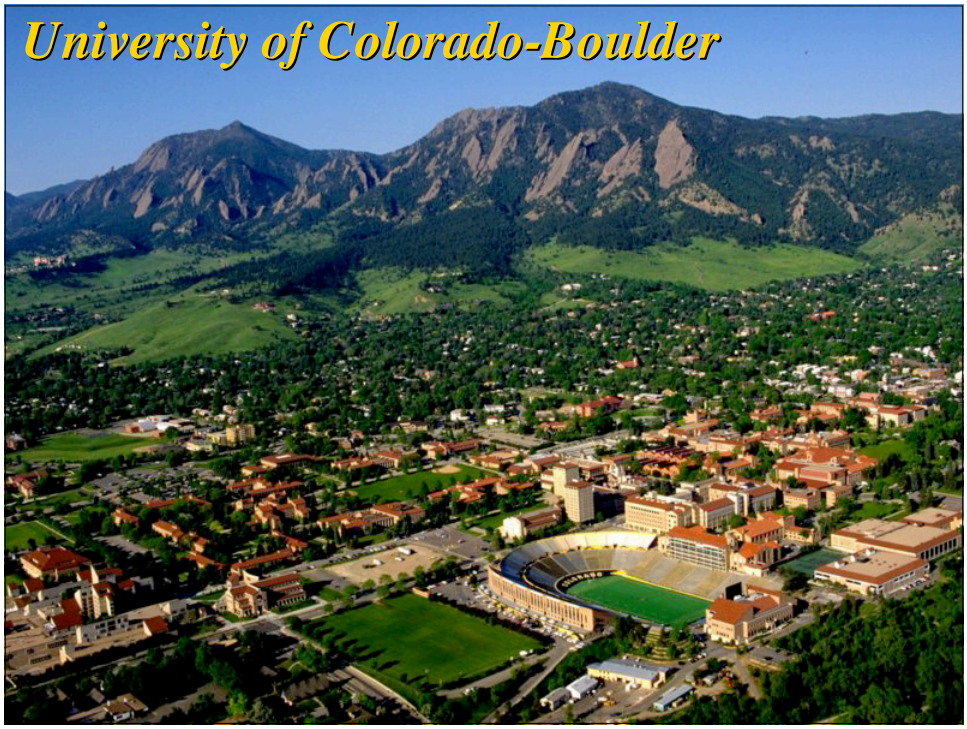
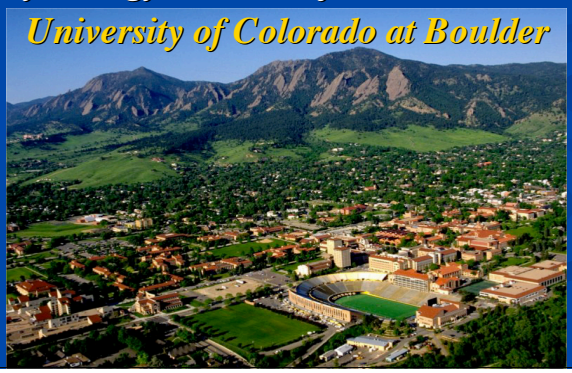


Glia as the "Bad Guys" in Dysregulating Pain & Opioid Actions: Implications for Improving Clinical Pain Control

Linda R. Watkins

Psychology & Center for Neuroscience

University of Colorado at Boulder



Global Concepts

- Views of pain & opioid effects are changing
- Glia (*microglia & astrocytes)* in CNS are key players in:
  * pain amplification, including pathological pain
  * making acute opioids (such as morphine) less effective for pain control
  * causing chronic morphine to lose effect, contributing to opioid tolerance
  * driving morphine dependence/withdrawal
  * driving morphine reward, linked to drug craving
  * driving other opioid-induced negative side effects
- Opioids activate glia via a *non-classical* opioid receptor

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Avigen

Neuropathic Pain

Glial Dysregulation of Pain

Activation of:

***Microglia**
***Astrocytes**

Release of:

***Interleukin-1**
***Interleukin-6**
***Tumor Necrosis factor**
•Each Enhance Pain
•Effects Synergize

Pain Amplification!

