1 Pain and impulse conduction

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According to the World Health Organisation pain is defined as an 'unpleasant sensation that occurs from imminent tissue damage'. From a physiological perspective, pain is a warning system. During dental treatment, patients will experience pain as something unpleasant.

1.1 Pain receptors

Pain stimuli are primarily generated by the relatively amorph sensory nerve endings of the Aδ and C fibres. These free nerve endings (nociceptors; see Figure 1.1) are sensitive to a variety of mechanical, thermal and chemical stimuli and are therefore called polymodal. Nociceptors do not display adaptation: nociceptive responses will occur as long as the stimulus is present. Nociceptors have a high threshold for activation. The detection of the stimulus is performed by the receptors, present on the sensory nerve endings, that convert the stimulus into an electric signal. This process is called transduction.

During tissue damage, several substances are released that are able to stimulate the nociceptors, such as histamine, serotonin, bradykinin, prostaglandin E_2 and interleukins. These substances activate the nociceptors and reduce their threshold (sensitisation).

Nociceptors are also present in the teeth and the oral cavity and are usually sensitive to a specific neurotransmitter. Most nerve fibres, however, contain various nociceptors.

The sensory nervous system also contains 'physiological' sensors. These are small end organs of the sensory nerves, such as the Krause, Meisner and Pacini bodies (see Figure 1.2). These 'physiological' sensors usually only respond to one specific stimulus (warmth, touch, smell, etc.) and are, as such, unimodal. Besides this, they exhibit the phenomenon of adaptation; the response to stimulus disappears during prolonged or persistent stimulation. In the case of excessive stimulation, these 'physiological' sensors may also initiate pain sensation.

Figure 1.1
Nociceptors.

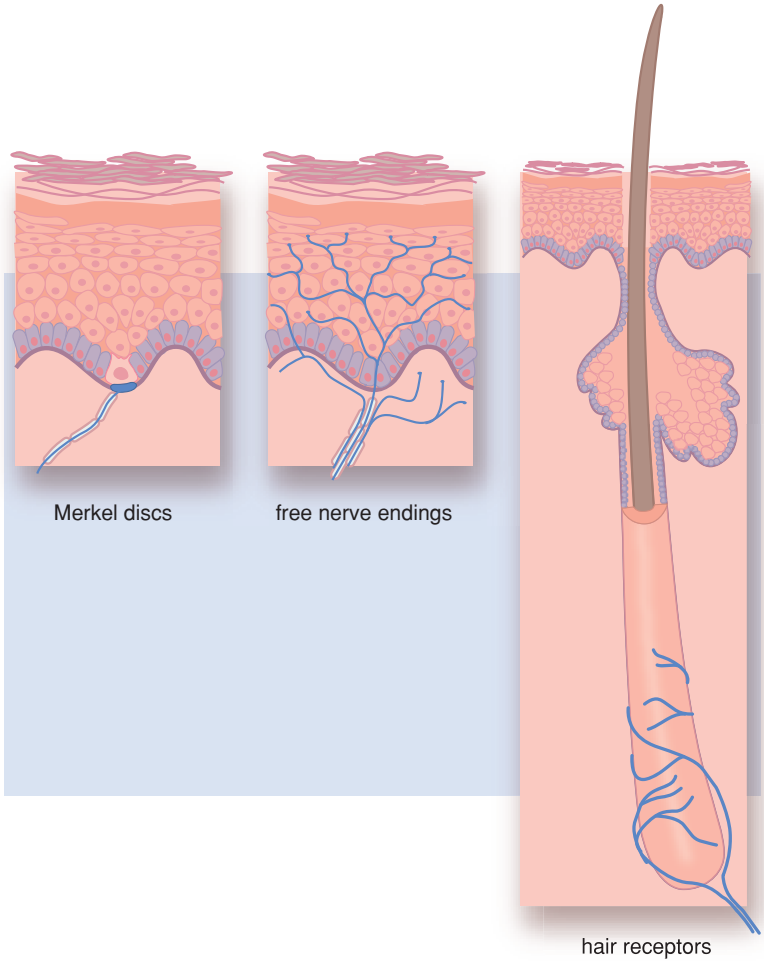
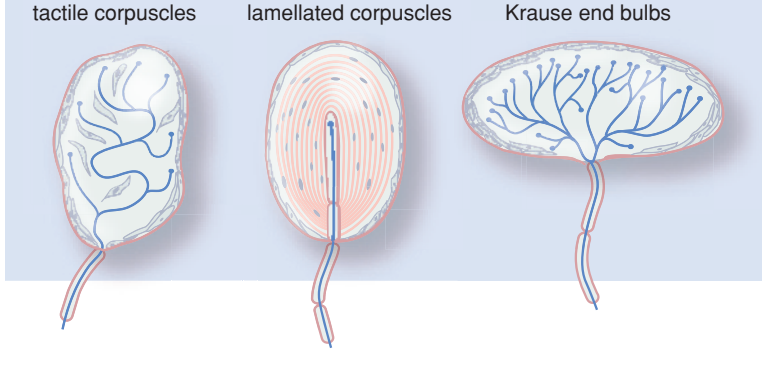


Figure 1.2
Physiological sensors.



