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

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Classification of Pain

- Good pain vs bad pain

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Good Pain

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

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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

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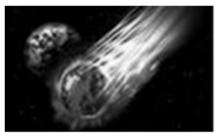
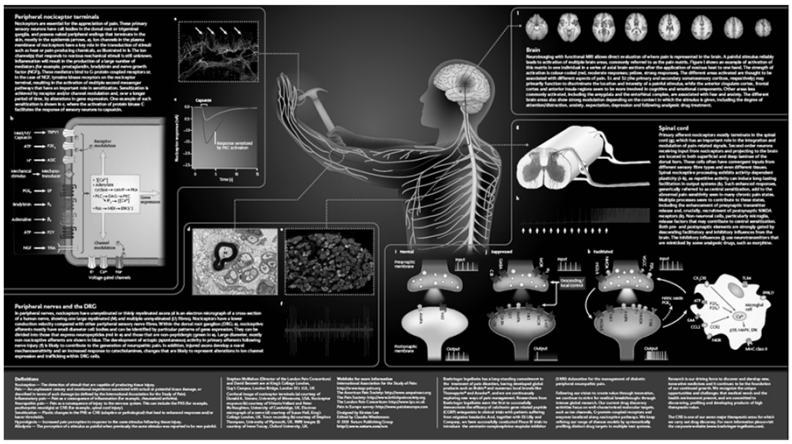
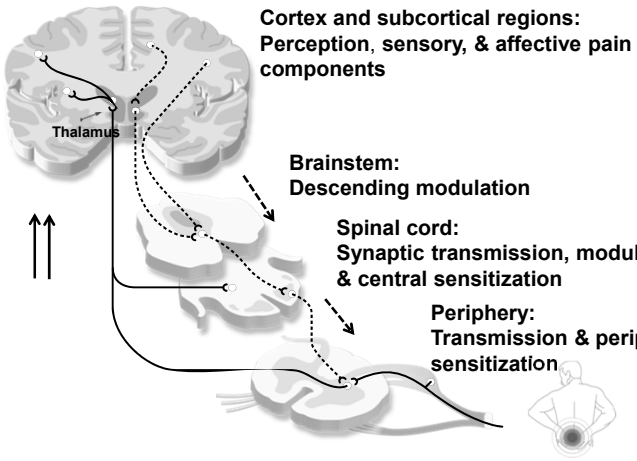
Pain Mechanisms





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

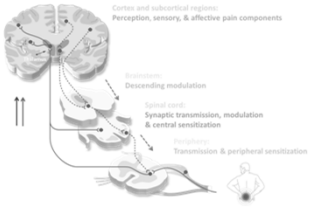
Periphery: Transmission & peripheral sensitization

- 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.

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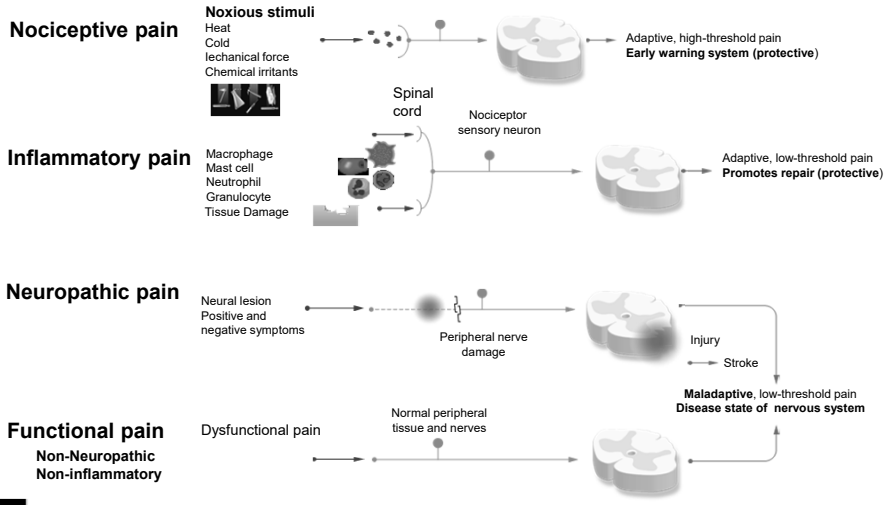
Common Types of Pain



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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.

