The Good, The Bad, And The Ugly: Principles Of Analgesia, Hyperalgesia, And Withdrawal
Overview

- Opioid pathophysiology
  - normal nociceptive pathways
  - opioid receptors and common agents
- Problems with long-term use
  - tolerance, withdrawal, and hyperalgesia
- Strategies to overcome limitations of therapy
  - change in dose or agent, and novel pharmacotherapy
Nociception

- Neural process by which we receive and interpret a stimulus as noxious
  - signal transduction
  - signal transmission
  - perception of pain
  - modulation of signaling pathways
Origins of Nociception

- Perception of pain is adaptive
  - pro-nociceptive pathways
- Elimination of pain is adaptive
  - anti-nociceptive pathways
Nociceptive Balance

Hyperalgesia

Analgesia
Opioid Receptors

- δ- receptor: OP₁
  - endogenous ligand = β-endorphin
- κ- receptor: OP₂
  - endogenous ligand = dynorphin
- μ- receptor: OP₃
  - endogenous ligand = enkephalin
- ORL₁- receptor: OP₄
  - endogenous ligand = nociceptin/orphanin FQ
  - naloxone insensitive
Receptor Distribution

- **Peripheral**
  - primary afferent neurons

- **Spinal**
  - pre- and post-synaptic in dorsal horn

- **Supraspinal**
  - Periaqueductal Grey Matter (PAG)
  - Rostral Ventromedial Medulla (RVM)
$G_{i/o}$-protein Coupled Receptor (GPCR)

- $\mu$-R
- $\beta\gamma$
- $\alpha$
- GDP
- GTP
- OP
- Adenylate cyclase
- ATP → cAMP
- $Ca^{2+}$
- $K^+$
$\text{G}_{i/o}$-protein Coupled Receptor (GPCR)
C-fiber

Interneuron

2nd order neuron

Pre-synaptic

Post-synaptic

Enkephalin

GABA

Excitatory amino acid/neuropeptide (EAA/NP) = glutamate, SP, CGRP

EAA/NP-R = NMDA-R, AMPA-R, CGRP-R, NK1-R

E. Brush, MD

3/15/2012
Common Examples

- $\mu$ and $\kappa$ agonist
  - morphine, hydrocodone, oxycodone, methadone, hydromorphone, fentanyl

- $\kappa$ agonist, $\mu$ antagonist
  - nalbuphine (Nubain®)

- $\mu$ partial agonist, $\kappa \delta$ antagonist, ORL$_1$ agonist
  - buprenorphine
Therapeutic Considerations

- Tolerance
- Withdrawal
- Dependence
- Addiction
- Opioid Induced Hyperalgesia
addiction  analgesia  euphoria  dysphoria

addiction  dependence  withdrawal

tolerance  hyperalgesia
Tolerance

- Diminished effect with repeated administration
- G-protein coupled receptor in response to prolonged agonism
  - Receptor phosphorylation via G-protein coupled receptor kinase
  - Uncoupling of receptor from G-protein mediated intracellular signaling
  - Receptor internalization/“downregulation”
Withdrawal

- Loss of normal inhibitory opioid effects
- Pro-nociceptive pathways predominate
  - pain
  - dysphoria
  - GI distress
Opioid Induced Hyperalgesia (OIH)

- Heightened perception of pain related to the use of opioids in the absence of disease progression or withdrawal state
Allodynia vs Hyperalgesia

- Allodynia
- Hyperalgesia
- Injury
- Normal

Pain Sensation

Stimulus Intensity

Innocuous

Noxious
Basic Model- Paw Withdrawal
Paw Withdrawal Latency

- **Baseline**
- **Day 1**
- **Day 2**
- **Day 3**
- **Day 4**
- **Day 5**
- **Day 6**
- **Day 7**
- **Day 8**
- **Day 9**
- **Day 10**

**Control**

**Opioid Infusion**

- **3/15/2012**
- E. Brush, MD
Acute on Chronic Pain

Pain

Withdrawal

Disease progression

Tolerance

Opioid-induced
Sorting Out The Problem

- **Tolerance**
  - Blunting of usual opioid anti-nociceptive effect

- **Withdrawal**
  - Loss of baseline anti-nociceptive effect: pro-nociceptive predominance

- **OIH**
  - Direct opioid induced facilitation of pro-nociceptive pathways
Tolerance vs OIH

A → B = OIH

A = Normal dose/response

A → C = Tolerance

A → B = OIH
Tolerance vs OIH

- A = Normal dose/response
- A → C = Tolerance
- A → B = OIH

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OIH in Humans

- Clinical features poorly defined
- Disease progression confounds data
- May apply to small subset of population
- Not detectable with all types of stimuli
- Chronic pain patients may have pre-existing hyperalgesia
- Primarily cohort studies
  - exposure to opioids not random
Evidence for OIH in Humans

- Review of existing human studies
  - Agency for Health Care Policy and Research criteria (AHCPR)
  - Level A
    - 5 studies: opioid infusion in normal volunteers produces hyperalgesia
  - Level B
    - 9 studies: chronic opioid use
      - decreased pain tolerance
      - decrease in pain threshold not consistent
Human Trial$^3$

