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# QUESTIONS

1. Discuss the physiology of sleep
2. Discuss the role of basal ganglia in coordinating movement

# ANSWERS

# PHYSIOLOGY OF SLEEP

Sleep is a state of reversible unconsciousness in which the brain is less responsive to external stimuli. We are functionally blind during sleep with no response to visual stimuli and a decreased threshold of response to auditory stimuli. Babies have been exposed to sound of up to 100 dB, which is above the legal limit for ear protection for employees, without waking up. In adults, the process is selective demon- strating continuing cortical function. For exam- ple, a sleeping mother is woken by her crying baby but not by other louder noises.

# DEFINITIONS OF SLEEP

Sleep is distinguished from unconsciousness and anaesthesia by a characteristic cycle of sleep phases with specific EEG patterns and physiological changes. Natural sleep is divided into two distinctive states: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is then further divided into 4 stages where stage 1 is the lightest and stage 4 the deepest level of sleep. REM sleep is divided into phasic and tonic phases. The two distinctive states follow a regular pattern called a sleep cycle which, in an adult, lasts about 90 min and comprises a period of NREM sleep followed by REM sleep. The cycles may be separated by a period of wakefulness and are repeated 3–6 times each night and are typically displayed as an hypnogram. The majority of deep (stage 4) NREM sleep occurs in the first and second cycles. As the night progresses, the pro- portion of REM sleep in a cycle increases and the NREM element is of lighter stage 2 sleep.

Age has a major effect on the duration of sleep and the ratio of NREM/REM sleep. Neonates sleep 16–18 h. It is widely distributed through- out the day with REM sleep accounting for 50% of total sleep time (TST). This may be even greater in premature babies. By the age of 2 yr, children should sleep 10 h per day, mainly at night with one or two naps during the daytime and REM sleep has declined to 20–25% of TST. Adults normally sleep 6–8 h per day with 15–20% REM sleep. With increasing age, TST changes little although sleep is more fragmented with more frequent and longer awakenings (decreased sleep efficiency) with less REM sleep and more light NREM sleep. Night-time sleep may be decreased if naps are taken during the day.

# FUNCTIONS OF SLEEP

The functions of sleep are still poorly under- stood. However, the observation that sleep (or, at least, an activity–inactivity cycle) is present in ll species and has been preserved throughout evolution and that sleep deprivation leads to a drastic deterioration in cognitive function and eventually to mental and physical morbidity proves its importance.

It has been suggested that sleep might conserve energy by reducing core temperature slightly and lowering metabolic rate by 10% compared with quiet wakefulness. Sleep would prevent perpetual activity as a response to environmental stimuli leading to excessive energy consumption. However, sleep is a state of starvation and there is no evidence that sleep is important for tissue repair. Sleep has been implicated as an important factor in storage of long-term memory. Facts learned during the day are usually better remembered the next morning whereas facts learned shortly before going to sleep are often poorly recalled.



# ELECTROPHYSIOLOGICAL CHARACTERISTICS OF SLEEP

The stages of sleep are characterised by typical patterns of electroencephalogram (EEG) electro-myogram (EMG) and electrooculogram (EOG) activity. Wakefulness with open eyes is characterised by an EEG with dominant low amplitude, high frequency beta activity of 16–25 Hz. Muscle tone is usually high with high-to-moderate EMG activity.

# STAGE 1

Sleep is usually initiated by a transition from wakefulness to a state of drowsiness with closed eyes and a shift from EEG beta activity to alpha activity of 8–12 Hz passing to Stage 1 NREM sleep with a mixed frequency EEG-pattern with low amplitude theta waves of 3– 7 Hz accompanied by slow rolling eye movements. Involuntary muscle clonus occurs frequently, resulting in jerky movement of the whole body (hypnic jerks) and EMG activity is moderate-to-low. This stage lasts typical- ly only 5–10 min, during which time minor auditory stimuli will cause arousal.

# STAGE 2

Stage 2 is characterised by short bursts of high frequency activity (12–15 Hz – sleep spindles) and K-complexes (large amplitude biphasic waves). Bodily movements continue and the EMG activity is low-to-moderate. This stage is generally short (10–20 min) in the first 1–2 cycles but predominates in

later cycles. It is the most abundant sleep stage in adults accounting for up to 50% of TST.