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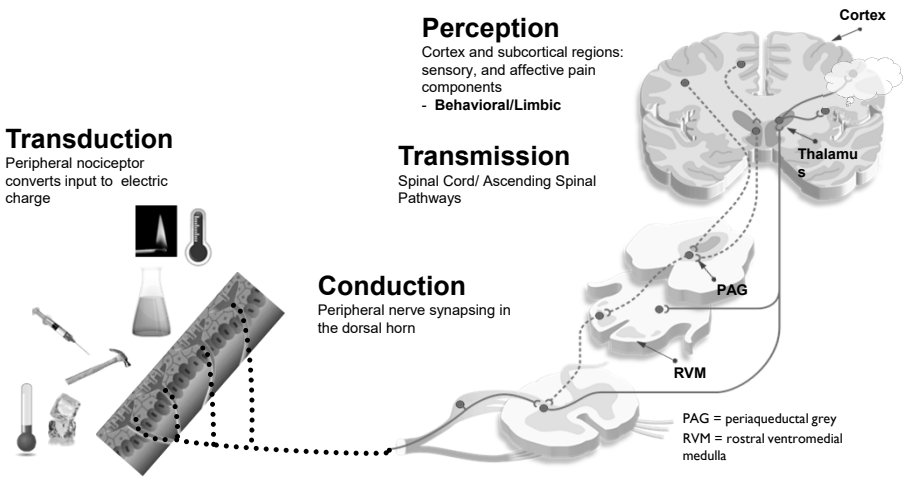
Pain Pathway Steps

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

Molecular Elements: Peripheral—Central

Transduction
TRPV1, TRPV2, TRPV3, TRPM8
ASIC, DRASIC
MDEG, TREK-1
BK_1, BK_2
$P2X_3$

Membrane excitability of peripheral afferents
Na_v 1.8, Na_v 1.9
K^+ channel

Peripheral sensitization
NGF, TrkA
TRPV1
Na_v 1.8
PKA, PKC isoforms, CaMK IV
Erk ½, p38, JNK
IL-1B, $cPLA_2$, COX2, EP1, EP3, EP4
TNFα

Synaptic Transmission
Presynaptic
VGCC
Adenosine-R
(mGlu-R)

Postsynaptic
AMPA/kainite-R, NMDA-R, mGlu-R
NK1
Na_v 1.3
K^+ channel

Central Inhibition
GABA, $GABA_A$-R, $GABA_B$-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

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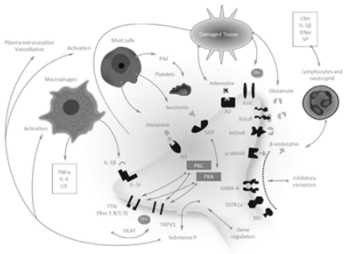
Adapted from Scholz J, Woolf CJ, Nature Neuroscience supplement Vol 5, 2002

Transduction: Processing at Peripheral Nerve Endings



- Conversion of mechanical, thermal or chemical stimuli into an electric charge
- Involves
  - Receptors activated directly by stimuli
  - Injury/inflammatory response

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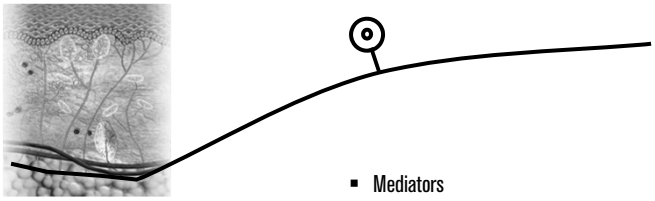
Adapted from Dougherty PM, et al. Neurochemistry of somatosensory and pain processing. In: Benzon H, et al, eds. *Essentials of Pain Medicine*. Philadelphia, PA; Saunders; 2011: chapter 2.

How is Pain Transduced?



- Nociception
  - Mechanical
  - Thermal
  - Chemical

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

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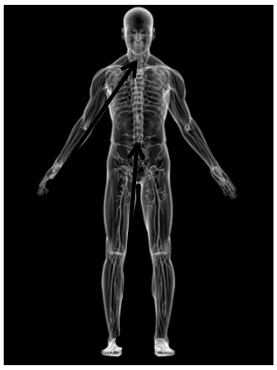
Conduction

- Conduction impulses from primary nociceptors to the spinal cord (dorsal horn) along the peripheral nerve



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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

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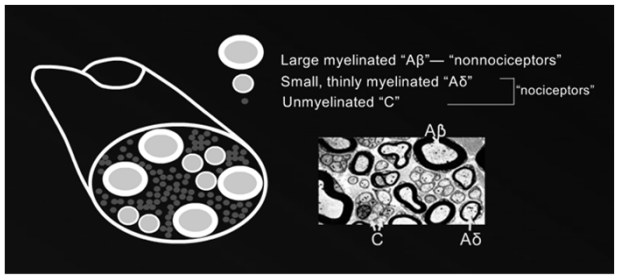
Peripheral Pain Nociceptors



Aβ - muscle spindle secondary endings, touch, and kinesthesia.
Aδ - pain, temperature, crude touch, and pressure.

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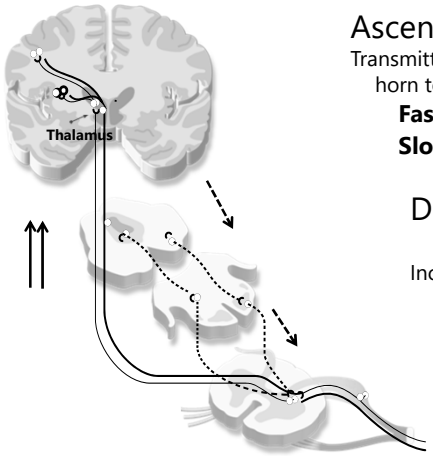
Bashbaum A, Jessell T, The perception of Pain, In Kendal E, Schwartz J, Principles of Neural Science 4th ed, New York, McGraw Hill, 2000, 482-483.

