

ANAESTHESIA, SLEEP AND DYSSOMNIAS - PART 1 ANAESTHESIA TUTORIAL OF THE WEEK 268

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QUESTIONS

Before continuing, try to answer the following questions. The answers can be found at the end of the article.

1. Which of the following statements regarding anaesthetic agents, analgesics and sleep are true?
 - a. Propofol induced anaesthesia creates sleep spindle activity on EEG recording
 - b. Dexmedetomidine's actions are akin to normal sleep
 - c. Propofol anaesthesia can help reverse the slept debt in sleep deprived individuals
 - d. Ibuprofen delays the onset of deeper stages of sleep

2. Which of the following physiological changes occur during sleep?
 - a. NREM sleep sees an increased heart rate
 - b. Urine output is decreased
 - c. Cortisol levels are highest at about midnight
 - d. GI peristalsis is decreased in sleep

INTRODUCTION

Sleep is a fundamental physiological process, crucial to health and wellbeing. It is observed in all mammals and birds and Humans spend approximately one third of their lives asleep. It can be defined simply as a reversible disengagement from environmental and external stimuli. This definition however, fails to describe the active physiological, psychological and environmental processes required.

This article describes the normal physiology of human sleep and explores the relationship between anaesthesia and sleep. Part two of this article will be published as a separate tutorial and will discuss dyssomnias and the associated anaesthetic implications.

NORMAL SLEEP

Sleep is a global state, controlled by a series of interdependent positive and negative feedback loops, exerting control over neuronal systems that in turn control movement, arousal, autonomic functions, cognition and behaviour¹. The importance of sleep cannot be underestimated. However a unifying theory as to its function is still unknown. Studies have demonstrated sleep's important role in memory and learning, and one broadly held theory is that it may allow for waking memories to be consolidated.

Prolonged deprivation can lead to behavioural and physiological disarray, such as impaired cognitive performance, temperature control, and immune function. In animal studies sleep deprivation leads ultimately to death.

Sleep is cyclical, and can be divided into two separate phases: rapid eye movement (REM) and non rapid eye movement (NREM) sleep. Each has a distinctly different constellation of physiological and neuro-biochemical changes. Normal sleep cycles between these two states approximately every 90 minutes, and is usually repeated between three and six times in a night. Generally, a normal night's sleep begins with roughly 80 minutes of NREM, followed by 10 minutes of REM. As the night progresses the amount of time spent in NREM stages 3 and 4 (see below) diminishes and the amount of time in REM sleep increases.

Sleep patterns and duration are influenced by age. Until adolescence, the average total night's sleep equates to about 10 hours. There is a precipitous drop in early adulthood, to about 7.5 hours, and a further drop into old age. The duration of sleep stages are similarly affected.

EEG recordings in an awake individual show two main waves. The alert and engaged person displays mainly beta (β) waves - desynchronized waves with low voltage and high-mixed frequency. A relaxed subject displays predominantly alpha (α) waves, characterised by a greater degree of synchronicity, but which remain low amplitude and mixed frequency.

NEUROCHEMISTRY OF SLEEP

The onset and maintenance of sleep is dependent on a complex gamut of neuro-chemical changes involving a wide range of centres in the brain. Neurotransmitters that promote wakefulness include the catecholamines (norepinephrine and dopamine), glutamate, histamine, hypocretin (orexin), and acetylcholine. Those predominantly associated with promoting slow wave sleep are serotonin and GABA.

Control for the onset of sleep is centred in the ventro-lateral pre-optic (VLPO) area of the anterior hypothalamus where activity increases during sleep. An increase in the production of inhibitory neurotransmitters, GABA and galanin causes inhibition of the wakefulness promoting regions of the brain (such as the locus ceruleus and dorsal raphe). Raphe and locus ceruleus discharge is maximal during wakefulness, falling during NREM sleep and ceasing in REM sleep. Serotonin and noradrenaline are the predominant neurotransmitters in these regions. Inhibition of their actions suppresses wakefulness.

