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

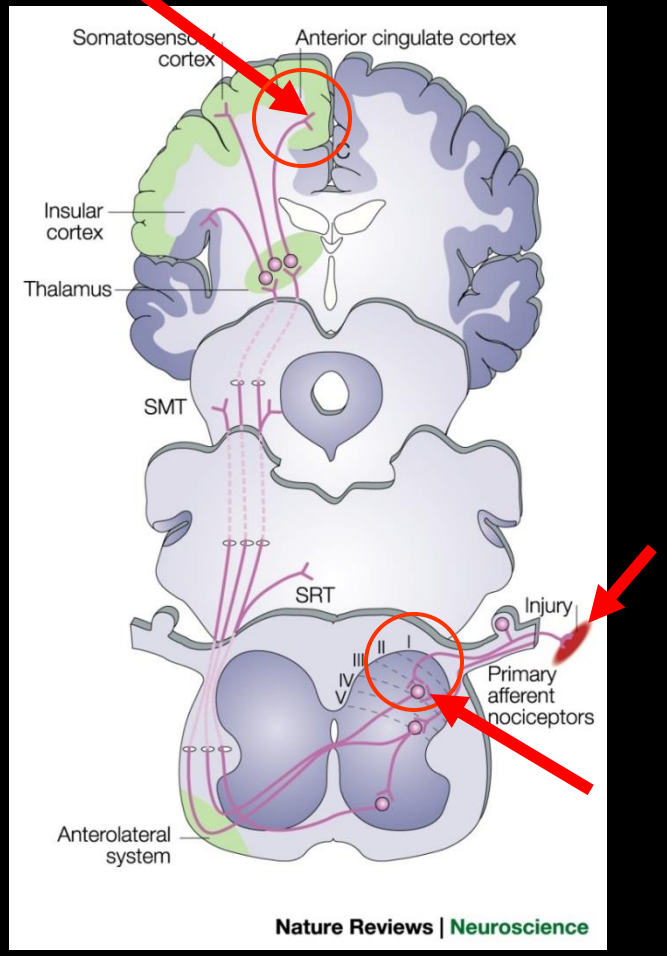
Why are Opioids so Widely Used?

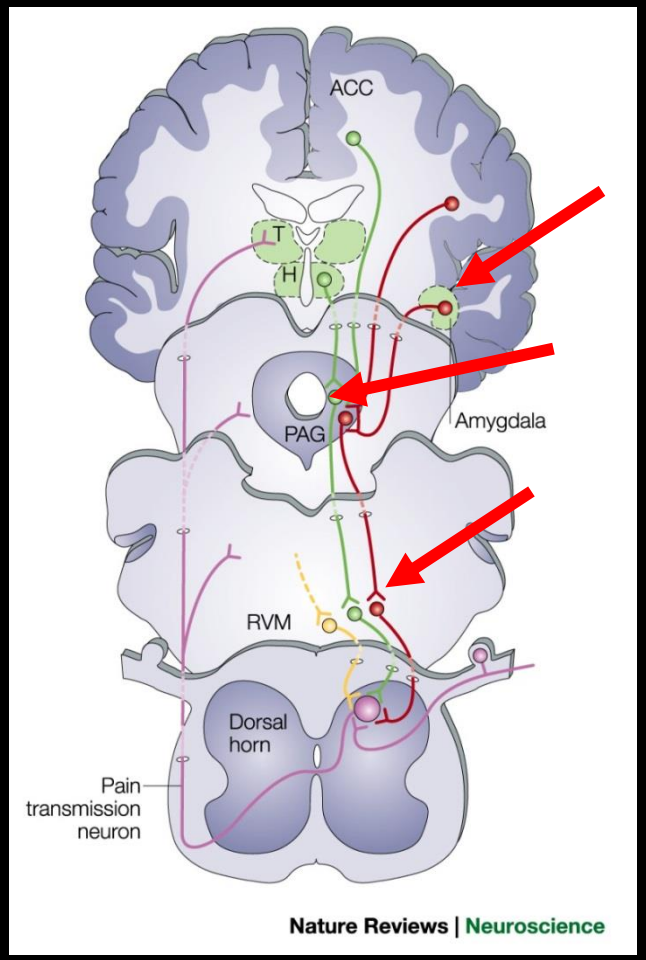
- Highly effective for acute severe pain
  - Rapid onset
  - Broad spectrum
  - Multiple routes of administration
    (oral, intramuscular, intravenous, subcutaneous, intranasal, rectal, sublingual, transmucosal, transdermal)
  - ↑ sense of well-being beyond pain relief