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)*

Increase or decrease volume control of incoming nociceptive signals reaching the brain

- 5-HT - Serotonin
- NE - Norepineherine

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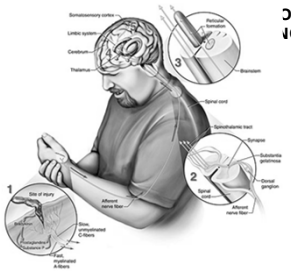
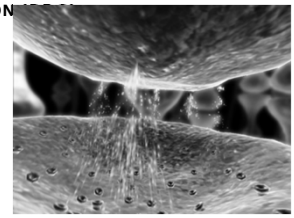
- Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012; 23;73(4):638-652.

How is Pain Conducted and Transmitted?



DORSAL ROOT GANGLION



- **Excitatory Transmitters**
  - Substance P
  - Calcitonin gene related peptide
  - Aspartate, Glutamate
- **Inhibitory Transmitters (descending inhibitory pathways)**
  - GABA
  - Glycine
  - Somatostatin
  - a2 agonists

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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

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How Acute Pain Becomes Chronic

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

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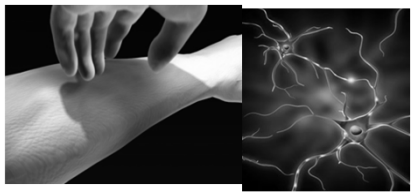
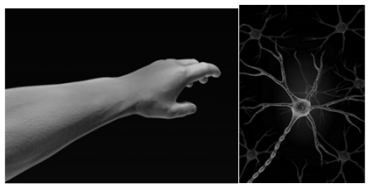
Definitions

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





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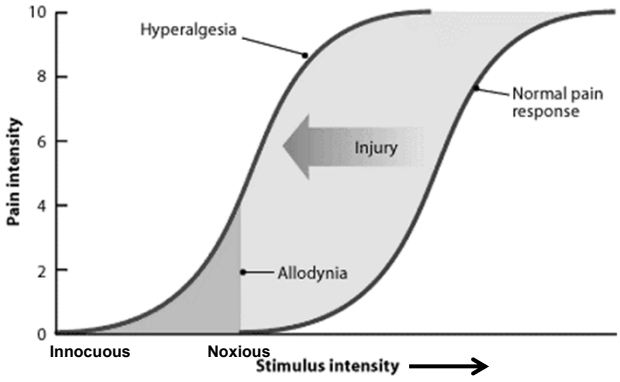
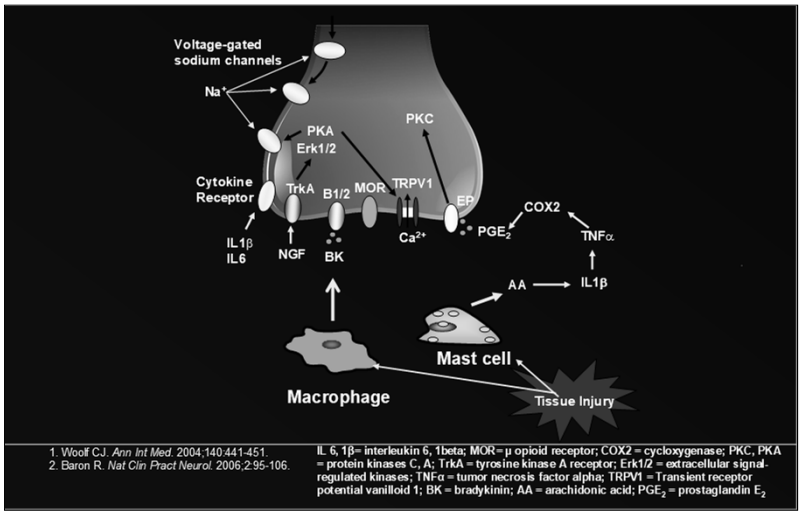
Neuroplasticity in Pain Processing



PAINWEEK

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

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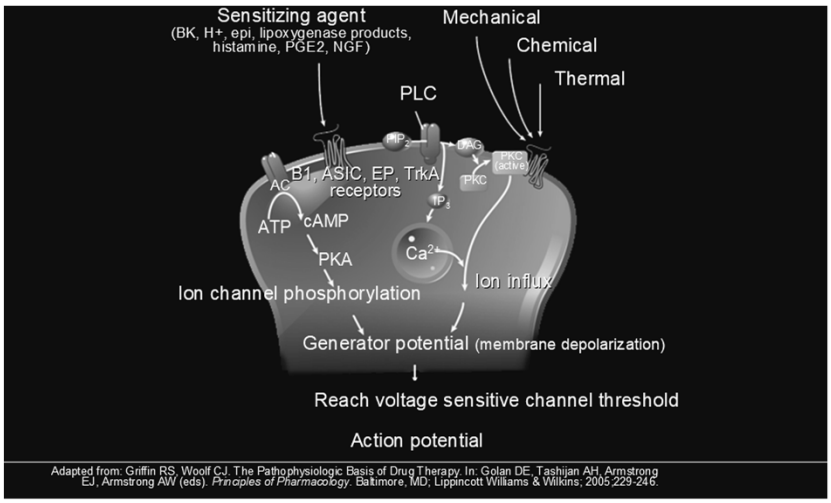
Peripheral Sensitization



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.

