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18 /MHS01 /383

MBBS 300LVL

PHYSIOLOGY ASSIGNMENT

QUESTION 1: Discuss the 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.

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 of 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 a hypnogram (Fig. 1).

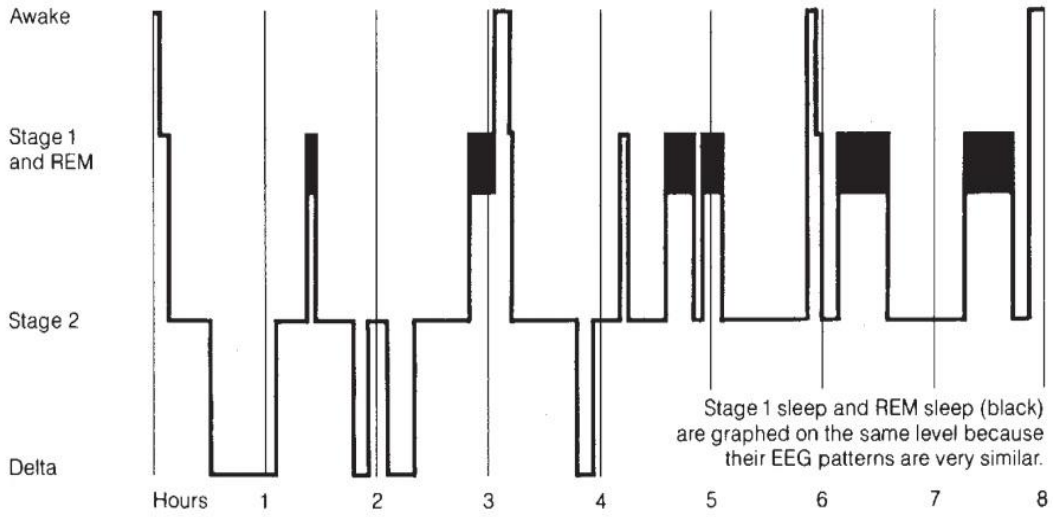

Fig. 1 Typical hypnogram of a young adult.

The majority of deep (stage 4) NREM sleep occurs in the first and second cycles. As the night progresses, the proportion 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 throughout 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 2yrs 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 understood. However, the observation that sleep (or, at least, an activity–inactivity cycle) is present in all 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.

NREM SLEEP

The NREM sleep is divided into four stages. The stages of sleep are characterised by typical patterns of electroencephalogram (EEG), electromyogram (EMG) and electro-oculogram (EOG) activity. Wakefulness with open eyes is characterised by an EEG with dominant low amplitude, high frequency beta activity of16–25 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 typically 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 disorientated and slow to react. Return to sleep is easy and short arousal (< 30 sec) are rarely remembered.

The ECG wave forms of the different NREM sleep stages and REM sleep are seen in fig 2.