# STAGES 3 AND 4

Deep NREM sleep stages 3 and 4, sometimes combined as slow wave sleep (SWS) are characterized by high amplitude low frequency delta waves (> 75 µV and 0.5–2 Hz) with stage 3 having between 20–50% and stage 4 more than 50% delta activity. EMG activity is low and eye movements are rare. Arousal through auditory stimuli from this stage of sleep is difficult and, if awakened, the individual is often disorientat- ed and slow to react. Return to sleep is easy and short arousals (< 30 sec) are rarely remembered.

# RAPID EYE MOVEMENT SLEEP

Non rapid eye movement(NREM) sleep is followed by REM sleep, the proportion increasing with each cycle. REM sleep is characterised by a fast mixed frequency low voltage EEG with sawtooth waves and rapid eye movements on the EOG. During the tonic phases of REM sleep, there is marked reduction of muscle tone and EMG- activity in skeletal muscles. The tonic phases of REM sleep are interrupted by short episodes of phasic REM sleep with increased EMG activity and limb twitches. The atonia of REM sleep affects all skeletal muscles, except the diaphragm and the upper airway muscles, and is associated with hyperpolarisation of the α-motor neurones. The purpose of this may be to prevent the acting out of dreams. About 10% of the population have experienced sleep paralysis (i.e. wakening from sleep and finding that the atonia has persisted into wakefulness). It can be frightening but is entirely harmless. Natural wakening usually occurs from REM sleep. Subjects woken from REM sleep are much more likely to recall dream content than those awakened from NREM sleep. NREM dreams are generally vague and formless in contrast to REM dreams.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | AWAK E | NONRAPIDEYEMOVEMENTSTAGE1 | NONRAPIDEYEMOVEMENTSTAGE2 | NONRAPIDEYEMOVEMENTSTAGE3 | NONRAPIDEYEMOVEMENTSTAGE4 | RAPDEYEMOVEMENT (REM) |
| EE G | Beta rhythm16-25Hz | Mixed frequen cy with thetawaves 3-12 Hz | Sleep spindles 12-14 Hz and highamplitud e Kcomplex es | Delta waves 0.5-2 Hz(20-50%) | Delta waves >50% | Desynchro nized low amplitude mixed frequency |
| EM G | High / moder ate | Moderat e/ low | Low/ moderat e | Low | Low | Absent except small muscle twitches in phasicREM sleep |
| EO G | Movewith gaze | Slowrolling | Rare | Rare | Rare | Bursts ofREM inphasicREM sleep |

**PHYSIOLOGICAL CHANGES DURING SLEEP**

# RESPIRATORY SYSTEM

During NREM sleep, there is a decrease in respiratory drive and a reduction in the muscle tone of the upper airway leading to a 25% decrease in minute volume and alveolar ventilation and a doubling of airway resistance accompanied by a small (0.5 kPa) increase in PaCO2 and decrease in PaO2. Hypercarbic and hypoxic ventilatory drives are reduced compared with wakefulness. The breathing pattern is regular except at the transition from wakefulness into sleep when brief central apnoeas are common.

During REM sleep there is a further decrease in hypercarbic and, particularly, hypoxic ventilatory drives. The breathing pattern is irregular especially during phasic REM sleep. The loss of skeletal muscle tone in REM sleep affects the intercostal and other muscles which stabilise the chest wall during inspiration. In infants, this may be seen as paradoxical movement of the rib cage and abdomen. In adults, there may be maldistribution of ventilation and impaired ventilation–perfusion matching with consequent arterial hypoxaemia. In normal subjects, this is unimportant but it may be very important in patients with chronic lung disease or abnormali- ties of the thoracic (e.g. kyphoscoliosis). The great majority of patients with impaired respiratory function will be at their worst during REM sleep.

# CARDIOVASCULAR SYSTEM

Blood pressure decreases during NREM and tonic REM sleep but may increase above waking values during phasic REM sleep. Cardiac output is generally decreased during all sleep phases. Systemic vascular resistance (SVR) and the heart rate are both reduced during NREM and tonic REM sleep and increased during phasic REM sleep.