Watkins et al., *Brain Research Reviews* 2007 in press

Glial Dysregulation of Opioids

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Release of:

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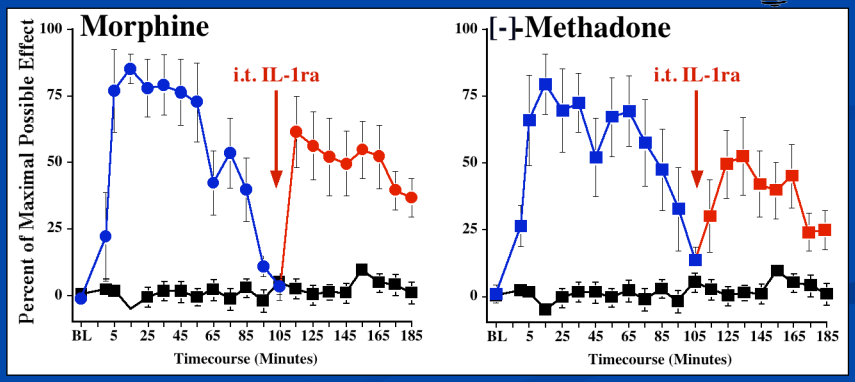
•Each Enhance Pain
•Effects Synergize

Results in:

*** ↓Analgesia**
*** Naïve tolerance**
*** ↑Tolerance**
*** ↑Dependence**
*** ↑Reward**
*** ↑Side Effects**

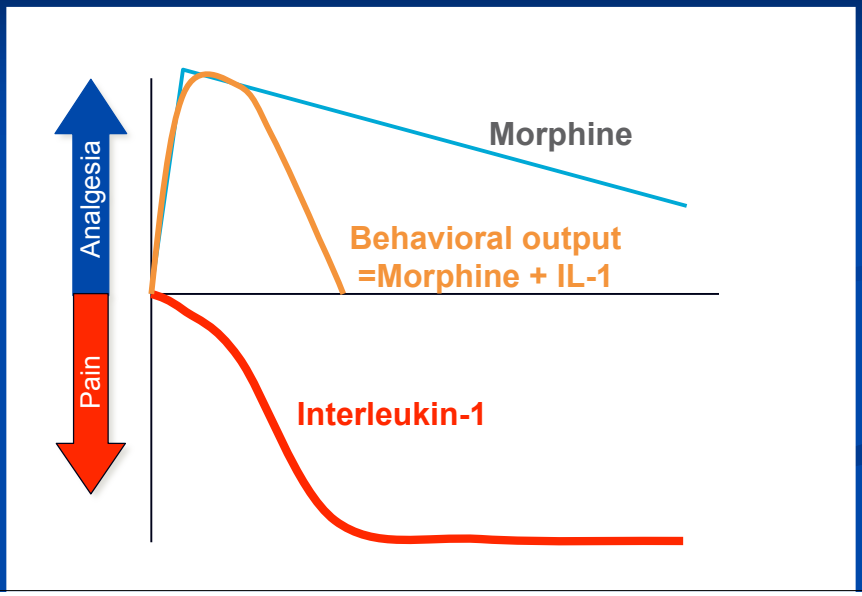
Hutchinson et al., *TheScientificWorldJournal* 2007 in press

Glial Activation Opposes the Analgesic Efficacy of Both Morphine & Methadone



Hutchinson et al., *MS in review* 2007

Intrathecal IL-1ra Unmasks Morphine Analgesia



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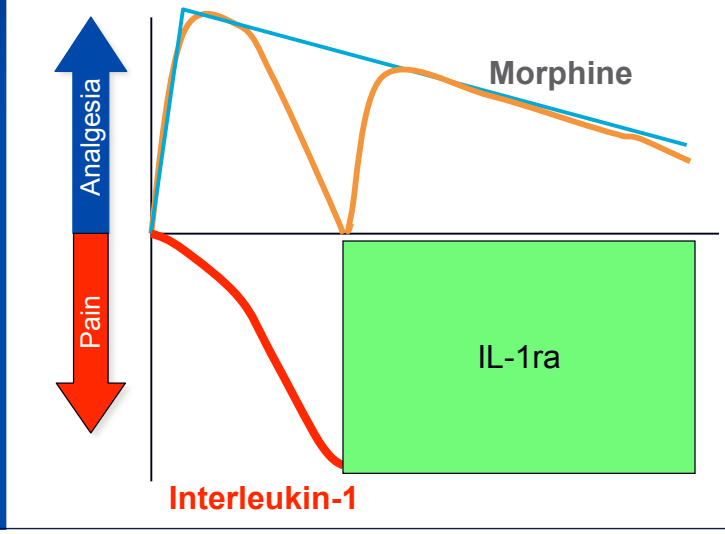
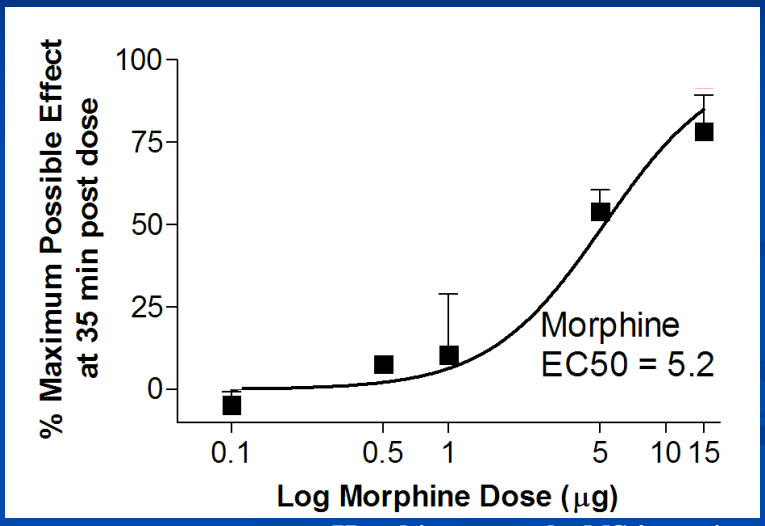


