ANALGESICS AND THEIR ACTIONS

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WHAT IS AN ANALGESIC DRUG?
ANALGESIC DRUG?

Class is defined by effect, not structure.

Tramadol
Gabapentin
Aspirin
Fentanyl
Amitriptyline
Butorphanol
Morphine
ANALGESIA vs ANESTHESIA

An-…(without) -algiesia…(pain)

vs

An-…(without) -esthesia ….(sensation)

WHAT IS AN ANALGESIC?

...a drug which specifically blocks pain

... leaves other sensations/consciousness unimpaired
ARE THERE DIFFERENT TYPES OF ANALGESIC DRUGS?
ANALGESIC DRUGS MAY BE BROKEN DOWN IN TERMS OF:

- NATURE OF PAIN STATE THEY CONTROL

- MECHANISM OF DRUG ACTION
HUMAN PAIN STIMULI

Acute (non injury)
- Thermal… > 42 °C / < 4°C
- Mechanical… Pinch

Tissue injury
- Post operative pain
- Arthritis

Nerve Injury
- Physical
- Chemical / Immune
HUMAN PAIN STATES

Acute (non injury)
- Thermal
- Mechanical

Tissue injury
- Post op pain...
- Arthritis

Nerve Injury
- Physical
- Chemical
- Immune

Stimulus dependent
Localized

Ongoing pain
2° Allodynia
1° Hyperalgesia
Examples of injury-induced hyperalgesia

**Sunburn**

Mild thermal stimulus...pain...Therm hyperalgesia

**Arthritis**

Normal joint rotation...pain...Mech hyperalgesia
ANALGESIC vs ANTI-HYPERALGESIC DRUGS

Tissue injury /inflammation leads to hyperalgesia

**Analgesic:**

**Anti-Hyperalgesic:**

<table>
<thead>
<tr>
<th></th>
<th>INFLAMMED PAW</th>
<th>NORMAL PAW</th>
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<tbody>
<tr>
<td>I.P. DOSE (mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>VEH</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>VEH</td>
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<tr>
<td>100</td>
<td>VEH</td>
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**Opiates**

**NSAIDS, NMDA antag, TCA, Anticonvulsants**
MECHANISMS OF ANALGESIC DRUGS

Analgesic drugs alter processing at one or more links in pathway over which information generated by tissue / nerve injury is carried.
PAIN PROCESSING

- Peripheral stimulus…injury
- Small afferent activation/persistent
- Spinal excitation…facilitation
- Ascending spinal projections to diencephalon (thalamus)
- Thalamic projections to sensory cortex limbic fore brain
MECHANISMS OF ANALGESIC DRUGS

OPIATES

- Morphine, hydromorphone
- Fentanyl
- Meperidine, methadone
- µ opioid receptor
- Brain stem / Spinal cord
- Blocks afferent transmission
- Analgesic
MECHANISMS OF ANALGESIC DRUGS

NSAIDS
Nonsteroidal anti-inflammatory drugs

- ASA, Ibuprofen, naproxan, Vioxx, Celebrex
- Inhibit cyclo-oxygenase (COX) at injury site and in spinal cord
- blocks prostaglandins synthesis
- prevents sensitization by PG’s
- Anti-hyperalgesic
MECHANISMS OF ANALGESIC DRUGS

ANTI CONVULSANT

• Gabapentin, topiramate, valproate
• Blocks sodium /calcium channels in sensory nerves / spinal cord
• Prevents increased excitability induced by nerve injury
• Anti-hyperalgesic / antiallodynic
MECHANISMS OF ANALGESIC DRUGS

TRICYCLIC ANTIDEPRESSANTS

- amitriptyline, nortriptyline
- Blocks uptake of norepinephrine in brain and spinal cord.
- Antidepressant reduces pain impact
- Reduces spinal pain traffic
- Anti-hyperalgesic / anti-allodynic
MECHANISMS OF ANALGESIC DRUGS

NMDA ANTAGONIST

• Ketamine

• Glutamate released in spinal cord by tissue and nerve injury initiates facilitated state by activating spinal NMDA receptor.

