Pain Pathways Made Simple

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Disclosures

- Nothing to disclose

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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 pharmacotherapy and nonpharmacologic treatments

Classification of Pain

- Good pain vs bad pain

Clinical Pearl

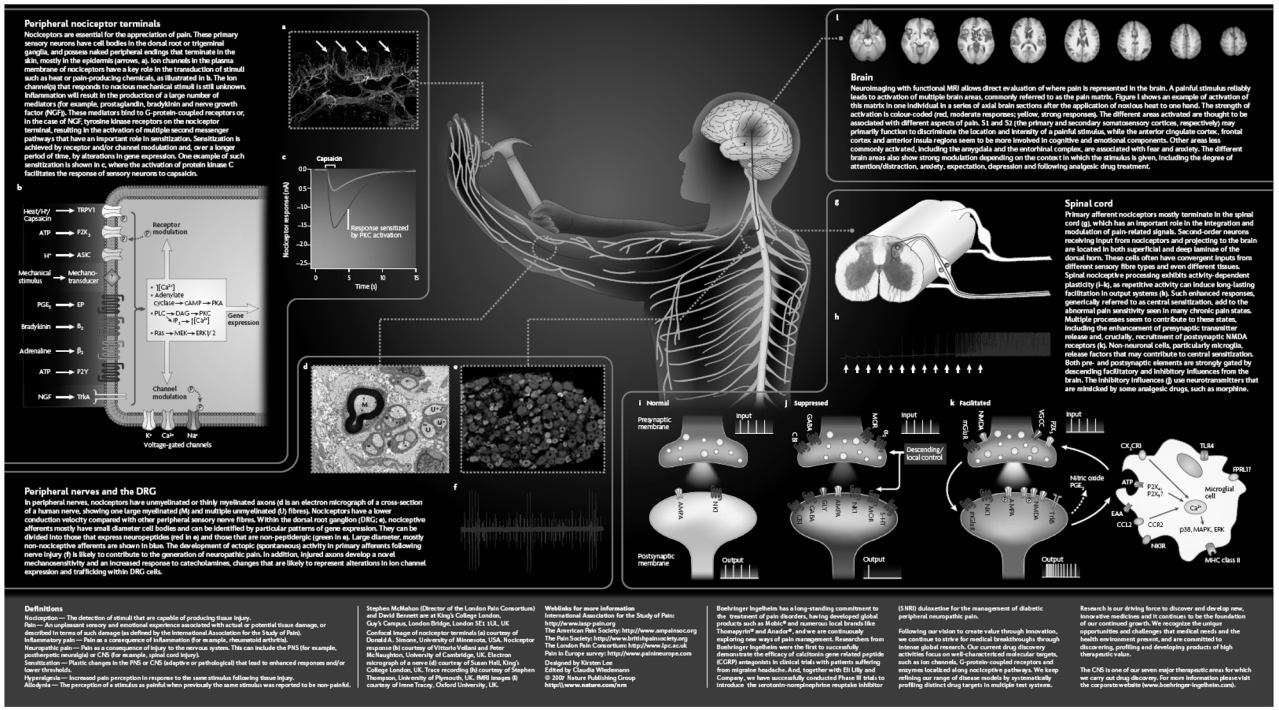
Good Pain

- **Nociceptive pain**: purposeful pain
  - **Eudynia:** being pain linked to normal tissue function or damage
  - Nonmaldynic pain
  - Adaptive

Bad Pain

- **Neuropathic pain**: Nonpurposeful 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



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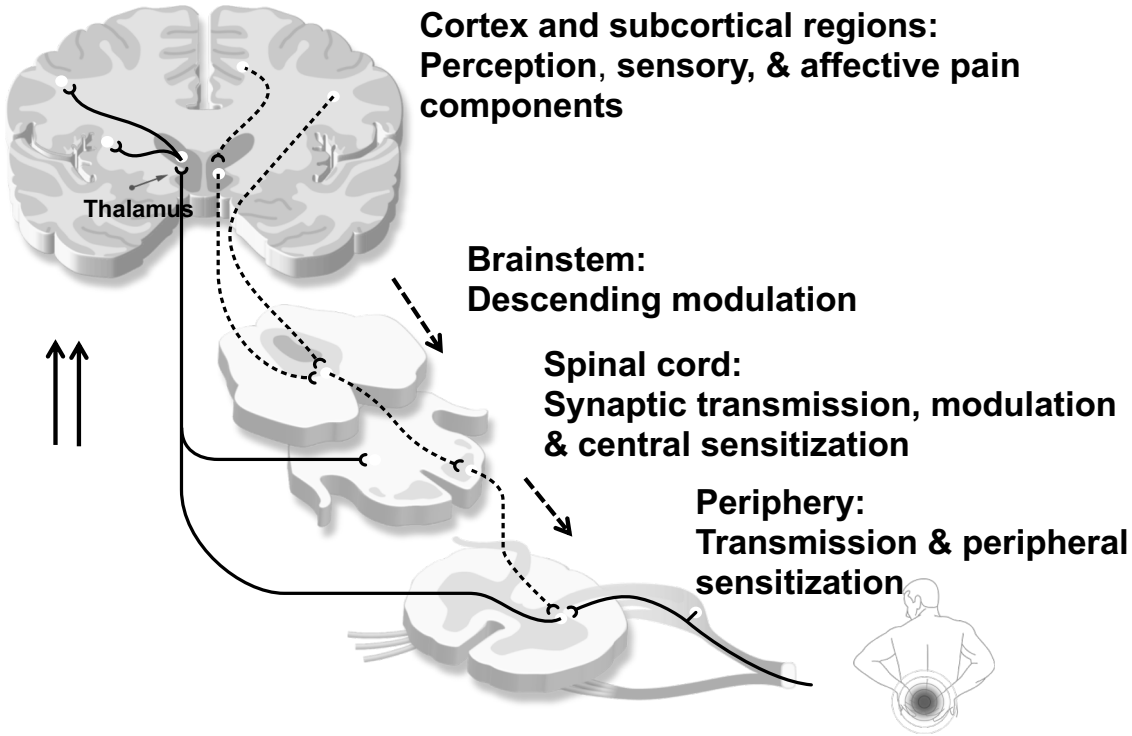
Adapted from Nature Reviews – Neuroscience, Stephen McMahon & David Bennett, 2007.

General Anatomy of Pain



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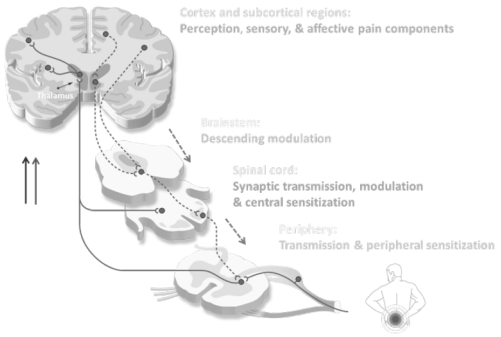
Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012; 23;73(4):638-652.

