



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



Classification of Pain

- Good pain vs bad pain



Good Pain

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

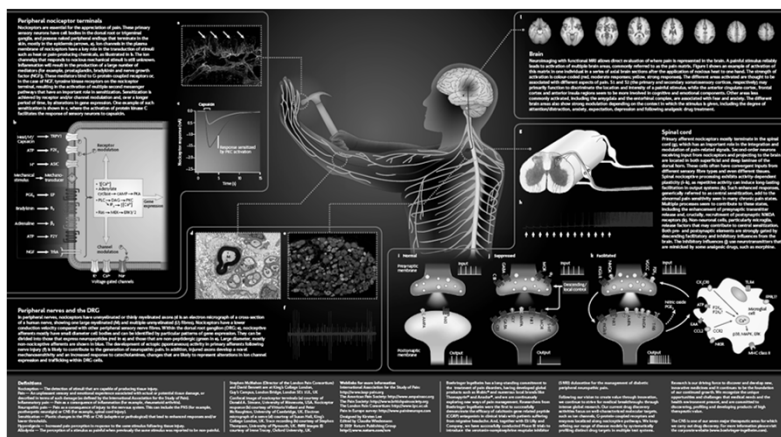
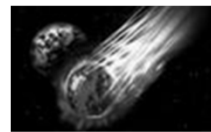
Painweek.

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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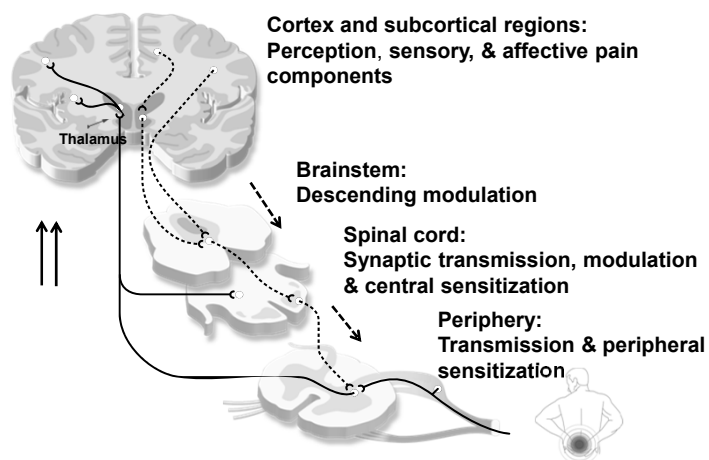
Pain Mechanisms



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

General Anatomy of Pain



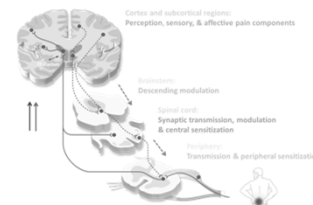
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Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012; 23;73(4):638-652.

Pain Roadmap:

Peripheral and Central Nervous System Landmarks

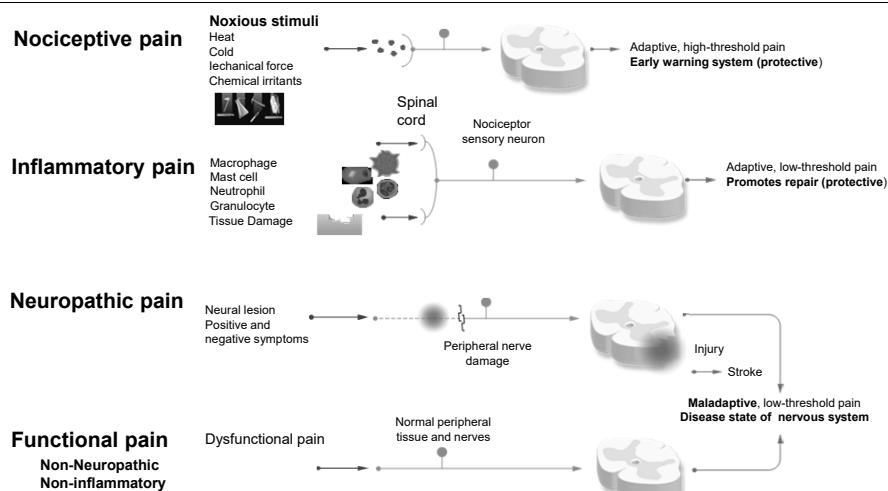
- Physiologic process involving multiple areas of the nervous system
- Bidirectional
- Involves normal as well as pathological processes
- A sensory experience associated with affective and cognitive responses
- Dynamic (i.e. occurring in real time)
- Adapts or changes in response to function—“neuroplasticity”



