Recent advances in neuropharmacology related to acute pain

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A struggle between the outer and inner worlds
Key types of pain

Nociceptive pain
Pain caused by an inflammatory or non-inflammatory response to a noxious stimulus
Tissue damage

Neuropathic pain
Pain initiated or caused by a primary lesion or disease in the peripheral or central nervous system
Nerve damage

Both types of pain can co-exist

Low back pain, cancer pain etc
Pain is unique

Sensory aspects of pain - 
threshold, intensity and location

Psychological aspects of pain - 
unpleasant, threatening, aversive

Social, economic issues 
depression, anxiety, sleep disorders etc
Activity generated within CNS pain circuits

- Higher centres
- Brain stem mechanisms and descending controls
- Spinal events
- Peripheral events
Inflammation – ongoing activation of pain sensors

- Sensitize, activate
- COX 1/2
- Capsaicin, heat
- ATP, H+, PGs
- Na+, K+, Ca²⁺ channels
- 5HT, NGF
- C-fibre
- Cytokines

Inflammation leads to the ongoing activation of pain sensors through various mechanisms involving neurotransmitters and enzymes such as COX 1/2 enzymes.
Tissue damage induces cyclooxygenase 2

Upregulation after tissue damage
Nerve Growth Factor - Direct peripheral, direct gene effects and indirect...


_Nat Clin Pract Rheumatol_ doi:10.1038/ncprheum0982
Tanezumab - humanized Monoclonal Antibody

10pM >100 hr stable binding
Prevents TrkA action

Excess of NGF in states of inflammation

Loss of NGF role in neuropathy
Neuropathy - nerves tend not to heal...

A-beta fibres
  Non-noxious
A-delta fibres
  Some noxious
C-fibres
  Noxious

Disordered conduction
Accumulations of channels
Ectopic and ephatic activity
De-novo channels

Calcium  Potassium  Sodium
Na$^{2+}$

DEPOLARISATION

Repolarisation

Slight Depolarisation

Fast Inactivated State

Classical Anticonvulsants

Local Anaesthetics

Na$^{2+}$

Lacosamide

Slow Inactivated State
Sodium channels

**Nav 1,7**
- Expressed in fine fibres
- Mutations cause sensory and autonomic changes in erythermyalgia - analgesia

**Nav 1,8**
- Unique to fine fibres
- Roles in pain in animals and esp mechanical

**Nav 1,3**
- Upregulated in DRG, cord after nerve injury - also in brain after SCI - central pains?

**Nav 1,5**
- Cardiac but implicated in visceral pain

Block multiple channels - TTX and 1.5?
## Channelopathic pain syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Channel</th>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited erythromyalgia</td>
<td>Nav 1.7</td>
<td>Lower threshold, enhanced responses</td>
<td>Attacks of burning pain and redness in extremities</td>
</tr>
<tr>
<td>Paroxysmal extreme pain disorder</td>
<td>Nav 1.7</td>
<td>Impaired inactivation, enhanced response</td>
<td>Episodes of lower body, ocular, jaw pain</td>
</tr>
<tr>
<td>Channelopathy associated insensitivity to pain</td>
<td>Nav 1.7</td>
<td>Loss of function</td>
<td>Inability to sense pain</td>
</tr>
<tr>
<td>Familial episodic pain syndrome</td>
<td>TRPA1</td>
<td>Enhanced response</td>
<td>Episodic upper body pain, triggered by fasting, cold, fatigue</td>
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</tbody>
</table>
A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome.

Irritant sensor

Upper body pain

Triggered by
- cold
- hunger
- fatigue
- exertion

Prodermal......pain 1.5 hrs......sleep

Normal acute pain

Channels are key to neuropathic pain

Major spinal increases in excitability

Damaged Zone

Electrical activity

α₂δ ligands

Release of transmitters

Carbamazepine

Lidocaine
Upregulated alpha-2 delta subunits in the spinal cord on the side of nerve injury

Pregabalin at effective doses prevents function of the subunit

Pregabalin and Alpha-2 Delta 1

- Traumatic neuropathy upregulates alpha-2 delta 1
- In all peripheral fibres and dorsal columns
- Corresponds to nerve territory
- Pregabalin has no gene effect
- Pregabalin at behavioural dose prevents movement of alpha-2 delta 1 to the membrane - trafficking
  If the channel is not in the membrane then it cannot function normally.....state-dependent effect
Primary hyperalgesia

PERIPHERAL ACTIVITY

Tissue damage

Nerve damage

PERIPHERAL ACTIVITY

Decreased threshold to peripheral stimuli

Increased spontaneous activity

Expansion of receptive field

Secondary hyperalgesia

Central sensitization

FMS

OIH

Hyperalgesia

Spontaneous pain

Allodynia

Secondary hyperalgesia
NMDA receptors and wind-up

NMDA-R mediated amplification & prolongation of response

Decay dependent on peripheral input

ketamine

secs - hours - weeks
(intensity and frequency of stimulus)

D’Mello RD, Dickenson AH. Br J Anaesthesia 2008;101:8-16

Increased excitability

Stimulus no.