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**"



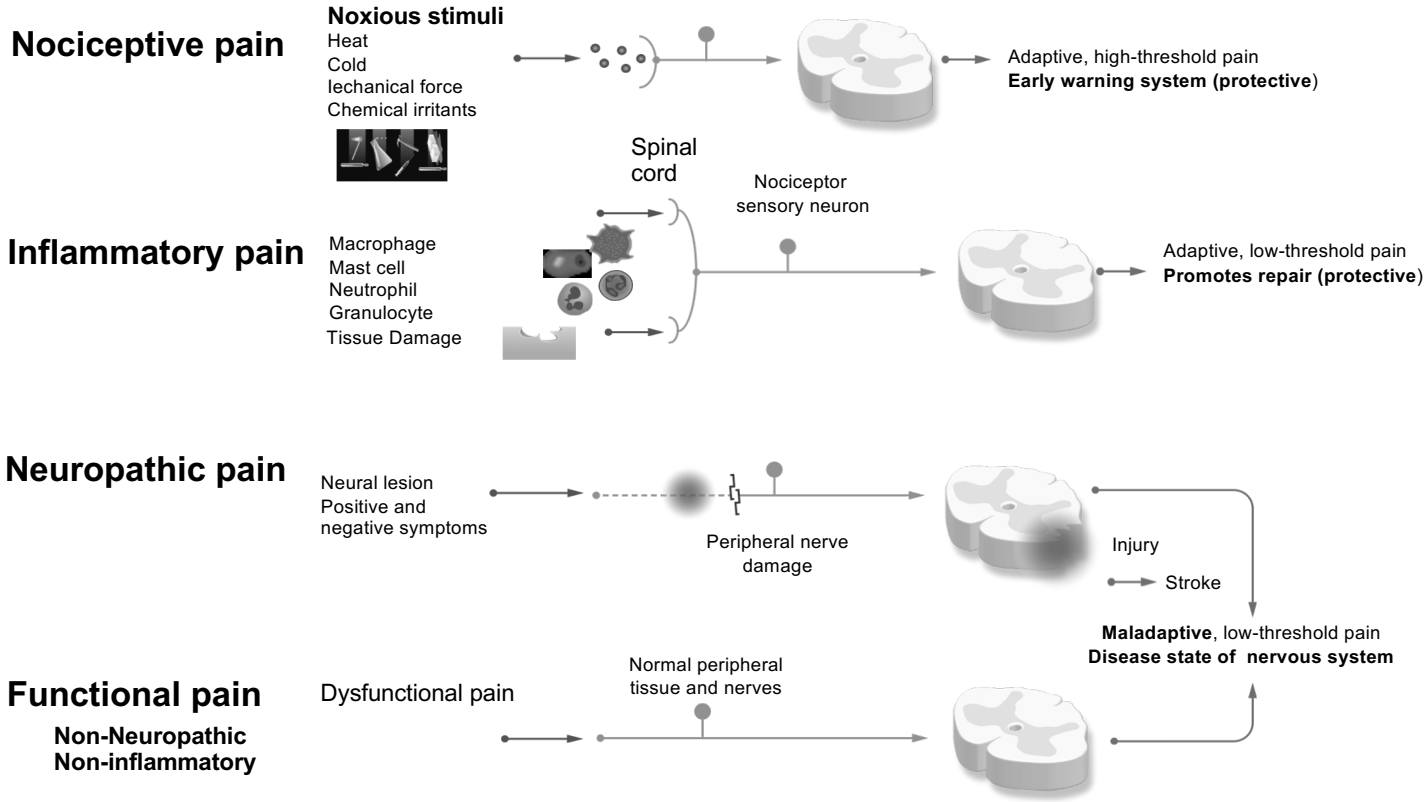
Gardner EP, et al. In: Kandel E, et al, eds. *Principles of Neural Science*. 4th ed. McGraw-Hill Medical; 2000; chapters 21-23.

Pathophysiologic Classification of Pain

- **Nociceptive –** purposeful pain
  - Somatic or visceral linked to normal tissue function or commensurate with identifiable tissue damage
- **Inflammatory pain –** Usually involves tissue damage
  - **Localized chemical soup of inflammatory mediators**
- **Neuropathic** – nonpurposeful pain
  - May be abnormal, unfamiliar pain, probably caused by dysfunction in PNS or CNS
- **Functional Pain** – dysfunctional pain
  - Non-neuropathic, non-inflammatory, often ill defined

IASP. Proposed taxonomy changes 2008. www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/ContentDisplay.cfm&ContentID=6633. November 2007.
Vadivelu N, et al. Pain pathways and acute pain processing. In: Sinatra RS, et al, eds. *Acute Pain Management.* New York, NY: Cambridge University Press; 2009:3-20.

Classification of Pain



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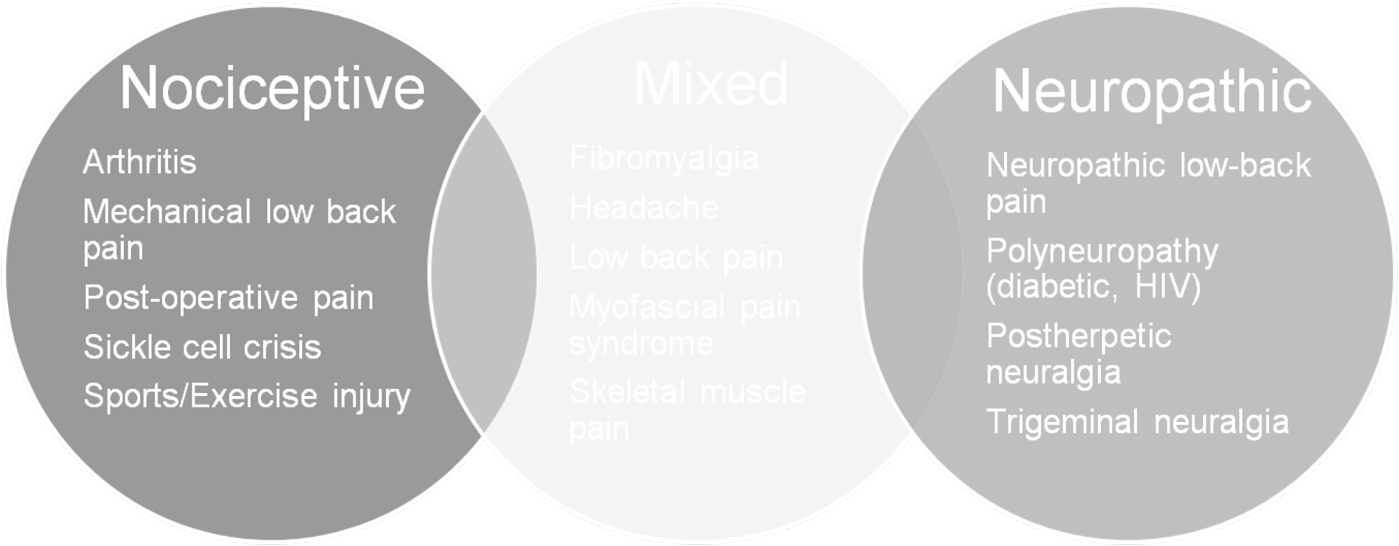
Adapted from: Woolf CJ. *Ann Intern Med.* 2004;140:441-451.

Nociceptive vs Neuropathic Pain



Portenoy RK, Kanner RM. In: Portenoy RK, et al, eds. Pain Management: Theory and Practice. Philadelphia, PA: FA Davis Company;1996:4.
Galer BS, Dworkin RH. A Clinical Guide to Neuropathic Pain. Minneapolis, MN: McGraw-Hill Companies Inc; 2000:8-9.

