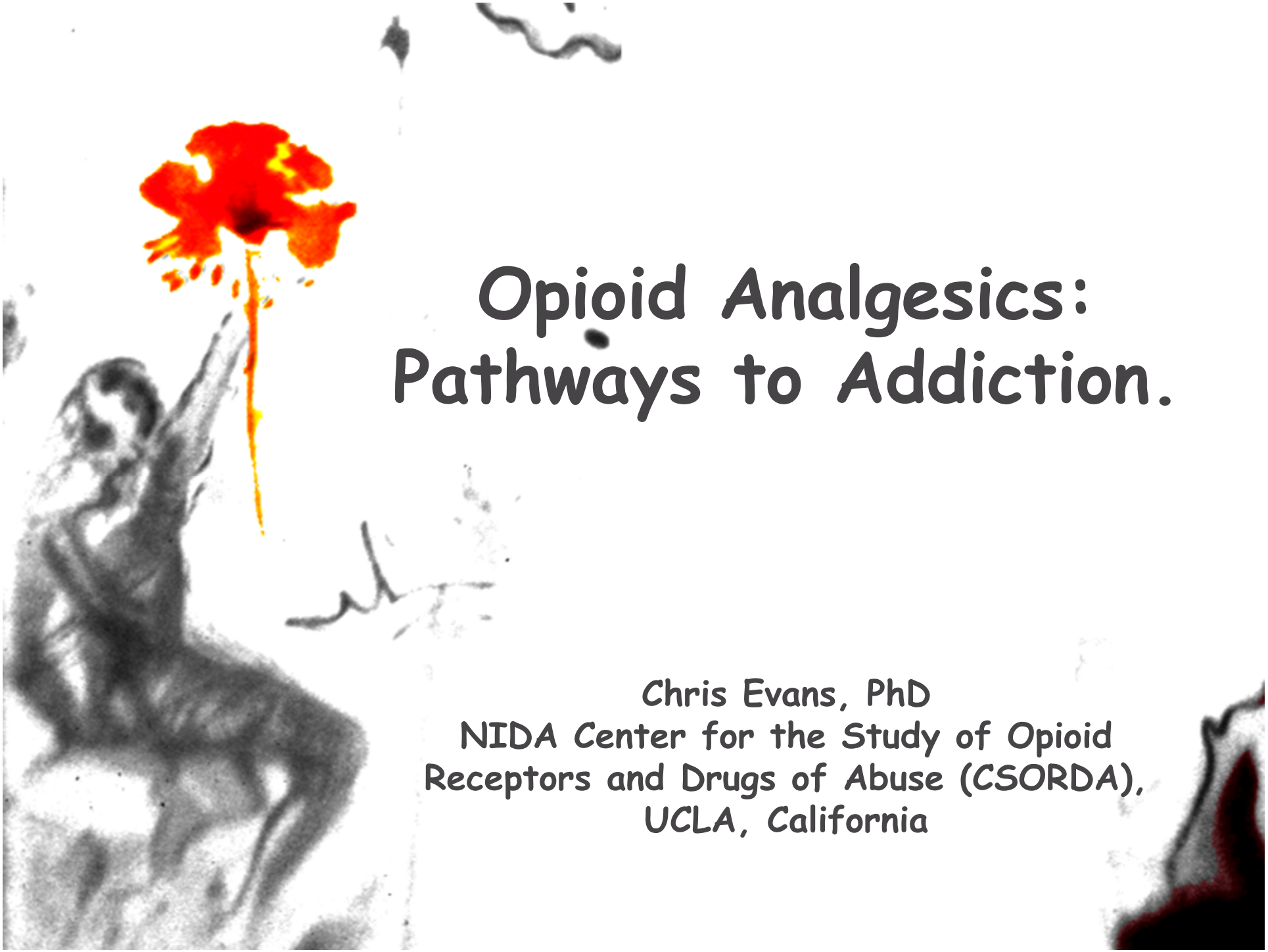


Opioid Analgesics: Pathways to Addiction.

Chris Evans, PhD
NIDA Center for the Study of Opioid Receptors and Drugs of Abuse (CSORDA), UCLA, California

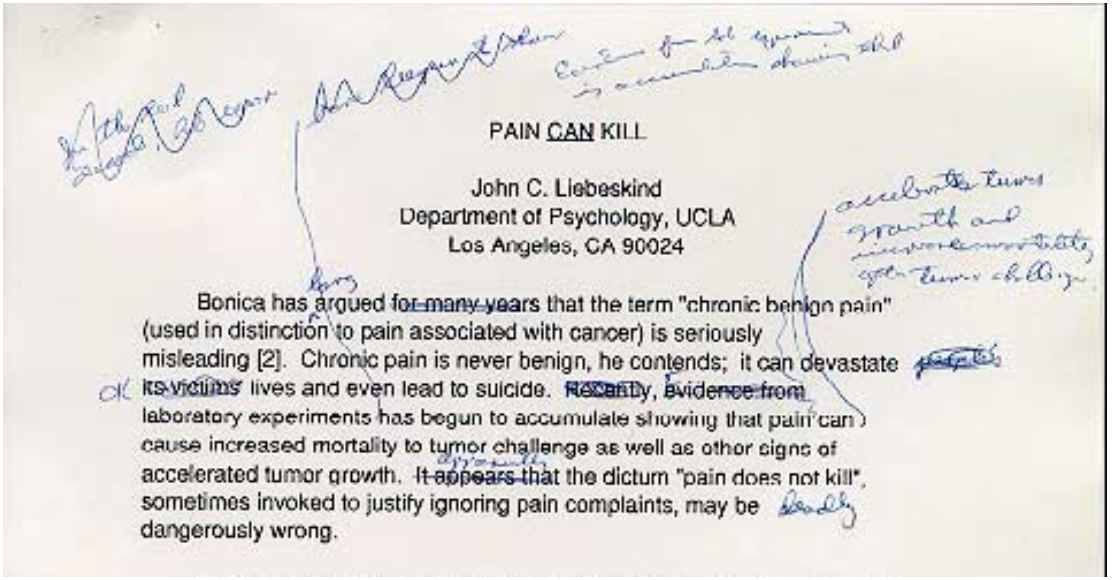
One side of the story

- 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



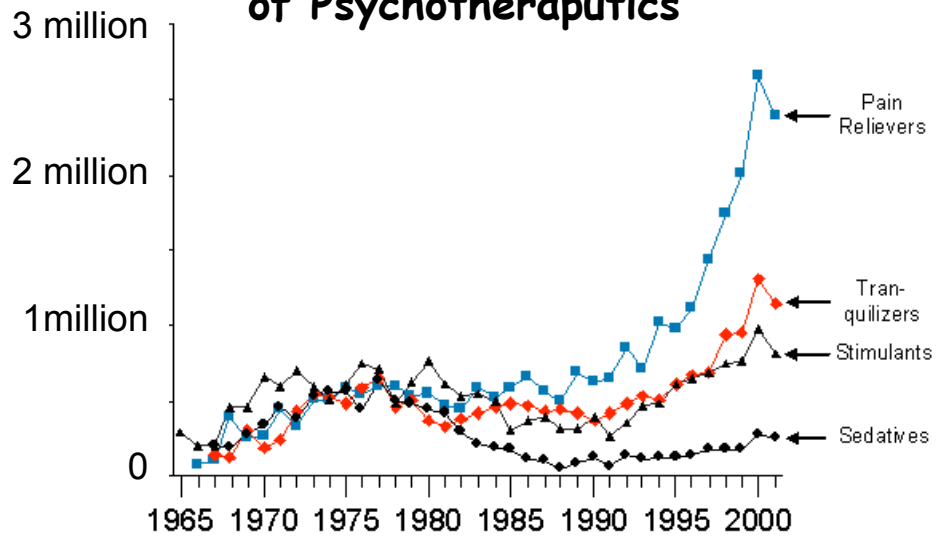
PAIN CAN KILL

John C. Liebeskind
Department of Psychology, UCLA
Los Angeles, CA 90024

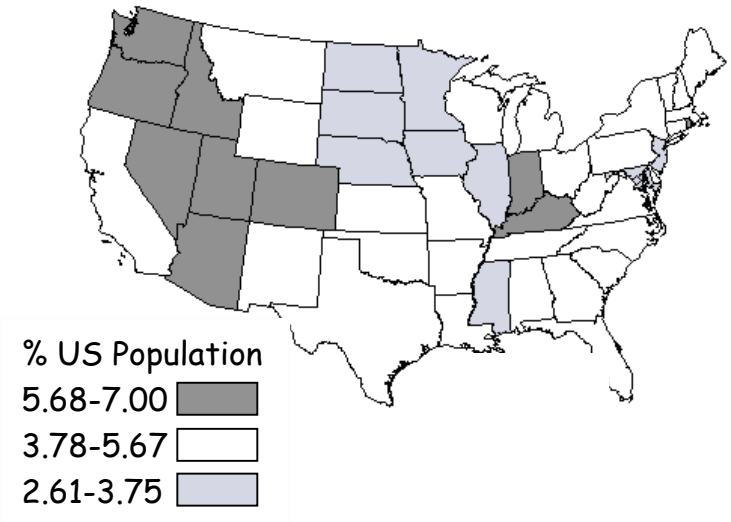
Bonica has argued for many years that the term "chronic benign pain" (used in distinction to pain associated with cancer) is seriously misleading [2]. Chronic pain is never benign, he contends; it can devastate its victims' lives and even lead to suicide. Recently, evidence from laboratory experiments has begun to accumulate showing that pain can cause increased mortality to tumor challenge as well as other signs of accelerated tumor growth. It appears that the dictum "pain does not kill", sometimes invoked to justify ignoring pain complaints, may be dangerously wrong.

The Other Side

Nonmedical New Users of Psychotheraputics



Past Year Nonmedical Use of Pain Relievers (% use 12 or Older, 02-04)



