Opioid Analgesia and Reward: Can They Be Separated?

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NAM Panel on Opioid Analgesia and Addiction
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The Ideal Analgesic
The Holy Grail of Pain Research

• Completely relieves severe pain of any cause
  – Rapid onset
  – Multiple routes of administration
  – Rapidly reversible (antagonist)

• No adverse effects
  – (e.g. opioids: respiratory depression, sedation, nausea, constipation, renal or GI toxicity)

• No tolerance, dependence or addictive potential
Why are Opioids so Widely Used?

• Highly effective for acute severe pain
  – Rapid onset
  – Broad spectrum
  – Multiple routes of administration
    (oral, intramuscular, intravenous, subcutaneous, intranasal, rectal, sublingual, transmucosal, transdermal)
  – ↑ sense of well-being beyond pain relief
What Makes Opioids so Effective?

• Act at **multiple sites**
  – Ascending pathways
    • Pain input converges →
    • Targets site mediating pain *suffering*
  – Pain modulating circuit
Opioids Hit both Transmission and Modulation Circuits

Fields, 2004
Limitations of Opioids

• Sedation, respiratory depression, constipation
• Tolerance and dependence
  • Loss of efficacy
  • Worsening of pain
• Diversion and Abuse
Opioid Dependence, Pain and Drug Seeking

- Opioid dependence
  - Aversive
  - $\uparrow$ motivation for opioids
  - $\downarrow$ opioid analgesia

- Chronic Pain
  - Aversive
  - $\uparrow$ motivation for opioids
  - $\downarrow$ opioid reward

e.g. Hipolito et al J Neurosci 2015
Ventral Tegmental Area
Critical for MOR Reward & Aversion

MOR agonists

MOR antagonists

drug room
Can We Keep Analgesic Potency, Reduce Adverse Effects and Avoid Dependence?
The Mu (morphine) Opioid Receptor (MOR)

1970s, Snyder, Simon, Goldstein, Terenius
30 Years of Progress

Opioid family of 7TMD GPCRs (1990s)

- MOR
- KOR
- DOR
- ORL

Brian Kobilka
Nature, 2012

MOR KO

Kieffer TIPS, 1999

Kieffer, 1999

MOR KO

- analgesia
- reward
- withdrawal
- respiratory depression
- immunosuppression
- constipation

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Canonical GPCR Signaling
(control synaptic function mediates analgesia)

Thanks Mark Schumacher
β-arrestin Signaling Specifically Enhances Respiratory Depression
Increasing G-protein Bias Reduces Respiratory Depression

Proof of Concept in Humans
Trevena Compound 130

Soergel et al Pain 2014
MOR Protein-Protein Interaction

- Heterodimer (DOR-MOR)
  - DOR KO or DOR antagonists reduce morphine tolerance
  - DOR antagonists enhance MOR agonist action
    - Phil Portoguese: MDANs (PNAS, 2005)
    - Lakshmi Devi: DOR antagonist enhances MOR Action (Br J Pharm, 2015)

Interaction of different GPCRs can change signaling

Clifford Woolf
Where Do We Go From Here?
Multiple Opioid Molecules in Current Human Use for Analgesia

Chemical Classes of Opioids

- PHENANTHRENES
- BENZOMORPHANS
- PHENYLPIPERIDINES
- DIPHENYLHEPTANES

MORPHINE
- RX EXAMPLES:
  - morphine
  - codeine
  - hydrocodone*
  - hydromorphone*
  - levorphanol*
  - oxycodone*
  - oxymorphone*
  - buprenorphine*
  - nalbuphine
  - butorphanol*

PENTAZOCINE
- pentazocine
- diphenoxylate
- loperamide

MEPERIDINE
- meperidine
- fentanyl
- sufentanil
- alfentanil
- remifentanil

METHADONE
- methadone
- propoxyphene

? relative efficacy, side effect profile, addictive potential

Courtesy of Dr. Jeffrey Fudin (FudinJ@gmail.com) Google
Re-examine Synthetic Opioids Effective in humans

• In theory you could design drug to separately enhance or reduce any biological action
• Systems/Synaptic Physiology
  – Different actions at different nervous system targets
• Cell Biology/signaling:
  – Relative Bias
  – Combinatorial action at several GPCRs
Structure Based Discovery of Novel Opioids

Kieffer Nature 2016
Optimize for Desired Characteristics

Strategy to Optimize Opioid Molecules

- Determine relevant signaling and protein-protein interaction in pain and reward circuit
- Determine changes with pain and opioid dependence
- Computationally model ideal docking in binding pocket
  - Optimize molecule for desired properties
  - Signaling bias
  - Protein protein interaction
Strategy Obvious: Who will Implement?

- NIH?
  - Development, not ‘innovative’
    - Study Section not likely to approve
    - RFA contract, In House?

- FDA?
  - Advanced Research and Development of Regulatory Science and Innovation? In House?

- Commercial Entities?
  - No IP, no $
    - Potentially useful molecules off patent
    - Computational approaches could optimize molecules and create IP, but optimization would require more neurobiology research