A Caress or a Slap: Understanding Sensory Amplification Systems in Chronic Pain

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Disclosure

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  - Elsevier
### Learning Objectives

- List mechanistic characterizations of pain
- Explain differential diagnosis of widespread pain
- Describe neuronal plasticity
- Assess the utility of skin biopsy to clarify small fiber neuropathies
- Recognize sensory amplification and its existence in more chronic pain conditions than previously recognized

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#### Understanding Sensory Amplification: Mechanistic Characterization of Pain

**Any combination may be present in a given individual**

<table>
<thead>
<tr>
<th>Peripheral (Nociceptive)</th>
<th>Peripheral Neuropathic</th>
<th>Central Neuropathic or Centralized Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Inflammation or mechanical damage in tissues</td>
<td>■ Damage or dysfunction of peripheral nerves</td>
<td>■ Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia)</td>
</tr>
<tr>
<td>■ NSAID, opioid responsive</td>
<td>■ Responds to both peripheral (NSAIDs, opioids, Na channel blockers) and central (TCA’s, neuroactive compounds) pharmacological therapy</td>
<td>■ Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission</td>
</tr>
<tr>
<td>■ Responds to procedures</td>
<td>■ Classic examples</td>
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<tr>
<td>■ Classic examples</td>
<td>■ Acute pain due to injury</td>
<td>■ Fibromyalgia</td>
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<tr>
<td>■ Classic examples</td>
<td>■ Osteoarthritis</td>
<td>■ Irritable bowel syndrome</td>
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<tr>
<td>■ Classic examples</td>
<td>■ Rheumatoid arthritis</td>
<td>■ TMJD</td>
</tr>
<tr>
<td>■ Classic examples</td>
<td>■ Cancer pain</td>
<td>■ Tension headache</td>
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</tbody>
</table>

**Mixed Pain States**
Neuropathic Pain Is Associated With Sensory Amplification

- Pain arising as a direct consequence of diseases affecting the somatosensory system
  - Grading system: definite, probable, possible
  - R-D Treede et al. Neurology 2008, Proposed by IASP Neuropathic Pain Special Interest Group
- In other words: pain from the nerves, spinal cord, or brain; not originating in the bones, muscles, organs

Differential Diagnosis—Widespread Pain

- Arthritis (OA, RA)
- Polymyalgia rheumatica
- Osteomalacia
- Myopathy
- Spondyloarthopathies
- Systemic lupus erythematosus
- Fibromyalgia
- Myelopathy
- Syringomyelia
- Multiple sclerosis
- Chiari malformation
- Spinal stenosis
- Radiculopathy
- Neuropathy
- Hypothyroidism
- Diabetes
- Vitamin disorders
- Various other autoimmune disorders
Chronic Widespread Pain: British Pain Society Guidelines

- CWP including fibromyalgia is highly prevalent
- Diagnosis should be based on the presence and distribution of signs and symptoms in the absence of another defined pathological process
- Comprehensive assessment
- Goals of guideline include: to reduce variations of standards of care and enable clinicians to help patients accept a diagnosis of CWP
- Use of opioids on chronic basis discouraged


Basic Neuropathic Pain Concepts

- The pain is caused by physiology gone awry
- Most nerve damage does not lead to ongoing pain
- Severity of the damage may not correlate with severity of pain
- No test tells us if a person has pain or how bad it is
- The entire nervous system can be involved
- How often can the “pain generator” be identified?
Burden of Illness Studies

- In a study characterizing burden of illness among adults with pDPN, those with pDPN demonstrated high pain levels, which were associated with poor sleep, function and productivity
- Utilization of health care was common and greater pain severity was associated with greater costs
- Burden of illness greater among those with greater pain severity


Burden of Illness Studies (cont’d)

- 2 observational studies: one regarding HIV related neuropathic pain and the other peripheral neuropathy with small fiber involvement were presented at the APS meeting 2013
- For both groups, many subjects experienced moderate to severe pain, the economic costs were substantial and the adverse effect on quality of life notable

