PATHOPHYSIOLOGY
Overview
Multiple pain mechanisms may coexist (mixed pain)

Nociceptive pain
- Somatic
- Visceral

Neuropathic pain
- Peripheral
- Central

Central sensitization/dysfunctional pain
What is neuropathic pain?

**Neuropathic Pain**

Pain caused by a lesion or disease of the somatosensory nervous system

- **Peripheral Neuropathic Pain**
  Pain caused by a lesion or disease of the peripheral somatosensory nervous system

- **Central Neuropathic Pain**
  Pain caused by a lesion or disease of the central somatosensory nervous system

# Nociceptive vs. Neuropathic Pain

<table>
<thead>
<tr>
<th>Nociceptive</th>
<th>Neuropathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Usually aching or throbbing and well-localized</td>
<td>• Pain often described as tingling, shock-like, and burning – commonly associated with numbness</td>
</tr>
<tr>
<td>• Usually time-limited (resolves when damaged tissue heals), but can be chronic</td>
<td>• Almost always a chronic condition</td>
</tr>
<tr>
<td>• Generally responds to conventional analgesics</td>
<td>• Responds poorly to conventional analgesics</td>
</tr>
</tbody>
</table>

Neuropathic Pain Is Characterized by Changes in Pain Response to Painful Stimuli

Pain intensity

10
9
8
7
6
5
4
3
2
1
0

Stimulus intensity

Hyperalgesia
(increased response to a stimulus that is normally painful)

Allodynia
(pain due to stimulus that does not normally provoke pain)

Injury

Normal pain response

Response after injury

Etiology
Neuropathic Pain Conditions May Affect Various Parts of the Somatosensory Nervous System

Lumbar Radiculopathy¹  
Carpal Tunnel Syndrome²  
Diabetic Peripheral Neuropathy³

Neuropathic Pain Has a Wide Variety of Etiologies

Complex Regional Pain Syndrome

• **What is it?**
  – Exaggerated response to trauma, characterized by intense prolonged pain, delayed recovery of function, vasomotor disturbances and trophic changes
  – Causes are unclear, but may include exaggerated local inflammatory response, nerve injury and involvement of the central and peripheral somatosensory nervous systems

• **How common is it?**
  – Thought to occur in 1 in 2000 cases of limb trauma

• **How should it be treated?**
  – Physiotherapy is the mainstay of treatment
  – Combination of pharmacological agents may be necessary

Pathophysiology
Development of Neuropathic Pain

Nerve damage

- Metabolic
- Traumatic
- Ischemic
- Toxic
- Hereditary
- Infectious
- Compression
- Immune-related

Mechanisms

- Spontaneous pain
- Stimulus-evoked pain

Etiology

- Nerve damage

Pathophysiology

- Etiology

Symptoms

- Pathophysiology

Syndrome

- Symptoms

Neuropathic pain

Pathophysiology of Neuropathic Pain

Peripheral mechanisms
- Membrane hyperexcitability
- Ectopic discharges
- Transcriptional changes

Central mechanisms
- Hyperexcitability
- Loss of inhibitory controls
- Reorganization

Sensitization
- Peripheral
- Central

Neuropathic pain

Mechanisms of Neuropathic Pain in Diabetic Peripheral Neuropathy

**Peripheral Mechanisms**
- Changes in sodium channel distribution and expression
- Changes in calcium channel distribution and expression
- Altered neuro-peptide expression
- Sympathetic sprouting
- Loss of spinal inhibitory control
- Altered peripheral blood flow
- Axonal atrophy, degeneration or regeneration
- Damage to small fibers
- Increased glycemic flux

**Central Mechanisms**
- Central sensitization
- Changes in the balance of facilitation/inhibition with descending pathways
- Increased thalamic vascularity

