1 *The Physiology of Pain*

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Key Messages

- Pain is still underdiagnosed and undertreated.
- Pain is a subjective experience and may even be present in the absence of any painful stimulus.
- Pain is multifactorial in nature and its management involves pharmacological, behavioural and psychosocial approaches.
- Transmission of nociceptive impulses depends on a balance of inhibitory and excitatory influences.
- With so many and diverse signalling mechanisms, there are numerous potential targets for analgesic therapies.

Introduction

Pain is an elaborate interaction between sensory, behavioural and emotional aspects, and past experiences of pain can dictate an individual's future response. In evolutionary terms, pain as a sensation serves to prevent ongoing trauma and to protect the injured area from harm whilst it is healing. However, there are situations where the painful experience far outlasts any tissue damage and does not convey any survival value but does prolong the suffering of the individual.

Definitions

There are many terms which require clarification in order to fully understand the processes involved when experiencing pain:

- *Nociception*
  The sensory process of detecting tissue damage. Nociceptors are the diverse group of receptors stimulated in this process.

- *Pain*
  The International Association for the Study of Pain defines this as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage' (Merskey & Bogduk 1994, p. 209).
  Thus, pain and nociception are not, despite common belief, the same. It is quite possible to experience pain without nociception and vice versa; nociception can occur without any pain being experienced.
- *Transduction*
  This is the conversion of one form of energy into another. This occurs at many stages in the pain pathway.
- *Transmission*
  Nociceptor excitation is conducted to its target via a combination of electrical and chemical transmitters.
- *Modulation*
  At all stages along the pain pathway, the transmitted signal is liable to amplification (upregulation) or dampening (downregulation).

In the example shown in Figure 1.1, the above terms are illustrated at various points along the pain pathway.

Nociceptors are excited not only by the physical trauma (such as pressure energy) to the tissue, but also by the consequent release of a multitude of chemical mediators (transduction). This information is further transduced into an electrical signal, which is transmitted along the primary afferent neurone to the dorsal horn of the spinal cord. The signal is transduced into quantal release of chemical neurotransmitters, which transmits the signal across the synaptic cleft to the second-order neurone. These events may be subject to presynaptic or postsynaptic modulation. Modulating influences may arise from primary afferent neurones, interneurones or descending pathways.

The majority of second-order neurones decussate at this point, crossing to the contralateral side of the spinal cord where they synapse again on third-order neurones, in anterolateral tracts, which ascend to the brainstem and sensory cortex.

Peripheral mechanisms

Peripheral receptors

It was once believed that painful stimuli were detected by the 'hyperstimulation' of receptors for other sensory modalities. We now know that in somatic tissues at least, this is not the case and painful stimuli are detected by specific receptors, called nociceptors. There is even a distinction between the fast 'sharp' pain transmitted along myelinated Aδ fibres and the slow 'dull' ache transmitted along non-myelinated C fibres.