1.2 Nerve impulse transmission

The stimuli, received by the nociceptors and converted into nerve impulses, eventually must be interpreted in the brain. The nerve impulse is transported within the sensory nervous system, wherein three nerve fibres are successively linked. The first nerve fibres form the peripheral nerve. The second and third are present in the central nervous system and form nerve bundles (pathways or tracts). The cell nuclei of the individual neurons are grouped together in ganglia and nuclei.

1.2.1 The structure of the peripheral nerve

Nociceptive stimuli are transported along sensory thinly myelinated Aδ and unmyelinated C fibres. Other types of nerve fibres are involved in the transport of other sensory stimuli (see Box 1.1).

A peripheral nerve is composed of nerve fibres from a group of neurons, enwrapped in a connective tissue network. The individual fibres may, or may not be, surrounded by an isolating myelin layer, Schwann's sheath. The cell body is the metabolic centre of the neuron (Figure 1.3) where most cell organelles are produced. Dendrites transport impulses towards the cell body and axons transmit signals away from the cell body. Some axons are surrounded by a myelin sheath, others are not. The axons and dendrites are elongated and form the nerve fibres. At the end of the dendrites, receptors are present that can receive signals. At the end of

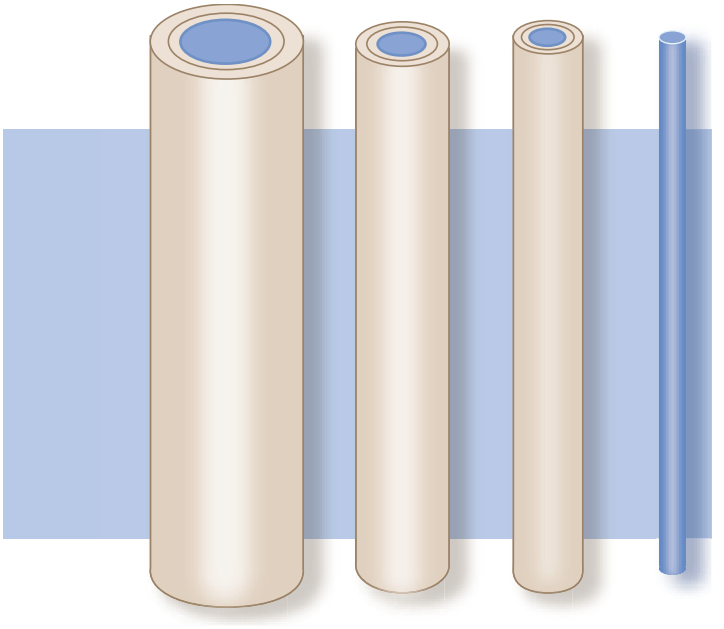
Box 1.1 Nociceptive pathways

In the body, nociceptive stimuli are received by nociceptors and then propagated via an Aδ or C fibre. The first are thinly myelinated with a fast transmission of stimuli, whereas the second are unmyelinated with a slow transmission.

The C fibres conduct impulses generated by temperature, pain and itching. The Aα fibres conduct motor impulses for the body's posture and movement; the Aβ fibres transport impulses generated by touch and signals from the skin mechano-receptors; and the Aδ fibres conduct pain impulses, temperature signals and signals to maintain the muscular tone.

The cell bodies of these primary neurons are located in the dorsal root ganglion. The axons run through Lissauer's tract to the dorsal horn of the spinal cord, where they connect to the secondary sensory neuron in Rexed's laminae. This secondary sensory neuron crosses the midline and ascends as the spinothalamic tract. The spinothalamic tract forms synapses with nuclei of the thalamus, where it projects onto the somatosensory cortex. Descending pathways from the somatosensory cortex modulate the nociceptive system. From these fibres, the neurotransmitters serotonin and noradrenalin are released.

Figure B1.1
Primary afferent axons.



the axons are synapses, where the impulse is transmitted to another nerve cell or to a cell of the end organ.

Nerves are bundles of nerve fibres held together by connective tissue (Figure 1.4). Each individual axon is surrounded by connective tissue (endoneurium). Bundles of nerve fibres form a fascicle, which is also held together by connective tissue (perineurium). A number of fascicles are held together again by connective tissue (epineurium), forming a nerve.

1.2.2 Impulse formation

The generation and conduction of impulses in nerve fibres is a complicated process. In order to excite electrical impulses, a change in electrical charge must take place. Cells are surrounded by a semipermeable membrane that is only permeable to water. A selective ion pump actively pumps potassium ions into the cell and sodium ions out of the cell. This results in a concentration gradient of sodium and potassium ions over the membrane. The cell cytoplasm contains a high concentration of negatively charged proteins, which give the cell a negative charge compared with its environment. Extracellularly, negatively charged ions are also present, primarily chloride ions. On both sides of the membrane, the electrical charge is balanced by positively charged ions (sodium, potassium, calcium). Because the concentration of anions on the inside is

