Mechanism of pain

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Pain is an unpleasant or emotional experience originating in real or potential damaged tissue.

Pain is an unpleasant phenomenon that is uniquely experienced by each individual; it cannot be adequately defined, identified, or measured by an observer.

May not be directly proportional to amount of tissue injury.

Highly subjective, leading to undertreatment.
The experience of pain

Three systems interact usually to produce pain:

1. sensory - discriminative
2. motivational - affective
3. cognitive - evaluative

1. Sensory - discriminative system processes information about the strength, intensity, quality and temporal and spatial aspects of pain.

2. Motivational - affective system determines the individual’s approach-avoidance behaviours.

3. Cognitive - evaluative system overlies the individuals learned behaviour concerning the experience of pain. It may block, modulate, or enhance the perception of pain.
Terminology of Pain

- **dysesthesia** - experience abnormal noxious sensation
  - **paraesthesia** - abnormal nonpainful sensation;
  - **hyperpathia** - exaggerated pain response to noxious or nonnoxious stimuli)
- **allodynia** - perception of nonnoxious stimuli as painful
Terminology of Pain

- Hyperalgesia - increased pain response to painful stimuli
- Hypoalgesia - decreased sensitivity to noxious stimuli
- Hyperesthesia and hypoesthesia - increase or decrease, respectively, in sensitivity to nonnoxious stimuli
Pain categories

1. Somatogenic pain is pain with cause (usually known) localised in the body tissue
   - a/ nociceptive pain
   - b/ neuropathic pain

2. Psychogenic pain is pain for which there is no known physical cause but processing of sensitive information in CNS is disturbed
<table>
<thead>
<tr>
<th>Nociceptive Pain</th>
<th>Neuropathic Pain</th>
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<tbody>
<tr>
<td>• Mechanical or inflammatory aetiology</td>
<td>• Pain generated &amp; perpetuated by the nervous system (pain conducting system)</td>
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<td>• May be somatic or visceral in origin</td>
<td>• May be initiated by a trivial injury to the central or peripheral nervous system</td>
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<td>• The degree of pain usually reflects the degree of tissue injury</td>
<td>• The pain becomes independent of the initial triggering injury</td>
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<td>• Usually well localised</td>
<td>• Not specific to a pathological condition</td>
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<td>• Response to analgesics predictable</td>
<td>• unpredictable</td>
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Nociceptive vs Neuropathic Pain

**Nociceptive Pain**
Caused by activity in neural pathways in response to potentially tissue-damaging stimuli

- Postoperative pain
- Mechanical low back pain
- Sports/exercise injuries

**Mixed Type**
Caused by a combination of both primary injury and secondary effects

- Postoperative pain
- Mechanical low back pain
- Sports/exercise injuries
- Sickle cell crisis
- Arthritis

**Neuropathic Pain**
Initiated or caused by primary lesion or dysfunction in the nervous system

- Neuropathic low back pain
- Distal polyneuropathy (e.g., diabetic, HIV)
- Postherpetic neuralgia
- Central post-stroke pain
- Trigeminal neuralgia
- CRPS

*CRPS indicates Complex Regional Pain Syndrome.*
## Acute vs Chronic Pain

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<thead>
<tr>
<th>Characteristic</th>
<th>Acute Pain</th>
<th>Chronic Pain</th>
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<tbody>
<tr>
<td>Cause</td>
<td>Generally known</td>
<td>Often unknown</td>
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<tr>
<td>Duration of pain</td>
<td>Short, well-characterized</td>
<td>Persists after healing, 3 months</td>
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<tr>
<td>Treatment approach</td>
<td>Resolution of underlying cause, usually self-limited</td>
<td>Underlying cause and pain disorder; outcome is often pain control, not cure</td>
</tr>
<tr>
<td>Onset</td>
<td>usually sudden</td>
<td>develops insidiously</td>
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Acute to chronic