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

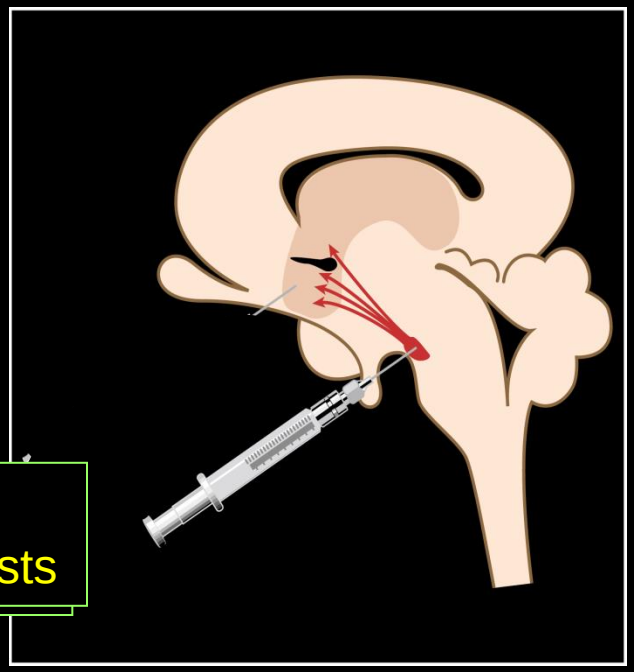
Opioid Dependence, Pain and Drug Seeking

- Opioid dependence
  - Aversive
  - ↑ motivation for opioids
  - ↓ opioid analgesia
- Chronic Pain
  - Aversive
  - ↑ motivation for opioids
  - ↓ opioid reward

