



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 common pharmacotherapy classes



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

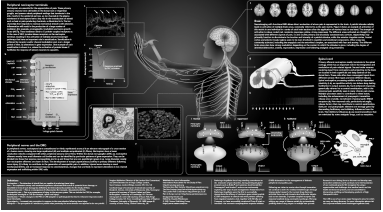
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Bad Pain

- **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

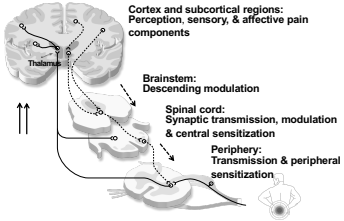
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Pain Mechanisms



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

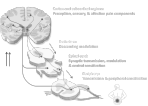
General Anatomy of Pain



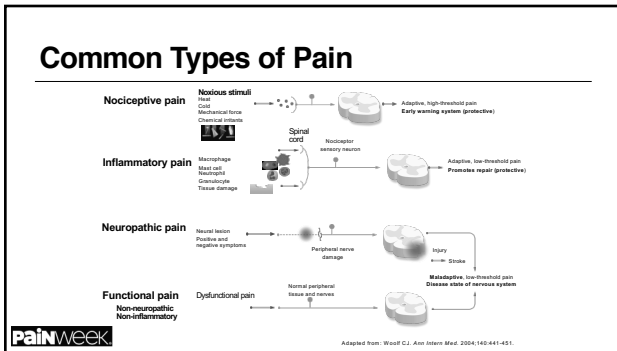
Adapted from Yun-Hahn C.A., Bacon W., Wiesel C.J. Deconstructing the neuroanatomic pain phenotype to reveal neural mechanisms. *Neuron* 90(1): 55-72(4): 638-652

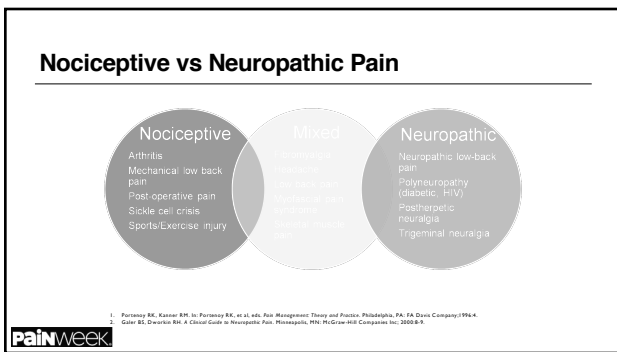
Pain Roadmap: Peripheral and Central Nervous System Landmarks

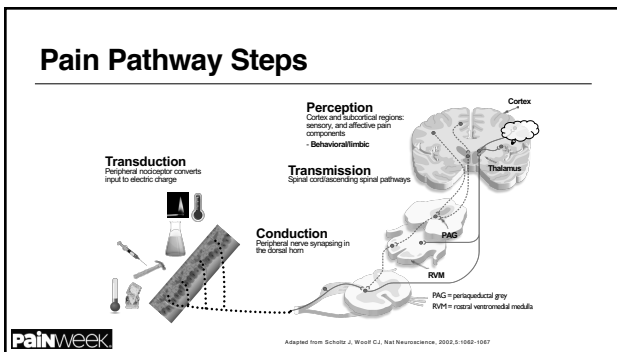
- Physiologic process involving multiple areas of the nervous system
- Bidirectional
- Involves normal as well as pathological processes
- A sensory experience associated with affective and cognitive responses
- Dynamic (ie, occurring in real time)
- Adapts or changes in response to function—"neuroplasticity"



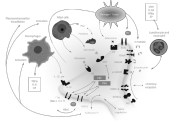
© Garland Science, in: Kandel E. et al. eds. *Principles of Neural Science*, 4th ed. McGraw-Hill Medical, 2005, chapters 21-23







**Transduction:
Processing at Peripheral Nerve Endings**

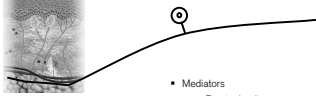


- Conversion of mechanical, thermal or chemical stimuli into an electric charge
- Involves
 - Receptors activated directly by stimuli
 - Injury/inflammatory response

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Adapted from Dougherty PM, et al. Neurochemistry of somatosensory and pain processing. In: Bonner G, 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

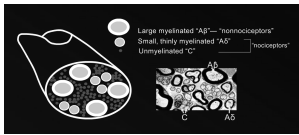
<ul style="list-style-type: none"> ▪ A-delta fibers <ul style="list-style-type: none"> - Small receptive fields - Thermal & mechanical - Myelinated - Rapidly conducting <ul style="list-style-type: none"> • 10-30 m/sec - Large diameter 	<ul style="list-style-type: none"> ▪ C-fibers <ul style="list-style-type: none"> - Broad receptive fields - Polymodal - Unmyelinated - Slower conducting <ul style="list-style-type: none"> • .5-2.0 m/sec - Cross sensitized - Small diameter
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Peripheral Pain Nociceptors

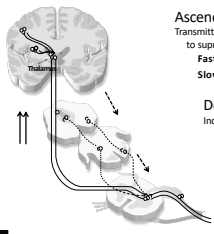


AB—muscle spindle secondary endings, touch, and kinesthesia
 AS—pain, temperature, crude touch, and pressure

Berkman A, Jessell T. The perception of Pain. In Kendal E, Schwartz J. Principles of Neural Science 4th ed. New York, McGraw-Hill, 2000, 452-453.