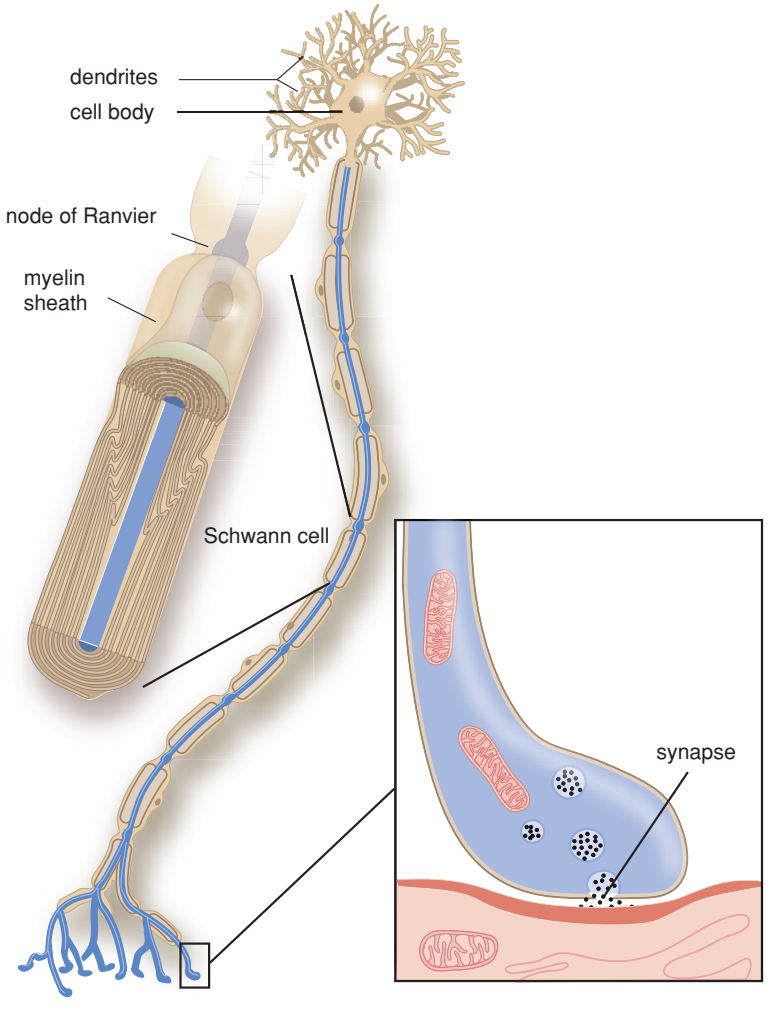


Figure 1.3
The nerve cell.

slightly higher than on the outside, the number of cations inside will therefore be higher than outside. This causes a transmembrane potential difference of –60 mV, called the resting potential.

The membrane contains ion channels with an open and closed state (Figure 1.5). These channels can be activated by an electrical stimulus ('voltage-gated') or by a chemical stimulus ('ligand-gated') (see Box 1.2). When ion channels are open, ions move along the concentration gradient. At rest, primarily potassium channels are open, so that potassium ions try to leave the cell. However, the relative overload of anions in the cell (proteins) counteracts the outflow of cations. When the sodium channels of the membrane open, sodium ions will move in: in other words, the membrane has a hole.

The inflow of sodium ions distorts the electrical equilibrium, so that a local depolarisation occurs and potassium ions can leave the cell. This

