrow$ distal PAN endings release the same type of neuropeptides (substance P and CGRP) that initiated the original nerve irritation

- “Chemical soup” affecting and activating other adjacent PAN endings $\rightarrow$ Dorsal Root Reflex

- Consequently, there is a decreased threshold to activate pain fibers, AND an additional population of pain fibers are “awakened” (silent nociceptor activation)
- A wave of depolarization enters the dorsal horn and adjacent terminals become depolarized. A greater population of dorsal horn neurons respond to a stimulus at the original site of injury.
- Small afferent fibers release neuropeptides (SP, CGRP) into the periphery, (antidromically)
- Thus, silent nociceptors are activated (40% of C-fibers, 30% of Aδ-fibers)
Peripheral Nociception Cascade

Schematic borrowed from Frank Willard, PhD
Peripheral Sensitization Sequelae

- Activated PAN stimulate spinal cord pathways via proximal release of:
  - Amino acids: Glutamate and Aspartate
    - into the dorsal horn
      - activates post-synaptic NMDA channels = second messenger system
  - Neuropeptides: Substance P and Calcitonin gene-related peptide
    - into the dorsal horn AND peripheral tissue
      - activates further mast cell degranulation, further vasodilation, & further immunocyte migration in the periphery
      - inflammatory chemical soup develops around adjacent PAN endings
      - activates phosphorylation cascade = second messenger system
Peripheral Sensitization Sequelae

“The peripheral mechanisms responsible for neuropathic pain are found in the altered gene/protein expression of primary sensory neurons [PANs]. With damage to peripheral sensory fibers, a variety of changes [“plasticity”] in pain-related gene expression take place in dorsal root ganglion neurons.”

Dorsal Root Entry Zone
Lateral (pain) & Medial (touch)

Lamina I (pain)

Lamina II and III (pain)

Lamina IV (touch)

Lamina V and VI (touch)

Lamina VII (touch)
Dorsal Horn Topography
the Laminas:

- I: prickling, tingling, coolness
- II/III: burning, itching, nociception
  - “substantial gelatinosa” = lamina II
  - generally does not project axons out of the cord, instead they help integration of multiple segments
- IV: light touch
- V/VI: referred pain, peripheral cutaneous, visceral input
- VII: proprioception from muscles, tendons

Implications: in pain states, second messenger systems cause large caliber (touch) fibers to sprout, forming collateral fibers to nociceptive lamina II
Spinal Cord Level Pathways

- Dorsal Horn receives input from:
  - Pain fibers
  - Touch fibers
  - **Wide dynamic range (WDR)**
    - Receive large receptive fields (Aβ, Aδ, C) and stimuli intensities
    - Modified by descending pathways
    - Selective activation leads to perception of discrete pain (normally)
Segmental Control

“Gate Control Theory”
- Large caliber fibers naturally yield collateral fibers, which synapse on inhibitory interneurons and presynaptic PAN terminals. Aδ-PAN terminals in the dorsal horn are surrounded by these GABAnergic synapses.

- Therefore, gentle touch inhibits our sensation of pain.
Spinal Facilitation

- Repetitive stimulation of a WDR neuron causes excitotoxicity and cell death.

- Receptor Field Dynamics
  - Facilitation causes sprouting of PAN terminals to other WDR neurons.
  - When PAN-1 sprouts to WDRN-2, WDRN-2 gains the afferent input from PAN-1’s receptor field in addition to input from PAN-2, thereby doubling its receptor field.
    - Detrimental if the receptor field of PAN-1 is already sensitized
  - May lead to further excitotoxicity of other inhibitory WDR neurons
Receptor Field Dynamics

WDRN 1 (dying) -> PAN 1 -> Receptor Field 1

Sprouting

WDRN 2 -> PAN 2 -> Receptor Field 2
Spinal Facilitation

“Wind-up”

- Increased Ca+ entry into dorsal horn neuron causes an increase in the cell’s Ca+ permeability, hyperexcitable state
- Gene induction initiating
  - synthesis of endogenous opioid (Dynorphin)
  - sprouting
- Ephaptic electrical cross talk spreads excitation to neighboring neurons
- Activity-dependent plasticity and structural re-organization: Large caliber (touch) fibers sprout, forming collaterals to nociceptive lamina II
- Altered activity of cord segment
  - Ventral Root Effects:
    - Changes in skeletal muscle tone, ROM, joint positioning
    - Enhanced sympathetic tone
Spinal Facilitation: Summary

