PainWeek®

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 pharmacotherapy and non-pharmacologic treatments

Classification of Pain

- Good pain vs. Bad Pain

Clinical Pearl

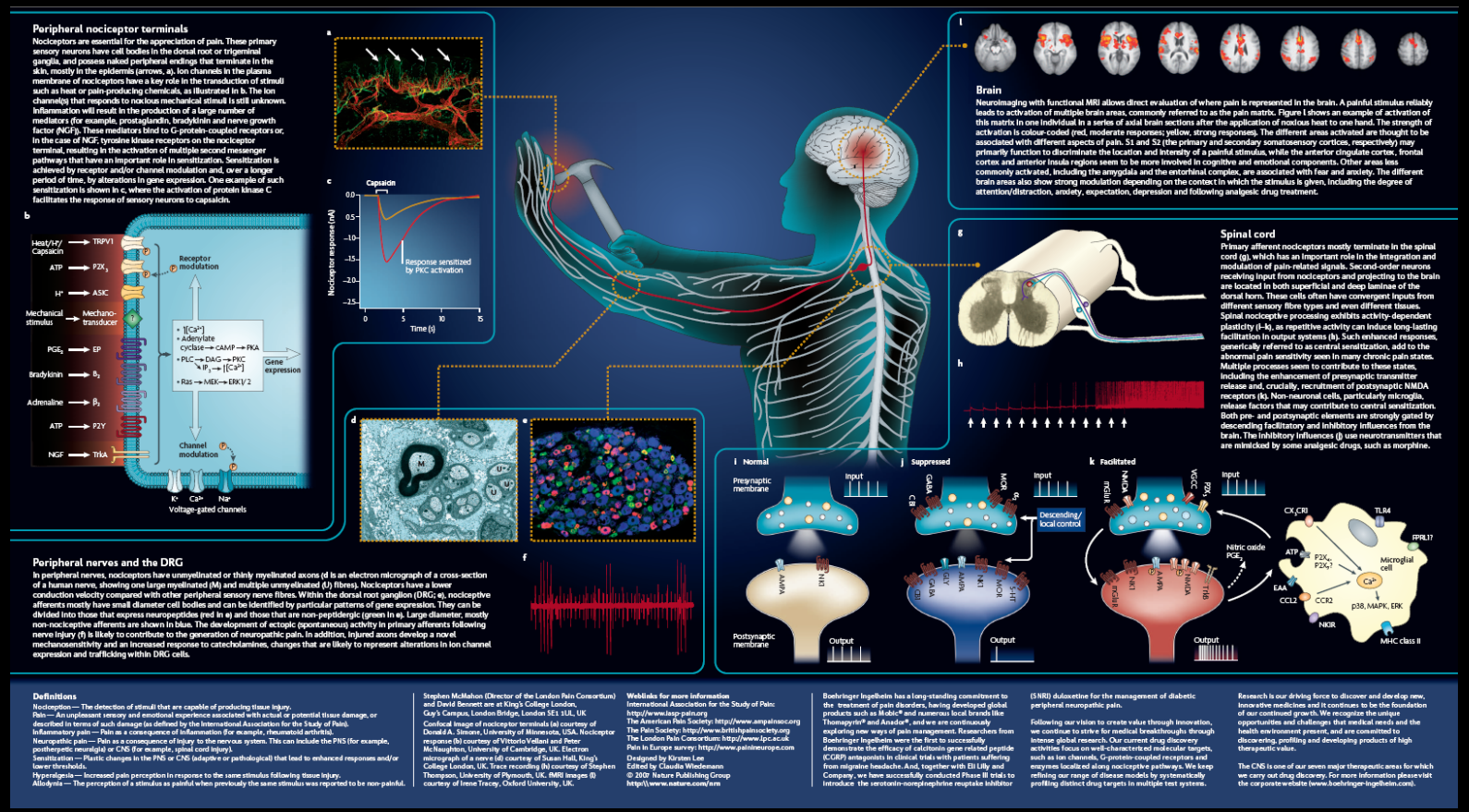
Good Pain

- **Nociceptive Pain**: Purposeful Pain
  - **Eudynia** - being pain linked to normal tissue function or damage
  - 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



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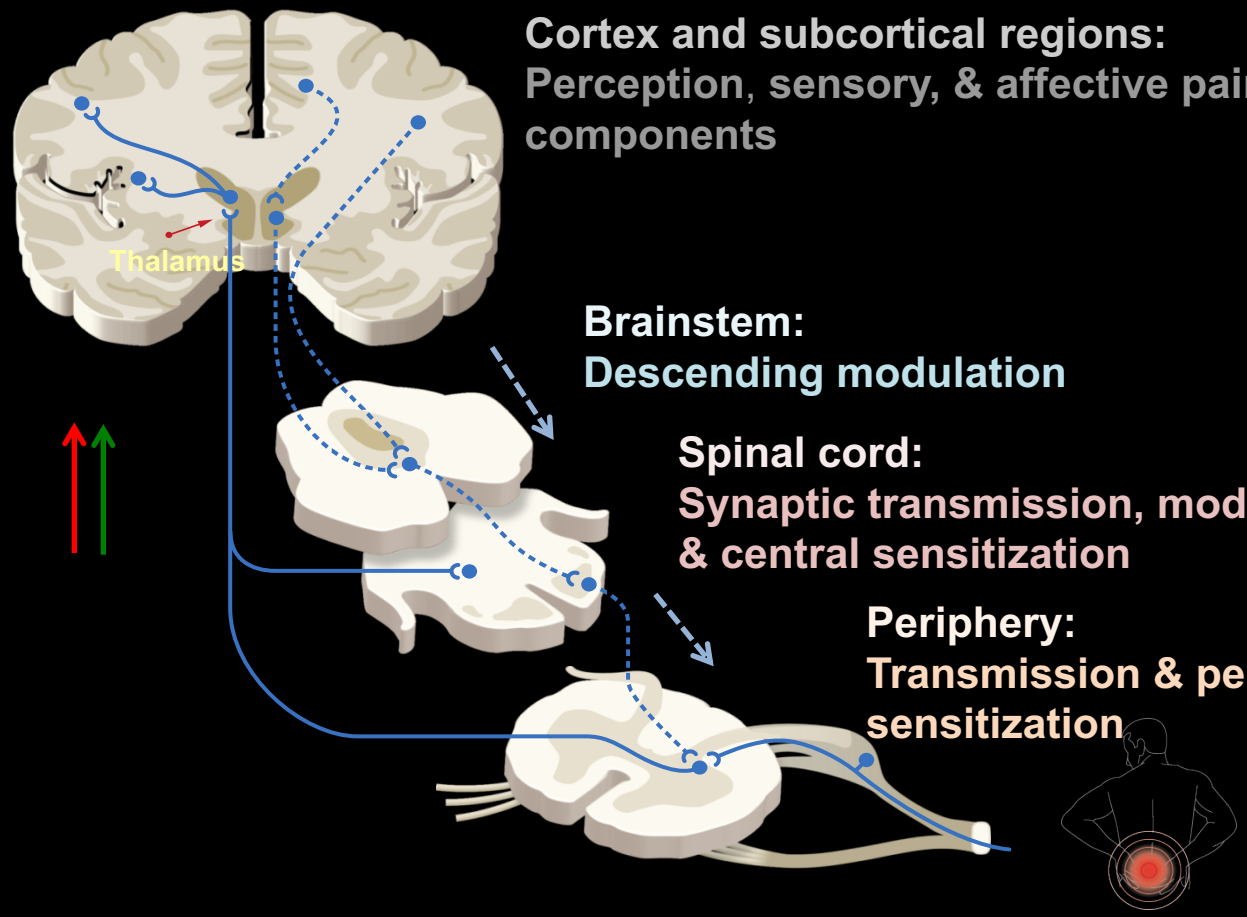
Adapted from Nature Reviews – Neuroscience, Stephen McMahon & David Bennett, 2007.

