Opioid Induced Hyperalgesia

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Disclosures

- Steve Prakken MD
  - Pfizer: Advisor
  - Radeas: Consultant

Learning Objectives

- Define and demonstrate evidence for the presence of OIH
- Define 2 likely mechanisms for OIH
- Recognize clinical clues for OIH in patients
- Formulate treatment options for patients with OIH

Outline

- DEFINITION
- DOES IT EXIST?
- WHAT IS IT?
  - Anatomical possibilities
  - Neurochemical possibilities
- CLINICAL PRESENTATION
- TREATMENT

Definition

- Opiate induced hyperalgesia (OIH) is best considered a state of nociceptive sensitization caused by exposure to opioids.

Chu 2008

Does OIH Exist

- Over 1500 articles related to OIH in humans and animals
- Animal studies, generally support the presence of OIH
- Human studies, some controversy, clinically relevant

Angst 2006, Fishbain 2009, Yi 2015

Does OIH Exist

HUMAN STUDIES

- Opiate addicts
  - Tends to support OIH
- Perioperative opiates
  - Mixed results
- Experimental exposure
  - Best evidence
- Controlled studies
  - Few

Opioid Addicts

- Former opiate addicts on methadone
- Found to have as increased sensitivity to cold pressor, though hyperalgesia to electrical or mechanical pain was weak or absent
- Confounded by
  - Effect of length of exposure
  - Pre-addiction quality of pain tolerance
  - Genetic predisposition

Khantzian 1985, 1997. Angst and Clark 2006, Fishbain 2009

Perioperative Opioid Exposure

- Fentanyl and remifentanil exposure primarily, with mixed outcome
  - —Preop exposure leads to increased postoperative opioid consumption, or peri-incisional wound allodynia and hyperalgesia (Joly 2005 Chia 1999)
  - —Preop exposure vs naïve, undergoing GYN or GI surgery with no difference in postoperative consumption of opioids (Lee 2005 Hansen 2005 Cortinez 2001)

Acute Opioids Exposure in Healthy Volunteers

- Opiate exposure in volunteers that are opiate naïve
  - Brief hyperalgesia to mechanical, cold pressor, and electrical stimuli
  - Usually lasting 30-90 minutes and resolve by the next day

- Fishbain literature review (2009)
  - This is primary model showing any significant evidence for OIH in the human literature

(Angst 2003 Koppert 2001,2003 Compton 2003,2004).

Prospective Observational Studies in Chronic Pain Patients

- Chu (2006), with a small N and using MS at 75 mg per day max for 1 month, found significant hyperalgesia and analgesic tolerance in cold pressor model but not in heat model

Prospective Observational Studies in Chronic Pain Patients (cont'd)

- OIH with hydromorphone
  - 30 patients over 4 weeks
  - Hydromorphone to 24 mg per day max
    - Washout from other opiates
    - ER hydromorphone
  - Clinical and experimental pain response
    - OIH measured by CP and heat
  - OUTCOMES
    - Analgesia and OIH concurrently
    - Dose dependent