Activity Dependent Plasticity

- Calcium influx (mediated by NMDA receptors) → decreased AP threshold, increased excitability, increased sensitivity
- Excitotoxicity → death of inhibitory interneurons
- Sprouting from PAN terminals to other WDR neurons → increased receptor field → excitotoxicity → death of other inhibitory interneurons
- Large fiber collaterals to nociceptive laminae, “wind-up” (due to the second messenger system and gene induction)
- Dorsal Root Reflexes: antadromic firing of PANs
Ascending Pathways

- **Lateral Pain Pathway**
  - Localization
  - SC(ALS) to VP thalamus to Primary and Secondary Sensory cortex

- **Medial Pain Pathway**
  - carries pain perceived as dull, throbbing, achy, diffuse
  - can be accompanied by nausea, vomiting, fear due to brainstem and limbic connections
  - SC(ALS) to Medial thalamus to Pre-frontal and Anterior Cingulate cortex (Limbic areas)
  - influences two Descending Pain Modulating Pathways
Descending Pathways
“Endogenous Pain Control”

- Limbic System influences dorsal horn and interneurons via a Serotonergic pathway.

- Norepinephrine stimulates the Arousal Center of the Hypothalamus, activating:
  - Sympathetic Nervous System
  - Hypothalamic-Pituitary Axis
    - Cortisol/Glucocorticoids released to facilitate wound healing
  - Oxytocinergic Pathway (?)
    - Selective blockade of Aδ and C-fibers, and glutamate activation
The Inflammatory Reflex:

-A neuro-physiological mechanism that regulates the immune system
- Inflammatory input activates an anti-inflammatory output
- Can be under conscious control via higher cortical functions

- Cholinergic anti-inflammatory mechanisms (activated by limbic system and hypothalamic projections)
  - Acetylcholine inhibits activation of macrophages and cytokine release (TNF-α, IL-1)
  - Ach binds receptors on macrophages and other cytokine producing cells. Binding suppresses pro-inflammatory cytokines.

- Vagus nerve (90% of fibers are afferents)
  - Stimulated by TNF and other cytokines, mechano- and chemo-receptors, temp sensors, and osmolarity sensors
  - Stimulation prevents inflammation and inhibits cytokine release
Summary: Normal Pain Fxn

- **Lateral Pain Pathway:**
  - Localization

- **Medial Pain Pathway:**
  - Activate inhibitory pathways for pain control
  - Activate arousal system for protection and wound healing

- **Inflammatory reflex acting in peripheral tissues**
  - Cholinergic neurons inhibit acute inflammation
  - “Health [is] restored when inflammation is limited by anti-inflammatory responses that are redundant, rapid, reversible, localized, adaptive to changes in input and integrated by the nervous system.” (Tracey 2002)

- Return to homeostasis
Summary: Abnormal Pain Fxn

- Perpetuation of inflammatory cascade
- Activation of “silent nociceptors” in the periphery
- Spinal sensitization: increased input of nociceptive dorsal horn cells
  - Loss of inhibitory interneurons 2° excitotoxicity
  - Increasing receptive field size as previously innocuous sites now evoke response at cord level
  - Wind-up: progressive and sustained partial depolarization of the cell, lowers its threshold, allowing smaller afferent impulses to result in action potentials.
- Impaired descending pain modulators, ie “inflammatory reflex”
- Failure to re-establish homeostasis
Pain Generators of the Spine

Figure 10.13  Innervation of the lumbar spine. A cross-sectional view incorporating the level of the vertebral body (VB) and its periosteum (p) on the right and the intervertebral disc (IVD) on the left. PM—psoas major. QL—quadratus lumborum. IL—iliocostalis lumborum. LT—longissimus thoracis. M—multifidus. altlf—anterior layer of thoracolumbar fascia. pltlf—posterior layer of thoracolumbar fascia. esa—erector spinae aponeurosis. ds—dural sac. zj—zygapophysial joint. pl—posterior longitudinal ligament. all—anterior longitudinal ligament. vr—ventral ramus. dr—dorsal ramus. m—medial branch. i—intermediate branch. l—lateral branch.svn—sinuvertebral nerve. grc—grey ramus communicans. st—sympathetic trunk.
Intervertebral Discs

HIZ on MRI: 89% specificity for symptomatic annular tear when present at the level of chronic LBP
Spinal Stenosis

- Healthy Cervical Spine
- Central Stenosis
- Foraminal Stenosis
- Herniated Disk
Boney Pathology

Compression Fracture

Spondylolysis

Spondylolisthesis
Zygopophysial (Facet) Joints innervated by Medial Branch Nerves
Referred Pain

Sacral Stress Fx: incidence 2-4% in athletes, up to 20% in runners
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Thank you.