- Continuous release of inflammatory mediators in the periphery sensitizes functional nociceptors and activates dormant ones.
  - decreased threshold for activation
  - increased rate of discharge with activation
  - increased rate of basal (spontaneous) discharge.
- Intense noxious input from the periphery may also result:
  - central sensitization ("persistent postinjury changes in the CNS that result in pain hypersensitivity")
  - hyperexcitability ("exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage").
- Such noxious input may lead to functional changes in the dorsal horn of the spinal cord and other consequences that may later cause postoperative pain to be perceived as more painful than it would otherwise have been.
  - certain receptors:
    - \(N\)-methyl-\(d\)-aspartate [NMDA]
    - substance P, protein kinase C-\(\gamma\)
- In spinal neurons such a progressive increase in output in response to persistent nociceptor excitation has been termed “wind-up.”
Neuroanatomy of pain

The portions of the nervous system responsible for the sensation and perception of pain may be divided into three areas:

1. afferent pathways
2. CNS
3. efferent pathways
• When peripheral tissue is damaged by a variety of thermal, mechanical, and chemical stimuli.
• Protons
• Sympathetic amines
• Adenosine triphosphate (ATP)
• Glutamate
• Neuropeptides (calcitonin gene–related peptide, substance P)
• Nerve growth factor
• Prostaglandins
• Bradykinin
• Proinflammatory cytokines
• Chemokines.
The afferent portion

is composed of:

a) nociceptors (pain receptors)
b) afferent nerve fibres
c) spinal cord network

Pain fibers

A-delta fibers

C-fibers

Afferent pathways terminate in the dorsal horn of the spinal cord (1st afferent neuron)
The small unmyelinated C- neurons are responsible for the transmission of diffuse burning or aching sensations.

Transmission through the larger, myelinated A- delta fibers occurs much more quickly. A - fibers carry well-localized, sharp pain sensations , transmits painful information that is often interpreted by the brain as burning or stinking pain.
The role of the spinal cord in pain processing

- Most afferent pain fibers terminate in the dorsal horn of the spinal segment that they enter. Some, however, extend toward the head or the foot for several segments before terminating.

- The A-β fibers, some large A-delta fibers and small C-fibers terminate in the laminae of dorsal horn and in the substantia gelatinosa.

- The laminae then transmit specific information (about burned or crushed skin, about gentle pressure) to 2nd afferent neuron.
• 2nd afferent neurons transmit the impulse from the substantia gelatinosa (SG) and laminae through the ventral and lateral horn, crossing in the same or adjacent spinal segment, to the other side of the cord. From there the impulse is carried through the spinothalamic tract to the brain. The two divisions of spinothalamic tract are known:

1. the neospinothalamic tract - it carries information to the mid brain, thalamus and post central gyrus (where pain is perceived)

2. the paleospinothalamic tract - it carries information to the reticular formation, pons, limbic system, and mid brain (more synapses to different structures of brain)
The brain

• The thalamus, sensitive cortex:
  - perceiving
  - describing
  - localising

\{ pain \}

• Parts of thalamus, brainstem and reticular formation:
  - identify dull longer-lasting, and diffuse pain

Thalamus
  - Lateral thalamic nucleus → somatosensory cortex “to feel” pain
  - Medial thalamic nucleus → frontal cortex “to realise” pain

• The reticular formation and limbic system:
  - control the emotional and affective response to pain

• Because the cortex, thalamus and brainstem are interconnected with the hypothalamus and autonomic nervous system, the perception of pain is associated with an autonomic response
FIG. 13-2. Nociceptors and spinal segment. A, Nociceptive and other afferent and efferent pathways in a spinal nerve at the dorsal horn. B, Small A-delta and C fibers from synapses primarily with cells in lamina V but also with cells in laminae IV and VI.
Efferent analgesic system

composed of the fibers connecting the reticular formation, midbrain, and substantia gelatinosa, are responsible for modulating pain sensation and inhibition of afferent pain signals

Mechanisms:
- pain afferents stimulates the neurons in periaqueductal gray (PAG) - gray matter surrounding the cerebral aqueduct in the midbrain results in activation of efferent (descendent) anti-nociceptive pathways
- from there the impulses are transmitted through the spinal cord to the dorsal horn
- there thay inhibit or block transmission of nociceptive signals at the level of dorsal horn
In response to stress, corticotropin-releasing factor, cytokines, chemokines, or catecholamines, leukocytes secrete opioids, which then activate peripheral opioid receptors and produce analgesia by inhibiting the excitability of nociceptors or the release of excitatory neuropeptides, or both.

