PAIN

Physiology of pain relating to pain management

What is pain?

An unpleasant sensory and emotional experience associated with actual or potential tissue damage.

(Melzac and Wall)

The generation of pain

- Pain is generated by the stimulation of nerve endings.
- Stimulation of these nerve endings generates an electrical signal in the afferent nerve fibre which is then transmitted to the central nervous system.

Sensory nerve endings

- There are several types of nerve endings whose stimulation may result in the perception of pain.
- There are specific nerve endings that when stimulated will always produce pain (nociceptors).
- Other nerve endings, when over-stimulated, will produce pain (pressure, temperature).

Nociceptors

- Present in skin and all organs (except the brain).
- Several types;
  Stimulated by chemicals.
  Stimulated by deformation.

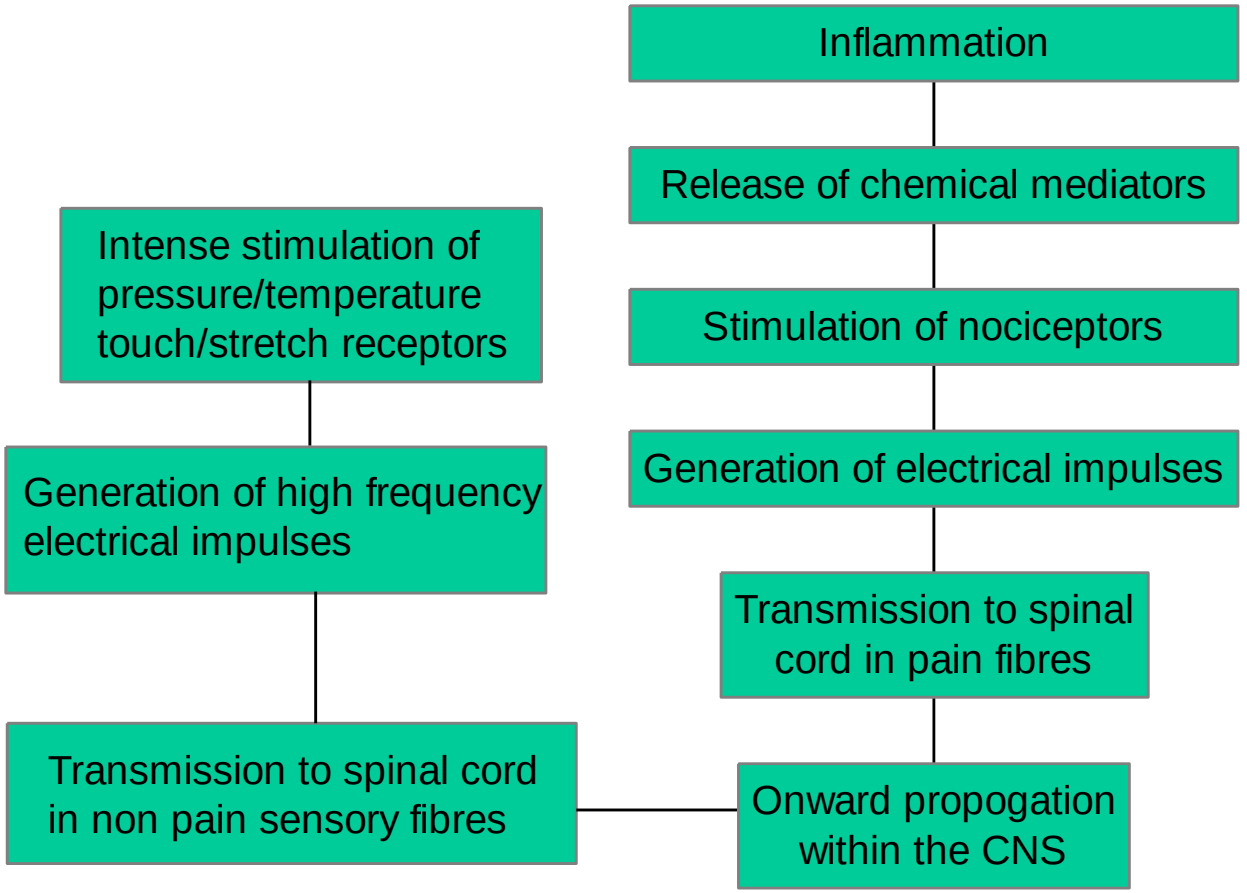
Chemical stimulation of nociceptors

- Stimulated by chemicals that are produced as a result of inflammation.
  Histamine
  Prostaglandins/prostacyclins
- Electrical impulses generated within the sensory nerve ending are then transmitted to CNS in pain nerve fibres.

