Central Sensitization and Ketamine Infusions

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Disclosure

- Nothing to disclose

Learning Objectives

- Discuss the landscape of pain management
- Discuss the various types of pain
- Discuss central sensitization
- Discuss ketamine and the mechanism of action
- Discuss ketamine infusions
- Discuss barriers to treatment

PAINWEEK

Definition of Pain

- According to the International Association for the Study of Pain (IASP), "pain" is defined as:
  - An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
- Central Sensitization: Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.
- Peripheral Sensitization: Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields.

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Other Definitions by IASP

- Allodynia: Pain due to a stimulus that does not normally provoke pain.
- Dysesthesia: An unpleasant abnormal sensation, whether spontaneous or evoked.
- Hyperalgesia: Increased pain from a stimulus that normally provokes pain.
- Hyperesthesia: Increased sensitivity to stimulation, excluding the special senses.
- Hyperpathia: A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.
- Neuralgia: Pain in the distribution of a nerve or nerves.
- Neuritis: Inflammation of a nerve or nerves.

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Other Definitions by IASP

- Neuropathic Pain: Pain caused by a lesion or disease of the somatosensory nervous system.
- Central Neuropathic Pain: Pain caused by a lesion or disease of the central somatosensory nervous system.
- Peripheral Neuropathic Pain: Pain caused by a lesion or disease of the peripheral somatosensory nervous system.
- Neuropathy: A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.
- Nociceptive Pain: Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.
- Sensitization: Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.

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Common Causes of Pain

- Low back pain and arthritis account for half of all musculoskeletal disease diagnoses[1]
- Low back pain is most commonly reported type of pain[2]
  - –Leading cause of disability among Americans <45 years of age[2,3]
  - –>26 million adults experience frequent back pain2
  - –~15% of Americans experience back pain lasting >2 weeks[1]
- Arthritis and chronic joint problems affect ~70 million individuals[1]
  - –~18 million affected by osteoarthritis
  - –~2 million suffer from rheumatoid arthritis

1. Emons MF. *Manag Care*. 2003;12(8 suppl):2-7.
2. Pain facts and figures. American Pain Foundation Web site. http://www.painfoundation.org/print.asp?file=Newsroom/PainFacts.htm. Accessed September 12, 2007.
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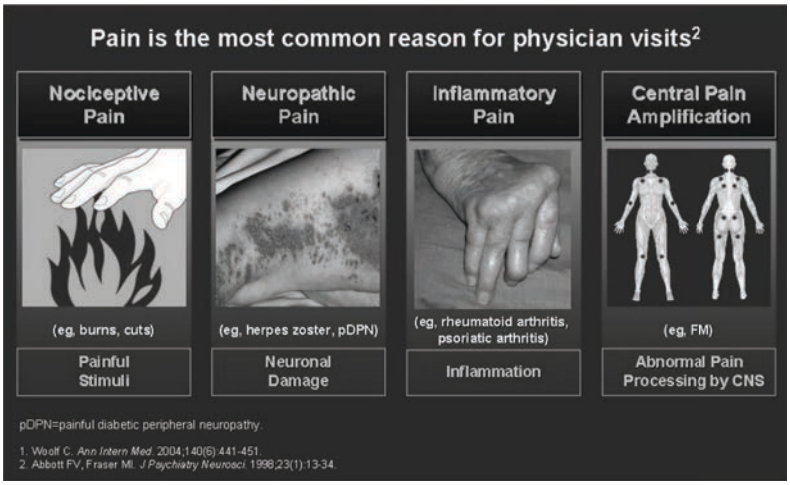
Types of Pain



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Categories of Pain

- While pain management crosses the health care spectrum, for the purposes of this assessment we have classified pain treatment services into three generally accepted categories:
  - Acute
    - Focused on symptomatic relief of acute pain (i.e. post-operative, obstetrical)
  - Chronic
    - Pain that persists beyond the time of normal healing and can last from 6 months onward (i.e. headaches, low back, pelvic pain, arthritis, RSD/CRPS)
  - Palliative
    - Severe pain in those suffering and dying from progressive diseases (i.e. cancer)