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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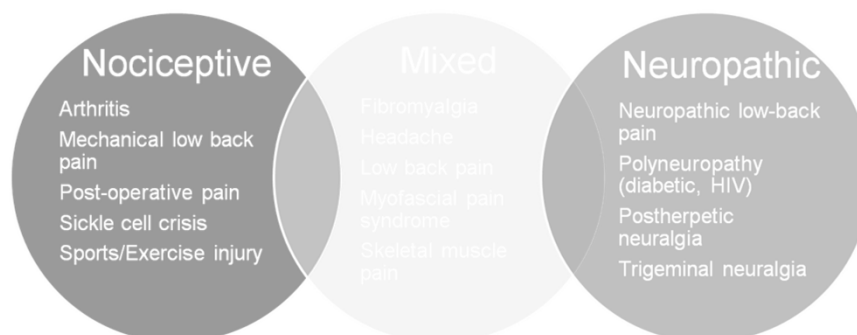
Common Types of Pain



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

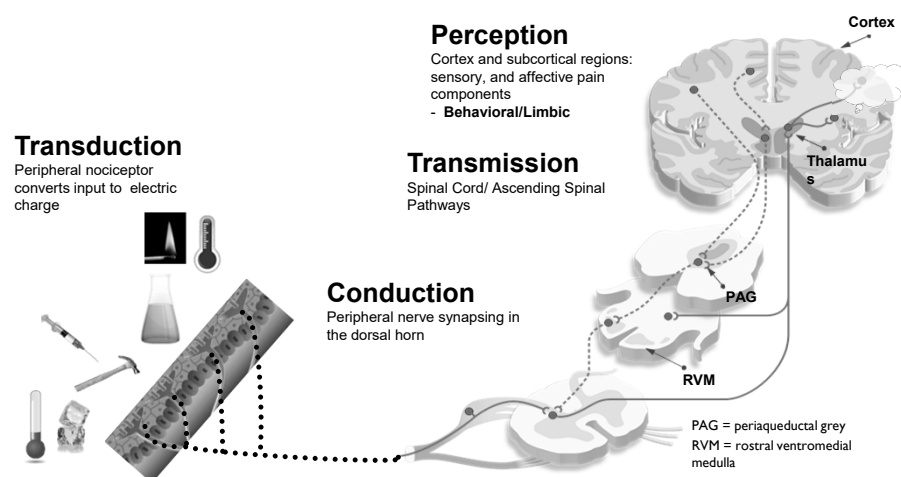
Nociceptive vs Neuropathic Pain



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



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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
BK₁, BK₂
P2X₃

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 1/2, p38, JNK
IL-1B, cPLA₂, COX2, EP1, EP3,
EP4
NF- κ B

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

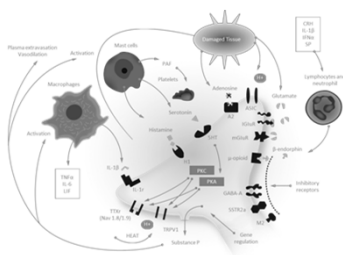
Gene expression

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

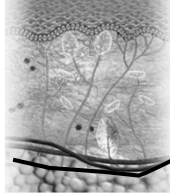


- Conversion of mechanical, thermal or chemical stimuli into an electric charge
- Involves
 - Receptors activated directly by stimuli
 - Injury/inflammatory response

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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



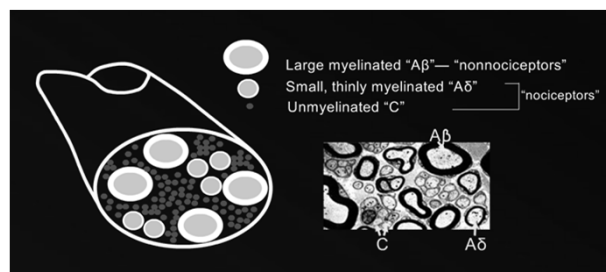
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▪ C-fibers

- Broad receptive fields
- Polymodal
- Unmyelinated
- Slower conducting
 - .5-2.0 m/sec
- Cross sensitized
- Small diameter



Peripheral Pain Nociceptors

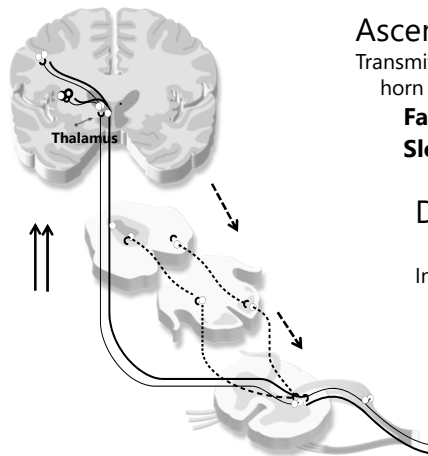


Aβ - muscle spindle secondary endings, touch, and kinesthesia.
Aδ - pain, temperature, crude touch, and pressure.

