

SESSION II

Chairman: PROFESSOR J. M. HINTON

The function of sleep

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Summary

Evidence is reviewed that points to sleep as a time during which synthetic processes for growth and repair are enhanced. REM (paradoxical) sleep seems especially related to increased synthetic processes in the brain.

Introduction

The 1960s saw a great volume of new knowledge about what happens during sleep. Some research workers felt it improper then to inquire what purpose or function might be served. The first explicit modern proposal that sleep was related to anabolic activity in the brain was made, so far as I know, by West (1969). He suggested that certain metabolic products would have to be dissipated and that this might happen mostly during a catabolic period while slow wave sleep (NREM sleep) was in progress and that then an 'anabolic phase occurs during fast-wave or paradoxical sleep' (REM sleep). Just at that time the implications of the Japanese discovery that growth hormone was secreted in large amounts during sleep (Takahashi, Kipnis and Doughaday, 1968; Honda *et al.*, 1969), and during slow-wave sleep in particular (Sassin *et al.*, 1969b) were beginning to dawn, and I was led to write of slow (NREM) sleep that 'its chief function is for bodily restitution, while REM sleep may be chiefly for brain repair' (Oswald, 1969). These themes were later developed (Oswald, 1970, 1973) and now Hartmann (1973) and Stern and Morgane (1974) have espoused the same general belief, but independently each suggests that REM sleep has a particular role of restoring or maintaining the functioning of catecholamine mechanisms within the brain. Hartmann points particularly to the fact that NREM sleep always precedes a shorter period

of REM sleep, that this demands explanation and he suggests that this can only be explained if one thinks of certain molecules being synthesized in the brain during NREM sleep and then being further processed during REM sleep.

There are of course those who will seek to explain sleep in behavioural terms, seeing the inertia as an adaptive response (Webb, 1974). Ideas of this nature are not incompatible with the notion that certain biochemical processes may be especially favoured during sleep. Nature is economical and in the course of evolution many purposes might have come to be best served during sleep.

We can see oscillations or rhythms of activity throughout nature—motor activity and motor inactivity, wakefulness and sleep. Organisms have both external and internal requirements for energy. Energy is sometimes directed to the outside world, and at other times must be used for such internal needs as repair and renewal of cells and synthesis for cellular division. Many enzymes can serve more than one function at one time, for example, promoting a catabolic process and, when conditions are slightly changed, an anabolic process. Since nature is economical some enzyme systems may function to direct energy expenditure towards the external world during wakefulness, but towards internal needs such as the synthesis of molecules during sleep.

Synthetic activity and sleep

Cell division is one customer for internal energy expenditure. Peaks of mitotic activity occur in human bone marrow and in human skin soon after the usual sleep onset time (Cooper, 1939; Killman *et al.*, 1962; Mauer, 1965; Fisher, 1968). In rats and mice cellular division in epidermis (Halberg and Barnum, 1961), bone marrow (Clark and Korst, 1969), pineal gland

(Renzoni and Quay, 1964), liver parenchyma (Halberg and Barnum, 1961), blood reticulocytes (Clark and Korst, 1969) and eosinophils (Halberg, 1960) shows circadian rhythms with maxima during the hours when the animals are predominantly asleep.

A further step in the inferential chain is provided by the new knowledge about hormone secretion during sleep. We now know that four important hormones concerned with the regulation of tissue growth and development, are sleep-dependent. Just because a hormone is present in greater amounts during sleep would not necessarily mean that it was sleep-dependent—corticosteroids rise during the later part of the sleep period, but they do so whether the individual is awake or asleep, and here the rise is a manifestation of a circadian rhythm and not of sleep-dependence. Sleep-dependent hormones are those which can be shown to be secreted in large amounts during sleep at the normal time, but not if the individual stayed awake, yet will be secreted if he sleeps, say, 6 hr or 12 hr later than the normal time. Human growth hormone is not merely sleep-dependent but requires the presence of slow-wave sleep Stages 3 and 4 (Sassin *et al.*, 1969a; Schnure, Raskin and Lipman, 1971). Also dependent on sleep, but not closely linked with any particular EEG-defined stage of sleep, are prolactin (Sassin *et al.*, 1973) and, in *early puberty only*, luteinizing hormone and testosterone (Boyar *et al.*, 1972, 1974). It seems a sensible provision of nature that maximal mitoses should be related in time to high blood levels of anabolic hormones. Growth hormone, especially, has been shown to increase the rate of synthesis of protein and RNA (Korner, 1965).

