

ANALGESICS AND THE CONTROL OF PAIN

• Introduction	155	• Opioids	159
• Pathophysiology and mechanism of pain	155	• Opioid antagonists	162
• Sites of action of analgesics	156	• Analgesics in terminal disease	162
• Drugs used to treat mild or moderate pain	156	• Management of post-operative pain	163

INTRODUCTION

Pain is a common symptom and is important because it both signals 'disease' (in the broadest sense) and aids diagnosis. Irrespective of the cause, its relief is one of the most important duties of a doctor. Fortunately, pain relief was one of the earliest triumphs of pharmacology, although clinicians have only recently started to use the therapeutic armamentarium that is now available adequately and rationally.

PATHOPHYSIOLOGY AND MECHANISM OF PAIN

Pain is usually initiated by a harmful (tissue-damaging, noxious) stimulus. The perception of such stimuli is termed 'nociception' and is not quite the same as the subjective experience of pain, which contains a strong central and emotional component. Consequently, the intensity of pain is often poorly correlated with the intensity of the nociceptive stimulus, and many clinical states associated with pain are due to a derangement of the central processing such that a stimulus that is innocuous is perceived as painful. Trigeminal neuralgia is an example where a minimal mechanical stimulus triggers excruciating pain.

The main pathways are summarized in Figure 25.1. The afferent nerve fibres involved in nociception consist of slowly conducting non-myelinated C-fibres that are activated by stimuli of various kinds (mechanical, thermal and chemical) and fine myelinated (A δ) fibres that conduct more rapidly but respond to similar stimuli. These afferents synapse in the dorsal horn of grey matter in the spinal cord in laminae I, V and II (the substantia gelatinosa). The cells in laminae I and V cross over and project to the contralateral thalamus, whereas cells in the substantia gelatinosa have short projections to laminae I and V and function as a 'gate', inhibiting transmission of impulses from the primary afferent fibres. The gate provided by the substantia gelatinosa can also be activated centrally by descending pathways. There is a similar gate mechanism in the thalamus. Descending inhibitory controls are very important, a key

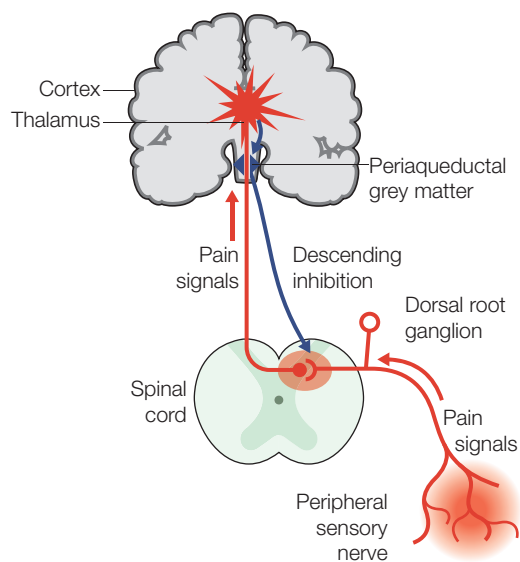


Figure 25.1: Neural pain pathways.

component being the small region of grey matter in the mid-brain known as the periaqueductal grey (PAG) matter. Electrical stimulation of the PAG causes profound analgesia. The main pathway from this area runs to the nucleus raphe magnus in the medulla and thence back to the dorsal horn of the cord connecting with the interneurons involved in nociception.

Key mediators of nociception are summarized in Figure 25.2. Stimulation of nociceptive endings in the periphery is predominantly chemically mediated. Bradykinin, prostaglandins and various neurotransmitters (e.g. 5-hydroxytryptamine, 5HT) and metabolites (e.g. lactate) or ions (e.g. K⁺) released from damaged tissue are implicated. **Capsaicin**, the active principle of red peppers, potently stimulates and then desensitizes nociceptors. The neurotransmitters of the primary nociceptor fibres include fast neurotransmitters – including glutamate and probably adenosine triphosphate (ATP) – and various neuropeptides, including substance P and calcitonin gene-related peptide (CGRP). Neurotransmitters involved in modulating the pathway include opioid peptides (e.g. endorphins), endocannabinoids (e.g. anandamide), 5HT and noradrenaline.