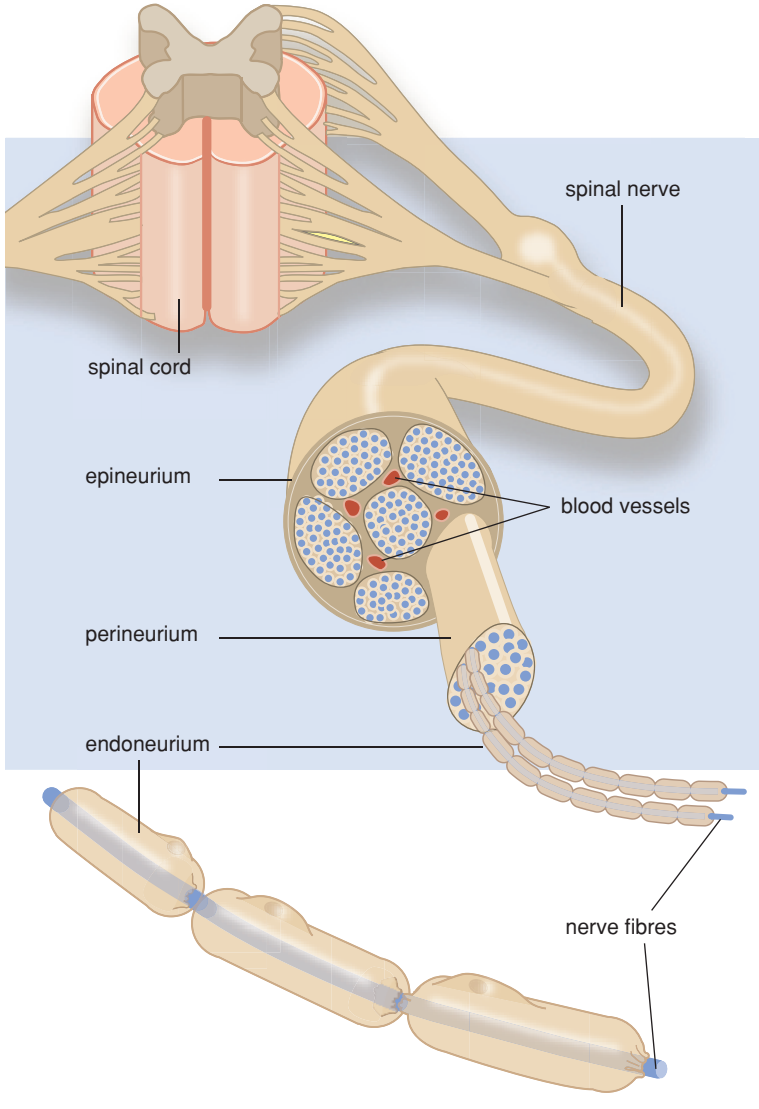


Figure 1.4
The peripheral nerve.

restores the balance between anions and cations (repolarisation). During depolarisation and the beginning of repolarisation, no new depolarisation can occur (refractory period).

When the local depolarisation is slight, the equilibrium is quickly restored (Figure 1.6). Only when the local depolarisation reaches a certain threshold value (approx. –50 mV), does an action potential appear. Thus there is an 'all-or-none' effect.

The height of the threshold value, necessary for an action potential to develop, is determined by several factors, such as the duration and strength of the depolarising stimulus and the status of the receptor. Through this, the voltage-gated sodium channels are opened, so that an influx of sodium occurs and the membrane polarity reverses.

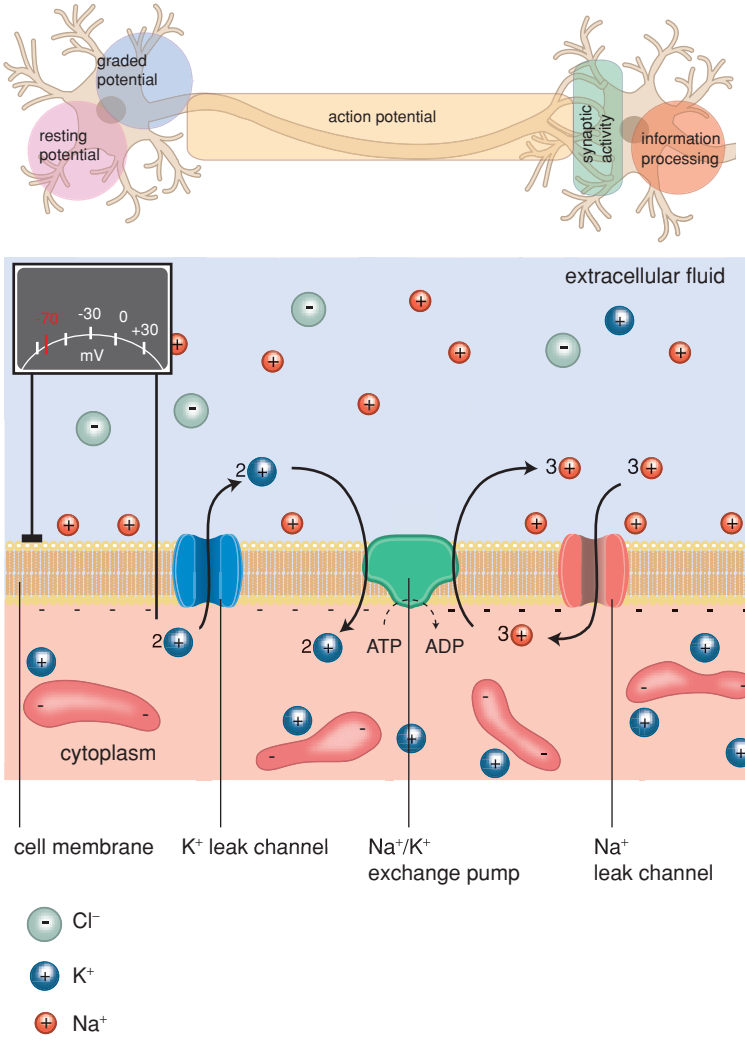


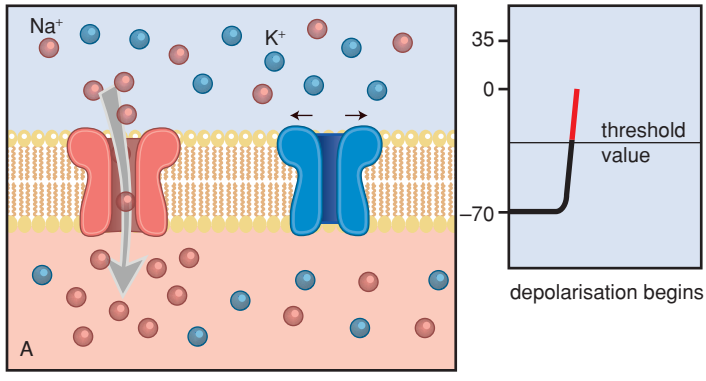
Figure 1.5
Semi-permeable membrane with ion channels.