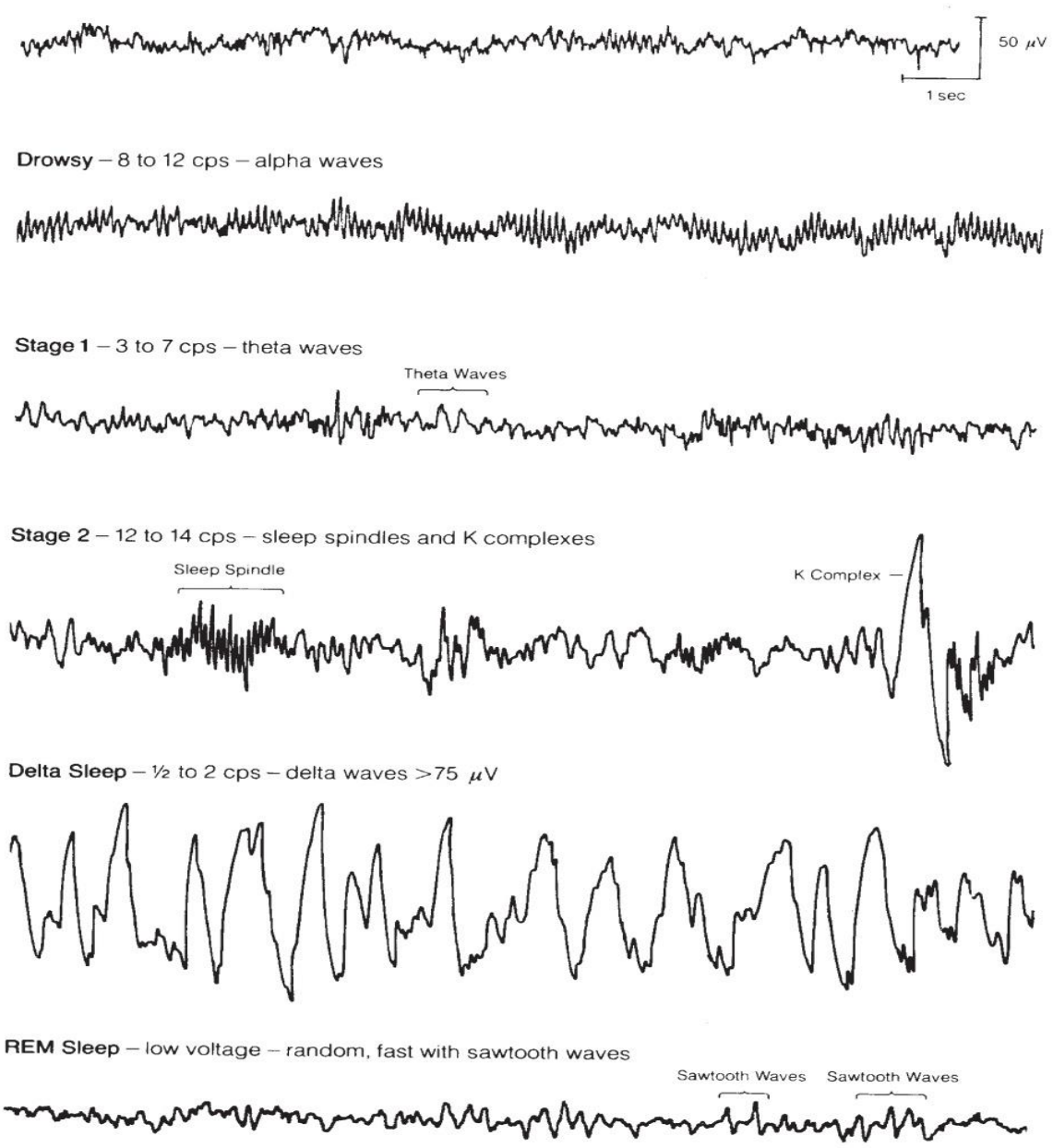

Fig. 2 EEG waveforms in different sleep stages.

REM SLEEP

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 saw-tooth 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 neurons. 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.

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 $PaCO_2$ and decrease in PaO_2. 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 abnormalities 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 greater during phasic REM sleep. Cerebral metabolic rate, oxygen 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 concentrated 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 4–5h 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 (‘opening the gate to sleep’) rather than as a 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.

Temperature control

In contrast to anaesthesia, thermoregulation is maintained during sleep. However, the shivering threshold is decreased and body core temperature decreases by about 0.5°C in humans and 2°C in hibernating mammals. Body temperature is linked to the circadian rhythm and reaches its nadir at about 3 am. Thermoregulation is quite good in human infants compared with other species.

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 illumination ('free running'), the wake/sleep cycle typically lengthens to about 24.5 h. Subjects who are born blind without any appreciation 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 chiasma. 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 disturbance (‘jet lag’) as the subject is trying to sleep during their circadian day. Light therapy can be helpful in re-setting the circadian clock.

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 pressure 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 wakefulness 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, and reduction of sensory 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 sensors and projects to the thalamus and the cortex. Its main neurotransmitters are acetylcholine, noradrenaline, dopamine and histamine which explains the sedative effect of antagonists to these substances. A decrease in its activity permits sleep to be initiated 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 barbiturates, which act through stimulation of GABA receptors in the CNS, induce sleep or anaesthesia. Cholinergic mechanisms initiate REM sleep through stimulation of pontine neurons in the lateral portion of the pontine tegmentum and the nucleus reticularis pontis oralis.

QUESTION 2: Discuss the role of basal ganglia in coordinating movements.

The basal ganglia are responsible for voluntary motor control, procedural learning, and eye movement, as well as cognitive and emotional function.