i.t. IL-1ra Enhances Morphine: Leftward Dose-Response Shift



Hutchinson et al., *MS in review*, 2007

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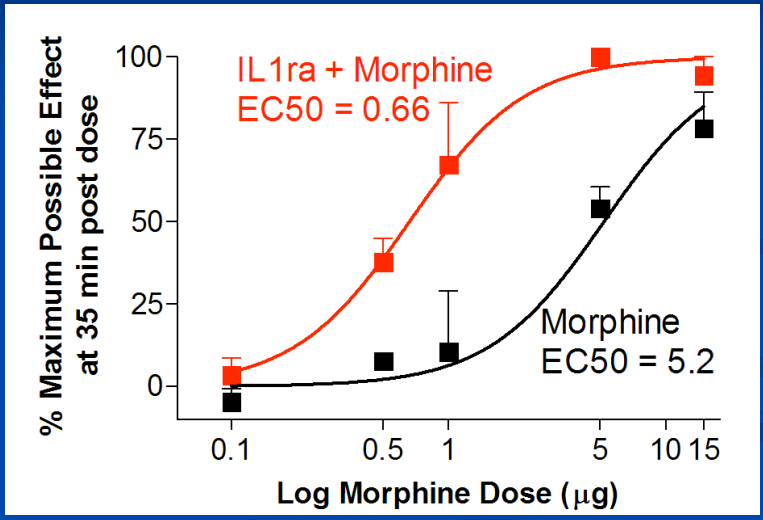
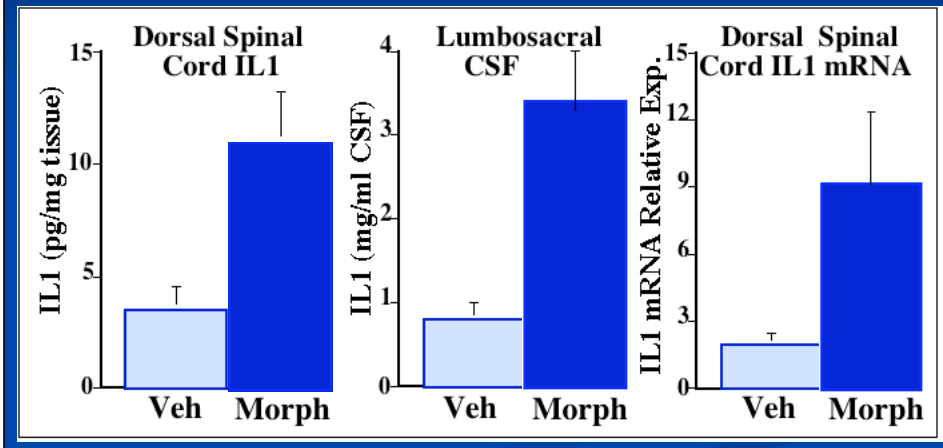


Hutchinson et al., *MS in review* 2007

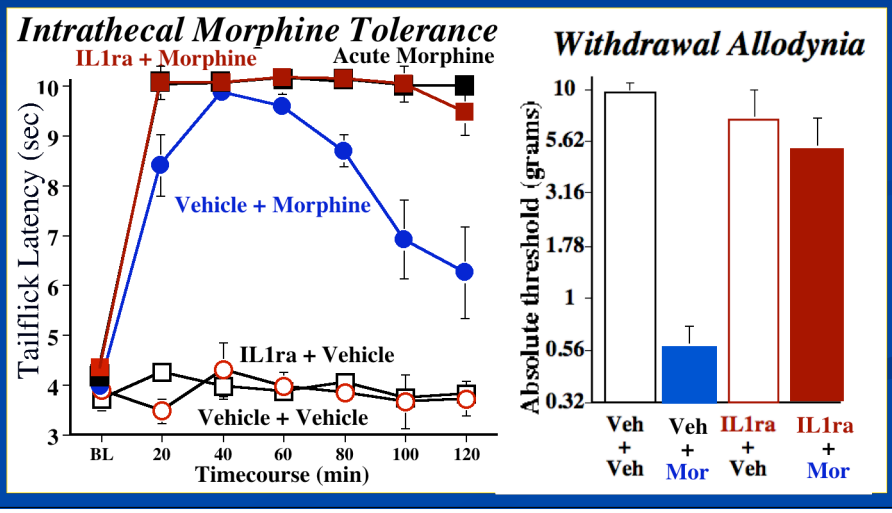
Chronic i.t. Morphine Increases Spinal Interleukin-1