Sandosky, APS 2013
Quality of Life, Real Patients

- Painful DPN: impacts function, mood, quality of life
- Patients often prescribed ineffective medications
- Severity of pain correlates with function, anxiety, depression, sleep
- Improvement in pain leads to less pain interference, improved health status


Neuronal Plasticity

- The capacity of neurons to change their function, chemical profile, or structure
- Types of neuronal plasticity
  - Activity-dependent
    - Progressive increase in response of the system to repeated stimuli, also called autosensitization
  - Modulation
    - Reversible changes in excitability of neurons
  - Modification: long-lasting alterations in:
    - Expression of transmitters, receptors, and ion channels, OR
    - Structure, connectivity, and survival of neurons
    - As a result, system is grossly modified, distorted
Role of Neuronal Plasticity in Pain

- Nervous system changes in
  - Neuronal structure
  - Connections between neurons
  - Quantity/properties of neurotransmitters, receptors, ion channels
- Decreases body’s pain inhibitory systems
  - Increased pain
- Injury, inflammation, and disease are culprits
- Produces short-term and permanent changes
- Pivotal to the development of hypersensitivity of inflammatory pain
  - Enables NS to modify its function according to different conditions

Neuroplasticity in Peripheral Pain Transmission

- Tissue Injury
  - AA = arachidonic acid; PGE2 = prostaglandin E2
  - COX2 = cyclooxygenase
  - PKC, PKA = protein kinases C, A
  - Erk1/2 = extracellular signal-regulated kinases
  - TRPV1 = Transient receptor potential vanilloid 1
  - BK = bradykinin
  - IL1β = interleukin 1β
  - α = tumor necrosis factor alpha
  - TNF = tumor necrosis factor
  - IL-6, 1β = interleukin 6, 1beta
  - MOR = opioid receptor
  - Na+ = sodium ion
  - Ca2+ = calcium ion
  - Macrophage
  - Mast cell

  Il-6, 1β interleukin 6, 1beta. MOR = opioid receptor. COX2 = cyclooxygenase. PKC, PKA = protein kinase C, A. TRPV1 = transient receptor potential vanilloid 1. BK = bradykinin. AA = arachidonic acid. PGE2 = prostaglandin E2.
How Acute Pain Becomes Chronic

- **Central sensitization**
  - One of the major causes of hypersensitivity to pain after injury
  - At first, it is triggered by nociceptor input into the spinal cord (acute phase)
  - Later, it is sustained beyond the first stimulus by molecular changes in the cell (late phase)
Central Sensitization in Knee Osteoarthritis

Sequential pressure stimulation (10 stimuli, 1-s duration, 1-s interval) was applied to affected knee and remote site (tibialis anterior) in 24 patients (knee pain on visual analog scale≥6) and 24 control subjects.


Mechanism Tidbits

- Multiple mechanisms, even for the same diagnosis
- Peripheral, spinal cord, brain stem, subcortical, cortical mechanisms
- Mediators, protein synthesis, altered connections, receptor activation/deactivation
- Sodium, calcium, potassium channels and their modulation
- Excitatory amino acids
- Immune system activation
- Conditioned pain modulation
- Many sites for the sustaining abnormality
- No treatments YET available based upon a mechanism model
Various Presentations

Common Diagnoses

- Diabetic peripheral neuropathy*
- Postherpetic neuralgia*
- Radicular pain
- Traumatic peripheral nerve injury
- Complex regional pain syndrome
- Chronic postop pain
- Phantom limb pain
- HIV related neuropathy
- Spinal cord injury*
- Poststroke pain
- Trigeminal neuralgia*
- Small fiber neuropathies

* FDA approved medications available
SFN Pathophysiology:
Possible Role of Sodium Channel Mutations

- Genetic variants in the structure/function of sodium channels may lead to either loss of pain sensitivity or enhanced pain
- Inactivating mutations in SCN9A, which encodes Nav 1.7 is associated with congenital insensitivity to pain
- Gain of function mutations in SCN9A may result in SFN
- Various mutations in TRPA 1 or NAvt.8(SCN10A) and Nav 1.9 (SCN11A) also may lead to SFN
- Might this information lead to new treatments?