# CENTRAL NERVOUS SYSTEM

Cerebral blood flow (CBF) increases by 50–100% above the level of resting wakefulness during tonic REM sleep and is even Table 2 Physiological changes in sleep greater during phasic REM sleep. Cerebral metabolic rate, oxy- gen consumption and neuronal discharge rate are reduced during NREM sleep but increased above resting values during REM sleep. The autonomic nervous system shows a general decrease in sympathetic tone and an increase in parasympathetic tone, except in phasic REM sleep.

# RENAL SYSTEM

The glomerular filtration rate and filtration fraction are reduced and ADH secretion is increased resulting in a low volume con- centrated urine.

# ENDOCRINE SYSTEM

The secretion of several hormones is directly linked to the sleep/wake cycle. Melatonin is released from the pineal gland under the control of the supra-chiasmatic nuclei (SCN) in a 4–5 h pulse, usually beginning at the onset of darkness (~9 pm). The pulse is inhibited or delayed by exposure to bright light in the evening. It is best regarded as being permissive of sleep (‘open- ing the gate to sleep’) rather than as an hypnotic, as it is possible to maintain wakefulness during this period. Growth hormone is mostly secreted during the first episode of SWS, particularly during puberty. Prolactin concentrations also increase shortly after sleep onset and decrease with wakefulness. Sleep phase delay delays secretion of both of these hormones. The secretion of cortisol decreases with the onset of sleep and reaches a trough in the early hours of the morning and a peak just after waking.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Non rapid eye movement sleep vs Wakefulness | Tonic rapid eye movement sleep vs Non rapid eyemovement sleep | Phasic rapid eye movement sleep vs Tonic rapid eye movement |
| EEG activity | ↓ | ↑ | ↑↑ |
| Cerebral blood flow | Unchanged | ↑ | ↑↑ |
| Heart rate | ↓ | Unchanged | ↑ and variable |
| Blood pressure | ↓ | Unchanged | ↑ and variable |
| Respiratory rate | ↓ | ↑ and variable | ↑ and variablewith central apnoeas |
| Airway resistance | ↑ | ↑ and variable | ↑ and variable |
| Responsivene ss of ↑CO2 | ↓ | ↓ | No difference |
| Upper airway |  | ↓ | ↓ |
| muscle tone |  |  |  |
| Penile andclitoraltumescence |  | ++ | +++ |

# CONTROL OF SLEEP

Sleep follows a circadian (~1 day) cycle, the periodicity of which is regulated by an independent genetically determined ‘intrinsic clock’ which is entrained to a 24 h cycle by external cues (Zeitgebers) such as light, darkness, clock time, working patterns and meal times. When a human being is deprived of all external time clues and is exposed to constant levels of illumi- nation (‘free running’), the wake/sleep cycle typically lengthens to about 24.5 h. Subjects who are born blind without any appre- ciation of light generally free run while those blinded in later life or who retain some perception of light remain entrained.

All living organisms, including plants and fungi, have been found to have clock genes and to show an inactivity/activity cycle. In mammals, control of the intrinsic clock is located in the SCN on either side of the third ventricle, just above the optical chiasm. In animal experiments, its destruction leads to a change from the normal sleep cycle into several shorter sleep/activity periods during the day. As noted above, melatonin secretion is prompted by the SCN just before the usual time of sleep onset. A mismatch of this pattern with sleeping time, as occurs in shift workers and after trans-meridian flights, leads to sleep distur- bance (‘jet lag’) as the subject is trying to sleep during their cir- cadian day. Light therapy can be helpful in re-setting the circadi- an clock and the interested reader is referred to the bibliography.

The propensity to fall asleep varies throughout the day and depends upon both circadian factors (process C) and time since the last sleep period (process S). The longer the time since the last sleep period, the greater will be process S. However, its propensity will be modulated by process C. The circadian pres- sure to sleep is greatest at ~2 am with a secondary peak at ~2 pm. It is least at ~6 am and ~6 pm. If a subject elects to stay awake throughout the night, they will feel most sleepy in the small hours of the morning but will get a ‘second wind’ as morning approaches and the circadian pressure to sleep declines. If wake- fulness is maintained, a second period of sleepiness and relative alertness will follow in early afternoon and early evening, respectively. Some of the 8-h sleep debt will be recovered that night but process C will ensure that awakening will occur at or shortly after the normal waking time. Sleep is normally an actively initiated and not a passive process. Unless a subject is sleep deprived, successful initiation of sleep depends both upon the phase of the circadian clock and external factors (recumbent position, darkness, reduction of sen- sory input). Over the years, considerable effort has been focused on a search for: (i) a ‘sleep centre’, a nucleus or region in the brain where stimulation or ablation would lead to sleep; and (ii) a hormone or transmitter which would reliably induce sleep. Neither have been found because the mechanisms resulting in sleep are complex and diffuse.