General Anatomy of Pain



Cortex and subcortical regions:
Perception, sensory, & affective pain components

Brainstem:
Descending modulation

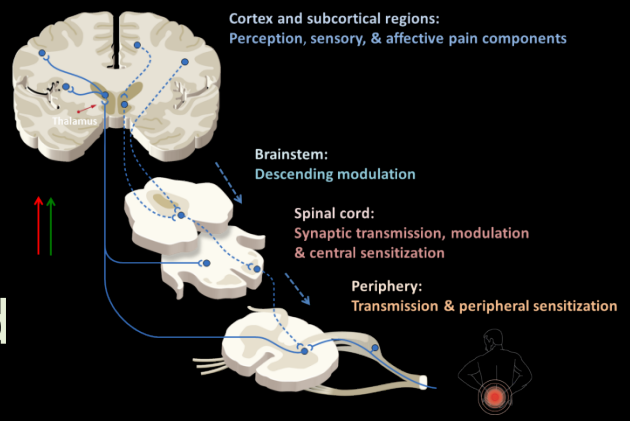
Spinal cord:
Synaptic transmission, modulation & central sensitization

Periphery:
Transmission & peripheral sensitization

- 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 (i.e. occurring in real time)
- Adapts or changes in response to function – "**Neuroplasticity**"



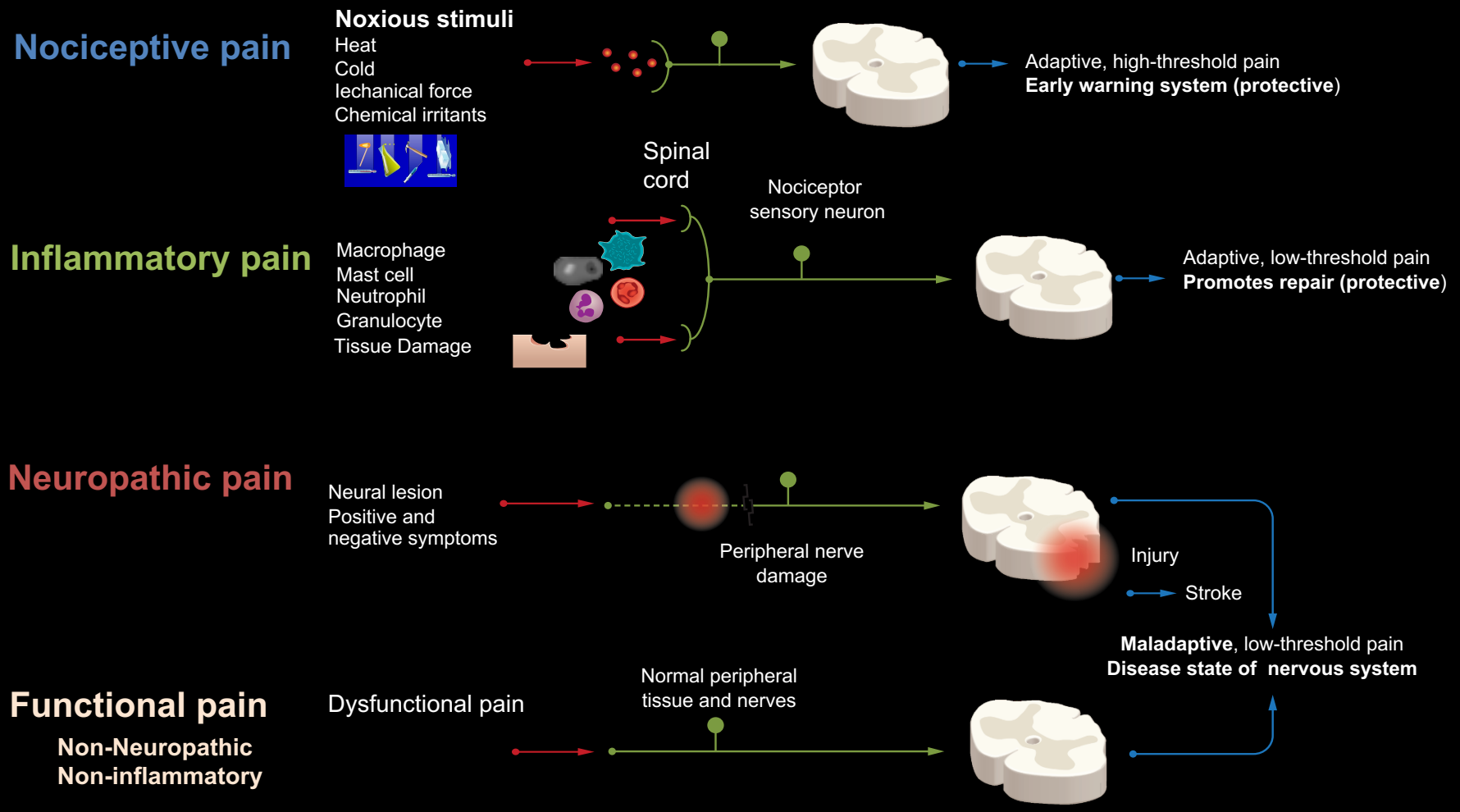
1. Gardner EP, et al. In: Kandel E, et al, eds. *Principles of Neural Science.* 4th ed. McGraw-Hill Medical; 2000; chapters 21-23.

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 -** Non-purposeful 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

1. IASP. Proposed taxonomy changes 2008. http://www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/ContentDisplay.cfm&ContentID=6633. Published November 2007. Accessed May 12, 2013. 2. 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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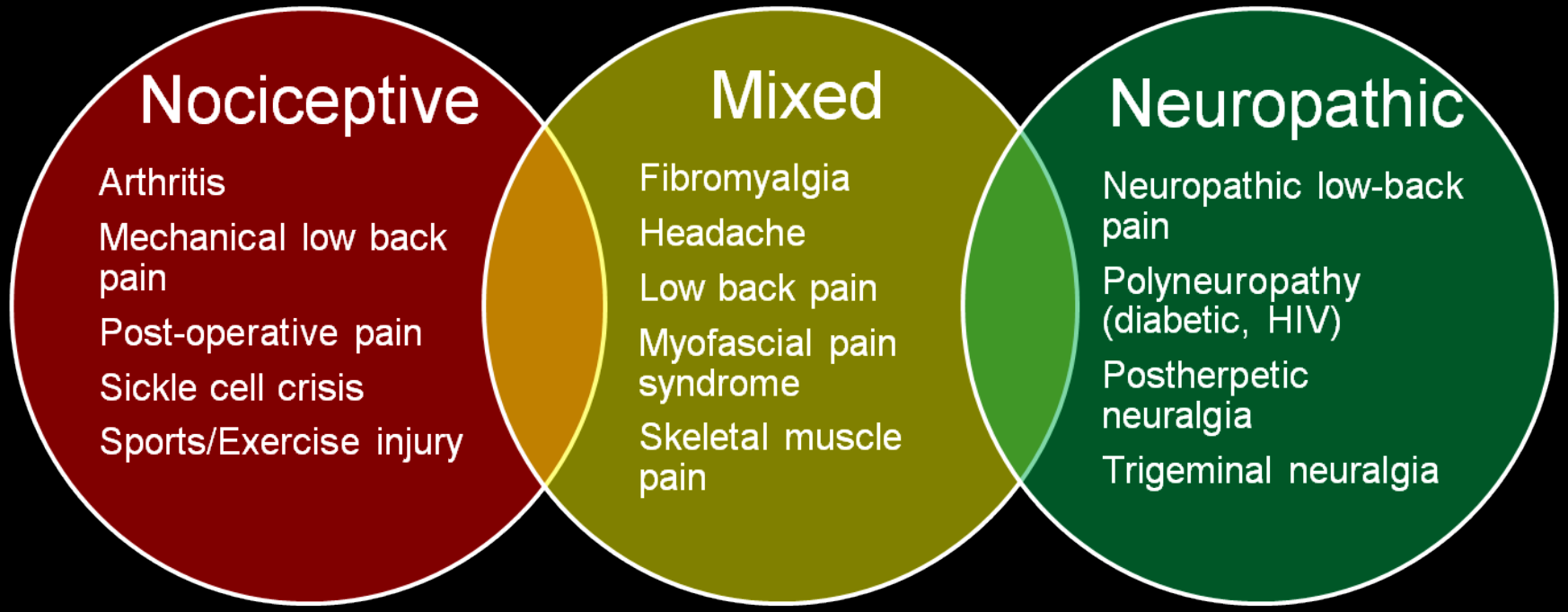
Adapted from: Woolf CJ. *Ann Intern Med.* 2004;140:441-451.