DPN Involves Small and Large Nerve Fibers

<table>
<thead>
<tr>
<th></th>
<th>Large fiber neuropathy</th>
<th>Small fiber neuropathy</th>
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<tbody>
<tr>
<td>Symptoms</td>
<td>Numbness, pins and needles, tingling, poor balance</td>
<td>Pain: burning, electric shocks, stabbing pain, numbness</td>
</tr>
<tr>
<td>Exam findings</td>
<td>Reflexes, proprioception Vibration, +/- motor</td>
<td>Thermal, pin-prick sensation, allodynia</td>
</tr>
<tr>
<td>Functional changes</td>
<td>Pressure, balance, fall risk</td>
<td>Nociception; protective sensation</td>
</tr>
<tr>
<td>Diagnostic test</td>
<td>EMG/NCV, sural nerve biopsy</td>
<td>QST, nerve biopsy, intraepidermal nerve fiber density (skin biopsy)</td>
</tr>
</tbody>
</table>
**Diagnostic Studies and Limitations**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Limitations of EMG/NCV</th>
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<tbody>
<tr>
<td>Blood studies</td>
<td>Insensitive in acute injury</td>
</tr>
<tr>
<td>X-ray, CT, MRI</td>
<td>Normal result does not rule out neuropathic pain</td>
</tr>
<tr>
<td>Electromyography (EMG)</td>
<td>Cannot assess function of small fiber nerves involved in most neuropathic pain</td>
</tr>
<tr>
<td>Nerve conduction velocity (NCV)</td>
<td></td>
</tr>
<tr>
<td>Quantitative sensory testing (QST)</td>
<td></td>
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<tr>
<td>Epidermal skin biopsy</td>
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**Skin Biopsy Assessment**

- Skin biopsy: has become widely accepted as a technique to evaluate the structure of small nerve fibers
- The standard is a 3-mm skin punch biopsy that can be taken from anywhere over the body
- Due to the need to compare to normal values the lower extremity is most commonly assessed, also length dependent SFN more common
- The results are expressed as the number of intraepidermal fibers per mm
- The sensitivity (78%-92%) and specificity (65%-90%) is fairly high for this technique

Loss of Skin Nerve Fibers in PHN

Think Sensitization

- This description: burning, tingling, electric, numb, or shooting
- Pain described as unusual or different than “normal” pain
- Hasn’t responded to treatment
- Take a pain history. Other pain associated with sensitization/nerves? Headache, IBS, carpal tunnel syndrome, radiculopathy, other nerve injury
Neuropathic Pain: Physical Examination

- **Appearance**
  - Red, blue, blotchy skin
  - Shiny, atrophic, loss of lines, hair, nails, sweat, edema
  - Guarding, loss of range of motion

- **Loss:** sensory deficits: light touch, vibration, monofilament, temperature

- **Positive findings:**
  - Allodynia: painful response to normally nonpainful stimuli—light touch, cold, vibration
  - Hyperalgesia: increased response to painful stimuli
  - Summation: repeated stimulus becomes more painful

Diagnostic Tests: Selective Use
Evaluate the CONDITION/DISEASE

- Abnormal Test ≠ Pain
- "Normal" Test ≠ No Pain

- Site of abnormal physiology may not be in the area of pain
- Minimal evidence that testing changes pain treatment
CWP and Multiple Sclerosis

- 10,176 MS patients responded to a questionnaire on pain
- 7579 reported experiencing pain during the month prior to the survey
- Increased pain intensity was associated with female gender, how constant the pain was and whether or not there were multiple sites of pain (more widespread)
- Those who responded with severe pain used more healthcare resources


CWP, SFPN, and Fibromyalgia

- 27 patients with fibromyalgia who satisfied the 2010 ACR criteria were compared to 30 matched controls
- 41% of skin biopsies from fibromyalgia subjects compared to 3% from controls were diagnostic for SFPN
- The Michigan Neuropathy Screening Instrument and Utah Early Neuropathy Scale scores were higher in fibromyalgia patients

