Beyond Pain

Edited by

PAT SCHOFIELD PHD
Senior Lecturer, School of Nursing and Midwifery,
University of Sheffield

WHURR PUBLISHERS
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For my mum.

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Preface

The subject of pain is a relatively new specialty. Since Melzack and Wall published their original account of the gate control theory in 1965, many advances have been made in the assessment and treatment of pain. However, chronic pain remains a contentious issue.

The main problem associated with chronic pain is the inability to confirm diagnosis, along with the impact the pain has on sufferers, their families, society, and the many healthcare professionals who may come into contact with them. In the past, management of chronic pain has tended to focus on the medical model of treatment and cure, which has resulted in the worldwide development of pain clinics.

Since 1965, it has been recognized that many factors are involved in the chronic pain experience, and that attempts at curative treatment (which is largely unsuccessful) have resulted in the development and perpetuation of pain behaviour. Such problems acknowledge the contribution that can be made by other members of the multidisciplinary team. Since the 1980s this team has included nurses, and over the last 20 years many people have gradually come to recognize the valuable contribution that nurses can make in terms of assessment and management of chronic pain.

This book is designed to raise awareness among nurses of the contribution they can make. The authors are leading nurse specialists in the field, who discuss various aspects of the chronic pain phenomenon. I hope the book will also provide a resource to help nurses understand the mechanisms by which chronic pain can occur and its the impact on patients, their families and society.

The book provides approaches that can be effectively used by practising nurses in order to help patients come to terms with their ongoing pain. In the final chapter, future developments for the nursing profession are highlighted.

Pat Schofield
Sheffield, April 2005

Contributors

Paul Bibby RN MA is currently working as a consultant nurse in pain management at Sherwood Forest Hospitals, North Nottinghamshire. He has worked full time in pain management since 1997, establishing the acute pain service at Doncaster, and has also worked at the University of Sheffield School of Nursing and Midwifery. His interest in spiritual pain was sparked by a growing problem on general wards at Doncaster with respect to the management of addicts and alcoholics with pain.

S. José Closs RGN DPhil is Professor of Nursing Research at the University of Leeds. She has been involved in clinically focused research for more than 20 years. Much of her work has been concerned with gaps in nursing care, with a particular emphasis on older people, and she has published widely in this field.

Margaret Dunham is a lecturer in nursing and pain in the School of Nursing and Midwifery at the University of Sheffield. Before that she worked in the field of pain management for over 5 years. She considers the improvement of knowledge and education of nurses in the pharmacology of pain and its application to practice to be an area of great importance.

Rachel Drago RN MSc PGDipEd DipTher is a lecturer in nursing at the University of the West of England, Bristol. She has staffed in hospitals in London, Leeds and Nottingham and worked as a lecturer in nursing since 1995, specializing in the teaching of physiology while working as a critical care practitioner. Rachel now teaches human physiology, functional anatomy and clinical pharmacology to nurses at all levels of study.

Linzi Fletcher BHSc MCSP works as a senior physiotherapist for the North Eastern Derbyshire PCT in Chesterfield. Since 1995 she has specialized in musculoskeletal injuries within NHS settings, private practice and industry, employing physical and behavioural approaches to treatment. This experience led her to set up a chronic pain management programme in 2003, that she has run with a psychologist. This education-based community programme is used to conduct a research programme as well as to set up patient-led network groups.

Amanda Howarth BMedSci MSc (Pain) is a non-clinical lecturer in the department of Community, Ageing, Rehabilitation, Education and Research in the School of Nursing and Midwifery at the University of Sheffield. Previously she has worked as a clinical nurse specialist in acute and chronic pain management at the Chelsea and Westminster Hospital in London and the Royal Hallamshire Hospital in Sheffield, where she ran clinics offering a variety of treatments including acupuncture and aromatherapy massage. She won the Nurse of the Year award in 2001 for her work in developing a pain service for people with multiple sclerosis, and is currently undertaking her PhD into the use of aromatherapy massage for people with multiple sclerosis who experience chronic pain.

Helen Macdonald RN (Mental Health) MSc is a cognitive-behavioural psychotherapist and psychologist. She trained as a behavioural psychotherapist at the Institute of Psychiatry in London. Her research has included a pilot study on self-help for chronic pain. Helen has been accredited by the British Association for Behavioural and Cognitive Psychotherapists since 1994, chartered as a Health Psychologist by the British Psychological Society in 2004 and is a full member of the Division of Health Psychology. She is on the board of directors of the British Association for Behavioural and Cognitive Psychotherapists (2001–2004) and a member of their accreditation panel and complaints and disciplinary procedures committee. After 20 years in the NHS, Helen now works in private practice.

Debbie Poole RN BA MSc has worked in the Pain Management Service since it began 10 years ago. Debbie has developed the nursing role within this multidisciplinary service, initiating nurse-led clinics, working closely with the psychologists to offer support and management and providing expert input into some of the more specialist interventional techniques for pain relief. She is also involved with teaching, research and audit, has spoken at the Annual Pain Society Meeting and co-facilitates an annual National TENS Course.