Stimulation of non-nociceptors producing pain

- Pressure/temperature/touch/stretch receptors.
- Increased intensity of stimulation leads to increased frequency of generation of electrical impulses which are transmitted to the CNS in sensory nerve fibres.
- When the frequency of generation of electrical impulses reach a critical level (the pain threshold), the sensation is perceived as pain.

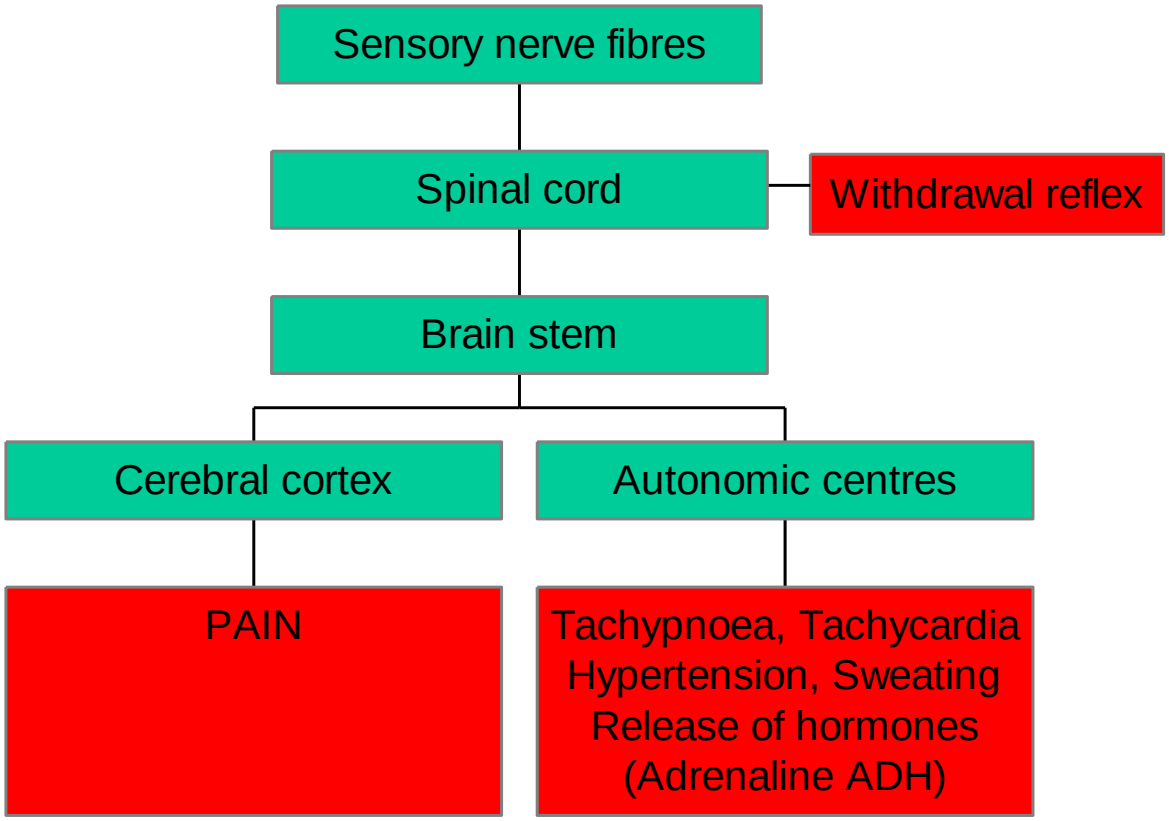
Generation of electrical impulses to produce pain



Transmission of impulses within the CNS

- The sensory nerve fibres enter the CNS via the spinal cord.
- The electrical signals are then transmitted up the spinal cord to the brain stem.
- There are also direct connections within the spinal cord between pain fibres and motor neurones. This initiates a withdrawal reflex in response to electrical signals produced from the nociceptors.
- From the brain stem the electrical impulses are then distributed to the cerebral cortex and autonomic centres.

Transmission of electrical impulses within the CNS



The Gate Theory

- Electrical signals arising as a result of a noxious stimulus can be modified within the CNS by the action of gating mechanisms.
- When the gate is open, information is transmitted to the cerebral cortex and perceived as pain. If the gate is partially or fully closed, the amount of information reaching the brain is reduced and hence the perceived pain is less.