During wakefulness, the CNS is dominated by activity of the ascending reticular activating system (RAS) in the brain stem. This formation receives sensory input from all peripheral sen- sors and projects to the thalamus and the cortex. Its main neuro- transmitters are acetylcholine, noradrenaline, dopamine and his- tamine which explains the sedative effect of antagonists to these substances. A decrease in its activity permits sleep to be initiat- ed by suppressing incoming external stimuli.

The induction of SWS is associated with the secretion of γaminobutyric acid (GABA) from basal forebrain neurones. Therefore, it is not surprising that benzodiazepines and barbitu- rates, which act through stimulation of GABA receptors in the CNS, induce sleep or anaesthesia. Cholinergic mechanisms ini- tiate REM sleep through stimulation of pontine neurones in the lateral portion of the pontine tegmentum and the nucleus reticu- laris pontis oralis. In animal experiments, injection of carbachol (acetylcholine agonist) induces instantaneous REM sleep. Recently, orexins (hypocretin) have been isolated in the hypo- thalamus and appear to be important in the control of REM sleep and appetite. CSF concentrations of orexins have been found to be very low in patients with narcolepsy.

# INFLUENCE OF SURGERY AND ANAESTHESIA ON SLEEP

Anaesthesia and surgery can have a profound effect upon sleep. On the first night after surgery, sleep architecture is severely disrupted with little or no SWS and REM sleep. The light Stage 2 sleep is fragmented with frequent awakenings. The degree of disruption appears to be related to the severity of the surgical insult. The mechanism is unclear but it is prob- ably due to a combination of the surgical stress and the effects of opioid analgesics. Recovery of lost SWS and REM sleep occurs on postopera- tive nights 2–5, being later after major surgery. This coincides with the nadir of postoperative pulmonary function and several studies have demonstrated marked hypoxaemia associated with the rebound of REM sleep. It was a logical step to attribute post- operative myocardial ischaemia, myocardial infarction, pul- monary embolism and cerebral impairment (delirium and cogni- tive impairment) to nocturnal hypoxaemia. However, a number of studies have failed to confirm these presumed associations, although this does not exclude the possibility that the that the hypox- aemia may be important in some individuals.

# CLINICAL ANATOMY

## A) Narcolepsy

Narcolepsy causes you to suddenly fall asleep at any time no matter where you are. Often times, you fall asleep uncontrollably during unusual circumstances, such as while eating. People with narcolepsy are unable to regulate their sleep-wake cycle. Treatment is via scheduled naps and medication.

## B) Restless Legs Syndrome

Restless Legs Syndrome (RLS) presents as an uncontrollable urge or desire to maneuver your legs while you’re resting. You could also experience unpleasant aching, tingling, burning, and a feeling that something is crawling in your calves. Sometimes you feel these uncomfortable sensations in other body parts. Medications and behavioral therapy can be used to treat RLS

## C) REM Sleep Behavior Disorder

When you have REM sleep behavior disorder, you act out your dreams while you sleep. You lack the muscle paralysis most people experience while asleep. When the condition causes danger to you or anyone around you, it’s taken particularly seriously. REM sleep behavior disorder is commonly treated with medications. Injury prevention is key if you're affected.

## D)Insomnia

Insomnia is the term for a difficulty getting to sleep or staying asleep. There are two different types of insomnia. Transient or short-term insomnia and chronic insomnia.

i)Transient or Short-Term Insomnia.This type of insomnia often occurs in the aftermath of a stressful life event — for example, losing a loved one or going through relationship issues. It can also happen if you work shifts or have jet lag. You might be unable to relax, experience disturbed sleep, and may be unable to pinpoint any real reason for your inability to sleep.

ii)Chronic Insomnia. Chronic insomnia is characterized by experiencing non-restorative sleep, having difficulty falling asleep and maintaining sleep for at least one month. You feel exhausted during the day. If you have chronic intermittent insomnia, you experience a sleeping pattern where you have a few nights of good sleep alternating with many nights of insomnia.