Nociceptive vs Neuropathic Pain



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

Pain Pathway Steps

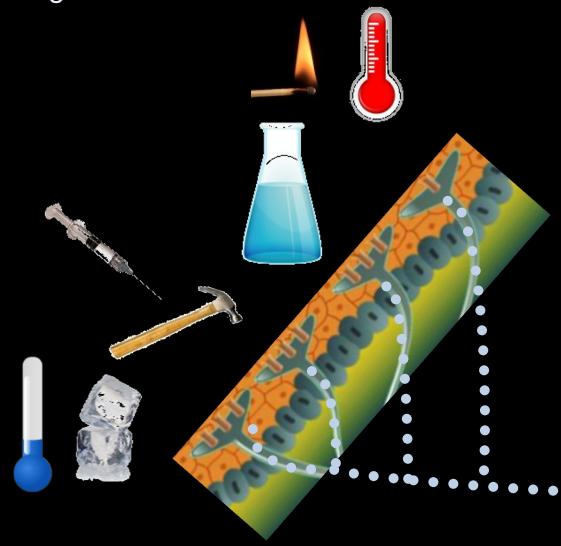
Perception

Cortex and subcortical regions: sensory, and affective pain components

- **Behavioral/Limbic**

Transduction

Peripheral nociceptor converts input to electric charge

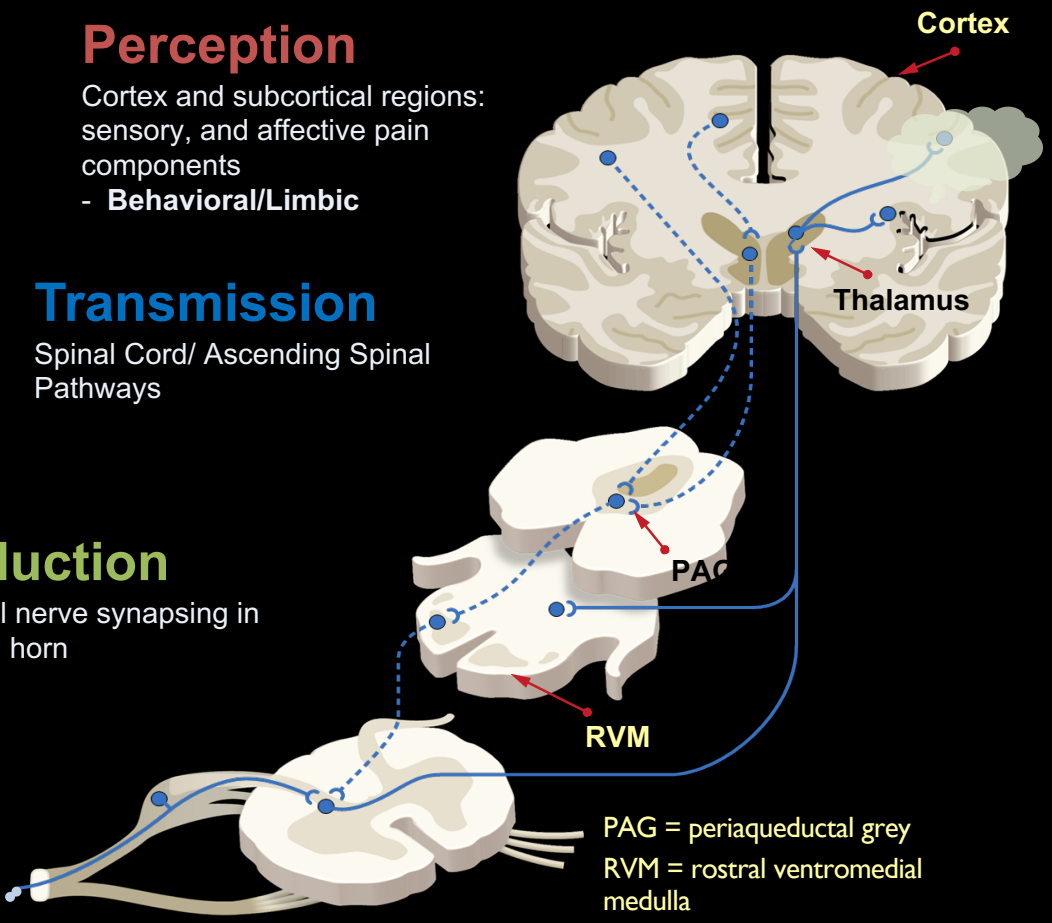


Transmission

Spinal Cord/ Ascending Spinal Pathways

Conduction

Peripheral nerve synapsing in the dorsal horn



PAG = periaqueductal grey

RVM = rostral ventromedial medulla

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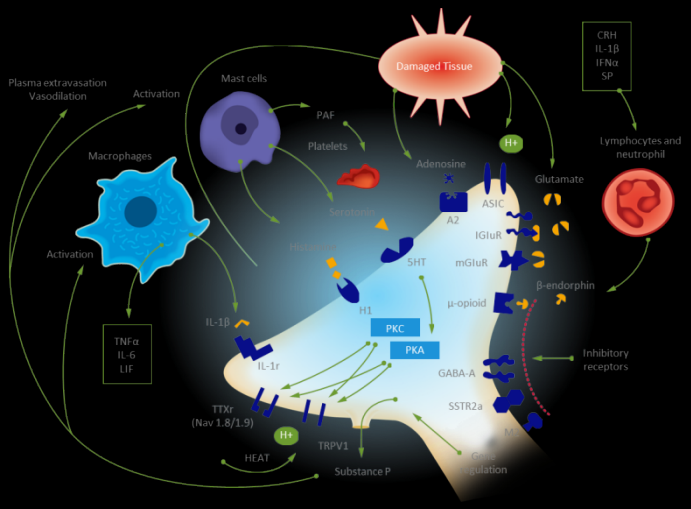
Adapted from Scholtz J, Woolf CJ, Nat Neuroscience, 2002,5:1062-1067

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.

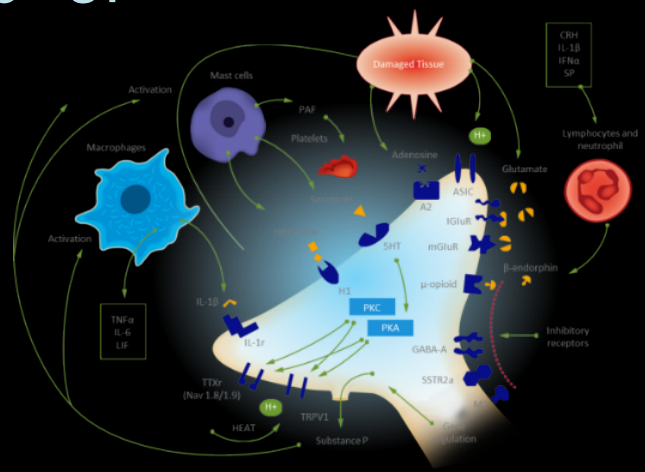
Peripheral Sensitization

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

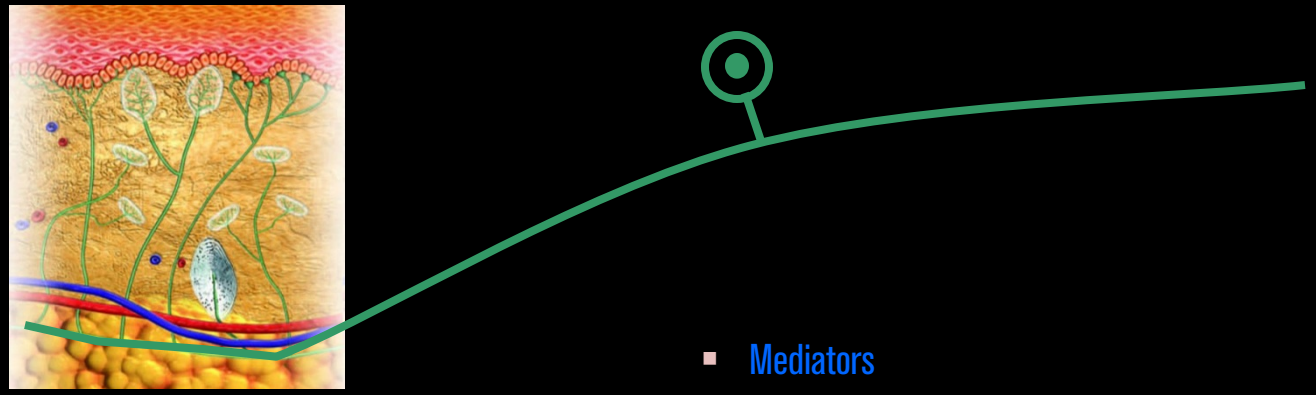
Mechanism of action*

- 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.



1. 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?

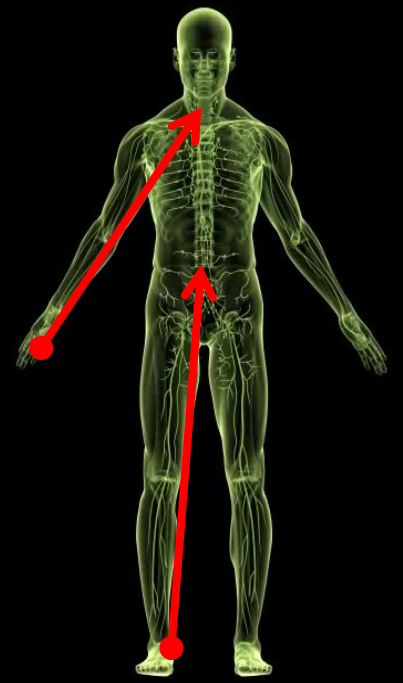


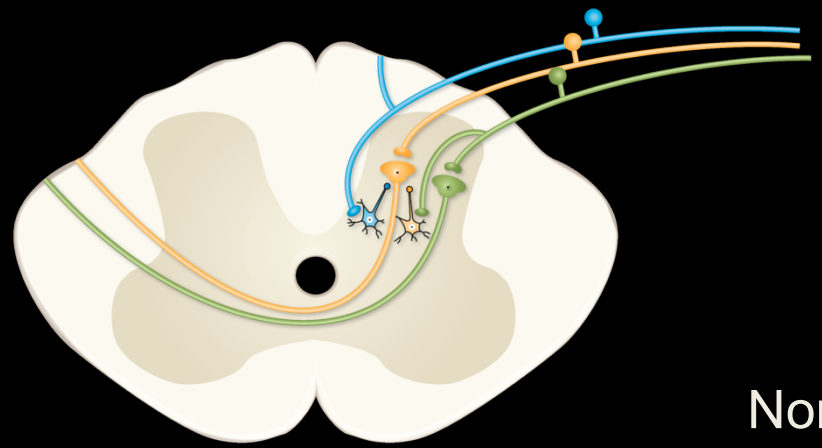
- Nociception
  - Mechanical
  - Thermal
  - Chemical