Louise Robson BSc PGDipAc MCSP MBAcC currently works part time as a musculoskeletal physiotherapist for North Eastern Derbyshire PCT and also practices acupuncture in private practice in Sheffield.

Joseph Robson DipAc MBAcC has a special interest in Japanese acupuncture. He practices acupuncture in private practice in Sheffield.

Pat Schofield RGN PhD PGDipEd DipN currently works as a senior lecturer in pain and nursing studies at the School of Nursing and Midwifery, University of Sheffield. Before entering the field of nurse education, she worked for 6 years as a clinical nurse specialist for chronic pain management, being among the first nurses appointed to this field in the UK. Pat was responsible for the development of the first education course for nurses on pain management and she has developed national conferences and networks for nurses. Her investigation of the use of the Snoezelen for the management of chronic pain was highly commended in the Nursing Times Innovations in Practice. She represents the British Pain Society on the Advisory Panel to NICE, and is working with the British Geriatric Society to develop guidelines for pain management in older people.

Sue Zmarzty RGN BSc MMedSci (Human Nutrition) DipN CertEd works as a Lecturer in Nursing in School of Nursing and Midwifery at the University of Sheffield. She has a special interest in the delivery of life sciences within the preregistration courses in nursing studies. She is passionately interested in human nutrition and has conducted research on the effects of food on pain perception in healthy human volunteers.

CHAPTER ONE

The anatomy and physiology of pain

RACHEL DRAGO

- What are pain and sensation?
- A simple neural pain pathway
- Gate control theory
- Pathological and chronic pain
- Conclusion

The human body is capable of experiencing a myriad of sensations, from the pleasing smooth, soft texture of velvet to the most extreme pain. The interpretation and appreciation of these sensations requires a close integration of physiological responses along designated anatomical pathways with the psychological interactions of the mind and behavioural responses (Wall and Melzack 1999).

Pain is a sensation that is common to us all, and is appreciated by most of us as an unpleasant phenomenon that the body and mind strive to avoid. It is a wholly subjective experience. The perceived intensity and discomfort for any one known controlled stimulus varies from person to person. The perception of pain requires the integration of sensory nerves and motor nerve pathways, the presence and quantity of pain-producing chemicals found at sites of tissue damage (local hormones), the genetic make-up of the individual, past experience and emotional condition. For the individual, the actual sensation of pain is therefore greater than the sum of its parts.

Although anatomical pathways, pain physiology and local hormone production play only a small part in the overall sensation of pain, the efficacy of analgesics and other pharmacological therapies is based on the modulation of the nervous system and its role in the sensation of pain. In order to make informed decisions on the therapeutic action of any analgesic and adjuvant treatments, the healthcare practitioner must have a good comprehension of theories of pain, the anatomy and physiology of pain, and factors such as local hormones that can increase or decrease the pain experience.

Learning point

You may need to revise some topics, such as

- the peripheral and central nervous system including the spinal cord, the sensory cortex of the parietal lobe and the simple spinal reflex
- the action potential and the function of the synapse, neurotransmitters and receptors
- sensory afferents
- motor and autonomic efferent
- the autonomic nervous system.

A knowledge of these topics will be assumed throughout this chapter. Details can be found in any good anatomy or physiology textbook.

What are pain and sensation?

Pain is an unpleasant sensation that warns of potential or actual tissue damage. The sensation of pain prevents bodily harm from becoming worse, or from occurring at all. It is a dramatic mixture of emotional and physiological reactions (Mountcastle 1980, Merskey 1986, Wall and Melzack 1999).

Physiological pain arises from the thermal, mechanical or chemical stimuli of the small-diameter sensory afferent fibres found in the tissues called **nociceptors**. There are two types: **Aδ** (A delta) fibres and **C fibres** (Cesare and McNaughton 1997). These differ from other sensory afferent nerve fibres in that the **noxious** stimulation has to be of a sufficient intensity and duration to bring about tissue damage. In other words, these fibres have a high stimulation threshold. Tactile sensory fibres such as the **Aβ (A beta) fibres**, on the other hand, have a low threshold and follow slightly different spinal tracts to the brain. The Aβ sensory fibres transfer information to do with pressure and texture, but not usually pain.

Imagine if pain was elicited by the simplest soft touch – this inappropriate nociceptor firing would make life miserable. Equally, if the nociceptor threshold is set too high then tissue damage will result before you can take action to halt the noxious stimuli. Hence the stimulation intensity is normally set to the appropriate threshold to prevent unnecessary discomfort or unnecessary tissue damage.

To modulate and regulate all this incoming information there are nerves that travel down from the brain to the spinal cord and help to analyse the sensations as they present at the spinal cord. These **descending tracts** regulate what sensations actually reach the brain, and allow you to divert your attention elsewhere. This is the rudimentary basis of the gate control mechanism of pain sensation and analgesia, and will be discussed later.