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Who Provides These Services

- Physician specialties involved with pain treatment include:
  - Anesthesiology
  - Emergency Medicine
  - General Surgery
  - Interventional Pain Management/Anesthesiology
  - Oncology
  - Neurology
  - Neurosurgery
  - Orthopedics
  - Physiatry
  - Psychiatry
  - Primary Care/Internal Medicine/Hospitalists
  - Radiology
  - Rheumatology
  - Trauma Surgery

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Other Providers

- In addition to physicians, Pain Management Services can be provided by:
  - Chiropractors
  - CRNAs
  - Nurse Practitioners
  - Physician Assistants
  - Physical Therapists
  - Massage Therapists
  - Acupuncturists
  - Holistic/Homeopathic "Doctors"
  - DME providers
  - Hospice and Home Health providers

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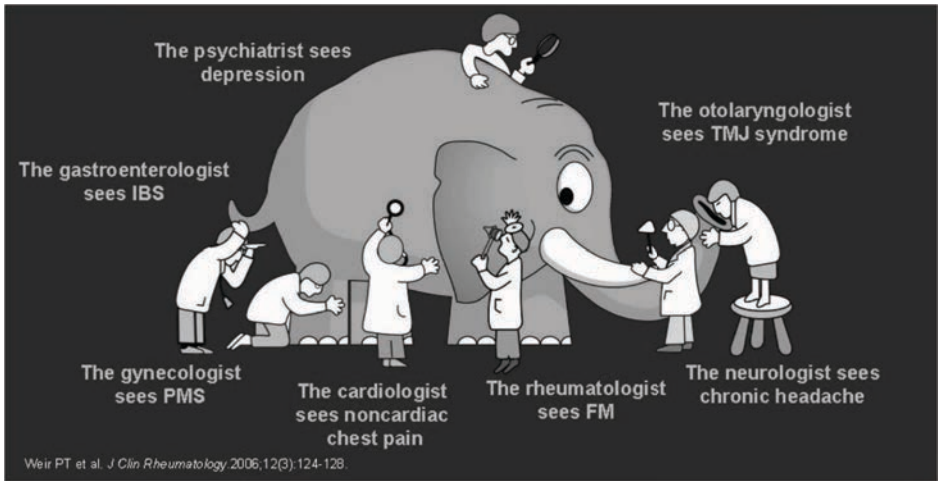
The Big Picture



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"Pain Specialist"

- A controversial and misunderstood title
- Board Certifications and Fellowships are available
- Interventional Pain Specialist is:
  - Typically Anesthesiologist who has done a fellowship in Interventional Pain Management
  - Can skillfully perform over 100 minimally invasive procedures
  - Diagnostician first
  - Multi-dimensional treatment options
  - Strong fund of multimodal pain knowledge
  - Practice with integrity holding patient safety and outcome as the priority

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Reality of Pain Management

- Of all "pain" doctors, over 90% have not had any accredited fellowships and board certifications in Pain Management
- Many pain board certifications can be bought and do not require accredited fellowships
- Fellowship programs have historically had variable quality of training
- Many unaccredited/counterfeit programs
- Many "pain physicians" have a variable practice patterns
- Interventional Pain Management recognized by Medicare only in 2002
- Few physicians, including Interventional Pain Management physicians, have been educated and trained on central sensitization and Ketamine Infusions

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Interventional Pain Options

- Epidural Steroid Injections (about 25 locations)
- Transforaminal Epidural Steroid Injections (theoretically over 50 locations)
- Facet Medial Branch Block (approximately 60 locations)
- Radiofrequency Ablation (well over 100 locations)
- Joint Blocks (multiple area)
- Nerve Blocks (multiple areas besides TFESI)
- Ganglion Blocks (multiple)
- Intrathecal Pumps
- Spinal Cord Stimulators
- Percutaneous Disc Decompression

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What is Central Sensitization