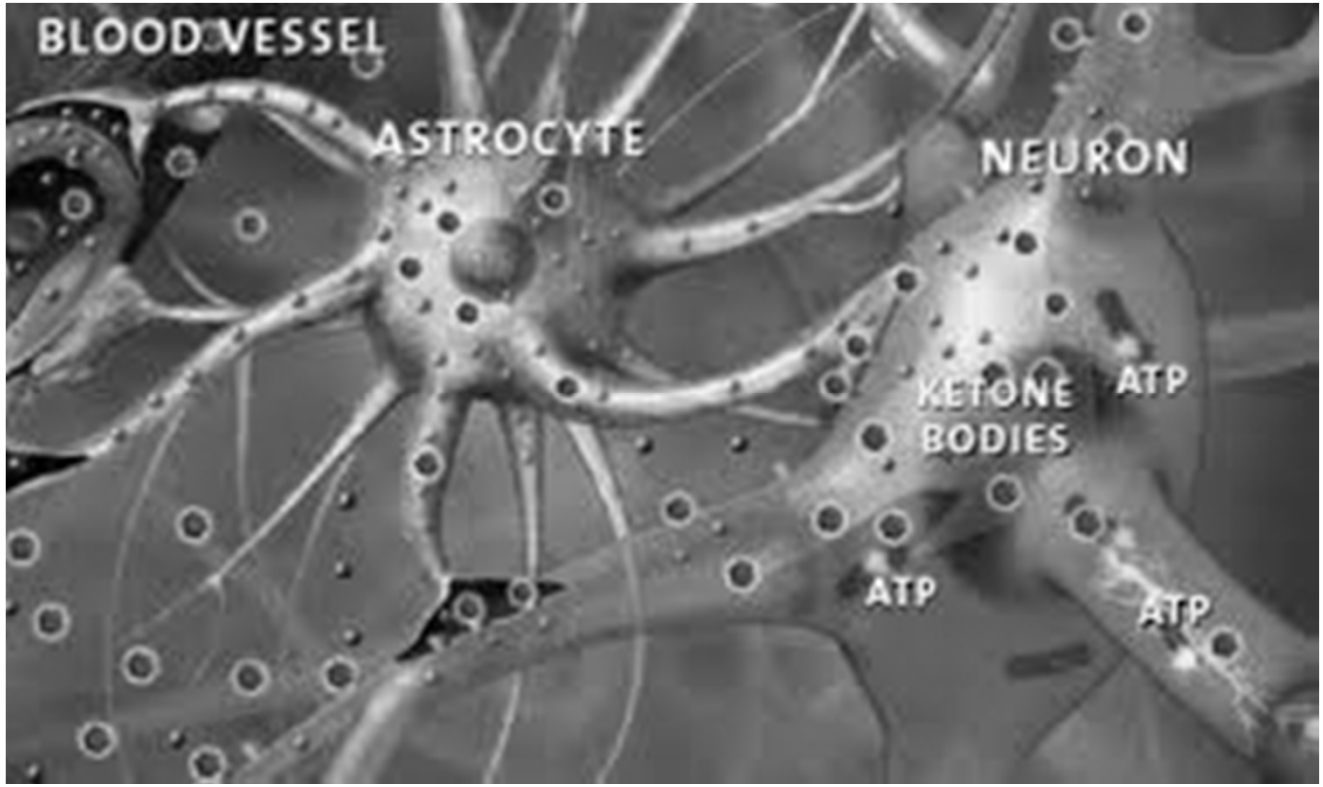
Suzan et al 2013

What is MOA

- Peripheral
  - TRP-V1, cytokines, beta-2 adrenergic receptors
- Spinal
  - NMDA, dynorphin, cytokines, substance P, 5HT3
  - Dorsal horn is primary site of action
- Supraspinal
  - PAG with 5HT, NE, opioid
  - RVM with opioid "on" cells, 5HT
  - Anterior cingulate
- Glial cell activation

Aley 1997 Liang 2006, Mao 1994,,2002 Sweitzer 2004, Johnston 2004, Li 2002, Belanger 2002

Glial Cell Activation



Glial Cell Activation (cont'd)

- Microglia > astrocytes
  - Activation causing cascade of events in both the brain and spinal cord
- Triggers
  - Nerve damage byproducts
  - Intracellular debris
  - Heat shock proteins
  - Inflammatory stressors
  - Opioids
  - ETOH

DeLeo 2004, Bianchi 2007)

Glial Cell Activation (cont'd)

- Activation releases
  - Proinflammatory cytokines (interleukin 1&6, TNF, ATP, NO, prostaglandins, substance P, etc)
- Increase neural activity due to
  - Upregulate AMPA, NMDA
  - Downregulate GABA and other modulating CNS activities
- Feedback loop
  - Ongoing activation of the CNS, including the "illness response"

Watkins 2007, 2009, Zhang 2008, Takeda 2008, Watkins 2012

Glial Cell Activation (cont'd)

- Appears to be independent of classic opiate receptors
  - —Toll like receptor 4 (TLR4)
  - —Nonstereoselective, unlike opioid receptors
  - —Unique treatment options
- Mu receptor may not be involved in OIH

Watkins 2009, 2012, Chu 2011

Alternative Mu Opioid Receptor

- Mu opiate receptor 1 (MOR1), G-protein receptor with 7 domains
  - Has standard inhibitory response, through decrease in Ca++, NO, and cAMP
- MOR1K is G-protein receptor with only 6 domains
  - Has atypical excitatory response, showing increase in Ca++, NO, and cAMP
  - Shown to cause OIH in mouse model

Diatchenko 2010, Folabomi 2015

Diffuse Noxious Inhibitory Control (DNIC)

- Endogenous pain inhibition
  - —Pain inhibits pain
- Nociceptive input form C and A delta
  - —Wide dynamic range neurons at DH inhibited
  - —Inhibition originates from upper CNS centers

DNIC Measurement

- Pressure pain threshold (PPT)
  - First pressure noted
- Pain tolerance (Ptol)
  - Intolerable
- Second painful stimuli applied to distant location and PPT measured again
  - Delta of PPT under both conditions is DNIC

Clinical Presentation

- OIH IS NOT
  - —Tolerance
  - —Progression of lesion
  - —Withdrawal pain
  - —Medication effects
    - Generic
    - Formulation changes (oxycodone ER)

Clinical Presentation

- OIH (for hours to days) with either acute or chronic opioid dosing
- OIH may be more prone in mechanical pain rather than electrical or thermal (though methadone addicts don't show this)
- OIH with high or low dose opioids (though larger doses were faster and longer)
- Route of administration not important
- Shorter half life tended to give more rapid tolerance and OIH
- Relative potency was not a factor
- Sensitization lasted long after direct OIH effects were resolved
- Pain at a site different than the original pain may be a marker for OIH. Generalized pain or flare of previously resolved pain

Angst and Clark 2006, Bekhit 2010

Clinical Presentation

- Rossback 1880

"When dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperesthesia, neuralgia, and irritability become manifest."