We can consider two categories of pain:

- **Physiological pain:** the pain response to high-intensity stimuli is transient if tissue damage is prevented by a simple spinal flexion reflex arc (Willer 1979). Imagine a just extinguished hot match head and the speed with which you let the match fall to the ground as you attempt to pick it up. This is a simple spinal reflex mediated by the high-intensity thermal stimulation of small sensory nerve endings in your fingers. The speed with which this reflex occurs allows you to suffer only a few moments of discomfort rather than deep tissue damage.
- **Pathological pain:** results from sensitization of the nerves in the periphery and in the spinal cord. The peripheral nerve endings are made more sensitive to noxious stimuli through tissue damage, action of local hormones such as prostaglandins, histamine, serotonin and bradykinin, and also by direct nerve damage; this is **peripheral sensitization**.

Central sensitization occurs when the **neurons** involved with transmission of the pain impulse along the spinal cord to the sensory cortex in the parietal lobe of brain are sensitized by a barrage of impulses from the site of tissue damage. The central nervous system nerve fibres now begin to respond to non-nociceptive impulses such as gentle touch as if these were pain impulses.

The resultant peripheral and central sensitization of the neural pathway produces pain without clear external stimulus, non-noxious stimuli such as gentle stroking produces pain (**allodynia**), and there is an exaggerated pain response to low-threshold noxious stimuli (**hyperalgesia**) (Woolf 1989, 1991; Rang, Dale and Ritter 1999). It is vital to note that in the acute injury phase this potentiation of pain serves an important purpose; it acts as a rate-limiting sensation, in that it prevents further tissue damage by ensuring immobilization and rest of the affected area (Woolf 1991). However, pain which persists after the acute phase, i.e. **chronic pain**, serves no useful purpose and becomes a clinical issue in its own right.

Summary

- Pain is an unpleasant sensation that warns of potential or actual tissue damage. It is a mixture of emotional and physiological reactions.
- Pain arises from the thermal, mechanical or chemical stimuli of the small diameter sensory nerves or **nociceptors** which are classified as Aδ fibres and C fibres.
- Tactile sensory fibres (Aβ fibres) transfer information to do with pressure and texture, but not usually pain.
- The physiological pain response to high intensity stimuli is transient if tissue damage is prevented by a simple spinal flexion reflex arc.

- Pathological pain results from sensitization of the nerves in the periphery and in the spinal cord.
- Peripheral sensitization occurs when peripheral nerve endings are made more sensitive to noxious stimuli through tissue damage or local hormone action.
- Central sensitization occurs when the central nervous system responds to tactile sensation and impulses from the Aβ fibres as if these were pain impulses.

A simple neural pain pathway

As mentioned previously, pain is detected essentially by two sensory (nociceptor) afferent fibres, which synapse with both **motor neurons** and **transmission** (sometimes called **relay**) **neurons** in the dorsal horn of the spinal cord. The nerve fibres within the dorsal (rear) horn carry information back to the spinal cord and brain. The ventral (front) horn carries autonomic efferents and motor nerves away from the spinal cord and brain and back to the body (Figure 1.1).

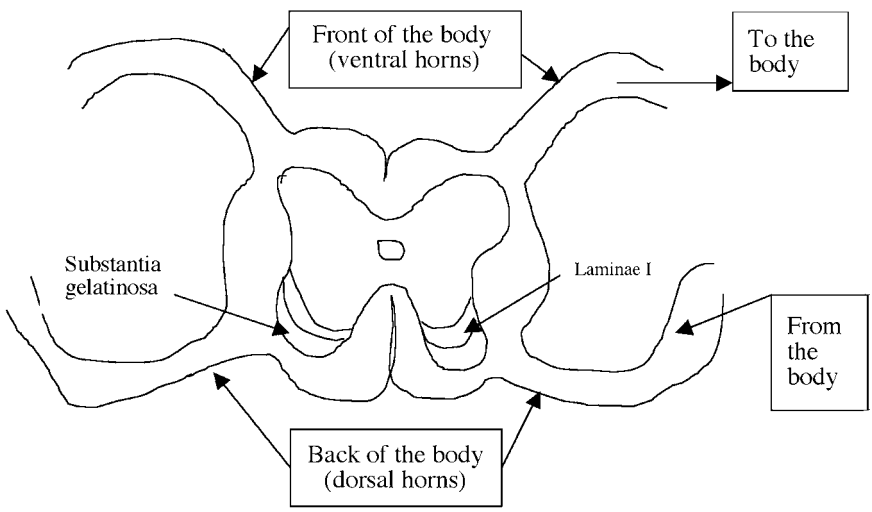

Figure 1.1 Cross-section of the spinal cord.

The terminal nerve endings of the sensory nociceptors release the neurotransmitters substance P and glutamate, which bind to specific receptors on the surface of the dendrites of the transmission neuron, propagating the pain signal either to a motor nerve or up the spinal cord to the brain.