- Central Sensitization:
  - Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.
- "Wind-Up":
  - Nervous system stays up-regulated and in a persistent state of high reactivity.
- Central vs. Peripheral
- Organic vs. Inorganic

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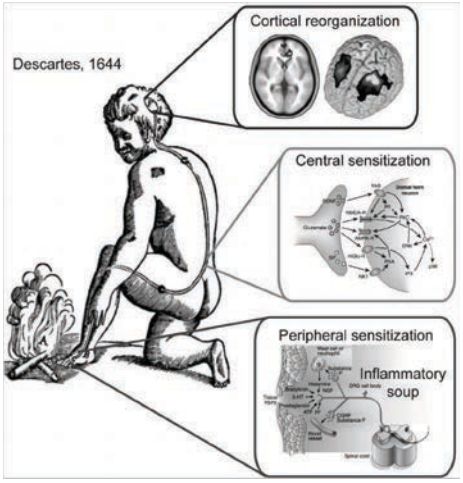
What is Central Sensitization



Descartes' Concept of Sensation Illustrates the Pain System and Its Reorganization Based on Modern Rodent Model Physiology and Human Brain Imaging Studies

(A) A stimulus is transmitted to a specific brain region where perception takes place.

(B) System undergoes reorganization following an injury that gives rise to a persistent or chronic pain state.

(C) End-organ injury gives rise to changes locally, collectively described as peripheral sensitization (adapted from Julius and Basbaum, 2001).

(D) Spinal cord circuitry undergoes a large number of changes, resulting in central sensitization (adapted from Scholz and Woolf, 2002), which includes enhanced glutamatergic signaling, changes in second-order messenger processes, and activation of microglia. At the level of the brain, human neuroimaging studies indicate anatomical and functional reorganization.

http://dx.doi.org/10.1016/j.neuron.2015.06.005

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What is Central Sensitization

- Central sensitization is:
  - A manifestation of activity-dependent plasticity due to an increase in synaptic strength, driven to a substantial extent, by N-methyl-d-aspartic acid (NMDA) glutamatergic receptors[1]
- Central sensitization operates after:
  - Noxious stimuli
  - Peripheral inflammation
  - Nerve injury in the spinal cord and higher brain centers
- It involves multiple presynaptic and postsynaptic changes producing changes in transmitter release and action, as well as synthesis of novel neuromodulators[2,3]

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3. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, Bonventre JV, Woolf CJ: Interleukin-1-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001; 410:471–5Samad, TA Moore, KA Sapirstein, A Billet, S Allchorne, A Poole, S Bonventre, JV Woolf, CJ

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What is Central Sensitization

- Many features of central sensitization resemble those that are responsible for memory[1]
- Central sensitization is produced by increases in excitability and reduction in inhibitory transmission, which may produce a persistent enhancement of pain sensitivity[2]
- It has been suggested that central neuronal sensitization plays an important role in postoperative pain[3]

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What Causes Central Sensitization

- Potential mechanisms implicated in central sensitization:
  - NMDA receptor activation[1]
  - Altered gene expression in dorsal horn neurons[1]
  - Decreased inhibition[2]
  - Microglial activation[3]
  - Thalamic and somatosensory cortex changes[4]

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2. Ossipov MH, et al. Ann NY Acad Sci.2000;909:12-24.
3. Wieseler-Frank J, et al. Neurosignals.2005;14:166-174.
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Types of Central Sensitization

- Anxiety
- Chronic Pain (In general)
- CRPS/RSD
- Depression
- Fibromyalgia
- Headaches
- Opioid Induced Hyperalgesia
- Phantom Limb Pain
- PTSD