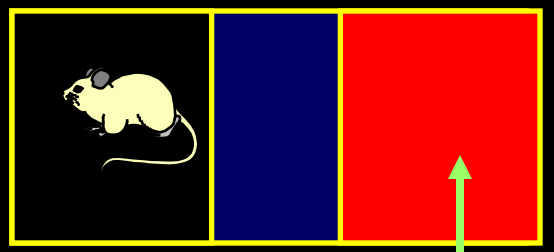
e.g. Hipolito et al
J Neurosci 2015

Ventral Tegmental Area

Critical for MOR Reward & Aversion



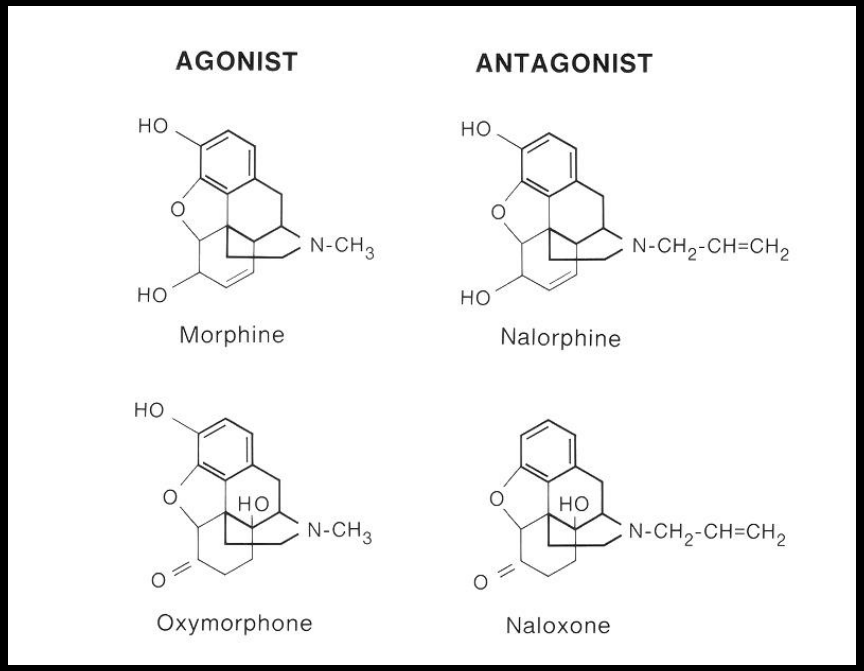
MOR antagonists

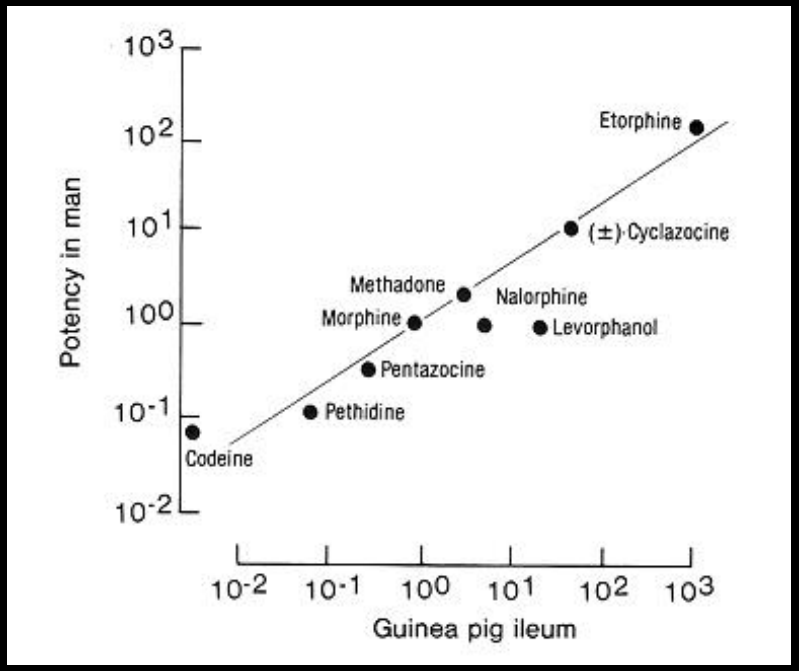


drug room

Can We Keep Analgesic Potency, Reduce Adverse Effects and Avoid Dependence?

The Mu (morphine) Opioid Receptor (MOR)