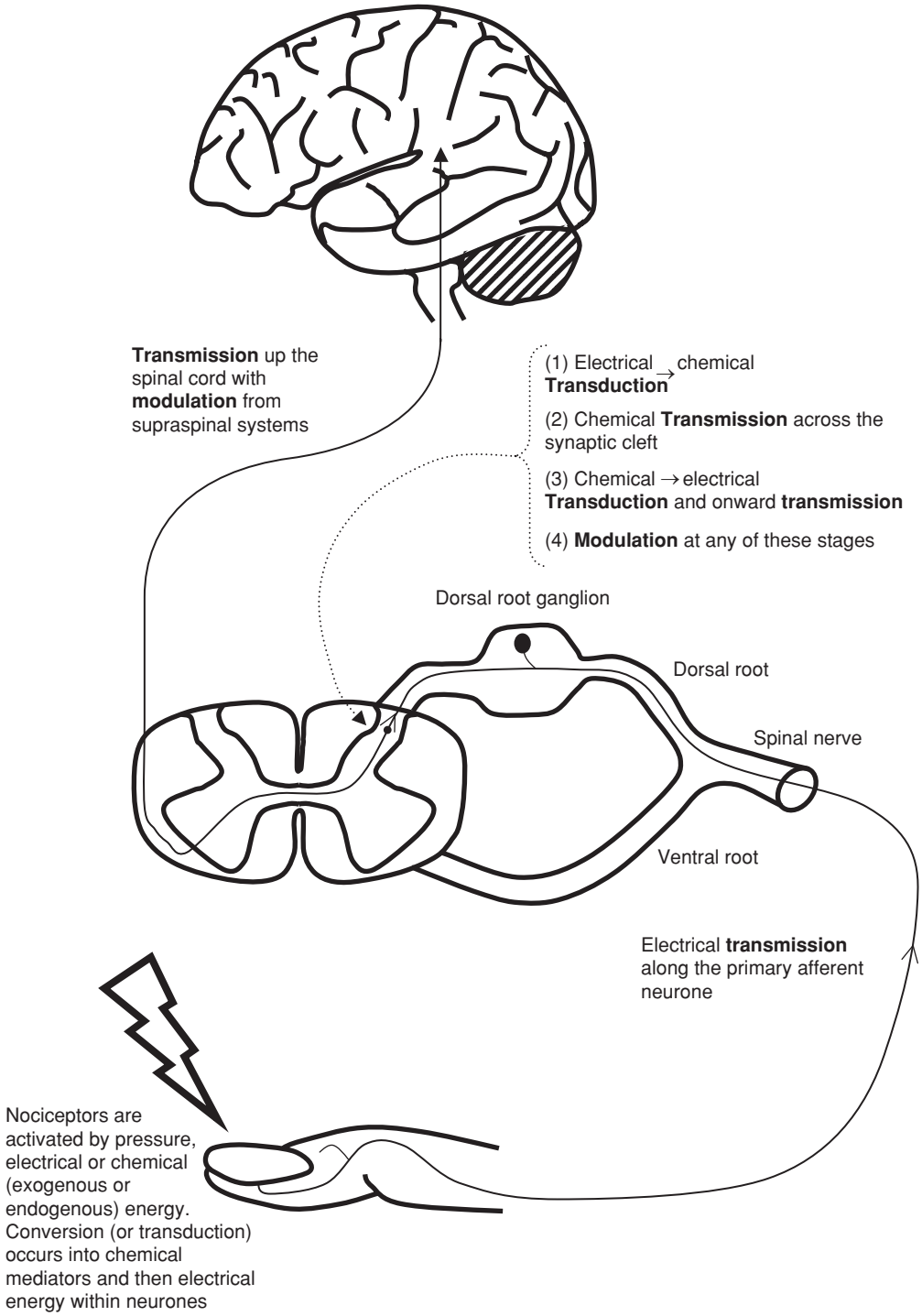

Figure 1.1 Transduction, transmission and modulation of a painful stimulus.

- *Cutaneous nociceptors*
  These are unlike other sensory receptors in that they are free nerve endings and respond to highly intense stimuli, i.e. those likely to cause injury to the tissue. The stimuli detected may be chemical, thermal or mechanical, hence their full title *polymodal* nociceptors. Information from cutaneous nociceptors (transmitted along C-fibre neurones) is responsible for the burning sensation in response to sufficient thermal stimulation (threshold usually about 44°C in humans).
- *Deep-tissue nociceptors*
  These are located in the deep structures such as joints, bones, muscles and viscera. Compared to their cutaneous counterparts, their receptive fields are much larger and pain experienced is more diffuse in nature. Moreover, visceral pain can also be referred to distant parts of the body, as is the case with cardiac pain referred to the left arm. This may be due to the primary afferent neurones from the heart entering the dorsal root entry zone at the same level as those cutaneous nociceptors which serve the left arm. As the brain can make no distinction between the two, it interprets the pain as coming from the superficial structure. The same mechanism is behind diaphragmatic pain being experienced in the shoulder tip.

Sensory neurones (primary afferent neurones)

There are numerous types of sensory neurones which are involved in conveying the information of the peripheral milieu to the central nervous system (CNS). A common classification is according to axon diameter, myelination and conduction velocity (Table 1.1).

A fibres differ grossly from C fibres in that they are of much larger diameter and are myelinated, hence their faster conduction velocities. Aβ fibres have a low threshold for activation, are cutaneous mechanoreceptors involved in

Table 1.1 Properties of different nerve fibres.

Fibre type	Function	Fibre diameter (mm)	Conduction velocity (m/sec)	Myelination
Aα	Motor	12–20	70–120	Yes
Aβ	Touch, pressure via cutaneous mechanoreceptors	5–12	30–70	Yes
Aγ	Muscle spindle afferents	3–6	15–30	Yes
Aδ	'Fast' pain, temperature	2–5	12–30	Yes
B	Autonomic preganglionic	<3	3–15	Yes
C	'Slow' pain	0.4–1.2	0.5–2.0	No

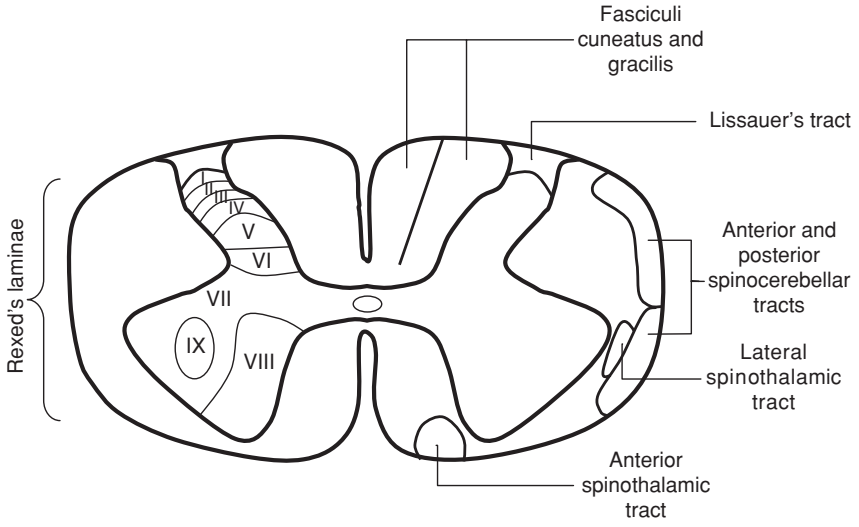

Figure 1.2 A cross section of the spinal cord, illustrating Rexed's laminae and the ascending tracts.

conveying the sensation of touch from somatic tissues and do not contribute directly to the sensation of pain.