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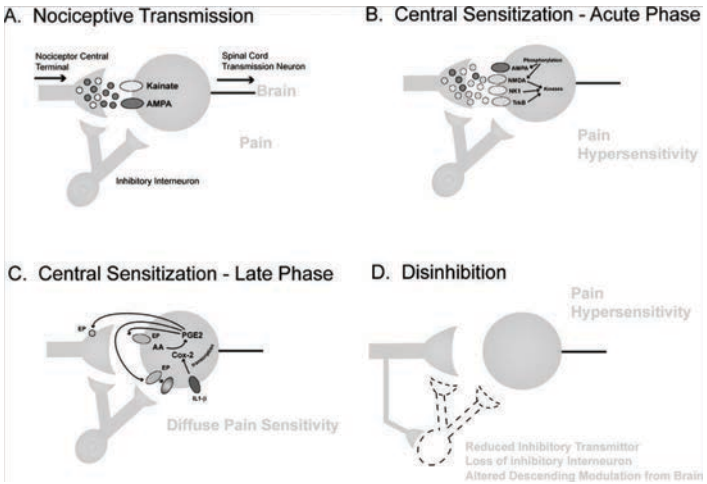
Neurophysiology of Central Sensitization



(A) Transfer of information about the intensity, duration, and location of peripheral noxious stimuli.

(B) Activity-dependent synaptic plasticity driven by high levels of nociceptor input that results in activation of intracellular kinases that phosphorylate ion channels and receptors, altering their distribution and function and increasing excitability and thereby pain sensitivity.

(C) Changes in transcription in dorsal horn neurons. Some alterations in gene expression are activity driven and others are widespread, like the induction of (Cox-2).

(D) Inhibitory interneurons play a major role in damping down sensory processing. After peripheral nerve lesions, there is a reduction in the action of inhibitory transmitters and a loss of γ-aminobutyric acid–mediated interneurons, resulting in a loss of inhibition (disinhibition) producing pain hypersensitivity.

AA = arachidonic acid; AMPA =α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; EP = prostaglandin receptor; IL1β= interleukin 1β; NK1 = neurokinin 1; NMDA = N -methyl-d-aspartic acid; PGE2 = prostaglandin E2; TrkB = tyrosine kinase

Woolf CJ: Pain: Moving from symptom control toward mechanism-specific pharmacologic management. Ann Inter Med 2004; 140:441–51; reproduced with permission.

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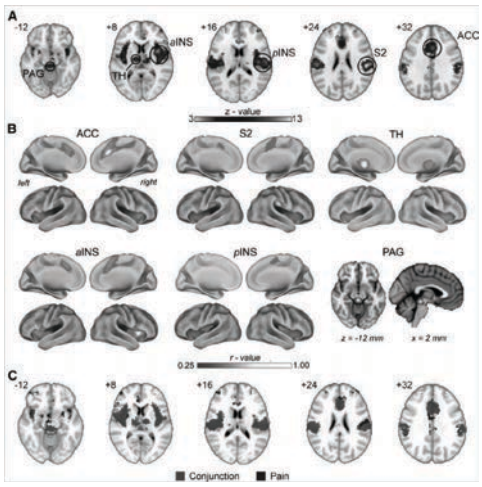
What is Central Sensitization



Constructing the Brain Acute Pain Representation Map from Resting State Brain Activity

(A) Brain regions identified by pain, which identifies 311 PubMed studies in the Neurosynth meta-analysis tool (Yarkoni et al., 2011). The map is localized to six brain regions: bilateral secondary somatosensory cortex (S2), anterior cingulate (ACC), bilateral anterior and posterior insula (aINS, pINS), thalamus (TH), and periaqueductal gray (PAG).

(B) Resting state functional connectivity associated with the term pain. Functional connectivity is derived from resting state activity from 1,000 subjects (Biswal et al., 2010), generated in Neurosynth. Essentially the same network is identified when ACC, aINS, or S2 are used as seeds. The pINS seed identifies bilateral pINS as well as posterior cingulate/supplementary motor area. The TH network is limited to bilateral thalamus, and PAG seed only shows connectivity limited to itself.