Johnston et al., *Journal of Neuroscience* 2004;
Watkins et al. *Trends in Neuroscience* 2005

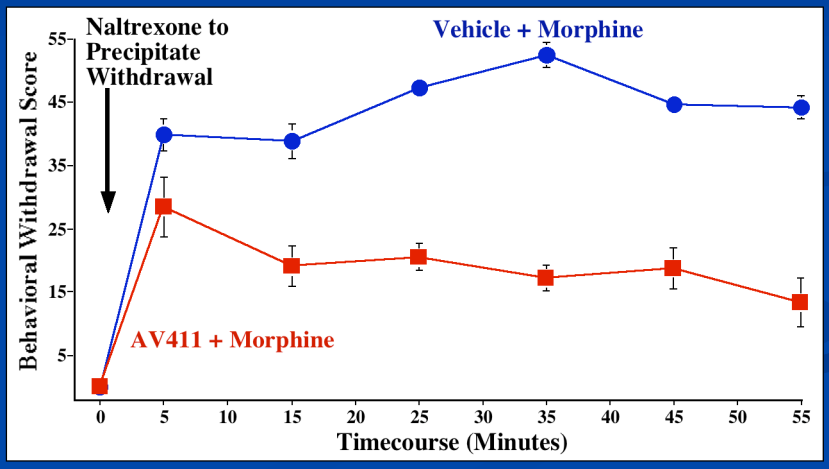
Spinal IL-1: i.t. Morphine Tolerance & Withdrawal-Induced Pain Facilitation

(Johnston et al. *Journal of Neuroscience, 2004;* Watkins et al., *Trends in Neuroscience, 2005*)



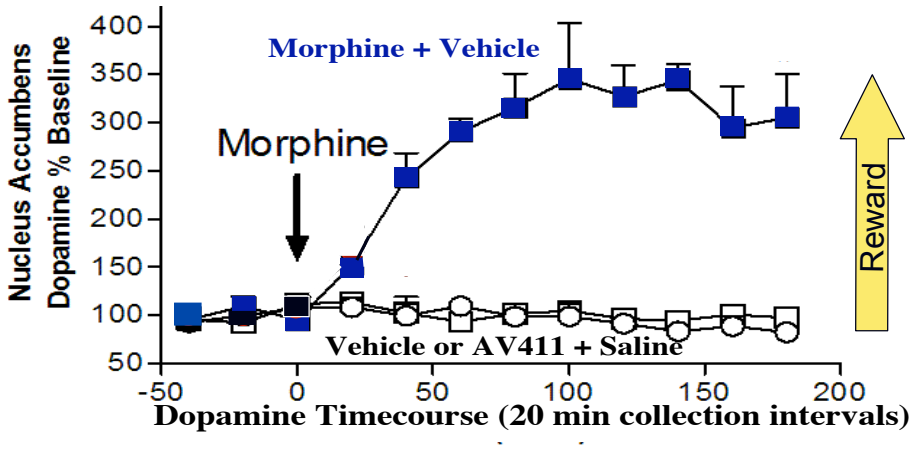
AV411, a Blood-Brain Permeable Glial Activation Inhibitor, Blocks Morphine Withdrawal

(Hutchinson et al., *Proc. Soc. NeuroImmunoPharmacology 2006*)



AV411 Blunts Morphine-Induced Release of Nucleus Accumbens Dopamine, by In Vivo Microdialysis