Aδ fibres in somatic tissues (e.g. skin) transmit the action potentials from excited high-threshold thermo/mechanoreceptors which respond to more noxious stimuli; i.e. they are thermal and mechanical *nociceptors*. However, in visceral tissues there are no Aβ fibres and small C and Aδ fibres must respond to all stimuli. Aδ fibres terminate in laminae I and V of the dorsal horn of the spinal cord and, by virtue of their myelination and diameter (compared to C fibres), are responsible for the 'first' or 'fast' pain that occurs following injury. It allows rapid and fine localisation of the stimulus so that it can be removed swiftly, thus limiting further damage.

C fibres are non-myelinated and relatively thin neurones which convey information from high-threshold polymodal nociceptors. These receptors are free nerve endings which respond to chemical, mechanical and thermal stimuli and are responsible for the 'second' or 'slow' pain, which is the main area of interest in postoperative pain management. C fibres terminate in laminae I and II (the *substantia gelatinosa*) (see Figure 1.2) but are subject to many modulating systems. It is also worth noting that approximately 15% of C-fibre nociceptors are 'silent' and can become active under inflammatory conditions.

Mechanisms of inflammatory pain

The degree of activation of nociceptors in a dynamic state is dependent on the degree of tissue injury and modulatory factors. For example, in areas of overt trauma or inflammation, nociceptor activity is heightened; i.e. the *threshold* for

nociceptor excitation and action potential generation is reduced. This results in a situation in which nociceptors are excited both in greater numbers and at a greater frequency for a given degree of stimulation. This phenomenon is referred to as *hyperalgesia*.

This reduced threshold for mechanical and thermal stimuli in the area of damage, *primary hyperalgesia*, manifests as tenderness and ongoing pain. When the reduced threshold extends beyond the area of damage (usually only to mechanical stimuli) and affects undamaged tissue, it is known as *secondary hyperalgesia*.

The mechanisms underlying each pathology are different.

- *Primary hyperalgesia*
  This results in part from the natural tissue-healing process. Inflammatory mediators are released from damaged cells and can act directly on nociceptors themselves. Examples of these include protons (H^+ ions), K^+ ions, adenosine triphosphate and bradykinin, which itself recruits mast cells and basophils to the damaged area.

  Mast cell degranulation results in the release of mediators including histamine and attracts platelets to the site of injury. Platelets are a rich source of serotonin (5-hydroxytryptamine, 5-HT), which is known to sensitise nociceptors to further activation via 5-HT_{2A} receptors present on the primary afferent terminal.

  The chemical mediators described are responsible for the classical signs of inflammation, namely:

  - Calor (warmth)
  - Tumour (swelling)
  - Rubor (redness)
  - Dolor (pain)

  Inflammation also brings about the breakdown of the membrane phospholipid, arachidonic acid, via the enzymes cyclooxygenase (COX) and lipoxygenase (LOX). The COX metabolites are the numerous prostaglandins, of which PGE_2 and PGI_2 have been identified as causing *peripheral sensitisation* of nociceptors afferents. The LOX pathway also produces nociceptor 'sensitisers', an area of current investigation. Inhibition of the COX enzyme is the target for *non-steroidal anti-inflammatory drugs* (NSAIDs), in a bid to reduce the production of prostaglandin metabolites.

  It is because of the huge number of chemical mediators (including those yet to be identified) involved in the inflammatory process that the term 'inflammatory soup' has been coined to collectively refer to these factors.

  A multitude of different receptors exist on the surface of nociceptive neurones. They include gamma aminobutyric acid (GABA), tachykinin, serotonin, histamine, prostaglandins, substance P (SP), H^+ ion, K^+ ion opioid and cannabinoid receptors, to name just a few. These receptors are

intimately involved in the modulation of activity in the peripheral portion of pain pathways.

- *Secondary hyperalgesia*
  This is the phenomenon of reduced nociceptor threshold to mechanical stimuli in the *undamaged* tissue surrounding the area of injury.

  Unlike primary hyperalgesia, which results from peripheral sensitisation of nociceptor afferents by the 'inflammatory soup', secondary hyperalgesia is thought to be mediated by a central mechanism, i.e. *central sensitisation*.

  Peripheral sensitisation, with increased primary afferent activity, results in increased frequency of dorsal horn activity in the spinal cord. This is liable to *modulation* – either amplification or inhibition of the signal before onward transmission up the spinal cord to the higher centres of the midbrain and cortex.

