Neuroanatomy and neurobiology of sleep

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The neurobiology of sleep

Sleep is a dynamic process involving complex neural activation. In 1929 the psychiatrist Hans Berger established that brain activity was different during wakefulness and sleep by recording cortical electrical potentials. He termed these recordings electroencephalograms and by the mid-1930s the cyclical patterns associated with NREM sleep had been categorised. The first observations of REM sleep occurred in the 1950s (Aserinsky et al., 1953). Understanding of the control mechanisms of NREM and REM sleep continues to develop.

The neural regulation of wakefulness and arousal from sleep

Neurons of the reticular activating system are central to the regulation of wakefulness. Specifically, there are two ascending pathways: one, a dorsal route from the cholinergic laterodorsal and pedunculopontine tegmental nuclei, activates thalamic neurons to promote EEG activity via glutamatergic thalamocortical projections (Saper et al., 2005). The ventral route through the hypothalamus includes the aminergic arousal system that originates from the brainstem with serotonergic (dorsal raphe nuclei), noradrenergic (locus coeruleus), histaminergic (tuberomammillary nucleus) and dopaminergic (ventral periaqueductal grey) neurons (Horner, 2008). Cortical activation during wakefulness is also influenced by orexinergic (hypocretin) neurons originating in the hypothalamus, and cholinergic neurons from the basal forebrain (fig. 1a).

During wakefulness these pathways allow sensory information to be transmitted to areas of the association cortex via the thalamic gate.

Key points

- Wakefulness is maintained by activation of the ascending reticular activating system involving several neurotransmitters including glutamate, acetylcholine and the monoamines.
- NREM sleep onset is associated with a reduction in activation of the ascending reticular activating system and an increase in neural activity within the ventrolateral pre-optic area, anterior hypothalamus and basal forebrain.
- REM sleep is triggered by activation of cholinergic neurons in the laterodorsal and pedunculopontine tegmental nuclei. The suppression of motor activity in REM sleep is generated by glutamate-mediated activation of descending medullary reticular formation.
- Cycles of NREM and REM sleep alternate throughout the night in a predictable manner.
- Ageing is associated with difficulty in maintaining sleep and more frequent arousals.

The neural regulation of NREM and REM sleep

The transition between wakefulness and sleep occurs through a process of reciprocal inhibition between arousal- and sleep-promoting neurons by way of a “flip-flop”
Figure 1. a) Wakefulness-, b) NREM sleep- and c) REM sleep-generating neuronal systems in the rat brain. Descending projections to the respiratory and hypoglossal motor neurons in the medulla are also shown. Solid lines indicate active neuronal groups and projections, respectively. Dashed lines and decreased symbol size indicate suppressed activity. Lines terminating with an arrow indicate excitatory projections, lines terminating with an oval indicate inhibitory projections and lines terminating in a diamond indicate mixed excitatory and inhibitory projections for acetylcholine. The progressive suppression of hypoglossal motor output to genioglossus muscle from wakefulness to NREM and REM sleep is illustrated by reduced line thickness. Figure adapted from Horner (2008), with permission from the publisher.
switch (McGinty et al., 2000). This is an all-or-nothing process that prevents the occurrence of intermediate conscious states. At sleep onset, neurons in the ventrolateral pre-optic area (VLPO), anterior hypothalamus and basal forebrain are activated and inhibit the arousal systems detailed previously. In particular, the VLPO neurons containing the inhibitory neurotransmitters $\gamma$-aminobutyric acid (GABA) and galanin, project to (and inhibit) the wake-promoting regions of the ascending reticular system (Sherin et al., 1998) and the descending brainstem arousal neurons (fig. 1b).

REM sleep occurs with activation of cholinergic neurons in the laterodorsal and pedunculopontine tegmental nuclei. This cholinergic activation occurs when withdrawal of the aminergic arousal systems (noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe nuclei) produces disinhibition. This causes the release of acetylcholine, which triggers the increased neural activity that is a feature of REM sleep. Suppression of motor activity, the other marker of REM sleep, is generated by glutamate-mediated activation of descending medullary reticular formation relay neurons (fig. 1c). The activity of these neurons is inhibitory to spinal motor neurons via the release of glycine and to a lesser extent GABA (Reinoso-Suarez et al., 2001).

The cycle of wakefulness and sleep The transition from wake to sleep can be difficult to determine as there are typically brief periods of drowsiness with transient bursts of wakefulness before sleep consolidation. NREM sleep is conventionally divided into three or four stages according to the guidelines laid out by the American Academy of Sleep Medicine in 2007. These stages approximately represent the depth of sleep and are analysed using standardised criteria (see chapter 5).

In adults sleep is most often initiated through NREM sleep and is marked by synchronisation of EEG activity (for further description of the EEG that defines the stages of sleep see chapter 5). The overnight sleep patterns in a healthy young adult are shown in figure 2. NREM predominates early in the night with episodes of REM sleep occurring in approximately 90-min intervals. The 90-min NREM–REM cycle is repeated approximately three to six times during the night, and the duration of REM sleep increases as the night progresses. The preferential occurrence of NREM sleep (particularly slow-wave sleep) early in the night is coincidental with sleep homeostasis, while the predominance of REM sleep later in the night is thought to be associated with the circadian rhythm of core body temperature.

Sleep cycles in ageing Sleep is essential for life in humans. Total sleep deprivation over 2–3 weeks impairs thermal regulation, energy balance and immune function, eventually causing death. The requirements for sleep vary with age. In infants, active (REM) sleep dominates in the first 1–2 months of life. After 3 months NREM sleep begins to dominate, and by 5 yrs of age adult sleep stages are established. The percentage of REM sleep is reduced to adult levels by 10 yrs of age.
In adults, optimal sleep duration varies. Sleep restriction to \( \leq 5 \) h per night causes a reduction in psychomotor vigilance (Dinges et al., 1997), a decline in mood and motivation and a worse performance on memory tests. Increasing sleep opportunity up to \( 10 \) h per night improves cognitive function. Most estimates suggest that \( 7.5–8.5 \) h of sleep are required for optimal performance.

Ageing influences sleep cycles, with older people reporting that they experience difficulty in maintaining sleep and increased awakenings (fig. 3). Morning preference also increases with age (Taillard et al., 2004); however, this may be due to changing work schedules or variation in social activities, as well as changes in the physiological requirements for sleep (Dijk et al., 2000). The increased number of arousals per night may be a consequence of the decline in the neural systems that regulate sleep or an age-related change in the arousal thresholds to external stimuli. Interestingly, although older adults experience more awakening during sleep, they do not seem to have any more problems returning to sleep once awake (Klerman et al., 2004).

By the age of \( 75 \) yrs there may be no deep sleep. The loss of the deep sleep with increasing age may be due to a reduction in the amplitude of delta waves detected on the EEG recordings, meaning that stage \( 3–4 \) sleep is not documented despite the presence of delta waves. Alternatively, disrupted synchronisation of neuronal activation may occur as a result of an age-related decline in the neural systems that regulate sleep. An increase in the lighter sleep partially compensates for the loss of deep sleep (Van Cauter et al., 2000) but there is also a reduction in the number of sleep spindles and K complexes. The duration of REM sleep tends to remain constant throughout adulthood (Landolt et al., 1996), although a reduction in the proportion of REM sleep has been reported by some (Van Cauter et al., 2000).

**Further reading**