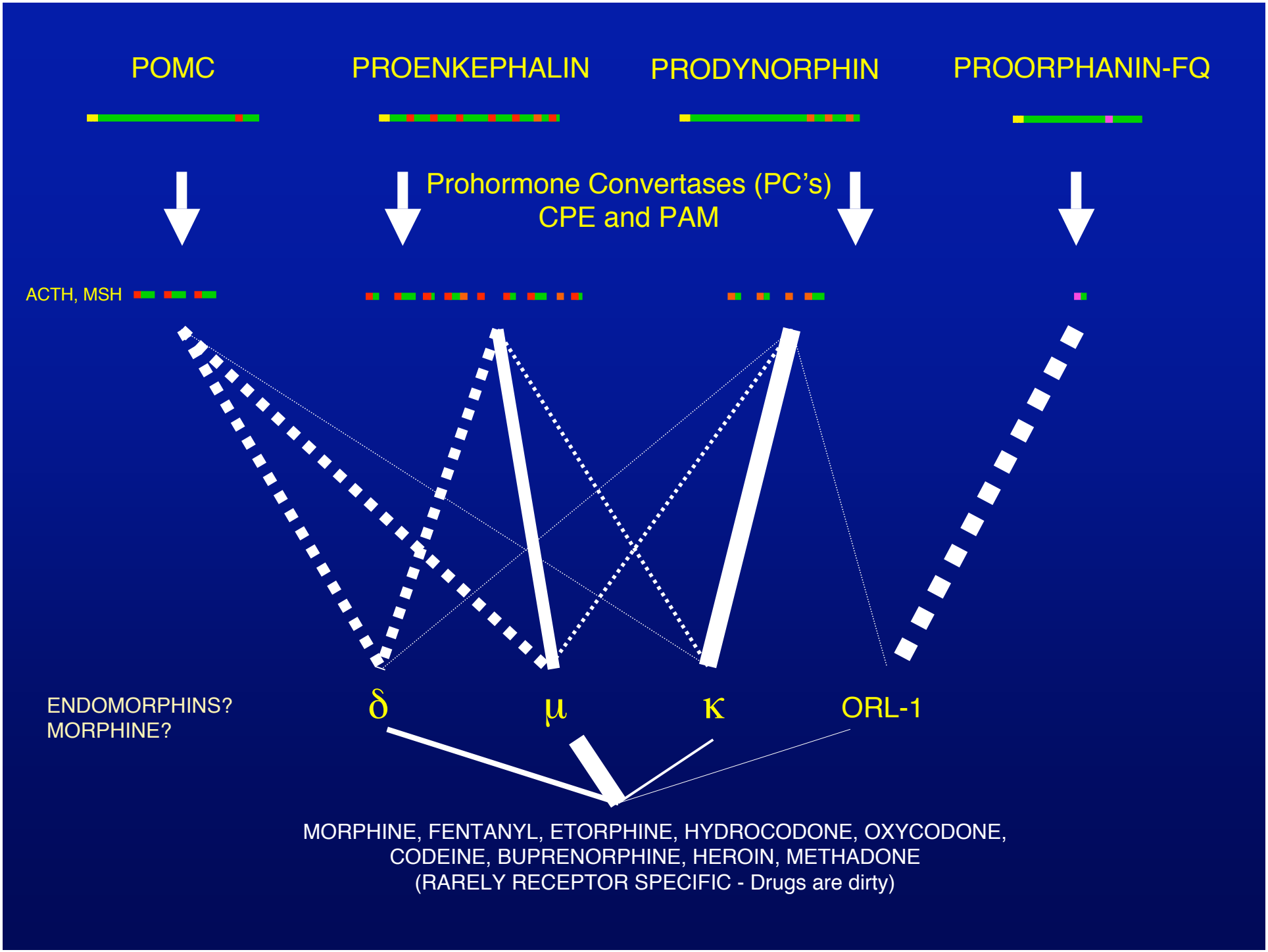
1) New Nonmedical Prescription Pain Reliever users Outnumbered New Marijuana Users (2002-2004)

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).

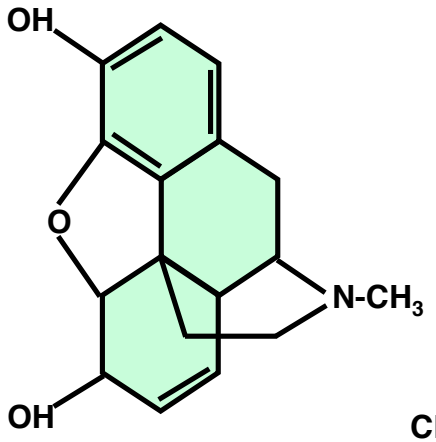
3) Estimated 415,000 Americans received treatment for pain reliever abuse in the past year.

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)

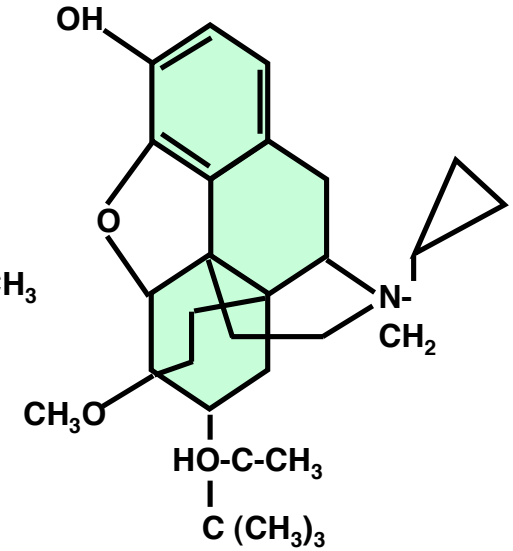
Data from the 2002, 2003 and 2004 National Surveys on Drug Use and Health


POMC
PROENKEPHALIN
PRODYNORPHIN
PROORPHANIN-FQ
Prohormone Convertases (PC's)
CPE and PAM
ACTH, MSH
ENDOMORPHINS?
MORPHINE?
δ
μ
κ
ORL-1
MORPHINE, FENTANYL, ETORPHINE, HYDROCODONE, OXYCODONE,
CODEINE, BUPRENORPHINE, HEROIN, METHADONE
(RARELY RECEPTOR SPECIFIC - Drugs are dirty)

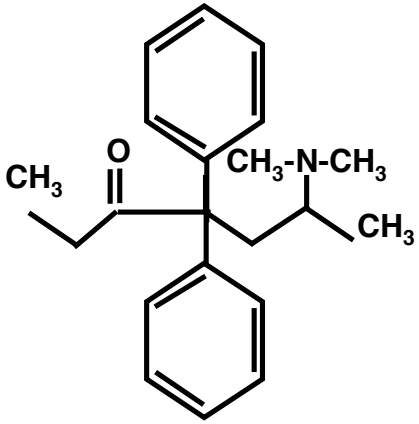
Morphine *(surgery)*



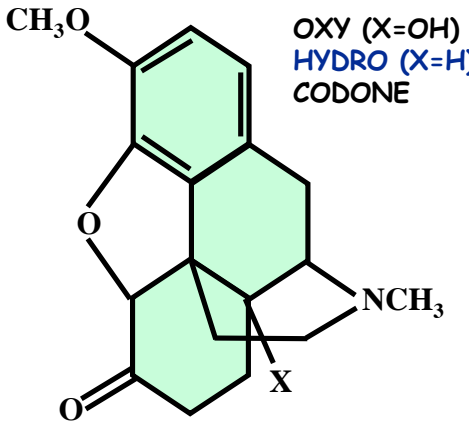
Buprenorphine *(addicts)*



Methadone *(addicts)*



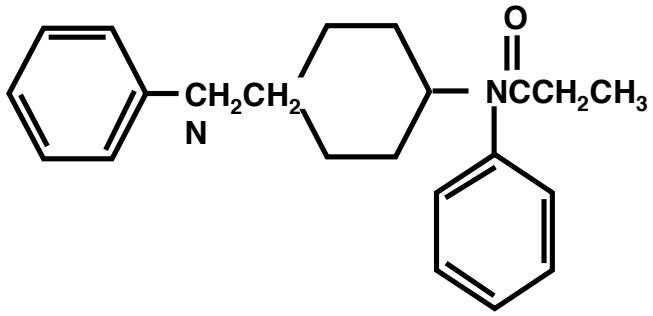
Oxy/hydrocodone *(pain)*



OXY (X=OH)
HYDRO (X=H)
CODONE

PERCOSET
PERCODAN OXYCODONE
OXYCONTIN
VICODIN HYDROCODONE

Fentanyl *(epidural, Moscow Siege Gas)*



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

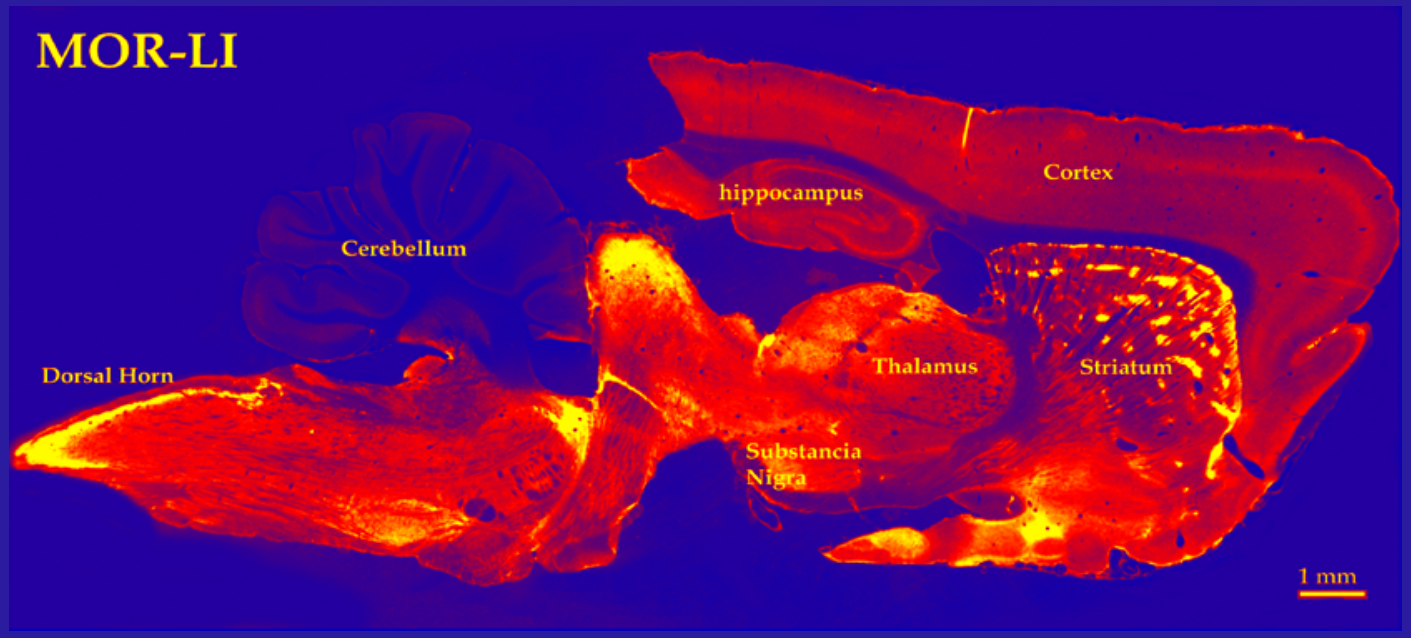
Agonists: aversive, hallucinogenic, analgesia

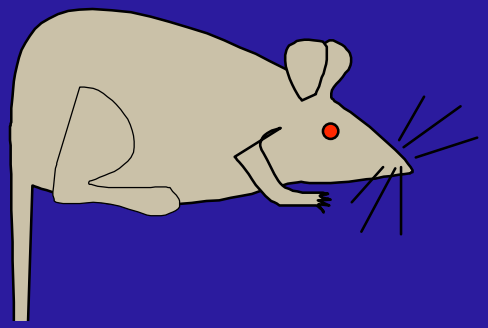
Antagonists: potential antidepressants/relapse

ORL-1

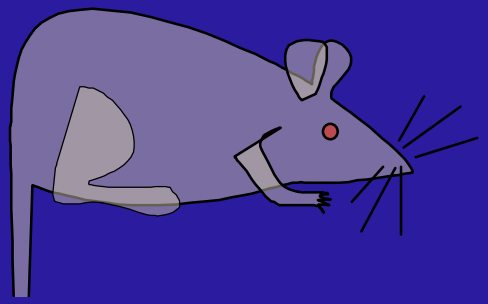
Agonists: Hyperalgesia* and block opioid analgesia