  Ongoing injury and inflammation will present the dorsal horn with unrelenting stimulation and can result in the phenomenon called *wind-up*, which leads to a state of spinal hyperexcitability. This reduces the threshold of nociceptors in surrounding undamaged tissue, by antidromic activation, and increases their receptive field. These nociceptors may now be excited by usually innocuous stimuli in areas adjacent to the area of injury.
- *Neurogenic inflammation*
  Stimulation of peripheral C fibres results in retrograde transport and local release of the neuropeptides calcitonin gene-related peptide (CGRP) and substance P (SP), which act on the surrounding vasculature to cause vasodilatation, mast cell degranulation and increased capillary permeability, which manifests as 'flare'.

Central mechanisms

Spinal cord modulation

Having established the receptors and neurones involved in the transmission of noxious stimuli to the spinal cord, we can now explore the routes which this information takes from entry into the spinal cord to being perceived as a painful experience in the higher centres of the brain. The cell body of the first-order neurone (primary afferent neurone) lies within the dorsal root and is called the dorsal root ganglion. A neurone projects from this cell body to the periphery and another projects to the dorsal horn where it synapses with a second-order neurone (see Figure 1.2). These second-order neurones then decussate to the contralateral side of the spinal cord and ascend in one of two main pathways/tracts. Depending on the ascending pathway, the second-order neurone synapses once more either in the midbrain or in the thalamus on a third-order neurone which will project onto higher cortical centres (see Figure 1.3). Each of these stages shall now be addressed individually.

The ascending pain pathways display evolutionary differences in that the 'older' *spinoreticulodiencephalic tract* (see Figure 1.4) is primarily involved in the

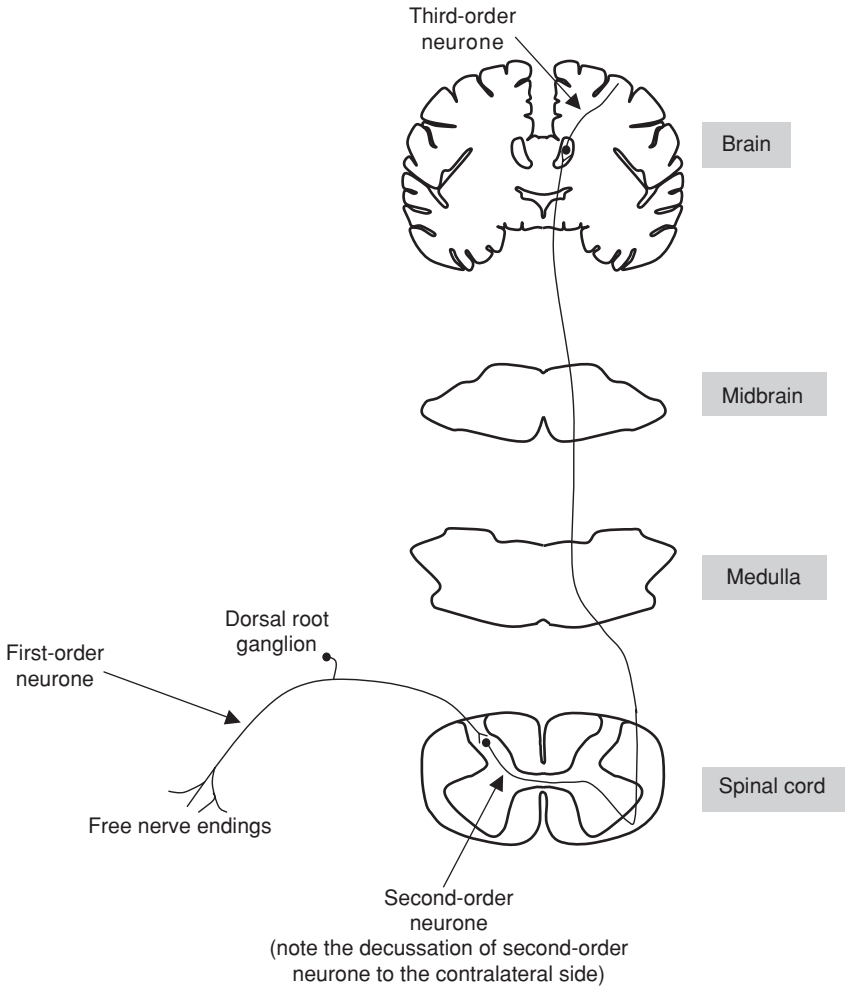

Figure 1.3 Schematic showing first-, second- and third-order neurones.

affective component of pain perception. Its fibres pass via the reticular formation, medial thalamic nuclei, and onto the secondary sensory cortex (S2), anterior cingulate gyrus, insula and limbic system.

In comparison, the phylogenetically advanced *spinothalamic tract* is responsible for the localisation of pain. Its fibres are highly organised and pass via the lateral thalamic nuclei onto the primary sensory cortex (S1), with specific areas of the body corresponding to specific areas of S1 cortex – the brain *homunculus*. In essence, the fibres of the spinoreticulodiencephalic tract convey the sensation that something is 'painful', whereas the spinothalamic tract conveys the exact location and the discriminatory quality of the painful stimulus.