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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 supraspinal targets

Fast (green) Neospinothalamic

Slow (yellow) Paleospinothalamic

Descending inhibitory tracts (blue)

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

5-HT - Serotonin

NE - Norepinephrine

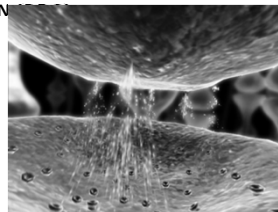
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Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012; 23,73(4):638-652.

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
- $\alpha 2$ 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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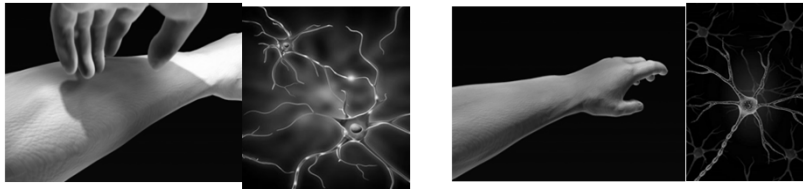
Definitions

▪ Hyperalgesia

- Lowered threshold to different types of noxious stimuli

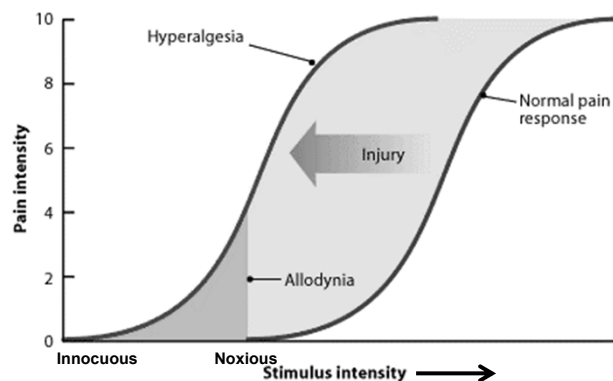
▪ Allodynia

- Painful response to what should normally be non-painful stimuli



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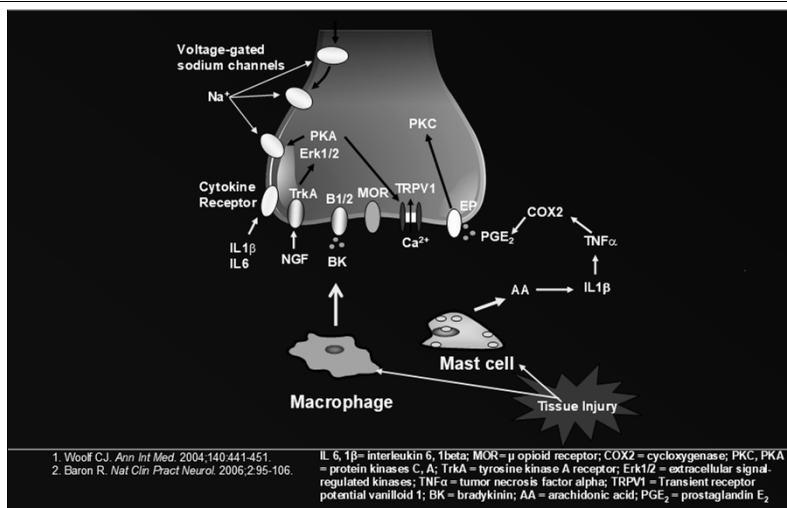
Neuroplasticity in Pain Processing



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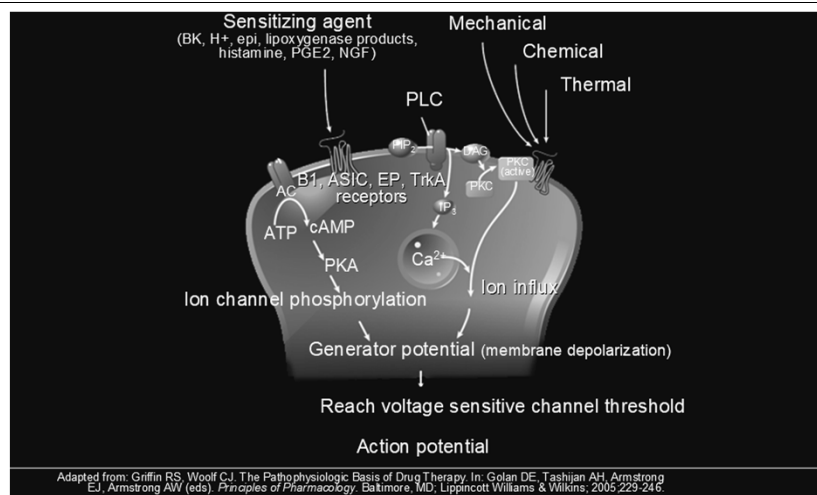
1. Woolf CJ, Salter MW. *Science*. 2000;288:1765-1768.
2. Basbaum AI, Jessell TM. The perception of pain. In: Kandel ER, Schwartz JH, et al. eds. *Principles of Neural Science*. 4th ed. New York, NY: McGraw-Hill; 2000:479.
3. Cervero F, Laird JMA. *Pain*. 1996;68:13-23.

