PATHOPHYSIOLOGY
Overview
Pain Is the 5th Vital Sign

Respiration  | Pulse  | Blood pressure  | Temperature

Pain
Overview of Pain

Protective role: vital early warning system
- Senses noxious stimuli
- Triggers withdrawal reflex and heightens sensitivity after tissue damage to reduce risk of further damage

Unpleasant experience:
- Suffering – physical, emotional and cognitive dimensions
- Continuous unrelieved pain can affect physical (e.g., cardiovascular, renal, gastrointestinal systems, etc.) and psychological states

Maladaptive response:
- Neuropathic and central sensitization/dysfunctional pain
- Not protective
- Lessens quality of life

The Pain Continuum

**Time to resolution**

**Insult**

**Acute pain**

- Normal, time-limited response to ‘noxious’ experience (less than 3 months)
  - Usually obvious tissue damage
  - Serves a protective function
  - Pain resolves upon healing

**Chronic pain**

- Pain that has persisted beyond normal tissue healing time (usually more than 3 months)
  - Usually has no protective function
  - Degrades health and function

Acute pain may become chronic

## Acute vs. Chronic Pain

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sudden, sharp, intense, localized</td>
<td>• Gnawing, aching, diffuse</td>
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<tr>
<td>• Usually self-limited (&lt;6 months)</td>
<td>• No definite beginning or end</td>
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<tr>
<td>• May be associated with physiologic changes (e.g., sweating,</td>
<td>• Varies in intensity; may remit briefly</td>
</tr>
<tr>
<td>increased heart rate, elevated blood pressure)</td>
<td>• Associated with psychological and social difficulties</td>
</tr>
<tr>
<td></td>
<td>• Acute pain may be superimposed</td>
</tr>
</tbody>
</table>

Acute Pain Can Become Chronic

Acute Pain Can Become Chronic

Life Cycle Factors Associated with Development of Chronic Pain

From birth
- Genetics
- Female sex
- Minority race/ethnicity
- Congenital disorders
- Prematurity
- Parental anxiety
- Irregular feeding/sleeping
- Parents’ pain exposure and reactions
- Personality

Childhood
- Physical/sexual abuse and other traumatic events
- Low socioeconomic status
- Emotional, conduct and peer problems
- Hyperactivity
- Serious illness or injury
- Separation from mother
- Acute or recurrent pain experience

Adolescence
- Changes of puberty
- Gender roles
- Education level
- Injuries
- Obesity
- Low levels of fitness

Adulthood
- Vivid recall of childhood trauma
- Lack of social support
- Accumulated stress
- Surgery
- Overuse of joints and muscles
- Occupation
- Chronic disease
- Aging

## Risk Factors for Chronic Post-operative Pain

### Pre-operative factors
- Moderate to severe pain, lasting >1 month
- Repeat surgery
- Psychologic vulnerability (e.g., catastrophizing)
- Pre-operative anxiety
- Female gender
- Younger age (adults)
- Workers’ compensation
- Genetic predisposition
- Inefficient diffuse noxious inhibitory control

### Intra-operative factors
- Surgical approach with risk of nerve damage

### Post-operative factors
- Moderate to severe acute pain
- Radiation therapy to area
- Neurotoxic chemotherapy
- Depression
- Psychological vulnerability
- Neuroticism
- Anxiety

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Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine.

Etiology
Common Causes of Acute Pain

Nociceptive Pain

Musculoskeletal injury

Burn pain

Infection, e.g., pharyngitis

Post-operative pain

Ischemic, e.g., myocardial infarction

Abdominal colic

Dysmenorrhea

Pathophysiology
Acute Pain: Normal Nociception Is Modified by Inflammation

Tissue damage zone

Activation and sensitization

Cytokines
TNFα, IL1, IL6

Growth factors
NGF, BDNF, etc.

Blood vessel

Vasodilation + plasma extravasation

PGs, H+

ATP, Bk

5HT

NGF

SP, CGRP

C fiber

5HT = serotonin; ATP = adenosine triphosphate; BDNF = brain-derived neurotrophic factor; Bk = bradykinin; CGRP = calcitonin gene-related peptide; IL = interleukin; PG = prostaglandin; NGF = nerve growth factor; SP = substance P; TNF = tumor necrosis factor.

What is nociceptive pain?