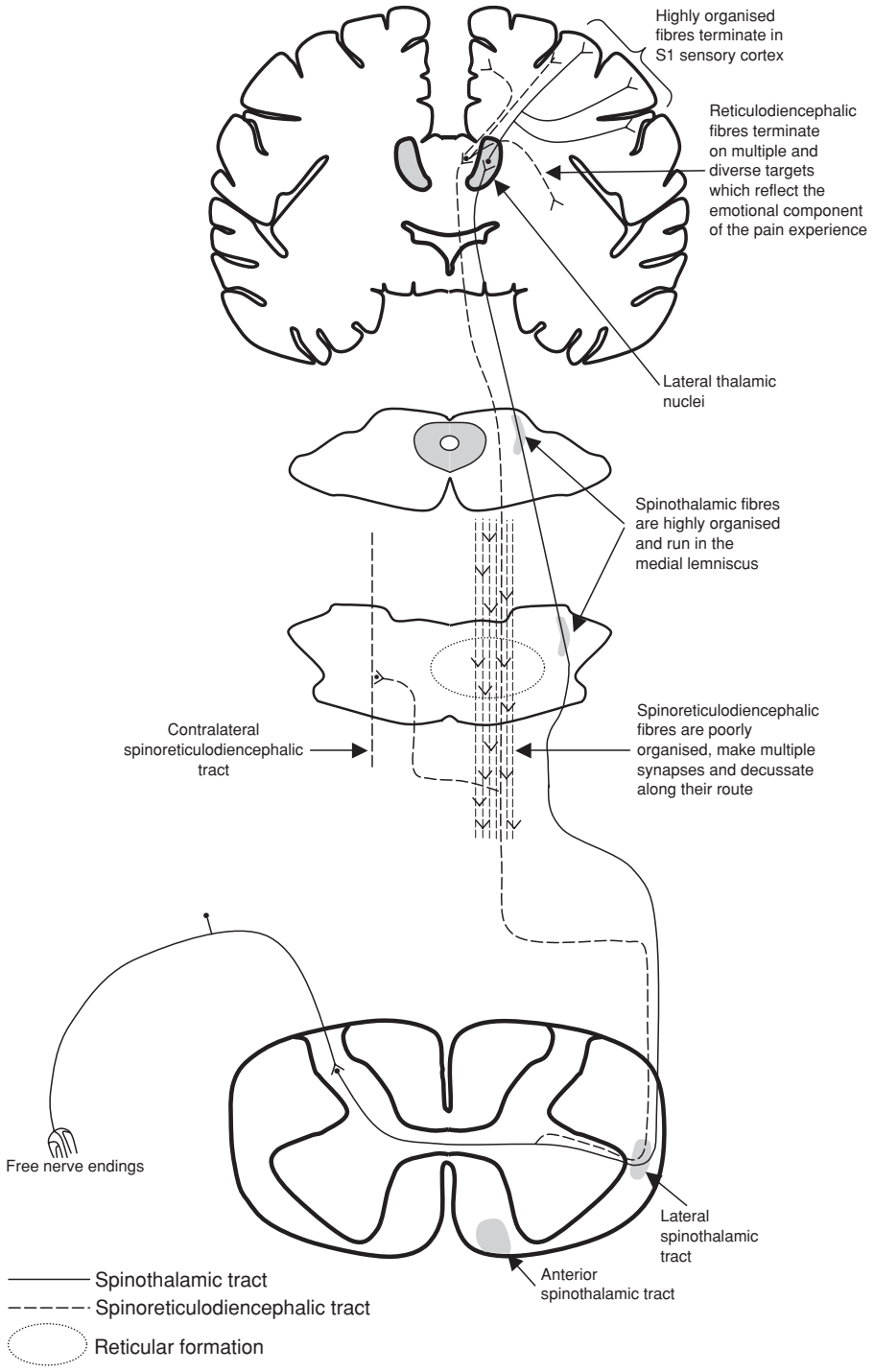

Figure 1.4 Ascending pain pathways.

Steps to consider include:

- Initial spinal connections
- Local spinal interneurones
- Ascending pathways
- Descending pathway – discussed later

The dorsal horn of the spinal cord plays a crucial role in integrating the many excitatory and inhibitory neurones, including interneurones and descending inhibitory pathways. Aδ- and C-fibre primary afferent neurones enter the dorsal horn and immediately ascend or descend one or two levels in a thin tract called Lissauer's tract, before synapsing with second-order neurones in the grey matter. The grey matter of the spinal cord contains the neuronal cell bodies and is highly organised into ten *laminae*.

The important laminae with reference to pain transmission are:

- *Laminae I and V*
  Many Aδ fibres terminate here.
- *Laminae I–V*
  Non-myelinated C fibres terminate here.
- *Laminae II and III* – substantia gelatinosa
  Many interneurones are present in these laminae and are involved in modulation of the pain signal. In fact, the majority of Aδ and C fibres synapse in this area.
- *Gate control theory*
  In 1965, Ron Melzack (a psychologist) and Pat Wall (a neuroscientist) postulated that perception of pain was influenced by the *pattern* of neuronal activity and proposed two classes of second-order neurones. The first class respond to non-noxious stimuli (e.g. touch carried via large-diameter, fast, myelinated Aβ fibres) and intense noxious stimuli (e.g. pain carried via small-diameter, slow, non-myelinated C fibres) – they are termed *wide dynamic range* (WDR) neurones. The second class respond solely to noxious stimuli and are termed nociceptive-specific neurones.