(C) Overlap between the map for the term ‘‘pain’’ and sum of six resting state networks. Blue is the same map shown in (A). Red is the sum of all functional connections identified in (B). The overlap between red and blue maps is 72% of the blue map.

http://dx.doi.org/10.1016/j.neuron.2015.06.005

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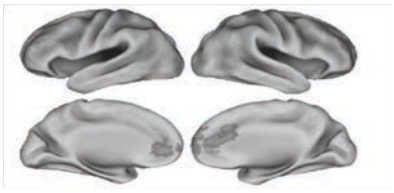
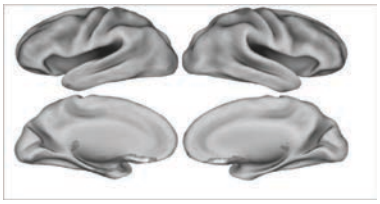
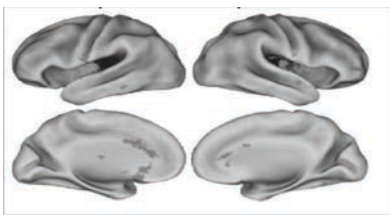
What is Central Sensitization



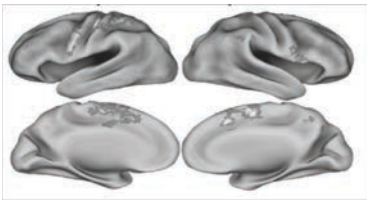
Low Back Pain



Osteoarthritis



Postherpetic Neuralgia



Pelvic Pain

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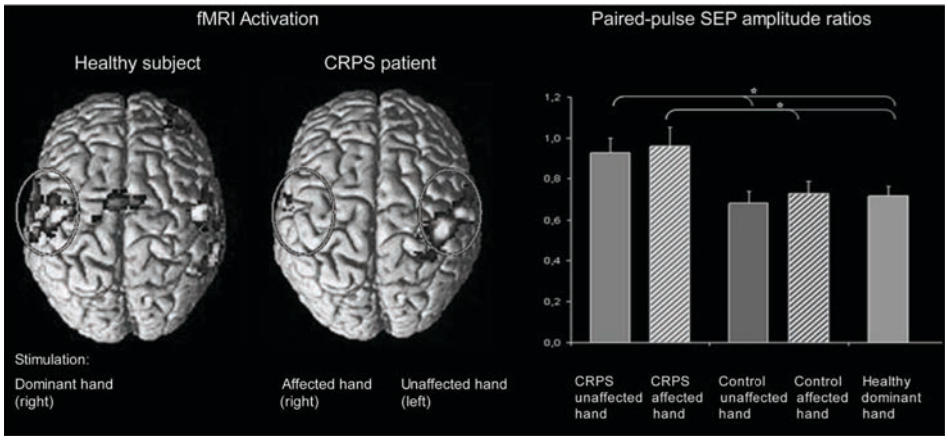
Corticostriatal functional connectivity predicts transition to chronic back pain, Baliki MN, Petre B, Torbey S, et. al., Nature Neuroscience 15, 1117–1119 (2012)

fMRI Imaging in CRPS (A Model for Central Sensitization)



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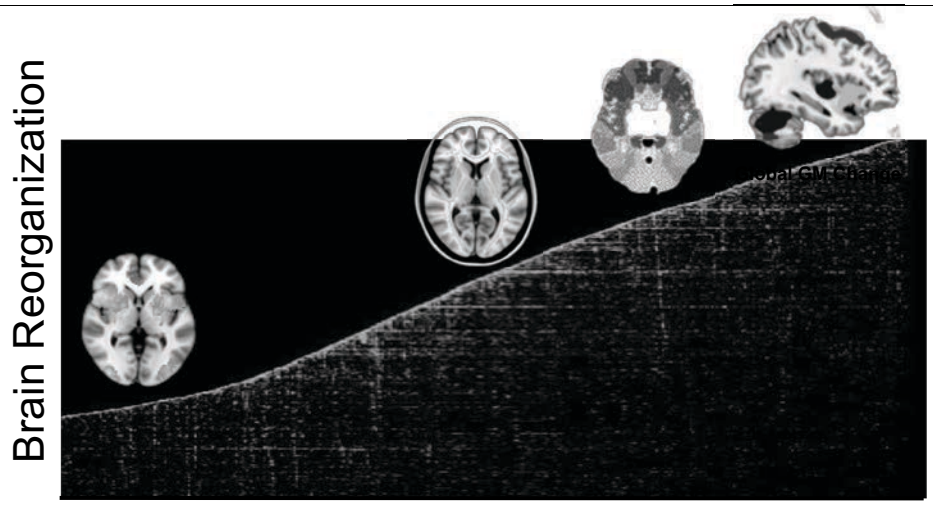
Lanz M, Höffken O, Stude P, Lissek S, Schwenkreis P, Reinersmann A, Frettlöh J, Richter H, Tegenthoff M, Maier C.: Bilateral somatosensory cortex disinhibition in complex regional pain syndrome type I. Neurology. 2011 Sep 13;77(11):1096-101. Epub 2011 Aug 31.

