Recent advances in pain management

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Outline

• Advances in basic sciences
• Implications on new pharmacological targets
• Recent technological innovations
Pain

- Protective (Nociceptive)
- Reparative (Inflammatory)
- Pathological (Neuropathic)

Basbaum AI. Current biology 1999;9:R429-431
A. Nociceptive Pain

Noxious Peripheral Stimuli
- Heat
- Cold
- Intense Mechanical Force
- Chemical Irritants

Pain Autonomic Response Withdrawal Reflex

Spinal Cord

Brain

B. Inflammatory Pain

Inflammation
- Macrophage
- Mast Cell Neutrophil Granulocyte
- Tissue Damage

Spontaneous Pain
- Pain Hypersensitivity
- Reduced Threshold: Allodynia
- Increased Response: Hyperalgesia

Brain

Spinal Cord

C. Neuropathic Pain

Spontaneous Pain
- Pain Hypersensitivity

Peripheral Nerve Damage

Spinal Cord Injury

Brain Stroke

Inflammatory soup

Peripheral sensitization

Wind-up

Repetitive afferent barrages in C-fibers induce discharges of dorsal horn neurons at progressively greater frequencies.

Central sensitization

A. Nociceptive Transmission

Nociceptor Central Terminal → Spinal Cord Transmission Neuron → Brain

Kainate AMPA

Pain

Inhibitory Interneuron

B. Central Sensitization—Acute Phase

Phosphorylation

AMPA,NMDA,NK1,TrkB

Kinases

Pain Hypersensitivity

Dorsal Horn

Recent pain targets

- Neurotransmitters – SNRI (duloxetine)
- Na channels – Lamotrigine
- Ca channels – Gabapentin, pregabalin
- Glu receptor antagonist – Topiramate
- COX-2 inhibitors – celecoxib, etoricoxib, parecoxib, lumiracoxib
Potential pharmacological targets under research and clinical trials
• COX-2 inhibitors
• Cytokine - IL1β
• Phospholipase A2
• PG synthase
• PG receptors

Lipoxygenase/Cyclooxygenase Pathway

Arachidonic acid

Phospholipase A2

12,15-LOX → Lipoxins
Inhibits bronchoconstriction, local antiinflammation

5-LOX → Leukotrienes
Inflammation, GI toxicity, antiplatelet function, Bronchoconstriction

COX-1 → Protective PGs
GI mucosa integrity, renal function, Platelet aggregation

COX-2 → Inflammatory PGs
Inflammation & Pain
Licofelone (ML3000)

- Dual 5-LOX / COX inhibitor
- Anti-inflammatory, analgesic, anti-pyretic, anti-asthmatic, reduces LTB4 production (decreases NSAID-induced gastrotoxicity), decrease cartilage degradation
- Phase III trial
- No known CVS, CNS toxicity
Target: TRPV-1 (VR1)

• Transient receptor potential vanilloid subfamily
• Mostly present in primary afferent neuron, recently found in brain
• Activated by noxious heat, capsaicin, protons
• Modulated by other inflammatory mediators
• Antagonists – IBTU, capsazepine
• TRPV-1 antagonism reduces thermal & mechanical hyperalgesia
  – migraine, chronic pain relief, irritable bowel
• Implications – hair growth, carcinogenesis, appetite regulation, GI epithelium

Szallasi A et al. Trends in Molecular Medicine 2006;12:545-54
Cannabinoids

- Marijuana, cannabis, ganja, hashish, weed, pot, grass, hemp - Cannabis sativa
- Endogenous cannabinoids
  - Anandamide, 2 arachidonyl glycerol
- Synthetic Tetrahydrocannabinol (THC)
- Anti-inflammatory, anti-hyperalgesia, analgesia, muscle relaxation, antiemetic, bronchodilation, anti-neoplastic, stimulate appetite, improve mood

Target: Cannabinoid receptors

- Cannabinoid receptors
  - CB1 (mainly central) – at nerve terminals, modulates NT release
  - CB2 (mainly peripheral) - on immune cells, modulates cytokine release
- Selective CB2 receptor activation anti-inflammatory, analgesia without CNS SE
- Central CB1 receptors activation causes CNS SE – ataxia, psychotrophic SE, catalepsy

Target: NMDA receptor

- Ketamine
- Dextromethorphan
- MK801
- CNS 5161
- Main problem with psychomimetic SE
- Aiming for targets beyond NMDA receptors eg PKC
Summary of mechanisms

Peripheral site of injury

Central spinal cord dorsal horn site

Pain targets ….. is a single magic bullet possible?
Biopsychosocial model

- Significant advancement
- Importance of fear avoidance belief, mood, distress, poor coping strategies, cognitive functioning, environmental factors
- Cognitive behaviour based pain management programme
  - Improves function & HRQOL
  - Reduce healthcare utilisation
  - Increase RTW