Antagonists: no obvious effects



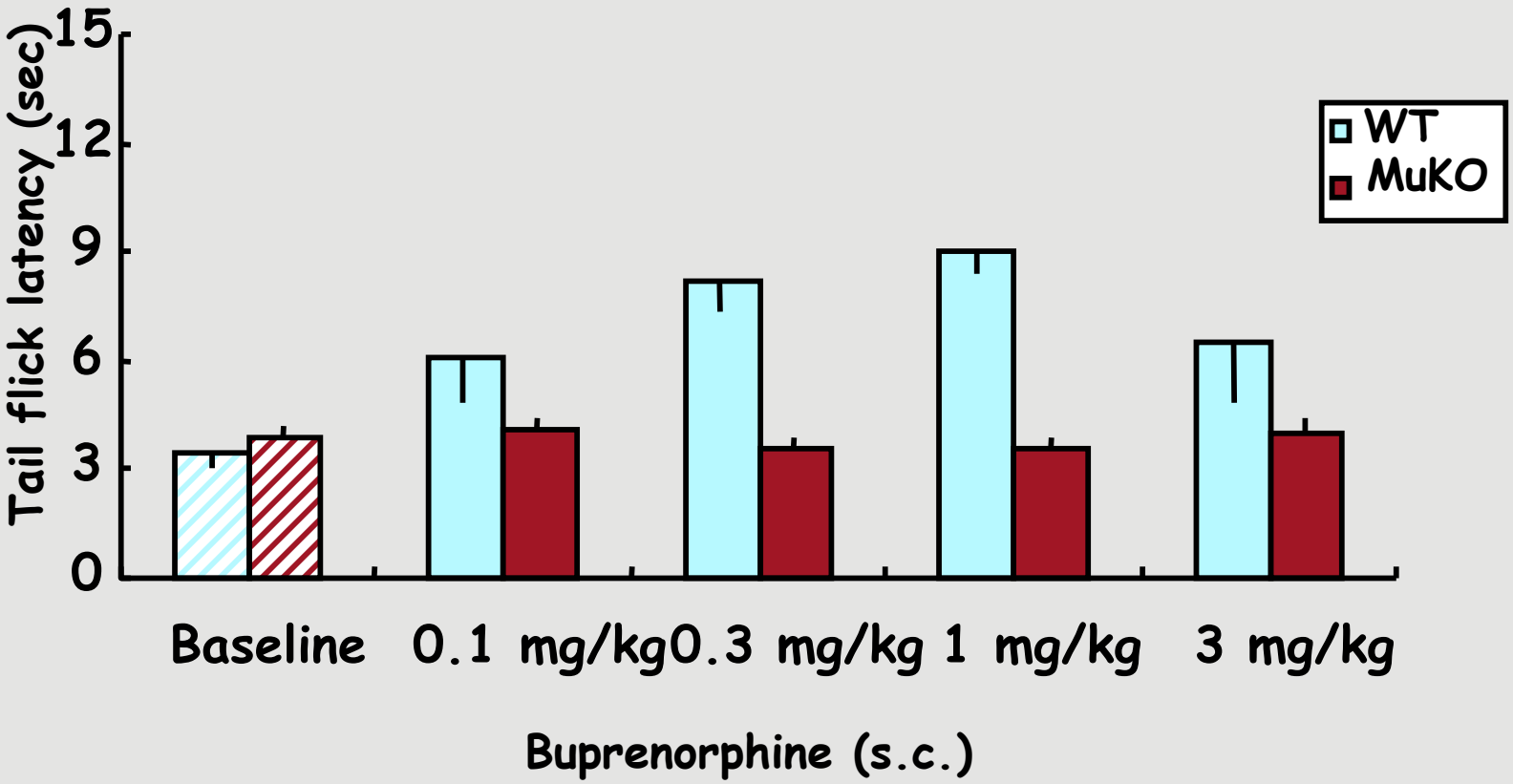


Homologous recombination

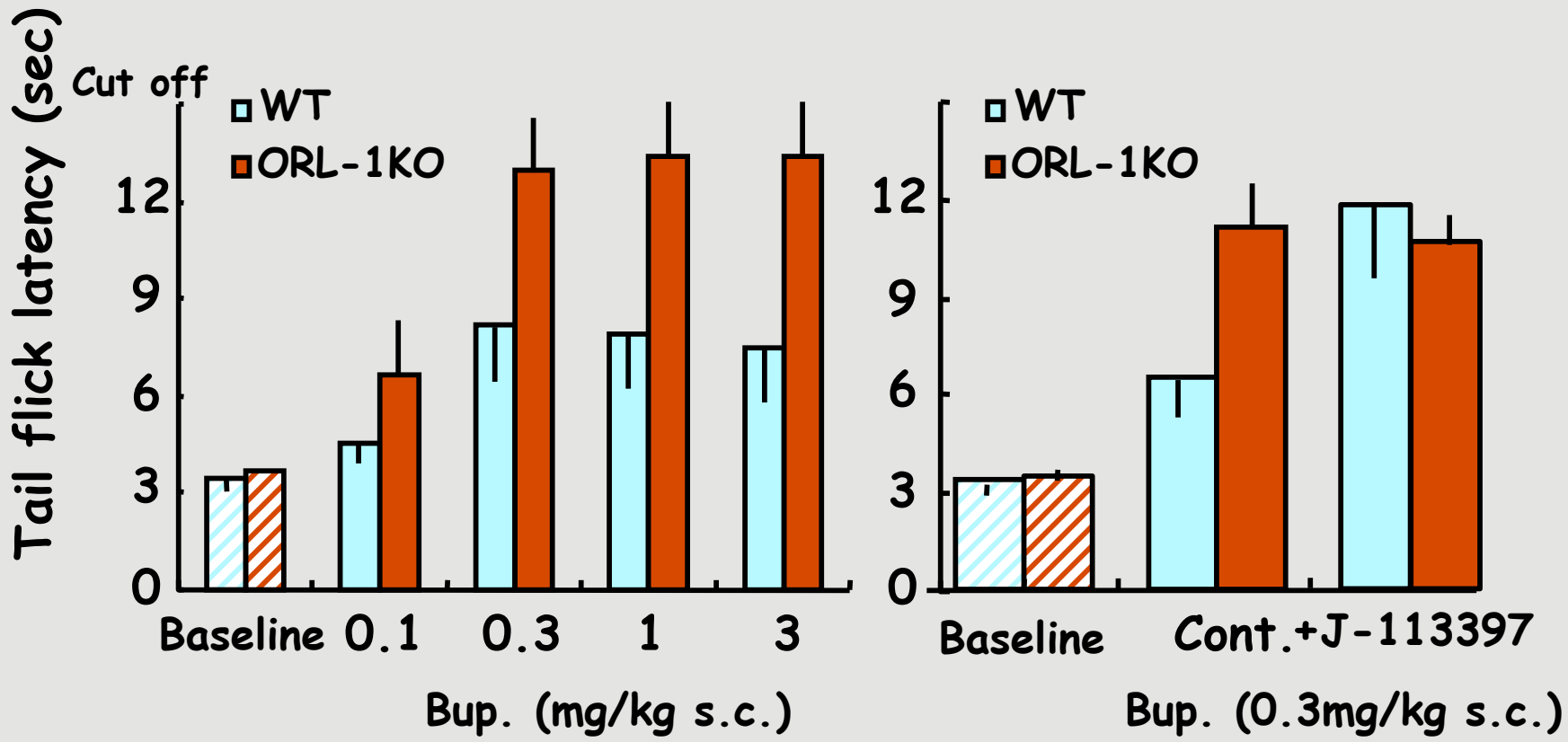


Mu KO mice have no classical morphine effects (analgesia, respiratory depression, reward, immune modulation). No longer are alcohol, nicotine or THC rewarding! Reviews by Kieffer's group Curr Opin Neurobiology, 2004

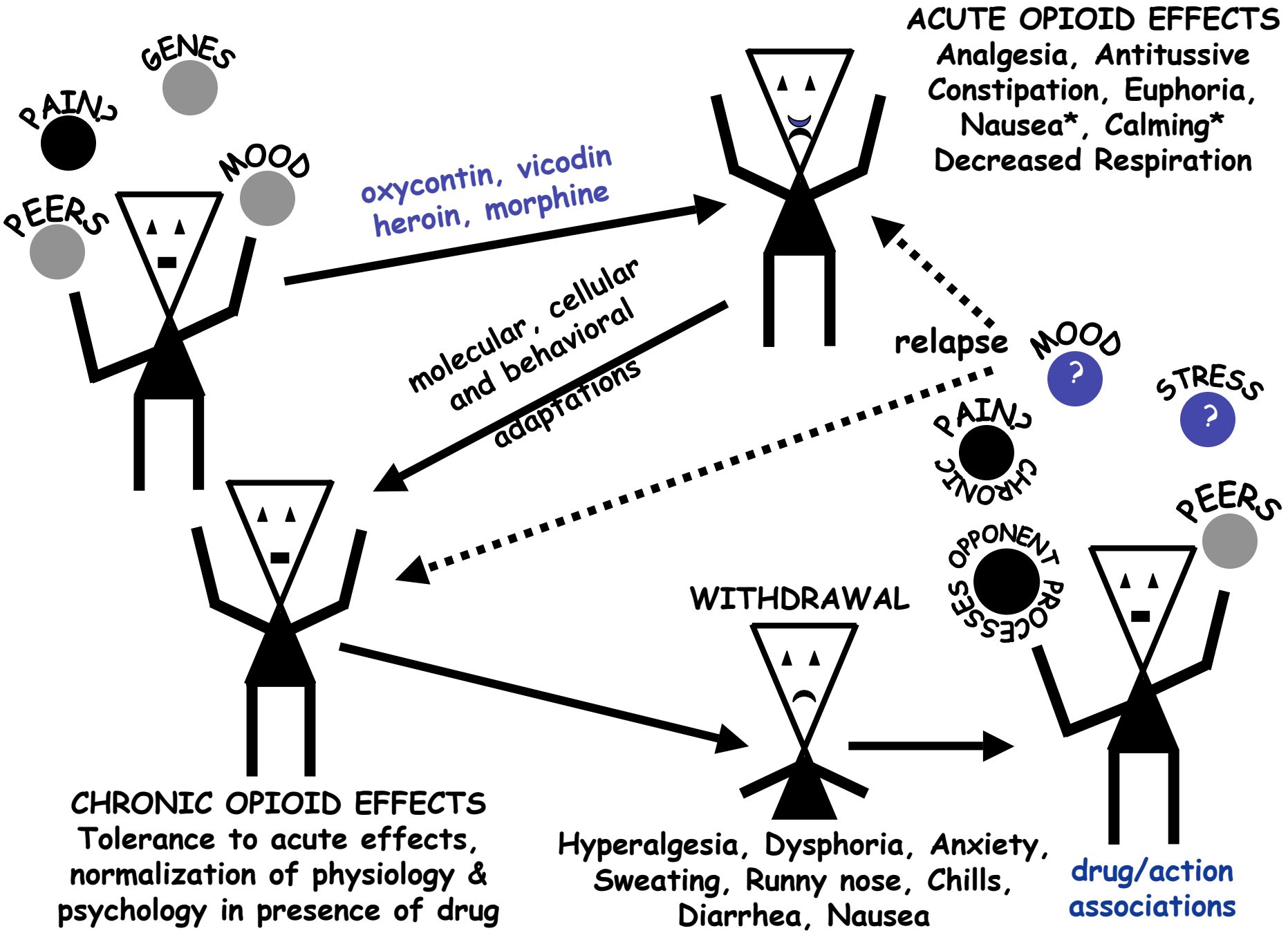
BUPRENORPHINE (κ antagonist, μ/δ /ORL-1 partial agonist) HAS NO ANALGESIC EFFICACY IN MU RECEPTOR KO MICE

