Opioid Analgesics: Pathways to Addiction.

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One side of the story

- Pain of all types is undertreated in our society. The pediatric and geriatric populations are especially at risk for undertreatment. Physicians' fears of using opioid therapy, and the fears of other health professionals, contribute to this problem.

- Opioid analgesics are generally safe medications when prescribed with appropriate monitoring. There is very little if any evidence of organ damage from the long term therapeutic use of opioids. With appropriate titration and stable dosing, tolerance develops to most of the side effects of opioid therapy, including cognitive impairment. Constipation is the most common persistent side effect and should be managed prophylactically.

Use of opioid analgesics for the treatment of chronic noncancer pain - A consensus statement and guidelines from the Canadian Pain Society 1998

John Liebeskind 1935-1997
2) 2.7% of the population 12 and older in 03 used prescription psychotherapeutic medications nonmedically in the month prior to surveyed. This included 4.7 million using pain relievers (compares to 166,000 Heroin users).
3) Estimated 415,000 Americans received treatment for pain reliever abuse in the past year.
4) Past year abuse of Vicodin 3.0% among 8th-graders, 7.0 % among 10th-graders, and 9.7% among 12th-graders in 2006, (stable since '02). Despite a drop in past year abuse of OxyContin among 12th-graders in '06, abuse among 8th-graders nearly doubled since 2002 (1.3% in '02 - 2.6 % in '06)

*Data from the 2002, 2003 and 2004 National Surveys on Drug Use and Health*
MORPHINE, FENTANYL, ETORPHINE, HYDROCODONE, OXOCODONE, CODEINE, BUPRENORPHINE, HEROIN, METHADONE
(RARELY RECEPTOR SPECIFIC - Drugs are dirty)

ACTH, MSH
POMC
PROENKEPHALIN
PRODYNORPHIN
PROORPHANIN-FQ

Prohormone Convertases (PC’s)
CPE and PAM

ENDOMORPHINS?
MORPHINE?

δ µ K ORL-1

MORPHINE, FENTANYL, ETORPHINE, HYDROCODONE, OXOCODONE, CODEINE, BUPRENORPHINE, HEROIN, METHADONE
(RARELY RECEPTOR SPECIFIC - Drugs are dirty)
Fentanyl \textit{(epidural, Moscow Siege Gas)}

Morphine \textit{(surgery)}

Buprenorphine \textit{(addicts)}

Methadone \textit{(addicts)}

Oxy/hydrocodone \textit{(pain)}

Opioid Receptor selectivity

Agonist/Partial Agonists

Activity at other receptors (NMDA)

Rate of onset/duration*

Route of Administration

Dependency/tolerance

Activity at mu opioid receptors
Mu
Agonists: analgesia, constipation, reward, nausea, respiratory depression - gender specific
Antagonists: aversive*, prevent reward

Delta
Agonists: not-rewarding, weak analgesia, seizure-inducing
Antagonists: no obvious effects

Kappa
Agonists: aversive, hallucinogenic, analgesia
Antagonists: potential antidepressants/relapse

ORL-1
Agonists: Hyperalgesia* and block opioid analgesia
Antagonists: no obvious effects
Homologous recombination

Mu KO mice have no classical morphine effects (analgesia, respiratory depression, reward, immune modulation). No longer are alcohol, nicotine or THC rewarding! Reviews by Kieffer’s group *Curr Opin Neurobiology*, 2004
BUPRENORPHINE (κ antagonist, μ/δ /ORL-1 partial agonist) HAS NO ANALGESIC EFFICACY IN MU RECEPTOR KO MICE
BUPRENORPHINE HAS INCREASED ANALGESIC EFFICACY IN ORL-1 RECEPTOR KO MICE

ORL-1 Receptor KO Mice Courtesy of Hiroshi Takeshima, J-113397 Ivy Carroll
ACUTE OPIOID EFFECTS
Analgesia, Antitussive
Constipation, Euphoria,
Nausea*, Calming*
Decreased Respiration

WITHDRAWAL
oxycontin, vicodin
heroin, morphine

ACUTE OPIOID EFFECTS
Analgesia, Antitussive
Constipation, Euphoria,
Nausea*, Calming*
Decreased Respiration

CHRONIC OPIOID EFFECTS
Tolerance to acute effects,
normalization of physiology &
psychology in presence of drug

Hyperalgesia, Dysphoria, Anxiety,
Sweating, Runny nose, Chills,
Diarrhea, Nausea

drug/action associations

molecular, cellular
and behavioral
adaptations

relapse
MOOD

PAIN

GENES

MOOD

PEERS

stress

withdrawal

chance opponent processes

PAIN

CHRONIC

T.

GENES

MOOD

PEERS
Liking
Taking the drug feels good - is rewarding and/or satisfies the reasons for taking the drug.