Pain Pathway Steps

Perception

Cortex and subcortical regions: sensory, and affective pain components

- **Behavioral/Limbic**

Transduction

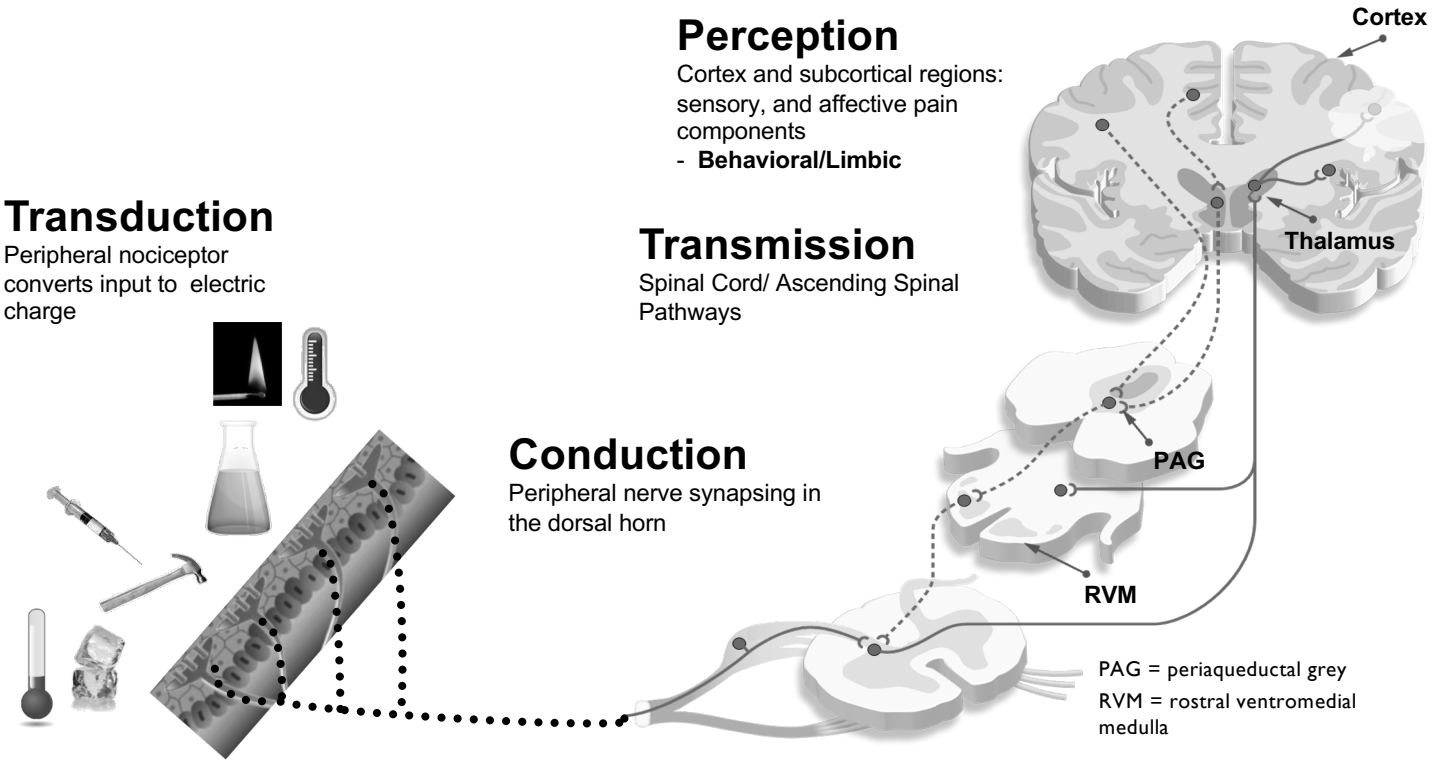
Peripheral nociceptor converts input to electric charge

Transmission

Spinal Cord/ Ascending Spinal Pathways

Conduction

Peripheral nerve synapsing in the dorsal horn



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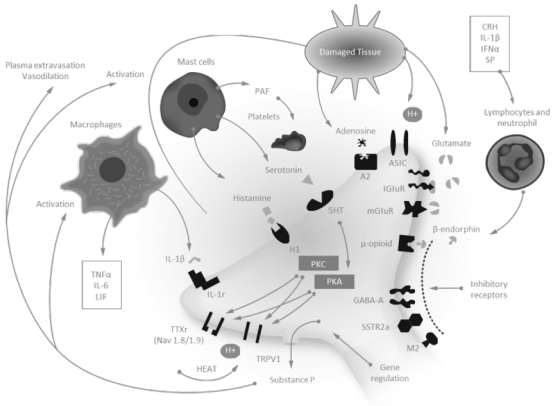
Adapted from Scholtz J, Woolf CJ, Nat Neuroscience, 2002,5:1062-1067.

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

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Adapted from Dougherty PM, et al. Neurochemistry of somatosensory and pain processing. In: Benzon H, et al, eds. *Essentials of Pain Medicine*. Philadelphia, PA; Saunders; 2011: chapter 2.

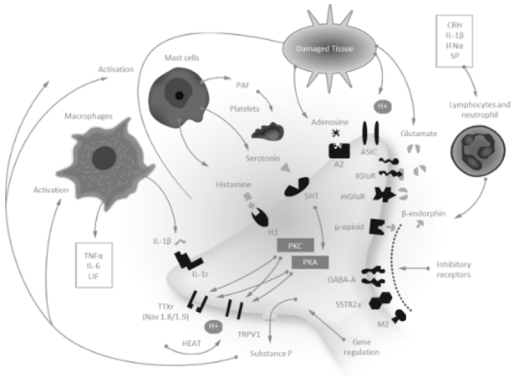
Peripheral Sensitization

After injury, a peripheral nervous system neuron becomes abnormally sensitive to stimuli, resulting in either or both

- Decreased threshold for activation
- Increased rate of firing

Mechanism of action*

- Tissue damage releases sensitizing “soup” of cytokines & neurotransmitters
- COX-mediated PGE2 release
  - These events are thought to be based on a number of changes at the cellular/molecular level, including changes in receptors and ion channels.



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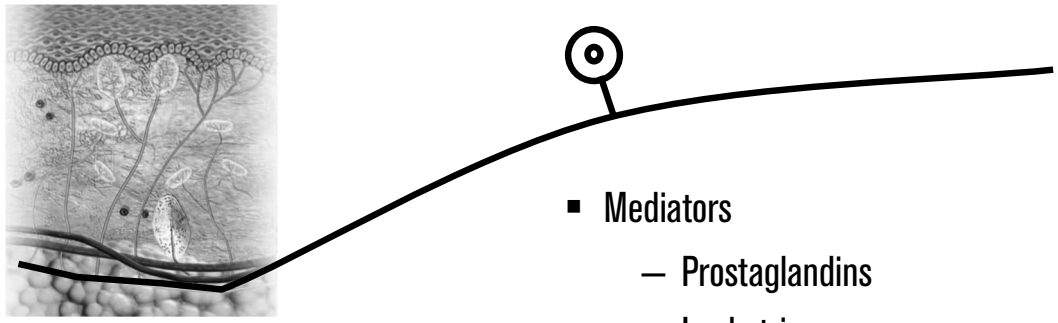
Baron R. Mechanisms of disease: neuropathic pain--a clinical perspective. *Nat Clin Pract Neurol*. 2006;2(2):95-106.
Figure: Adapted from Dougherty PM, et al. Neurochemistry of somatosensory and pain processing. In: Benzon H, et al, eds. *Essentials of Pain Medicine*. Philadelphia, PA; Saunders; 2011: chapter 2.

How Is Pain Transduced?

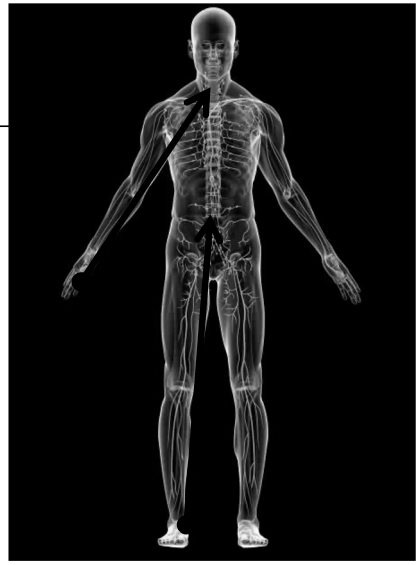


- Nociception
  - Mechanical
  - Thermal
  - Chemical

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

Conduction

Transfer of noxious impulses from primary nociceptors to cells in the spinal cord dorsal horn along the peripheral nerve.