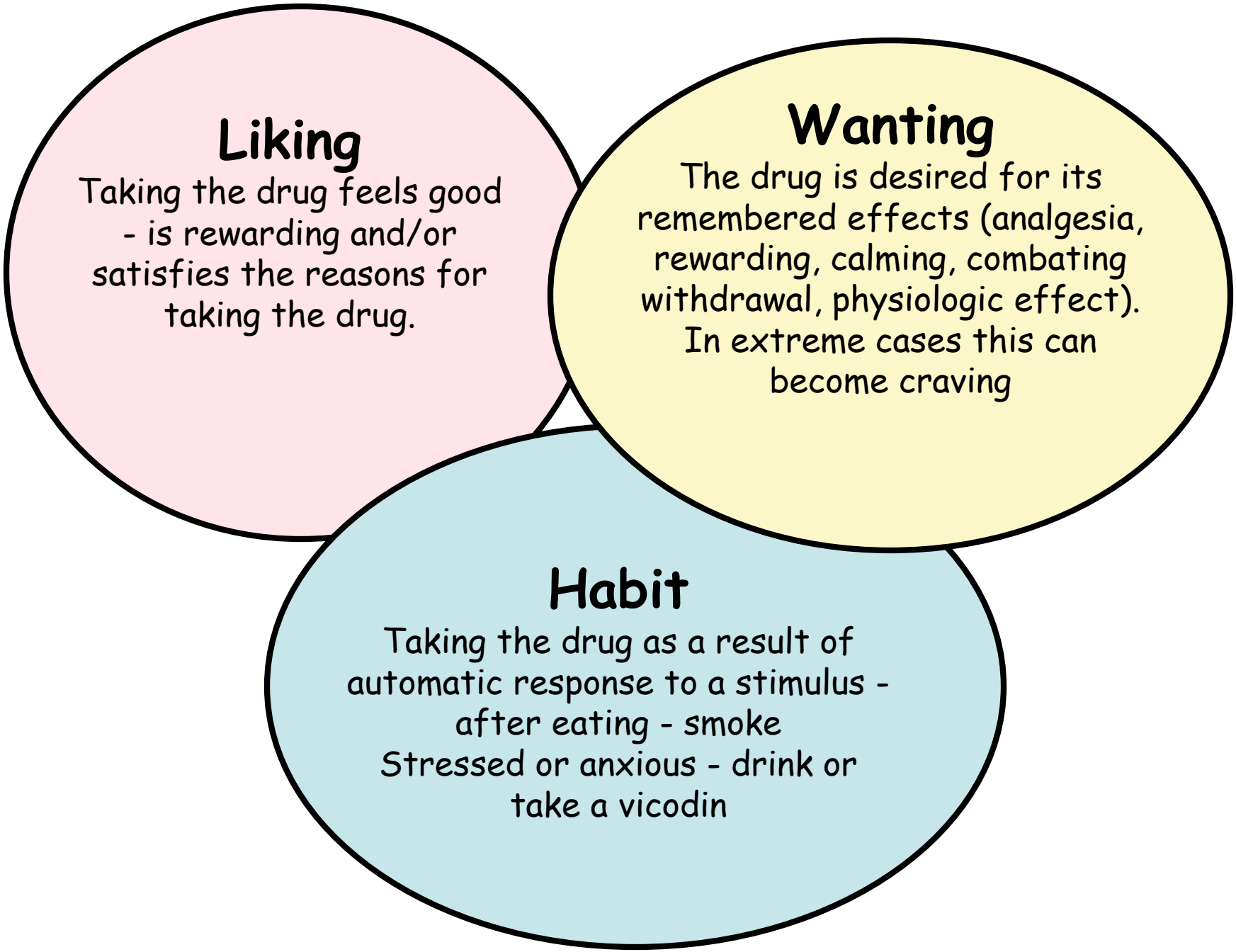


BUPRENORPHINE HAS INCREASED ANALGESIC EFFICACY IN ORL-1 RECEPTOR KO MICE

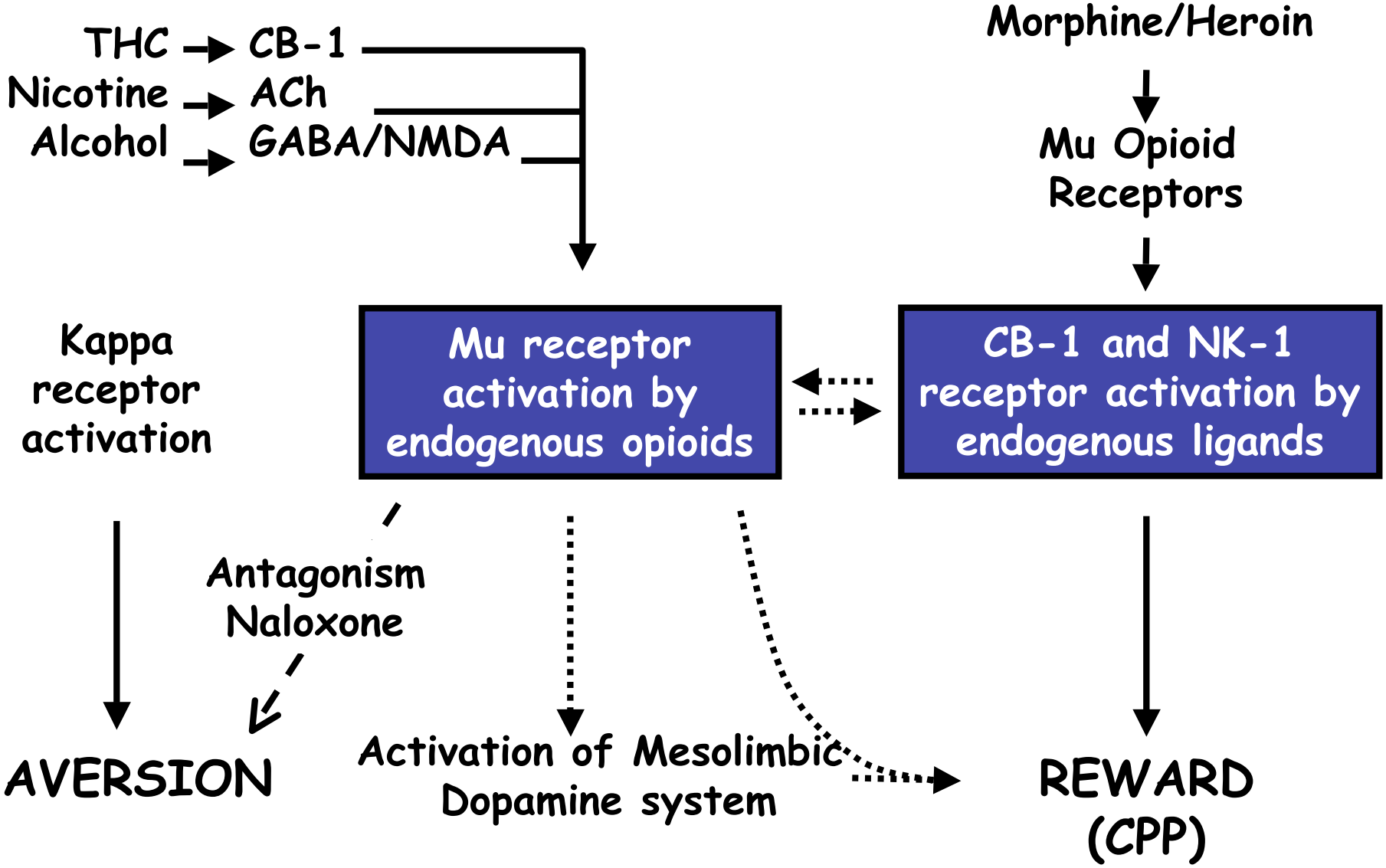


ORL-1 Receptor KO Mice Courtesy of Hiroshi Takeshima, J-113397 Ivy Carroll

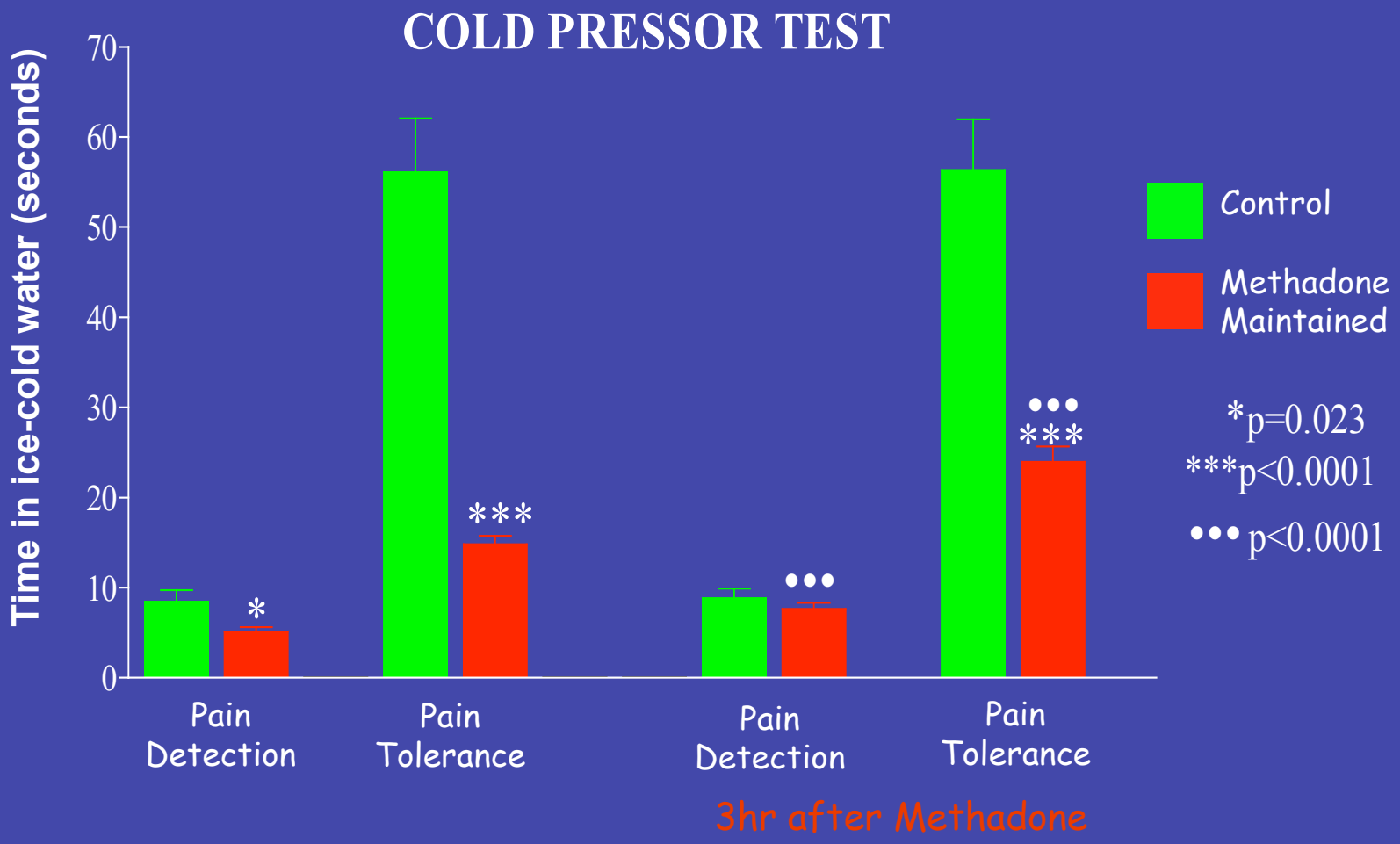

GENES
PAIN
MOOD
PEERS
oxycontin, vicodin
heroin, morphine
ACUTE OPIOID EFFECTS
Analgesia, Antitussive
Constipation, Euphoria,
Nausea*, Calming*
Decreased Respiration
molecular, cellular
and behavioral
adaptations
relapse
MOOD
?
STRESS
?
PAIN
CHRONIC
OPPONENT PROCESSES
PEERS
WITHDRAWAL
CHRONIC OPIOID 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