STRUCTURE

The basal ganglia are a cluster of subcortical nuclei deep to cerebral hemispheres. The largest component of the basal ganglia is the corpus striatum which contains the caudate and lenticular nuclei (the putamen, globus pallidus externus, and internus), the subthalamic nucleus (STN), and the substantia nigra (SN). These structures intricately synapse onto one another to promote or antagonize movement

Divisions of the Basal Ganglia:

1. **Corpus Striatum**- (The largest subcortical brain structure of the basal ganglia is the striatum with a volume of approximately 10 cm). It is a heterogeneous structure that receives afferents from several cortical and subcortical structures and projects to various basal ganglia nuclei. Within the striatum, there are two main divisions
    - Dorsal striatum (DS). Primarily involved in control over conscious motor movements and executive functions. The dorsal striatum consists of the caudate nucleus and the putamen. A white matter, nerve

tract (the internal capsule) in the dorsal striatum separates the caudate nucleus and the putamen.

- Ventral striatum, responsible for limbic functions of reward and aversion. Consists of nucleus accumbens and the olfactory tubercle.

2. Internal and External segments of **Globus Pallidus** NB until the first half of the 19th century the globus pallidus and putamen were considered one structure, collectively referred to as the lentiform or lenticular nucleus.
3. **Subthalamic Nucleus** (STN) - a lens-shaped cell group that makes up the largest part of the subthalamus.
4. **Substantia Nigra** (SN) - ("black substance" in Latin) is a long nucleus located in the midbrain but considered functionally a part of the basal ganglia because of its reciprocal connections with other brainstem nuclei. It consists of two components, the pars compacta and the pars reticulata, which have different connections and use different neurotransmitters

CONTROL OF MOVEMENT

1. *Regulation of Voluntary Movements*: during voluntary motor activity are initiated by cerebral cortex. However, these movements are controlled by basal ganglia, which are in close association with cerebral cortex. During lesions of basal ganglia, the control mechanism is lost and so the movements become inaccurate and awkward. Basal ganglia control the motor activities because of the nervous (neuronal) circuits between basal ganglia and other parts of the brain involved in motor activity. Neuronal circuits arise from three areas of the cerebral cortex:
    - Premotor area
    - Primary motor area
    - Supplementary motor area.

All these nerve fibers from cerebral cortex reach the caudate nucleus. From here, the fibers go to putamen. Some of the fibers from cerebral cortex go directly to putamen also. Putamen sends fibers to globus pallidus. Fibers from

here run towards the thalamus, subthalamic nucleus of Luys and substantia nigra. Subthalamic nucleus and substantia nigra are in turn, projected into thalamus. Now, the fibers from thalamus are projected back into primary motor area and other two motor areas, i.e. premotor area and supplementary motor area.

2. *Regulation of Conscious Movements*: Fibers between cerebral cortex and caudate nucleus are concerned with regulation of conscious movements. This function of basal ganglia is also known as the cognitive control of activity. For example, when a stray dog barks at a man, immediately the person, understands the situation, turns away and starts running.
3. *Regulation of Subconscious Movements*: Cortical fibers reaching putamen are directly concerned with regulation of some subconscious movements, which take place during trained motor activities, i.e. skilled activities such as writing the learnt alphabet, paper cutting, nail hammering, etc.

CLINICAL CORRELATES

1. *ATHETOSIS*: Athetosis is another type of abnormal involuntary movement, which refers to slow rhythmic and twisting movements. It is because of the lesion in caudate nucleus and putamen.
2. *CHOREOATHETOSIS*: Choreoathetosis is the condition characterized by aimless involuntary muscular movements. It is due to combined effects of chorea and athetosis.
3. *HUNTINGTON CHOREA*: Huntington disease is an inherited progressive neural disorder due to the degeneration of neurons secreting GABA in corpus striatum and substantia nigra. This disease starts mostly in middle age. It is characterized by chorea, hypotonia and dementia. In severe cases bilateral wasting of muscles occurs. It is otherwise called Huntington disease, chronic progressive chorea, degenerative chorea or hereditary chorea.

REFERENCE

1. British journal of anaesthesia/CEPD reviews/volume 3 number 3 2003
   The board and management of the british journal of anaesthesia 2003
2. K sembullingham-Essential physiology text.