  They suggested that stimulation of low-threshold, myelinated Aβ afferent fibres would result in activation of an inhibitory interneurone in the substantia gelatinosa synapsing on the WDR second-order neurone, thus decreasing the output from the WDR neurone up the spinal cord. Smaller, non-myelinated C fibres would inhibit the inhibitory interneurone, thus allowing onward transmission of the 'pain signal' by the WDR neurone.

  They named this the gate control theory because stimulation of Aβ fibres in the painful area activated inhibitory interneurones and *closure of the gate* to C-fibre transmission (Figure 1.5). It explains the phenomenon of 'rubbing it better', as fast Aβ touch fibres are stimulated and block WDR neuronal transmission of the slower C-fibre input. It is also the principle behind *transcutaneous electrical nerve stimulation*, which utilises high-frequency, low-amplitude current to stimulate large peripheral Aβ fibres.

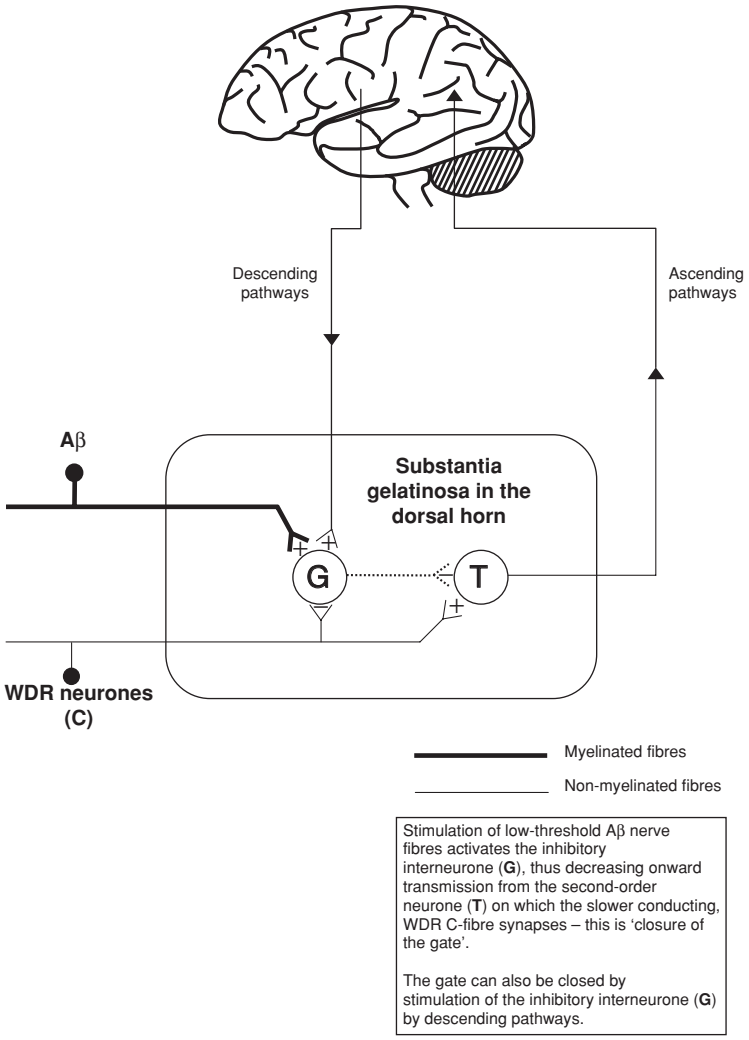

Figure 1.5 Gate control theory of pain. (© R. Melzack, reproduced with permission.)

- *Dorsal horn inhibitory mechanisms*
  Descending inhibitory pathways (see Figure 1.6) from higher centres in the brain can also close the gate. Descending neurones synapse on the dorsal horn inhibitory interneurones releasing excitatory neurotransmitters, including norepinephrine and serotonin. The excited inhibitory interneurones secrete opioid peptides, in particular enkephalins, which inhibit the transmission of pain signals by blocking the release of SP (an excitatory neurotransmitter) from the primary afferent neurone and by blocking SP receptors on WDR neurones.