Neuroplasticity in Peripheral Pain Transmission



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Peripheral Sensitization



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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



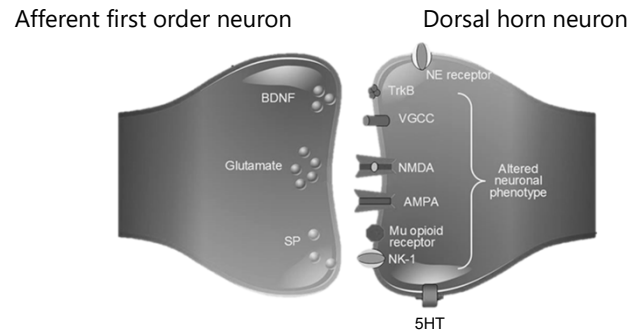
Definitions

- 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.

Central Sensitization



NK-1 = Neurokinin 1 receptor; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartic acid; VGCC = voltage gated sodium channel; TrkB = tropomyosin receptor kinase B; BDNF = Brain derived neurotrophic factor; SP = substance P

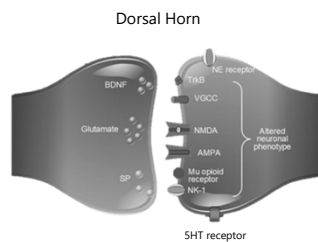
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Adapted from Schlotz J, Woolf CJ. Nat Neuroscience. 2002;5:1062-1067

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

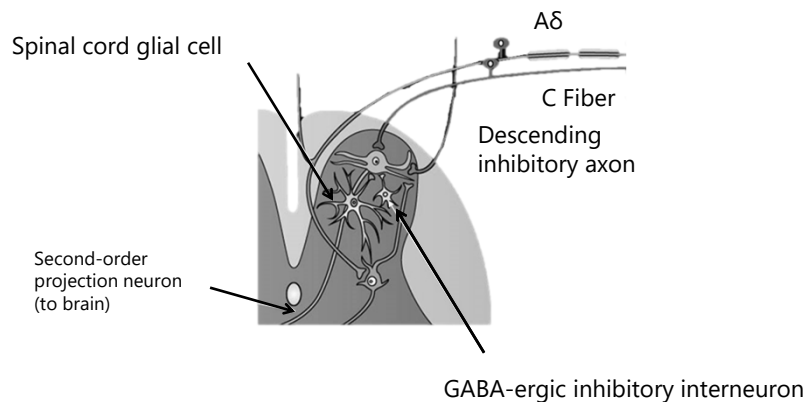


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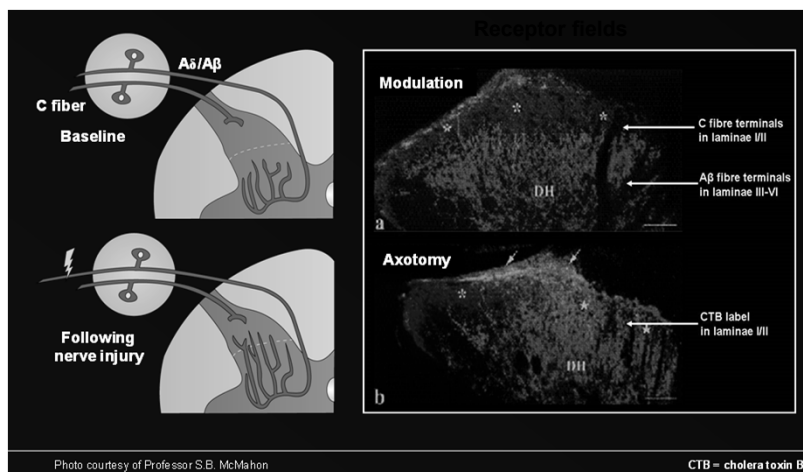
Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing^{1,2}



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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.