Serotonin has a dual role in both promoting sleep as well as wakefulness. It achieves both these roles probably by acting at multiple sites at many receptor subtypes. Serotonin originates mostly in the cells of the raphe nuclei in the reticular formation. Serotonergic cells are activated when we are awake and aroused. During slow wave sleep their firing is greatly reduced, and activity stops right after REM sleep. Noradrenaline cells arise in the locus ceruleus, and also have a role in vigilance. Firing of noradrenaline releasing cells in this region virtually stops during REM sleep.

Sleep disorders, including excessive daytime somnolence and sleep disturbances, are common in sufferers of Parkinsons disease. This has led to postulation that dopamine also plays a role in wakefulness and sleep. However the exact mechanism remains unclear.

Cholinergic neurotransmission is known to modulate levels of arousal, and has an active role to play during sleep. It has been shown that levels of cortical acetylcholine are elevated in both the awake individual and in REM phase sleep. NREM sleep sees diminished levels of acetylcholine, which is also seen during anaesthesia

Studies into narcolepsy have elicited a further neuro-chemical system called hypocretins or orexins. This system has an important role in the maintenance of wakefulness. Discovered almost simultaneously by two separate groups, the system encompasses two peptides, hypocretin (orexin) A and B, as well as neurones that have widespread excitatory projections to all monoaminergic and cholinergic cell groups. They function to activate waking-active neurons in the hypothalamus and brain stem regions to maintain a long, consolidated awake period. They are inhibited by the VLPO in NREM sleep, and excite the cholinergic pedunculo- pontine neurons in REM sleep.

These processes themselves are under the influence of both circadian and physiological factors. Circadian input flows from the suprachiasmatic nucleus (SCN), which is akin to the cardiac pacemaker.

It is driven by photic (light) input via the retina. The physiological input is a complicated milieu of positive and negative feedback mechanisms. The final common pathway is suggested to be due to accumulation of somnogens (sleep promoting agents). Principle among these is adenosine. During prolonged wakefulness adenosine accumulates, and acts to switch off the GABA containing neurones that suppress the sleep active areas of the VLPO. Caffeine is an adenosine receptor antagonist, which probably explains its function in maintaining wakefulness.

NREM Sleep

In short NREM sleep can be described as a relatively inactive brain in a moveable body. Classically it is subdivided into four stages (N1-4), which correlate with increasing depth of sleep and increasing arousal thresholds. These stages can be discerned on EEG recordings of the sleeping individuals, and are distinctly different to that of an individual in a wakeful state.

Stage 1 is the first phase of sleep entered, and persists for a few minutes. During this stage arousal is easy and there is increased α wave activity on EEG. Theta wave activity also occurs at around 4-7 hz frequency. Bursts of high synchronicity occur in the sleep of children and adolescents a pattern not seen in adults unless during emotional stress. Some suggest these may represent evidence of memory consolidation. If sleep continues, stage 2 is entered. This accounts for about 50% of total sleep time and is seen on the EEG as low voltage activity with mixed but slowing frequency and the inclusion of sleep spindles. The sleep spindle is a slow sinusoidal wave with bursts of high amplitude peaks.

As stage 3 and then 4 of sleep are entered, the EEG becomes synchronised, displaying delta wave activity (high amplitude and low frequency). Together these two stages are termed slow wave sleep (SWS), and occur for about 15% of total sleep. Auditory arousal thresholds are at their highest during slow wave sleep. SWS has physiological importance. A recent study² has shown that the percentage of time spent in SWS is inversely associated with incidental hypertension in aging men. Deprivation of SWS may thus contribute to adverse blood pressure in older men.