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

SYSTEM INTERDEPENDANCE FOR REWARD

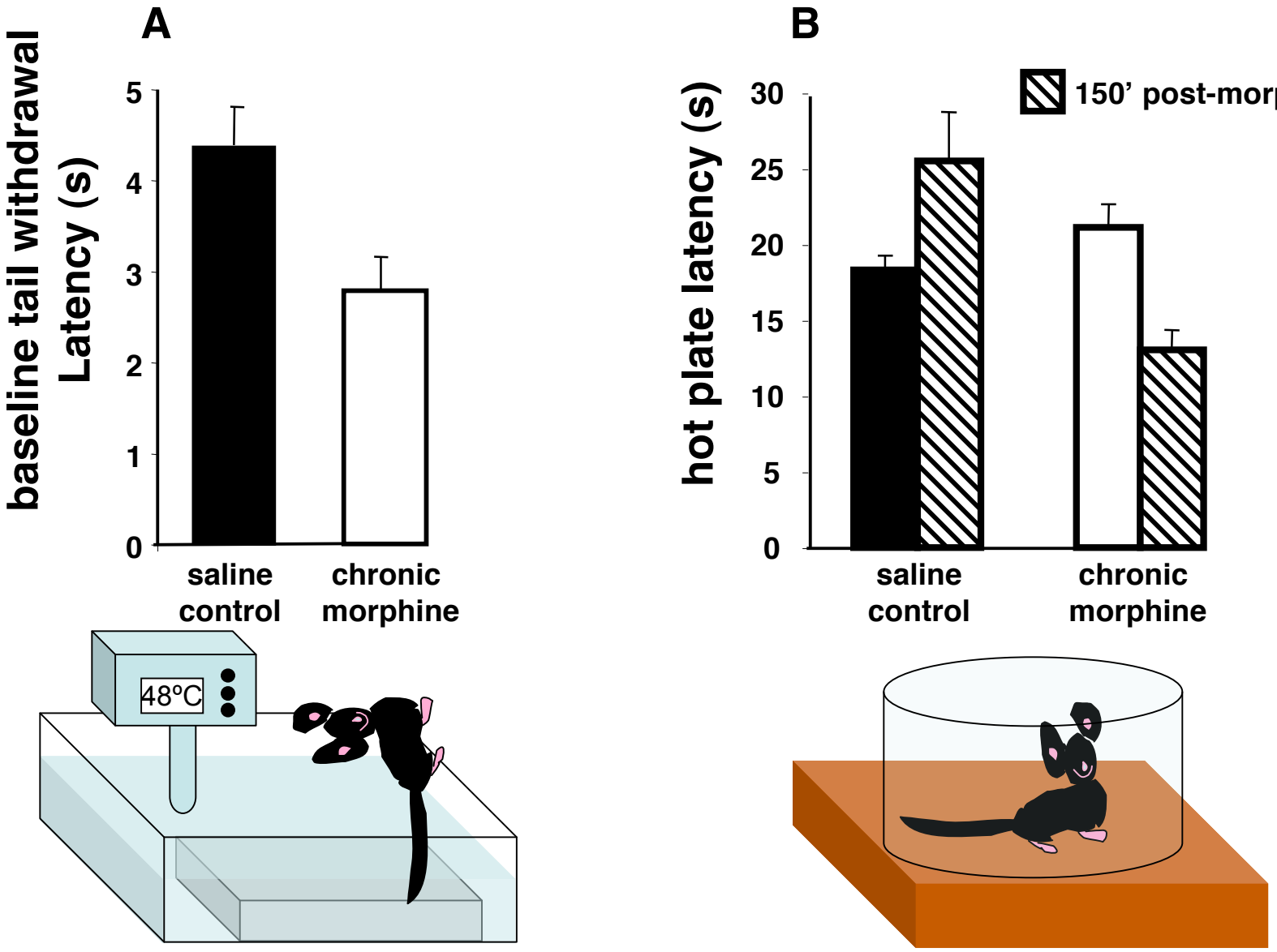


Methadone Maintained Patients are Hyperalgesic in Cold Pressor Test.

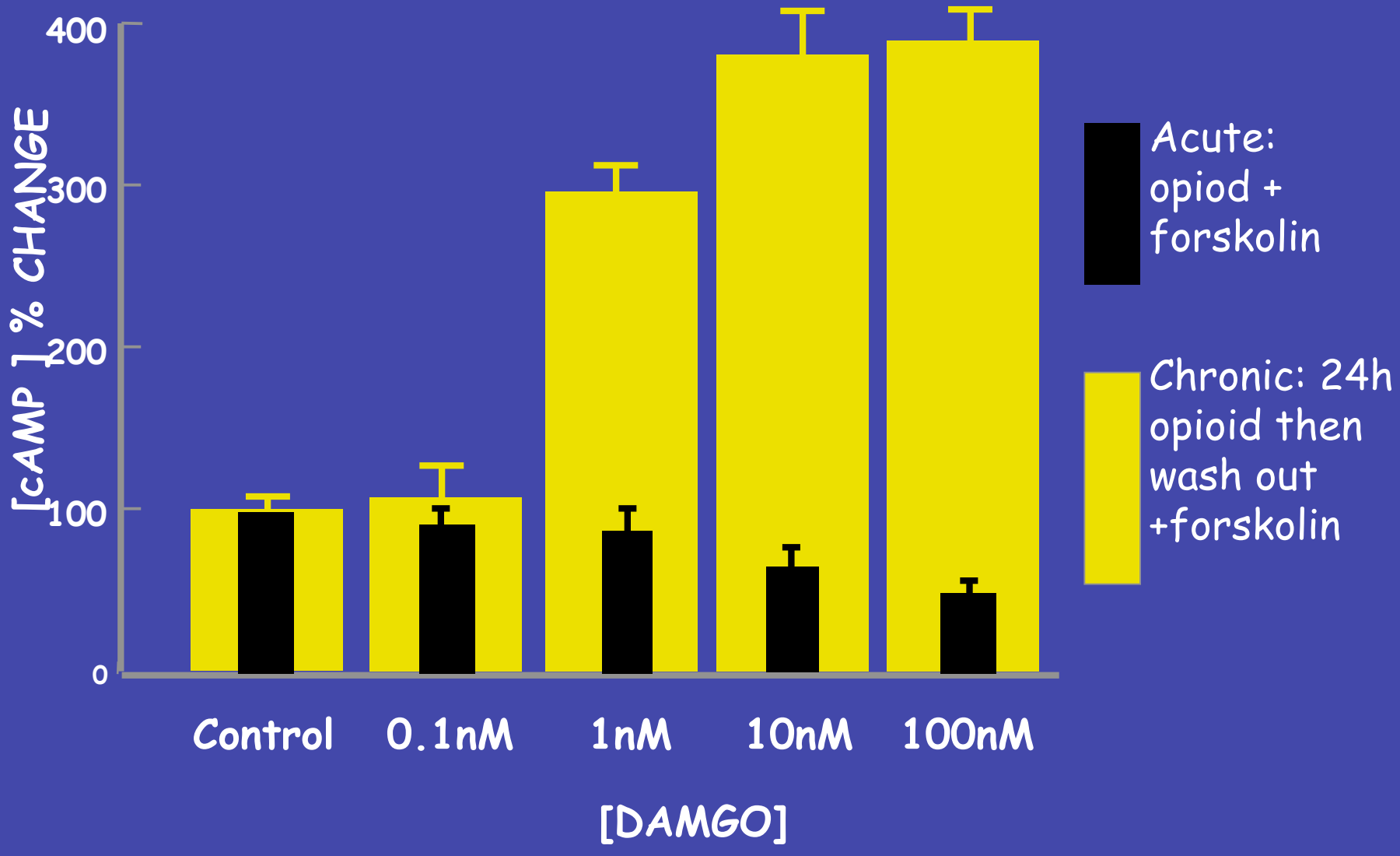


Slide kindly provided by Walter Ling, UCLA

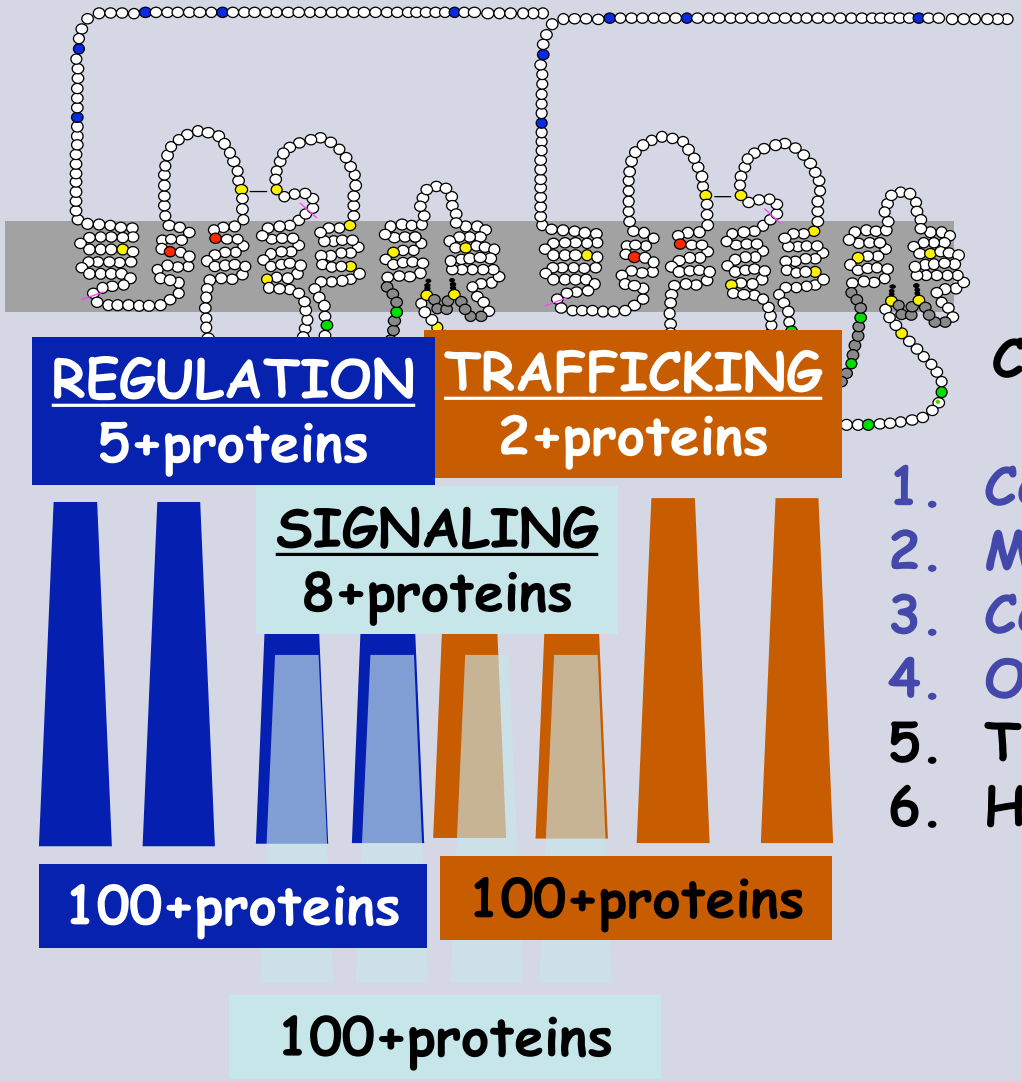
Hyperalgesia Following Chronic Morphine (TAD)- Pain Paradigm Specific



FORSKOLIN-STIMULATED cAMP ACCUMULATION FOLLOWING ACUTE AND CHRONIC OPIOID TREATMENT - CYCLASE SUPERSENSITIVITY



MU OPIOID RECEPTOR COMPLEX (diversity)