C fibres

These are fine (0.23–1.5 μm in diameter) unmyelinated fibres with a conduction velocity of less than 2.5 m/second (Wall 1999). They are sometimes called **C polymodal fibres** as they respond to chemical, mechanical and thermal stimuli, i.e. they have more than one mode of stimulation. Their main neurotransmitters at the synapse are substance P and glutamate.

C fibres are thought to be involved with dull, diffuse pain. As well as sending electrical messages to the spinal cord by the movement of potassium and sodium ions into and out of the axon, C fibres are responsible for the absorption of inflammatory chemicals (local hormones such as bradykinin) from the site of tissue damage and the subsequent transport of these chemicals along the length of the axon to be released within the spinal cord at the synapse with the transmission neuron (Wall and Melzack 1999) (Figure 1.2). This process provides the dull, diffuse and profound ache that follows some relatively minor injuries and may last for days. In the case of a sprained ankle, for example, it will make the whole of the lower leg painful to touch and impossible to walk on.

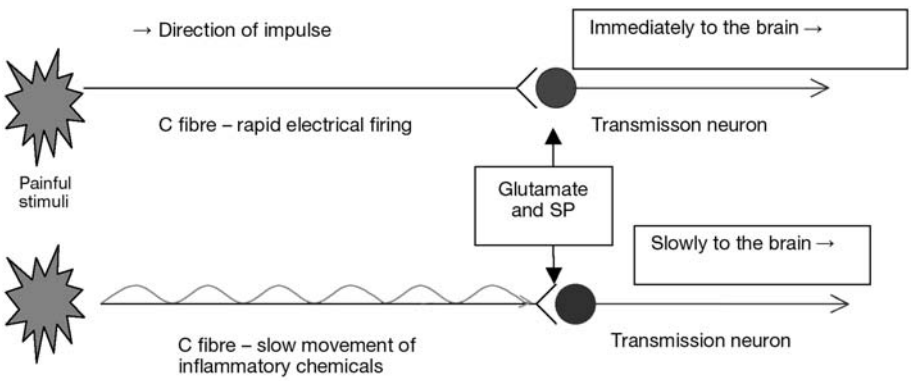

Figure 1.2 The rapid and slow effects of the C fibre in the dorsal horn.

Aδ fibres

These are medium-sized neurons (1–5 μm in diameter), myelinated and fast acting with a conduction velocity of more than 2 m/second. They are assumed to cause the sensation of well-localized, sharp and intense pain (Rang, Dale and Ritter 1999). Aδ fibres are similar in function to the C polymodal fibres, but are more rapid in reaction and are sensitive to heat and mechanical stimuli rather than to chemical stimuli.

Consider a needle prick to your finger: initially you can feel the exact location of the needle stab and can pinpoint it with accuracy (Aδ fibres), but a few minutes later the pain is a dull, diffuse throb and the exact site of tissue damage is unclear (C fibres).

Both Aδ and C fibres are found in large numbers in the skin, but C fibres predominate within the internal organs, muscles and viscera. Both types of fibres respond to potential tissue threat by setting off a series of action potentials along the axon length to the synapse with a number of transmission neurons within the dorsal root of the spinal cord, and along tracts to the brain (Figure 1.3).

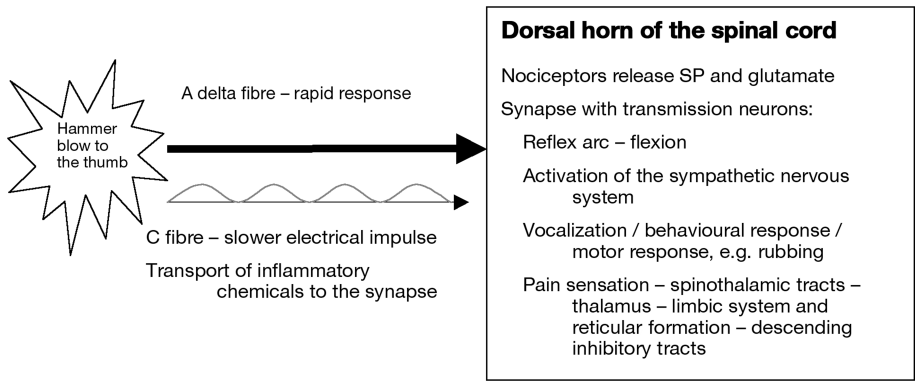

Figure 1.3 Physiological pain responses.

Dorsal roots

The **dorsal roots** are made of layers or laminae into which the sensory nerve fibres, including nociceptors, penetrate. Synapses are made with the transmission neurons that direct the impulse across the spinal cord to motor neurons and can elicit a reflex flexion arch from the offending source of the noxious stimuli or ascend the cord to the brain.

All sensory fibres have to cross a neuron-rich area called the **substantia gelatinosa** before forming a synapse with spinal neurons in the various laminae. The Aδ and C fibres connect predominantly in the first three layers (laminae I, II and III).