## Sensory Processing and Neuropathic Pain

<table>
<thead>
<tr>
<th>Nerve function</th>
<th>Stimulus</th>
<th>Primary afferent</th>
<th>Sensation</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Innocuous Mechanical</td>
<td>A(\beta)</td>
<td>Normal touch</td>
<td>Normal function</td>
</tr>
<tr>
<td>Structural</td>
<td>Noxious Mechanical Thermal Chemical</td>
<td>A(\delta) nociceptor C nociceptor</td>
<td>Normal sharp pain Normal burning pain</td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>Innocuous Mechanical</td>
<td>A(\beta)</td>
<td>Tactile hypoanesthesia</td>
<td>Decreased transmission of impulses</td>
</tr>
<tr>
<td>Structural</td>
<td>Noxious Mechanical Thermal Chemical</td>
<td>A(\delta) nociceptor C nociceptor</td>
<td>Mechanical Heat or cold hypoalgesia</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Innocuous Mechanical</td>
<td>A(\beta)</td>
<td>Dynamic mechanical alldonyia</td>
<td>Many theories (e.g., sensitization)</td>
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<tr>
<td>Structural</td>
<td>Noxious Mechanical Thermal Chemical</td>
<td>A(\delta) nociceptor C nociceptor</td>
<td>Mechanical Heat or cold hyperalgesia</td>
<td>Many theories (e.g., wind-up, peripheral sensitization)</td>
</tr>
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Neuropathic Pain: $A\beta$, $A\delta$ and $C$ Fibers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$A\beta$ fibers</th>
<th>$A\delta$ fibers</th>
<th>$C$ fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter</td>
<td>Large</td>
<td>Larger</td>
<td>Small</td>
</tr>
<tr>
<td>Myelination</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>Rapid</td>
<td>Intermediate</td>
<td>Slow</td>
</tr>
<tr>
<td>Activation stimuli</td>
<td>Non-noxious mechanical</td>
<td>Noxious</td>
<td>Noxious</td>
</tr>
</tbody>
</table>

Mechanisms of Neuropathic Pain

Nerve lesion/disease

Spinal cord Nociceptive afferent fiber

Loss of inhibitory control

Central sensitization

Ectopic discharge

Descending modulation

Peripheral sensitization

Nerve lesion/disease

Nociceptive afferent fiber

Brain

Spinal cord

Ectopic Discharges

Nerve lesion induces hyperactivity due to changes in ion channel function.

Perceived pain

Descending modulation

Ascending input

Nerve lesion

Nociceptive afferent fiber

Ectopic discharges

Spinal cord

References:
Ectopic Discharges

- Sodium channel expression increased
- Primary excitatory afferent nerve fiber
- Conduction frequency amplified

Peripheral Sensitization

Innocuous stimulus → Neuropeptide release → Nerve growth factor (NGF) → Dorsal horn neurons → Pain

References:
Central Sensitization

After nerve injury, increased input to the dorsal horn can induce central sensitization.

- Nerve lesion
- Nociceptive afferent fiber
- Tactile stimuli
- Intact tactile fiber
- Abnormal discharges induce central sensitization

Central Sensitization

Believed to result from excessive release of 2 important neurotransmitters:

- Substance P
- Glutamate
Central Sensitization after Nerve Injury

Innocuous stimulus

NORMAL

NERVE INJURY

No pain

PAIN

Central Sensitization

Dorsal horn neuron

C fiber terminal

Inhibitory Inter-neuron

Glutamate

Substance P

AMPAT (+)

NMDA (-)

Glycine receptors

PKC (+)

COX-2 induction

PGE2

GABA

Glycine

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid;
GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate; prostaglandin E; PKC = protein kinase C

Central Sensitization

Dorsal horn neuron

C fiber terminal

Inhibitory inter-neuron cell death

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid;
GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate; prostaglandin E; PKC = protein kinase C

Central Sensitization

Establishment of aberrant excitatory synaptic connection

Dorsal horn neuron

New A fiber forming synapse

Inhibitory inter-neuron cell death

Dorsal horn neuron

Loss of inhibitory effects of inter-neurons

C fiber terminal

Glutamate

Substance P

PGE₂

Inhibitory inter-neuron

Cell death

AMP A = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid;
GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate; prostaglandin E; PKC = protein kinase C

Loss of Inhibitory Control: Disinhibition

Pain treatment options
- $\alpha_2\delta$ ligands
- Antidepressants

Loss of Inhibitory Controls

Normal

Innocuous or noxious stimulus

Injured

Spontaneous firing

Exaggerated pain response

Dorsal horn neuron

Descending

To brain

Summary
Pathophysiology: Summary

• Neuropathic pain is pain caused by a lesion or disease of the somatosensory system.
• It is characterized by positive and negative sensory symptoms.
• Peripheral and central mechanisms mediate neuropathic pain independent of etiology:
  – Hyperexcitability
  – Sensitization
  – Loss of inhibitory controls