Box 1.2

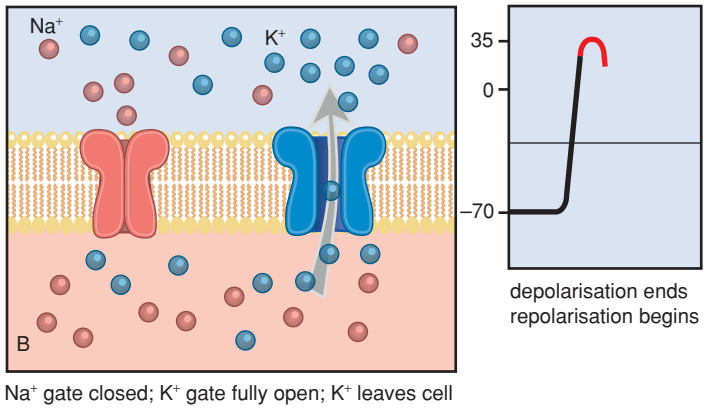
Ion channels are of great importance for the generation, conduction and transfer of nerve impulses. Activation of these receptors may occur by an electrical stimulus (voltage-gated channels) or by a neurotransmitter (ligand-gated channels). Once activated the channel opens, which allows the passage of ions, causing a depolarisation of the cell membrane.

Voltage-gated ion channels are, amongst others, the fast sodium channels and calcium channels involved in impulse formation in the heart and in impulse conduction in the nerve fibres. Examples of ligand-gated ion channels are acetylcholine receptors, glutamate receptors and GABA receptors.

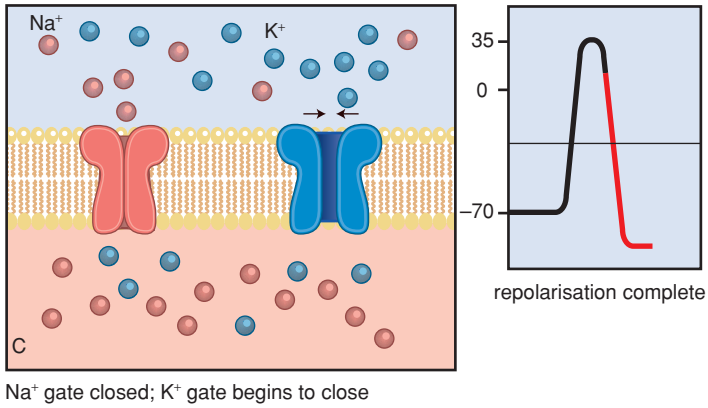
Figure B1.2 A–C



Na^+ gate open; Na^+ enters the cell; K^+ gate begins to open



Na^+ gate closed; K^+ gate fully open; K^+ leaves cell



Na^+ gate closed; K^+ gate begins to close

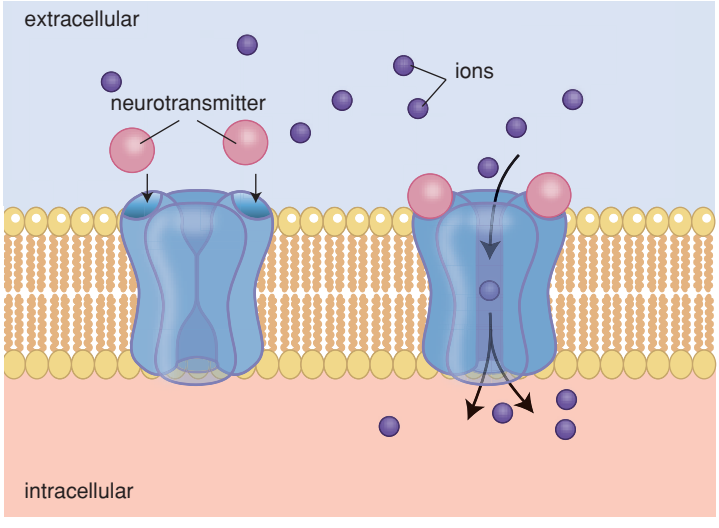


Figure B1.2 D
Activation of a ligand-gated ion channel.

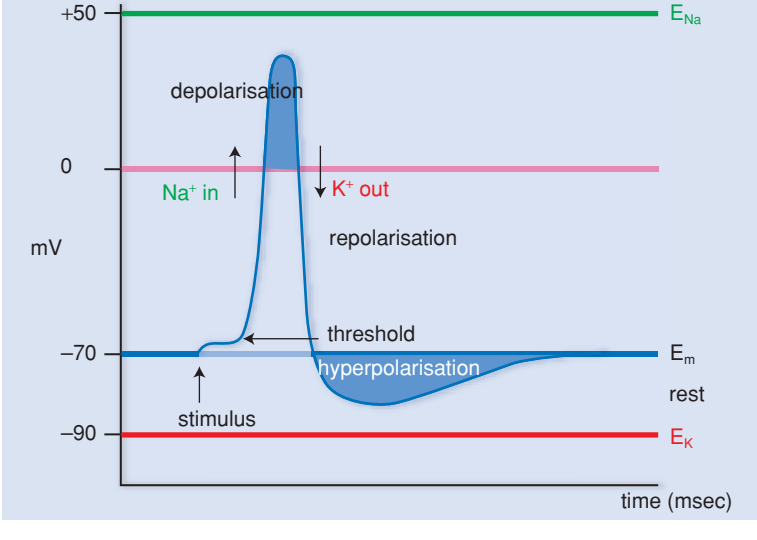


Figure 1.6
The action potential.