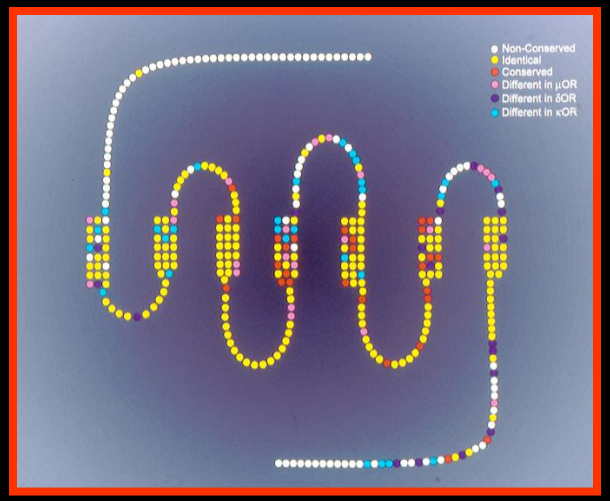


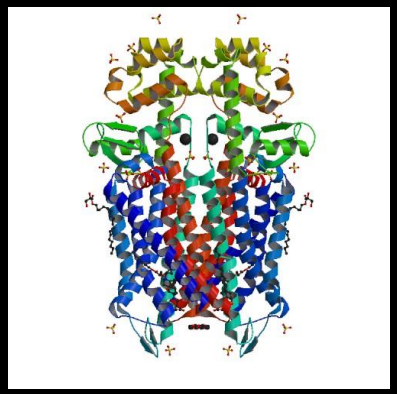
1970s, Snyder, Simon, Goldstein, Terenius

30 Years of Progress

Opioid family of 7TMD GPCRs (1990s)