- 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

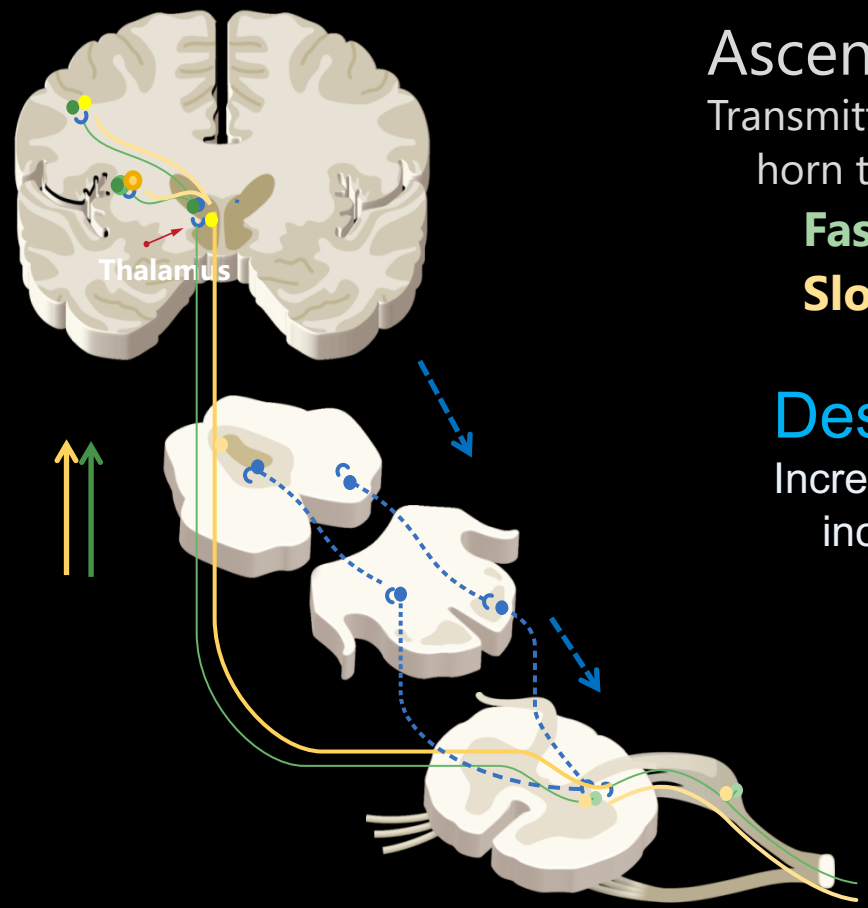
Vadivelu N, et al. Pain pathways and acute pain processing. In: Sinatra RS, et al, eds. *Acute Pain Management*. New York, NY: Cambridge University Press; 2009:3-20.
Figure adapted from Binder A, et al. Disease mechanisms in neuropathic itch. *Nat Clin Pract Neurol*. 2008;4(6):329-333.

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

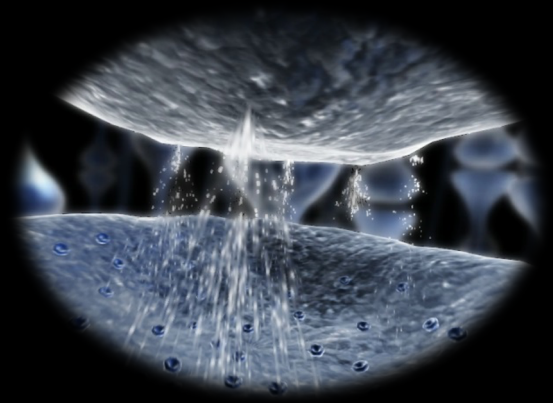
- 5-HT – **Serotonin - both excitatory & inhibitory*** (*may not lead to pain relief*)
- NE – **Norepinephrine - Inhibitory**

- 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

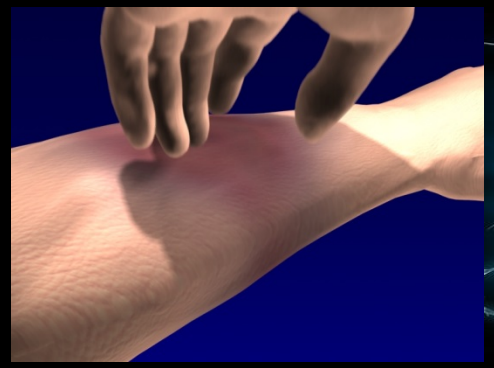
- Enables NS to modify its function according to different conditions or demands placed upon it.

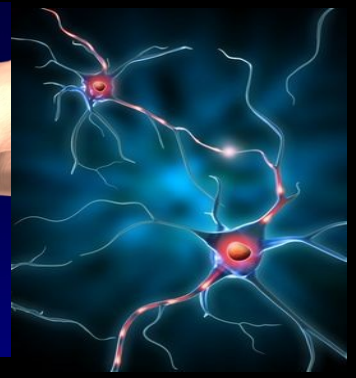
How Acute Pain Becomes Chronic

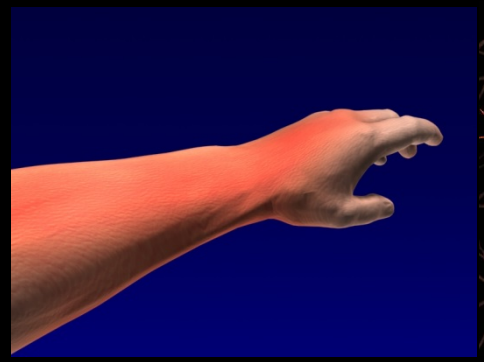
- Peripheral Sensitization
  - Tissue damage releases sensitizing “soup” of cytokines & neurotransmitters
  - COX-mediated PGE2 release
  - Sensitized nociceptors exhibiting a decreased threshold for activation & increased rate of firing
- Central Sensitization –Resulting from noxious input to the spinal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