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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

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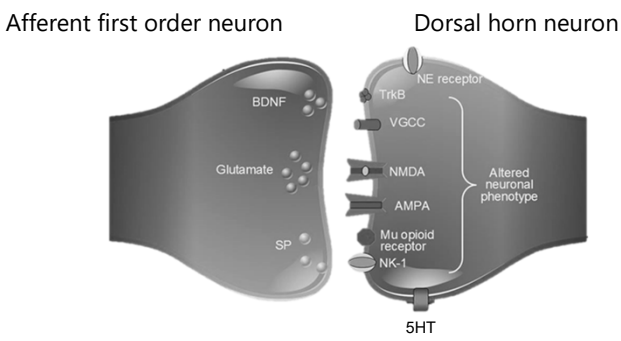
Definitions

- 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]

PAINWEEK

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.

Central Sensitization



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

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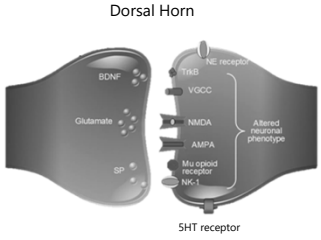
Adapted from Schlotz J, Woolf CJ. Nat Neuroscience. 2002;5:1062-1067

Central Sensitization (cont'd)



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

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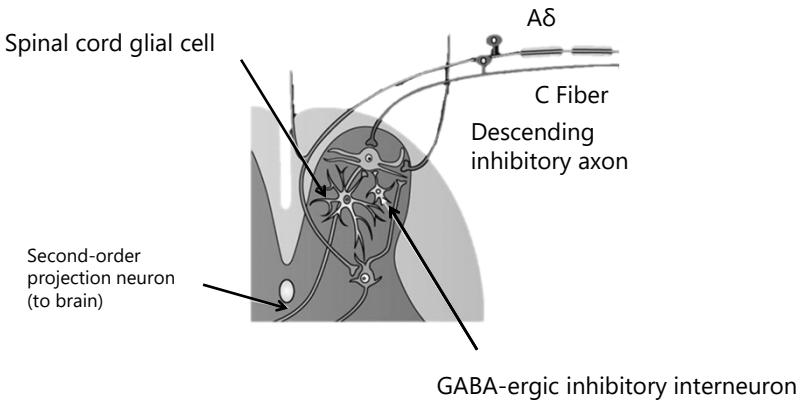
Adapted from Schlotz J, Woolf CJ. Nat Neuroscience. 2002;5:1062-1067

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



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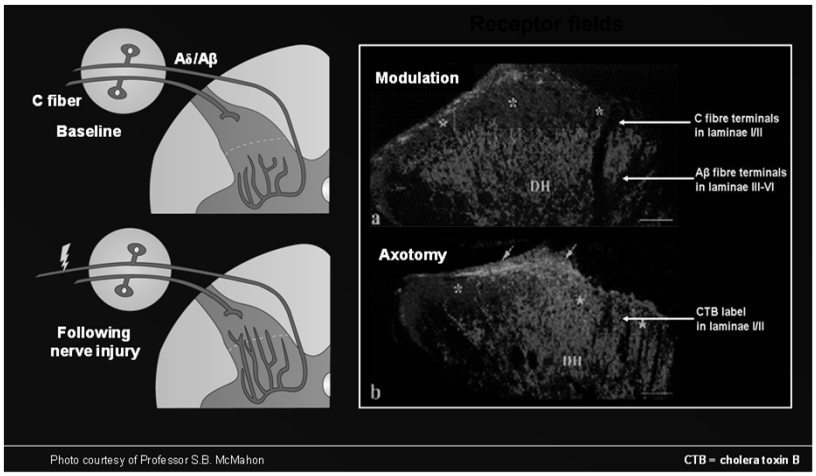
Adapted from 1. Baron R. Mechanisms of disease: neuropathic pain-a clinical perspective. *Nat Clin Pract Neurology*. 2006;2:95-106.
2. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Int Med*. 2004;140:441-451.