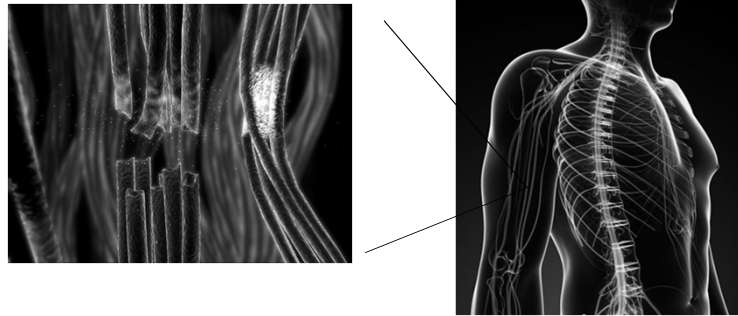
Neuroplasticity: Neural Reorganization



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CTB = cholera toxin B

Neuroplasticity: Cross Talk



CTB = cholera toxin B

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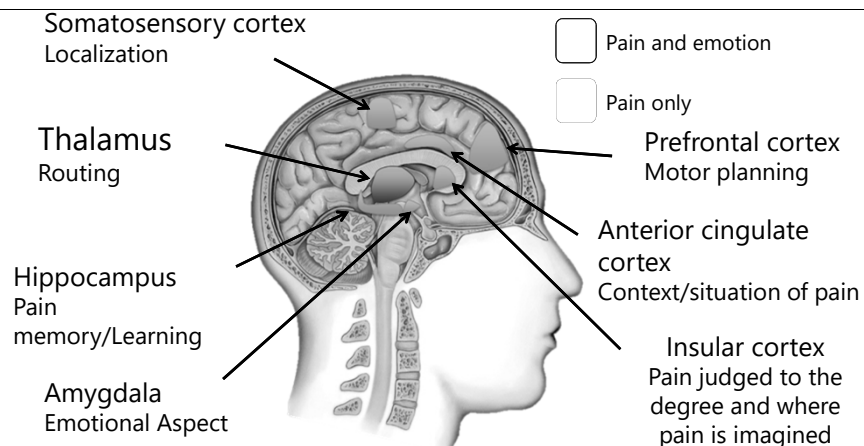
Central Sensitization: Neuroplasticity in Spinal Cord Processing

- 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 pathways²
 - Activation/migration of glial cells into the spinal cord³
 - Changes in the thalamus and primary somatosensory cortex⁴

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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.

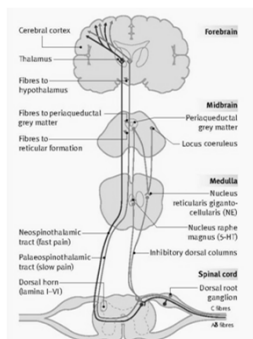
Brain Regions Involved in Pain Processing



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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 opioids
- α_2 agonists
- NMDA receptor antagonists
- NSAIDs
- NO inhibitors
- K^+ channel openers

Perception

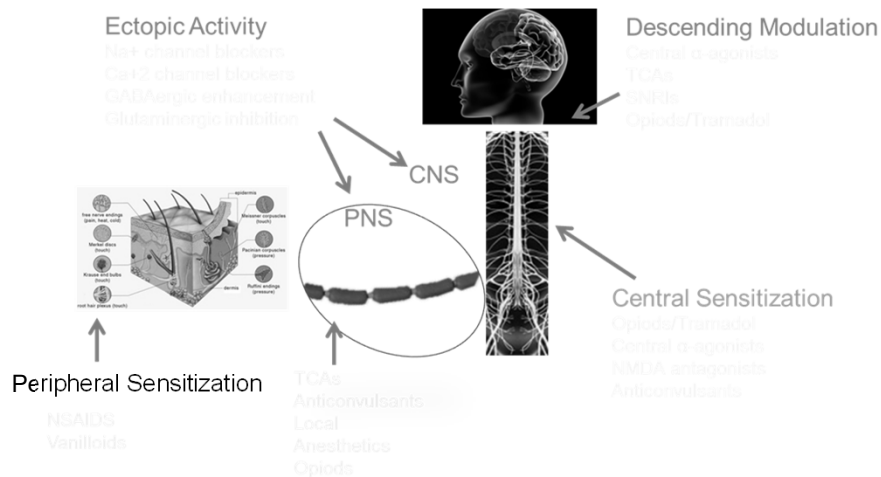
- Parenteral opioids
- α_2 agonists
- General anesthetics

Conduction

- Local anesthetics
 - Peripheral nerve, plexus, epidural block

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Pharmacological Targets in Pain