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Transmission & Modulation



Ascending nociceptive pathways
 Transmitting nociceptive impulses from the dorsal horn to supraspinal targets

Fast (green) neospinothalamic
 Slow (yellow) paleospinothalamic

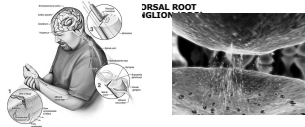
Descending inhibitory tracts (blue)
 Increase or decrease volume control of incoming nociceptive signals reaching the brain

5-HT—serotonin
 NE—norepinephrine

Adapted from Yun-Ho Cho, CA, Bruce R. Wolf, C.J. Deconstructing the nociceptive pain pathway to reveal neural mechanisms. *Nature* 2012; 485:416-421

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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



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



Peripheral Sensitization

Sensitizing agent
(BK, H⁺, etc. lipopolysaccharide products, histamine, PGE₂, NGF)

Mechanical
Chemical
Thermal

PLC
PKC
EP
TRPA
receptors

ATP
GAMP
PKA
Ca²⁺
ion influx

Ion channel phosphorylation

Generator potential (membrane depolarization)

Reach voltage sensitive channel threshold

Action potential

Adapted from Curtis DJ, Woolf CJ. The Pathophysiology Basis of Drug Therapy. In: Gilen DE, Tashan Ali, Anesthetist EJ, Anesthetist AN (eds). Principles of Pharmacology. Baltimore, MD: Lippincott Williams & Wilkins, 2008:220-242.

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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); 2000:472-481.
2. Millan MJ. Progress in Neurobiology. 1998;57:1-164.
3. Dickenson AH. Brit J Anaesth 1995;75:193-200.
4. Quasthoff S and Dickenson AH. Neuroreport 2000;11:1817-21.

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Central Sensitization

NMDA = N-methyl-D-aspartate receptor; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartate receptor; VGCC = voltage-gated calcium channel; SHT = 5-hydroxytryptamine receptor; BDNF = brain-derived neurotrophic factor; SP = substance P

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Adapted from Scholz J, Woolf CJ. Nat Neurosci. 2003;5:1063-1067

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 (SHT)
- Mu opioid receptor

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Adapted from Scholz J, Woolf CJ. Nat Neurosci. 2003;5:1063-1067

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

Spinal cord glial cell

Second-order projection neuron (to brain)

GABA-ergic inhibitory interneuron

Aδ

C Fiber

Descending inhibitory axon

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Adapted from: 1. Baron R. Mechanisms of disease: neuropathic pain: a clinical perspective. Nat Clin Pract Neurol. 2005;1:105-116.
 2. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacological management. Ann NY Acad Sci. 2004;104:1-11.

Neuroplasticity: Neural Reorganization

Photo courtesy of Professor S.R. McMahon

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⁺/Ca²⁺ (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. McMahon SB, Woodruff CJ. *Curr Opin Neurol*. 2005;18(2):123-130. 2. Chubb RW, et al. *Ann NY Acad Sci*. 2005;1060:12-24. 3. Wesseler Frank J, et al. *NeuroReport*. 2002;13(16):174. 4. Q. Zhang G, et al. *Exp Brain Res*. 1992;92:227-235.

Brain Regions Involved in Pain Processing

- Somatosensory cortex** (Pain and emotion): Localization
- Thalamus** (Pain and emotion): Routing
- Hippocampus** (Pain and emotion): Pain memory/learning
- Amygdala** (Pain and emotion): Emotional aspect
- Prefrontal cortex** (Pain only): Motor planning
- Anterior cingulate cortex** (Pain only): Context/situation of pain
- Insular cortex** (Pain only): Pain judged to the degree and where pain is imagined

Painweek 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 agonists
 - NMDA receptor antagonists
 - NSAIDs
 - NO inhibitors
 - K^+ channel openers
- Perception**
 - Parenteral opioids
 - α agonists
 - General anesthetics
- Conduction**
 - Local anesthetics
 - Peripheral nerve, plexus, epidural block

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Pharmacological Targets in Pain

- Peripheral Sensitization** (PNS): NSAIDs, Vanilloids
- Ectopic Activity** (PNS): V_{α} -channel blockers, Ca^{2+} channel blockers, Ca^{2+} channel antagonism, G-protein/coupled inhibition
- Central Sensitization** (CNS): $TCAs$, Anticoagulants, Local Anesthetics, Opioids
- Descending Modulation** (CNS): Central α -agonists, $TCAs$, β -blockers, Opioids/Tramadol

