SESSION I

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The neurophysiological aspects of sleep

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Definition

Although about a third of our life span is spent in sleep, the sleeping state is difficult to define. It may be regarded as a recurring state of inactivity accompanied by loss of awareness and decrease in responsiveness to the environment. It can be distinguished from coma due to disease, drugs or alcohol, and unconsciousness caused by general anaesthesia, by the ease with which the sleeping subject can be aroused. Stupor, a condition occurring in some mental illnesses and certain brain lesions, is also associated with unresponsiveness and immobility. However, disorder in stupor is one of motility, not consciousness, for the stuporose patient is fully aware of the environment though not responsive to it. Finally, there are a number of conditions of dissociation of consciousness such as hypnotic trances and fugue states, that are intermediate, possessing some of the features of both sleep and wakefulness. In these states, however, the affected individual, although amnesic for his actions, behaves for the most part as if fully in touch with the external world.

Electrophysiological aspects of sleep

Polygraphic studies (EOG, EMG and EEG) of nocturnal sleep have demonstrated that there is not one, but two opposing states of sleep (Freeman, 1972). One sleep state, non-rapid eye movement (NREM) sleep, contains slow waves, spindles and K-complexes in the EEG recording. No eye movements occur except slow eyeball oscillation during drowsiness and in the lighter stages of NREM sleep. Cardiorespiratory activity is steady with slower heart and respiration rates and during quiet wakefulness. The electrical activity of the chin EMG decreases, but falls further, almost to zero, during the other type of sleep. This second type of sleep, called rapid eye movement sleep (REM), is characterized by a

low voltage mixed frequency EEG pattern with bursts of rapid conjugate eye movements (REMs) and profound abolition of tone in the neck muscles. The phenomena in the REM state can be classified into the following two groups: tonic (continuous physiological changes) and phasic (periodic changes). The main tonic events, which persist continuously through the REM state, are the low voltage mixed frequency EEG pattern similar to that accompanying arousal, hippocampal theta rhythm and the abolition of nuchal muscle tone. The phasic phenomena include bursts of rapid eye movements and, in the cat, high voltage spikes, isolated or grouped in volleys that appear in the pons, lateral geniculate nucleus and occipital cortex. These are known as ponto-geniculo-occipital (PGO) spikes. They make their appearance about 0.5-1 min before the occurrence of the tonic phenomenon and subsequently accompany the bursts of REM. The PGO spikes come at a remarkably constant rate; about 60-70 min, or 1400/day (Jouvet, 1967). The organism is in a state of intense physiological activity during the REM state. Cerebral blood flow is greater than that during wakefulness. Heart rate, respiration and blood pressure become highly variable with higher mean levels. The penis is in a state of tumescence.

When awakened from REM sleep the subject is likely to report vivid dreams with much visual imagery. This contrasts with the mentation reported on waking from NREM sleep, which tends to consist of specific thoughts, devoid of dramatic story content, with minimal sensory imagery, those images that are present being vague, static or fragmentary (Freeman, 1972; Rechtschaffen, 1973). Both REM and NREM mentation slip rapidly from the memory unless rehearsed immediately on reawakening. Hence, a subject may deny having any dreams or interruption with his previous night's sleep, only to

find to his surprise that he not only had vivid REM mentation but was awakened and gave a detailed dream report (Baekeland and Lasky, 1968).

NREM sleep can be classified into a number of stages according to criteria formulated by a Committee of the Association for the Psychophysiological Study of Sleep (Rechtschaffen and Kales, 1968). These are as follows: stage 1, a relatively low voltage mixed frequency EEG without rapid eye movements; stage 2, 12–14 Hz sleep spindles and K-complexes on a background of relatively low voltage, mixed frequency EEG activity; stage 3, moderate amounts of high amplitude slow wave activity are present with 20–50% of the epoch consisting of waves of 2 Hz or less, with a peak-to-peak amplitude of 75 μ V or more; stage 4, large amounts of high amplitude activity are present, more than 50% of the epoch consisting of waves of 2 Hz or less with peak-to-peak amplitude of 75 μ V or more. Sleep spindles and K-complexes may or may not be present in stages 3 and 4. Stages 3 and 4 are often referred to as delta wave sleep, or slow wave sleep (SWS).