Factors influencing the gate

1) Past physical and emotional experience of pain
2) Anxiety & fear
3) Coexisting non-noxious stimulation;- rubbing a painful area often reduces the perception of pain in that area.

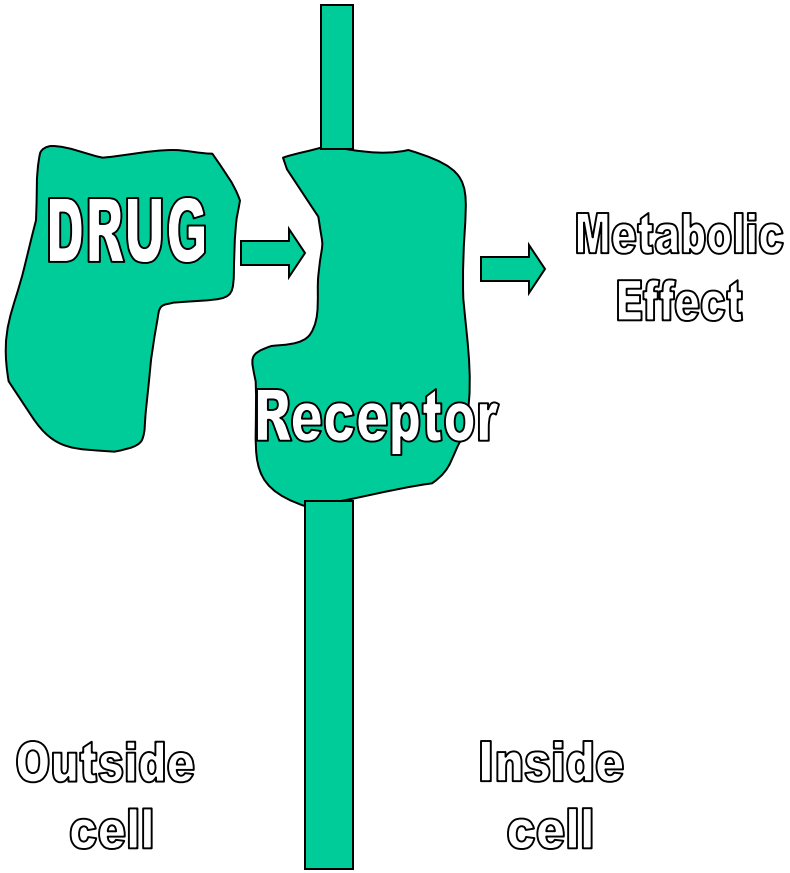
Gating mechanisms (chemical)

- The gate is closed by the production of chemicals within the CNS that modify the transmission of electrical impulses along nerve fibres within the CNS.
- Endorphins/enkephalins
- GABA
- These chemicals act via receptors on the nerve fibres.

Receptors

When a compound combines with its receptor, a conformational change occurs.

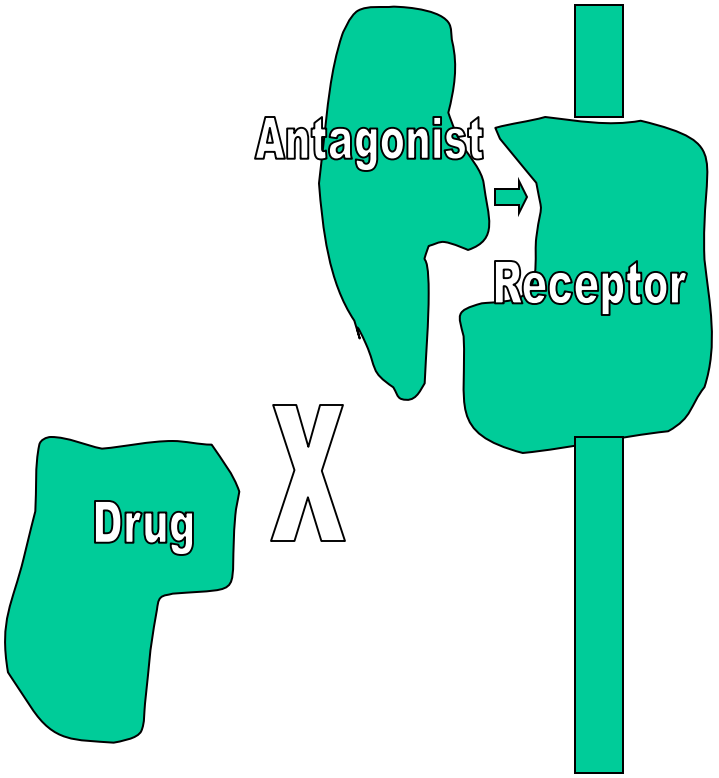
This results in an activation or inhibition of intracellular mechanisms producing a metabolic effect.