• Ketamine blocks NMDA receptor and prevents facilitated state

• Reduces spinal pain traffic

• Anti-hyperalgesic / antiallodynic
# ANALGESIC DRUG ACTIONS

- Multiple mechanisms
- Differential effects upon components of pain state

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>MECHANISM</th>
<th>Acute Stim</th>
<th>Tissue Injury*</th>
<th>Nerve injury*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiate</td>
<td>μ opiate receptors on pain fibers, blocks excitatory input</td>
<td>X</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>NMDA antag</td>
<td>Blocks glutamate-r spinal facilitation</td>
<td>O</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NSAID</td>
<td>Inhibit PG synthesis, blocks terminal / spinal sensitization</td>
<td>O</td>
<td>X</td>
<td>O</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>Reduces spontaneously active spinal neurons</td>
<td>O</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TCA</td>
<td>Increases brain and spinal catecholamine levels</td>
<td>O</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>CB1/2 receptors reduce inflammation/pain x-mission</td>
<td>O</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* Hyperalgesia / allodynia
WHY DO WE NEED SO MANY ANALGESIC DRUGS?
CLINICAL PAIN...

MULTIPLE MECHANISMS

• Burn
• Cancer
• Mechanical Trauma
• Post herpetic neuralgia
• Diabetic neuropathy
PAIN SECONDARY TO CANCER.....
......Not mono-mechanistic....

- Multiple etiologies.. Tissue injury / nerve injury
- Multiple pharmacologies

<table>
<thead>
<tr>
<th>Iatrogenic:</th>
<th>Tissue injury</th>
<th>Nerve injury</th>
</tr>
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<tbody>
<tr>
<td>Chemotherapy</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td>X</td>
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<tr>
<td>Surgery</td>
<td>X</td>
<td>X</td>
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<table>
<thead>
<tr>
<th>Disease</th>
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<tbody>
<tr>
<td>Tumor compression</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Release of active factors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Immune response</td>
<td>X</td>
<td>X</td>
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</tbody>
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PAIN SECONDARY TO CANCER.....

No single drug acts upon all pain mechanisms

Typical cancer pt is typically on 3 - 4 pain medications

- **OPIATE**
  Maintenance: PO Morphine (slow release)
  Rescue: Buccal fentanyl

- **NSAID**
  Naproxen

- **ANTICONVULSANT**
  Gabapentin

- **ANTIDEPRESSANT**
  Amitriptyline
FACTORS GOVERNING ANALGESIC REQUIREMENTS.

Role of pain intensity in drug selection

Graded analgesic therapy (World Health Organization ladder).
- Weak to strong opiates
- Combination analgesic therapy (e.g. NSAIDs + opiates)
- Adjuvants to manage side effects.

World Health Organization (WHO) Ladder

MILD PAIN
- NSAIDS

MODERATE PAIN
- NSAIDS
- “Weak” Opiates

SEVERE PAIN
- NSAIDS
- “Strong” Opiates
- Anticonvulsant
- Adjuvants
- Laxatives
- Stimulants
- Antidepressant
WHAT IS A “STRONG” VS A “WEAK” OPIATE?
“STRONG vs WEAK OPIATE…..

Opiate agonists bind at opioid receptor

**AFFINITY**: How strongly does it bind?

Once it binds, it activates the receptor

**EFFICACY**: Once bound, how well does it activate?

Drugs binds strongly to receptor:

…does not activate: **ANTAGONIST**: Naloxone

… activates weakly: **WEAK AGONIST**: Codeine/Tramadol

…activates strongly: **STRONG AGONIST**: Morphine, methadone, hydromorphone, fentanyl
PAIN INTENSITY AND OPIATE ACTIVITY

• Opiates dose dependently diminish a pain state
• As stimulus intensity rises, dose response curve shifts to right.

Mild pain… weak agonist may be fully effective as strong agonist.