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Woolf C, Max M Anesthesiology 2001

The Chronic Pain Armamentarium

Nonopioids

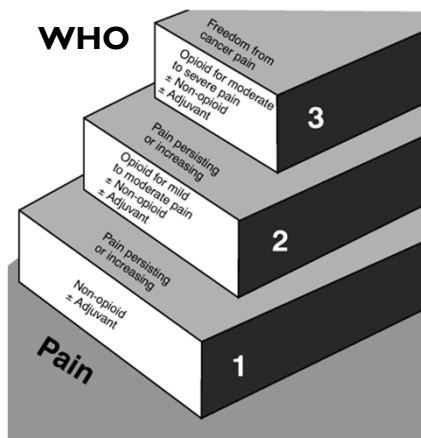
- Acetaminophen
- NSAIDs
- COX-2 inhibitors

Opioids

- Mu-opioid agonists
- Mixed agonist-antagonists

Adjuvant analgesics

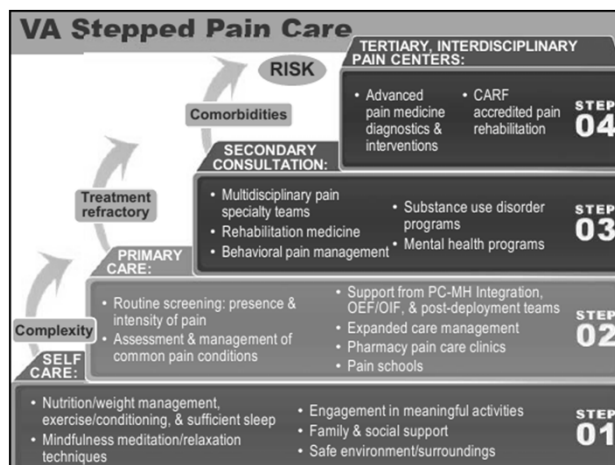
- Antidepressants
- Anticonvulsants
- Topical agents/local anesthetics



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

VA DoD Stepped Pain Care Model

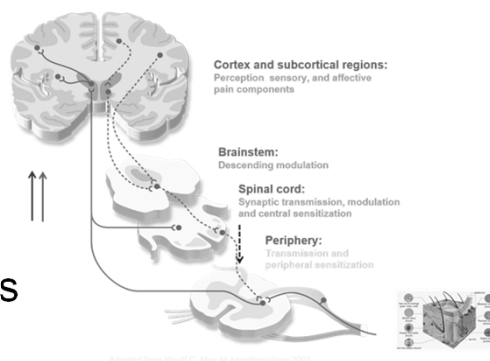


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PCSS-O Webinar Implementation of the National Pain Strategy and Safer Opioid Prescribing:
A Military Perspective, Buckenmaier C (COL) ret, Aug 24, 2016
JAMA Intern Med. 2015;175(5):682-689. doi:10.1001/jamainternmed.2015.97

Common Pharmacologic Therapies

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



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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



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)



Opioids

Examples

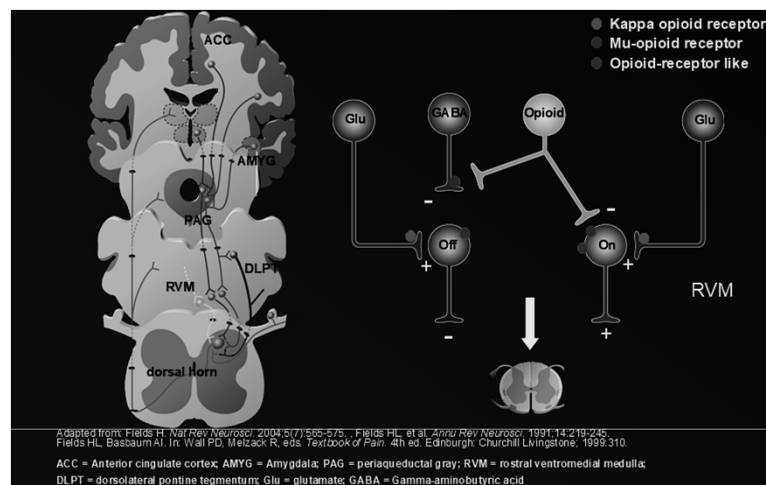
- Morphine, hydromorphone, fentanyl, oxycodone, oxymorphone, meperidine, codeine, methadone, tramadol

