Pain system: nociception
Distinct receptors and pathways mediate mechanical stimulation and pain perception or nociception.
**TABLE 9.1** Somatic Sensory Afferents that Link Receptors to the Central Nervous System

<table>
<thead>
<tr>
<th>Sensory function</th>
<th>Receptor type</th>
<th>Afferent axon type(^a)</th>
<th>Axon diameter</th>
<th>Conduction velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprioception</td>
<td>Muscle spindle</td>
<td></td>
<td>13–20 μm</td>
<td>80–120 m/s</td>
</tr>
<tr>
<td>Touch</td>
<td>Merkel, Meissner, Pacinian, and Ruffini cells</td>
<td>I, II, Aβ</td>
<td>6–12 μm</td>
<td>35–75 m/s</td>
</tr>
<tr>
<td>Pain, temperature</td>
<td>Free nerve endings</td>
<td>Aδ</td>
<td>1–5 μm</td>
<td>5–30 m/s</td>
</tr>
<tr>
<td>Pain, temperature, itch</td>
<td>Free nerve endings</td>
<td></td>
<td>0.2–1.5 μm</td>
<td>0.5–2 m/s</td>
</tr>
</tbody>
</table>

\(^a\)During the 1920s and 1930s, there was a virtual cottage industry classifying axons according to their conduction velocity. Three main categories were discerned, called A, B, and C. A comprises the largest and fastest axons, C the smallest and slowest. Mechanoreceptor axons generally fall into category A. The A group is further broken down into subgroups designated α (the fastest), β, and δ (the slowest). To make matters even more confusing, muscle afferent axons are usually classified into four additional groups—I (the fastest), II, III, and IV (the slowest)—with subgroups designated by lowercase roman letters!

(After Rosenzweig et al., 2005.)

*NEUROSCIENCE, Fourth Edition, Table 9.1*
Different types of pain detected by different types of nociceptors

**Primary afferent axons**

- **Aα and Aβ fibres**
  - Myelinated
  - Large diameter
  - Proprioception, light touch
  - Thermal threshold: None

- **Aβ fibre**
  - Lightly myelinated
  - Medium diameter
  - Nociception (mechanical, thermal, chemical)
  - Thermal threshold: ~53°C Type I, ~43°C Type II

- **C fibre**
  - Unmyelinated
  - Small diameter
  - Innoxious temperature, itch
  - Nociception (mechanical, thermal, chemical)
  - Thermal threshold: ~43°C

**Graph**

- Voltage over time
  - Aαβ
  - Aβ
  - C

- First pain
- Second pain
Specificity of nociception

(A) Heat stimulus

(B) Nociceptor
Stimulus
Non-nociceptive thermoreceptor

(C) Magnitude of afferent response (action potentials per second)

Thermoreceptor
Nociceptor

Temperature (°C)
0 40 45 50

NEUROSCIENCE, Fourth Edition, Figure 10.1
Arrangement for transcutaneous nerve recording

(A)
The same rate of firing of

(B)

<table>
<thead>
<tr>
<th></th>
<th>Nociceptor</th>
<th>Stimulus</th>
<th>Non-nociceptive thermoreceptor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Stimulus Graph" /></td>
<td></td>
</tr>
</tbody>
</table>

(C)

Magnitude of afferent response (action potentials per second)

![Graph](image)

**NEUROSCIENCE, Fourth Edition, Figure 10.1 (Part 2)**
2 categories of pain perception: sharp first pain & diffuse 2nd pain
Capsaicin nociception

(A) Habañero

(B) Capsaicin

(C) Molecule structure of Capsaicin

(D) Capsaicin interaction with VR-1 receptor
Peppers!

(A) Habañero
Jalapeño
Red chile

(B) Capsaicin

(C) Molecular structure of Capsaicin

NEUROSCIENCE, Fourth Edition, Box 10A (Part 1)
VR-1/capsaicin receptor channel
TRPV1 expression in dorsal horn and DRG neurons
Diversity of signal transduction mechanisms of nociceptors (b) vs. other sensory neurons (a)
Functions of TRP receptors
The pain pathway: anterolateral system
Primary nociceptive afferent: from DRG to dorsal horn
Lissauer’s track showing branched afferents connecting second-order neurons
Dissociated sensory loss due to SC lesions

- Dorsal column
- Anterolateral column
- Lesion (lower thoracic)
- Nociceptive afferents
- Mechanoreceptive afferents

- Normal sensation
- Lesion
- Zone of complete loss of sensation
- Reduced sensation of two-point discrimination, vibration, and proprioception

Right Left

NEUROSCIENCE, Fourth Edition, Figure 10.4
Parallel pain pathways

Sensory–discriminative

- Somatosensory cortex (S1, S2)
- Ventral posterior nucleus

Affective–motivational

- Anterior cingulate cortex
- Insular cortex
- Amygdala
- Hypothalamus
- Periaqueductal grey
- Superior colliculus
- Reticular formation
- Midline thalamic nuclei