In the spinal cord, inhibition is mediated by the release of opioids, γ-aminobutyric acid (GABA), or glycine from interneurons, which then activate presynaptic opioid or GABA receptors (or both) on central nociceptor terminals to reduce the release of excitatory transmitters.
Action of endorphins (ED)

All ED act by attaching to opiate receptors on the plasma membrane of the afferent neuron. The result than is inhibition of releasing of the neurotransmitter, thus blocking the transmission of the painful stimulus.
Descendent antinociceptive system

Enk – enkephalinergic
PAG – paraaqueductal gray
EAA – excitatory amino acids
RVM – rostral ventro-medial medulla
FIG. 13-3. Spinal cord and CNS pathway. Stimuli are transmitted from pain receptors through sensory nerves into the dorsal root ganglia. The impulse enters the spinal cord, forms a synapse, crosses the cord, and rises to the spinothalamic tract.
FIG. 13-5. Descending pathway and endorphin response. The biologic receptors of the enkephalins and endorphins are located close to known pain receptors in the ascending and descending pain pathways.
Acute effect

• the neuroendocrine stress response:
  • a combination of local inflammatory substances (e.g., cytokines, prostaglandins, leukotrienes, tumor necrosis factor-α) and systemic mediators of the neuroendocrine response.
  • The dominant neuroendocrine responses to pain involve hypothalamic-pituitary-adrenocortical and sympathoadrenal interactions.
  • Suprasegmental reflex responses to pain result in increased sympathetic tone, increased catecholamine and catabolic hormone secretion (e.g., cortisol, adrenocorticotropic hormone, antidiuretic hormone, glucagon, aldosterone, renin, angiotensin II)
  • decreased secretion of anabolic hormones
  • The effects:
    • sodium and water retention
    • increased levels of blood glucose, free fatty acids, ketone bodies, and lactate.
  • A hypermetabolic, catabolic state occurs as metabolism and oxygen consumption are increased
Acute effect

• development of hypercoagulability.
• Enhancement of coagulation (i.e., decreased levels of natural anticoagulants and increased levels of procoagulants)
• inhibition of fibrinolysis
• increased platelet reactivity and plasma viscosity
• elevated incidence of postoperative hypercoagulable-related events such as deep venous thrombosis, vascular graft failure, and myocardial ischemia.
• The stress response may also potentiate postoperative immunosuppression
• Hyperglycemia from the stress response may contribute to poor wound healing and depression of immune function.
Acute effect

• activate the sympathetic nervous system
• increase myocardial oxygen consumption, which may be important in the development of myocardial ischemia and infarction,
• decrease myocardial oxygen supply through coronary vasoconstriction and attenuation of local metabolic coronary vasodilation
• delay return of postoperative gastrointestinal motility, which may develop into paralytic ileus.
Harmful Effects

Cardiovascular and respiratory systems are significantly affected by the pathophysiology of pain

- adrenergic stimulation
- hypercoagulation, leading to DIC
- ↑ heart rate
- ↑ cardiac output
- ↑ myocardial oxygen consumption
- ↓ pulmonary vital capacity
- ↓ alveolar ventilation
- ↓ functional residual capacity
- arterial hypoxemia
- suppression of immune functions, predisposing trauma patients to wound infections and sepsis
Intermittent pain produces a physiologic response similar to acute pain. Persistent pain allows for adaptation (functions of the body are normal but the pain is not relieved).

Chronic pain produces significant behavioural and psychological changes.

The main changes are:
- depression
- an attempt to keep pain-related behaviour to a minimum
- sleeping disorders
- preoccupation with the pain
- tendency to deny pain
Good luck