Within the substantia gelatinosa are short nerve fibres or **interneurons** which regulate the transmission of impulses from the nociceptors and other sensory nerve fibres. The interneurons are rich in neurotransmitters which resemble opiates and are therefore very important in the modulation of nociception through an opiate receptor mechanism. They act as gatekeepers, allowing the transmission of some impulses to take priority over others.

The interneurons inhibit the response of the transmission neuron to stimulation from an Aδ fibre when impulses generated by an Aβ fibre are also arriving at the synapse with the transmission neurons. At a time of high input from the nociceptors, the large Aβ fibres, which respond to mechanical and pressure stimuli, are preferentially filtered through the substantia gelatinosa in the dorsal horn of the spinal cord. For example, if you rub the sore area, the rubbing sensation is felt rather than the pain experience. Rubbing really does make it better! An understanding of the physiology behind this has enabled the development of transcutaneous nerve stimulation (TENS) as a pain-relieving technique (see Chapter 7).

Learning point

Revise the autonomic nervous system.

From spinal cord to brain

The sensation of pain occurs as the impulse moves along the anteriolateral spinothalamic tracts and through the mid brain, which includes the **thalamus**, the **reticular formation** and the **limbic system**. Sensory information is directed through the **cerebral cortex** and on to the **sensory cortex** in the parietal lobe. Concurrently the sympathetic nervous system is aroused, increasing blood pressure, heart rate and local blood flow and bringing about a sense of heightened psychological arousal or wakefulness. The sympathetic nervous system only dominates the regulation of the body during so-called 'E' situations (emergency, excitement and embarrassment): it prepares the body for 'fight or flight'. The adrenal medulla secretes adrenaline into the blood stream, and sympathetic nerves at the site of tissue damage release noradrenaline directly into the injured tissue.

The vocalization and behavioural responses from higher brain centres occur instantaneously (it is amazing how the use of expletives can have a major analgesic effect on physiological pain!).

The arousal and emotional effects of pain are also influenced by the areas of the brain the nociceptor impulses pass through. The reticular formation is concerned with consciousness and the filtering of sensations through to the cerebral cortex; the limbic system is linked with primal needs or drivers and with base emotions.

Descending tracts and the substantia gelatinosa

Descending tracts are efferent fibres which leave the reticular formation within the brain, travel along the spinal cord and synapse with transmission and interneurons within the substantia gelatinosa. The role of the descending

tracts is to modulate the incoming messages from the peripheral nerves. In essence, they act as a filter and as a partial inhibitor of the messages ascending the spinal cord from the nociceptors, thus limiting rather than preventing the transmission of peripheral impulses from the sensory Aδ and C fibres along the transmission fibres.

The descending nerve pathways derive from the **periaqueductal grey** within the reticular formation and flow into the **medulla** (brainstem). From the specific area called the **nucleus raphe magnus** in the medulla, impulses then pass down the dorsolateral tracts in the spinal cord to connect with transmission neurons and interneurons in the substantia gelatinosa of the spinal cord (see Figure 1.1) (Fields and Basbaum 1994). The major neurotransmitter from the descending tracts is serotonin, which stimulates interneurons within the substantia gelatinosa to release peptides, noradrenaline and endogenous opiates such as endorphin, enkephalin and dynorphine.

It is important to note that these descending tracts, the brain and spinal cord areas involved with pain perception and modulation are rich in opiate receptors, which may explain the actions of a number of our analgesic preparations.

The pain pathway is a cycle of events within the central nervous system, interpreting and modulating the impulses that are generated in the peripheral nerves of the body.

Learning point

Revise the peripheral nervous system and the central nervous system, i.e. the brain and spinal cord, 12 pairs of cranial nerves and 31 pairs of spinal nerves.

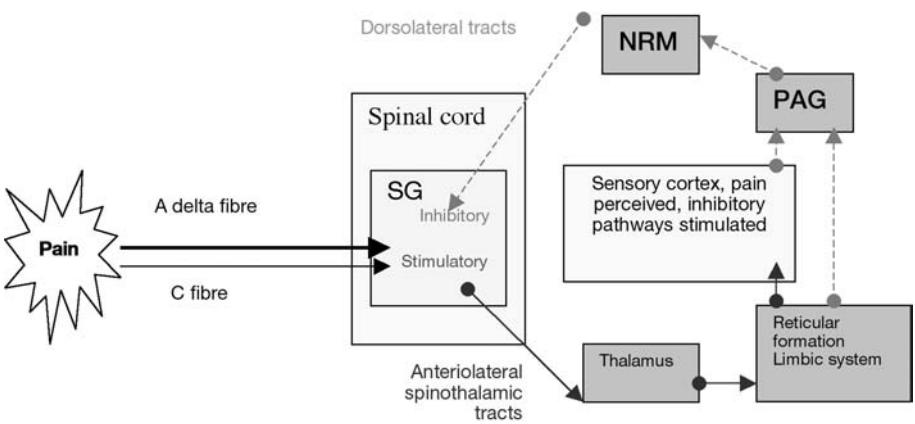

Figure 1.4 The **ascending pathways** and descending inhibitory pathways.
SG, substantia gelatinosa, laminae I–III, transmission neurons; PAG, periadquaductal grey; NRM, nucleus raphe magnus. The dashed lines represent pain modulation pathways (descending) and the solid lines are pain sensation pathways (ascending).