CWP, SFPN, and Fibromyalgia (cont’d)

- 25 patients with fibromyalgia were compared to 10 depressed patients and controls
- Small fiber evaluation included QST, pain-related evoked potentials and quantified intraepidermal nerve fiber density and regenerating IENF of the lower leg and upper thigh
- Compared with control subjects fibromyalgia patients BUT not depressed patients had impaired small fiber function


CWP, SFPN, and Fibromyalgia (cont’d)

- Skin biopsy findings demonstrated that total and regenerating IENFs at the lower leg and upper thigh were reduced in patients with fibromyalgia compared with controls
- A reduction in unmyelinated nerve fiber bundles was seen in patients with fibromyalgia compared with depressed and control subjects
- The authors concluded that the results point towards a neuropathic nature of fibromyalgia

CWP, SFPN, and Fibromyalgia (cont’d)

- At the ACR annual meeting in 2012, 56 patients who met the 2010 ACR diagnostic criteria for fibromyalgia underwent skin punch biopsies at proximal and distal lower limb sites
- 61% of these had findings consistent with SFPN using PGP 9.5 immunolabeling

Levine T and Saperstein D. ACR 2012

CWP and Opioid-Induced Hyperalgesia

- 9/10/13: FDA announces new “safety” measures for ER/LA opioids including requiring that manufacturers conduct further studies of already approved ER/LA opioids to assess the prevalence of opioid-induced sensitivity to pain
- Multiple mechanisms including numerous molecular and cellular mechanisms of OIH have been proposed BUT precise data is lacking
- A national study is underway with the aim to better understand the true incidence of OIH

### 4 Recent Patients—1

- 47-year-old man with history of intractable migraine, unresponsive to ALL medical, interventional, and noninterventional treatments with severe burning pain in both lower extremities and less severe complaints over upper body
- Diagnosis of Ehlers-Danlos syndrome made
- 3mm skin punch biopsy of left leg and thigh demonstrates reduced intraepidermal nerve fiber density
- Recent publication suggests high prevalence of small fiber neuropathy changes is EDS
- Do these findings explain this person’s sensory amplification?


### 4 Recent Patients—2

- 70-year-old woman complaining of chronic widespread pain as well as more localized trigeminal neuralgia pain
- Diagnoses include fibromyalgia
- Detailed evaluation revealed no specific etiology
- Skin punch biopsies demonstrate reduced IENF density
4 Recent Patients—3

- 22-year-old woman with 20-year history of pelvic pain
- Symptoms have been identified as being caused by pelvic flood dysfunction
- Exercise and botulinum toxin injections worsen the pain
- Skin punch biopsy revealed reduced IENF density at both lower extremity sites

4 Recent Patients—4

- 79-year-old woman with recent stroke who several months later developed widespread pain complaints
- Referred for “pain management”
- Skin punch biopsies demonstrate reduced IENF density in lower extremity

Pathologies in Vascular Innervation Associated With Fibromyalgia

- Excessive Peptidergic Sensory Innervation of Cutaneous Arteriole-Venule Shunts (AVS) In the Palmar Glabrous Skin of Fibromyalgia Patients: Implications for Wide-Spread Deep Tissue Pain and Fatigue
- Phillip J. Albrecht, Quanzhi Hou, Charles E. Argoff, James R. Storey, James P. Wymer, Frank L. Rice

Females With Fibromyalgia Have Excessive Innervation of Cutaneous Arteriole-Venule Shunts (AVS)

AVS profiles labeled with anti-PGP in sections of hypothenar skin biopsies from control subjects (A, C, E, G, I) and from comparable age FM patients (B, D, F, H, J)
Summary

- Multiple medical conditions are associated with sensory amplification states.
- The mechanism(s) of such sensory amplification and site(s) of initiation and maintenance are uncertain most of the time.
- Recognizing sensory amplification and its existence in perhaps more conditions than previously recognized may lead to improved treatment approaches.