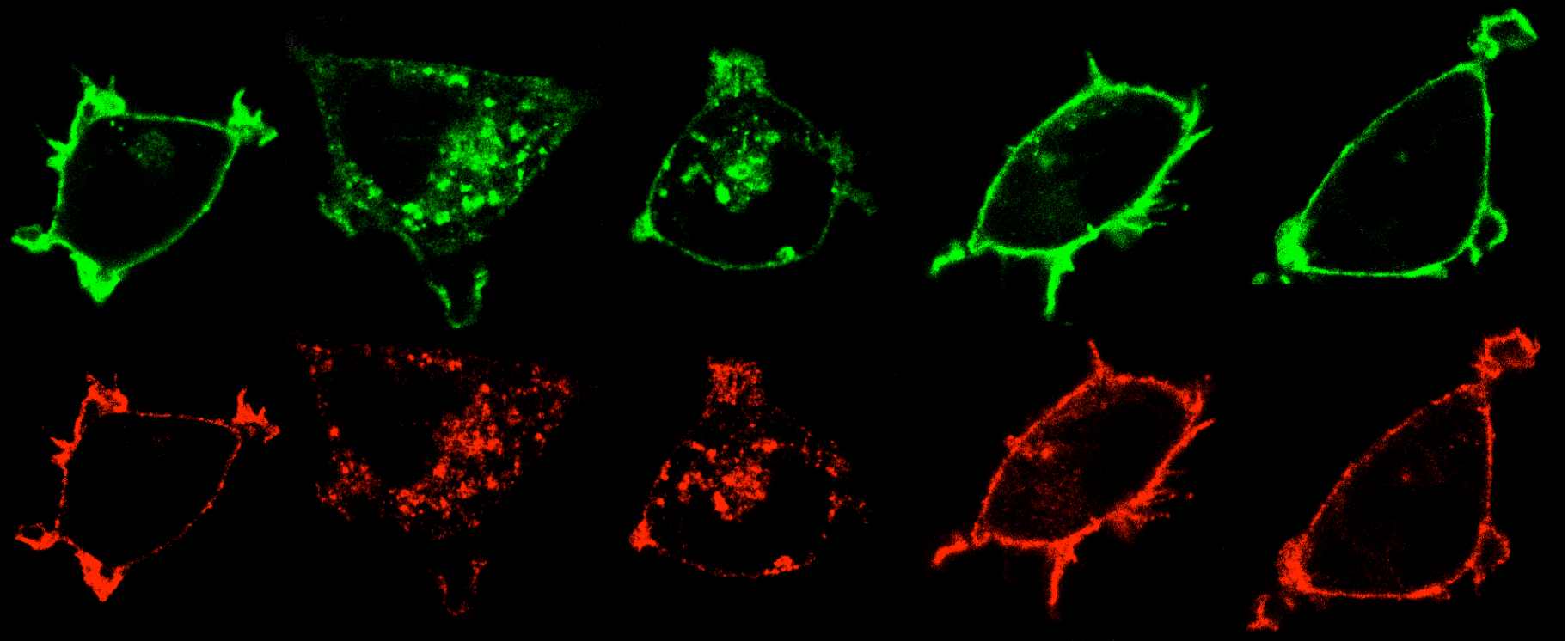


COMPLEX DETERMINATION

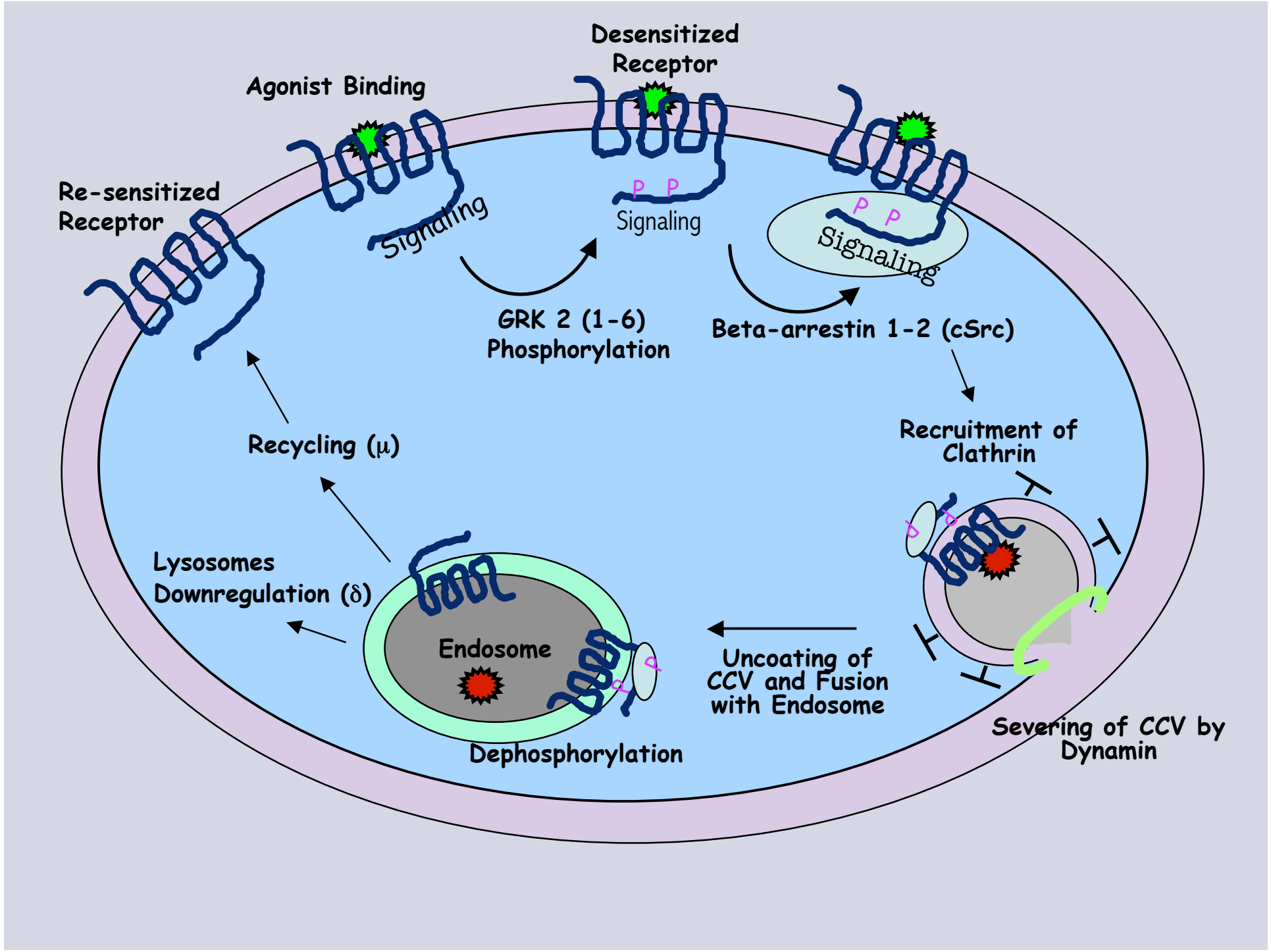
1. Cellular Proteome
2. Mu receptor alternative splicing
3. Cellular Compartment
4. Oligomerization (Hetro/Homo)
5. The Receptor Activation State
6. History of Receptor/Environment

Arrestins/G-proteins/GRK's/Src's/RGS's

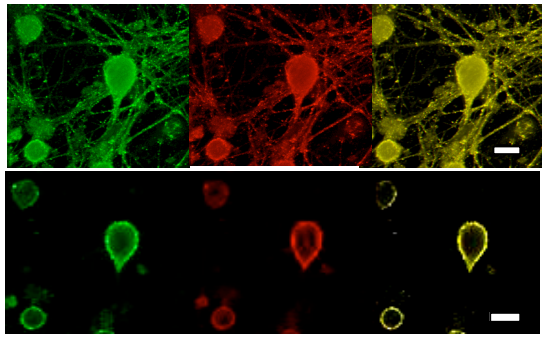
FLAG & MOR-C12 STAINING OF 293-CELLS TRANSFECTED WITH MU RECEPTORS



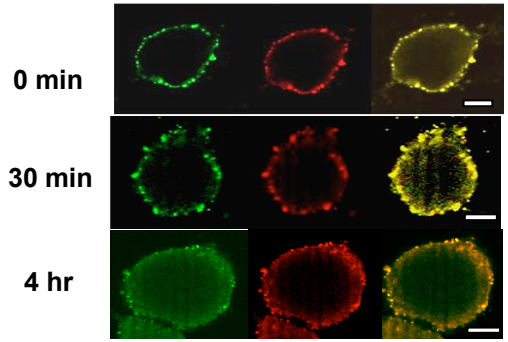
CONTROL | ETORPHINE (100nM) | DAMGO (100nM) | ETOR/NALOX (100nM/10μM) | MORPHINE (20μM)


Desensitized Receptor
Agonist Binding
Re-sensitized Receptor
Signaling
P P
Signaling
P P
Signaling
GRK 2 (1-6) Phosphorylation
Beta-arrestin 1-2 (cSrc)
Recruitment of Clathrin
Recycling (μ)
Lysosomes Downregulation (δ)
Endosome
Uncoating of CCV and Fusion with Endosome
Severing of CCV by Dynamin
Dephosphorylation

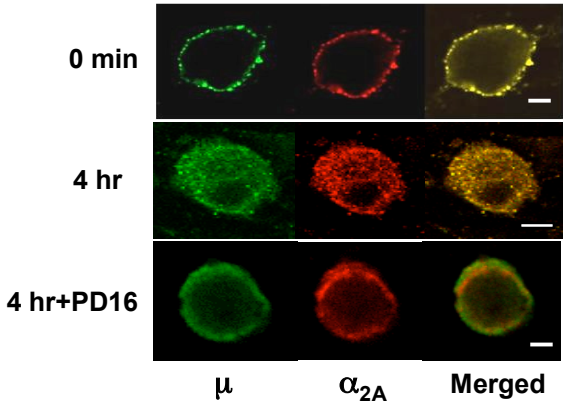
Mouse Dorsal Root Ganglion Cells
Express mu and alpha2A receptors

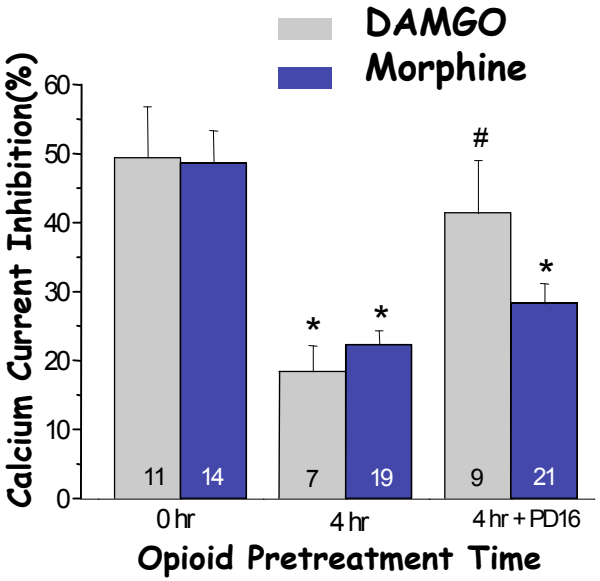


Morphine
(No internalization)



DAMGO
(Internalization)