Summary

- Nociceptors synapse with motor neurons and transmission neurons in the dorsal horn of the spinal cord.
- Transmission fibres within the dorsal horn carry information back to the spinal cord and brain.
- The dorsal horn is made up of layers or laminae which contain many transmission neurons.
- Aδ and C fibres predominately synapse with transmission neurons in the first three layers (laminae I, II and III).
- Nociceptors release the neurotransmitters substance P and glutamate.
- The substantia gelatinosa is a neuron-rich area through which all nociceptors must cross before forming a synapse with spinal neurons in the various laminae.
- The interneurones in the substantia gelatinosa regulate the transmission of impulses from the nociceptors and other sensory nerve fibres to the various laminae. They are rich in neurotransmitters that resemble opiates and are therefore important in the modulation of nociception through an opiate receptor mechanism.
- C fibres are unmyelinated fibres which respond to chemical, mechanical and thermal stimuli. They are thought to be involved with dull, diffuse pain.
- Aδ fibres are myelinated fibres, which are assumed to cause the sensation of well-localized, sharp and intense pain.

Gate control theory

First put forward by Melzack and Wall (1965), this is now the most widely accepted theory of pain sensation and inhibition. It explains a great many of the pain phenomena that humans experience, but it is by no means complete, and experimental work continues to be carried out. The **plasticity** of the nervous system – its ability to become desensitized and sensitized – also adds an extra dimension to the theory.

Aδ and C nociceptor fibres synapse within the dorsal horn of the spinal cord with both transmission fibres and interneurons. Aβ sensory fibres follow a similar pathway and also synapse with the same neurons (Figure 1.5).

Tissue damage produces high intensity messages to move along the nociceptors to the transmission neuron. The nociceptor also forms synapses with small excitatory interneuron.

Concurrent stimulation of the excitatory interneuron as well as the transmission neuron will augment the nociceptor output, and hence potentiate the pain experienced. Rubbing the affected area will also stimulate the

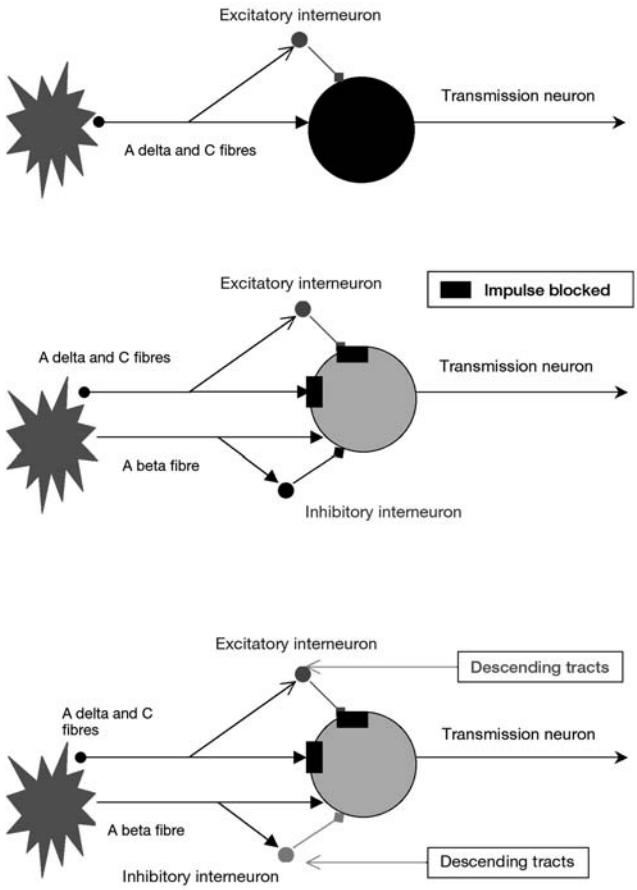

Figure 1.5 A simple pain pathway.

low-threshold Aβ sensory fibres. They synapse with an **inhibitory interneuron**, which decreases the sensitivity of the transmission neuron to the nociceptor outputs.

The descending pathways from the periaqueductal grey will attempt to modulate the activity of the interneuron. By stimulating the inhibitory interneurons to release endogenous opiates, the nociceptive pathway is again blocked.

Learning point

As a healthcare professional, can you hypothesize how the use of heat, cold, TENS, opiates and NSAID analgesics have an effect on the physiological properties of acute pain perception?