Chronic Pain and Central Sensitization



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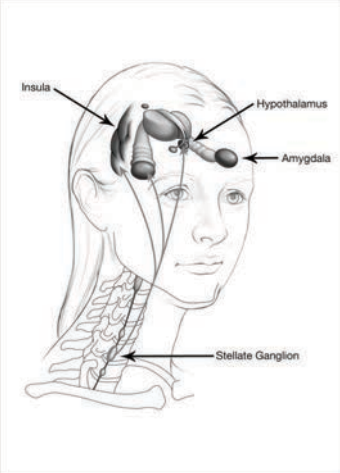
Neural Connection Between the Stellate Ganglion and Central Sensitization



Neural connections between the stellate ganglion and the hypothalamus, amygdala, and regions of the prefrontal cortex, in particular the insular cortex, might explain the effect of stellate ganglion block on Central Pain conditions.

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Effects of stellate-ganglion block on hot flushes and night awakenings in survivors of breast cancer: a pilot study. Lipov EG1, Joshi JR, Lancet Oncol. 2008 Jun;9(6):523-32. doi: 10.1016/S1470-2045(08)70131-1.

Treatments for Central Sensitization and CRPS

- Therapy Based:
  - Physical therapy
  - Mirror box therapy
  - Graded motor imagery
  - Tactile discrimination training
  - Sensory discrimination training
- Neuropsych Based:
  - EEG Biofeedback
  - Cognitive Behavioral Therapy
  - Relaxation Techniques
  - Hypnosis

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Treatments for Central Sensitization and CRPS

- Medications:
  - Alpha- or beta-adrenergic-blocking compounds
  - Anti-inflammatories (corticosteroids, COX-inhibitors)
  - Bisphosphonates
  - Botulinum Toxin
  - Calcium-regulating drugs
  - GABA analogs
  - Ketamine
  - Local Anesthetics
  - Opioids
  - SNRIs
  - Vasodilators

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Treatments for Central Sensitization and CRPS

- Interventional:
  - Epidural Blockade
  - Intravenous immunoglobulin
  - Intravenous regional sympathetic block
  - Ketamine Infusion
  - Selective sympathetic ganglion nerve blocks
  - Spinal cord stimulators

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Ketamine History

- Ketamine was first synthesized in 1962 by Calvin L. Stevens
- Ketamine was introduced to testing in human prisoners in 19641,2
- FDA approval in 1970
- Ketamine is a "core" medicine in the World Health Organization's Essential Drugs List, a list of minimum medical needs for a basic healthcare system3

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Properties of Ketamine

- Highly lipophilic (44% non-ionized at physiological pH)
- Racemic mixture of two stereoisomers: S(+) and R(-)
- Onset: IV: 30 seconds; IM: 3-4 minutes
- Duration: IV: 5-15 minutes; IM: 12-25 minutes
- Half-Life - Elimination half-life: 2.5 hours; Distribution half-life: 11-16 hours
- Metabolism: Hepatic via hydroxylation and N-demethylation; the metabolite norketamine is 33% as potent as parent compound
- Excretion: primarily urine