Bland *et al. NIDA Miniconvention '07*



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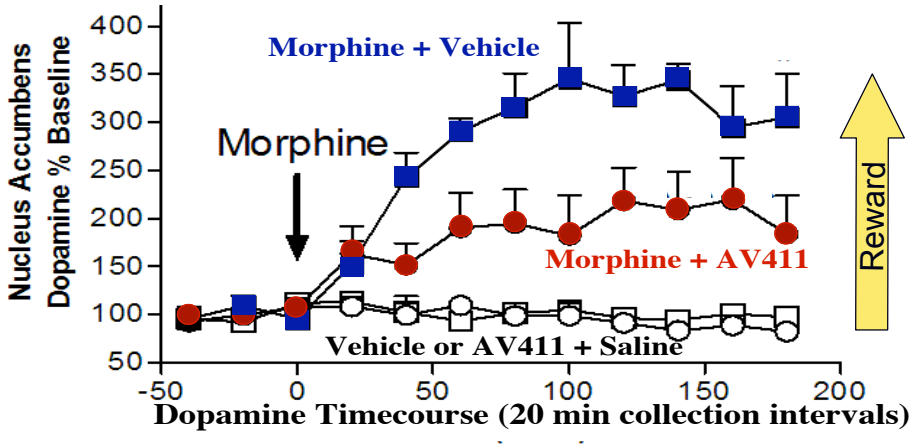
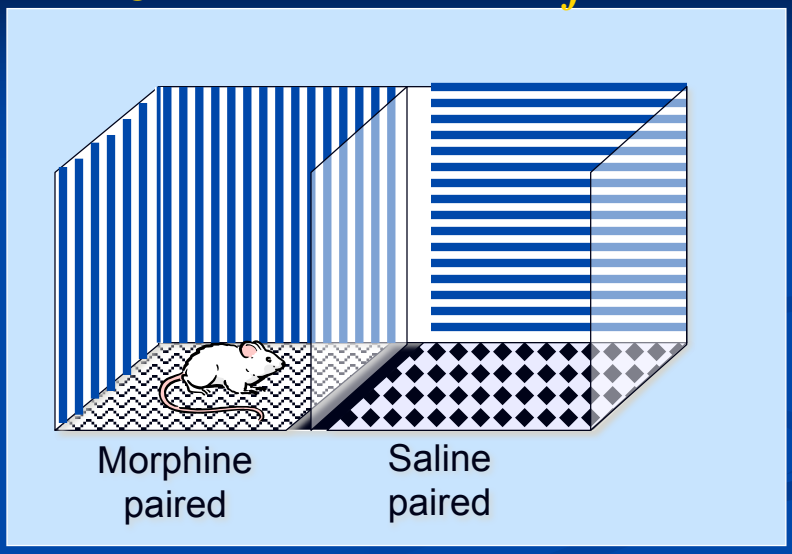
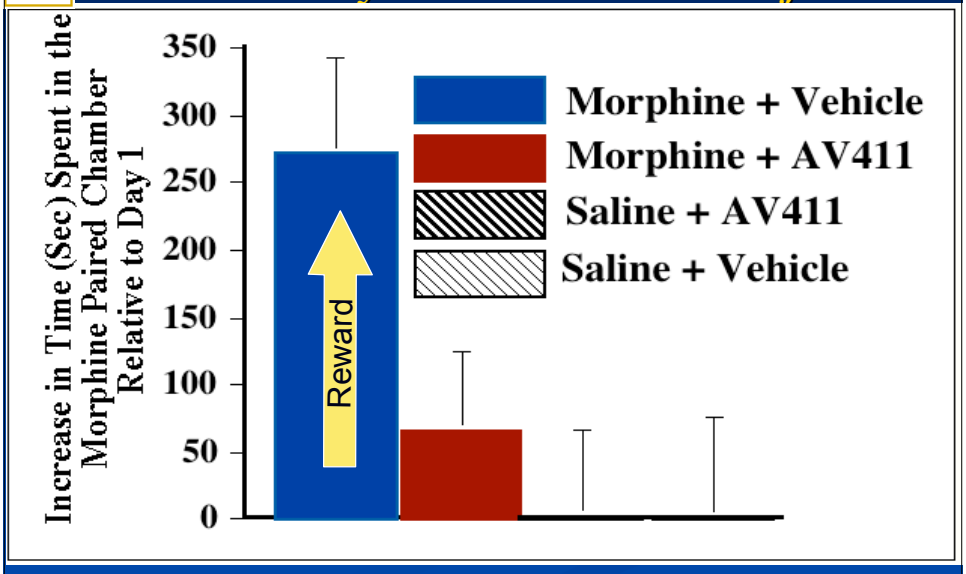