Stimulus number

Neuronal response
Spinal mechanisms - central hypersensitivity

Wind-up - temporal summation
Long-term potentiation

Peripheral and descending pathways converge …
Genes related to memory processes, responses to the outside world etc.

Rygh LJ et al. Eur J Neurosci 2006; 761-72
Differential development of central hypersensitivity and a measure of spinal cord hyperexcitability following whiplash injury

Sterling M. Pain 2010 in press
Non-neuronal cell changes - the issue of timing.....

![Graph showing post-operative pain and gliosis over time]

- Priming - dormant?
- Trigger?
Noradrenaline and 5HT

Limbic System
Amygdala
Hypothalamus

Periaqueductal grey

Rostroventral medial medulla

Mood, fear, anxiety, rage, panic, sleep-wake….

Locus coeruleus

Neutral Cell

On-Cell

Off-Cell

Inhibitory and excitatory controls
Pain changes our brain functions

- Difficulty sleeping: 60%
- Lack of energy: 55%
- Drowsiness: 39%
- Concentration difficulties: 36%
- Depression: 33%
- Anxiety: 27%
- Poor appetite: 18%

% patients with moderate to very severe discomfort due to symptoms (n=126)

Brain stem mechanisms and descending controls

Neuropathy - loss of NA inhibition - gain of 5HT facilitation

5HT - anxiety, sleep issues

NA - depression, sleep issues

Hyperexcitability through spinal events

Peripheral transduction
Excitations up – Inhibitions down
Time ..... The pain moves....

Could there be time-related events in neuropathic pain?

Bee LA, Dickenson AH. *Pain* 2008;140:209-23
GBP reduces hyperalgesic signals in human brainstem etc
Iannetti et al
PNAS 2006
Psychophysical and Functional Imaging Evidence Supporting Presence of Central Sensitisation in a Cohort of Osteoarthritis Patients

Modes of action
Tapentadol vs. Tramadol

Tramadol - mu opioid binding/ NA and 5HT uptake block
Direct opioid receptor inhibition via metabolite
Isomers acting on monoamines

Tapentadol - mu opioid and NA only – removes pro-pain 5HT - single entity

NA

5HT - pain, nausea and GIT issues

Mu opioid

Synergy

NA

Mu opioid
Tapentadol + Intense pain

Brainstem

Supraspinal opioid action

Noradrenaline

Increased NA inhibition

MOR - NRI

Spinal opioid action

Alpha-2

5HT₁

5HT₂,₃
Severe pain

Tapentadol

MOR - NRI

MOR

NRI

MOR
Tapentadol – Two mechanisms on neurons

Naloxone

Mu opioid

Same receptor structure
Similar mechanisms
Similar potassium channels

Mechanical SNL

Atipamezole

NA alpha-2
• Increases in efficacy on spinal neuronal hypersensitivity after nerve injury
  • Increased effects on brush and heat
• Equal potency, greater efficacy than morphine in nerve injury
  • Opioid and alpha-2 adrenoceptor synergy
• Move to greater alpha-2 adrenoceptor actions after nerve injury

Systemic tapentadol modulates spinal opioid function and increases spinal NA
**Targets for therapy**

**Trauma**

**Genes may protect or predispose**

**Multiple mechanisms**

**Signs and symptoms**

![Diagram showing PWT (g) over days and weeks post nerve ligation with data points for Harlan: Sham, Harlan: Ligated, Holtzman: Sham, and Holtzman: Ligated with N=4-21.](image)
Symptoms

Mechanism

ongoing
Calcium channel function increases. Wind-up and long-term potentiation are induced. Brain facilitations up, inhibitions down.

Peripheral level: Altered nerve function.

CNS level: Calcium channel function increases. Wind-up and long-term potentiation are induced. OPIOIDS (Tapentadol).

Multi-drug: Lidocaine, Lacosamide, Tanezumab, Qutenza, CBZ. NMDA blockers. GBP PGB. TCA duloxetine.