Sleep

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The science of sleep

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Half our days are spent in the shadow of the earth and the brother of death exacteth a third part of our lives.

Sleep, 'the brother of death', in the words of the 17th century physician Sir Thomas Browne, is more than a bland intermission in the business of life: it is a structured physiological process which influences, and is influenced by, a wide range of medical and psychiatric disorders. Every physician should have a working knowledge of the biology and pathologies of sleep, yet opportunities for the necessary education have traditionally been rare. A survey in 1998 indicated that undergraduate courses devoted a median of five minutes to sleep and its disorders.[1]

This introductory article will cover the following topics:

- an outline of the basic neurobiology of sleep
- some clinically important interactions between sleep, cardiorespiratory, neurological and psychological functions
- the contemporary classification of sleep disorders
- an explanation of the choice of topics for the four CME articles which follow.

The neurobiology of sleep

The structure of sleep

Normal sleep is a highly regulated and temporally structured process, as revealed by 'polysomnography' (Fig 1).[2–4] This is a well-established sleep laboratory technique which monitors overnight breathing and blood oxygen saturation, the brain's surface electrical activity and muscle activity including limb and eye movements.

Slow wave sleep. In the first hour of sleep in adults, brain activity descends through a series of stereotyped stages into 'slow wave sleep' (stages 3 and 4), in which the EEG is dominated by large amplitude slow theta and delta activity (<8 cycles/second). Slow wave sleep is associated with slowing of cardiac and respiratory rate, lowered blood pressure, marked but not total muscular relaxation and a reduction in the brain's metabolic rate to about 70% of normal waking levels (Fig 2).[5] Sleepers woken from slow wave sleep can be confused (so-called 'sleep drunkenness') and typically report that their minds are empty.

Rapid eye movement sleep. The brain's electrical activity re-ascends through stages 4 to 1 after about half an hour in slow wave sleep, moving into a state with electrical appearances and cerebral metabolic rate similar to those of wakefulness, accompanied by rapid eye movements and a profound relaxation of limb muscles. A sleeper woken in this stage of sleep is likely to report a dream. This is 'rapid eye movement' (REM) or 'paradoxical' sleep.

Recent functional imaging techniques examining regional brain activity during REM sleep have shown that limbic regions, associated with emotional behaviour and experience, are strongly activated in REM sleep, while regions of the frontal cortex required for rational thought and memory formation are deactivated. These observations help to explain the bizarre and evanescent quality of dreams, not dissimilar to the state of delirium. The profound muscular relaxation or atonia of REM sleep results from an active process of descending neuromuscular inhibition which prevents us from acting out our dreams – a mechanism which fails in REM sleep behaviour disorder (see article on parasomnias).

The cyclical alternation of non-REM (NREM) and REM sleep stages repeats itself four or five times during the course of the night, with decreasing amounts of

Key Points

- **Normal sleep is a highly structured physiological process**
- **Periods of non-rapid eye movement sleep alternate with periods of rapid eye movement sleep with 4-5 cycles in an average night**
- **Neurones in the upper stem, thalamus, hypothalamus and basal forebrain control the sleep–wake cycle**
- **The neurotransmitters involved in sleep regulation include histamine, noradrenaline, serotonin, acetylcholine and the recently discovered hypocretin**
- **Circadian and homeostatic factors influence the timing and duration of sleep**
- **Sleep interacts with many general medical, neurological and psychiatric disorders**