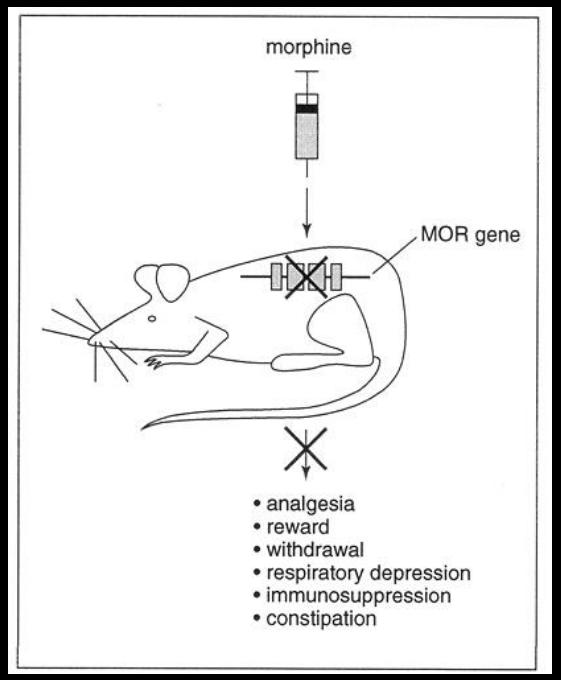
MOR
KOR
DOR
ORL





Brian Kobilka
Nature, 2012

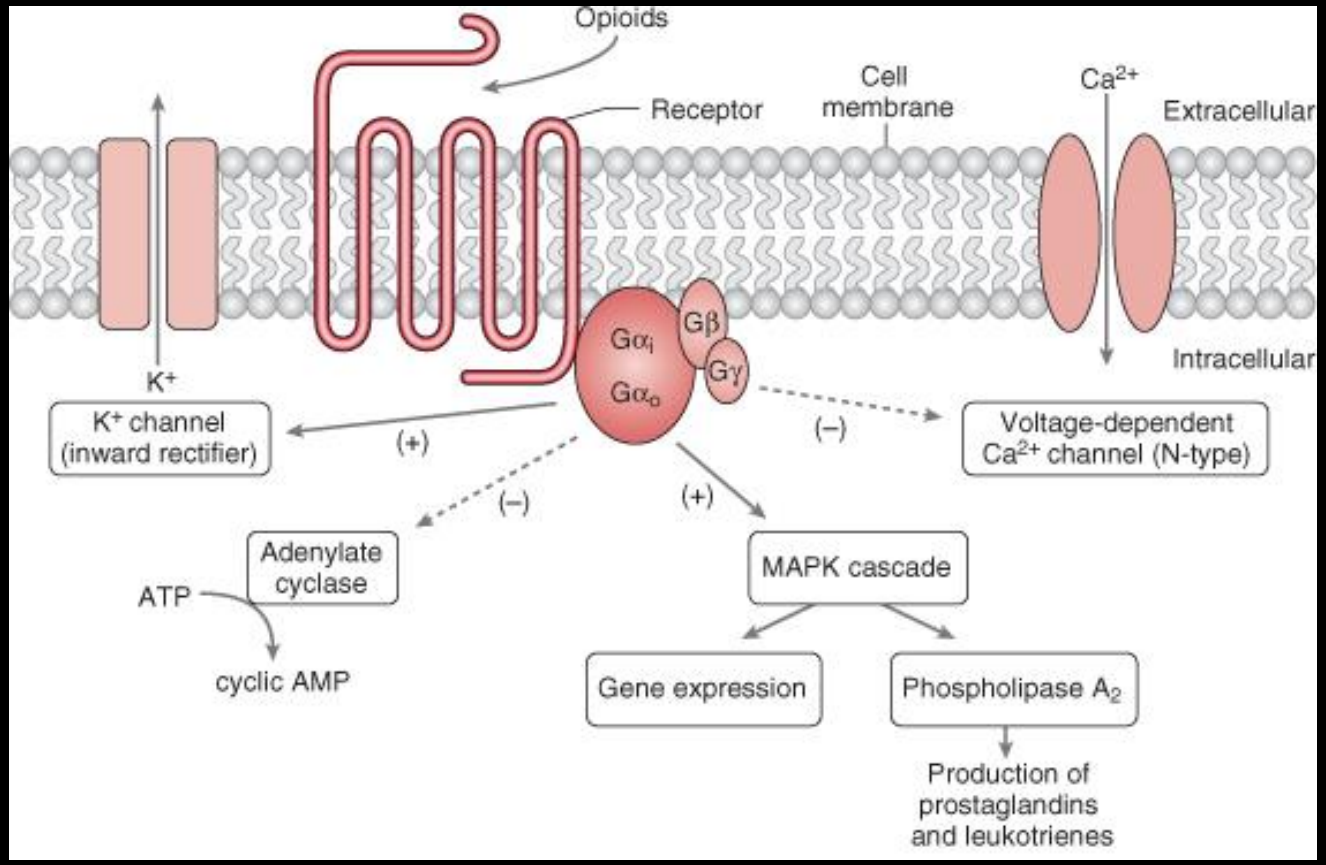
MOR KO



Kieffer TIPS, 1999

Canonical GPCR Signaling

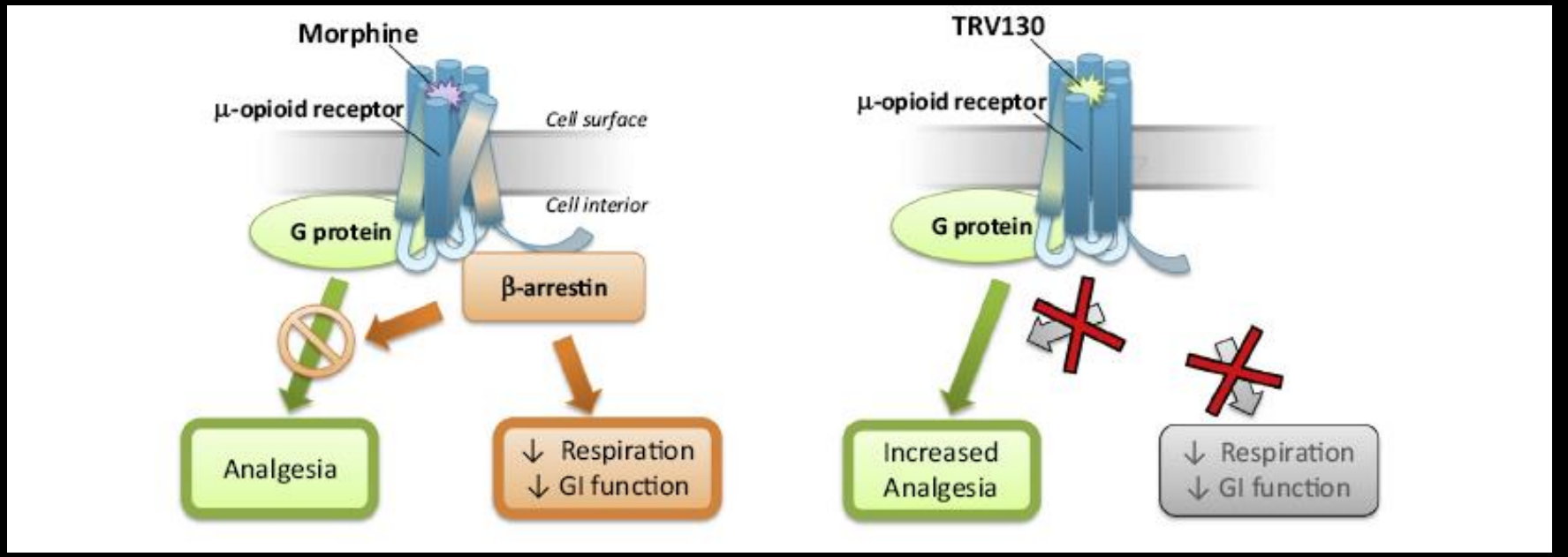
(controls synaptic function mediates analgesia)