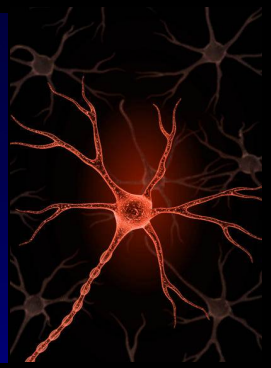
Definitions

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

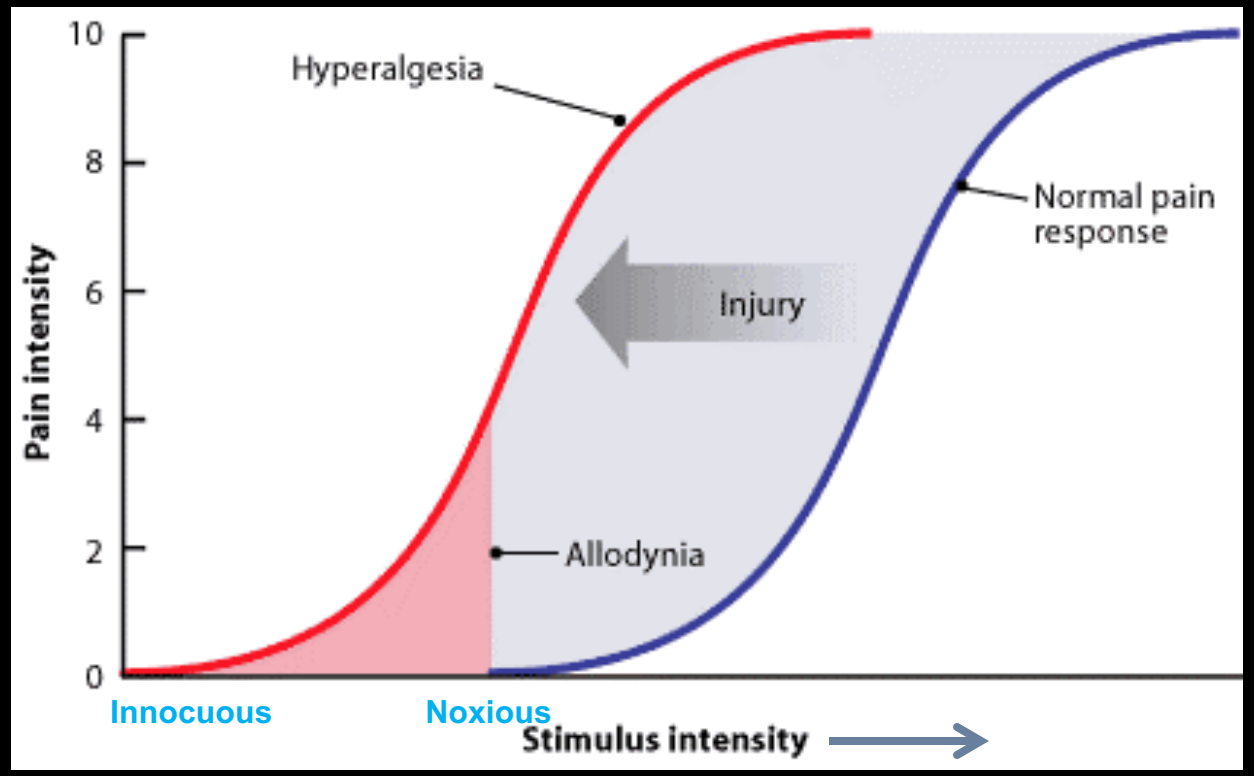






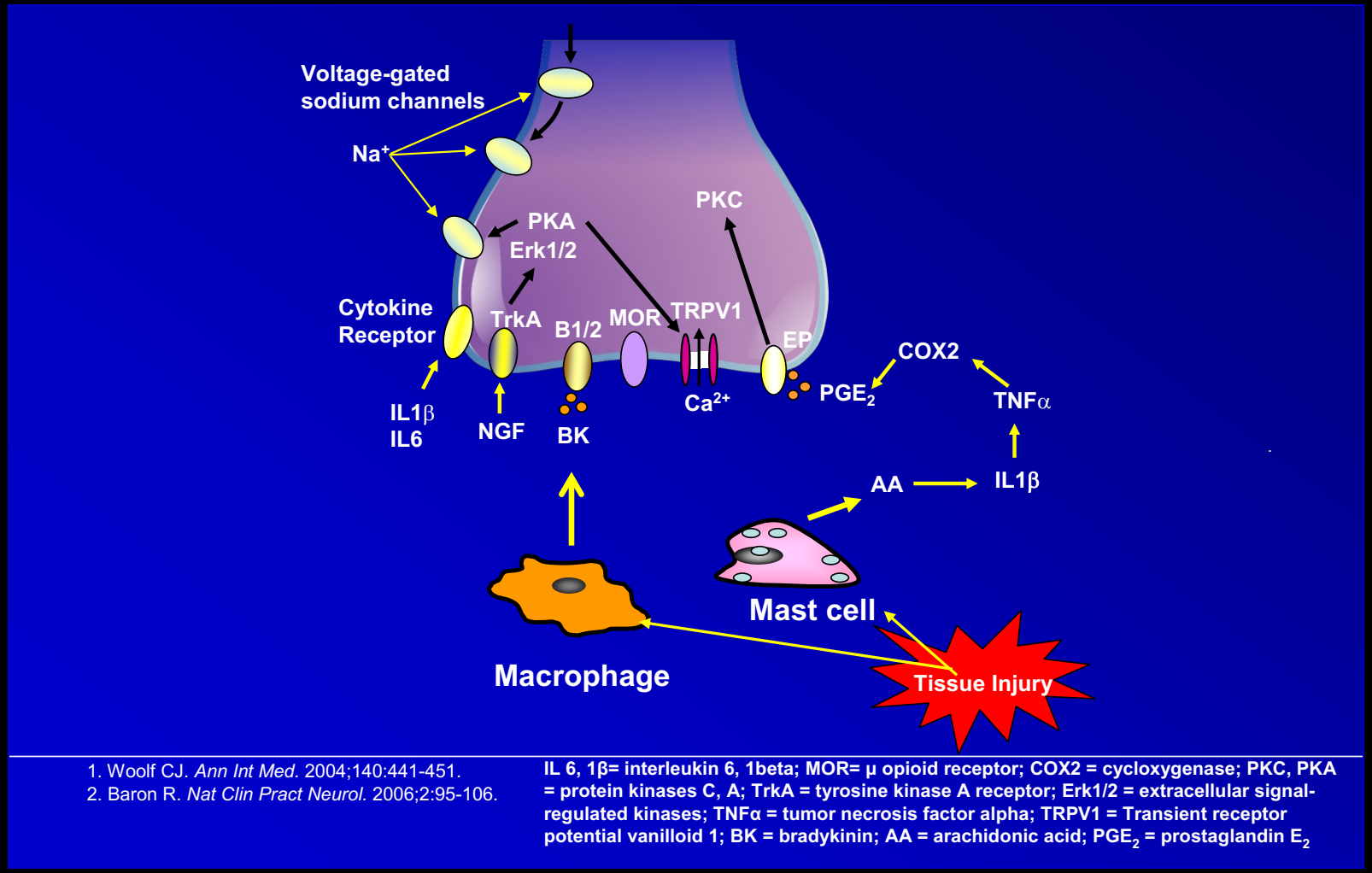


Neuroplasticity in Pain Processing



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.

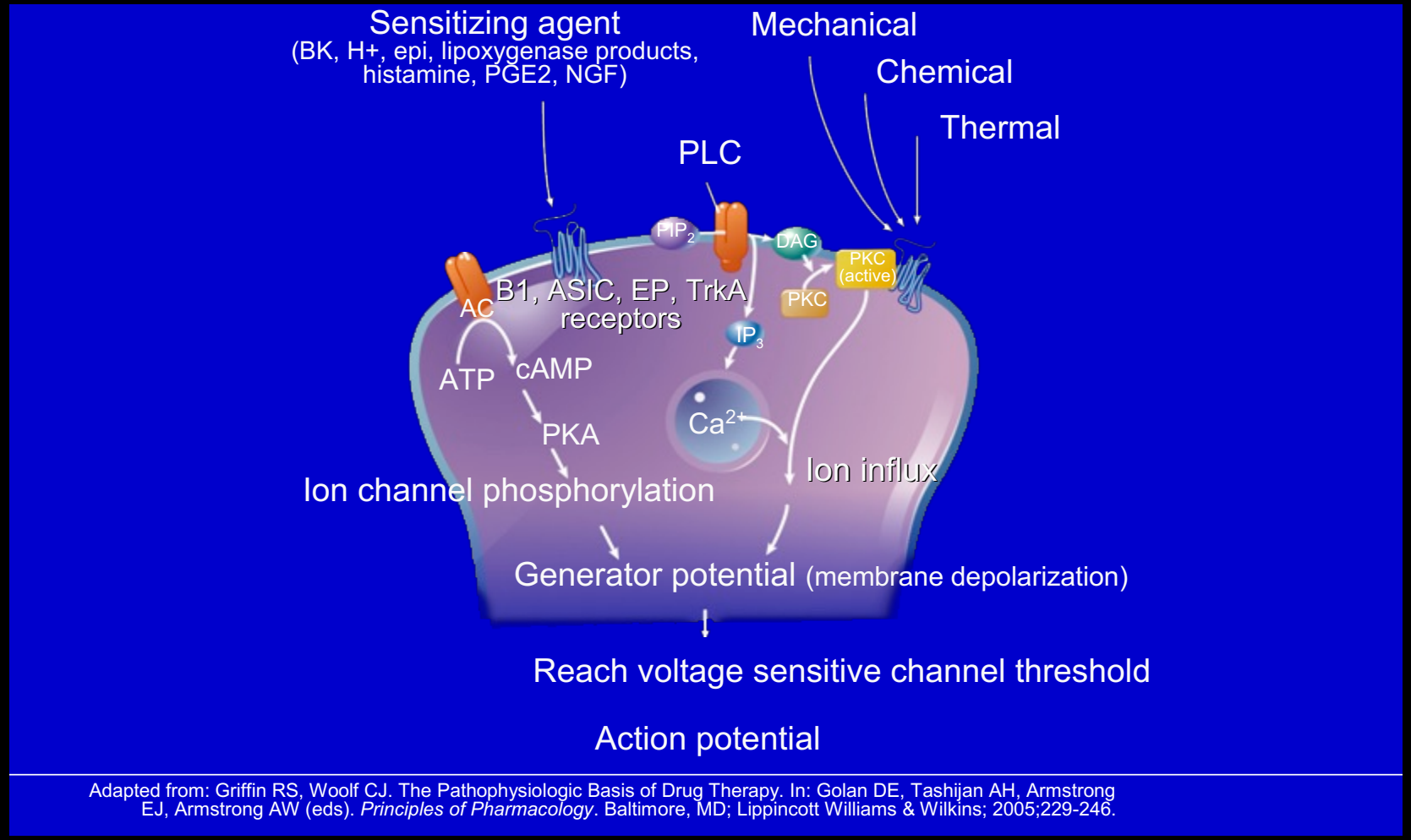
Neuroplasticity in Peripheral Pain Transmission