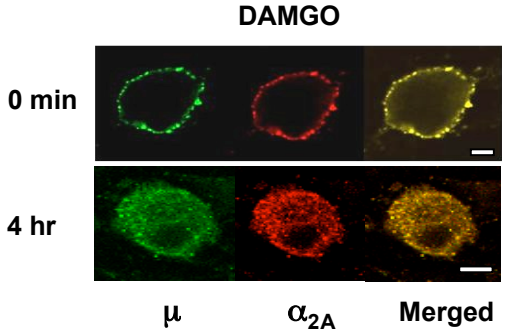


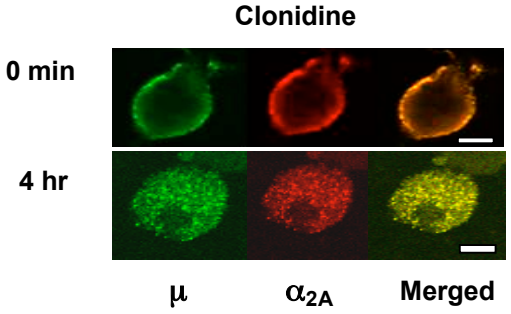


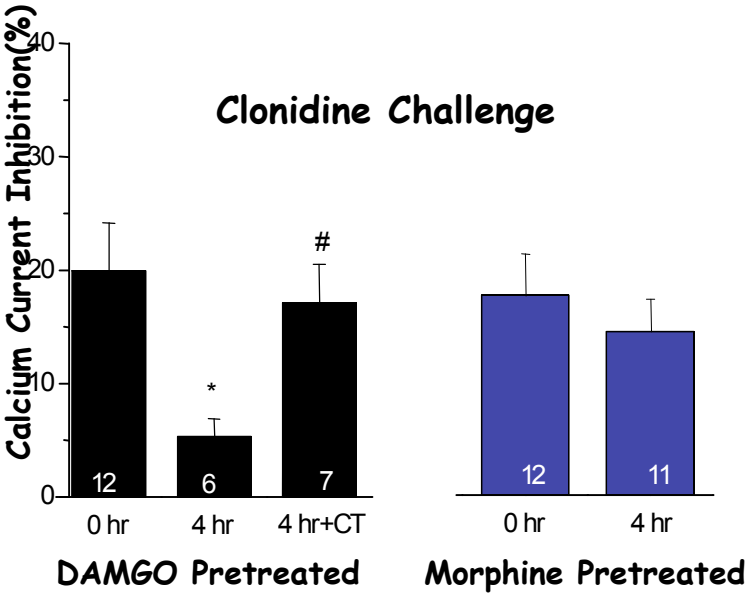
-Blocking internalization with the P38 inhibitor PD169316 blocks calcium signaling desensitization via DAMGO but not morphine
- The alpha 2A receptor internalizes with DAMGO treatment - blocked by PD169316

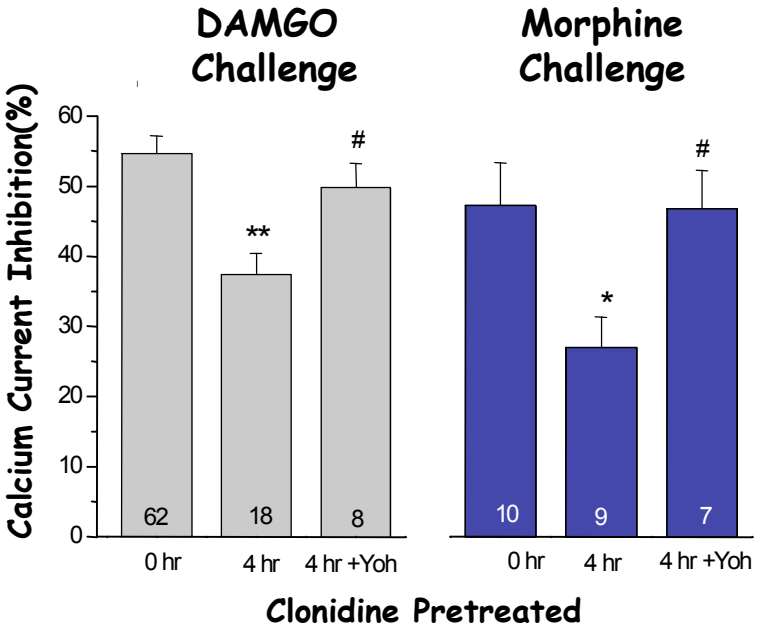
Tracy Xie CSORDA Lab 2006, submitted

Clonidine and DAMGO but not morphine induce both mu and alpha2A internalization and desensitization.



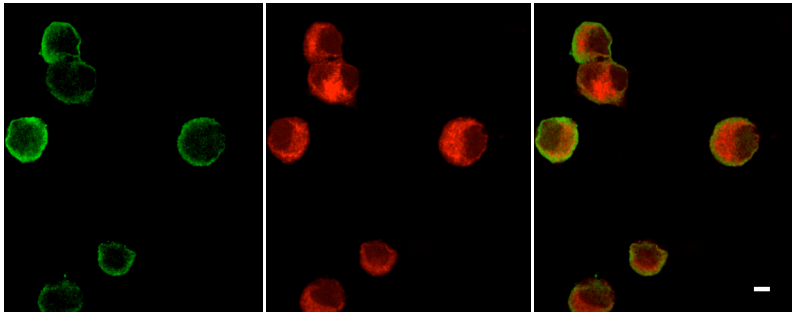


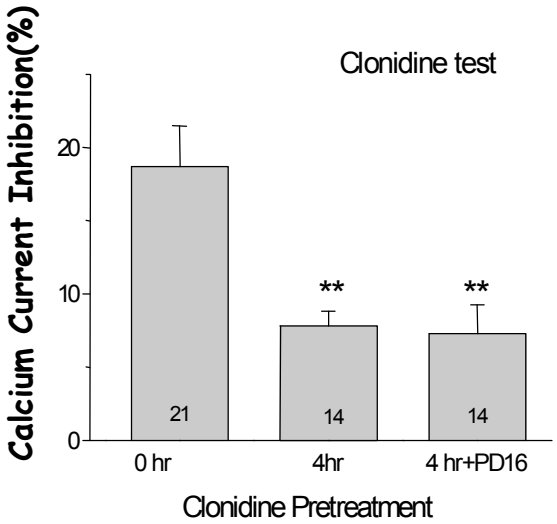


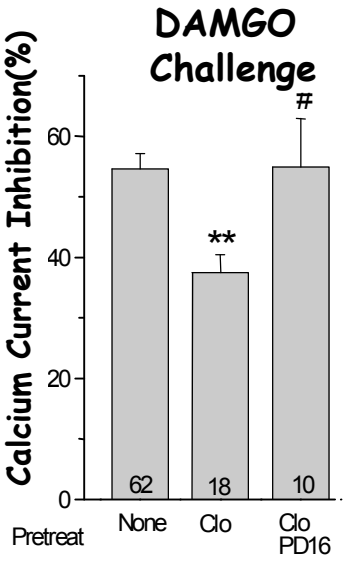


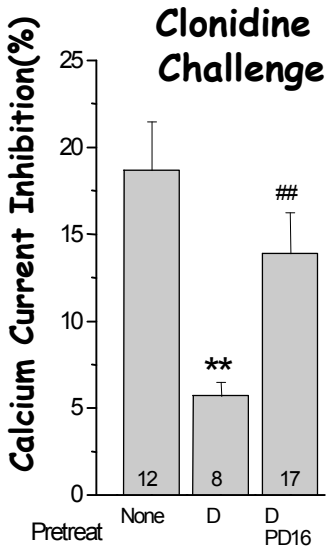
P38 inhibition blocks mu internalization but not Clonidine-induced alpha2A internalization and desensitization.

4 hr Clonidine Treatment + P38 inhibitor PD169316









Summary

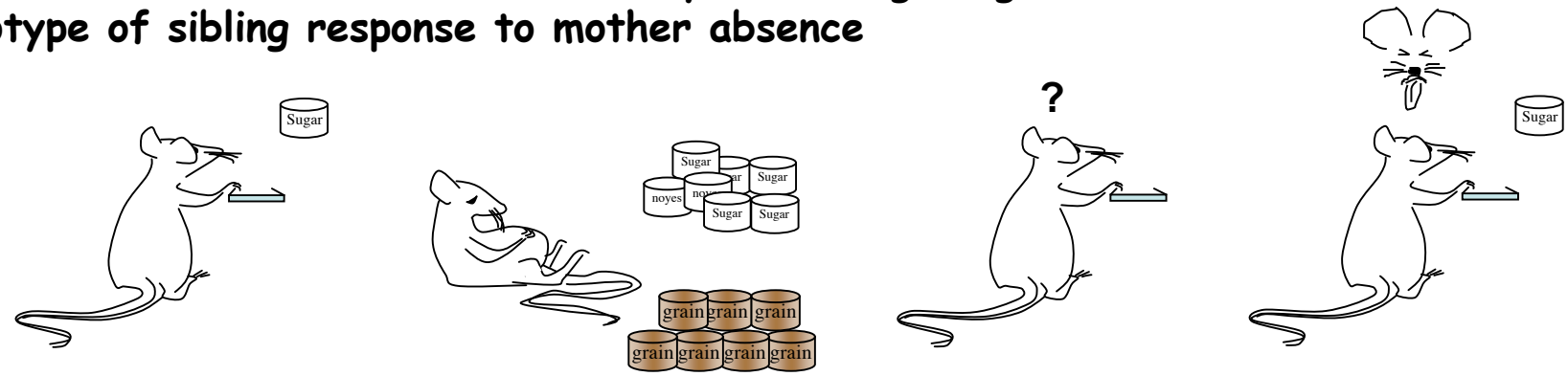
-Functional implications of mu and Alpha2A adrenergic association in endogenously expressing nociceptive neurons

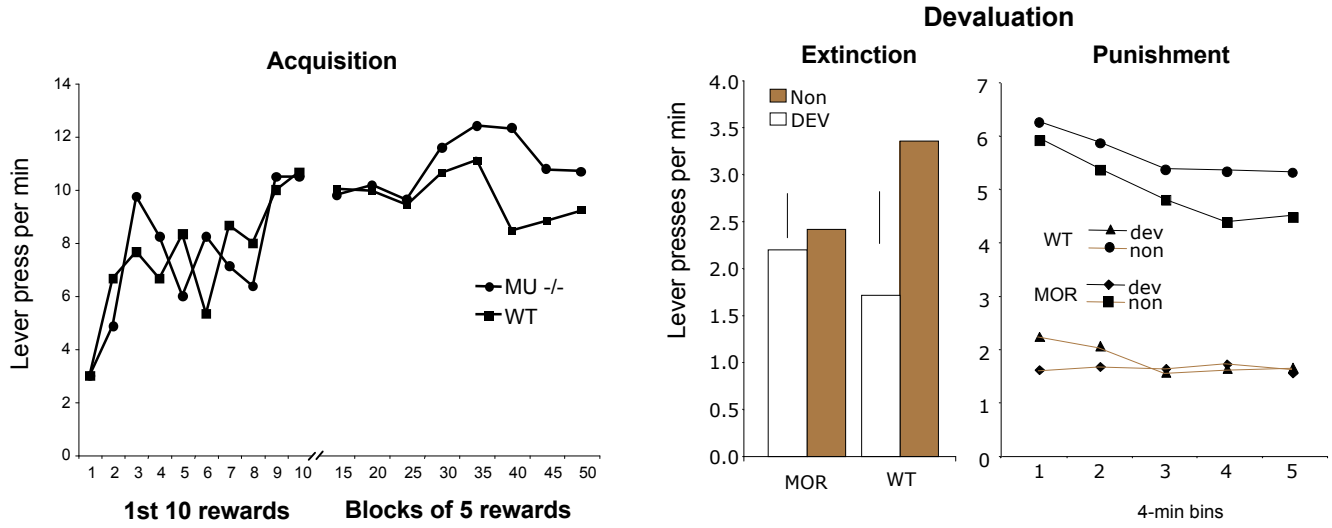
-Mu agonist specific cross-desensitization of Alpha2A adrenergic signaling

Role of Opioid System in Habit and Goal-Directed Behaviors

Mu opiate receptor knockout mice.