Neuroplasticity: Neural Reorganization



CTB = cholera toxin B

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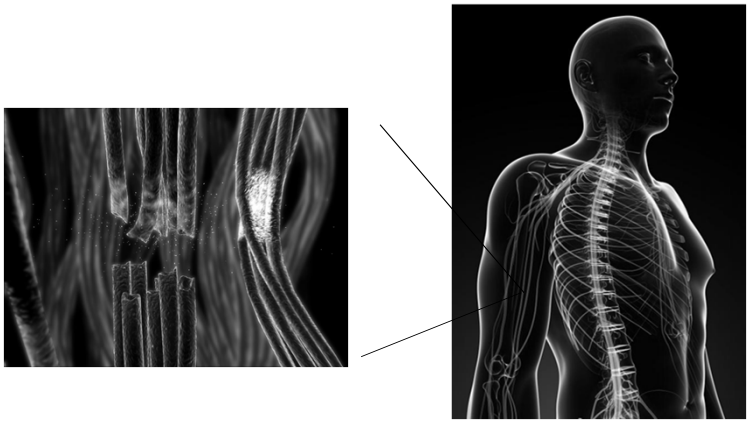
Neuroplasticity: Cross Talk



CTB = cholera toxin B

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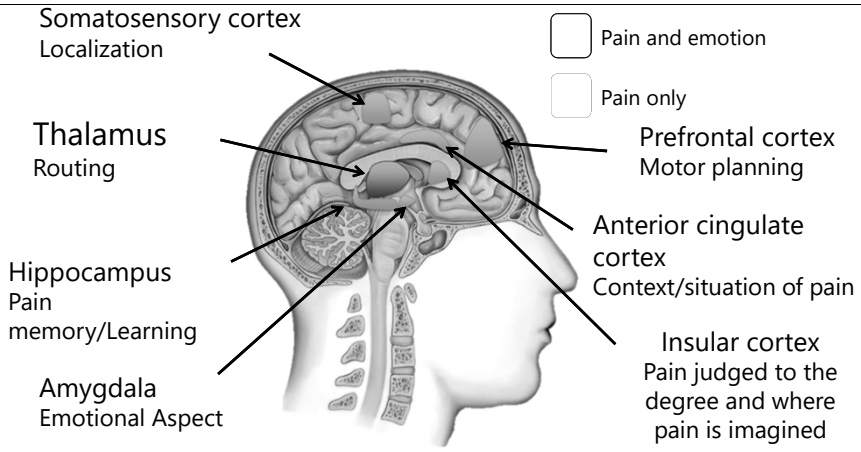
1. Mannion RJ, Woolf CJ: *Clin J Pain.* 2000;16(3):S151-S153. 2. Ossipov MH, et al. *Ann NY Acad Sci.* 2000;909:12-24.
3. Wieseler-Frank J, et al. *Neurosignals.* 2005;14:166-174. 4. Guilbaud G, et al. *Exp Brain Res.* 1992;92:227-245.

Brain Regions Involved in Pain Processing



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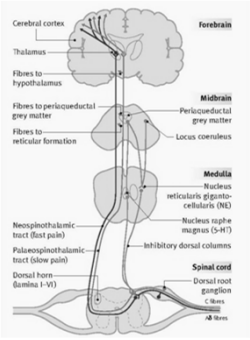
Apkarian AV et al, Eur J Pain 2005;9:463-484

Analgesics That Modify Pain Processes



- Transduction
  - NSAIDs
  - Antihistamines
  - Membrane stabilizing agents
  - Local anesthetic cream
  - Opioids
  - Bradykinin & Serotonin antagonists
- Transmission/Modulation
  - Spinal opiods
  - α_2 **agonists**
  - **NMDA receptor antagonistis**
  - **NSAIDs**
  - **NO inhibitors**
  - **K^+ channel openers**
- Perception
  - Parenteral opiods
  - α_2 **agonists**
  - **General anesthetics**
- Conduction
  - Local anesthetics
    - Peripheral nerve, plexus, epidural block

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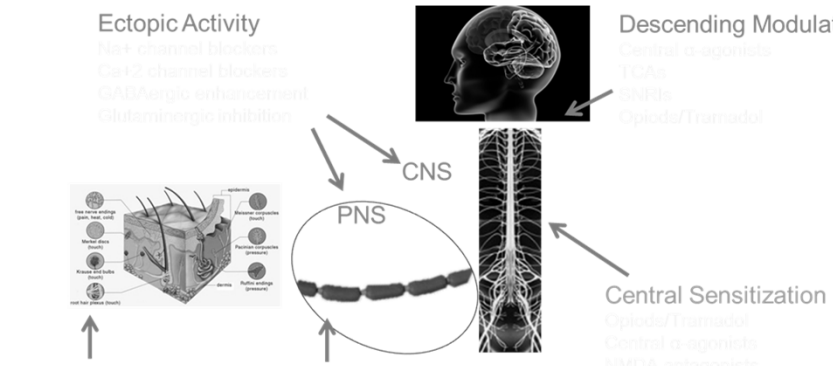
Pharmacological Targets in Pain