KEY WORDS: sleep, sleep regulation, sleep stages, sleep–wake cycle

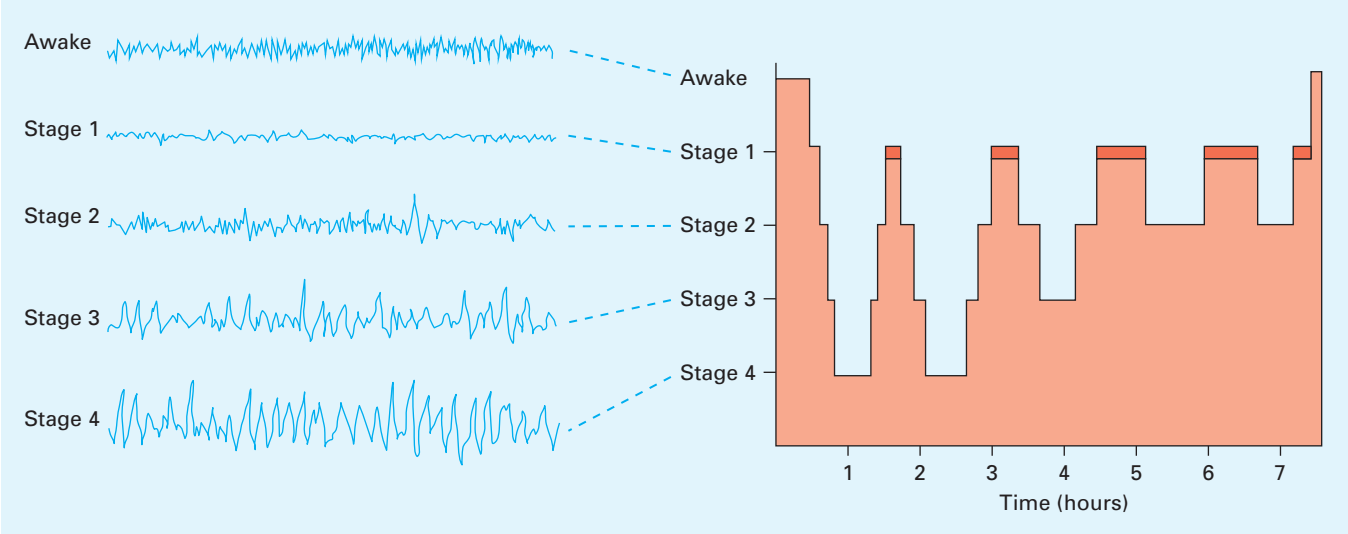

Fig 1. An idealised version of the stages of sleep with associated EEG activity, as assessed by polysomnography. Rapid eye movement (REM) sleep periods are indicated by the dark bars.

slow wave sleep and increasing amounts of REM sleep in successive cycles. The three principal states of consciousness, wakefulness, NREM and REM sleep, are normally well demarcated and the transitions between them relatively rapid. Failure to maintain the normal boundaries between these states underlies a number of sleep disorders (Fig 3).[6]

The regulation of sleep: anatomy, pharmacology and physiology

Sleep and wakefulness are regulated from the brainstem, diencephalon (thalamus and hypothalamus) and basal forebrain by a set of interacting neuronal subsystems (Fig 4).[3,4] These are the contemporary descendants of the 'ascending reticular activating system', the network of neurones identified in the 1950s as the brainstem control system for the arousal level of the cerebral hemispheres. The subsystems are most clearly identified by their neurotransmitters:

- noradrenaline from the locus caeruleus
- serotonin from the raphé nuclei
- acetylcholine from a number of sites in the brainstem and basal forebrain
- histamine and hypocretin from the hypothalamus.

All play a part in the regulation of the sleep–wake cycle. These systems innervate the cortical mantle directly and via the thalamus, and all reduce their levels of activity around the time of sleep onset. REM sleep is facilitated by a resurgence of activity in acetylcholinergic neurones, later being inhibited by a relative recovery of activity among noradrenergic and serotonergic neurones. There are no single 'on' and 'off' switches for sleep. However, damage to the arousal structures of the midbrain and thalamus can sometimes selectively impair arousal, inducing a state akin to sleep. Regions in the medulla and particularly the anterior hypothalamus (Fig 4) may play a key role in sleep induction.

Two processes are thought to be involved in the regulation and timing of sleep onset and duration:

1 '*Process C*' is a central circadian rhythm, governed by a circadian oscillator in the suprachiasmatic nucleus of the hypothalamus, that can be 'reset' by a direct projection

Fig 2. Brain metabolism during sleep. Positron emission tomography studies of the three main states of consciousness. There is a substantial decrease in cerebral metabolic rate in slow wave sleep, while whole brain metabolism in REM sleep is similar to that in wakefulness.[5]

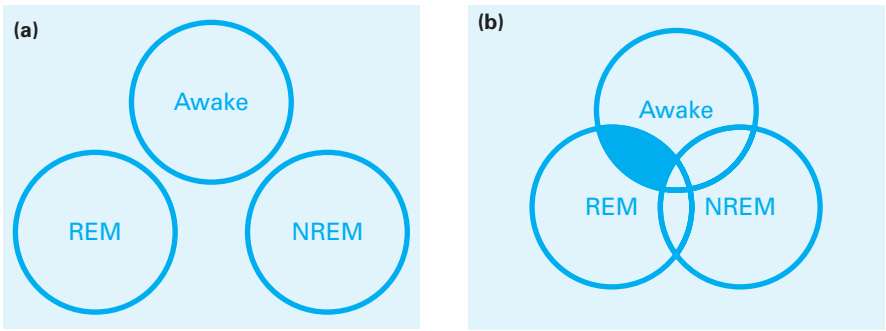

Fig 3. (a) Wakefulness (Awake), slow wave sleep (SWS) and rapid eye movement (REM) sleep are normally well demarcated states, but (b) many parasomnias can be understood as the result of overlaps between these states. For example, overlap states between Awake and REM (shaded area) give rise to such phenomena as sleep paralysis, nightmares and REM-sleep behaviour disorder.

from the retina. This 'master' clock mechanism influences many metabolic systems, both directly and indirectly, via the diurnal secretion of hormones from the pituitary and pineal glands. These contribute to our normal preference for going to sleep at 'bedtime', a time usually, of course, defined by the daily cycle of light and darkness.

