Targeting the CNS for drug discovery for pain

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Jean-Joseph-Xavier Bidaud (1758-1846) Vien: Siege of a City(1795)
Central targets

- Avoid potential redundancy of peripheral targets
- Potentially blunt pain co-morbidities
- Broader actions
- Increase inhibitions and decrease excitations

- Tolerability
- Multiple roles - GABA, AMPA-R etc
- Compensations
- Dependence issues
Persistent post-surgical pains

Understanding 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 distribution

Generalized pain
No tissue or nerve damage

Cancer pain, Low Back Pain

Persistent post-surgical pains
Activity generated within CNS pain circuits

Higher centres

Brain stem mechanisms and descending controls

Spinal events

Peripheral events

Inflammation

Neuropathy
**Limbic brain**
**Affective aspects of pain**
Fear, anxiety, sleep

**Spinal cord**
Integrates, amplifies and modifies incoming messages
Output to brain

**Descending controls**
Allow top-down processes to alter pain - link mood, sleep and pain

**Incoming peripheral nerves**
- Convey touch, temperature
- Convey painful messages - heat, mechanical, chemical
- Are altered by tissue and nerve damage

PN – pontine nuclei
NC – nucleus coeruleus
PBN – parabrachial nucleus
RVM – rostral ventromedial medulla
NTS – nucleus tractus solitarius
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
Right CeA has a higher response to stimuli in late SNL animals, independently of the side of surgery.

SNL animals increase evoked activity changes throughout post surgery time – higher in the right CeA, 14 days after.
Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. Caterina Mainero MD, PhD¹, Jasmine Boshyan BS¹, Nouchine Hadjikhani MD, PhD¹,²,*
Visual analogue scale (VAS)

A Nociceptive specific

B Wide dynamic range

Threshold

No pain

Worst possible pain

Action potentials

von Frey (g)

Heat (Joules)

Spikes (total in 1-10s)

NRS

No pain

Worst possible pain

Threshold

Visual analogue scale (VAS)
Into the CNS ...
Marked changes in calcium channel function
Pregabalin on spinal neurones - partial reduction - state dependent
GBP reduces hyperalgesic signals in human brainstem etc

Iannetti et al. PNAS 2006
Spinal Mechanisms - Central Hypersensitivity

Wind-up - temporal summation
NMDA receptor activation

Peripheral and descending pathways converge ...

Early C-fibre inputs

Subsequent inputs

Altered pain states
Stimulus no.

1 6 12 16

Increased excitability

Peripheral contribution
spinal events
what the brain receives

Ketamine modulates
PERIPHERAL ACTIVITY

Tissue damage

Nerve damage

CREASED threshold to peripheral stimuli

Expansion of receptive field

Increased spontaneous activity

CENTRAL SENSITIZATION

Hyperalgesia

Spontaneous pain

Allodynia

Tissue damage

Nerve damage

Decreased threshold to peripheral stimuli

Expansion of receptive field

Increased spontaneous activity
OIH with morphine
7 days

Enhanced mechanical and thermal coding - spinal neurones

Completely normal periphery
Increased wind-up and spread of pain in knee OA patients.
A small group of spinal NK1 R neurones...required for wind-up via spinal mechanisms
Noradrenaline and 5HT

Limbic System
Amygdala
Hypothalamus

PAIN

Periaqueductal grey

Rostroventral medial medulla

Locus coeruleus

On-Cell

Off-Cell

Noradrenaline and 5HT

Inhibitory and excitatory controls

Mood, fear, anxiety, rage, panic, sleep-wake….
Pain sensitivity in fibromyalgia is associated with catechol-O-methyltransferase (COMT) gene.

Serotonin transporter gene (SLC6A4) polymorphism in patients with irritable bowel syndrome and healthy controls.

Descending controls
Allow top-down processes to alter pain - link mood, sleep and pain

Incoming peripheral nerves
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Spinal cord
Integrates, amplifies and modifies incoming messages
Output to brain
Descending inhibitions in humans......
Descendent facilitations in humans

Translation to patients

Psychophysical and Functional Imaging Evidence Supporting Presence of Central Sensitisation in a Cohort of Osteoarthritis Patients

PAG activation

Patients > Controls

High PainDETECT > Low PainDETECT

% change of BOLD signal (vmax) within PAG mask

Diffuse noxious inhibitory controls (DNIC)

- Extra-segmental inhibitions - via brain
- Maximal in primary insomnia
- Slowed in chronic fatigue disorder
- Reduction relates to chronic post-op pain
- Reduced in fibromyalgia
- Altered by gender, age....
- Reduced in opioid hyperalgesia
Descending excitations, descending inhibitions

Promotes

Protects

5-HT

NA
Excitations up – Inhibitions down

Reduced NA function - mood and sleep change
Increased 5HT function - anxiety, fear, sleep change
Spinal - brainstem - spinal loops - increase - 5HT promotes

Inhibitions

RVM 5HT

Facilitations

5HT3

Hyperalgesia

PERIPHERAL NEUROPATHY
SPINAL INJURY
CHEMICAL NOCICEPTION
CANCER INDUCED BONE PAIN
OPIOID HYPERALGESIA
FMS, IBS etc ??

NOXIOUS innocuous
Neuropathy - endogenous 5HT promotes pain

Ipsilateral hindpaw

Contralateral hindpaw

Deplete 5HT
Reduce allodynia
Descending facilitations allow hypersensitivity.
Descending inhibitions protect....

<table>
<thead>
<tr>
<th>Strain 1</th>
<th>Normal</th>
<th>Strain 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNL Surgery</td>
<td>No Surgery (from Strain 1)</td>
<td>SNL Surgery</td>
</tr>
<tr>
<td>85% mechanical hypersensitivity</td>
<td></td>
<td>50% mechanical hypersensitivity</td>
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Opioid mechanisms

C-fibre

Substance P etc

Glutamate

Descending controls

To the brain

Opioid

Spinal cord neurone
Bench to bedside

- Triptans
- COX-2 inhibitors
- CGRP blockers
- ABT - nACR
- GBP in pain
- Ketamine analgesia
- TCA, SNRI etc analgesia
- Sodium and TRP channel subtypes - inherited pain syndromes
  - (Lacosomide)
  - NGF ab
- NK1 antagonists
- NMDA antagonists
- Channel blockers
Tapentadol – Two mechanisms on neurones

Naloxone               Yohimbine/Atipamezole

Mu opioid             NA alpha-2

Same receptor structure
Similar mechanisms
Similar potassium channels

Mechanical SNL
Tapentadol: Analgesia and Antihyperalgesia in Opioid Receptor Knock-Out Mice

Activity in OPRM1 KO and WT mice

Antinociceptive and antihyperalgesic efficacy of Tapentadol partially retained in MOR knock-out mice

Koegel B, Neuroscience Letters 2011
Calcium channel function increases.

Wind-up and long-term potentiation are induced.

Brain facilitations up, inhibitions down.

Peripheral level
- Altered nerve function
- Tissue damage

CNS level
- Wind-up and long-term potentiation are induced

Multi-drug

OPIOIDS
- Tapentadol

NMDA blockers
- Lidocaine
- Lacosomide
- Tanezumab
- Quetenza
- CBZ
- COX I
- TCA duloxetine
- GBP PGB

TCA duloxetine

Multi-drug

CNS level
- Brain facilitations up, inhibitions down