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

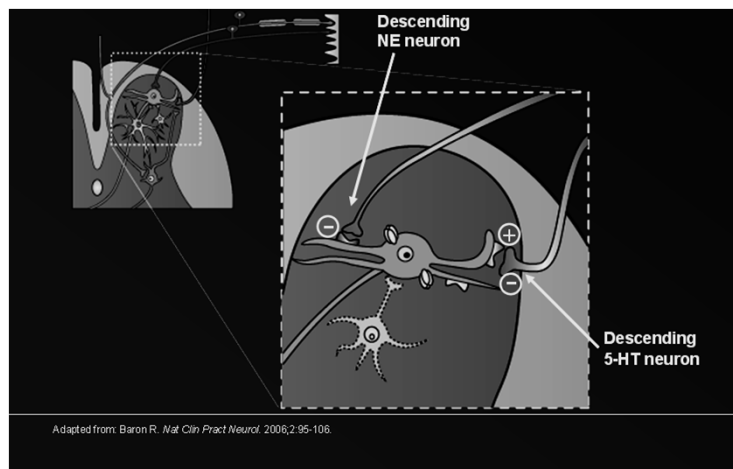
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Overview of Descending Pain Inhibitory Pathways and Modulation of Pain Response



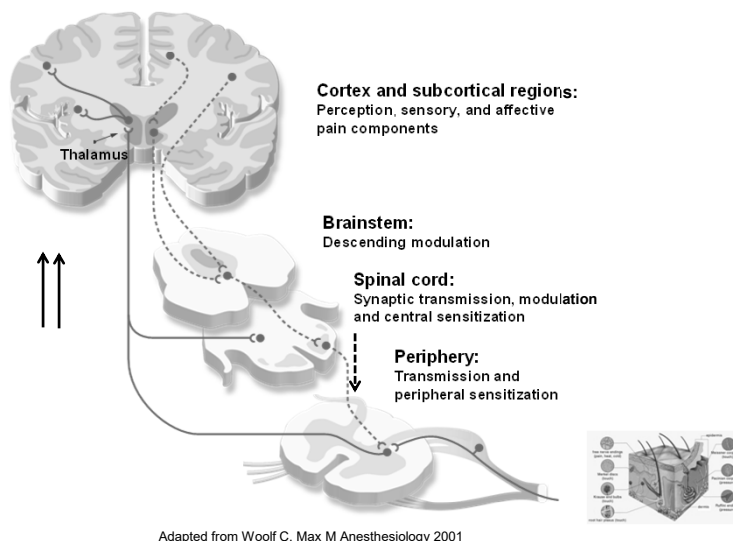
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Modulation of Central Sensitization by 5-HT & NE Descending Pathways



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Mechanism of Action: Opioids



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Adjuvant Analgesics: Tricyclic Antidepressants

Examples

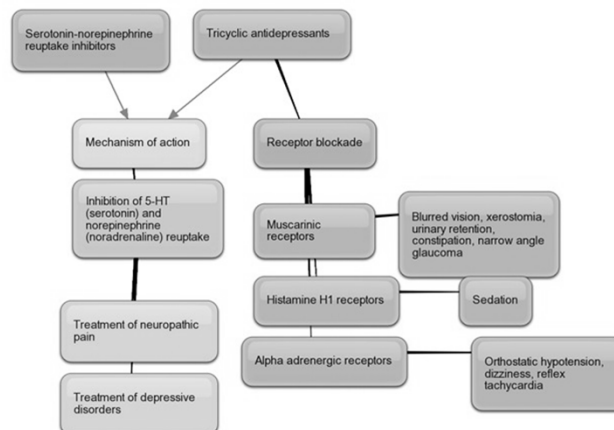
– Amitriptyline, desipramine, doxepin, imipramine, nortriptyline

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)



TCAs and SNRIs Pharmacological Properties



<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!

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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

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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

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

Serotonin/5-HT Receptors (cont'd)

- 5-HT_{1a} (Blood Vess/CNS)
 - Addiction
 - Aggression
 - Anxiety
 - Appetite
 - BP
 - Cardiovascular function
 - Emesis
 - Heart rate
 - Impulsivity
 - Memory
 - Mood
 - Nausea
 - Nociception
 - Penile erection
 - Pupil dilatation
- 5-HT_{1a} (*cont*)
 - Respiration
 - Sexual behavior
 - Sleep
 - Sociability
 - Thermoregulation
- 5-HT_{5a} & 5-HT₆ (CNS)
 - Locomotion
 - Sleep
 - Anxiety
 - Cognition
 - Learning
 - Memory
 - Mood

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

SNRIs (Serotonin/Noradrenaline Reuptake Inhibitors)

