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

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Psychology & Center for Neuroscience
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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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Neuropathic Pain
**Glial Dysregulation of Pain**

Activation of:
* Microglia
* Astrocytes

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

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

**Glial Dysregulation of Opioids**

Activation of:
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* Tumor Necrosis factor
  • Each Enhance Pain
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Results in:
* ↓ Analgesia
* Naïve tolerance
* ↑ Tolerance
* ↑ Dependence
* ↑ Reward
* ↑ Side Effects

Glial Activation Opposes the Analgesic Efficacy of Both Morphine & Methadone

Hutchinson et al., *MS in review* 2007

Intrathecal IL-1ra Unmasks Morphine Analgesia

Interleukin-1

Behavioral output = Morphine + IL-1
Intrathecal IL-1ra Unmasks Morphine Analgesia

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

Hutchinson et al., *MS in review*, 2007
**i.t. IL-1ra Enhances Morphine: Leftward Dose-Response Shift**

![Graph showing dose-response shift](Image)

- **IL1ra + Morphine** EC50 = 0.66
- **Morphine** EC50 = 5.2

Hutchinson et al., *MS in review* 2007

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**Chronic i.t. Morphine Increases Spinal Interleukin-1**

![Bar charts showing interleukin-1 levels](Image)

- **Dorsal Spinal Cord IL1**
  - Veh: 0.5 pg/mg tissue
  - Morph: 1.0 pg/mg tissue

- **Lumbosacral CSF**
  - Veh: 0.1 mg/ml CSF
  - Morph: 0.3 mg/ml CSF

- **Dorsal Spinal Cord IL1 mRNA**
  - Veh: 0.6 Relative Exp.
  - Morph: 1.2 Relative Exp.

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)

**Intrathecal Morphine Tolerance**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tailflick Latency (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL1ra + Morphine</td>
<td>10 (± 1)</td>
</tr>
<tr>
<td>Vehicle + Morphine</td>
<td>9 (± 1)</td>
</tr>
<tr>
<td>IL1ra + Vehicle</td>
<td>8 (± 1)</td>
</tr>
<tr>
<td>Vehicle + Vehicle</td>
<td>7 (± 1)</td>
</tr>
</tbody>
</table>

**Withdrawal Allodynia**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Absolute threshold (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veh</td>
<td>0.56 (± 0.1)</td>
</tr>
<tr>
<td>Veh + Mor</td>
<td>1.62 (± 0.1)</td>
</tr>
<tr>
<td>IL1ra + Veh</td>
<td>1.78 (± 0.1)</td>
</tr>
<tr>
<td>IL1ra + Mor</td>
<td>3.16 (± 0.1)</td>
</tr>
</tbody>
</table>

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


**Behavioral Withdrawal Score**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Behavioral Withdrawal Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone + Vehicle</td>
<td>55 (± 5)</td>
</tr>
<tr>
<td>Vehicle + Morphine</td>
<td>45 (± 5)</td>
</tr>
<tr>
<td>AV411 + Morphine</td>
<td>35 (± 5)</td>
</tr>
</tbody>
</table>
AV411 Blunts Morphine-Induced Release of Nucleus Accumbens Dopamine, by In Vivo Microdialysis

Bland et al. NIDA Miniconvention ‘07

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Bland et al. NIDA Miniconvention ‘07
**Glia & Opioid Reward:**

*Conditioned Place Preference*

Morphine paired

Saline paired

**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

Minute Volume
Inspiratory Force

Area Under the Curve: Minute Volume
Area Under the Curve: Inspiratory Force

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
Opioid Effects are Different for Neurons & Glia

**Neuronal Receptors are Stereoselective:**

<table>
<thead>
<tr>
<th>Enantiomer</th>
<th>Action</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>[-]-Naloxone:</td>
<td>Active</td>
<td>Antagonist</td>
</tr>
<tr>
<td>[-]-Naloxone:</td>
<td>Inactive</td>
<td>Antagonist</td>
</tr>
</tbody>
</table>

This Point is KEY

**Glial Receptors are Not Stereoselective!**

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<td>Agonist</td>
</tr>
<tr>
<td>[+]-Methadone:</td>
<td>Active</td>
<td>Agonist</td>
</tr>
</tbody>
</table>

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

Glial opioid receptor -- Fits BOTH [-] & [+] enantiomers
**Glial Non-Stereoselectivity Extends to Opioid Antagonists!**

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

Analgesia

(-)-Opioid

(+)-naloxone

ANALGESIA
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

**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

Hutchinson et al., Unpub. Obs.
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