- 32 patients
  - Methadone Maintenance Therapy (MMT), N=16
  - Control, N=16

- Cold Pressor Test (CPT)
  - measured pain threshold and tolerance
  - testing at projected methadone trough and peak (time 0hr and 3hr after daily dose)
Methadone Trough

Detection: p=0.023
Tolerance: p<0.0001

seconds

Control
Methadone
Methadone Peak

- Detection: p = 0.369
- Tolerance: p < 0.0001

Control vs. Methadone
Analysis of CPT Results

- Pain threshold same between methadone patients and controls
- Patients on MMT may be more “annoyed” by pain (affective response)
  - cocaine addicts have similar decrease in pain tolerance with CPT
Altered Pain Tolerance? ⁴

- 110 Patients
  - Group 1 (N=73) - chronic pain on maintenance opioids
  - Group 2 (N=37) - chronic pain not on opioids

- Diffuse Noxious Inhibitory Control Test (DNIC)
  - Measures subjects’ ability to dampen pain signals when co-administered noxious stimuli
    - Home remedy: hold an ice cube in your hand when you have a toothache
DNIC

- Pain rated (NPS) after heat stimulus to left arm
- NPS after same stimulus when co-administered with CPT to opposite hand
- Measured magnitude of change in NPS
- Magnitude of change in NPS much smaller in opioid tolerant subjects
  - anti-nociceptive inhibitory mechanisms impaired with chronic opioid administration
Compartmental View

Peripheral increase in signal transduction
- Increased expression of ion channels in nerve terminals producing enhanced transduction of painful stimuli

Spinal sensitization to nociceptive input
- Paradoxical PK and AC activation - increased SP and CGRP, ion channel modulation
- Enhanced spinal dynorphin stimulates SP and CGRP release: NMDA receptor dependent

Central sensitization
- Enhanced descending facilitation of nociception from RVM via CCK
Excitatory amino acid/neuropeptide (EAA/NP) = glutamate, SP, CGRP

EAA/NP-R = NMDA-r, AMPA-r, CGRP-r, NK1-r
Medulla

Midbrain

OP

PAG

CCK

RVM

On

Off

Primary afferent

Spinal Cord
Treating Tolerance and OIH

- Dose escalation
  - overcome tolerance
- Dose reduction
  - aim to eliminate OIH
- Opioid rotation
  - various receptor affinities may increase analgesia and decrease side effects
- Add novel agent
  - NMDA receptor antagonist
Dose Escalation

- Beware of increased adverse effects
  - morphine-3-glucoronide accumulation with renal disease
  - fentanyl delirium and myoclonus
  - GI effects
  - respiratory suppression

- Special consideration to methadone
  - increase only after 5 or more days at new dose
Opioid Rotation

- Analgesia and adverse effects may vary between individuals
- Evidence largely anecdotal
- Best approach for optimal outcome unknown
- Useful if dose escalation limited by adverse effects
- Methadone most commonly used and best studied
Proposed Mechanisms

- Accumulation of metabolites
  - renal failure (morphine-3-glucoronide)

- Pharmacogenetics
  - CYP2D6 – 10% Caucasians cannot methylate codeine to morphine
  - receptor polymorphisms
    - varied binding affinity for opioids
Proposed Mechanisms

- **Pharmacokinetics**
  - poor versus extensive metabolizers
    - PM may require higher doses due to inadequate conversion to active drug

- **Incomplete cross-tolerance**
  - high tolerance to opioid #1, but lower tolerance to opioid #2
Approach to Rotation

- Change drug class
  - Phenanthrene: morphine, hydrocodone, hydromorphone, oxycodone
  - Phenylpiperidine: fentanyl
  - Diphenylpropylamine: methadone
    - Weak NMDA-r antagonist
  - Buprenorphine paradox
    - precipitated withdrawal
General Advice

- Use one equianalgesic guideline consistently
- Caution with certain conversions
  - Methadone ratio varies with morphine equivalent (ME) dosing
  - ME <100mg, 10:1
  - ME 100-300mg, 15:1
  - ME >300mg, 20:1
- Conservative dosing with PRN available
Addition of Novel Agent

- NSAIDs
- Gabapentin
- NMDA-r antagonists
  - ketamine, amantadine, dextromethorphan
Dextromethorphan

- 829 patients with chronic pain treated with morphine (MS) or morphine/dextromethorphan (MS/DM 1:1 ratio, MorphiDex®)
  - A: stable dose 3 months. Measured change from baseline in average pain intensity
  - B&C: self-titration to maintain analgesia. Measured change from baseline in morphine dose with MS vs MS/DM
Dextromethorphan\textsuperscript{5}

- No significant effect from addition of DM
- 1:1 ratio of MS to DM may have limited effect
  - relatively low doses of DM
Managing Pain Effectively

- High variability between individuals
  - pain tolerance
  - genetic profile
  - disease states
- Difficult to sort of root cause of pain
  - tolerance, withdrawal, OIH, disease progression
- Consistent approach
  - plan for long-term optimization
References