The sodium channels remain open only for approx. 1 millisecond, after which they close again. The potassium channels are then still open, and the outflow of potassium through voltage-gated potassium channels restores the electrical equilibrium, and even hyperpolarisation takes place. Then the voltage-gated potassium channels close and the sodium–potassium pump restores the starting situation. The number of sodium and potassium ions that has to be moved in order to generate an action potential is only very small.

1.2.3 Impulse conduction and transfer

Once a stimulus is converted into an action potential, the action potential must be propagated along the nerve. This occurs through sequential depolarisations along the membrane, which are initiated by the activation of fast sodium channels. In myelinated nerves, sodium channels are only present at the gaps in the myelin sheath, the nodes of Ranvier, which causes a jumping (saltatory) conduction (Figure 1.7A). In unmyelinated nerve fibres, the conduction is a continuous process (Figure 1.7B).

Because the sensory nervous system consists of three successive neurons, the stimulus must be transferred from one nerve cell to another. This transmission is conducted by neurotransmitters in synapses. The neurotransmitter is released presynaptically and activates postsynaptic

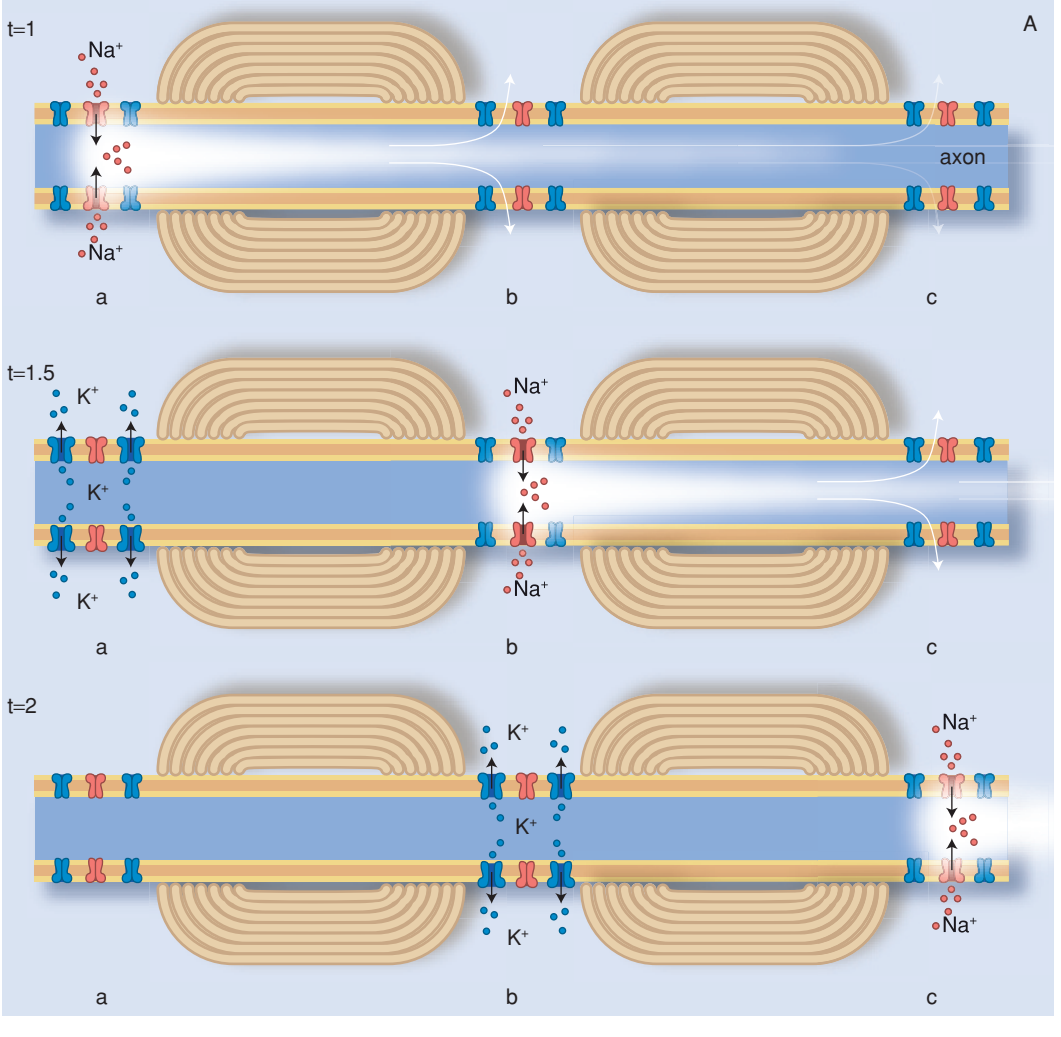


Figure 1.7 A
Saltatory conduction.