Evidence

- Lindstrom I. Spine 1992
- Nicholas M. Pain 1992
- Flor H. Pain 1992
- McQuay H. 1997
- Jensen T. Pain 1998
- Morley S. Pain 1999
- Van Tulder M. Spine 2001
- Guzman D. 2001 (BMJ) 2002 (Cochrane Collaboration)
- Mc Cracken L. Spine 2002
- Linton SJ. Spine 2006
- Airaksinen O. Eur Spine J 2006
- Koes BW. BMJ 2006
### Table 1. Self-Reported Pain, Function, Fear and Medication Usage at the 5-Year Follow-Up for the Cognitive Behavioral and Information Comparison Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cognitive Behavioral</th>
<th>Information Comparison</th>
<th>( P ) (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average back pain (3 mos) (mean 0–10)</td>
<td>3.69</td>
<td>4.28</td>
<td>0.05*†</td>
</tr>
<tr>
<td>Worst back pain (0–10)</td>
<td>5.10</td>
<td>6.01</td>
<td>0.01*†</td>
</tr>
<tr>
<td>Back pain past wk (0–10)</td>
<td>3.82</td>
<td>4.04</td>
<td>0.63†</td>
</tr>
<tr>
<td>Activities of daily living (0–60; 60 = maximum function)</td>
<td>42.87</td>
<td>37.43</td>
<td>0.001*†</td>
</tr>
<tr>
<td>SF-36 Function (0–3)</td>
<td>2.17</td>
<td>1.66</td>
<td>0.001*†</td>
</tr>
<tr>
<td>Fear mFABQ (0–24)</td>
<td>14.69</td>
<td>15.45</td>
<td>0.67†</td>
</tr>
<tr>
<td>Medication use (No. ds/wk used)</td>
<td>0.99</td>
<td>1.58</td>
<td>0.04*†</td>
</tr>
</tbody>
</table>

*Statistically significant.
†Mann-Whitney \( U \) test.
Supraspinal mechanisms

Dynamic cortical pain processing

fMRI slices at same time point during separate forearm and leg stimulation
**Insular cortex**

- Most frequently activated structure in fMRI studies of pain
- Electrical stimulation of posterior insula causes pain and thermal sensation in distinct site on contralateral body
- Damage to insula causes asymbolia ie pain without suffering (affective quality lost)
- Convergence of neuroanatomy and multidimensional nature of pain – site of sensory affective integration

Anticipation of pain on fMRI

Increases activities in PAG, VTA, ACC, entorhinal cortex, posterior insula

Anticipation & Belief

• Provides functional evidence that mere expectation of pain and injury can influence pain perception
• Fear-avoidance belief, catastrophizing (negative orientation) attitude, mood likely similar effect
• Must be addressed in pain mx

Spinal cord stimulation

- Technology advances
- Systematic review
  - 67% overall had >50% pain reduction > 6mths
  - Effective in CRPS (83%), PHN (82%), limb ischaemia (77%), peripheral neuropathy (67%), FBSS (62%), PLP (62%)

Deep brain stimulation

- Meta-analysis 1966-2003 (Jan)
- PAG-PVG + sensory thalamus/internal capsule 79-87%
- DBS effective for nociceptive pain, FBSS, less so for neuropathic pain
- Invasive procedure
- Will newer technology of neuroimaging & neuromodulation improve results?

Transcranial magnetic stimulation

• Mechanism due to
  – inhibition of limbic system - secondary activation of pain and mood regulating regions eg cingulate gyrus, insula, hippocampus

• Prefrontal rTMS
  – Facial pain, FMS, post-gastric bypass

• Motor cortex rTMS

Iontophoresis transdermal system

- Electrotransport delivery platform technology (E-TRANS/IONSYS)
- Low-intensity direct current
- Hydrogel reservoir into the skin
- No depo in skin

Koo PJ. Am J Health Syst Pharm 2005;62:1171-6
Fentanyl iontophoretic PCTS

- Patient-controlled transdermal system
- Bolus dose 40 ug
- Dose interval 10 min
- Designed for max dose 80 times or 24h
- Audible beep & LED light indicator

IONSYS by Ortho-McNeil Pharmaceutical (formerly E-Trans)
Liposome-encapsulated preparations

- Liposome-encapsulated extended release morphine
  - Single epidural injection lasting 48h
  - SE – vomiting, pruritus, O2 desaturation
- Intranasal opioid aerosols
  - Fentanyl, Morphine
  - Breath activated nebuliser
  - Rapid onset, deep-lung dosing
  - Variable bioavailability
  - SE

The non-concentric vesicles are surrounded by a lipid membrane, and each contains an internal aqueous chamber with morphine sulfate solution.

1. SkyePharma Website. DepoFoam™ overview  
Intravenous Paracetamol

Frequency of administration
15-minute infusions every 4-6 hours (maximum 4 per day)

Suggested time of first administration
In the operating theatre because the analgesic effect peaks one hour after injection

Dosing
Adults
• 1 g per infusion
(→ maximum 4 g per day from all sources of paracetamol)

Children (≤ 33 kg)
• 15 mg/kg (1.5 mL/kg) per infusion
(→ maximum 60 mg/kg per day)
• neonates (< 10 days) 7.5 mg/kg
(0.75 mL/kg) per infusion (→ maximum 30 mg/kg per day)
• minimum interval between infusion – 6 hrs

Elderly patients
No dose adjustment required
Advances in pain relief treatment concept

- Traditionally target disease mechanism or symptomatic relief
- Pain not driven by disease but by pain mechanisms
- Assess pain related symptoms and signs to determine mechanisms involved
- Psychosocial & environmental factors important
Conclusion

• PAIN
  – Complex problem
  – Major advances in understanding pain
  – New technology
  – Brighter future in pain management
Thank you