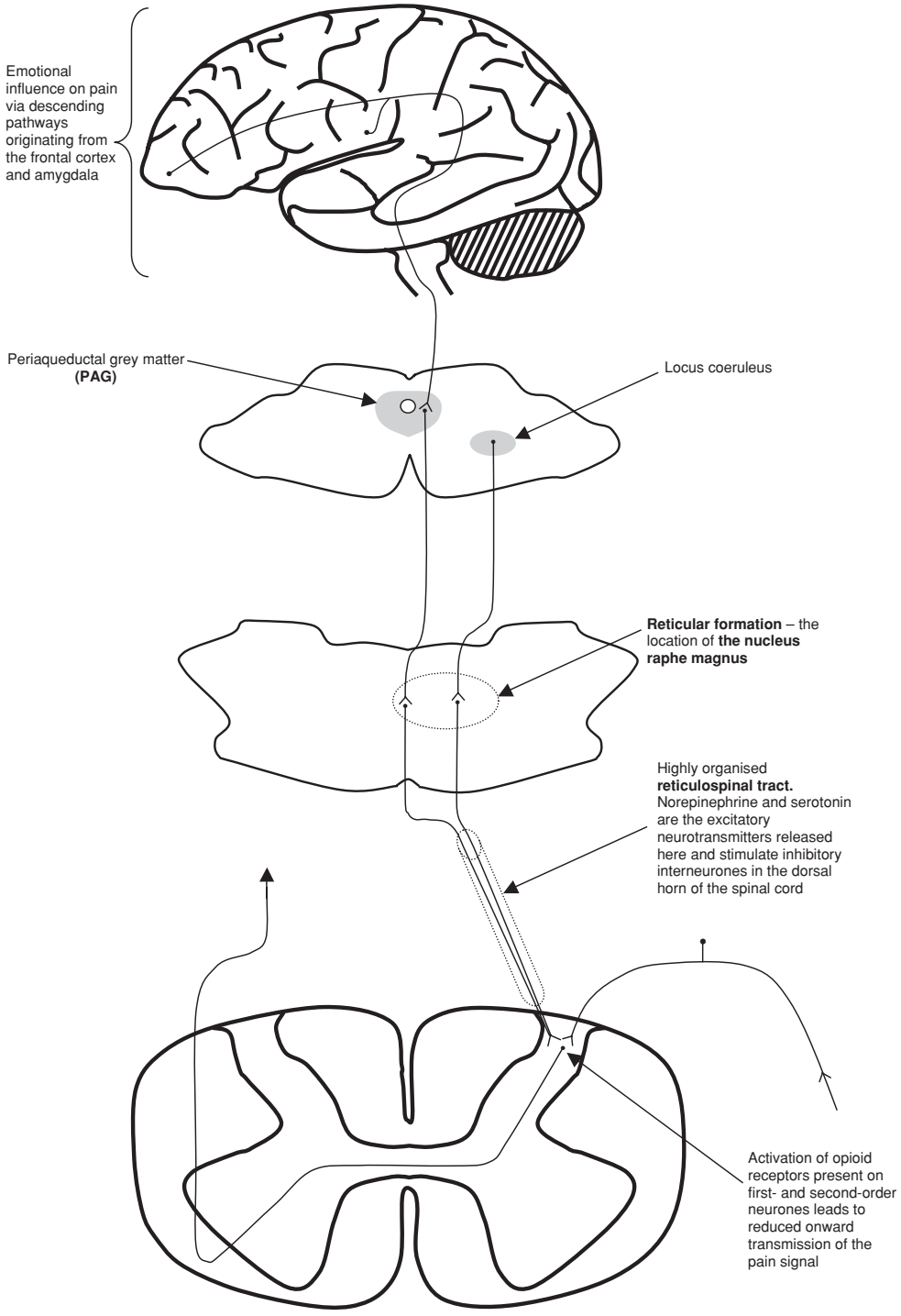

Figure 1.6 Descending pain pathways.

There are an abundance of opioid receptors in the superficial dorsal horn on both presynaptic primary afferent neurone terminals and postsynaptic second-order neurones. Activation of these receptors results in the opening of K^+ ion channels leading to hyperpolarisation of the neurone and consequent increased activation threshold. Thus, it is more difficult for nociceptive activity to be transmitted.

- *Central sensitisation and wind-up*

Pain signals are subject to modulation (augmentation or inhibition) both peripherally and centrally. When peripheral sensitisation occurs, pain signals arriving in the CNS are of greater amplitude and frequency. This increased barrage of *high-frequency* afferent activity can result in a state of *central sensitisation* in which the threshold of central neurones is decreased; allowing ordinary sensory information, such as innocuous touch and pressure, is perceived as painful.

Glutamate is the primary excitatory neurotransmitter involved in pain transmission and it exerts its effects on the *NMDA* (*N*-methyl-D-aspartate) and *AMPA* (α-amino-3-hydroxy-5-methyly-4-isoxazolepropionic acid) receptors. It is the NMDA receptor which is of great interest with regard to the phenomenon of *wind-up*.

Wind-up describes the situation in which dorsal horn second-order neurones are sensitised, increasing their output in response to *repeated* stimulation. Thus, although the strength of the repeated stimulation remains the same, the dorsal horn output increases.

Both low- and high-threshold, sensory, afferent fibres release glutamate when stimulated. This binds to both AMPA and NMDA receptors, although at different levels of activity. Normal noxious stimuli cause glutamate to bind to AMPA receptors and open a fast voltage-gated Na^+ ion channel, which results in short-lived postsynaptic depolarisations. When glutamate binds to NMDA receptors, a large Ca^{2+} channel is opened, allowing a large Ca^{2+} influx. Such large amounts of Ca^{2+} influx can be detrimental to cells and for this reason the channel is 'guarded' by Mg^{2+} ions while 'resting'. Only in the presence of continuous, unrelenting noxious stimuli is the 'Mg^{2+} block' from the Ca^{2+} channel of the NMDA glutamate receptor removed.