Wanting
The drug is desired for its remembered effects (analgesia, rewarding, calming, combating withdrawal, physiologic effect). In extreme cases this can become craving

Habit
Taking the drug as a result of automatic response to a stimulus - after eating - smoke Stressed or anxious - drink or take a vicodin
Reward

Activation of Mesolimbic Dopamine system

CB-1 and NK-1 receptor activation by endogenous ligands

Morphine/Heroin
Mu Opioid Receptors

THC → CB-1
Nicotine → ACh
Alcohol → GABA/NMDA

Kappa receptor activation

Antagonism Naloxone

AVERSION

Mu receptor activation by endogenous opioids

Activation of Mesolimbic Dopamine system

REWARD (CPP)

SYSTEM INTERDEPENDANCE FOR REWARD
Methadone Maintained Patients are Hyperalgesic in Cold Pressor Test.

<table>
<thead>
<tr>
<th>Time in ice-cold water (seconds)</th>
<th>Pain Detection</th>
<th>Pain Tolerance</th>
<th>Pain Detection</th>
<th>Pain Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>*</td>
<td>***</td>
<td>*</td>
<td>***</td>
</tr>
<tr>
<td>Methadone Maintained</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Time in ice-cold water (seconds):

- **Control**: *p=0.023***
- **Methadone Maintained**: ***p<0.0001***
- **Pain Detection**: *p<0.0001***
- **Pain Tolerance**: ***p<0.0001***

Slide kindly provided by Walter Ling, UCLA
Hyperalgesia Following Chronic Morphine (TAD)-Pain Paradigm Specific

A

Baseline tail withdrawal latency (s)

saline control chronic morphine

B

Hot plate latency (s)

saline control chronic morphine

150’ post-morphine
Forskolin-Stimulated cAMP Accumulation Following Acute and Chronic Opioid Treatment - Cyclase Supersensitivity

Acute: opioid + forskolin

Chronic: 24h opioid then wash out + forskolin

[Graph showing forskolin-stimulated cAMP accumulation following acute and chronic opioid treatment.]

- Control
- 0.1nM
- 1nM
- 10nM
- 100nM [DAMGO]
MU OPIOID RECEPTOR COMPLEX (diversity)

COMPLEX DETERMINATION
1. Cellular Proteome
2. Mu receptor alternative splicing
3. Cellular Compartment
4. Oligomerization (Hetro/Homo)
5. The Receptor Activation State
6. History of Receptor/Environment

REGULATION 5+proteins
TRAFFICKING 2+proteins
SIGNALING 8+proteins

100+proteins
100+proteins
100+proteins

Arrestins/G-proteins/GRK’s/Src’s/RGS’s
FLAG & MOR-C12 STAINING OF 293-CELLS TRANSFECTED WITH MU RECEPTORS

CONTROL
ETORPHINE
(100nM)
DAMGO
(100nM)
ETOR/NALOX
(100nM/10µM)
MORPHINE
(20µM)
Agonist Binding

Re-sensitized Receptor

Recycling (µ)

Lysosomes Downregulation (δ)

Endosome

Dephosphorylation

Uncoating of CCV and Fusion with Endosome

Severing of CCV by Dynamin

Recruitment of Clathrin

GRK 2 (1-6) Phosphorylation

Beta-arrestin 1-2 (cSrc)

Desensitized Receptor

Signaling

Signaling

Signaling

GRK 2 (1-6) Phosphorylation

Beta-arrestin 1-2 (cSrc)
Mouse Dorsal Root Ganglion Cells
Express mu and alpha2A receptors

Morphine
(No internalization)

DAMGO
/Internalization

-Blocking internalization with the P38 inhibitor PD169316 blocks calcium signaling desensitization via DAMGO but not morphine
- The alpha 2A receptor internalizes with DAMGO treatment - blocked by PD169316

Tracy Xie CSORDA Lab 2006, submitted
Clonidine and DAMGO but not morphine induce both mu and alpha2A internalization and desensitization.
P38 inhibition blocks mu internalization but not Clonidine-induced alpha2A internalization and desensitization.

Summary

- Functional implications of mu and Alpha2A adrenergic association in endogenously expressing nociceptive neurons
- Mu agonist specific cross-desensitization of Alpha2A adrenergic signaling
Role of Opioid System in Habit and Goal-Directed Behaviors

Mu opiate receptor knockout mice.
- Lack reward-directed behaviors to many rewarding drugs
- Phenotype of sibling response to mother absence

Maidment and Balleine Labs CSORDA 2006
Enkephalin knockout mice.

Instrumental Acquisition

Specific satiety - consumption test

Devaluation - extinction test

Devaluation - Punishment test

Sugar piles up in food tray in Enk-KO trials
Summary

**Mu** -/- appear to have a problem with retrieving reward value: They are sensitive to changes in value but are unable to retrieve changes in a test of free recall but can when the outcome is delivered.

**pENK** -/- are unable to control their actions when faced with lack of salience. They appear to have a specific problem with goal-directed actions. Performance is likely controlled by a stimulus-response process and is habitual.
WITHDRAWAL
Symptom alleviation NK-1 antagonist hyperalgesia

1) +NK-1/CB-1 antagonist
2) Slow on and off rate +/-
3) Partial agonist - safety

REWARD/ANALGESIA

Kappa antagonists? (JD-Tic)

PLASTICITY
ENVIRONMENT
DRUG ACCESS

Adaptive Changes. Tolerance. Salience for rewards likely disrupted
Partial Agonists?
Mu-agonists that show selective signaling and trafficking

WITHDRAWAL
Symptom alleviation NK-1 antagonist hyperalgesia