When a healthy person retires for the night drowsiness develops with increased muscular relaxation, slow eye-ball oscillation and disappearance of the alpha rhythm. Subsequently rapid development of NREM sleep of progressively increasing depth occurs, stage 4 being reached within the first 30–60 min. Gradual slowing of heart and respiration rates, reduction of muscle tone and increasing thresholds of arousal are observed. This sequence of events is interrupted after about 90 min by the sudden appearance of the REM state with bursts of rapid eye movements, abolition of nuchal muscle tone, skeletal muscular twitches, a variable rapid heart rate, shallow irregular respirations and penile tumescence. The first REM period is brief, usually 5–10 min, with fewer eye movements than later REM periods (Verdone, 1965). Four to six REM periods occur during the night in 80–100 min cycles, alternating with NREM sleep. Each lasts 10–30 min, the first three REM periods tending to increase progressively in length as the night goes on. Thus, longer periods of REM sleep occur later in the night. In contrast, the bulk of stage 3 and 4 sleep occurs early, while in the latter part of the night NREM sleep consists mainly of stage 2. In fact, most stage 4 occurs during the first NREM period.

The young adult spends 20 to 25% of the night in REM, about 5% in stage 1, around 50% in stage 2, 7–8% in stage 3 and 10–16% in stage 4 (Williams, Agnew and Webb, 1964, 1966; Agnew and Webb, 1968a; Kales *et al.*, 1967a, b, c). In the neonate, the sleep cycle is much shorter, 40–45 min, and REM sleep much more abundant, about 50% of total sleep time (TST). Moreover, sleep onset directly into the REM state may occur and the sleep is dispersed

throughout the 24-hr period. The percentage of REM sleep decreases progressively after birth, reaching 20–25% of TST at the end of the first year. The sleep patterns of children, young adults and elderly differ mainly in total sleep time and stage 4 sleep. Children have considerably more stage 4 sleep (20–30%) while this percentage decreases to 10–16% in young adults with a further dramatic reduction in middle and old age (0–6%). The elderly also show a substantial decrease in total sleep time owing to frequent awakenings during the night. REM percentage shows a slight fall to around 20% in the middle-aged and elderly. While the first three REM periods of children and young adults increase successively in length, the REM periods of the elderly remain fairly uniform in duration (Kales *et al.*, 1967; Feinberg, Koresko and Heller, 1967; Feinberg, 1974). The effects of ageing on sleep are accentuated in elderly patients with diffuse brain pathology.

Most psychoactive drugs also affect REM sleep, the most common response being a varying degree of suppression with a compensatory rebound on withdrawal. The suppressant effect may be temporary, normal REM percentages reappearing with continued administration. Only a few compounds have been shown to increase REM sleep. However, the drug effects on REM sleep are complex and dose-dependent. For example, small doses of monoamine oxidase inhibitors (MAOIs) can result in a transient initial increase in REM time while larger doses cause marked reduction. Slow wave sleep is also reduced by certain drugs, especially the benzodiazepine derivatives (Oswald, 1973).

Hormone secretion during sleep

As well as the autonomic changes which occur during sleep, important alterations in endocrine function have been reported in recent years. Sleep is the most important stimulus for human growth hormone (HGH) secretion. Except for increases following hypoglycaemia, exercise and psychic stress, human growth hormone maintains a relatively low constant serum level during wakefulness (Catt, 1970). A peak of growth hormone activity appears shortly after sleep onset and is triggered by the first nightly appearance of slow wave sleep, NREM stages 3 and 4 (Takahashi, Kipnis and Daughaday, 1968; Parker *et al.*, 1969). This physiologically maximal HGH release in slow wave sleep has been taken as evidence that slow wave sleep has an anabolic protein sparing restorative function (Oswald *et al.*, 1973).

The relationship of other pituitary hormones secretion to the sleep waking cycle and to sleep stage is less dramatic. Sassin *et al.* (1972) have also noted a marked diurnal variation in human plasma prolactin, with highest values during sleep. However,

periods of episodic release occurred throughout the 24 hr. The concentration of ACTH in the plasma cannot be assayed, but the plasma cortisol level is highest in the early morning hours and lowest in the late evening in the human being, with a well established circadian sleep waking cycle. Cortisol begins to be secreted in large episodic bursts during the 3 or 4 hr before time of waking. Although this is also the time of maximum REM activity, there is no clear relationship between REM sleep and cortisol secretion (Weitzman, 1972).