Primary Nociception Fibers

Aδ – Fast/first pain
Large diameter

C-fibers – slow/second pain
Small diameter

Non-nociception fibers
(Proprioception)

Aβ – Muscle spindle, touch & kinesthesia
Larger diameter, myelinated

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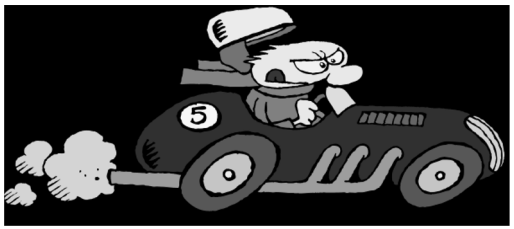
Vadivelu N, et al. Pain pathways and acute pain processing. In: Sinatra RS, et al, eds. *Acute Pain Management.* New York, NY: Cambridge University Press; 2009:3-20.
Figure adapted from Binder A, et al. Disease mechanisms in neuropathic itch. *Nat Clin Pract Neurol.* 2008;4(6):329-333.

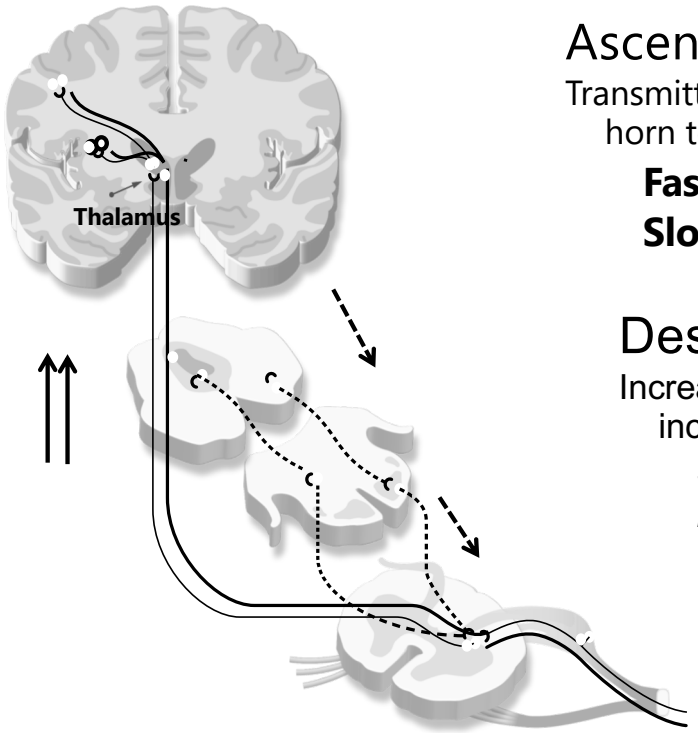
Primary Nociception

- **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

Transmission & Modulation



Ascending nociceptive pathways

Transmitting nociceptive impulses from the dorsal horn to surpaspinal targets

- **Fast** *(green)* Neospinalthalamic
- **Slow** *(yellow)* Paleospinalthalamic

Descending inhibitory tracts *(blue)*

Increased activation leads to a decrease in volume control of incoming nociceptive signals reaching the brain

- 5-HT – **Serotonin - both excitatory & inhibitory*** (*may not lead to pain relief*)
- NE – **Norepinephrine - Inhibitory**

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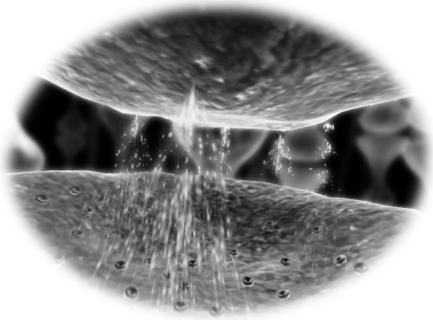
Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012; 23;73(4):638-652.

Transmission & Modulation

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

- **Inhibitory Transmitters**
  (descending inhibitory pathways)
  - GABA
  - Glycine
  - Somatostatin
  - a_2 agonists



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

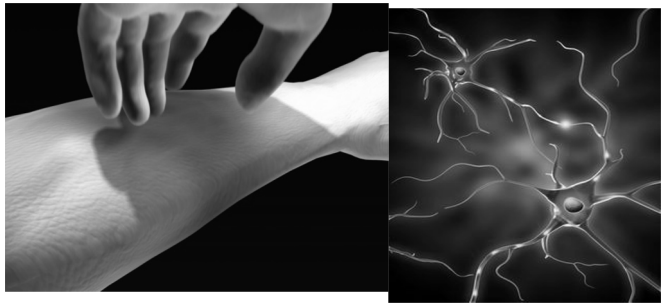
- Enables NS to modify its function according to different conditions or demands placed upon it

How Acute Pain Becomes Chronic

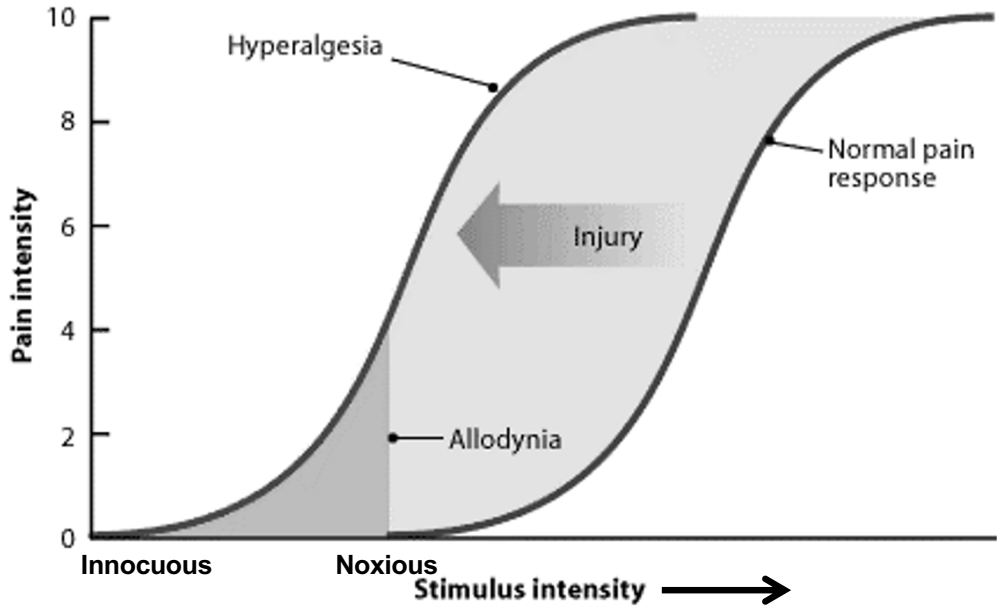
- Peripheral sensitization
  - Tissue damage releases sensitizing “soup” of cytokines & neurotransmitters
  - COX-mediated PGE2 release
  - Sensitized nociceptors exhibiting a decreased threshold for activation & increased rate of firing
- Central sensitization
  - Resulting from noxious input to the spinal cord
  - Resulting in hyperalgesia, & allodynia

Definitions

- **Hyperalgesia**
  - Lowered threshold to different types of noxious stimuli
- **Allodynia**
  - Painful response to what should normally be nonpainful stimuli