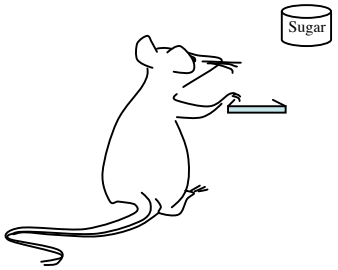
- **Lack reward-directed behaviors to many rewarding drugs**
- **Phenotype of sibling response to mother absence**

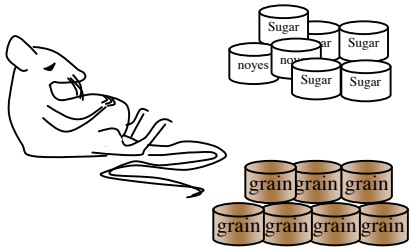


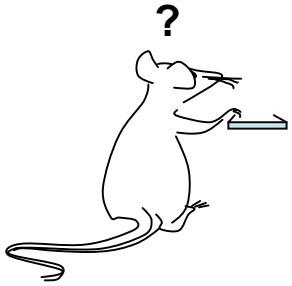


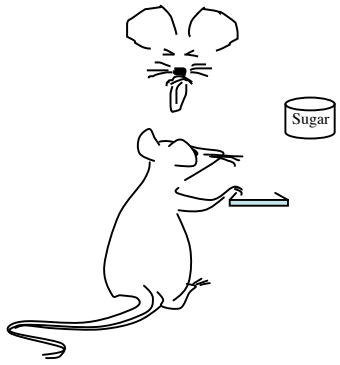
Maidment and Balleine Labs CSORDA 2006

Enkephalin knockout mice.

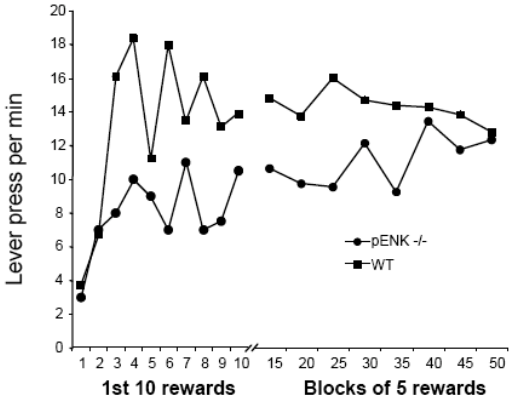




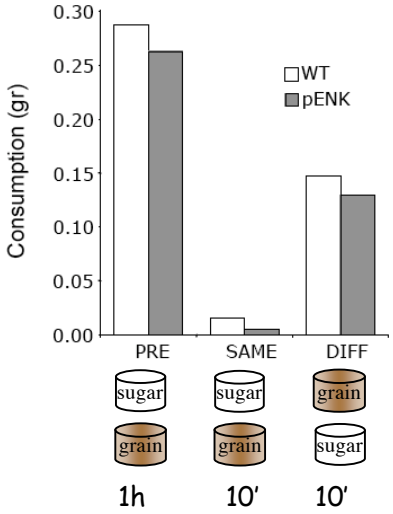




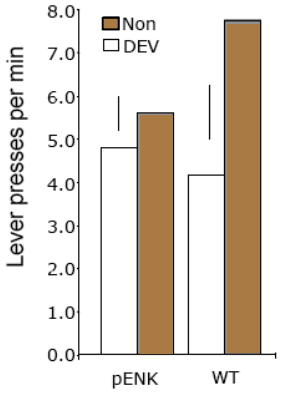
Instrumental Acquisition



Specific satiety - consumption test

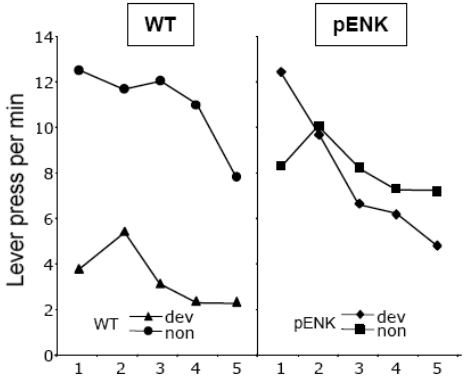


Devaluation - extinction test



No food

Devaluation - Punishment test



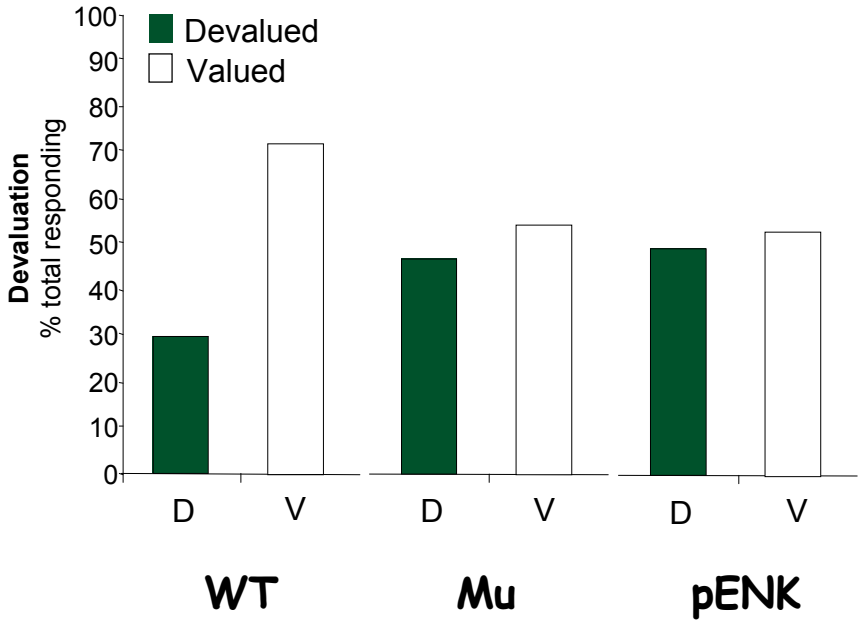
Sugar piles up in food tray in Enk-KO trials

Summary

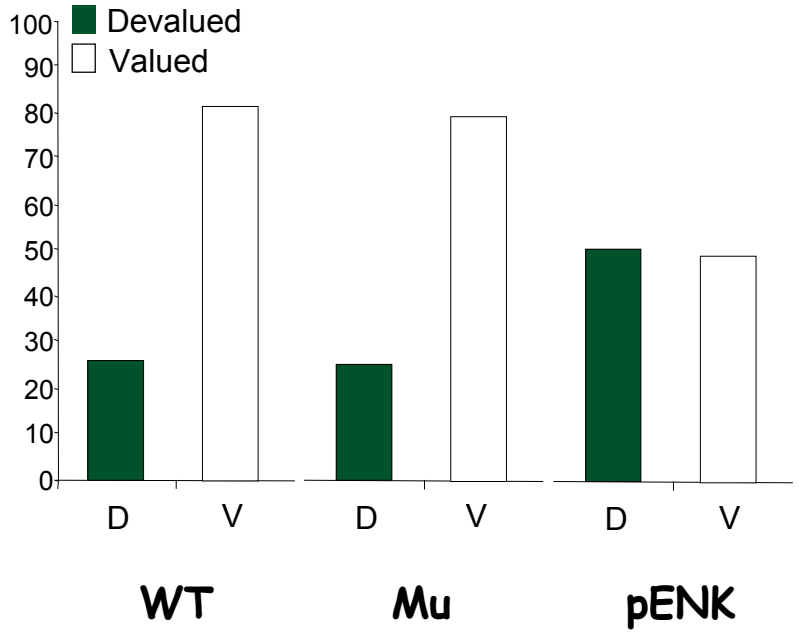
Mu -/- appear to have a problem with retrieving reward value:
They are sensitive to changes in value but are unable to retrieve changes in a test of free recall but can when the outcome is delivered.

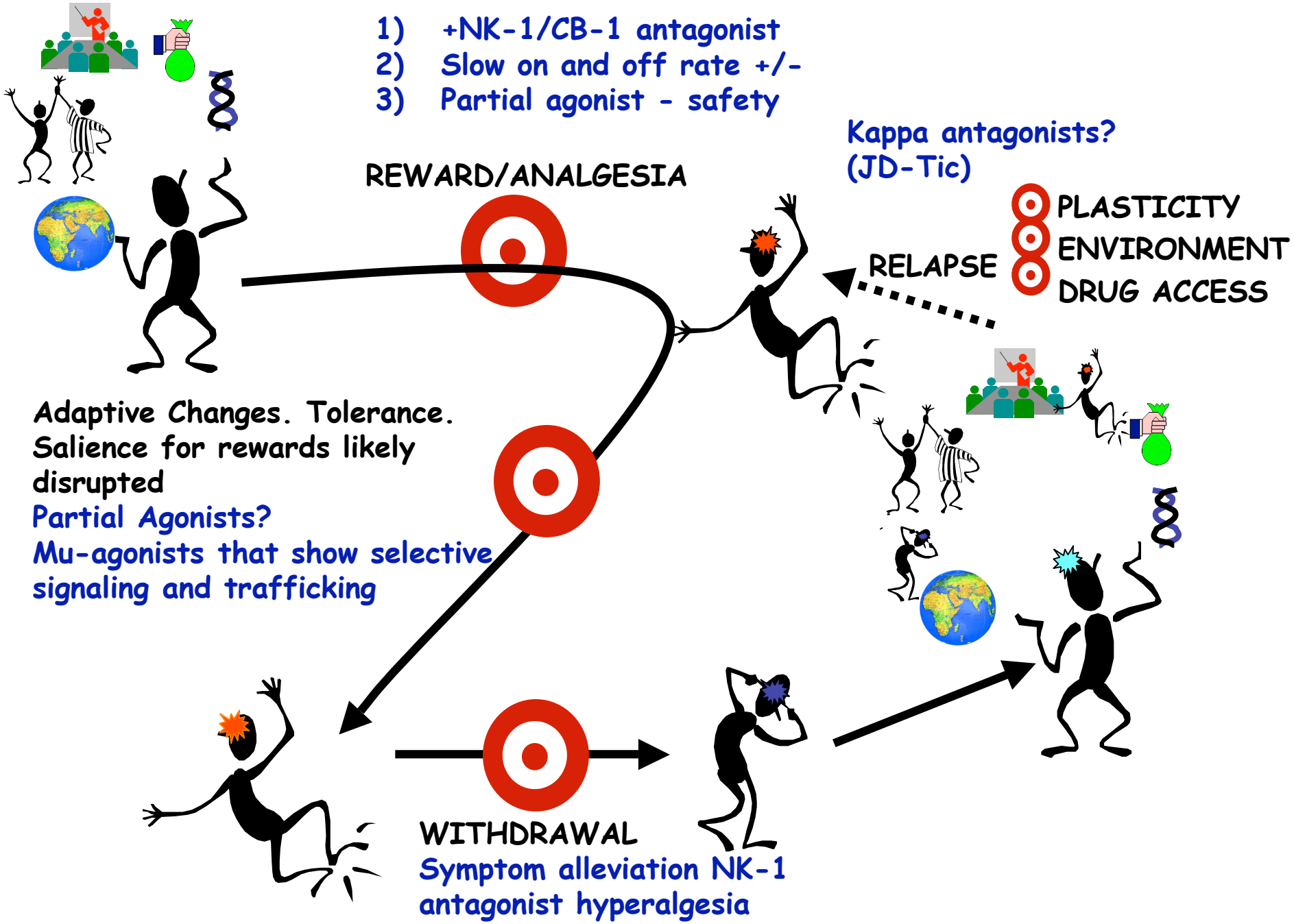
pENK -/- are unable to control their actions when faced with lack of salience. They appear to have a specific problem with goal-directed actions. Performance is likely controlled by a stimulus-response process and is habitual.

Retrieved value: Extinction



Punishment




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
RELAPSE
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