**Definition**
- Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
- Can be somatic or visceral

**Pain Quality**
- Usually aching or throbbing
- Usually time-limited (resolves when damaged tissue heals)
- Usually well localized if somatic
- May be referred if visceral
- Can become chronic

## Somatic vs. Visceral Pain

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<thead>
<tr>
<th><strong>Somatic</strong></th>
<th><strong>Visceral</strong></th>
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<tbody>
<tr>
<td>• Nociceptors are involved</td>
<td>• Involves hollow organ and smooth muscle nociceptors that are sensitive to stretching, hypoxia and inflammation</td>
</tr>
<tr>
<td>• Often well localized</td>
<td>• Pain is usually referred, poorly localized, vague and diffuse</td>
</tr>
<tr>
<td>• Usually described as throbbing or aching</td>
<td>• May be associated with autonomic symptoms (e.g., pallor, sweating, nausea, blood pressure and heart rate changes)</td>
</tr>
<tr>
<td>• Can be superficial (skin, muscle) or deep (joints, tendons, bones)</td>
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Referred Pain
Nociception: Neural Process of Encoding Noxious Stimuli

Consequences of encoding may be autonomic (e.g., elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior). Pain perception is not necessarily implied.

Nociceptive Pain

Transduction
- Transduction of noxious mechanical and chemical stimuli into electrical signals in nociceptors

Transmission
- Neuronal signals are transmitted up via the spinal cord to higher centers where they are perceived as “pain”

Modulation
- Nervous system can alter pain sensitivity via inhibition or facilitation

Transduction via Endogenous Mediators

**Noxious stimuli**
- Mechanical
- Thermal
- Chemical

**Mediators**
- Prostaglandins
- Leukotrienes
- Substance P
- Histamine
- Bradykinin
- Serotonin
- Hydroxyacids
- Reactive oxygen species
- Inflammatory cytokines and chemokines

**Receptors/channels on nociceptors**

Transmission via Neurotransmitters

1. Impulses reach terminals of presynaptic neuron
2. Glutamate is released into synaptic cleft
3. Glutamate binds to AMPA receptor
4. Impulse is transmitted to postsynaptic neuron

**Substance P**
**Presynaptic neuron**
**Synaptic cleft**
**Glutamate**
**NMDA receptor blocked by Mg^{2+}**
**AMPA receptor**
**NMDA receptor**
**NK-1**

**AMPA** = 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid; **NK** = neurokinin; **NMDA** = N-methyl-D-aspartate

Pain Modulation

- Pain is modulated via **ascending nociceptive** and **descending inhibitory/facilitatory** spinal tracts.

<table>
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<tr>
<th>Ascending Nociceptive</th>
<th>Descending Inhibitory/facilitatory</th>
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<tr>
<td>C fibers</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Aδ fibers</td>
<td>Norepinephrine</td>
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<tr>
<td></td>
<td>Dopamine</td>
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Pain Perception

• Spinal cord transmits pain signals to specific nuclei in the thalamus, and from there to wide variety of regions in the brain – collectively known as the “pain matrix”

• Pain perception can also be altered without any external stimuli (i.e., through emotion, distraction, placebo, etc.)

Inflammation

- Nociceptive afferent fiber
- Inflammation
- Damaged tissue
- Inflammatory cells
- Tumor cells
- Changed responsiveness of nociceptors (peripheral sensitization)

Brain

- Inflammatory chemical mediators
- Prostanoids
- Cytokines
- Growth factors
- Kinins
- Purines
- Amines
- Ions

Spinal cord

- Changed responsiveness of neurons in CNS (central sensitization)

CNS = central nervous system
Central Sensitization

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

C fiber terminal

New A fiber forming synapse

Inhibitory inter-neuron cell death

Dorsal horn neuron

Loss of inhibitory effects of inter-neurons

Establishment of aberrant excitatory synaptic connection

Dorsal horn neuron

COX-2 induction

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
Summary
Pathophysiology of Acute Pain: Summary

• In acute pain, normal nociception is modified by inflammation

• Acute pain may develop into chronic pain through modulation of synaptic transmission
  – Repeated activation of C fiber nociceptors and peripheral inflammation can lead to increased expression of COX-2, iNOS and c-Fos in the secondary neuron and microglia
  – Peripheral injury can generate pain hypersensitivity in neighbouring, uninjured tissues (secondary hyperalgesia) via central sensitization

iNOS = inducible nitric oxide synthase