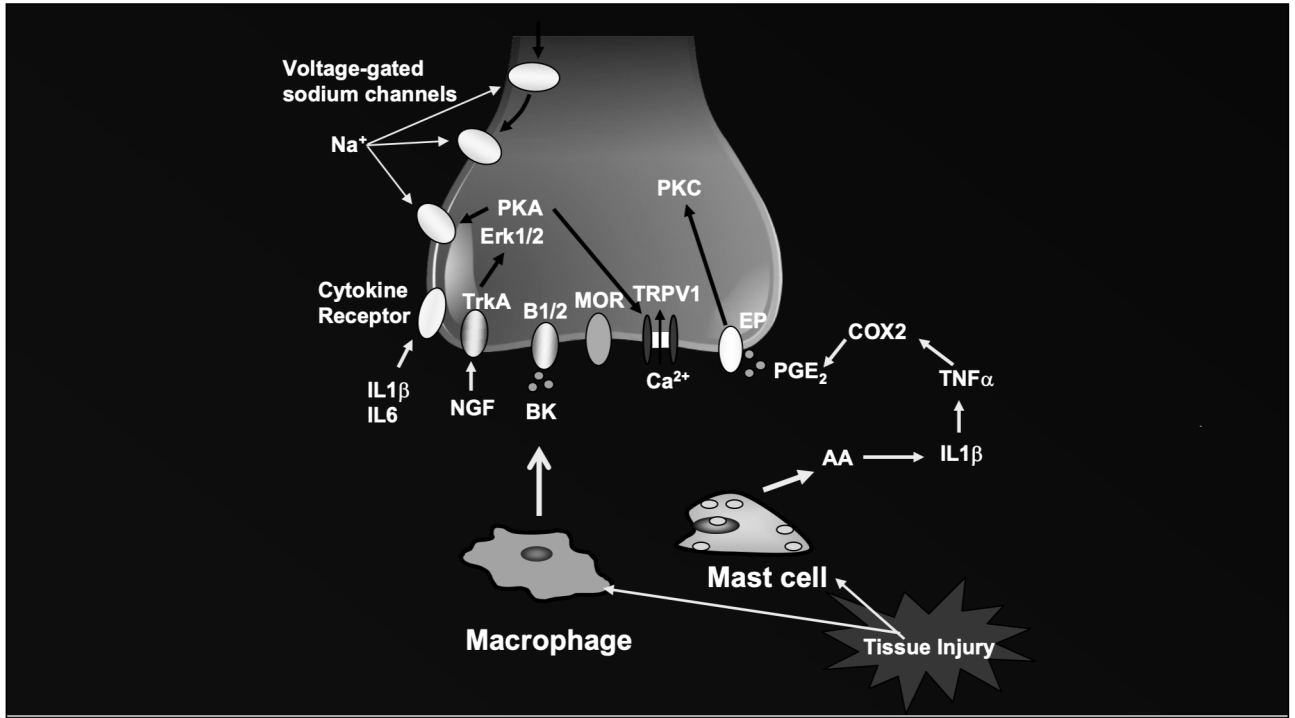


Neuroplasticity in Pain Processing



1. Woolf CJ, Salter MW. *Science*. 2000;288:1765-1768.
2. Basbaum AI, Jessell TM. The perception of pain. In: Kandel ER, Schwartz JH, et al. eds. *Principles of Neural Science*. 4th ed. New York, NY: McGraw-Hill; 2000:479.
3. Cervero F, Laird JMA. *Pain*. 1996;68:13-23.

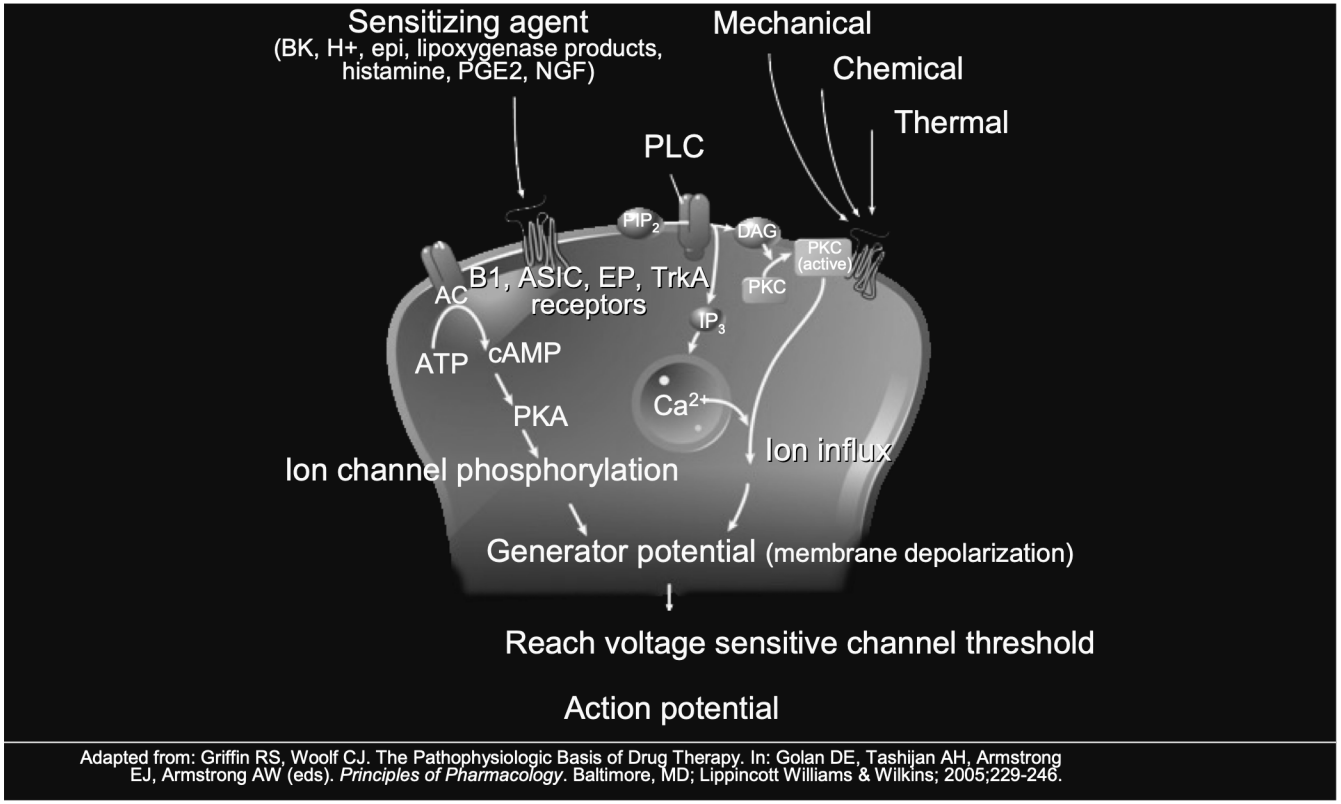
Neuroplasticity in Peripheral Pain Transmission



1. Woolf CJ. *Ann Int Med.* 2004;140:441-451.
2. Baron R. *Nat Clin Pract Neurol.* 2006;2:95-106.

IL 6, 1β= interleukin 6, 1beta; MOR= μ opioid receptor; COX2 = cycloxygenase; 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; PGE_2 = prostaglandin E_2

Peripheral Sensitization



Adapted from: Griffin RS, Woolf CJ. The Pathophysiologic Basis of Drug Therapy. In: Golan DE, Tashijan AH, Armstrong EJ, Armstrong AW (eds). *Principles of Pharmacology*. Baltimore, MD; Lippincott Williams & Wilkins; 2005;229-246.

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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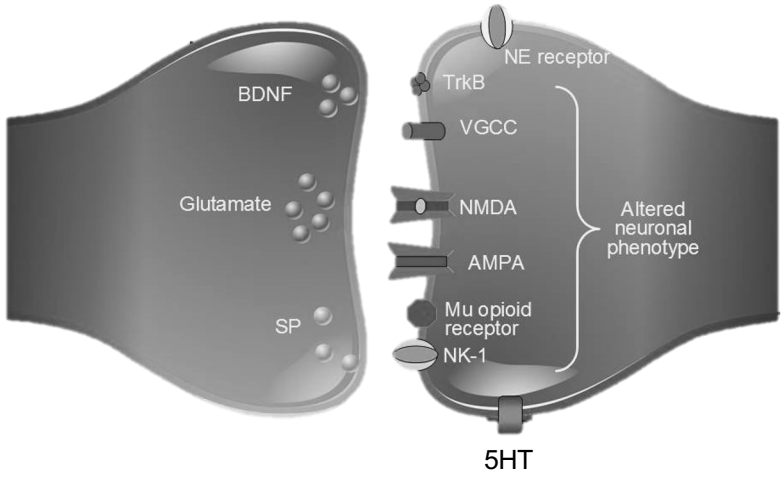
1. Kandel ER, Schwartz JH, Jessell TM, editors. Principles of Neural Science (Fourth Edition). New York: McGraw Hill (Health Professions Division). 2000;472-491.
2. Millan MJ. Progress in Neurobiology 1999;57:1-164.
3. Dickenson AH. Brit J Anaesthesia 1995;75:193-200.
4. Suzuki R and Dickenson AH. Neuroreport 2000;11:R17-21.