It has been known for many years that if it was a long time since the last sleep had occurred then slow wave sleep Stages 3 and 4 had immediate priority (Berger and Oswald, 1962). It is now widely recognized that whereas the amount of REM sleep seems to be governed chiefly by the circadian cycle, the amount of slow wave sleep at any given age is determined by the need for sleep as judged by the number of hours of continuous wakefulness that have elapsed. An especial role for this kind of sleep in promoting restoration was further suggested by the report of Baekeland and Lasky (1966) that when athletes had exercised hard during the day they got more slow-wave sleep at night, and by the report of Hobson (1968) that when cats had been obliged to take extra physical exercise, they too got a significant excess of subsequent slow wave sleep. A variety of authors have failed to confirm the finding of Baekeland and Lasky but none of us has exactly repeated their experiment by using athletes. Nevertheless, Adamson and his colleagues (1974) found that there is a significant increase of growth hormone during

sleep in men who have taken strenuous exercise during the day compared with days when they have taken only an ordinary amount of exercise. They also found that on the nights when the anabolism-promoting growth hormone was increased the catabolism-promoting corticosteroids were significantly reduced.

Another way of increasing the metabolism of tissue reserves is by starvation and under these circumstances an increase in the protein conserving growth hormone in the blood has been observed by Parker, Rossman and Vanderlaan (1972). Acute starvation is, at the same time, associated with a significant increase in the amount of slow wave sleep Stages 3 and 4 (MacFadyen, Oswald and Lewis, 1973; Karacan *et al.*, 1973).

Yet another condition that increases demands on tissue reserves is hyperthyroidism. Its converse, hypothyroidism was found to be associated with loss of Stages 3 and 4 sleep that returned during treatment (Kales *et al.*, 1967). We have found greatly increased amounts of Stage 3 and 4 slow wave sleep in hyperthyroidism and suspect that there is also an increase in growth hormone secretion (Dunleavy *et al.*, 1974). Where loss of weight is induced by the anorectic drug, fenfluramine, there is also an increase of Stage 3 and 4 sleep (Lewis *et al.*, 1971) and there can be increase of nocturnal growth hormone (Dunleavy, Oswald and Strong, 1973).

Even the extra demands of an additional hour of wakefulness in the middle of the night leads to a significant increase in the amount of Stage 3 and 4 sleep and of plasma growth hormone in the remainder of the night (Beck *et al.*, 1975). It is as if the extra wakefulness demands extra amounts of the sleep of high restorative value.

REM sleep and cerebral synthetic processes

It has been repeatedly shown that cerebral blood flow during paradoxical sleep is considerably increased, even to well above the levels of wakefulness (Townsend, Prinz and Obrist, 1973). Since blood flow through a tissue is normally proportional to oxidative metabolism and since during REM sleep the brain could hardly be working strenuously in order to cope with the external environment, one can only suppose that internal metabolic needs are being met and this is in keeping with the report by Van den Noort and Brine (1970) that brain ATP rises during the sleep of rats and that RNA synthesis in rabbit cortex increased as the sleep EEG became less synchronized (Vitale-Neugebauer *et al.*, 1970). There is, moreover, a lot of evidence suggesting that the high proportion of REM sleep or its equivalent in young animals is related in time to the period of most rapid brain growth, whereas senility, with its failure of cerebral synthetic processes and shrivelling of the brain, is associated with decreased REM sleep

(Feinberg, 1968) and there is also the deficit of REM sleep in mental defectives (Petre-Quadens and Lee, 1970; Feinberg, 1968). One might suppose that in mental defectives less synthetic processes are required for turnover and maintenance. There have been a number of animal experimenters who have reported that extra learning tasks are associated with more REM sleep in rats and that lack of REM sleep impairs learning performance, but most of these experiments are open to uncertainties of interpretation. We were unable to find that massive learning through the wearing of distorting spectacles caused any increase of REM sleep in man (Allen *et al.*, 1972) but since most cerebral protein synthesis must be for the maintenance of existing tissue this is not really very surprising. Another telling line of evidence stems from the fact that when the brain recovers from poisoning there is no excess of slow wave sleep during the subsequent weeks but there is usually a very large excess of REM sleep (Haider and Oswald, 1970; Oswald *et al.*, 1973).

In the Soviet Union, Demin and Rubinskaya (1974) have measured protein and RNA in cerebral neurones and found them to be decreased in association with REM-deprivation, and one of their colleagues, Dr A. Panov, has since repeated the work and confirmed that this is so even when the REM-deprivation procedure is relatively short and insufficient to cause any corticosteroid signs of a stress reaction. In Rostov-on-Don, Kogan *et al.* (1975) have now been able, with most elegant technique, to determine the rate of protein and RNA synthesis in small cerebral biopsies in relation to the stages of sleep of the cat, and they find a 30% reduction below waking levels during slow wave sleep and a rise of about 7% above waking levels during REM sleep.

Stern and Morgane (1974) point to diminished responsiveness of catecholamine systems following REM sleep deprivation and to greatly increased REM time where substances are given that depress catecholamine activity, such as reserpine. Whether brain catecholamines really are in a special category in regard to brain synthetic processes during REM sleep only time will tell. Although the most crucial experiments, which would have to involve incorporation of labelled amino acids, still remain to be done, we may by this time conclude that there is strong evidence for regarding sleep as a time specially important for synthetic processes in the body, with REM sleep being particularly important for synthetic processes in the brain.

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