Cannabinoids and Neuropathic Pain

Perry G. Fine, M.D.
Professor of Anesthesiology
Pain Management and Research Centers
School of Medicine
University of Utah
and
Chief Medical Officer
ISA Scientific, Inc.
What is pain?

“...an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

The International Association for the Study of Pain

Multiple Types of Pain

A. Nociceptive Pain
   - Noxious Peripheral Stimuli
   - Brain

B. Inflammatory Pain
   - Inflammation
   - Brain

C. Neuropathic Pain
   - Peripheral Nerve Damage
   - Brain

D. Non-inflammatory/Non-neuropathic Pain
   - No Known Tissue or Nerve Damage
   - Abnormal Central Processing
   - Brain

- Patients may experience multiple pain states simultaneously

“When we wish to perfect our senses, neuroplasticity is a blessing; when it works in the service of pain, plasticity can be a curse”

—Norman Doidge, MD

Neuroplasticity in Spinal Cord Processing: Central Sensitization

- **Definition:** Heightened dorsal horn excitability due to increased peripheral nociceptor activity

- **Features of central sensitization**¹:
  - Reduced threshold for dorsal horn neuron activation
  - Increased receptive field of dorsal horn neurons
  - Increased response of dorsal horn neurons to painful stimuli

- **Potential mechanisms implicated in central sensitization**:
  - NMDA receptor activation¹
  - Altered gene expression in dorsal horn neurons¹
  - Decreased inhibition²
  - Microglial activation³
  - Thalamic and somatosensory cortex changes⁴

Brain Regions Involved in Pain Processing

Somatosensory Cortex

Prefrontal Cortex

Insular Cortex

Anterior Cingulate Cortex

Thalamus

Amygdala

Brain image courtesy of ATI
Traditional WHO Step Ladder:

Step 1
- Aspirin
- Acetaminophen
- NSAIDs
- ± Adjuvants

Step 2
- APAP/Codeine
- APAP/Hydrocodone
- APAP/Oxycodone
- APAP/Dihydrocodeine
- Tramadol
- ± Adjuvants

Step 3
- Morphine
- Hydromorphone
- Methadone
- Levorphanol
- Fentanyl
- Oxycodone
- ± Adjuvants

The Current "Analgesic Formulary"

- **Descending Modulation**
  - Anticonvulsants
  - Opioids
  - Tricyclic/SNRI Antidepressants

- **Central Sensitization**
  - Anticonvulsants
  - Opioids
  - NMDA-Receptor Antagonists
  - Tricyclic/SNRI Antidepressants

- **Peripheral Sensitization**
  - Local Anesthetics
  - Topical Analgesics
  - Anticonvulsants
  - Tricyclic Antidepressants
  - Opioids
Neuropathic Pain

- Definition: “Pain initiated or caused by a primary lesion or dysfunction in the nervous system.”

- Syndromes: peripheral and central
  - PHN, PDPN, PLP, Post-stroke, Cancer, HIV, etc.

- Population prevalence: 6.9 – 10%

Loeser J, Treed R-D. The Kyoto Protocol of basic IASP terminology. PAIN 2008; 137(3):473-7
### Peripheral Nociceptor Hyperexcitability and Sensitization

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Symptoms</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperexcitability</strong></td>
<td></td>
<td></td>
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<tr>
<td>Ectopic impulse generation; oscillations in dorsal root ganglion</td>
<td>Spontaneous pain (shooting)</td>
<td>Sodium channels, CB$_2$ receptors</td>
</tr>
<tr>
<td><strong>Sensitization: Inflammation within nerves</strong></td>
<td></td>
<td></td>
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<tr>
<td>Cytokine release</td>
<td>Spontaneous pain (ongoing)</td>
<td>Cytokines, α3 glycine receptor (CBD)</td>
</tr>
<tr>
<td><strong>Sensitization: Reduced activation threshold</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced threshold to heat or cold</td>
<td>Heat allodynia or cold allodynia</td>
<td>TRPV1 receptor (anandamide)</td>
</tr>
<tr>
<td>Reduced threshold to mechanical stimuli</td>
<td>Static mechanical allodynia</td>
<td>ASIC receptor</td>
</tr>
<tr>
<td>Reduced threshold to histamine or norepinephrine</td>
<td>Sympathetically maintained pain</td>
<td>CB$_1$, CB$_2$ receptors, histamine and α receptors,</td>
</tr>
</tbody>
</table>