Receptor antagonists

These compounds bind to the receptor and prevent activation of the receptor by another compound.

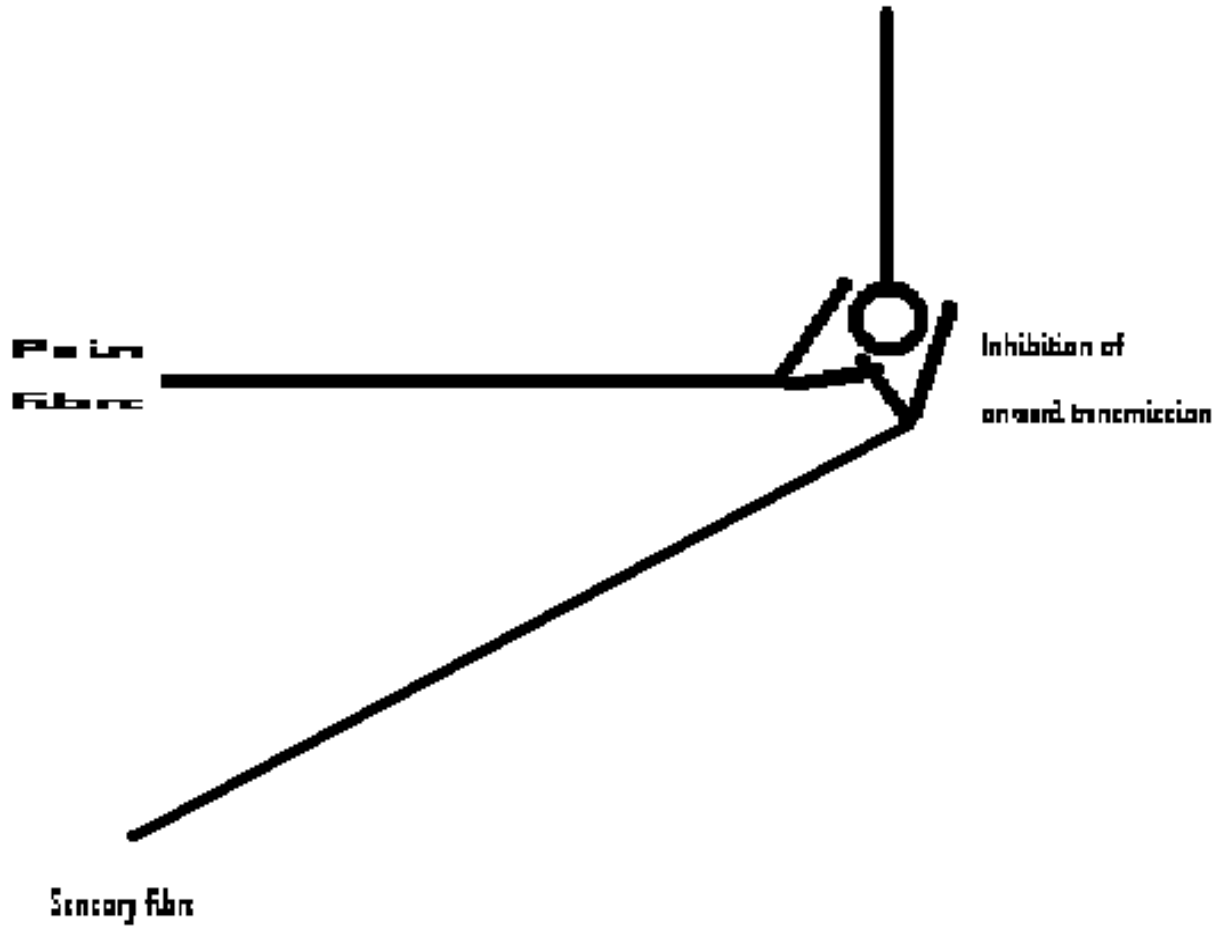
They do not produce a conformational change in the receptor and hence the metabolic effects are not initiated.



Endorphins & encephalins

- Endorphins and encephalins are receptor agonists.
- They reduce the perception of pain.
- Naturally occurring within the CNS.
- Levels can be modified by emotional factors.

Gating mechanisms (neural)



Treatment of pain

The sensation of pain can be modified by interference with the transmission of the electrical signal at any point in this pathway, or by altering the processing of these signals in the cerebral cortex.