2 '*Process S*' is an independent homeostatic process controlled by the time spent awake: after a night on call, we are sleepy the next morning despite encouragement from our circadian rhythms to stay awake. The 'sleep drive', which builds during long periods of wakefulness, is thought to depend on the accumulation of 'somnogens' in the brain. Rising extracellular adenosine concentrations in the basal forebrain during wakefulness have been identified as one key determinant of sleepiness.

The functions of sleep

Sleep occurs throughout the animal kingdom, but the understanding of its functions is rather poor. Ecological theories suggest that a 'sleep instinct' was evolved simply to keep us out of harm's way during the hazardous hours of darkness. Reparative theories (not necessarily incompatible with ecological ones) propose that sleep enables the body to conduct essential repairs. There is current interest in the possibility that during sleep the brain engages in complex information processing, such as memory consolidation, which might be more difficult to accomplish while awake. There are probably elements of truth in several of these ideas.

Sleep deprivation. Studies indicate that even minor degrees of sleep deprivation have significant effects on cognition and behaviour. A 'sleep debt' incurred during a period of sleep deprivation needs to be repaid, but not necessarily in full. During recovery, the structure of sleep changes at the expense of the lighter stages: sleepers make good most of their lost stage 4 sleep and up to half their lost REM.

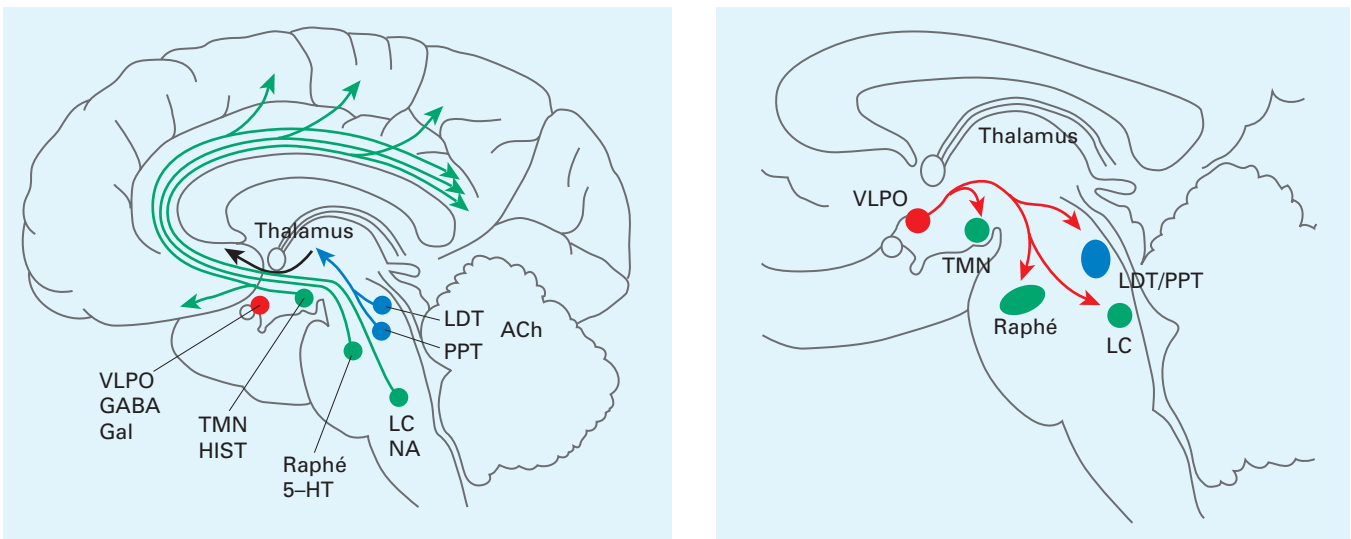

Fig 4. Neurochemistry of sleep, illustrating many of the principal brainstem and hypothalamic nuclei involved in sleep regulation. The green and blue systems are active in wakefulness, the red nucleus is thought to play a key role in controlling sleep onset and the blue nuclei are active in relative isolation during rapid eye movement (REM) sleep. The hypocretin-secreting neurones of the lateral hypothalamus and the acetylcholine (Ach) secreting neurones of the basal forebrain are not shown. LC = locus coeruleus, associated with noradrenaline (NA); LDT/PPT = laterodorsal tegmental and pedunculopontine nuclei, associated with Ach; raphé = raphé nuclei, associated with serotonin (5HT); Gal = galanin; HIST = histamine; TMN = tuberomamillary nucleus, associated with histamine; VLPO = ventrolateral preoptic nucleus, thought to control sleep onset, associated with the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