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NMDA Receptor

- NMDA receptor, a specific inotropic glutamate receptor, mediates neuronal signaling and regulates gene expression
- Present in all neurons in the CNS - specifically in the dorsal horn of the spinal cord
- Highly permeable to and allows flow of Na and Ca into cell and K out of cell
- Mg blocks NMDA channels
- NMDA signaling is important in anesthesia: involved in pain processing, neuronal plasticity and generation of central sensitization
- The NMDA receptor is very important for controlling synaptic plasticity and memory function
- NMDAR antagonists reduce neuropathic, wind-up and spontaneous pain

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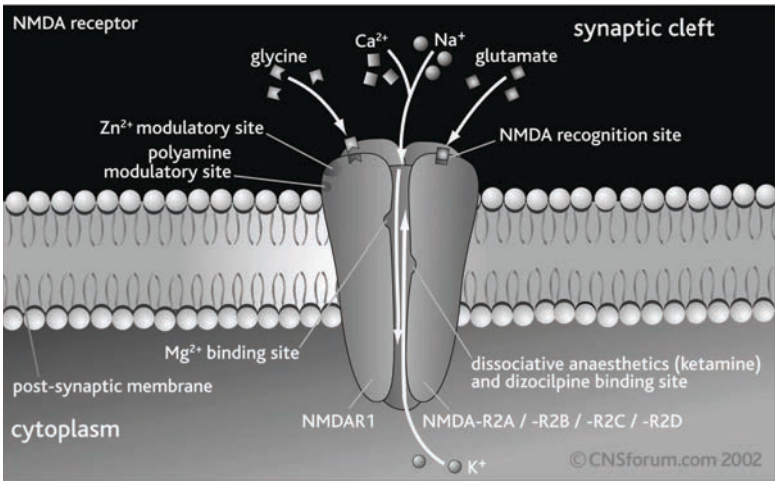
NMDA Receptor



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Ketamine Mechanism of Action

- Various NMDAR compounds have differing relative potency on the different NMDA receptor subtypes
  - GluN1, GluN2A, GluN2B, GluN2C, and GluN2Debut also called NR1, NR2A-D
- Ketamine has been shown to result in suppression of immediate early gene expression at the site of mechanical injury
  - zif/268, c-fos, junB, fosB, c-jun, junD
- Ketamine alters the regulation of NMDA receptor phosphorylation 22 and NMDA receptor mRNA expression in rat and mouse models
- Ketamine limits astrocytic and microglial activation
  - Effects that correlate with a reduction in neuropathic pain.

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Ketamine Mechanism of Action

- At concentrations within the clinical dose range, ketamine directly affects a wide range of cellular processes, including:
  - Blockade of NMDA channels
  - Neuronal hyperpolarisation-activated cationic currents
  - Nicotinic acetyl-choline ion channels
  - Delta and mu-opioid agonism and opioid potentiation
  - Nitric-oxide (NO) cyclic guanosine-mono-phosphate (cGMP) system
  - Non-NMDA glutamate receptors (a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA))
  - Metabotropic glutamate receptors (mGluR)
  - Brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) protein levels
  - Reduction in cholinergic neuromodulation
  - Increased release of aminergic neuromodulators (dopamine and noradrenaline)
  - Neurosteroids
  - L-type Ca2þ channels.

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Ketamine Mechanism of Action

- Norketamine has been shown to actually have anti-analgesic effects and ketamine may actually facilitate endogenous pain pathways in some circumstances.
- In the setting of chronic neuropathic pain syndromes, there is some evidence for prolonged post-drug analgesia that markedly outlasts the effective drug levels, which would be mediated by downstream mechanisms
- Ketamine's pre-emptive reduction in neuropathic pain is a corollary of its antidepressant effect which endures well after the drug has been eliminated
- Ketamine's analgesia is not reduced by naloxone; which would argue against the primary opioid mechanisms of action.