Regarding the pituitary gonadotrophins, Rubin (1972) has described unrelated random peaks of LH (luteinizing hormone) and FSH (follicle stimulating hormone) during sleep, with the plasma LH being slightly higher in REM sleep in adult males. The observation of a modest but definite increase in plasma LH level in sleep in adult males was confirmed by Rubin *et al.* (1973) while FSH secretion was found to have no clear relationship to sleep stages. No significant circadian rhythm during sleep for either LH or FSH was apparent. Nankin and Troen (1972) have observed that the pituitary release of LH occurs as repetitive abrupt discharges in healthy adult men during the night with highest levels in the early morning. Kapen (1972) has studied several females at various phases of the menstrual cycle. During menstruation, the episodic release of LH is infrequent, with low amplitude peaks. Just before ovulation the episodic release of LH is more prominent, with high amplitude peaks of secretion occurring, half of which occur in REM periods. The secretory episodes also seem to be more frequent with high amplitude peaks in the latter part of the follicular phase. Finkelstein *et al.* (1973) have reported, that plasma LH output is synchronized with sleep at the beginning of puberty with the secretion during sleep being greatly augmented during puberty. These workers observed that, when sexual maturation is complete, the rise in LH secretion during sleep is lost. A more recent study from the same laboratory has sampled plasma LH and testosterone levels at 20-min intervals for 24 hr in nine pubertal boys and three sexually mature young men (Boyar *et al.*, 1974). In all nine pubertal boys the plasma testosterone concentration fluctuated and was significantly higher during normal nocturnal sleep as compared to daytime waking. This increased testosterone during sleep was temporally linked to the pubertal sleep augmentation of LH secretion. Reversal of sleep in three of the boys showed that the plasma testosterone concentrations were now augmented during the reversed daytime sleep period. Measurement of the plasma LH and testosterone levels in the three sexually mature young men showed episodic secretion peaks of LH and testosterone both during waking and sleep periods. There was no

consistent increase of LH or testosterone secretion during sleep in the young adult males, nor was there any relationship between plasma LH and testosterone levels, neither during sleep nor wakefulness. Other all-night studies of adult males have reported a decline in plasma testosterone levels with sleep onset, with a subsequent increase in the latter part of the night, reaching a peak in the early morning between 6 and 7 a.m., with many fluctuations, which tend to occur at or before onset of REM periods (Evans *et al.*, 1971; Rowe *et al.*, 1974).

Ban (1972) has reported a diurnal fluctuation in triiodothyronine ^{131}I resin sponge uptake (T_3RSU) with its peak during sleep. On the other hand plasma thyroxine concentrations sampled at 20-min intervals throughout the 24 hr have revealed slightly higher levels during wakefulness than during sleep (O'Connor *et al.*, 1974). Disturbance in thyroid function certainly affects slow wave sleep, a marked reduction occurring in hypothyroidism (Kales *et al.*, 1967) and an increased percentage in hyperthyroidism (Dunleavy *et al.*, 1974). The parathyroid hormone shows a maximum output between the hours of 2 and 4 a.m. (Jubiz *et al.*, 1972).

Neural mechanisms of sleep

The neural mechanisms of sleep and waking are complex and still the subject of much debate. The present position has been elegantly reviewed by Moruzzi (1972). The ascending reticular system and a group of neurones lying in the posterior hypothalamus appear to be endowed with a tonic activating influence and are concerned with the maintenance of wakefulness. In contrast, the lower brainstem (middle and upper middle pons in the region of the solitary tract) and basal forebrain (pre-optic region of the anterior hypothalamus) contain structures with an opposing function. These actively inhibit the more rostral portions of the mid-brain reticular formation with consequent synchronization of cortical rhythms and the induction of sleep accompanied by NREM EEG patterns.

The trigger for REM sleep has been located in the pons by a series of coagulation studies in which complete destruction of the nucleus reticularis pontis caudalis has been shown to eliminate REM sleep without affecting NREM sleep. The ascending route from this centre to the cortex has not yet been defined. Bilateral destruction of the locus coeruleus, a pontine nucleus rich in noradrenaline, abolishes the tonic atonia of the REM state due to interference with the descending inhibitory system, which *via* the reticulo spinal pathways inhibits the spinal anterior horn cells (Jouvet, 1972). The neural basis of the phasic REM components appears to be separate, involving the lateral vestibular nuclei and ocular motor control centres (Pompeiano and Morrison, 1965).

