PAINWEEK

Pain Pathways Made Simple

David M Glick, DC, DAAPM, CPE

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 common pharmacotherapy classes

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Classification of Pain

- Good pain vs bad pain

Clinical Pearl

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Good Pain

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

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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

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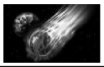
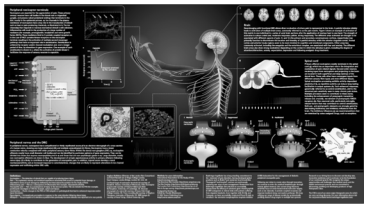
Pain Mechanisms





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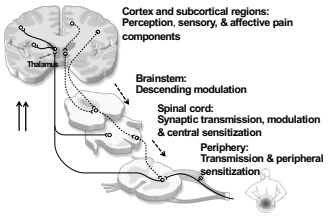
Adapted from Nature Reviews – Neuroscience, Stephen McMahon & David Bennett, 2007.

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

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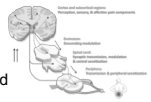
- Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012; 23;73(4):638-652.

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"



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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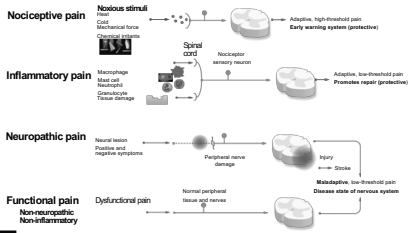
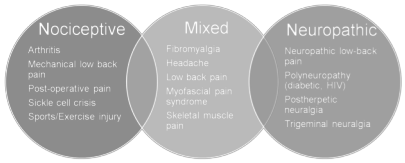
Common Types of Pain



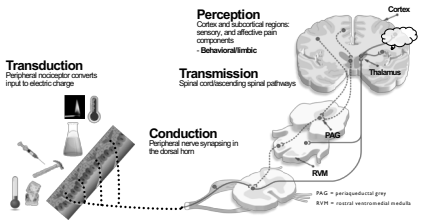
Adapted from: Woolf CJ. *Ann Intern Med.* 2004;140:441-451.

Nociceptive vs Neuropathic Pain



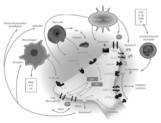
1. Portenoy RK, Kanner RM. In: Portenoy RK, et al, eds. *Pain Management: Theory and Practice*. Philadelphia, PA: FA Davis Company;1996:4.
2. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, MN: McGraw-Hill Companies Inc; 2000:8-9.

Pain Pathway Steps



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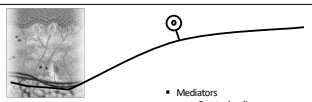
Adapted from Dougherty PM, et al. Neurochemistry of somatosensory and pain processing. In: Benzon H, et al, eds. *Essentials of Pain Medicine*. Philadelphia, PA: Saunders; 2011: chapter 2.

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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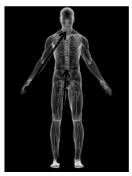
Conduction

- 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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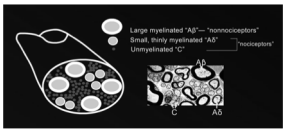
Peripheral Pain Nociceptors



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

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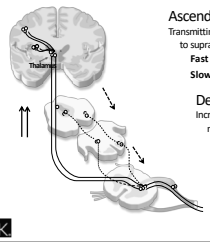
Bashbaum A, Jessell T, The perception of Pain, In Kendal E, Schwartz J, Principles of Neural Science 4th ed, New York, McGraw Hill, 2000, 482-483.

Transmission & Modulation



Ascending nociceptive pathways
Transmitting nociceptive impulses from the dorsal horn to supraspinal 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—norepinephrine

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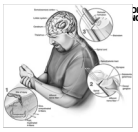
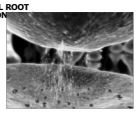
Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron. 2012; 73(4):638-652.

How is Pain Conducted and Transmitted?





