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Chapter 26.
DRUGS FOR MIGRAINE

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26.1 Migraine
Migraine affects 10-15% of the population, being more common in females, and with peak prevalence between 35 and 45 years of age. Migraine symptoms comprise a unilateral (sometimes contralateral), localized, throbbing headache that may persist for 72 hours, often accompanied by nausea and vomiting, photophobia (light sensitivity) and phonophobia (sound sensitivity). Roughly 20% of sufferers experience an “aura” preceding the headache. The aura may involve visual disturbances such as scintillating zig-zag lines, scotoma (blind spot), or blurred vision, accompanied by transient aphasia, chills, vertigo, or unilateral paraesthesia (numbness or weakness).

The actual cause of migraine is unknown, and it can be triggered by almost anything, but most commonly psychosocial, environmental, neurochemical and neuroendocrine changes. Known triggers in susceptible individuals include cheese, chocolate, alcohol, chemicals, sunlight, hormones, and the contraceptive pill.

26.2 Pathogenesis of Migraine
While the biochemical initiators of migraine or underlying abnormality that predisposes some individuals are not well known, migraine is now recognized to have neural and vascular involvement, highlighting the important interaction between nerves and the cerebral vessels. The headache originates from pain-sensitive extracerebral structures such as the meninges and large arteries, which are innervated by nociceptive sensory nerves of the trigeminal system, paving the way for the neurogenic inflammation. Another important phenomenon that occurs in migraine is cortical spreading depression, thought to explain the aura or increased susceptibility to migraine.

26.3 Cortical Spreading Depression
Cortical spreading depression can be viewed as a wave of transient neural inhibition (spontaneous and evoked activity) that progresses slowly over the cortex at 2-6 mm per minute. This wave of depression is preceded by a transient wave of intense excitation associated with very high extracellular K\(^+\) and reduced blood flow. Although the trigger of excitability is not known, accumulation of extracellular K\(^+\) due to enhanced excitation depolarises adjacent neurons, causing the phenomenon to spread. Changes in blood flow or spreading excitation and depression may initiate the headache. Moreover, the localised spreading depression may activate the trigeminal nucleus caudalis (of the central pain pathway), sensitising the central pain pathway.

### 26.4 Neurogenic Inflammation Theory

The trigeminocerebrovascular system comprises the ophthalmic trigeminal ganglia, the cells of which innervate major vessels regulating cerebral blood flow, smaller meningeal (especially dura mater) vessels, the meninges, and centrally projecting sensory fibres synapsing on to the trigeminal nucleus caudalis in the caudal brainstem and cervical spinal cord. The pain sensitive structures include the blood vessels and meninges, thus trigeminal fibres afford a conduit for nociceptive information originating in the blood vessels and meninges to the central nervous system.

Stimulation of the trigeminal fibres, which are nociceptive C fibres, causes pain directly, as well as release of neuropeptides such as calcitonin gene-related peptide (CGRP), substance P and neurokinin, and also nitric oxide, leading to vasodilation. Following sufficient activation resulting perhaps from cortical excitation, blood vessel constriction or lowered sensitisation threshold to certain stimuli, inflammatory events occur including plasma extravasation (leakage from vessels), platelet activation, 5-HT secretion, mast cell degranulation and secretion of bradykinin, histamine and prostaglandins. This provides a localised “inflammatory soup” that continues to sensitise and activate the C fibres, contributing to neurogenic inflammation of the dura mater and blood vessels.

CGRP release is thought to regulate normal blood flow, since vasoconstriction triggers antidromic (feed forward) release of CGRP from trigeminal nerves, leading to vasodilation. Interestingly, CGRP is released in correspondence with the pain of migraine and its concentration has been shown to correlate with headache intensity. CGRP is also a marker of trigeminal activity. Thus, migraine may involve a lowered threshold of trigeminal activation, and hypersensitivity to local neuropeptide release, including CGRP, which not only causes vasodilation in pain-sensitive structures, but causes chemical irritation and may lower the pain threshold to previously innocuous stimuli.

Figure 26.1 schematically depicts the trigeminocerebrovascular pathways and highlights the important neuropeptides and neurotransmitters involved in these pathways.
26.5 Role for 5-HT in Migraine

5-HT is thought to be intrinsically linked to migraine. Evidence shows a sharp increase in urinary 5-HIAA (the catabolic product of 5-HT) and a fall in blood 5-HT concentration during a migraine attack. Moreover, migraine sufferers display perturbed 5-HT metabolism and transmission. 5-HT<sub>1B</sub> and 5-HT<sub>2</sub> receptors are found on extracerebral blood vessels. Stimulation of 5-HT<sub>2</sub> receptors indirectly causes vasodilation via release of nitric oxide, while activation of 5-HT<sub>1B</sub> receptors leads to vasoconstriction. As highlighted in Figure 1, 5HT<sub>1B,1D</sub> and 1F receptors, located on trigeminal nerve fibres and the trigeminal nucleus caudalis, become important regulators of the trigeminocerebrovascular system, since their activation would have an inhibitory effect on neurotransmission.