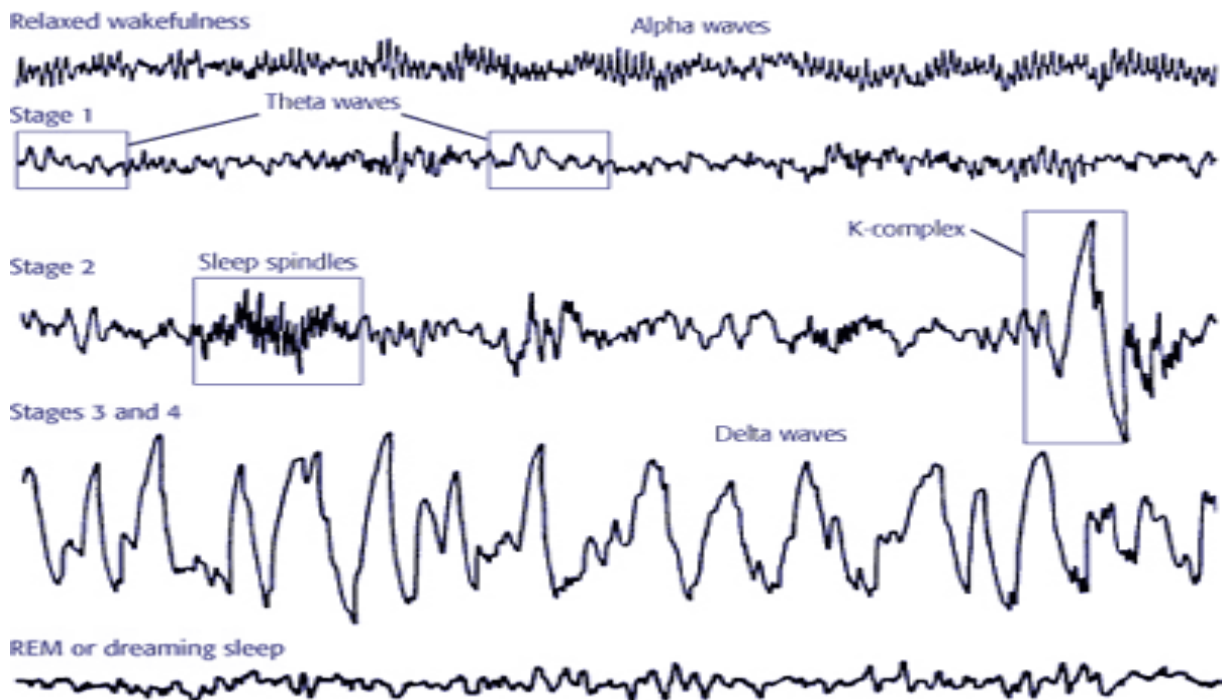


Figure1: EEG traces from different sleep stages

REM Sleep

In REM sleep, so named for its characteristic eye movements, EEG activation and muscle atonia occur, creating a highly activated brain in a paralysed body. It is during the REM phase that we dream, and arousal from this state leads to vivid recollection of a high proportion of dream content.

In adults 20-25% of sleep is REM sleep. In infants REM sleep duration may take up to 50% of total sleep time. As we age, the duration of REM sleep decreases, mirroring the decrease in total sleep. It would appear that REM sleep plays a role in neuronal maturation, hence its high proportion when the brain is most plastic. Absolute hours of REM sleep may also correlate with intellectual function into old age. Measures of cerebral blood flow and glucose utilization during REM sleep correlate with those of an awake individual. REM sleep is generated by the REM "on" neurones, mediated by cholinergic neurotransmitters, chiefly from the mesencephalic and pontine neurones. Characteristically we see desynchronized cortical output or low voltage mixed frequency waves on EEG recording. REM sleep is terminated by the REM "off" array of neurotransmitters (noradrenaline, serotonin and histamine) from the locus ceruleus and dorsal raphe.