- **Excitatory transmitters**
  - Substance P
  - Calcitonin gene related peptide
  - Aspartate, glutamate
- **Inhibitory transmitters** *(descending inhibitory pathways)*
  - GABA
  - Glycine
  - Somatostatin
  - α_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 & 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

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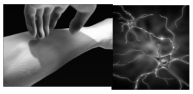
Definitions

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



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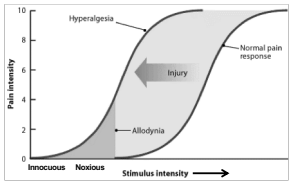
Neuroplasticity in Pain Processing



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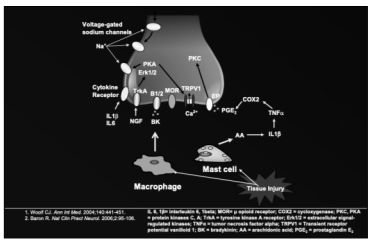
1. Woolf CJ, Salter MW. Science. 2000;288:1765-1769.
2. Ramilowski PA, Howell TW. The perception of pain. In: Kandel ER, Schwartz JH, et al, eds. *Principles of Neural Science*. 4th ed. New York, NY: McGraw-Hill; 2000:479.
3. Cervero F. *Lancet JMA Pain*. 1998;68:13-23.

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 1β= interleukin 6, 1beta; MOR= μ opioid receptor; COX2 = cyclooxygenase; PKC, PKA = protein kinases C, A; TRA = tyrosine kinase A receptor; ERK1/2 = extracellular signal-regulated kinase 1, 2; TRPV1 = transient receptor potential cation channel 1; BK = bradykinin; AA = arachidonic acid; PGE_2 = prostaglandin E_2

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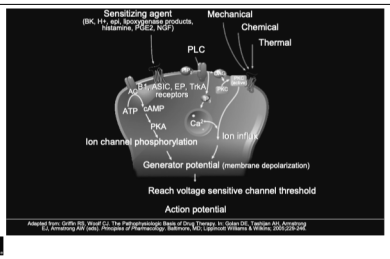
Peripheral Sensitization



Adapted from: Griffin RS, Woolf CJ. The Pathophysiologic Basis of Drug Therapy. In: Golan DE, Tashjian AH, Armstrong EJ, Armstrong AW (eds). *Principles of Pharmacology*. Baltimore, MD: Lippincott Williams & Wilkins, 2005:228-242

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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

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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]

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.

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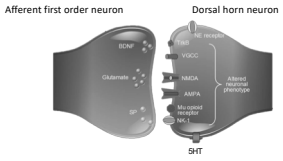
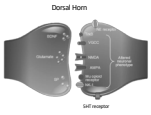
Central Sensitization



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

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

Central Sensitization



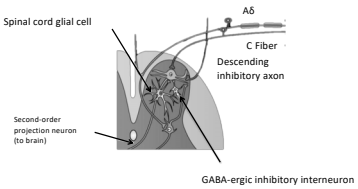
Key influences upon signal propagation

- 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

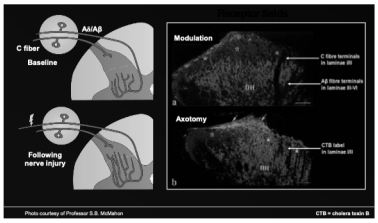
Adapted from Schlotz J, Woolf CJ. Nat Neuroscience. 2002;5:1062-1067

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



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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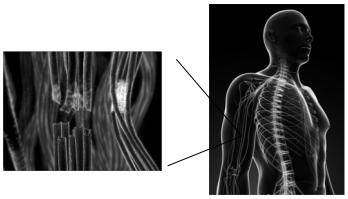
Neuroplasticity: Cross Talk



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 affecting 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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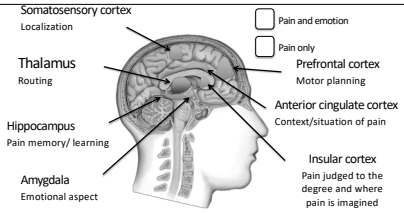
1. Mannion RJ, Woolf CJ. *Clin J Pain.* 2000;16(3):S151-S153. 2. Ossipov MH, et al. *Ann NY Acad Sci.* 2000;909:12-24.
3. Wieseler-Frank J, et al. *Neuroscignals.* 2005;14:166-174. 4. Guilbaud G, et al. *Exp Brain Res.* 1992;92:227-243.