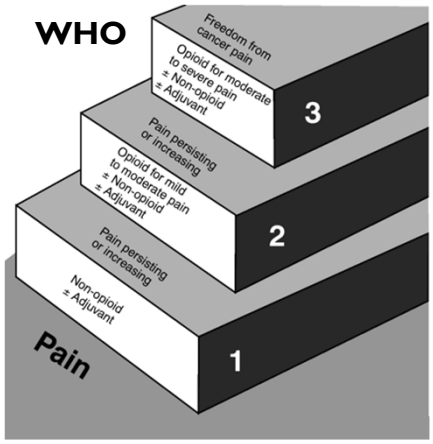
Woolf C, Max M Anesthesiology 2001

The Chronic Pain Armamentarium

Nonopioids
- Acetaminophen
- NSAIDs
- COX-2 inhibitors

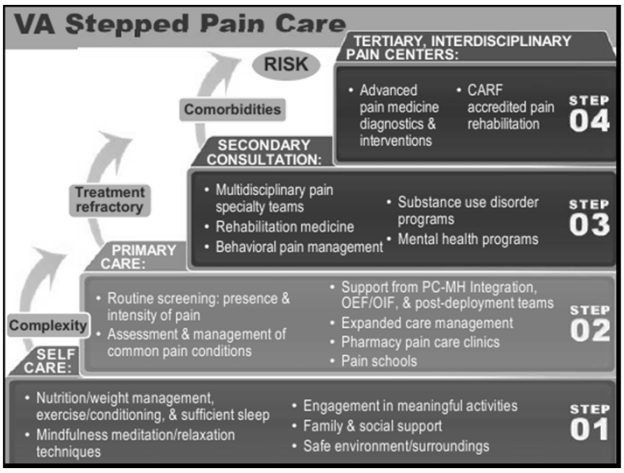
Opioids
- Mu-opioid agonists
- Mixed agonist-antagonists

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



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

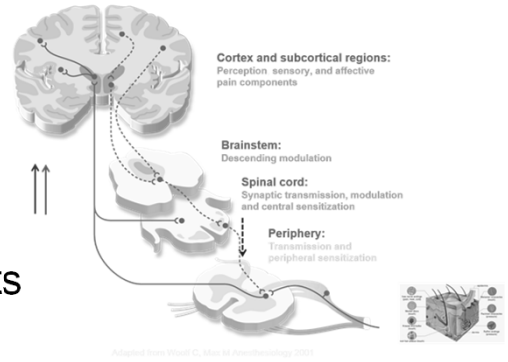
VA DoD Stepped Pain Care Model



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

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 and toxic epidermal necrolysis

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Nonopioids: NSAIDs

Examples

- Acetylated (aspirin); nonacetylated (diflunisal); acetic acid (diclofenac); propionic acid (naproxen); fenamic acid (mefenamic acid); enolic acids (piroxicam); nonacidic (nabumetone); 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
- Lipoxins (signaling resolution of inflammation)

PAINWEEK

Opioids

Examples

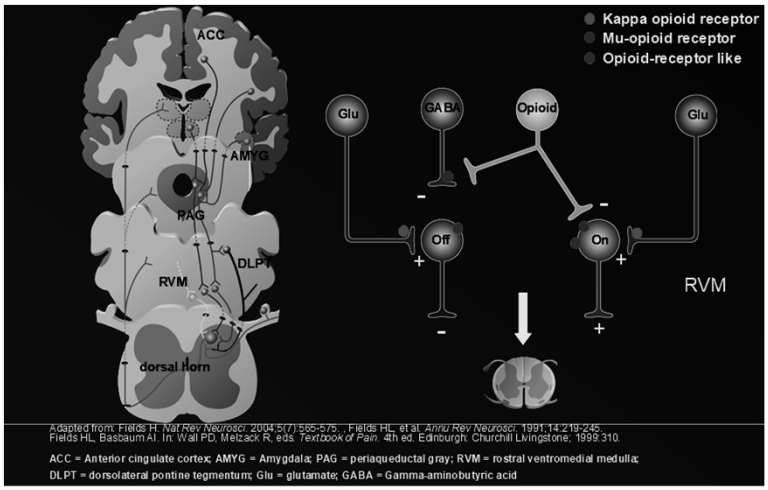
- Morphine, hydromorphone, fentanyl, oxycodone, oxymorphone, meperidine, codeine, methadone, tramadol