First Order Synapse – Dorsal Horn

Afferent first order neuron

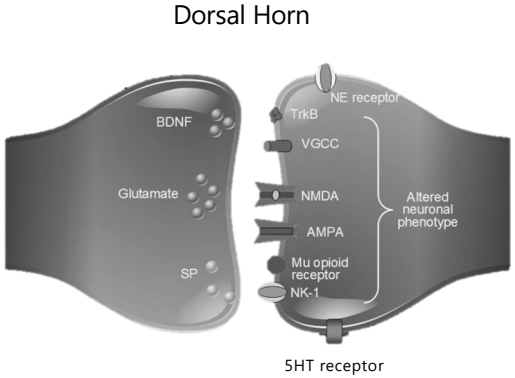
Dorsal horn neuron



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



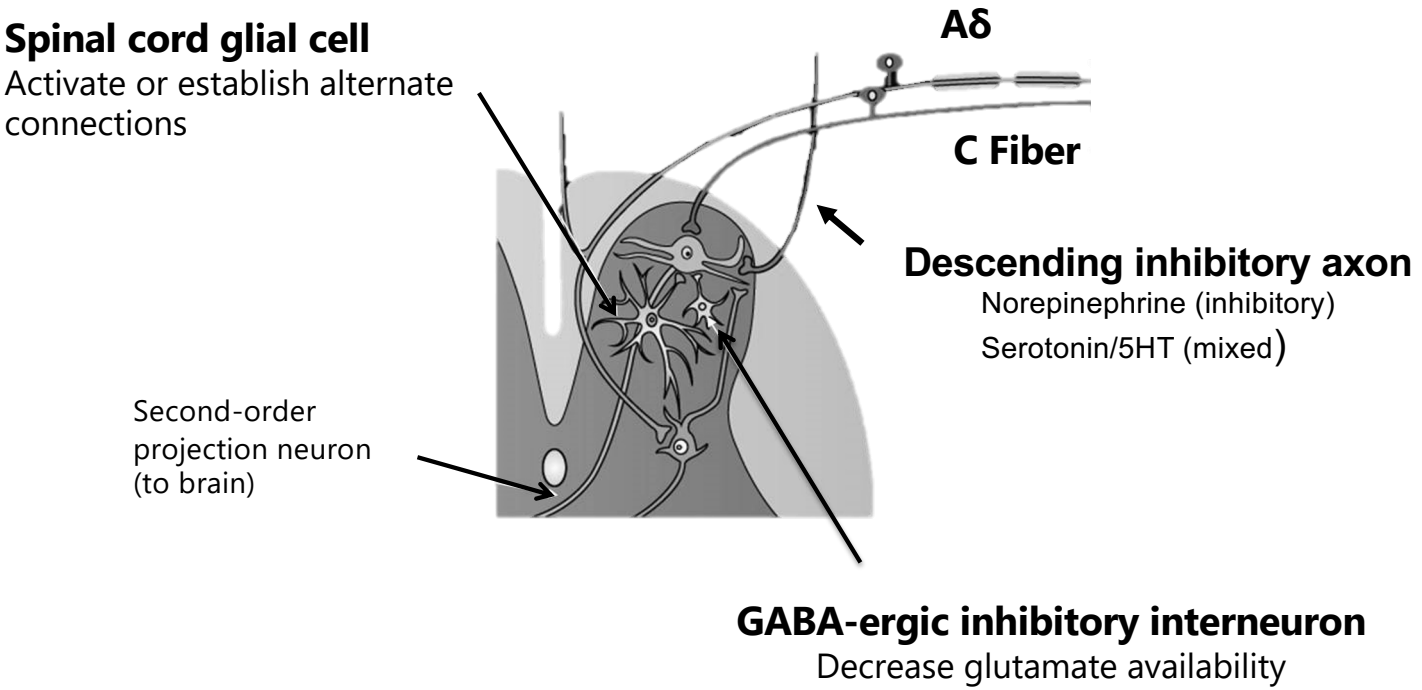
Key influences upon signal propagation

- 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-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; CRGP = Calcitonin gene related peptide

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

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



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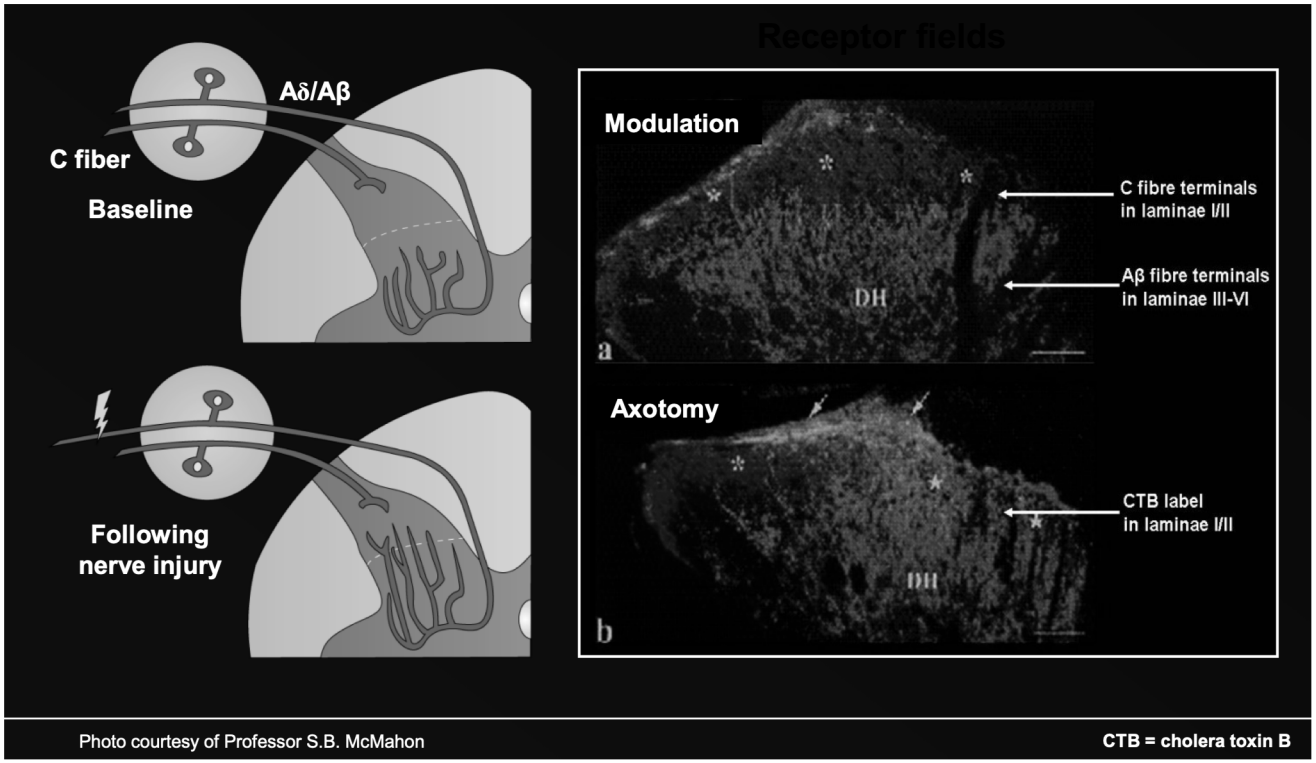
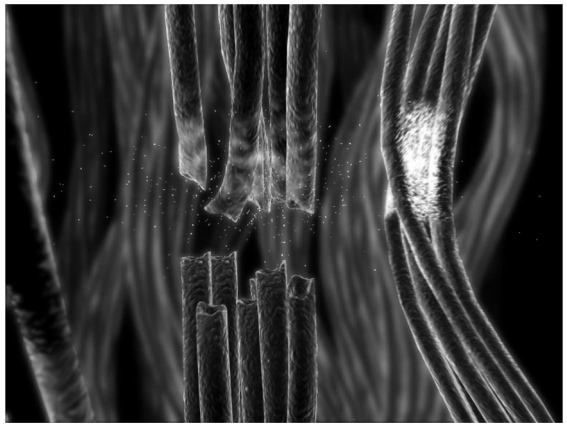
Adapted from 1. Baron R. Mechanisms of disease: neuropathic pain-a clinical perspective. *Nat Clin Pract Neurology.* 2006;2:95-106.
2. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Int Med.* 2004;140:441-451.