Summary

- The gate control theory is the most widely accepted theory of pain sensation and inhibition. However, it is not by any means a complete theory and it is worth noting that other theories exist but are hard to support through scientific enquiry.
- Plasticity is the ability of the nervous system to become sensitized and desensitized.
- Aδ and C nociceptor fibres and Aβ sensory fibres synapse with the same interneurons.
- Painful stimuli excite the nociceptors, which in turn excite the transmission neuron and excitatory interneurons.
- Rubbing the affected area excites Aβ sensory fibres. These synapse with an inhibitory interneuron, which decreases the sensitivity of the transmission neuron to the nociceptor outputs.
- The descending tracts modulate the pain sensation by stimulating the inhibitory interneurons to release endogenous opiates, blocking the nociceptive pathway.

Pathological and chronic pain

Chronic pain is a reminder that we do not fully understand the sensory phenomenon that is pain. The simple pain pathway and gate control theory described in previous sections do not adequately explain the ramifications and issues that arise from chronic pain, or from pain that has no obvious cause.

The pain pathways travel through many different regions of the brain, which may go some way to account for the psychologically depressing and unpleasant nature of pain, and the arousal of the sympathetic nervous system and inability to find sleep or comfort that chronic pain sufferers describe. But this cannot be the whole story. The plasticity of the central nervous system and the change in sensitivity of both peripheral nerves and central pathways also add support to the signs and symptoms explained and experienced by patients with chronic pain. Thus in the treatment of chronic pain we must look beyond the accepted analgesics and seek novel treatments that would not be considered in the treatment of acute pain.

Peripheral sensitization

Tissue damage results in the release of phospholipids from the plasma cell membrane (Figure 1.6). Enzymes present in the tissue fluid, such as phospholipase A_2, catalyse their conversion to arachidonic acid, which is further modified by other enzymes (cycloxygenase 1 and 2, and lipoxygenase) to

produce a family of chemicals known as **eicosanoids**. These are often termed **local hormones** and include substances such as prostaglandins, leukotrienes, lipoxins, chemotaxins and thromboxanes. These eicosanoids increase the sensitivity of the C fibres, which are responsive to chemicals, heat and mechanical action, and thus increase the unpleasant experience of pain. The C fibres also absorb a great many of these chemicals and transmit them along the axon length to release them within the dorsal horn of the spinal cord (see Figure 1.2).

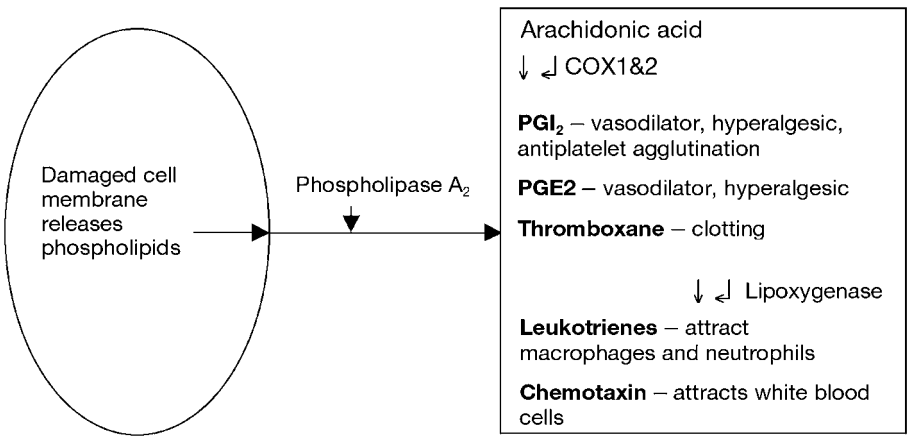

Figure 1.6 Cell damage and arachidonic acid.

To add impact to the action of local hormones, the nociceptors also release inflammatory mediators into the surrounding tissue (Figure 1.7). Hence, when stimulated by high-intensity heat, chemical or mechanical activity, the nociceptors also release calcitonin gene related peptide (CGRP) and substance P (Brain and Williams 1985). These chemicals act directly on mast cells (connective tissue cells containing granules of histamine), causing the release of histamine and serotonin. CCRP and substance P also act on the local blood vessels and cause vasodilatation and increase in capillary permeability.

The sympathetic nerves in the area of damage add to this inflammatory chemical cocktail by releasing prostaglandin I_2 and monoamines such as noradrenaline (also called norepinephrine).

This inflammatory cocktail of prostaglandins, histamine, bradykinins and noradrenaline (Figure 1.8) alters the threshold of the peripheral nociceptors to create a more sensitive neuron. It does this through a variety of mechanisms, including coupling to receptors on the neuron and opening ion channels, thus lowering the action potential threshold; or indirectly increasing the number of ion channels within the nociceptor membrane.