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

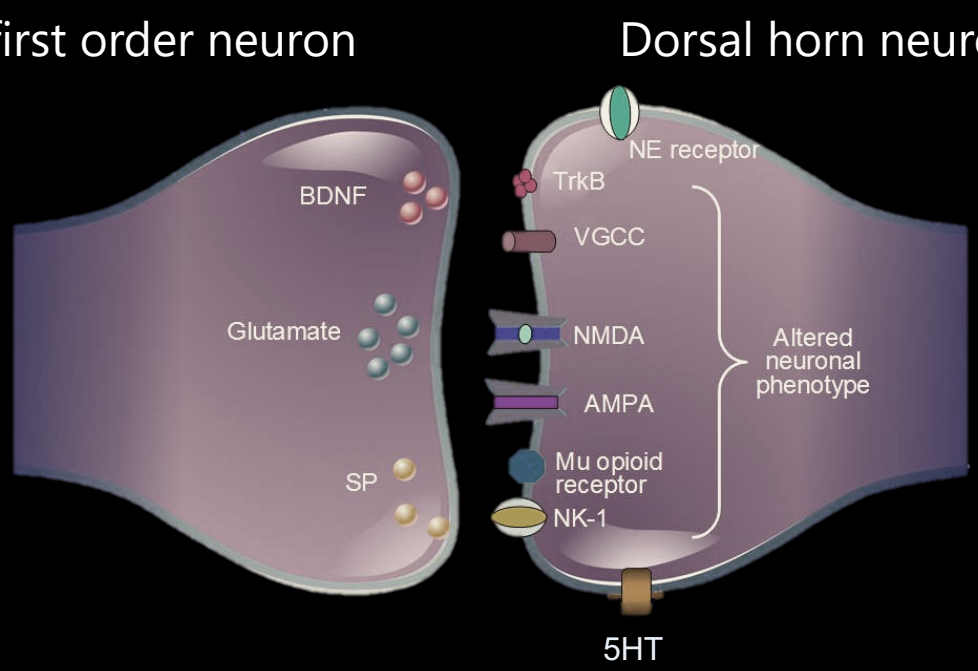
Prime role in chronic pain, particularly neuropathic pain

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

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.

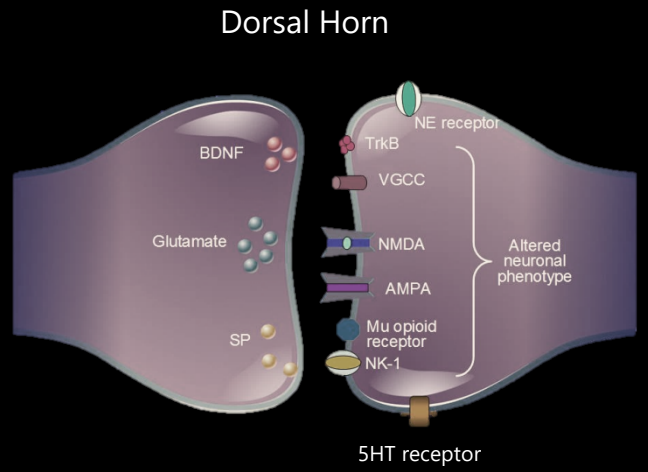
First Order Synapse – Dorsal Horn



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

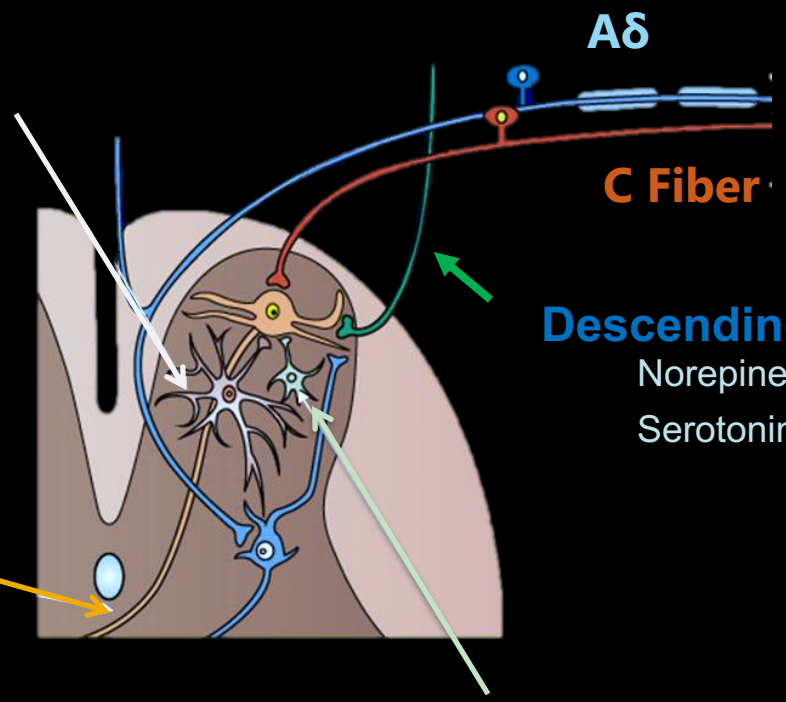
- Excitatory Neurotransmitters
  - Substance P, CGRP, Glutamate
- NMDA Channel Activity
  - Glutamate binding
  - Altering channel activity
- Descending inhibitory tracts
  - NE/Serotonin (5HT)
- Mu opioid receptor

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]

Spinal cord glial cell
Activate or establish alternate connections



Descending inhibitory axon
Norepinephrine (Inhibitory)
Serotonin/5HT (Mixed)

Second-order projection neuron (to brain)

GABA-ergic inhibitory interneuron
Decrease glutamate availability

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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