Brain Regions Involved in Pain Processing



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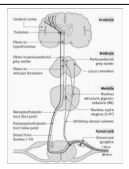
Apkarian AV et al, Eur J Pain 2005;9:463-484

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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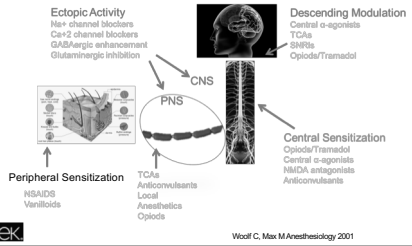
Pharmacological Targets in Pain



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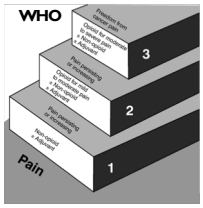
Woolf C, Max M Anesthesiology 2001

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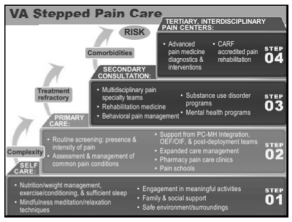
IC Ballantyne Oncologist 2003;8(6):567-75 © AlphaMed Press; WHO 2005

VA DoD Stepped Pain Care Model



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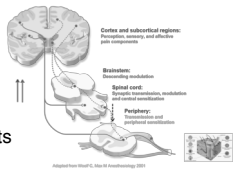
PCSS-O Webinar Implementation of the National Pain Strategy and Safer Opioid Prescribing: A Military Perspective, Buckenmaier C (COL) ret, Aug 24, 2016
JAMA Intern Med. 2015;175(5):682-689. doi:10.1001/jamainternmed.2015.87

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 & 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; anti-inflammatory and analgesic effects
- Inhibition of cyclooxygenase and prostaglandin production
- Inhibition of leukotriene B4 production
- Lipoxins (signaling resolution of inflammation)

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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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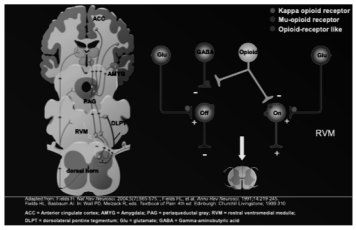
Overview of Descending Pain Inhibitory Pathways and Modulation of Pain Response



ACC = Anterior cingulate cortex, AMYG = Amygdala, PAG = periaqueductal gray, RVM = rostral ventromedial medulla; DLPT = dorsolateral pontine tegmentum, Glu = glutamate, GABA = Gamma-aminobutyric acid

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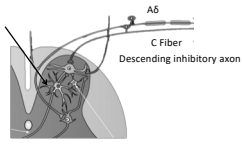
Modulation of Central Sensitization by 5-HT & NE Descending Pathways



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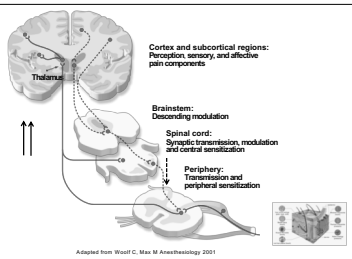
Mechanism of Action—Opioids



Adapted from Woolf C, Max M Anesthesiology 2001

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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)

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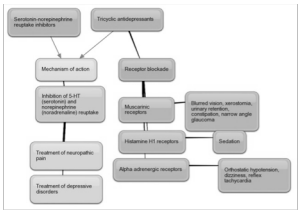
TCAs and SNRIs Pharmacological Properties



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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

- 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'd)*
  - Respiration
  - Sexual behavior
  - Sleep
  - Sociability
  - Thermoregulation
- 5-HT5a & 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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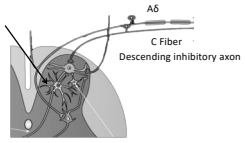
Modulation of Central Sensitization by 5-HT & NE Descending Pathways



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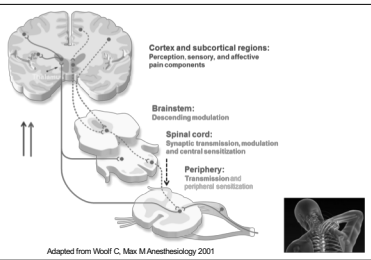
Site of Action—SNRIs



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Adapted from Woolf C, Max M Anesthesiology 2001

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

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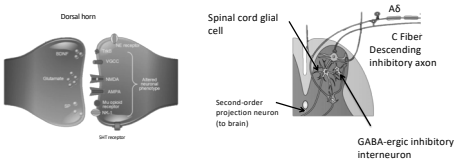
Site of Action—Antiepileptics



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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

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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 (barbiturate like effects), tizanidine (α-2 agonist), baclofen (GABA agonist), orphenadrine (diphenhydramine/antihistamine)
- Common adverse effects
  - Sedation, lethargy & confusion (cyclobenzaprine), dependence (carisoprodol)

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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

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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 nonpharmacologic 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