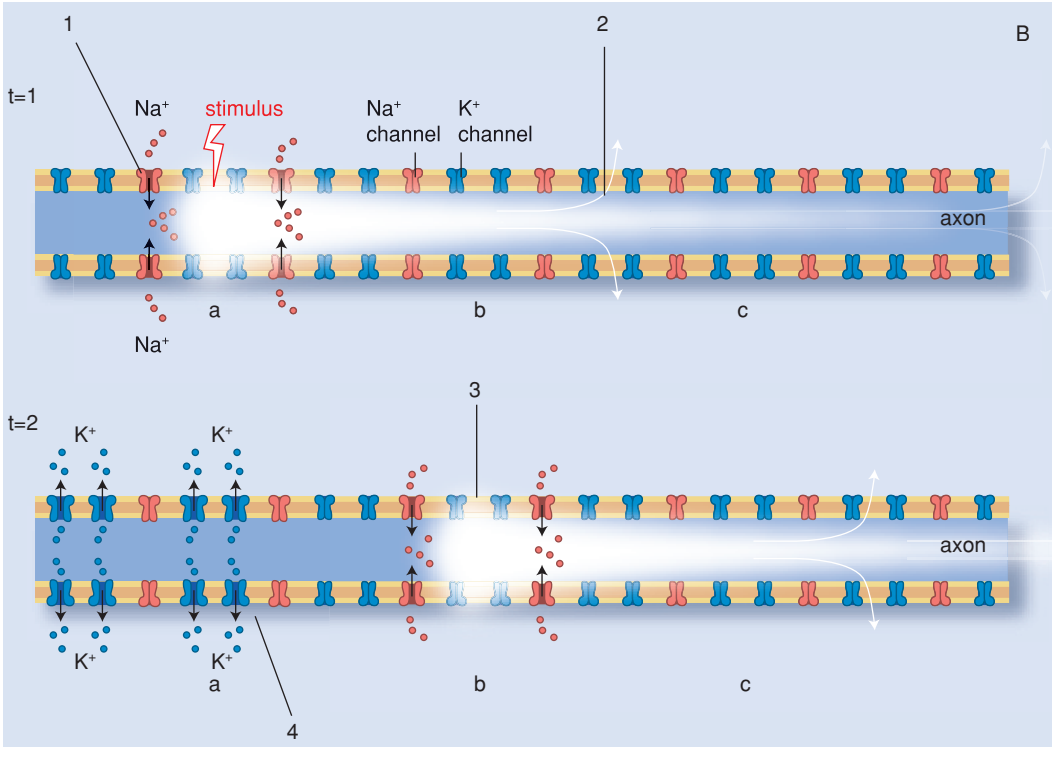


Figure 1.7B
Continuous conduction.

receptors. These postsynaptic receptors consist of ion channels that open once activated, which depolarises the cell membrane, creating an electrical stimulus again, that is propagated along the nerve fibre.

1.2.4 Modulation of the impulse

At the sites where impulses are transferred to other nerves, the impulse stimulus can be enhanced or subdued. This process is called neuromodulation. This can occur both peripherally as well as at connection points in the central nervous system.

One of the most frequent forms of neuromodulation is that affecting the voltage-gated sodium channels involved in the formation and conduction of action potentials. Excitatory neurotransmitters lower the resting potential (hypopolarisation). Consequently, the threshold level can be reached more easily, through which an action potential can occur more quickly. Inhibitory transmitters will only cause an opening of potassium channels, which induces hyperpolarisation of the membrane and an action potential will develop less easily. These mechanisms affect the transmission of impulses. The release of neurotransmitters can also be influenced by presynaptic receptors. Many receptors are involved in these systems, usually selective ion channels (see Box 1.3).

Box 1.3 Modulation of nociceptive stimuli

Various ion channels are involved in the modulation of nociceptive stimuli. They are present, among other places, in the peripheral endings involved in the stimulus perception where they modulate the sensitivity: heat sensitive ion channels (vanilloid receptors, VR1), acid sensitive channels (proton activated receptors) and purine sensitive ion channels (P2X receptors). Besides these, there are also voltage-gated receptors that especially allow passage of sodium or potassium and ligand-gated channels that primarily affect the release of neurotransmitters.

The neurotransmitters are released from the presynaptic nerve ending in large amounts and are able to change the polarity of nerve membranes by opening ion channels. This creates a postsynaptic potential that, depending on the nature, causes either a depolarisation (excitatory postsynaptic potential) or a hyperpolarisation (inhibitory postsynaptic potential). When neurotransmitters open cation channels the nerve is excited (depolarisation). When they open anion channels, inhibition occurs (hyperpolarisation). The most important excitatory neurotransmitter in the nociceptors is glutamate. Substance P plays an important role in peptidergic fibres. Neuropeptides not only have a role in modulating the input to spinal nociceptive neurons and autonomic ganglia, but also cause vasodilation, contraction of smooth muscles, release of histamine from mast cells, chemoattraction of neutrophil granulocytes and proliferation of T lymphocytes and fibroblasts.