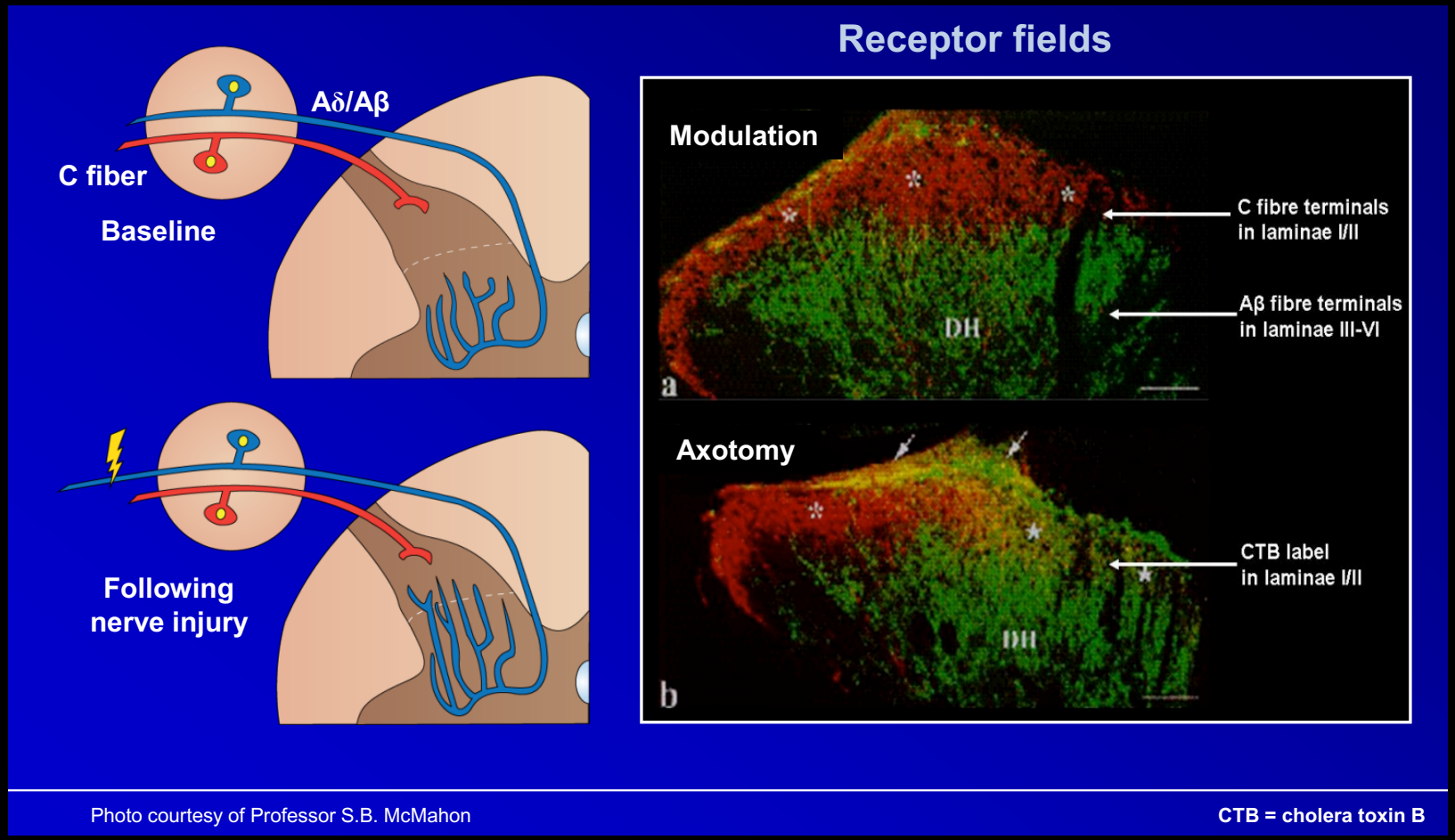
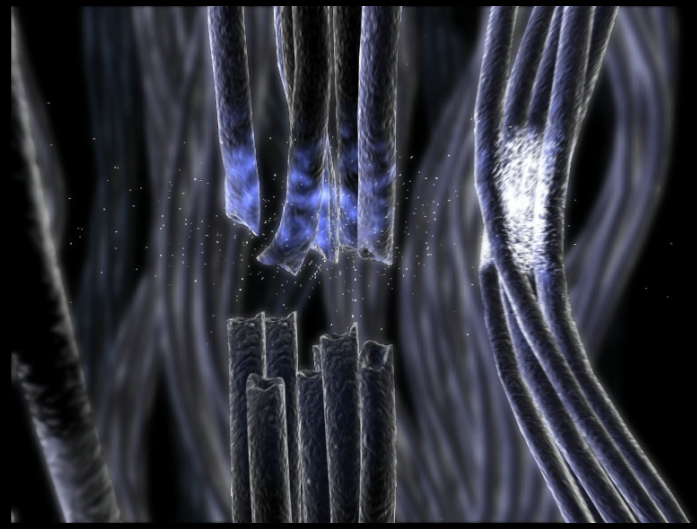
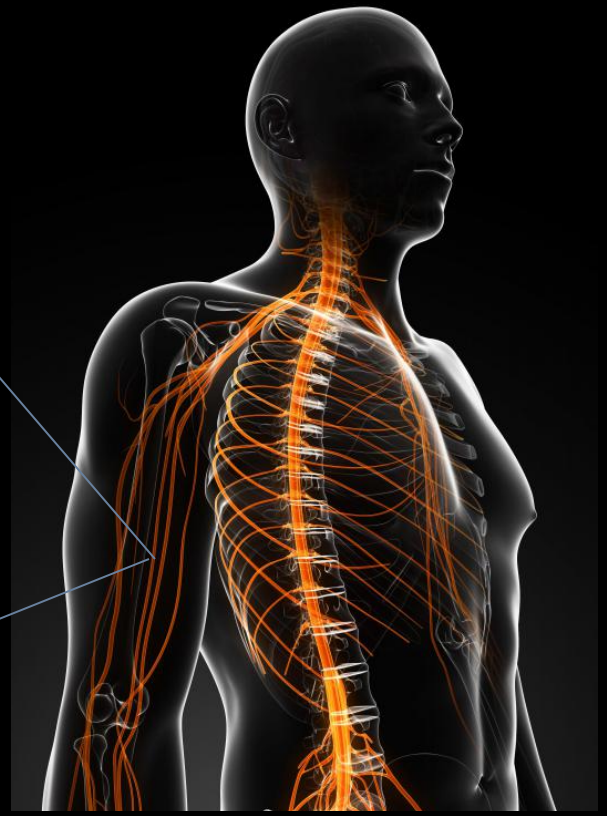


Photo courtesy of Professor S.B. McMahon

CTB = cholera toxin B

Neuroplasticity: Cross Talk



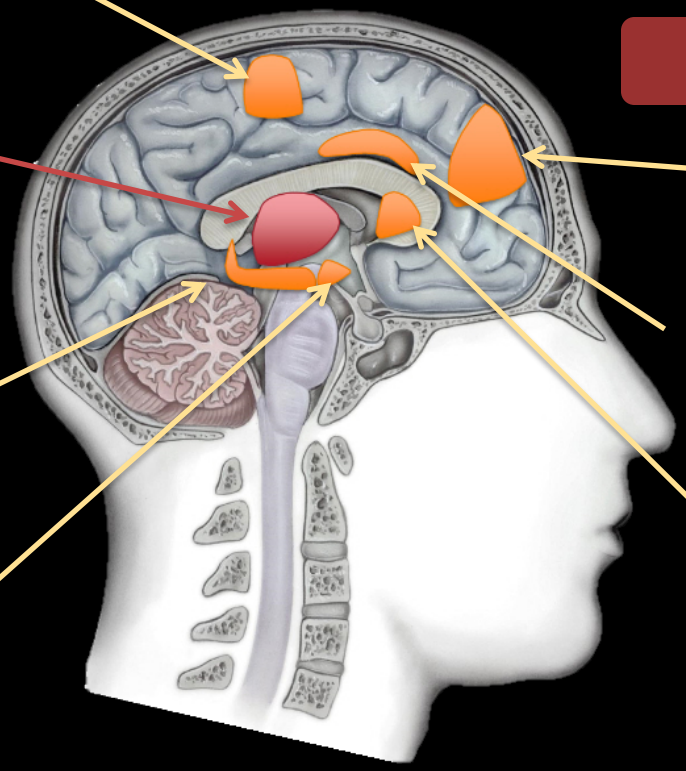


Central Sensitization:
Neuroplasticity in Spinal Cord Processing

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

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



Pain and emotion

Pain only

Somatosensory cortex
Localization

Thalamus
Routing

Hippocampus
Pain memory/Learning

Amygdala
Emotional Aspect

Prefrontal cortex
Motor planning

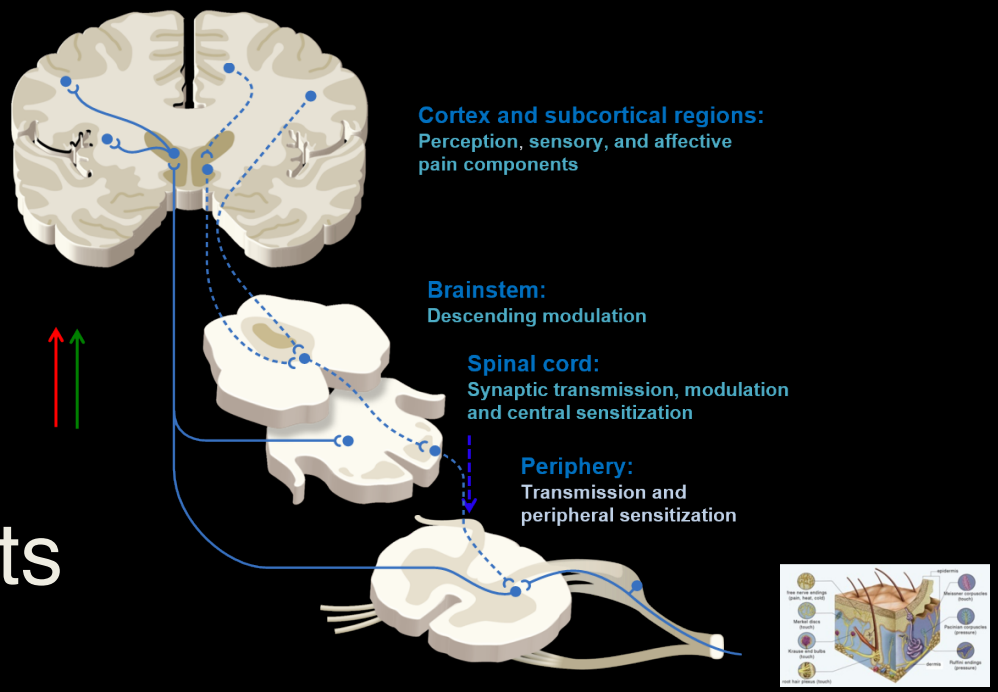
Anterior cingulate cortex
Context/Situation of pain

Insular cortex
Pain judged to the degree and where pain is imagined

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

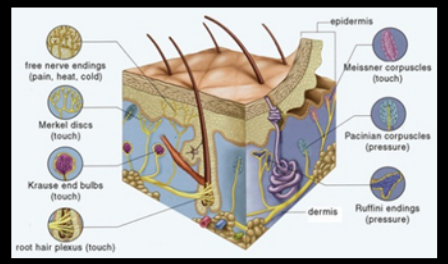
Pharmacological Targets in Pain

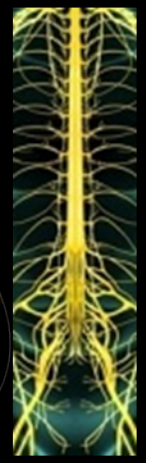
Ectopic Activity
Na+ channel blockers
Ca+2 channel blockers
GABAergic enhancement
Glutaminergic inhibition