26.5 Acute Treatment of Migraine

It is important to distinguish between drugs that are used to treat acute migraine attacks, and drugs used in migraine prophylaxis, required for cases of at least two migraine attacks per month.

Acute attacks are treated with non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and paracetamol, ergotamines, and more commonly, triptans. NSAIDs are usually effective for mild attacks and when taken shortly after the onset of pain.
For over 70 years ergotamines such as ergotamine tartrate and dihydroergotamine were the classical treatment for migraine. These drugs can relieve the pain of migraine even when taken more than four hours after onset. Ergotamines are partial agonists at 5-HT\textsubscript{1D} receptors, thus blocking trigeminal nerve transmission, however they act at many additional monoamine receptors, including 5-HT\textsubscript{1B}, 5-HT\textsubscript{2}, dopamine D\textsubscript{1} and D\textsubscript{2}, noradrenergic α\textsubscript{1} and α\textsubscript{2} receptors. Subsequently, their usefulness is limited by their propensity to cause vasoconstriction, including of the coronary vessels, and foetal damage. They also cause nausea and vomiting due to activation of area postrema.

Triptans have become first line treatment for acute severe migraine, replacing ergotamines. A number of triptans are available, including sumatriptan (the prototype), zolmitriptan, almotriptan and naratriptan. The differences between these drugs lie in their plasma half life and time to peak plasma levels. Moreover, sumatriptan does not cross the blood brain barrier, while the other drugs do. Up to 80\% of patients respond to triptans within two hours of administration, and up to 40\% experience headache recurrence within 24 hours of initial relief.

All triptans are 5-HT\textsubscript{1B/1D} agonists, and their effects on migraine are numerous. Activation of these receptors on trigeminal ganglia and trigeminal nucleus caudalis cells inhibits transmission of nociceptive information from the blood vessels and meninges to the brainstem and central pain pathways. Additionally, stimulation of presynaptic 5-HT\textsubscript{1B/1D} autoreceptors on trigeminal cell bodies inhibits release of neuropeptides from trigeminal ganglia cells, thus reducing neurogenic inflammation. Moreover, on extracerebral blood vessels, activation of 5HT\textsubscript{1B/1D} receptors causes vasoconstriction, thus facilitating restoration of normal vascular tone. Finally, triptans relieve the nausea associated with migraine. One drawback, however, is their ability to cause vasoconstriction of coronary arteries via 5-HT\textsubscript{1B} receptors, thus they are contraindicated in cardiovascular disease.

26.6 Prophylactic Treatment of Migraine

Drugs used in prophylactic treatment of migraine include β-adrenoceptor antagonists, 5-HT\textsubscript{2} receptor antagonists, anticonvulsants and calcium channel antagonists. The type of prophylactic drug is chosen on the basis of factors such as contraindications, co-morbid conditions and tolerability. Even when used, only 50\% of sufferers can expect a reduction in migraine frequency.

β-adrenoceptor antagonists such as propranolol and metoprolol have been used successfully in the prophylactic treatment of migraine. The mechanism of prophylaxis is unknown, but it may be due to vasoconstrictor effects. These drugs are contraindicated in respiratory diseases such as asthma, and side effects include fatigue and bronchoconstriction.

5-HT\textsubscript{2} antagonists such as pizotifen, cyproheptadine and methysergide act by preventing 5-HT\textsubscript{2} receptor-induced vasodilation, secondary to nitric oxide production, and consequent inflammation. Adverse effects include weight gain and methysergide is now rarely used owing to the risk of retroperitoneal fibrosis and renal failure with long-term use.
Anticonvulsants such as sodium valproate, gabapentin and topiramate are thought to prevent migraine by increasing inhibitory GABAergic and Ca$^{2+}$ channel activity, thus reducing cortical excitability and possibly the threshold for triggering migraine attacks. These drugs may reduce cortical spreading excitation, hence depression, and trigeminal neurotransmission, however they are teratogens thus their use is excluded during pregnancy and lactation.

Finally, calcium channel antagonists like nifedipine and verapamil have shown some efficacy, and act to decrease cellular excitability by reducing Ca$^{2+}$ entry into cells.

The need remains for improved drugs, with greater selectivity and fewer side effects, for treatment of migraine. Drugs that act selectively on 5-HT$_{1D/1F}$ receptors would remove 5-HT$_{1B}$-induced constriction of coronary and cerebral arteries. The role of CGRP in regulation of vascular tone and in the pathogenesis of migraine is being increasingly recognised, and CGRP antagonists such as olcegepant.