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

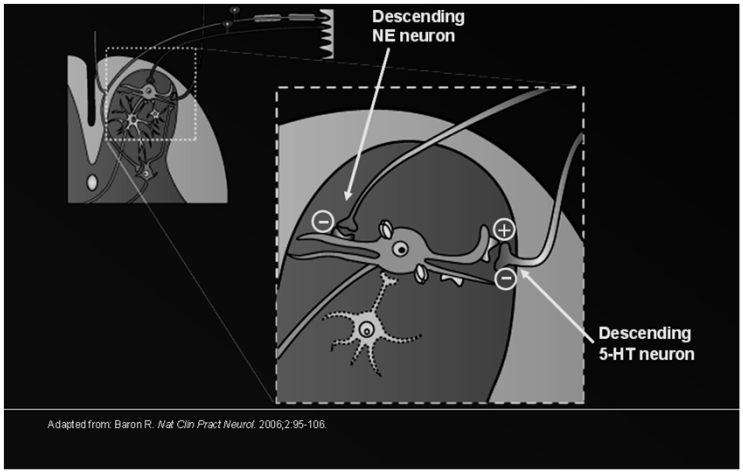
PAINWEEK

Overview of Descending Pain Inhibitory Pathways and Modulation of Pain Response



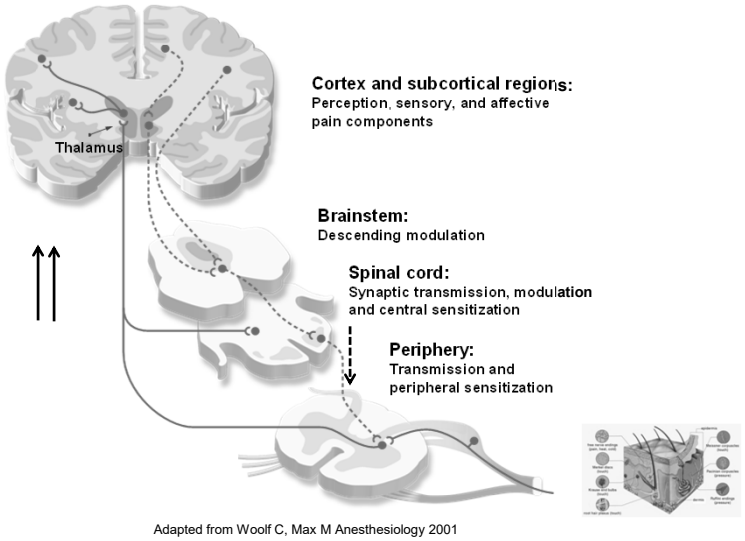
PAINWEEK

Modulation of Central Sensitization by 5-HT & NE Descending Pathways



PainWeek

Mechanism of Action: Opioids



PainWeek

Adapted from Woolf C, Max M Anesthesiology 2001

Adjuvant Analgesics: Tricyclic Antidepressants

Examples

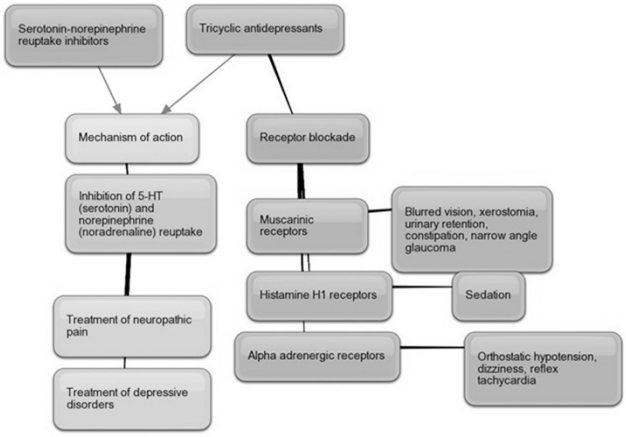
- Amitriptyline, desipramine, doxepin, imipramine, nortriptyline

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)

PAINWEEK

TCAs and SNRIs Pharmacological Properties



PAINWEEK

http://pharmacologycorner.com

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!

PAINWEEK

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

PAINWEEK

Serotonin/5-HT Receptors

Family	Type	Mechanism	Potential
5-HT$_1$	G_i/G_o-protein coupled.	Decreasing cellular levels of cAMP.	Inhibitory
5-HT$_2$	G_q/G_{11}-protein coupled.	Increasing cellular levels of IP_3 and DAG.	Excitatory
5-HT$_3$	Ligand-gated Na^+ and K^+ cation channel.	Depolarizing plasma membrane.	Excitatory
5-HT$_4$	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT$_5$	G_i/G_o-protein coupled.[4]	Decreasing cellular levels of cAMP.	Inhibitory
5-HT$_6$	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT$_7$	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory

PAINWEEK

http://en.wikipedia.org/wiki/5-HT_receptor

Serotonin/5-HT Receptors (cont'd)

- 5-HT1a (Blood Ves/CNS)
  - Addiction
  - Aggression
  - Anxiety
  - Appetite
  - BP
  - Cardiovascular function
  - Emesis
  - Heart rate
  - Impulsivity
  - Memory
  - Mood
  - Nausea
  - Nociception
  - Penile erection
  - Pupil dilatation
- 5-HT1a *(cont)*
  - Respiration
  - Sexual behavior
  - Sleep
  - Sociability
  - Thermoregulation
- 5-HT5a & 5-HT6 (CNS)
  - Locomotion
  - Sleep
  - Anxiety
  - Cognition
  - Learning
  - Memory
  - Mood

PAINWEEK

http://en.wikipedia.org/wiki/5-HT_receptor

SNRIs (Serotonin/Noradrenaline Reuptake Inhibitors)