Severe pain… All drugs show an increase in dose requirement… but weak agonist may fail to produce pain relief equivalent to strong agonist (plateau).
WHY DO ANALGESIC DRUG DOSES VARY SO WIDELY?
FACTORS GOVERNING ANALGESIC DOSE

Analgesic requirements vary across population

- 3,170 post op patients (orthopedic)
- Morphine range for analgesia: 0.02-0.83mg/kg
- Correlation of initial pain and dose = 0.34

Aubrun, et al, 2003
FACTORS GOVERNING ANALGESIC DOSE

Pain Type
- Some pain states are less sensitive to a given analgesic mechanism

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>PAIN MECHANISMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs:</td>
<td>Tissue injury $&gt;&gt;$ acute stimuli $=$ nerve injury $= 0$</td>
</tr>
<tr>
<td>Opiates:</td>
<td>Tissue injury $=$ acute stimuli $&gt;/=$ nerve injury $&gt; 0$</td>
</tr>
<tr>
<td>Anticonvulsant:</td>
<td>Nerve injury $&gt;&gt;$ Tissue injury $=$ acute stimuli $= 0$</td>
</tr>
</tbody>
</table>
FACTORS GOVERNING ANALGESIC DOSE

Pain Intensity

• As stimulus intensity rises, dose response curve shifts to right.

Example of “adequate analgesic doses” of Fentanyl

**RAT:** Thermal stimulus: 48°C: 1-3µg/kg

60°C: 20µg/kg

**HUMAN:** Thoracotomy incision: 30 µg/kg

Resting post operative pain: 3-5 µg/kg

Burn patient: 10-15 µg/kg
FACTORS GOVERNING ANALGESIC DOSE

Individual variability

• Heritability of pain traits

\[ V_{\text{Phenotypic}} = V_{\text{Genetic}} + V_{\text{Environmental}} \]

Human Studies

• migraine: 40-65%
• irritable bowel syndrome: 45-57%
• back/neck pain: 30-57%
• menstrual pain: 55%
• carpal tunnel syndrome: 46%
• sciatica: 21%
• joint pain (OA): 12%
• widespread pain (in kids): 10%
• experimental pressure pain: 10%

Mouse Studies

• nociception: 21-69% (mean: 46%)
• antinociception: 23-76% (mean: 50%)

Moghil, 2004
FACTORS GOVERNING ANALGESIC DOSE

Individual variability

- Pain responsiveness varies across population: REAL?

Pain stimulus to forearm.. Assessment by patient.. Measurement by fMRI of brain response

FACTORS GOVERNING ANALGESIC DOSE

Tolerance

• Reduction in drug effect over time or increase in dose required to yield given response after repeated opiate doses

  Tolerance can be extreme. (10 mg PO in naïve Pt is high dose vs 1-3 grams IV in a severely tolerant individual producing only minor sedation)

  Analgesic tolerance is controversial… (1000 advanced cancer patients: only 5% required a daily increase of > 10% over 6 months)

  Different effects…different rates of tolerance

  euphoria > sedation > analgesia > nausea > constipation > miosis
TOLERANCE

Loss of analgesic response in chronic pain patients could be secondary to:

i) **Increased pain**
   - increased pain stimulus requires higher dose

ii) **Pharmacokinetics**
   - increased metabolism or clearance….unlikely

iii) **Pharmacodynamics**
   - Reduced receptor number/loss of second messenger coupling….controversial.

iv) **System level changes**
   - Chronic opiates may initiate a facilitated state

iv) **Development of non-opioid sensitive pain**
   - less effective in neuropathic pain

v) **Suffering vs pain**
   - Removal of the stimulus may be necessary, but not sufficient to control suffering.
OPIATES:

Tolerance Dependence Addiction
DEPENDENCE

• State of pharmacodynamic adaptation produced by continued drug exposure.

• Manifested by drug class specific withdrawal syndrome produced by abrupt cessation (e.g. by drug abstinence), and/or administration of antagonist (Naloxone).