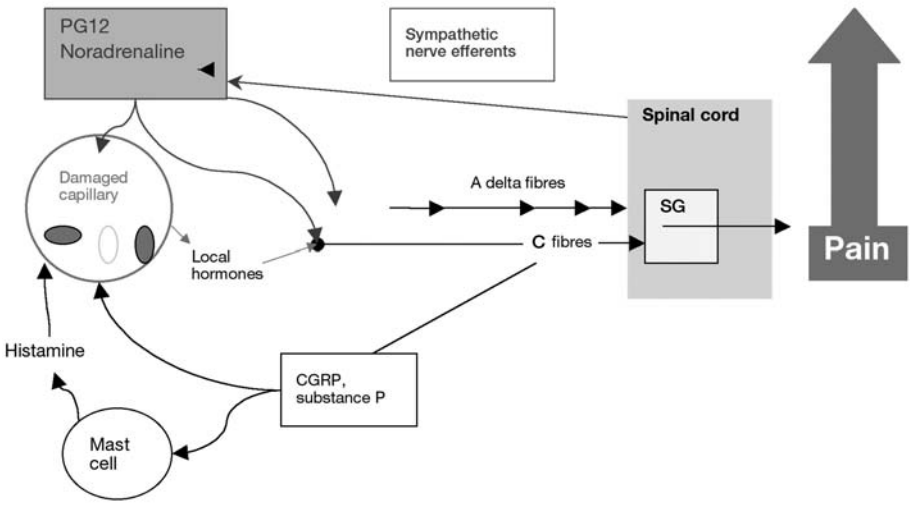

Figure 1.7 Peripheral sensitization by the sympathetic efferents, local hormones and local release of nociceptor-derived substance P.

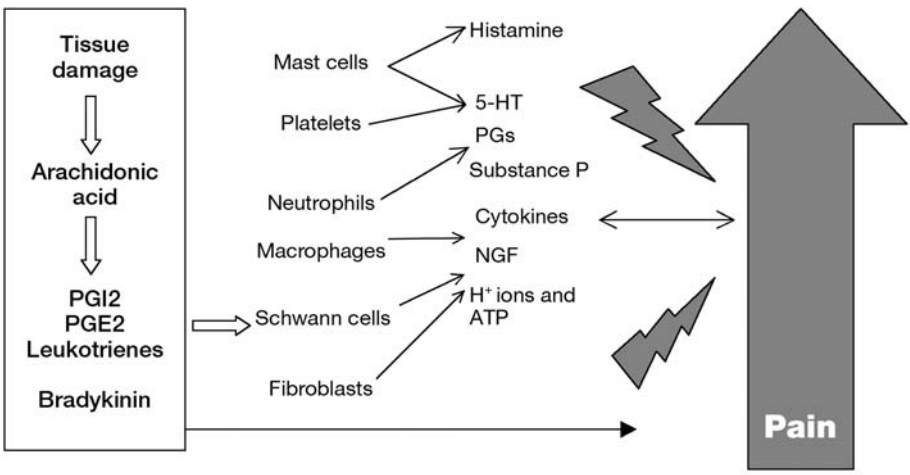

Figure 1.8 The inflammatory chemical cocktail and increased peripheral pain perception.

The inflammatory-mediated peripheral sensitization mechanism explains the anti-inflammatory and analgesic effect of non-steroidal anti-inflammatory drugs (NSAIDS) and glucocorticoids (steroids), which inhibit the lipoxygenase and cycloxygenase enzymes and so reduce the quantity of prostaglandins and leukotrienes at the site of tissue damage.

Summary

- Phospholipase A_2 catalyses the break down of cell membrane phospholipids into arachidonic acid.
- Arachidonic acid is the chemical precursor of many inflammatory mediators or eicosanoids, of which leukotrienes and prostaglandins are examples.
- Cycloxygenases are the enzymes that catalyse the breakdown of arachidonic acid to prostaglandins.
- Prostaglandins are a family of inflammatory chemicals that are also involved with pain potentiation, platelet agglutination and vascular resistance. They are absorbed by C fibres and transmitted along the axon length to be release within the dorsal horn.
- Nociceptors also release CGRP and substance P into the surrounding damaged tissue which potentiates the action of the inflammatory mediators by increasing mast cell degranulation, histamine release and vasodilatation.
- The sympathetic nerve endings in the damage tissue augment the inflammatory chemical cocktail by releasing prostaglandin I_2 and noradrenaline.
- NSAIDS and glucocorticoids (steroid drugs) inhibit the lipoxygenase and cycloxygenase enzymes respectively and so reduce the quantity of prostaglandins and leukotrienes at the site of tissue damage.

Table 1.1 Sources and action of local hormones

Substance	Released from	Action
Hydrogen Ions	Intracellular fluid	Excites nocioceptors
ATP	Intracellular Fluid	Acts on ATP receptors on macrophages inducing macrophage degranulation
Histamine	Macrophages, mast cells, basophils, histaminocytes (in the stomach) and histaminergic neurones	Vasodilatation, increases plasma permeability Increase gastric acid secretion Smooth muscle contraction with the exception of vascular smooth muscle
Bradykinin	Cleaved from kininogens found in tissue fluid	Activates sensory neurones, fibroblasts, endothelial cell secretion, liberates arachidonic acid.