Descending Modulation
Central α-agonists
TCAs
SNRIs
Opioids/Tramadol

CNS

PNS





Peripheral Sensitization
NSAIDS
Local Anesthetics

TCAs
Anticonvulsants
Local Anesthetics
Opioids

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

PAINWEEK®

Woolf C, Max M Anesthesiology 2001

Non-Pharmacologic Treatments Reliant Upon Pain Pathways

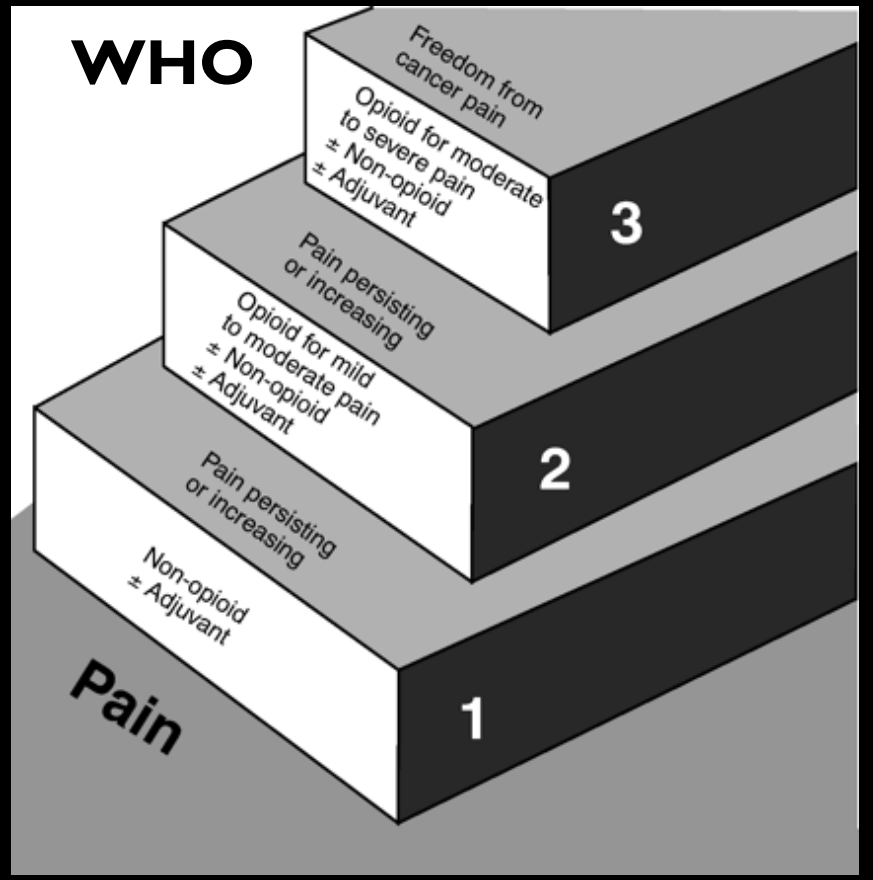
- Classic Neuromodulation (Implantable spinal and extraspinal)
- External devices (Transcutaneous)
  - Quell – Musculoskeletal pain (neck, back, etc.)
  - Nerivio Migra – Acute migraine
  - Cefaly – Acute migraine without aura
  - Livia – Menstrual cramps
  - ActiPatch – Musculoskeletal pain
  - ClearUP – Sinus pain
  - gammaCore – Migraine & cluster HA (Covid-19 emergency use respiratory system/asthma)

The Chronic Pain Armamentarium

Nonopioids
- Acetaminophen
- NSAIDs
- COX-2 inhibitors

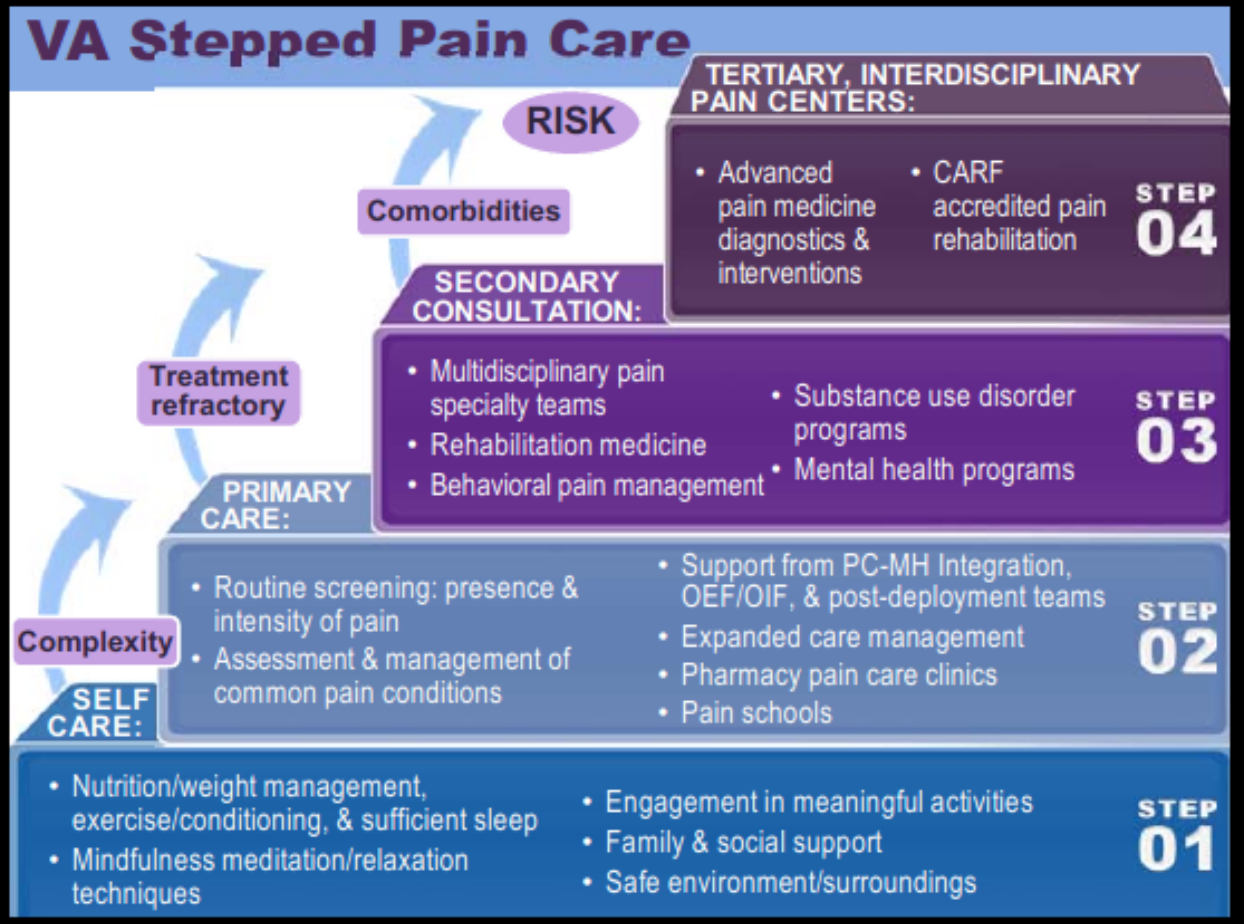
Opioids
- Mu-opioid agonists
- Mixed Agonist-antagonists

Adjuvant analgesics
- Antidepressants
- Anticonvulsants
- Topical agents/local anesthetics



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

VA DoD Stepped Pain Care Model



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

Objectives for Treating Pain

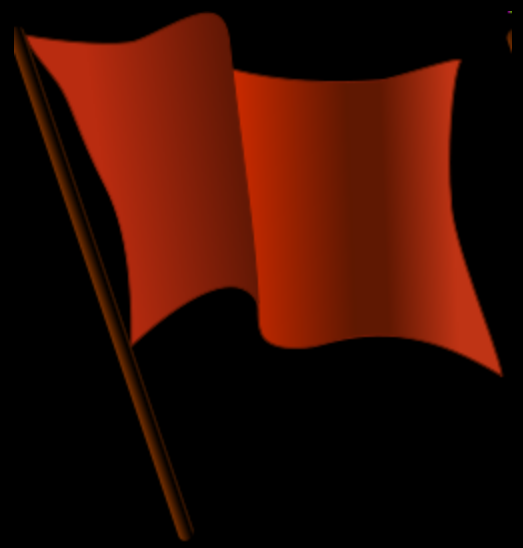
- Reduce overall signal by addressing the source
  - Treatment by eliminating the pathology
  - Mitigate the response at the source
- Interrupt or interfere with the signal within the pathway
  - Directly addressing steps in the pathway
- Reduce the overall excitatory response
- Increase the inhibitory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

Neuroplasticity Considerations

- Neuroplasticity can be a two 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 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