NEUROPATHIC PAIN: A REVIEW

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NEUROPATHIC PAIN: DEFINITION

“Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”

International Association for the Study of Pain (Treede et al. 2007)

- What about “peripheral or central origin”?
NEUROPATHIC PAIN: CLASSIFICATION

- painful peripheral neuropathies (trauma, toxic, metabolic....)
- central pain syndromes (stroke, MS....)
- CRPS
- mixed-pain syndromes (radiculopathy)

Jensen TS, Pain 2003
NEUROPATHIC PAIN: DIAGNOSIS

Not painful findings:
1. Area of maximum pain is coextensive with or within an area of sensory deficit (numbness)
2. Paresthesia

Painful findings:
1. Spontaneous pain (i.e. shooting)
2. Evoked pain (stimulus-induced pain, mechanical hypersensitivity)

Allodynia: pain in response to a nonnociceptive stimulus

Hyperalgesia: increased pain sensitivity to a nociceptive stimulus.

Summation: progressive worsening of pain evoked by slow repetitive stimulation with mildly noxious stimuli
1) Pain sensations: unmyelinated (C) and small myelinated (Aδ) fibers

2) After disease-trauma: hypersensitization!

3) Result of increased expression of messenger RNA for voltage gated sodium channels:
   - Two voltage-gated sodium channel genes (Nav1.8 and Nav1.9)
   - An embryonic channel (Nav1.3) gene
   - Accumulation of Na⁺ lowers the action potential threshold at the:
     - Periphery (site of stimulation)
     - Centrally (within the intact dorsal root ganglion)

4) Increase expression of functional α1- or α2-adrenoceptors on cutaneous afferent fiber
   - Intravenous adrenaline or physiological noradrenaline release can excite afferent nociceptors
Uninjured fibers running in a partially lesioned nerve may also take part in pain signaling.

Spontaneous activity is present in A and C-fibers after nerve injury and this can lead to central sensitization.

In addition to spontaneous electrical activity there is upregulation of a number of genes:

1. mRNA for the vanilloid receptor
2. mRNA for calcitonin gene-related
3. a sodium channel subunit that is resistant to tetrodotoxin
4. α2A adrenergic receptors

Messages from injured nerves are not essential for neuropathic pain to occur.

NEUROPATHIC PAIN: MECHANISM

- **Peripheral sensitization**
  - Myelinated mechanosensitive fibers
    1. traumatic nerve lesions, entrapment neuropathies, or radiculopathies
    2. A-fibers
  - **Phantom limb pain**
    1. spontaneous ectopic activity in afferent A- and C-fibers projecting into the neuroma
    2. Ectopic excitation is at multiple sites in damaged sensory neurons
  - **Burning pain and heat hyperalgesia,**
    1. Erythromelalgia
    2. sensitized C-nociceptors
    3. mutation in the Nav1.7 sodium channel

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Lidocaine on the stump

Spontaneous activity

After tap on neuroma

residual activity probably comes from the dorsal root ganglia

Nystrom B, Neurosci Lett 1981
NEUROPATHIC PAIN: MECHANISM

- Peripheral sensitization
- Postherpetic neuralgia
  1. Heat hyperalgesia
  2. Changes in the density of cutaneous innervation
  3. Increased TRPV1 expression
  4. Abnormal sodium channel
NEUROPATHIC PAIN: MECHANISM

• Central sensitization:

“increased responsiveness of nociceptive neurons in the CNS to their normal afferent input”

By

1. increase of neuronal activity to noxious stimuli,
2. expansion of the size of neuronal receptive fields,
3. spread of spinal hyperexcitability to other segments
NEUROPATHIC PAIN: MECHANISM

- **Central sensitization:**
  - **Step 1:** pathological activity of C-fibers
  - **Step 2:** release of glutamate on NMDA receptors and neuropeptide substance P resulting in sensitization of second-order spinal cord dorsal horn neurons
  - **Step 3:** central neuronal voltage-gated neural-type calcium channels located at the presynaptic site facilitate the release of glutamate and substance P
  - **Step 4:** dorsal horn neurons abnormally express Nav1.3
  - **Step 5:** sensitized neurons in the thalamus and primary somatosensory cortex
HYPERALGESIA

- **MECHANICAL ALLODYNYA**
  1. A-fiber mechanoreceptors, in the presence of central sensitization, gain access to the nociceptive system
  2. These large myelinated axons normally encode non-painful tactile stimuli

- **HYPERALGESIA TO PINPRICK**
  1. Signaled by non-sensitized, heat-insensitive, Aδ-nociceptors
  2. Sensitive skin area expands widely into the secondary zone indicating CNS changes
BRAIN AND HYPERALGESIA

Pin-prick pre capsaicin
A

Pin-prick post capsaicin
B

Thermal pre capsaicin
C

Thermal post capsaicin
D

S2: secondary somatosensory cortex; MFC: middle frontal cortex; PA: parietal association cortex; SFC: superior frontal cortex.

Maihofner C, NeuroImage, 2005
BRAIN AND HYPERALGESIA

**Pin-prick post capsaicin**

**Thermal post capsaicin**

“pin-prick hyperalgesia” minus “pin-prick stimulation” and “thermal hyperalgesia” minus “thermal stimulation”: stronger activation of ACC, contralateral MFC and anterior insula.

S2: secondary somatosensory cortex; MFC: middle frontal cortex; PA: parietal association cortex; SFC: superior frontal cortex; ACC: anterior cingulated cortex.

Maihofner C, NeuroImage, 2005
PHARMACOLOGICAL OPTIONS

- **Calcium-Channel modulators:**
  1. Gabapentin and Pregabalin bind to the α2δ-subunit of presynaptic calcium channels
  2. Ziconotide: intrathecal
      (conotoxin derived from the sea snail, Conus magus or “cone snail)

  They both inhibit the release of nociceptive neurochemicals like glutamate, calcitonin gene-related peptide (CGRP), and substance P in the brain and spinal cord
PHARMACOLOGICAL OPTIONS

- **Opioids (??????):**
  1. Tramadol: noradrenaline and serotonin reuptake inhibitor with a major metabolite that is a \( \mu \)-opioid agonist.
  2. Tapentadol: similar mechanism

- **NMDA-Receptor Antagonists (???):**
  1. Ketamine

**LETS FORGET ABOUT THIS ONE:**

( High-concentration capsaicin patch)
• American Academy of Neurology
  1. Pregabalin and Duloxetine
  2. Tricyclic antidepressants and Gabapentin

• International Association for the Study of Pain
  1. Tricyclic antidepressants and Duloxetine
  2. Gabapentin and Pregabalin
  3. If localized: lidocaine patches
  4. Tramadol and opioids in general
TREATMENT GUIDELINES

• International Association for the Study of Pain

If everything fails try:

1. certain antidepressant medications (eg, bupropion, citalopram, and paroxetine),
2. certain antiepileptic medications (eg, carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid),
3. topical low concentration capsaicin,
4. dextromethorphan, memantine,
5. mexiletine

Dworkin RH, Mayo Proceedings, 2010
ADHERENCE TO RECOMMENDED GUIDELINES

Commercial Claims and Encounters (Commercial) and Medicare databases: patients with PHN:

- 13% of patients: no treatment
- 30% of patients did not start with prescribed treatment
- 25% started with 1st line recommended treatment
- 25% started with 3rd line recommended treatment or non-recommended treatment (i.e. steroids, NSAID’s, acetaminophen)
- 50% started with 2nd line recommended treatment

Dworkin RH, Pain, 2012