Examples

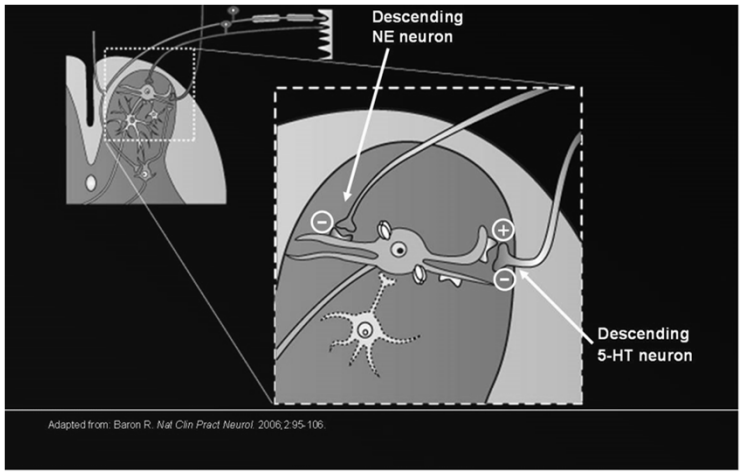
- Duloxetine, milnacipran, and venlafaxine

Mechanism of action

- Block reuptake of 5-HT and NA
  - Better tolerated, lower tendency for drug-drug interactions, better overdose safety

PAINWEEK

Modulation of Central Sensitization by 5-HT & NE Descending Pathways



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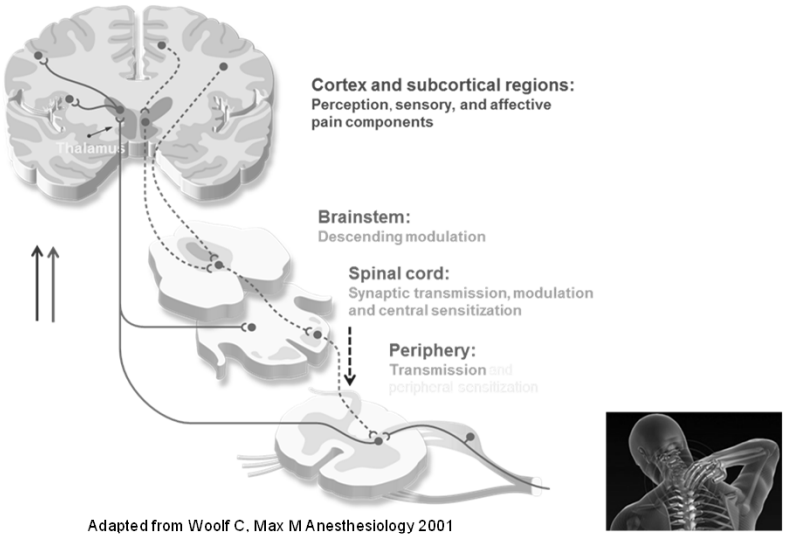
Site of Action: SNRIs



Adapted from Woolf C, Max M Anesthesiology 2001

PAINWEEK

Adjuvant Analgesics: Antiepileptics

Examples

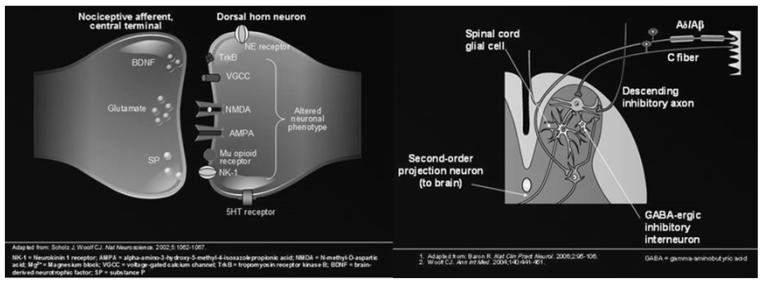
- Gabapentin, pregabalin*, carbamazepine, phenytoin, divalproex sodium, clonazepam, levetiracetam, topiramate, lamotrigine

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
  - Binds the α2δ subunit of voltage gated Ca+ channels, inhibit NT release

PAINWEEK

Site of Action: Antiepileptics



PAINWEEK

Adjuvant Analgesics: Topicals

Examples

- Lidocaine patch 5% , eutectic, mixture of lidocaine and prilocaine
- Capsaicin cream/patch
- Diclofenac (cream/liquid/gel/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

PAINWEEK

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

PAINWEEK

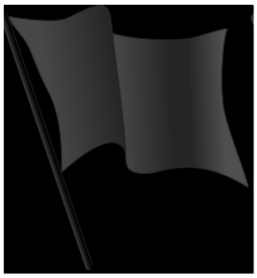
Muscle Relaxants: Spasmolytics

- 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, tizanadine (α-2 agonist), baclofen (GABA agonist), orphenadrine (benzodiazepine)
- Common adverse effects
  - Sedation, lethargy & confusion (cyclobenzaprine), dependence (carisopradol)

PAINWEEK

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



PAINWEEK

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

PAINWEEK