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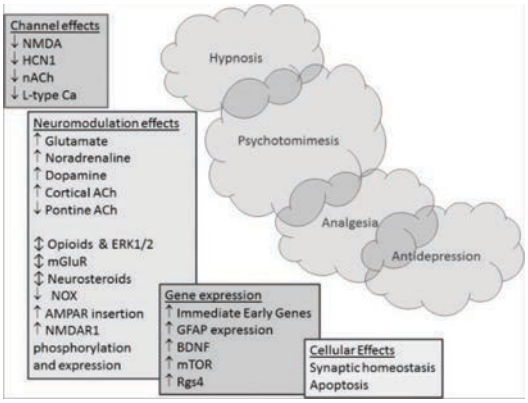
Ketamine Mechanism of Action



Ketamine – More mechanisms of action than just NMDA blockade, Jamie Sleigh, Martyn Harvey, Logan Voss, Trends in Anaesthesia and Critical Care, Volume 4, Issue 2, Pages 76-81 (June 2014) DOI: 10.1016/j.tacc.2014.03.002

Effects of Ketamine

- Preventing central sensitization in the dorsal horn neurons (interfere with pain transmission in spinal cord)
- CV
  - Inhibits reuptake of catecholamines (NE) at nerve terminals
  - Increase HR, BP, CO
- Pulmonary
  - Stimulation of B2 adrenergic receptors
  - Bronchial smooth muscle relaxant (bronchodilation)
  - Increases salivary and tracheobronchial secretions (esp in kids)
  - Does not lead to ventilatory depression
- Neurological
  - Increases cerebral blood flow, metabolism and ICP
  - Seizure threshold unaltered
- Causes sensory and perceptual illusions, vivid dreams and “emergence reactions”

Ketamine Perioperatively

- Bell et al. (2006) reviewed 37 RCT (over 2240 participants)
  - Found perioperative ketamine reduces rescue analgesic requirements or pain intensity or both
- Ketamine in subanesthetic doses is effective in reducing morphine requirements in the first 24 hours after surgery
- Loftus et al. (2010) found intraoperative ketamine reduces opioid consumption (morphine) in the 48 hour postoperative period in opioid-dependent patients with chronic back pain
- Implications:
  - Reduced acute pain
  - Reduced chronic pain
  - Reduced peripheral sensitization
  - Reduced central sensitization
  - Reduced opioid induced hyperalgesia
- Ketamine applied around the time of surgery as a single infusion has even been reported to limit the development of chronic pain up to 180 days postoperatively

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Ketamine and PTSD

- Ketamine infusion was associated with significant and rapid reduction in PTSD symptom severity, compared with midazolam
- Ketamine was also associated with reduction in comorbid depressive symptoms and with improvement in overall clinical presentation
- Ketamine was generally well tolerated without clinically significant persistent dissociative symptoms.
- To date, few pharmacotherapies have demonstrated sufficient efficacy in PTSD; selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and other medications are associated with significant levels of nonresponse and persistent residual symptoms, even in responders.
- Accumulating evidence for the role of glutamate in mediating stress responsivity, the formation of traumatic memories, and the pathophysiology of PTSD, suggests a potential benefit for ketamine for PTSD

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Ketamine Infusions

- Ketamine infusions for pain have been used for decades
- Inpatient protocols
- Outpatient protocols
- Multiple adjunctive medications
- Dosing time
- Fixed dose protocols vs. custom individual protocols
- Growing awareness and ketamine infusion clinics
- Counterfeit clinics
- Possible ketamine epidemic

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Challenges to Treatment

- Physician Lack of Education
- Physician Stereotypes
- Physician Egos
- Physician Laziness
- Facility Logistical Issues
- Complexity of Science
- Complexity of Treatment
- Lack of Coverage
- Minimal Reimbursement

In the USA there is some following, even absent "FDA approval" for use of ketamine infusions, in documented CRPS-criteria meeting cases. Ms. [redacted] did not meet diagnostic criteria for CRPS and therefore, use of ketamine infusions was not indicated. She also does not have "central sensitization" (purely speculative diagnosis) nor does she have peripheral neuropathy (all EMGs are normal). She therefore is NOT a candidate for ketamine infusions.

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