Neurotransmitters and sleep

Jouvet (1972) has reviewed the role of monoamines and acetylcholine containing neurones in the regulation of sleep. He hypothesizes that the 5-hydroxytryptamine (5-HT)-rich neurones in the anterior raphe system* are responsible for behavioural and slow wave sleep. The 5-HT neurones in the caudal raphe nuclei prime REM sleep mechanisms by sending terminals to the caudal two thirds of the locus coeruleus. This in turn is responsible for total inhibition of muscle tone associated with REM. On the other hand the medial third of the locus coeruleus (pontine pace maker) is responsible for both the phasic and tonic ascending REM components. The 5-HT priming mechanisms may trigger the locus coeruleus thus causing the onset of REM while terminals from the locus coeruleus in turn suppress re-uptake of 5-HT thus allowing the REM state to develop. Acetylcholine and noradrenaline are concerned with the maintenance of REM while PGO activity appears to be inhibited by 5-HT. Alterations between slow wave sleep and REM sleep are produced by alternating 5-HT release (SWS) and re-uptake (REM). The anterior noradrenaline-containing cells of the locus coeruleus in the pons cause waking. According to Jouvet, the neurotransmitter involved with the maintenance of wakefulness is acetylcholine.

However, the biochemical findings in recent human sleep studies (Wyatt, 1972) do not readily conform to Jouvet's elegant model of the control of sleep and waking based on animal work. For example, parachlorophenylalanine (PCPA), which decreases brain 5-HT, decreased REM sleep without affecting NREM sleep. 5-Hydroxytryptophan (5-HTP), the immediate precursor of 5-HT, reversed the PCPA effect and elevated REM sleep in healthy subjects. The twice removed precursor of 5-HT, tryptophan, had a marked soporific effect in patients with insomnia and increased SWS in normals. Tryptophan also decreased REM sleep in normals. The observation that tryptophan produced the opposite effect on sleep from that of 5-HTP suggests that tryptophan-induced sleep is not caused by its effect on 5-HT metabolism. Other metabolic pathways may be involved. The finding that PCPA enhanced tryptophan's soporific effect is further evidence to support this view.

Thus the hypothesis that 5-HT is primarily involved in initiating and sustaining NREM sleep is not supported by human sleep studies.

In fact, the available evidence points to 5-HT metabolites having a role in triggering the REM

state. Monoamine oxidase inhibitors (MAOIs), which prevent the metabolism of 5-HT, markedly reduce or abolish REM sleep. PCPA blocks the synthesis of 5-HT and reduces REM sleep, an effect which can be reversed by giving 5-HTP, the immediate precursor of 5-HT. These results suggest that interruption of the normal metabolism of 5-HT causes REM reduction and support the 5-HT REM triggering hypothesis. Against this view is the finding that low doses of MAOIs, which should decrease 5-HT metabolites, increase rather than decrease REM sleep. Thus REM reduction is not invariably due to a fall in the brain concentration of 5-HT metabolites.

As hypothesized by Jouvet, the adrenergic system may also play a role in REM control. α -Methyl-paratyrosine (AMPT) and α -methyl-phenyl-alanine (AMPA) are both tyrosine hydroxylase inhibitors and decrease the content of brain catecholamines. Both were found to increase REM sleep time, while L-dopa, a catecholamine precursor, decreased REM sleep. Thus, in man, it appears that high brain catecholamine concentrations decrease REM, while lowering catecholamine levels augments REM.

Wyatt (1972) claims that these findings indicate that the REM state is controlled by an interaction between the serotonergic and adrenergic systems, with 5-HT augmenting and catecholamines reducing the REM state. There is considerable biochemical evidence that catecholamines can modify 5-HT metabolism.

Humoral factors

Humoral factors may play a role in the genesis of sleep. Recipient rabbits infused with a dialysate from the cerebral sinuses of sleeping donor rabbits (sleep being induced by stimulation of the ventromedial intralaminar thalamic nuclei) developed SWS (Monnier and Hatt, 1971; Monnier *et al.*, 1972). Fencf, Koki and Pappenheimer (1971) have also isolated a factor derived from sleep-deprived goat C.S.F. which increases sleep time and decreases locomotor activity in rats.

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* The raphe system is a collection of midline nuclei situated in the brain stem, clustered in nine groups from the nucleus raphe obscurus in the medulla to the nucleus linearis in the mesencephalon.

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