TCA = Tricyclic antidepressant; TNF-α = tumor necrosis factor-α; NSAID = Nonsteroidal anti-inflammatory drug; ASIC = Acid-sensing ion channel; TRPV1 = Transient receptor potential vanilloid 1
## Central Dorsal Horn Hyperexcitability

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<th>Mechanisms</th>
<th>Symptoms</th>
<th>Targets</th>
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<tr>
<td><strong>Central sensitization, increased synaptic transmission</strong></td>
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</tr>
<tr>
<td>Amplification of C-fiber input, gating of Aβ-fiber and Aδ-fiber input</td>
<td>Spontaneous pain (ongoing), dynamic mechanical alldynia, punctate mechanical hyperalgesia</td>
<td>CB₁, CB₂ receptors, µ, receptors, calcium channels (α2-δ), NMDA receptors, NK1 receptors, sodium channels, intracellular cascades</td>
</tr>
<tr>
<td><strong>Intraspinal inhibitory interneurons decreased</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA-ergic or opioidergic interneurons decreased</td>
<td>Spontaneous pain (ongoing), dynamic mechanical alldynia, punctate mechanical hyperalgesia</td>
<td>GABA₉ receptors or µ receptors</td>
</tr>
<tr>
<td><strong>Changes in supraspinal descending modulation</strong></td>
<td></td>
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</tr>
<tr>
<td>Inhibitory control (5-HT, noradrenaline) decreased</td>
<td>Spontaneous pain (ongoing), dynamic mechanical alldynia, punctate mechanicalhyperalgesia</td>
<td>5-HT receptors, α2 receptor, CB₁, CB₂ receptors</td>
</tr>
</tbody>
</table>


NMDA = N-methyl-D-aspartic acid; NK-1 = neurokinin; GABA₉ = Gamma-aminobutyric acid receptor – subtype B; 5-HT = 5-hydroxytryptamine (serotonin) receptor; α2 = alpha 2 adrenergic receptor
Cannabinoids and Neuropathic Pain
Rahn EJ, Hohman AG. Cannabinoids as pharmacotherapies for neuropathic pain: from bench to the bedside. Neurotherapeutics 2009;6:713-37

- Chronic constriction injury
- Partial sciatic nerve ligation
- Spinal nerve ligation
- Chemically-induced diabetic neuropathy
- Chemotherapy-induced neuropathy
- HIV-associated neuropathy
- Demylenation-induced neuropathy
- Post herpetic neuralgia (PHN)
Clinical Trials of Cannabinoids

- HIV (n=50): Abrams et al
- Chronic NP pain (n=61) Notcutt et al, Karst et al
- MS (n=875) Zajicek et al, Svendsen et al, Wade et al, Rog et al
- Brachial plexopathy (n=48) Berman et al
- Peripheral neuropathy (n=125) Nurmmikko
Pain Physiology – Pretty Complicated

Plasma Extravasation
Vasodilation

Tissue Damage

Hea

Pressure

Mast Cell
Macrophage

5-HT
Histamine
PGE$_2$
Bradykinin

IL1β
NGF
ATP
H$^+$
P2X
ASIC

VR1
5-HT
H1
EP
B1/B2
IL1-R
TrkA

TTX$_r$
(PKC)
PKA
PKC

Gene Regulation

Sub P

TTX$_r$
(TTXs)

Ref: J Gudin
People/Patients – More Complicated..
Spot the Receptor Type

Who Responds Best??
How Do You Know When You Have Succeeded?
The “Analgesic Formulary” of the Future

Descending Modulation
- Cannabinoids
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- Local Anesthetics
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- Opioids

BRAIN
- SPINAL CORD

Dorsal Horn

PNS

CNS
References for Clinical Trials

References for Clinical Trials