PHYSIOLOGICAL CHANGES DURING SLEEP

Cardiovascular

During NREM there is a reduction in heart rate, blood pressure and cardiac output, attributed to loss of vasomotor tone. In REM sleep the reverse is seen with increased heart rate and blood pressure, attributable to the generalised vasoconstriction in skeletal muscle.

Respiratory

Functional residual capacity (FRC) is diminished during sleep. This is due to the supine position and also loss in respiratory muscle tone. Resultant atelectasis is seen in dependent areas. The ventilatory response to increased arterial partial pressure of carbon dioxide (PaCO_2) is blunted, leading to a higher PaCO_2 . Haemoglobin saturation and arterial oxygen tension falls, coupled with an overall reduction in oxygen consumption.

NREM sleep sees a regular respiratory pattern. There is a slight increase in tidal volume and a decrease in respiratory rate with an overall decrease in minute volume as each stage is entered. Decreases of up to 15% can occur in SWS. Respiratory control in NREM sleep is subject to chemo and mechanoreceptor influence.

REM sleep sees an increase in respiratory rate and variability, with lower tidal volumes. There is generalised postural muscle atonia and the maintenance of ventilation is solely derived from the activity of the diaphragm. There is a further reduction in the response to hypercapnia during the REM phase. The upper airway musculature also has a tendency to collapse, especially during REM sleep, but there is a wide inter-individual variation. Higher cortical control predominates in the control of REM sleep. Superimposed on patients with existing disease, these respiratory changes can lead to a profound reduction in minute volume.

Renal

During all sleep phases the production of urine is reduced, creating smaller more concentrated volumes. There is a decrease in glomerular filtration rate and renal plasma flow. Aldosterone and anti-diuretic hormone production is also reduced.

GI tract

Saliva production is reduced during sleep. This may explain the sensation of a dry mouth upon waking. Swallowing frequency is the same as in the awake person during NREM sleep, but markedly reduced in REM sleep. Reduced saliva production prolongs the time it takes for gastric pH normalisation. Gastro-oesophageal reflux occurs with more frequency during sleep. This is due to several factors, such as reduction in GI peristalsis and loss of postural drainage.

Endocrine system

Various hormone secretion patterns are displayed during sleep. During the first half of the night growth hormone predominates. At about midnight cortisol production is at its nadir. Thereafter there is a slow increase in cortisol levels, reaching its peak at about 0900. Nocturnal awakenings are associated with pulsatile cortisol releases. Distinct from nocturnal awakenings, there is a marked and rapid rise in cortisol and ACTH that occurs and continues for about a 60-min period after cessation of sleep, termed the awakening response. Hypercortisolaemia plays a role in the sleep disturbances associated with depression. During sleep body temperature falls, with thermoregulation ceasing during REM phase sleep.

SLEEP AND ANAESTHESIA

It remains a common colloquialism to equate anaesthesia with sleep. Indeed the motto of the association of anaesthetist of Great Britain and Ireland (AAGBI) is “in somno securitas” (safe in sleep). However strictly speaking anaesthesia differs from sleep; as a “drug induced, reversible condition producing unconsciousness, amnesia and akinesia”³.

There are many behavioural similarities between sleep and anaesthesia, suggesting a connection between the two. Many of the anaesthetic agents have some of the same effects on the neuro-chemical cascade of normal sleep. Propofol’s actions are attributed to its enhancement of GABA-a mediated inhibition of pyramidal neurones in the cortex and subcortical areas. Positron emission tomography (PET) scanning of people in NREM sleep and propofol induced anaesthesia show deactivation of the same areas (the thalamus, cingulate gyri and precuneus). It has also been shown⁴ that EEG recordings of NREM sleep and propofol induced anaesthesia share similarities. The slow waves propagated by propofol follow the same pathways as spontaneous sleep slow waves. Crucially however there seems to be no sleep spindle activity with propofol sedation, separating it from spontaneous NREM sleep. Propofol administration in rats leads to a reduction in acetylcholine release from the cortex, mirroring NREM sleep. In addition, reversal of propofol anaesthesia can be brought about by administering physostigmine (acetylcholinesterase inhibitor), in much the same way as REM sleep can be altered by the administration of cholinergic agonists and antagonists.