Continuous noxious stimulation results in dorsal horn release of the neuropeptides SP and CGRP. SP acts on neurokinin$_1$ (NK_1) receptors, which are abundant in the dorsal horn of the spinal cord. Activity of these receptors is essential for central sensitisation to occur but not for the normal transmission of painful stimuli. The key elements in the establishment of wind-up are the activation of the NMDA receptor, successful depolarisation and subsequent generation of increased levels of intracellular Ca^{2+}. A cascade of events then follows, which include activation of many Ca^{2+}-dependent second-messenger systems, such as protein kinases, and consequent phosphorylation of the AMPA receptor, which increases NMDA receptor sensitivity to released glutamate and the probability of NMDA receptor channel opening.

The increased strength of the chemical synapse following NMDA activation can last from minutes to days, and is referred to as *long-term potentiation*. It is postulated to be one of the mechanisms involved in forming memories, including those of pain.

Supraspinal modulation

Descending pathways can close the 'gate' in the dorsal horn, as described above. In addition, they can inhibit pain transmission independently of the dorsal horn 'gate'. They originate from three main areas:

- Cortex
- Thalamus
- Brainstem – especially the *periaqueductal grey* (PAG) area

and descend in the dorsolateral columns of the spinal cord to terminate in dorsal horn regions. Release of norepinephrine, 5-HT and enkephalin opioids results in antinociceptive effects.

The PAG is crucial in integrating information from higher centres such as the frontal cortex and amygdala (both of which are involved in emotion) and from ascending afferent activity from the dorsal horn of the spinal cord.

Neurones pass from the PAG to the *reticular formation* of the *rostroventromedial* (RVM) medulla. The reticular formation is the collective term for the many nuclei that lie in the RVM and make synapses with descending fibres from the PAG. The most important of these nuclei is the *nucleus raphe magnus* (NRM).

The descending neurones from the PAG to the NRM are serotonergic in nature and fibres pass on to the dorsal horn via the *reticulospinal tract*. Activation of this pathway causes inhibition of ascending pain impulses by releasing enkephalins, which hyperpolarise the postsynaptic membrane of second-order ascending neurones, reducing the amount of SP released by the presynaptic neurone.

A second pathway utilising norepinephrine runs from the *locus coeruleus* in the pons to the spinal cord, via the brainstem. As with fibres in the reticulospinal tract, they act to modulate afferent impulses in the spinal cord and enhance the action of endogenous opioids. This is the principle behind the use of the exogenous α_2-agonist clonidine, which acts in a similar way to norepinephrine although is limited by its side effects, which include hypotension and sedation.

The abundance of opioid peptide transmitters and receptors in all aspects of the descending pathways is of particular interest. Enkephalinergic neurones are prevalent in the PAG, NRM, locus coeruleus and dorsal horn and in part explain the analgesic mechanisms of opioid drugs such as morphine and codeine.

These descending pathways are under tonic GABAergic inhibition and opioids not only reduce this inhibitory tone but also increase the synthesis and release of norepinephrine and 5-HT along the pathways, which in turn augment the action of opioids.

Pain perception

All of the stages in the pain pathway which have been explained so far are part of the process of nociception. The final stage of the ascending pathway is the conscious experience and perception of the noxious stimulus as being painful. This experience will vary between individuals and depend on the context in which the injuries occur. A given degree of noxious stimulation does not equate with a predetermined pain response. For example injuries sustained in the battlefield or those during competitive sport may go unnoticed at the time they occur. In evolutionary terms, this has obvious survival benefits, and descending inhibitory pathways utilising norepinephrine may also play a role in these scenarios.

Recent functional imaging studies of the brain have illustrated the numerous and diverse areas which are involved in pain processing – areas such as the thalamus, S1 and S2 sensory cortex, primary motor and supplementary motor cortex, anterior cingulate gyrus, insula and the limbic system. The anterior cingulate gyrus, insula and limbic system are all known to be involved in emotion and explain why psychological factors such as arousal, attention, past experience and expectation can influence CNS circuits involved in modulation. Areas of the brain involved in processing emotion project down to the PAG and activate descending inhibitory pathways, such as the spinoreticular tract. The manipulation of these psychological factors is the basis behind the placebo effect, hypnosis and the Lamaze technique for pain during labour. It is also the reason why psychotherapy and cognitive behavioural therapy can play a crucial role in the multidisciplinary treatment of pain.

Finally, pain may be experienced in the absence of nociception. An example is the 'thalamic syndrome' which can occur following a stroke, where pain is experienced despite any injury, probably due to the loss of descending inhibitory signals from the thalamus.

Summary

Pain is a complex interaction between sensory, behavioural and emotional aspects of the experiencing person, yet it can occur in the absence of a stimulus. Past experiences of pain can dictate an individual's future response. Effective pain management requires the use of appropriate pharmacological, behavioural and psychosocial approaches.

Further reading

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Useful websites

The Digital Anatomist: *http://sig.biostr.washington.edu/projects/da/*.
The Whole Brain Atlas: *http://www.med.harvard.edu/AANLIB/home.html*.
International Association for the Study of Pain: *http://www.iasp-pain.org*.