Glia & Opioid Reward: Conditioned Place Preference



Bland *et al. NIDA Miniconvention '07*

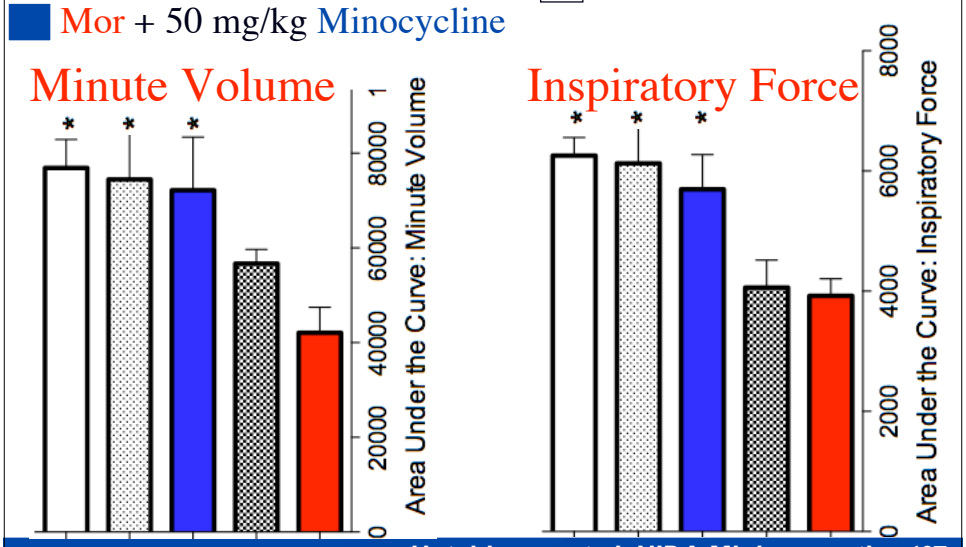
AV411 Suppresses Morphine Reward as Measured by Conditioned Place Preference



Bland *et al. NIDA Miniconvention '07*

Glial Inhibitor Suppresses Respiratory Depression

Morphine + Vehicle
Mor + 25 mg/kg Minocycline
Mor + 50 mg/kg Minocycline
Veh + 50 mg/kg Mino
Vehicle + Vehicle



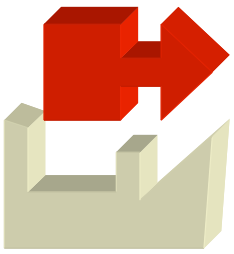
Hutchinson *et al. NIDA Miniconvention '07*

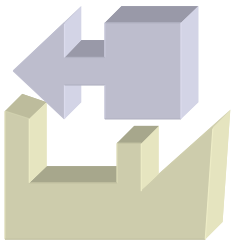
Opioid Effects are Different for Neurons & Glia

Neuronal Receptors are Stereoselective:

[-]Methadone:
Active Agonist
at Classical Opioid Receptor

[+]Methadone:
INActive Agonist
at Classical Opioid Receptor





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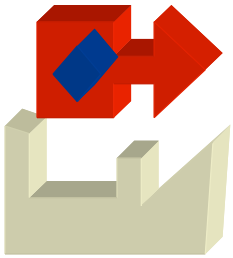
Neuronal Receptors are Stereoselective:

[-]-Naloxone:
Active Antagonist
at Classical Opioid Receptor



[+]-Naloxone:
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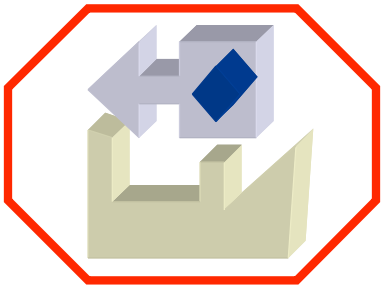


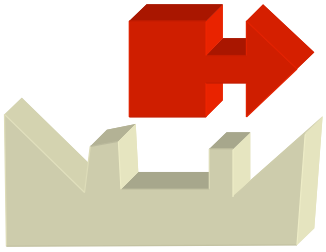
This Point is KEY

Opioid Effects are Different for Neurons & Glia

GLIAL Receptors are Not Stereoselective!

[-]& [+] Isomers have EQUAL effects on glia

[-]-Methadone:
Active Agonist
at Glial Opioid Receptor



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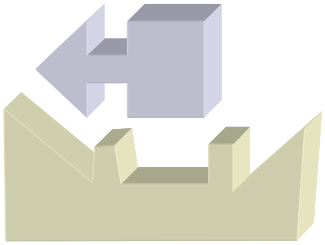

Glial opioid receptor -- Fits BOTH [-] & [+]-enantiomers

Glial Non-Stereoselectivity Extends to Opioid Antagonists!