• Withdrawal characterized by exaggerated appearance of physiological signs which are suppressed by additional opiate agonists.
# DEPENDENCE

Dependence-Withdrawal syndrome observed at all levels of biological organization responsive to opiates

<table>
<thead>
<tr>
<th>MODEL</th>
<th>Opiate effect</th>
<th>+ Naloxone</th>
</tr>
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<tbody>
<tr>
<td>Isolated tissue</td>
<td>Suppression of ileum contraction</td>
<td>Enhanced contractility</td>
</tr>
<tr>
<td>Neuron</td>
<td>Block of activity</td>
<td>Enhanced activity/x-mitter release</td>
</tr>
<tr>
<td>Animal</td>
<td>Bradycardia Constipation Pupil constriction Analgesia Euphoria</td>
<td>Tachycardia Diarrhea Pupil dilation Hyperalgesia Dysphoria</td>
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ADDICTION

- Drug seeking behavior ....strong efforts to obtain drug for non-therapeutic self delivery....defined in terms of intrinsic rewarding properties of drug.

- Characterized by behaviors that include: impaired control over drug use, continued use despite harm, and reported craving.

- Aberrant behaviors .... prescription forgery, stealing drugs from others, and obtaining prescription drugs from non-medical sources are indicators of addiction disorder.
Historical perspective: Medicinal use of opiates.

- Widely used in the US Civil war.
- “Soldier’s disease”…laudanum/morphine abuse by Civil War wounded (1865-1880).

"... The returning veteran could be... identified because he had a leather thong around his neck and a leather bag (with) Morphine Sulfate tablets, along with a syringe and a needle issued to the soldier on his discharge.... (T)his was called the "Soldier’s Disease." (Starkey, 1971:482-84)1"

- Heroin synthesis to develop a “non-addictive” morphine (1890-1900).
EUPHORGENIC MECHANISMS OF OPIATES

Opiates → Brain μ opiate receptor activation...

**positive** re-enforcing properties.

- Opiate receptors in **n. Accumbens** inhibit local inhibitory (GABA) interneurons which regulate activity of (n. Accumbens) meso-limbic dopamine-releasing terminals
- Increased **dopamine release** is reinforcing.
- Opiates with rapid onset of action have higher rewarding properties (e.g. lipid soluble agents such as heroin, 3,6 diacetyl morphine)
ADDICTION

Addiction……or …Pseudo-addiction…

• Analgesics-seeking behavior..
• May occur in the setting of continuous pain when inadequate doses are utilized or excessive dosing intervals are employed.
• Patient may aggressively seek analgesics because they are in pain.
Among the remedies which it has pleased almighty God to give to man to relieve his sufferings, none is so universal and efficacious as opium............Sydenham, 1680.

Opium Poppy: morphine

Phylomedusae sauvagei: dermorphin
# NEURAXIAL SYSTEMS REGULATING PAIN TRANSMISSION

<table>
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<tr>
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<tbody>
<tr>
<td>µ/K opioid ag*</td>
<td>δ opioid ag</td>
<td>α2 adren ag subtype</td>
</tr>
<tr>
<td>Na ch blkr</td>
<td>K opioid ag</td>
<td>NPY ag</td>
</tr>
<tr>
<td>α2 adren ag</td>
<td>Muscarinic ag</td>
<td>COX inhibitor*</td>
</tr>
<tr>
<td>GABA-B ag</td>
<td>Nicotinic ag</td>
<td>Steroid</td>
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<tr>
<td>COX inhibitor*</td>
<td>Cannabinoids (CB1)</td>
<td>N-type Ca Ch blkr*</td>
</tr>
<tr>
<td>Na ch blkr*</td>
<td>AChase inhib*</td>
<td>P-type Ca Ch blkr</td>
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<tr>
<td>Steroid</td>
<td>Neurotensin ag</td>
<td>NK1 ant</td>
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<td>Adenosine A1 ag*</td>
<td>Purine-r ant (P2X/P2Y)</td>
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<tr>
<td></td>
<td>Adenosine kin inhib</td>
<td>COX 2 inhib</td>
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<td>Gabapentinoids(α,2δ)</td>
<td>PG (EP1) antag</td>
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<td>NMDA-r ant subtype*</td>
<td>PLA2 inhib-isozymes</td>
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<td>Glycine site ant</td>
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<td>AMPA ant subtype</td>
<td>MAPK inhib</td>
</tr>
<tr>
<td></td>
<td>Na ch subtype</td>
<td>VR1 ant</td>
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- Microglial inhib
- siRNA
- Transfection vectors
- Antisense
- Cyclodextrin
- Liposomes
- SP-Saporin
- Botulinum toxin