Thanks Mark Schumacher

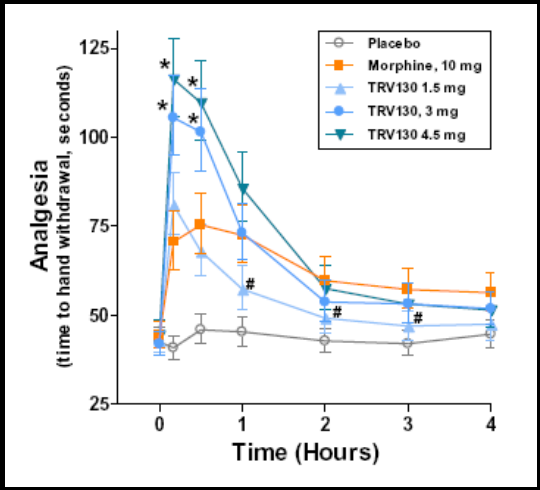
β-arrestin Signaling

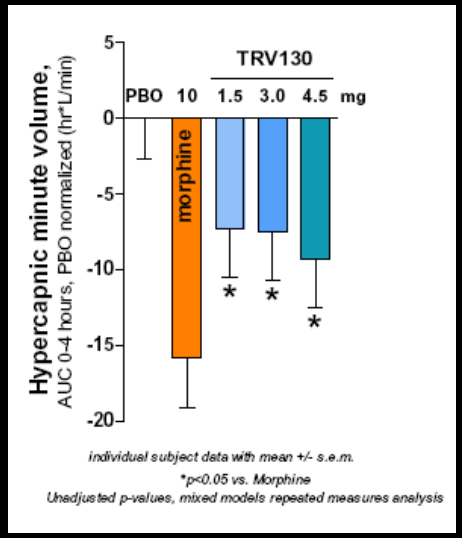
Specifically Enhances Respiratory Depression