1) Preventing the generation of impulses by the sensory nerve endings.

2) Preventing the transmission of electrical impulses along sensory nerves to the spinal cord and thence to the brain

3) Altering the modulation of electrical impulses within the CNS and hence the appreciation of pain, including psychological management

The modern approach is termed balanced analgesia using a combination of the above.

Preventing chemical activation of sensory nerve endings

Prevent production of the chemicals produced by inflammation;
NSAIDs
(Anti-histamines)

Non steroidal anti-inflammatory drugs (NSAIDs)

The NSAIDs inhibit the activity of enzymes (cyclo-oxygenases) that manufacture some of the pain inducing chemicals and hence prevent the chemical activation of the sensory nerve endings. Similar enzymes also exist in most tissues and control other vital functions, the inhibition of these enzymes resulting in many of the side effects seen with NSAIDs.

Side effects of NSAIDs

- Bleeding as a result of the inhibition of enzymes involved in the production of the sticky surface of platelets. These drugs should not be used in patients at high risk of haemorrhage (eg following vascular surgery)
- Peptic ulceration as a result of the inhibition of enzymes that produce the protective mucous coating that lines the stomach and helps it resist attack from the acid it produces in gastric digestive juice.
- Bronchospasm can be precipitated by NSAIDs in susceptible individuals and should not be used in asthmatic subjects.
- Acute renal failure especially in patients with pre-existing renal disease. Usually reversible on cessation of treatment.

Some of the newer NSAIDs produce less side effects due higher specificity of enzyme inhibition. (COX 2 inhibitors e.g. Viox)

Contraindications to NSAID therapy

- 1) Known hypersensitivity to NSAIDs
- 2)Pre-existing renal disease
- 3) Potential renal impairment as a result of surgery or drug therapy
- 4)Asthmatic patients who have not received NSAID therapy previously without incident (includes aspirin)
- 5)Patients with coexisting peptic ulcer disease or symptoms of dyspepsia
- 6) Patients with known bleeding disorders or at high risk of haemorrhage

Prevent transmission of electrical impulses along nerve fibres

- Local anaesthetics
  Local infiltration
  Nerve blocks
  Spinal/epidural
- Modulating the gate
  TENS

Altering modulation of electrical impulses within the CNS

- Opioids
- Ketamine

Opiates

These drugs act by combining with specific receptors in the CNS. This drug/receptor interaction alters the processing of the electrical information received by the cerebral cortex and in this way alters the perception of pain. Opioid receptors within the spinal cord may also influence gating mechanisms. Receptors are related to those for the naturally occurring endorphins/encephalins.

There are also opiate receptors at other sites and their combination with opiate drugs results in the side effects seen.

Opiate side effects

- Respiratory depression due to interaction with opiate receptors in the respiratory centres of the brain stem, thus reducing sensitivity to carbon dioxide and reducing respiratory drive.
- Sedation due to interaction with opiate receptors in the limbic system of the brain stem.
- Euphoria due to interaction with receptors in the brain stem and cerebral cortex. The feel good factor.
- Nausea and vomiting due to effects on the vomiting centre and chemoreceptor trigger zone in the brain stem, and due to a slowing of gastric emptying.

Opiate side effects

- Constipation due to a reduction in gastrointestinal motility.
- Addiction Not a problem in the short term use of opiates for analgesia in the presence of acute pain.
- Histamine release can occur with some opiates (eg morphine) in susceptible individuals producing bronchospasm, hypotension and itching. These opiates should thus be used with care in such patients.

Treatment of opiate side effects

- All can be reversed by the use of naloxone, a drug that separates an opiate from its receptor at any site. Thus treatment of side effects with naloxone will also reverse the analgesia. Naloxone has a very short half life, shorter than most opiate drugs, therefore a single dose will usually wear off before the opiate has been cleared from the body resulting in a return of its effects.
- Itching can be treated by the use of antihistamines (eg piriton)
- Nausea and vomiting can be treated with anti emetics that reduce the activity of the vomiting centre (eg cyclizine) Metaclopramide has the additional effect that it also speeds up gastric emptying thereby further reducing the nauseating stimulus.
- Respiratory depression may be treated by the use of doxapram, a non specific respiratory stimulant.

Ketamine

- Acts via NMDA receptors in the brain.
- As well as analgesia it produces hypertension, sedation, and often precipitates severe nightmares.
- Not often used due to the severity of the nightmares.