ANTEROLATERAL SYSTEM
Pathways mediating pain and temperature: A. body; B: face
Pain modulation
Modulation of ascending pain signals by the descending systems
A visceral pain pathway: dorsal column pathway
Refered pain: from a visceral disorder refered to cutaneous regions
Referred Pain

- Damage to visceral produces pain which appears to come from a cutaneous site
- Cutaneous location may be far from the visceral organ
- Learn to suspect a visceral injury when no surface injury is apparent to explain the pain
- Mechanism:
  - Both cutaneous and visceral afferents of same dorsal roots converge on deep cells in dorsal horns
  - When ascending tracts reach the somatotopic map in sensory cortex, location is interpreted as coming from skin surface
Phantom limbs and phantom pain
Classification of major pain syndromes

<table>
<thead>
<tr>
<th></th>
<th>Nociceptive pain</th>
<th>Inflammatory pain</th>
<th>Neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus</td>
<td>Noxious</td>
<td>Inflammation</td>
<td>Neural damage and ectopic firing</td>
</tr>
<tr>
<td>Sensory neuron</td>
<td>Nociceptor</td>
<td>Nociceptor and non-nociceptor</td>
<td>Nociceptor and non-nociceptor</td>
</tr>
<tr>
<td>Site</td>
<td>PNS</td>
<td>PNS and CNS</td>
<td>PNS and CNS</td>
</tr>
<tr>
<td>Involvement of TRP channels</td>
<td>TRP</td>
<td>TRP</td>
<td>TRP?</td>
</tr>
<tr>
<td>Clinical setting</td>
<td>Acute trauma</td>
<td>Post-operative pain</td>
<td>PNS and CNS lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arthritis</td>
<td>Diabetic neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lumbar radiculopathy</td>
</tr>
<tr>
<td>Function</td>
<td>Protective</td>
<td>Healing/repair</td>
<td>Pathological</td>
</tr>
<tr>
<td>Pain sensitivity</td>
<td>High threshold</td>
<td>Low threshold</td>
<td>Low threshold</td>
</tr>
</tbody>
</table>
Roles of TRP channels in peripheral and central nociceptor terminals
Sensitization: Hyperalgesia & Allodynia

Unlike other somatosensory modalities, which show adaptation to continuous presentation of a stimulus, the sensation of pain becomes greater when a painful stimulus is presented repeatedly due to lowering of threshold for both mechano- and thermal nociceptors:

“hyperalgesia”
- includes a primary effect at site of injury; and a secondary effect in undamaged surrounding tissue.

“allodynia” - a related phenomenon in which non-noxious stimuli produce painful responses. Example: pain produced by lightly touching burned skin.
Nociceptor signaling in hyperalgesia

Components of Nociceptor Signaling

Parallel vs. convergent signaling models
Response complexity of primary afferent nociceptors to inflammatory mediators

- Anti-inflammatories
  - NGF
  - Bradykinin
  - Serotonin
  - ATP
  - H+
  - Lipids
  - Prostaglandins
  - Heat
  - Pressure

- Local anesthetics
  - CGRP
  - Substance P

- Opiates
  - Blood vessel
  - Spinal cord

- NSAIDs

Stimulus | Representative receptor
--- | ---
NGF | TrkA
Bradykinin | BK₂
Serotonin | 5-HT₃
ATP | P₂X₃
H⁺ | ASIC3/VR1
Lipids | PGE₂/CB1/VR1
Heat | VR1/VRL-1
Pressure | DEG/ENaC?
Changes in TRP channels produced by inflammation

Phenotypic switch:
- Inflammation (+ growth factors)  
  ↑TRPV1
- Axonal injury (− growth factors)  
  ↓TRPV1

Peripheral sensitization

Sensitizers  Receptors  Signal transduction  Cell body

Bradykinin  PGE2  NGF  TNFα  Substance P  Prokinetican  Endothelin  Trafficking

Phosphorylation  [P]

TRPV1  TRPA1  B2  EP  ETAR  PAR1  PKCε  PKA  PI3K  ERK  PKR

Ca²⁺  Anterograde transport  NGF/GDNF  Transcription  Translation  Trafficking

Peripheral terminal  Dorsal root ganglion

Nature Reviews | Drug Discovery
TRP channel antagonists and agonists as analgesics
TRP drugs under development as analgesics

- **Preclinical**
  - TRPV1 antagonists: Renovis/Pfizer, Sanofi-Aventis, Amphora, Johnson & Johnson, Renovis, Therapeutics
  - TRPV3 antagonists: Hydra Biosciences, Glenmark
  - TRPV4 antagonists: Renovis
  - TRPA1 antagonists: Abbott, Amgen, Hydra Biosciences, Genomics Institute of the Novartis Research Foundation

- **Preclinical/Phase I TRPV1 antagonists**
  - AMG628
  - AMG517
  - A0T102

- **Phase II TRPV1 antagonists**
  - GRC 6211 (Patent example)
  - SB-705498
  - MK-2295 (NGD-8243) (Patent example)

- **Phase III TRPV1 agonists**
  - NGX 4010 (capsaicin), transdermal patch
  - Zucapsaicin
  - Capsaicin, sustained-release injection

Nature Reviews | Drug Discovery