Increasing G-protein Bias Reduces Respiratory Depression

Proof of Concept in Humans
Trevena Compound 130

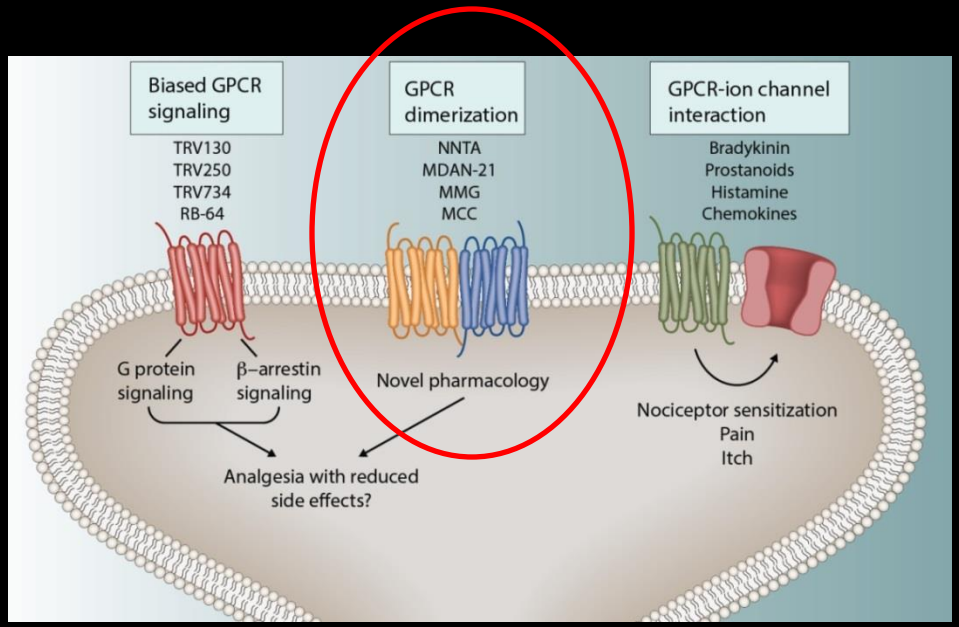




Soergel et al Pain 2014

MOR Protein-Protein Interaction

Interaction of different GPCRs can change signaling



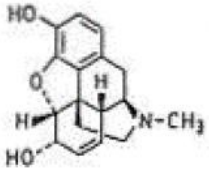
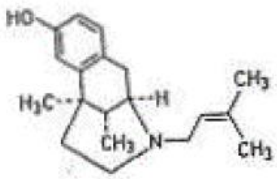
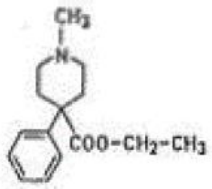
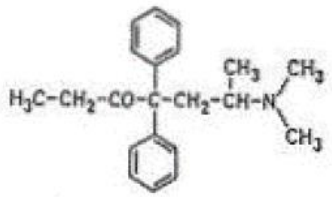
Clifford Woolf

- 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)

Where Do We Go From Here?

Multiple Opioid Molecules in Current Human Use for Analgesia

Chemical Classes of Opioids

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES
			
MORPHINE	PENTAZOCINE	MEPERIDINE	METHADONE
Rx EXAMPLES > morphine codeine hydrocodone* hydromorphone* levorphanol* oxycodone* oxymorphone* buprenorphine* nalbuphine butorphanol*	pentazocine diphenoxylate loperamide	meperidine fentanyl sufentanil alfentanil remifentanil	methadone propoxyphene

MOR/KOR

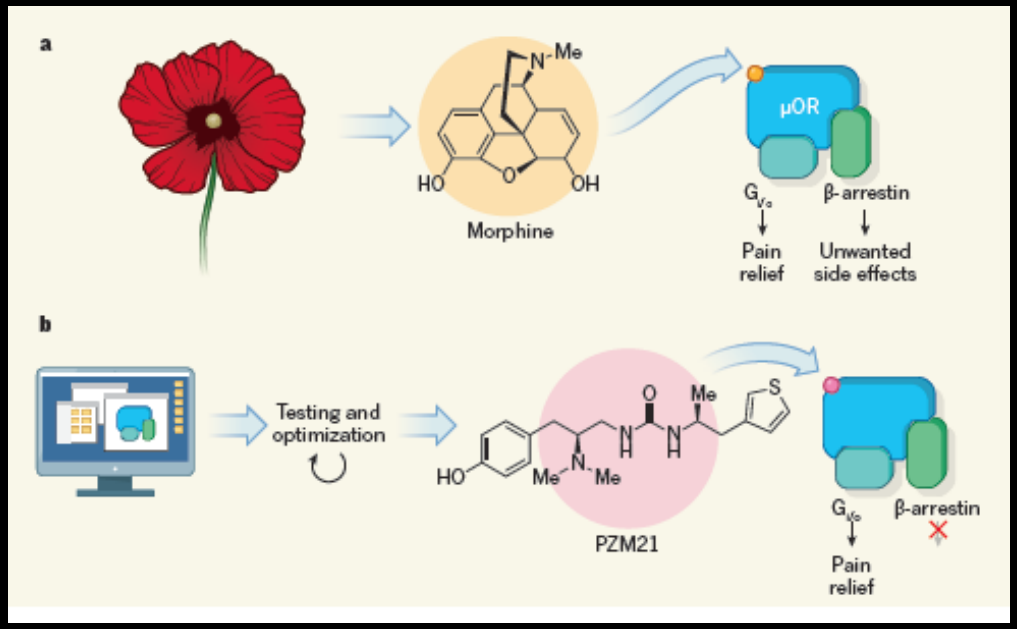
Courtesy of Dr. Jeffrey Fudin (FudinJ@gmail.com) Google