Modulation of impulse conduction can also happen through cellular second messengers. An example of this is prostaglandin E_2, which is released during tissue damage. Prostaglandin E_2 increases the sensory transduction via a G protein (protein kinase A). This facilitates the inflow of sodium and the outflow of potassium, changing the electrical charge over the membrane; thus the nerve cell will be stimulated more easily. As a result, a nociceptive stimulus will be propagated more easily. There is, therefore, a local amplification system. On the other hand, afferent fibres exist that have a subduing effect on transduction. For example, activation of μ-receptors (opioids) increases the stimulus threshold that negatively modulates transmission. Pharmacological treatment of pain often intervenes in these modulation systems (Figure 1.8).

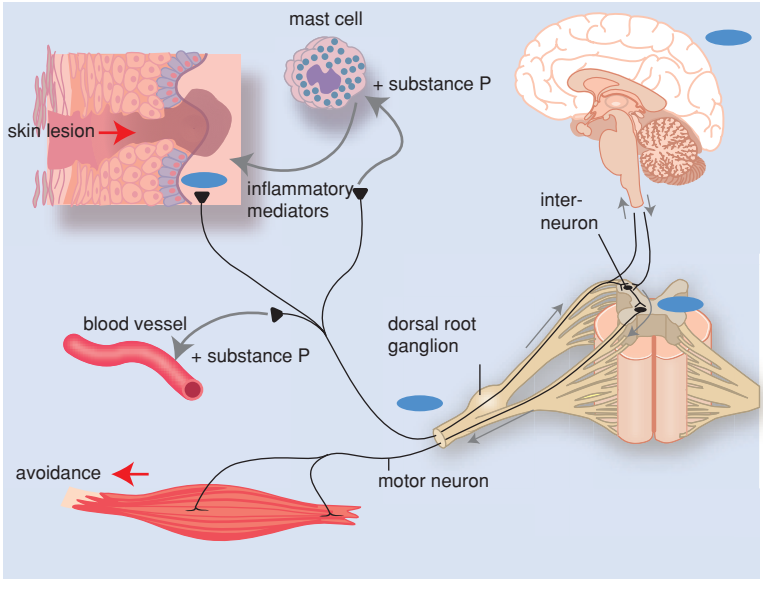


Figure 1.8
Intervention sites for analgesics.

1.3 Perception of pain

Consciousness is a requisite of the perception of pain. Ultimately, the nociceptive stimuli reach the primary sensory cortex, whereby pain is experienced and a physiological response is induced. Pain leads to the release of hormones, such as cortisol and catecholamines, which stimulate the catabolism. Respiration and circulation also increase. Fear and emotion are caused by the transfer of the stimulus to the limbic system.

There are great differences in pain perception between men and women. Women have a lower pain threshold and a lower tolerance for nociceptive stimuli than men. Furthermore, there are great sociocultural differences in the sensation of pain: one patient may experience no pain, while another may cry out from pain, though stimulated by the same stimulus. The emotional state of the patient and environmental factors play an important role in the experience of pain. Fear and excitement have a large influence on the individual pain experience. Fear mobilises the organism to take action in order to avoid or reduce impending damage. As a result, fear causes hypoalgesia. Excitement has the opposite effect.

Aromas have a great impact on mood; this influence is much greater than that of music, which is often used in dental practices in order to influence the sensation of pain. Additionally, the effect of aromas takes place much faster than that of sound or visual stimuli. It has recently been shown that scents, by a change in mood, indeed have a fast and positive influence on the experience of pain.

1.4 Nociception in the orofacial area

The process of transduction, transmission, modulation and perception also occurs in the head and neck area. Tooth pain is caused by stimulation of the polymodal nociceptors in the dental pulp that respond to mechanical and thermal activation. The intensity of the pain is determined by the frequency of the sensory stimulation and by the number of nerve fibres that are excited. Temperature stimulations induce immediate pain responses through the Aδ fibres. When a tooth is stimulated mechanically, fluid moves in the pulpa, which alters the form of the nerve membrane and a stimulus is excited slowly (via C fibres). After application of something cold, the stimulus extinguishes after a while, because vasoconstriction induces lack of oxygen in the nerve. Electrical stimulation induces ion transport, resulting in the stimulation of nerve endings. The same process occurs in osmotic stimulation, for example by sugar and salt. Chemical inflammatory mediators cause the stimulation of nociceptors on the C fibres in the pulpa. Substance P, calcitonin gene-related peptide and neurokinin A have been found in the periodontium and in the pulp of teeth. In painful teeth, the concentration of these inflammatory mediators is increased. They are released from the nerve fibre endings during stimulation and activate the nociceptors. The stimuli are thus propagated by primary Aδ and C fibres, primarily in the trigeminal nerve. At the Gasserian ganglion, they synapse onto secondary fibres that run to the brainstem trigeminal nuclei. From there, they project to the thalamus and the cerebral cortex.

The secondary C fibres end in the most caudal part of the ventrobasal thalamus, run from there to the intralaminar nucleus of the thalamus (forming the activating part of the reticular formation) and project to the cerebral cortex and hypothalamus. The secondary Aδ fibres terminate in the caudal nucleus, where they activate pain tracts to the most caudal part of the ventrobasal thalamus. From there, tertiary tracts run to other parts of the thalamus and somatosensory cortex.