Painweek 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

WHO

Pain

1

2

3

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VA DoD Stepped Pain Care Model

VA Stepped Pain Care

STEP 04 TERTIARY, INTERDISCIPLINARY PAIN CLINICS

- Advanced pain medicine (epidemiology & interventional)
- CARF accredited pain rehabilitation

STEP 03 SECONDARY CONSULTATION

- Multidisciplinary pain specialty teams
- Substance use disorder programs
- Rehabilitation medicine
- Behavioral pain management
- Mental health programs

STEP 02 PRIMARY CARE

- Routine screening, presence & severity of pain
- Assessment & management of common pain conditions
- Support from PC-MH integration, OEF/OIF, & post-deployment teams
- Expanded care management
- Pharmacy pain care clinics
- Pain schools

STEP 01 SELF CARE

- Nutrition/weight management, exercise/conditioning, & sufficient sleep
- Mindfulness meditation/relaxation techniques
- Engagement in meaningful activities
- Family & social support
- Safe environments/soundings

RISK

COMORBIDITIES

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PCSS-O Webinar Implementation of the National Pain Strategy and Safer Opioid Prescribing: A Military Perspective. Buckenmaier C, Ockler, 8th Aug 24, 2015. JAMA Intern Med. 2015;175(5):882-889. doi:10.1001/jamainternmed.2015.97

Common Pharmacologic Therapies

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

Cortex and subcortical regions: Perception, sensory, and affective pain experience

Brainstem: Breathing, swallowing, etc.

Spinal cord: Sensory, motor, and autonomic

Periphery: Pain receptors and nociceptors

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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

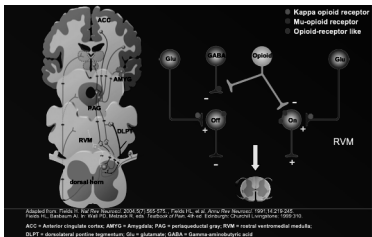
- Morphine, hydromorphone, fentanyl, oxycodone, oxymorphone, meperidine, codeine, methadone, tramadol

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

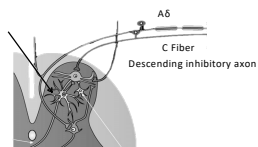
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Overview of Descending Pain Inhibitory Pathways and Modulation of Pain Response



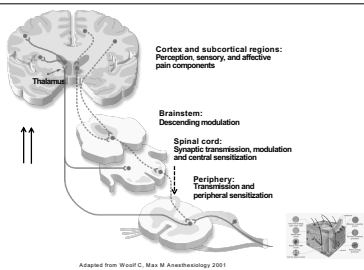
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Modulation of Central Sensitization by 5-HT & NE Descending Pathways



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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)

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TCA and SNRI Pharmacological Properties

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    graph TD
      Root[TCAs and SNRIs Pharmacological Properties] --> MA[Mechanism of action]
      Root --> RB[Reuptake blockade]
      MA --> I5HT[Inhibition of 5-HT reuptake and norepinephrine reuptake]
      I5HT --> TNP[Treatment of neuropathic pain]
      I5HT --> TD[Treatment of depressive disorders]
      RB --> MR[Muscarinic receptors]
      RB --> HR[Histamine H1 receptors]
      RB --> AR[Alpha adrenergic receptors]
      MR --> MR_Effects[Blurred vision, xeroderma, urinary retention, constipation, narrow angle glaucoma]
      HR --> HR_Effects[Sedation]
      AR --> AR_Effects[Orthostatic hypotension, tachycardia, reflex tachycardia]
    
```

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!

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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 (**GPCBs**) 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 ₁₂ /14-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

- 5-HT_{1a} (blood ves/CNS)
 - Addiction
 - Aggression
 - Anxiety
 - Appetite
 - BP
 - Cardiovascular function
 - Emesis
 - Heart rate
 - Impulsivity
 - Memory
 - Mood
 - Nausea
 - Nociception
 - Penile erection
 - Pupil dilatation
- 5-HT_{1a} (*cont'd*)
 - Respiration
 - Sexual behavior
 - Sleep
 - Sociability
 - Thermoregulation
- 5-HT_{5a} & 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

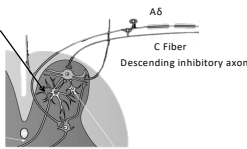
- Duloxetine, milnacipran, and venlafaxine

Mechanism of action

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

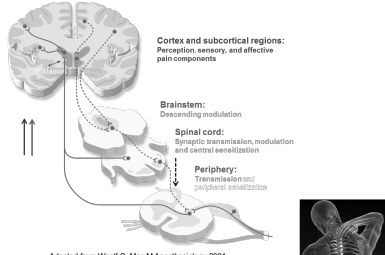
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Modulation of Central Sensitization by 5-HT & NE Descending Pathways



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Site of Action—SNRIs



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

Brainstem:
Descending modulation

Spinal cord:
Synaptic transmission, modulation and central sensitization

Periphery:
Transmission and peripheral sensitization

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



Site of Action—Antiepileptics




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



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



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 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