? relative efficacy, side effect profile, addictive potential

Re-examine Synthetic Opioids Effective in humans

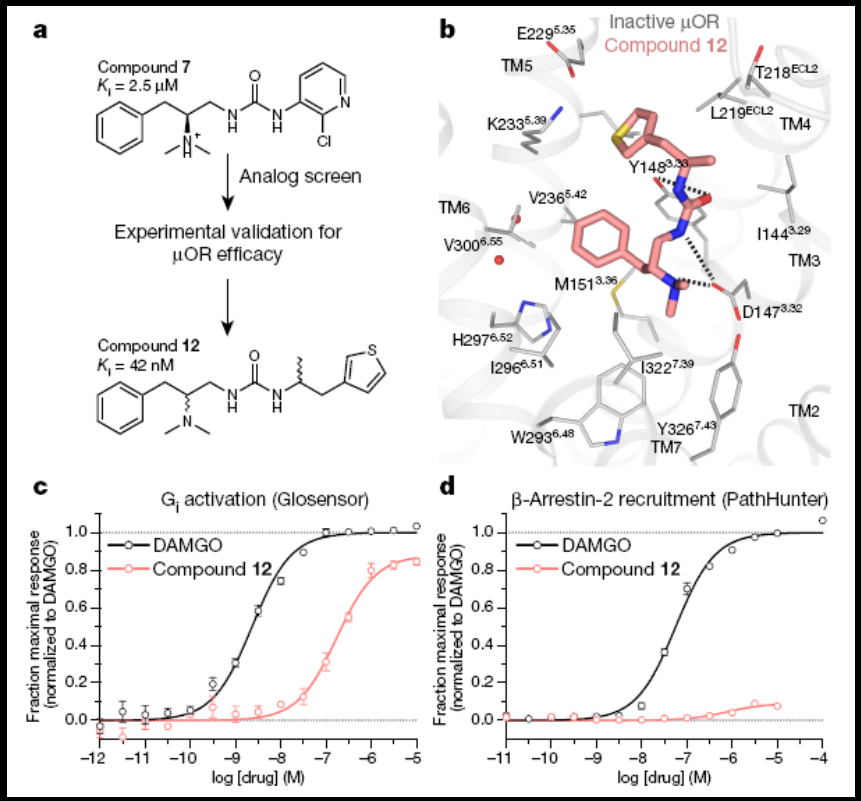
- In theory you could design drug to separately enhance or reduce any biological action
- Systems/Synaptic Physiology
  - Different actions at different nervous system targets
- Cell Biology/signaling:
  - Relative Bias
  - Combinatorial action at several GPCRs

Structure Based Discovery of Novel Opioids



Manglik et al Nature August 2016
Kieffer Nature 2016

Optimize for Desired Characteristics



Manglik et al
Nature 2016

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