There are various reasons you can develop insomnia. These include:

* Poor sleep hygiene
* Sleep-related breathing disorders
* Medical conditions
* Disrupted sleep-wake schedule
* Hormonal changes
* Limb movements during sleep
* Circadian rhythm disorders

Medications tailored to your own specific needs are prescribed. For instance, if anxiety or depression are the underlying cause of your condition, your physician may prescribe you with antidepressants or anti-anxiety medications. Medications for sleep can be used as well, but are typically prescribed to be used on a short-term or as-needed basis.

* Non-medical methods, such as cognitive behavior therapy, hypnosis, sleep restriction, stimulus control, and relaxation techniques, can also be used to treat insomnia. Lifestyle changes, such as avoiding caffeine and alcohol, are also advised.

## 2) ROLE OF BASAL GANGLIA IN COORDINATING MOVEMENT

Basal Ganglia are a group of subcortical nuclei or bodies that together are primarily engaged in influencing motor(movement) control along with the motor cortex and the spinal cord.

## MOVEMENT

In order to execute purposeful movements, a small number of motor plans in the brain need to be promoted and integrated, while others that impair or stop the execution of the desired movement must be suppressed. Action selection is facilitated by the nature of the parallel pathways, the number of neurons involved in the processing of information as it progresses through the basal ganglia, and the manner in which these neurons are arranged. The input and output nuclei generally contain the largest and smallest numbers of neurons, respectively. As information progresses through the basal ganglia, each neuron integrates information that has been transmitted from many other neurons in preceding nuclei; hence, the signal becomes increasingly focused and specific as it passes through the basal ganglia. The process of determining which signals are promoted occurs early in the basal ganglia circuit—at the striatum; the neuromodulator dopamine plays a key role in signal promotion.



Parallel pathways within the basal ganglia circuits facilitate signal

promotion and signal inhibition. Neighbouring pathways carrying

information about elements of the same desired movement successively amplify the promoted signal as it progresses through the basal ganglia.

More often, however, neighbouring pathways act to reduce unwanted signals, ensuring that an accurate, precise, and optimized action plan is developed. In the absence of action selection, all motor plans are promoted and many muscles around the body are activated, leading to a failure to execute desired actions.

Coordinating motivation with body movement. Specifically, the basal ganglia inhibits individual behavior in a complex social interaction and also inhibits small voluntary movement.The basal ganglia are considered to be necessary for voluntary control of body movements . This idea is derived mainly from the clinical observations that lesions in the basal ganglia lead to movement disorders ranging from the inability to initiate a movement to the inability to suppress involuntary movements.

The greatest source of insight into the functions of the basal ganglia has come from the study of two neurological disorders, Parkinson’s disease and Huntington’s disease. For both of these disorders, the nature of the neural damage is wellunderstood and can be correlated with the resulting symptoms.

Parkinson’s disease involves the major loss of dopaminergic cells in the substantial nigra. Huntington’s disease involves the massive loss of medium spiny neurons in the striatum.

The symptoms of the two diseases are virtually opposite: Parkinson’s disease is characterised by a gradual loss of the ability to initiate movement, whereas Huntington’s disease is characterised by an inability to prevent parts of the body from moving unintentionally. It is noteworthy that, although both diseases have cognitive symptoms, especially in their advanced stages, the most salient symptoms relate to the ability to initiate and control movement. Thus, both are classified primarily as movement disorders.A different movement disorder, called Hemiballismis , may result from damage restricted to the sub thalamic nucleus. Hemiballismus is characterised by violent and uncontrollable flinging movements of the arms and legs.

**Function in Eye Movement**

One of the most intensively studied functions of the basal ganglia is their role in controlling eye movements. Eye movement is influenced by an extensive network of brain regions that converge on a midbrain area called the superior colliculus (SC). The SC is a layered structure whose layers form two-dimensional retinotopic maps of visual space. A bump of neural activity in the deep

layers of the SC drives eye movement toward the corresponding point in space.