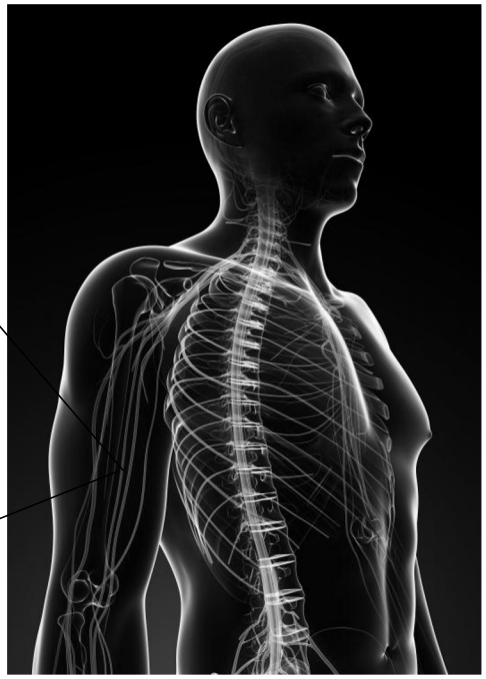
Neuroplasticity: Neural Reorganization



CTB = cholera toxin B

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 pathways[2]
  - Activation/migration of glial cells into the spinal cord[3]
  - Changes in the thalamus and primary somatosensory cortex[4]

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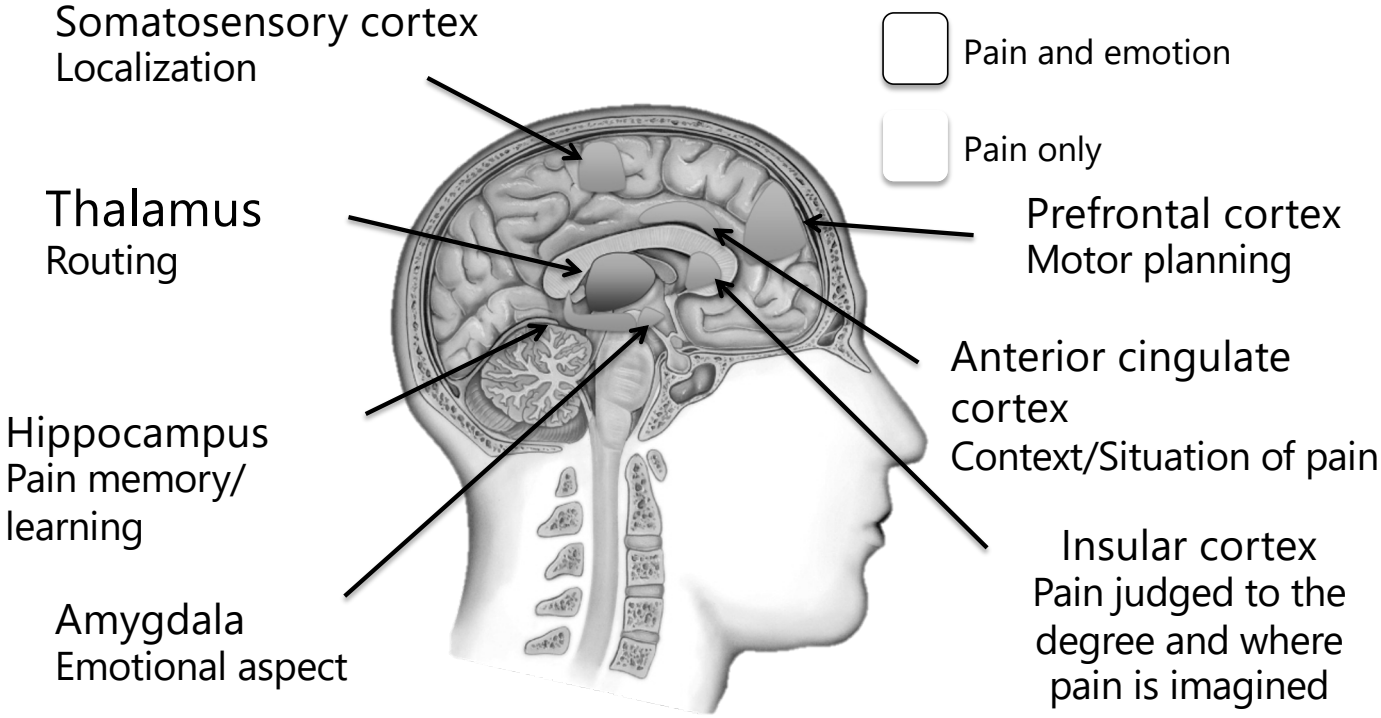
1. Mannion RJ, Woolf CJ: *Clin J Pain.* 2000;16(3):S151-S153. 2. Ossipov MH, et al. *Ann NY Acad Sci.* 2000;909:12-24.
3. Wieseler-Frank J, et al. *Neurosignals.* 2005;14:166-174. 4. Guilbaud G, et al. *Exp Brain Res.* 1992;92:227-245.

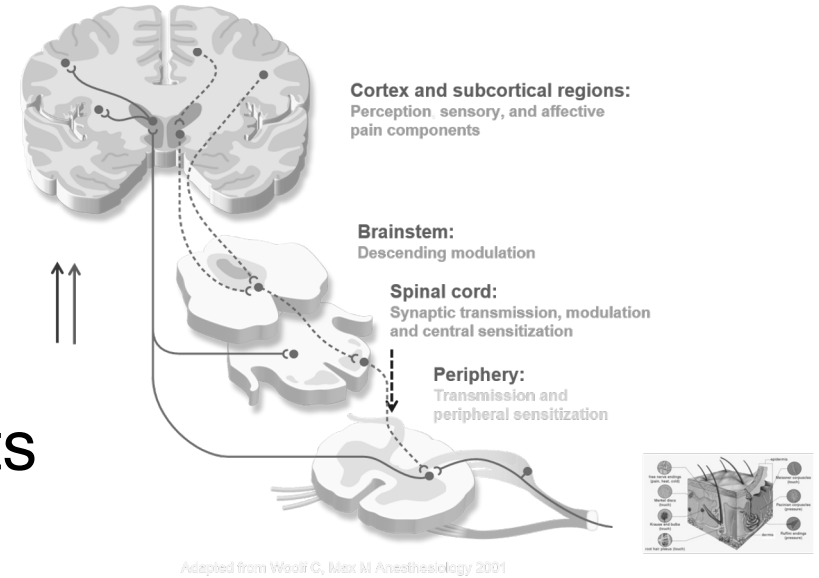
Brain Regions Involved in Pain Processing