[-]-Naloxone:
Active Antagonist
at Glial Opioid Receptor

[+]-Naloxone:
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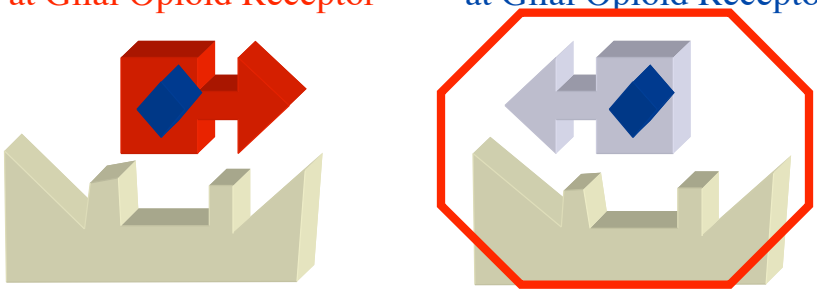
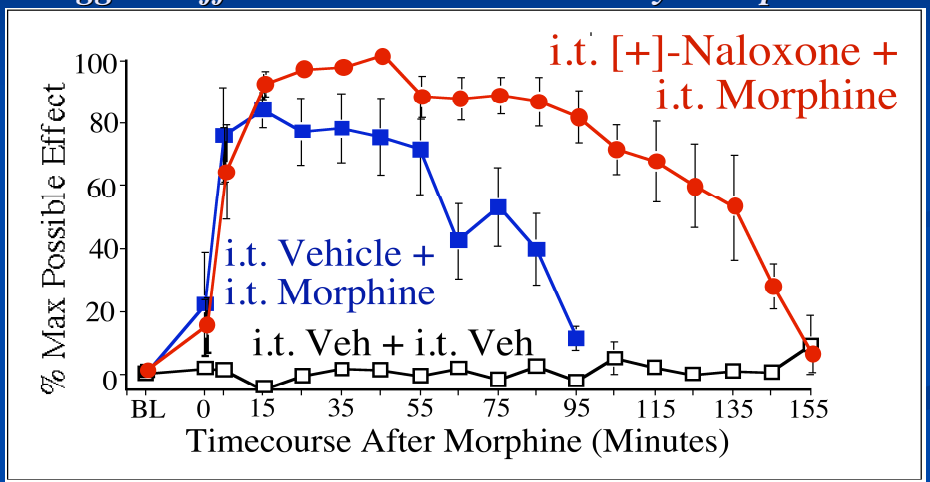
at Glial Opioid Receptor



[+]-Naloxone should *POTENTIATE* morphine analgesia by:
(a) *NOT* blocking morphine effects on neurons, yet
(b) Removing glial activation that *OPPOSES* analgesia!

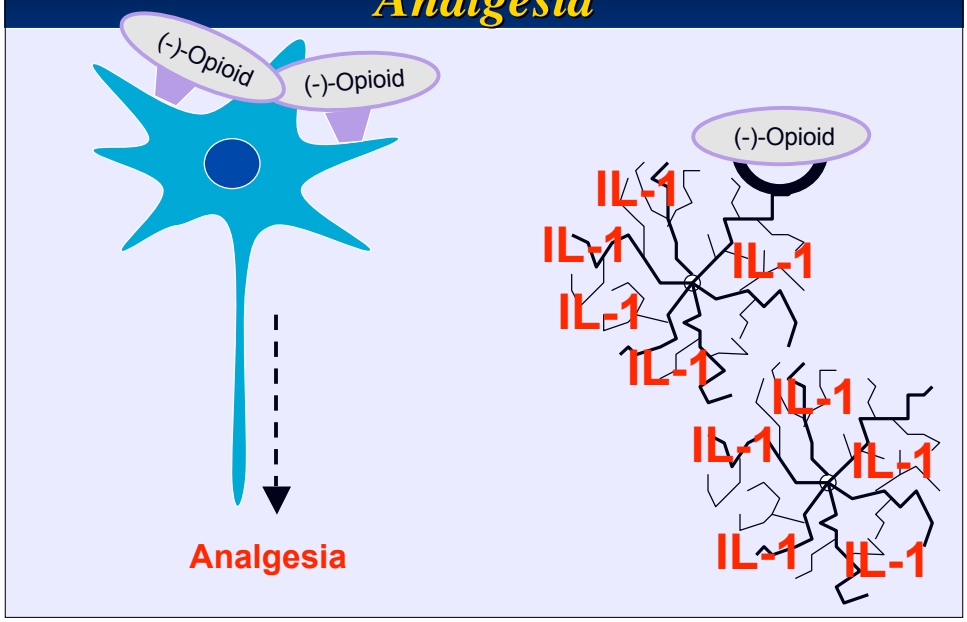
Neuronally INACTIVE [+]-Naloxone Potentiates Morphine Analgesia!

Suggests Effects on Glia & Neurons May be Separable!