Clinical Presentation

- Sleep reduced consistently
- Irritability
- Thoughts racing
- Physical agitation
  - Myoclonic jerking
  - Night time movements
- Distractible
- Impulsivity

Irritable Mania, DSM V Criteria

- Distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least 1 week

- With 3 (or more) of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
  - More talkative than usual or pressure to keep talking
  - Flight of ideas or subjective experience that thoughts are racing
  - Distractibility
  - Increase in goal-directed activity or psychomotor agitation
  - Excessive involvement in pleasurable activities that have a high potential for painful consequences

- Sufficiently severe to cause marked impairment in occupational or usual social activities or relationships
- The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment)

Clinical Presentation

- Not to be given the dx of bipolar disease
  - —Type I, II, III
- Looks like Cluster B, some obsessive or mixed mood
- Clinically associated with:
  - —Family history of mood instability consistent with BAD
  - —Personal mood instability
    - Personality d/o
    - Severe mood variability
    - Bipolar dx

Adjunctive Treatment

- NMDA receptor antagonists (NMDARAs)
  - Ketamine
  - Dextromethorphan
    - 3 RCTs with 1:1 MS and dextro, no different than MS alone
    - Nuedexta
  - Memantine
    - Open channel NMDARA
- GABA-A antagonist
  - Propofol
- Alpha-2 agonist
  - Clonidine
  - Dexmedetomidine

Elia 2005, Bell 2003, 2006, De Kock 2001, Stubhaug 1997, Angst 2003, Joly 2005, Koppert 2003, Galer 2005, Sinis 2007, Schifitto 2006, Sang 2002, Eisenberg 1998, Nikolajsen 2000, Patill 2011, Kapural 2010, Collins 2011, Welters 2011, Mei 2011, Ramasubbu 2011

Opioid Treatment

- Opioid rotation
- Opioid reduction
- Methadone (levorphanol)
  - NMDA receptor antagonist
- Buprenorphine

Callahan 2004, Sjogren 1994, 1998, Lawlor 1997, Mercadante 2005, Woolf 1981, Mercadante 2003, Koppert 2005, Chu 2008

TLR-4 Treatment

ANTAGONIST

- Ibudilast
  - —Asthma and stroke tx, now AV411
- Amitriptyline
- Imipramine
- Cyclobenzaprine
- Naloxone/naltrexone

Glial Cell Inhibitors

REDUCE MIGRATION

- Minocycline (TCN derivative)
- Cannabinoids (CBR2 in particular)

Clinical Approach

- OIH as unintended clinical outcome
- OIH as tool
- OIH as club

Clinical Approach (cont'd)

- Identify
  - —Sleep disturbance primary
    - Medicated?
  - —Reported stimulation from the opiate
  - —Irritability
    - Collateral, inconsistent history, staff reactions
  - —Impulsivity
    - Medication, behavioral dysregulation

Clinical Approach (cont'd)

- Educate, enlist cooperation
  - —Predict outcome
  - —Curious about change in behavior with opiates
    - Collateral information supporting change in behavior
  - —Not about opiate use per se

Clinical Approach (cont'd)

- Rotate
  - Oxycodone, fentanyl, hydrocodone
  - Oxymorphone
  - MS, hydromorphone, methadone, levorphanol
  - Buprenorphine
  - Tapentadol
- Mood stabilize
  - Lamotrigine, aripiprazole
  - Duloxetine
- Stimulating agents to help DC of opioids
  - Replacement
  - Bupropion, modafinil, atomoxetine
  - Dextroamphetamine, methylphenidate

Clinical Approach (cont'd)

- Opioid holiday
  - Tapering schedules
  - Effective "holiday" time unknown
  - Is OIH reversible
  - Pain management in the interim
  - PRN opiates

Summary

- OIH exists
- Varied mechanisms
  - Multiple mechanisms
  - Glial cell activation as common denominator?
- CNS is primary
  - Cord and brain
- Clinical appearance
  - Increasing pain with increasing opioid activation
- Treatment options
  - Rotation, education, replacement, holiday trial

THANK YOU