Examples

– Duloxetine, milnacipran, and venlafaxine

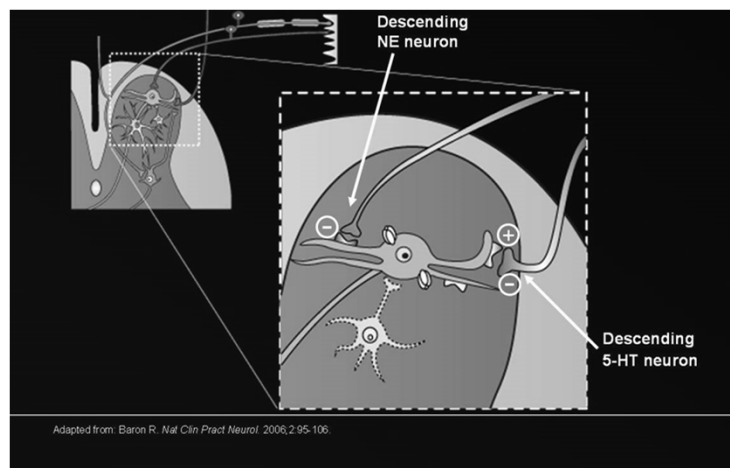
Mechanism of action

– Block reuptake of 5-HT and NA

- Better tolerated, lower tendency for drug-drug interactions, better overdose safety

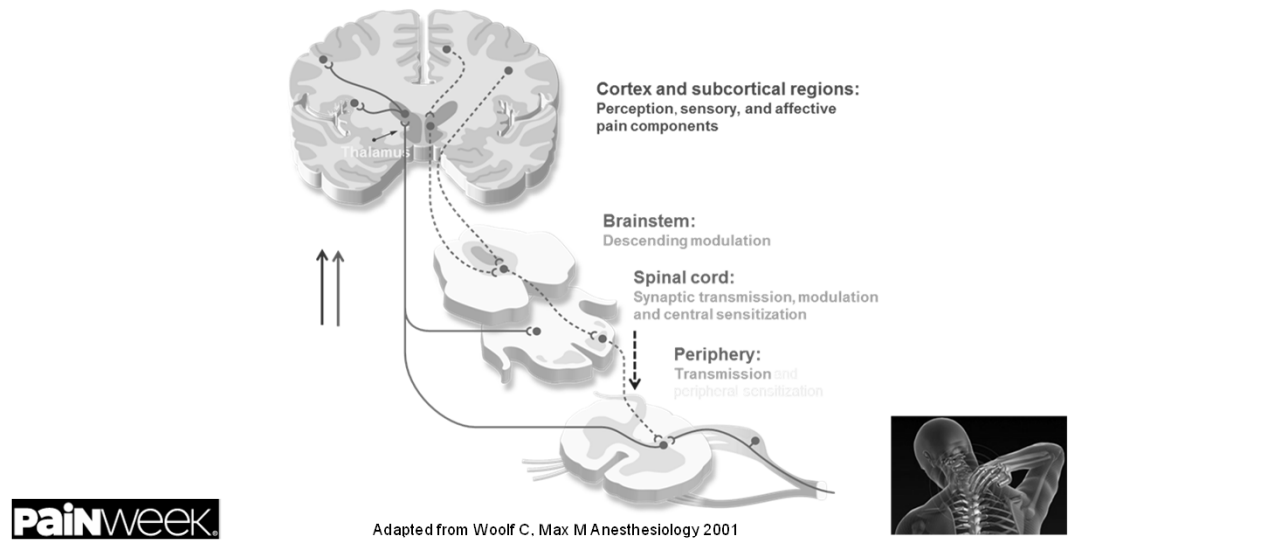
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Modulation of Central Sensitization by 5-HT & NE Descending Pathways



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Site of Action: SNRIs



Adjuvant Analgesics: Antiepileptics

Examples

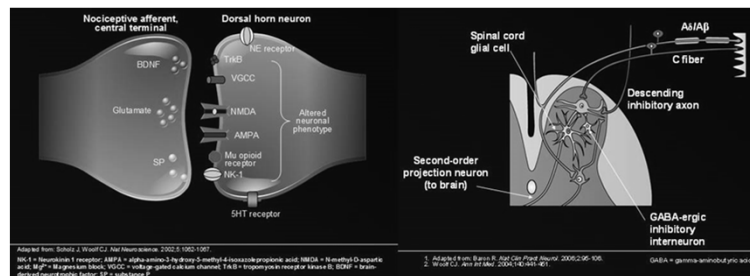
- Gabapentin, pregabalin*, carbamazepine, phenytoin, divalproex sodium, clonazepam, levetiracetam, topiramate, lamotrigine

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 $\alpha 2\delta$ subunit of voltage gated Ca^{++} channels, inhibit NT release

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Site of Action: Antiepileptics



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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

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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



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 (carisoprodol)



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.