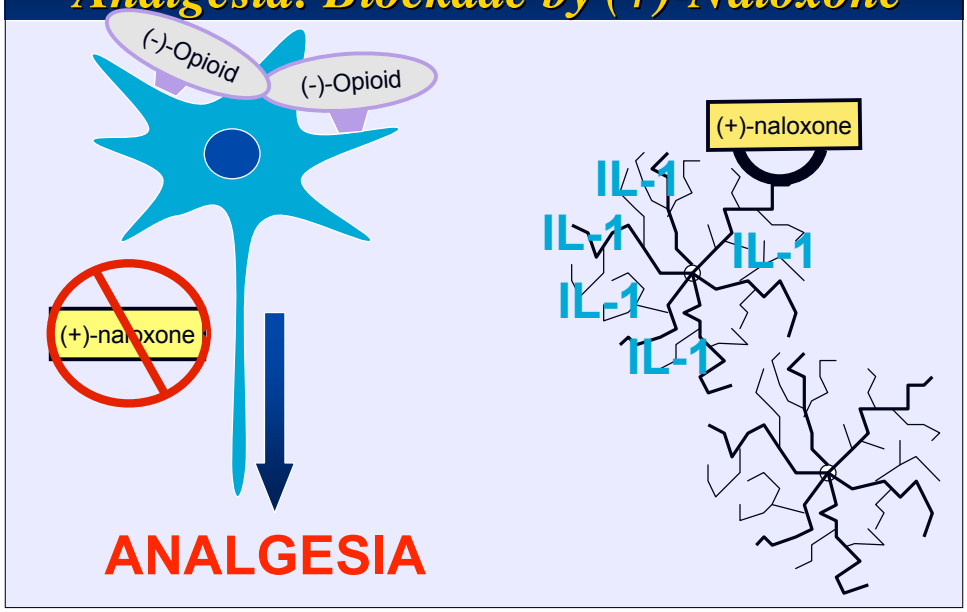


Hutchinson et al., MS in review '07

Opioid Activation of Glia Suppresses Analgesia



Opioid Activation of Glia Suppresses Analgesia: Blockade by (+)-Naloxone



Soooooo…….

What's the mystery opioid receptor on glia?

To target it, one must know what it is

Toll-Like Receptors (TLRs):

Classically….

"not me, not right, not OK" receptors

Toll-Like Receptors (TLRs) detect:

***pathogens (bacteria, viruses, etc.)**

***endogenous danger signals (damage/death)**

**** All classes of opioids used clinically***

Hutchinson et al., *TheScientificWorldJournal* 2007 in press

TLR4 Induced Glial Activation

TLR4 expression is upregulated by:

- *** Neuropathy**
- *** Opioids, *non-stereoselectively***

TLR4 is activated by:

- *** Neuropathy**
- *** Opioid agonists, *non-stereoselectively***

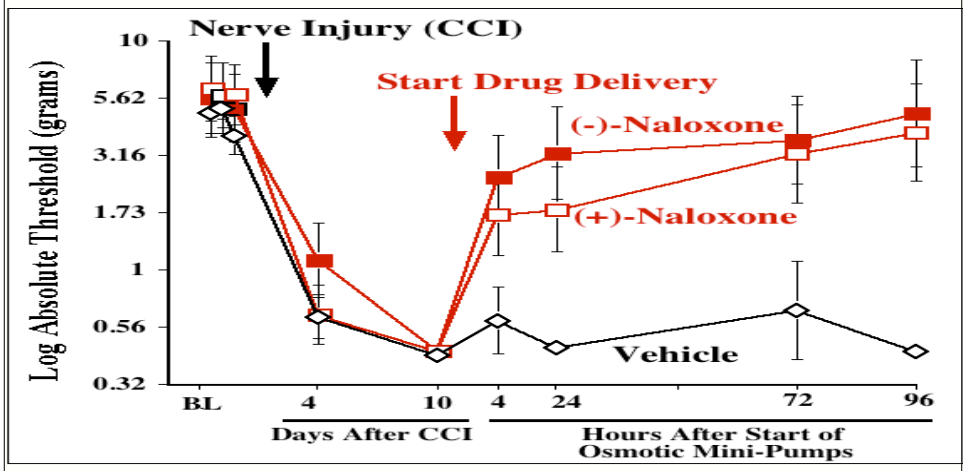
TLR4 is blocked by:

- *** Naloxone, *non-stereoselectively***

Hutchinson et al., *TheScientificWorldJournal* 2007 in press

Toll Like Receptor-4 (TLR4):

Naloxone, a TLR4 antagonist, non-stereoselectively reverses neuropathic pain



Hutchinson et al., Unpub. Obs.

Conclusions - 1

So, Taken Together Our Data Predict That Suppressing Glial Activation Will:

- Suppress neuropathic pain, etc.
- Improve opioid analgesia
- Suppress opioid tolerance
- Suppress opioid dependence
- Suppress opioid reward linked to drug craving/drug seeking
- Suppress other negative side effects

Conclusions - 2

Opioid Activation of Glia is Fundamentally Different Than Neurons:

- Glial receptors are ***not*** stereoselective
- Opioid effects on glia ***must*** be via different receptors than for neurons: TLR4
- Effects on glia & neurons should be separable
- To increase the efficacy of opioids:
  - Modify opioids so they don't bind glia &/or
  - Create long-lasting versions of [+]-naloxone

With Thanks to my Collaborators, NIDA, NIDCR, NINDS, IASP, Avigen & the grant review panels!

CU-Boulder:

Sondra Bland, coPI
Ben Coats
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Kim Brown
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David Martin