Sleep and medicine

Sleep, breathing and the circulation

An increase in parasympathetic tone and decrease in sympathetic tone are associated with NREM sleep. Heart rate, blood pressure, respiratory rate and tidal volume all decrease. REM sleep is associated with autonomic instability, with corresponding fluctuations in heart rate and blood pressure. The muscles of the upper airways relax during sleep, causing snoring and predisposing to the significant airways obstruction which underlies the obstructive sleep apnoea/hypopnoea syndrome (see the article on the assessment and management of excessive daytime sleepiness). Sleep interacts with several cardiorespiratory disorders: unstable angina, exacerbations of asthma and respiratory failure in neuromuscular disease are all particularly common during sleep.

Sleep and neurological disease

The brain remains active in sleep. Certain neurological disorders are particularly prone to occur during sleep. Epileptic seizures commonly occur from sleep, usually during slow wave stages. Sleep deprivation increases diagnostic interictal abnormalities in the EEG, the basis for the 'sleep-deprived recording'. Raised intracranial pressure must be considered in anyone with a recent onset of nocturnal headaches, but cluster headache typically occurs in the early hours. The parasomnias, disturbances of experience and behaviour during sleep, are more fully discussed in the article on parasomnias. In addition to primary sleep disorders such as narcolepsy, neurological conditions such as Parkinson's disease and multiple sclerosis can be associated with daytime sleepiness.

Sleep and the psyche

The quality, timing and structure of sleep are all sensitive to psychological state, particularly to mood. Anxiety commonly inhibits sleep, while depression is associated with increased amounts of REM sleep and early morning wakening or sometimes with excessive sleep. Antidepressants typically suppress REM sleep. There is a renaissance of interest in using short-term sleep deprivation as a treatment in drug-resistant depression.

The classification of sleep disorders

A simplified version of the International Classification of Sleep Disorders (ICSD) is shown in Table 1. The dyssomnias are disorders primarily associated with insomnia or excessive sleepiness. They are subdivided into those with 'intrinsic' and 'extrinsic' causes, with a third subgroup due to disturbances of circadian rhythm. The parasomnias are a miscellany of disorders of behaviour and experience occurring during sleep. The third main subdivision of the ICSD comprises sleep disorders occurring in the context of another medical or psychiatric disorder.

The general physician is likely to encounter three common groups of symptoms relating to sleep:

- excessive daytime sleepiness
- insomnia
- peculiarities of experience or behaviour during sleep, the parasomnias.

The three following articles have been organised accordingly, with a final article placing sleep and sleep disorders in a broader social context.

References

1 Stores G, Crawford C. Medical student education in sleep and its disorders. *J R Coll Physicians Lond* 1998;**32**:149–53.

2 Chokroverty S (ed). An overview of sleep. In: *Sleep disorders medicine*, 2nd edn. Boston: Butterworth Heinemann, 1999.

3 Hobson JA, Pace-Schott EF. The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. Review. *Nat Rev Neurosci* 2002;**3**:679–93.

4 Pace-Schott EF, Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. Review. *Nat Rev Neurosci* 2002;**3**:591–605.

5 Macquet P, Dive D, Salmon E, Sadzot B *et al.* Cerebral glucose utilization during

Table 1. The International Classification of Sleep Disorders.

Sleep disorder	Examples
Dyssomnias:	
Intrinsic sleep disorders	Narcolepsy, obstructive sleep apnoea/hypopnoea syndrome, idiopathic insomnia
Extrinsic sleep disorders	Insufficient sleep syndrome, inadequate sleep hygiene, altitude insomnia
Circadian rhythm sleep disorders	Shift work sleep disorder, jet lag syndrome, delayed sleep-phase syndrome
Parasomnias:	
Wake–sleep transition disorders	Sleep starts ('hypnic jerks')
Phenomena arising from light sleep	Sleep talking, sleep-related panic attacks
Arousal disorders (typically from slow wave sleep)	Sleep walking, sleep terrors
REM-sleep parasomnias	Nightmares, REM-sleep behaviour disorder, sleep paralysis
Other parasomnias	Snoring, nocturnal dissociative disorder
Sleep disorders associated with medical or psychiatric disorders:	
Mental	Mood disorders, psychoses
Neurological	Sleep-related headaches, sleep-related epilepsy
Other medical	Sleep-related asthma, sleep-related gastro-oesophageal reflux/peptic ulcer disease, nocturnal cardiac ischaemia

NREM = non-rapid eye movement; REM = rapid eye movement.