Apkarian AV et al, Eur J Pain 2005;9:463-484

Common Pharmacologic Therapies

- Acetaminophen
- NSAIDS
- Antiepileptics
- TCAs
- SNRIs
- Topicals
- Muscle relaxants
- Opioids



Adapted from Woolf C, Max M Anesthesiology 2001

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Pharmacological Targets in Pain

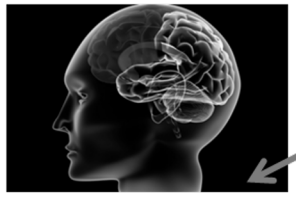
Ectopic Activity

Na+ channel blockers

Ca+2 channel blockers

GABAergic enhancement

Glutaminergic inhibition



Descending Modulation

Central α-agonists

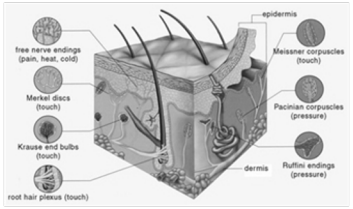
TCAs

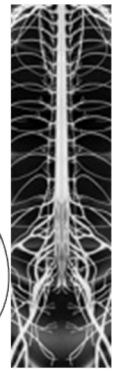
SNRIs

Opioids/tramadol

CNS

PNS





Central Sensitization

Opioids/Tramadol

Central α-agonists

NMDA antagonists

Anticonvulsants

Peripheral Sensitization

NSAIDS

Local Anesthetics

TCAs

Anticonvulsants

Local Anesthetics

Opioids

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Woolf C, Max M Anesthesiology 2001

Nonpharmacologic Treatments Reliant on Pain Pathways

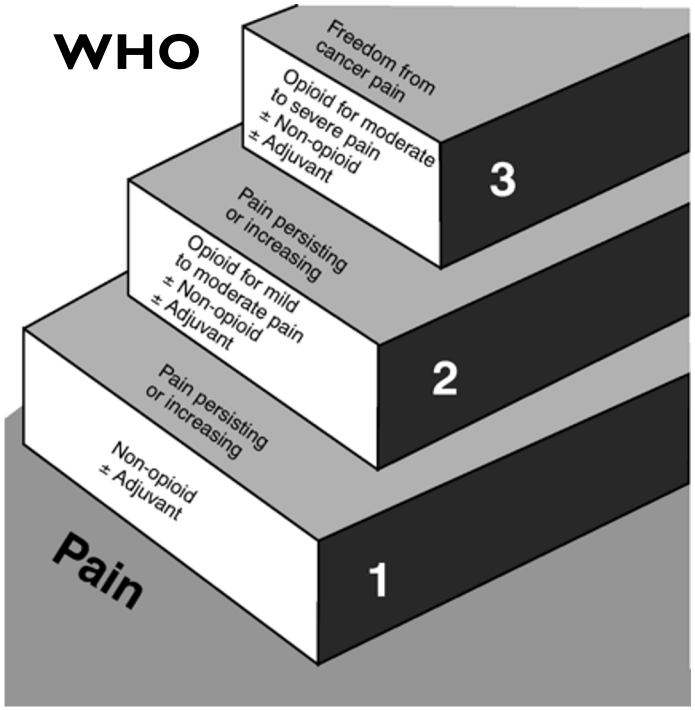
- Classic neuromodulation (Implantable spinal and extraspinal)
- External devices (transcutaneous)
  - Quell – musculoskeletal pain (neck, back, etc)
  - Nerivio migra – acute migraine
  - Cefaly – acute migraine without aura
  - Livia – menstrual cramps
  - ActiPatch – musculoskeletal pain
  - ClearUP – sinus pain
  - gammaCore – migraine & cluster HA (COVID-19 emergency use respiratory system/asthma)

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



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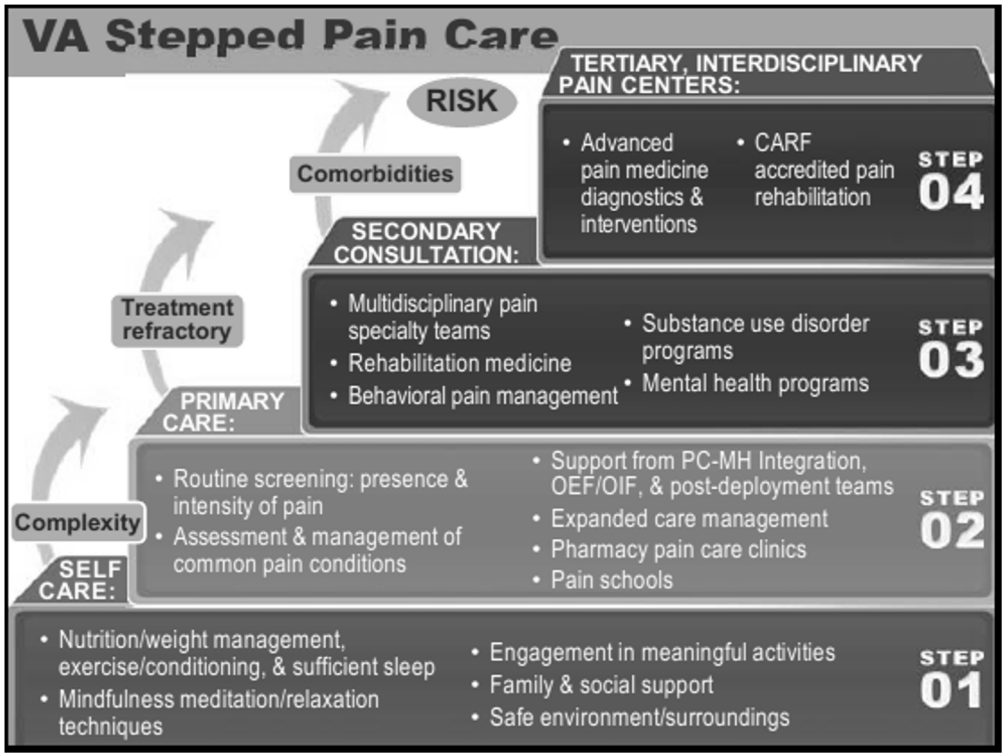
JC Ballantyne Oncologist 2003:8(6):567-75. © AlphaMed Press; WHO. 2005.

VA DoD Stepped Pain Care Model



PainWeek

PCSS-O Webinar Implementation of the National Pain Strategy and Safer Opioid Prescribing: A Military Perspective, Buckenmaier C (COL) ret, Aug 24, 2016

JAMA Intern Med. 2015;175(5):682-689. doi:10.1001/jamainternmed.2015.97

Adjuvant Analgesics: Topicals

Examples

- Lidocaine patch (patch/gel)
- Capsaicin cream/patch
- Diclofenac (cream/liquid/gel/patch)
- Rubefacient (cream/patch/spray)

Mechanism of action

- Block sodium channels, inhibit generation of abnormal impulses by damaged nerves
- Depletion of peripheral small fibers and therefore Substance P release from sensory nerve endings, $TRVP_1$ receptor agonist
- Target local inflammatory response
- Counterirritation, some with mild anti-inflammatory action

Objectives for Treating Pain

- Reduce overall signal by addressing the source
  - Treatment by eliminating the pathology
  - Mitigate the response at the source
- Interrupt or interfere with signal within pathway
  - Directly addressing steps in the pathway
- Reduce the overall excitatory response
- Increase the inhibitory response
- Decrease perception of the signals

Neuroplasticity Considerations

- Neuroplasticity can be a 2 way process, and should be considered reversable
- Can delay or slow the perceived response to pain treatment
- May play a role in amplification of pain perception in the presence of comorbidities
- Is often overlooked when caring for the patient

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
    - Methocarbamol
    - Tapentadol
    - Acetaminophen and propoxyphene
    - Zolpidem
    - Diclofenac topical
    - Acetaminophen