Dream recall following anaesthesia may occur in up to 30% of patients. There is some discrepancy in recall between those receiving the longer acting inhalational agents, and those receiving solely propofol anaesthesia. Most likely this effect is due to slow emergence from anaesthesia, proven elegantly by Leslie et al¹, who showed dream recall to be similar amongst patients rapidly recovered following either desflurane or propofol.

Further research has also shown that sleep deprived animals are more susceptible to the effects of general anaesthesia (intravenous and inhalational). Strengthening the link between neuronal networks facilitating sleep and playing a role in the anaesthetized state. Sleep deprivation may also partly explain the variability in patient response to anaesthesia.

Dexmedetomidine, an α -2 receptor agonist has demonstrated a positive action on the VLPO whilst reducing the activity in the locus ceruleus, akin to normal sleep.

There is a marked reduction in the amount of NREM slow wave sleep in individuals given opioids. Similarly, although benzodiazepines decrease sleep latency and increase total sleep time, they increase spindle activity and decrease overall slow wave sleep.

The effects of anaesthesia on subsequent normal sleep are also of interest. There are several studies that have shown that sleep debt does not accrue during prolonged propofol anaesthesia, and that sleep deprived individuals who undergo subsequent anaesthesia lose their need for “recovery” sleep, effectively leading to recovery from sleep deprivation.

This could be of interest to intensive care practice. Often prolonged ICU sedation leads to significant sleep deprivation, a state shown to increase morbidity and mortality. Levels of sedation approaching anaesthesia may therefore have a physiological benefit by reversing sleep deprivation, however there would likely be detrimental cardiovascular effects to consider.

The relationship between sleep and volatile agents is less clear. Pick et al looked at the effects of sevoflurane, isoflurane and halothane on sleep deprived mice. Following a six hour anaesthetic, they demonstrated that, in contrast to propofol, volatile agents led to a significant REM debt, and so cannot be said to substitute for normal sleep.

Various medications given concurrently with anaesthesia may have detrimental effects on sleep. Dexamethasone, often used as an antiemetic, can reduce both the duration of REM and SWS, as well as inducing nightmares. Antiemetics displaying dopamine antagonism such as domperidone and metoclopramide can also cause sleep disturbances. Non-steroidal anti-inflammatory drugs (NSAIDs)

reduce sleep efficiency and increase the absolute number of awakenings. Ibuprofen has the added effect of delaying the onset of deeper sleep stages⁵. There may also be a decrease in melatonin secretion with NSAID use. Ranitidine and other H2 receptor antagonists, along with the PPIs can cause insomnia.

Studies have looked at the combined effects of anaesthesia and surgical insult on sleep. There is a categorical reduction in both REM and NREM sleep⁶, with the magnitude of surgery directly correlated to the degree of sleep disruption. Up to one week can pass before sleep reverts to a normal pattern. Many reasons have been postulated, but no definitive answer yet found. Pain and opioids may affect the patients' sleep, but these are by no means the only factors.

In conclusion, there can be no doubt of an intrinsic link between normal sleep and general anaesthesia. Unravelling these mechanisms may help the development of future anaesthetic agents. We should also be mindful of the effects that anaesthesia, the surgical insult and ill health play on normal sleep.

IMPORTANT POINTS

- Sleep is vital, producing an array of physiological effects, and being a product of a complex gamut of neuro-chemical processes.
- Anaesthesia and sleep share similar pathways, exploration of these may bring better understanding of both.
- Anaesthesia, analgesia and operative stress can all affect normal sleep patterns.

ANSWERS TO QUESTIONS

1: F, T, T, T

2: F, T, F, T

FURTHER READING

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