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Sleep and its Interaction with Endocrine Rhythms

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Rhythmic variations with frequences from fractions of seconds to years characterise a wide variety of biological processes (Aschoff, 1979). Biological rhythms can be observed, not only in the individual of the species, but also in the cells which comprise the organism and the populations of which it is a member. These regular fluctuations can be endogenously generated by some form of internal oscillator, or alternatively may passively reflect exogenous environmental alterations. An important group of rhythms combines both endogenous and exogenous inputs with an internal oscillator or oscillators which are capable of being influenced by some external change. In this situation, the internal rhythm is kept in harmony with an environmental cycle by a change in the outside world acting as a synchroniser or zeitgeber. In this type if the animal is artificially isolated from its normal external synchroniser, the rhythm will continue, but free running, with a periodicity which is a close approximation to the duration of the environmental cycle to which it is normally tied. These rhythms normally synchronised to an environmental cycle but capable of being self-sustaining at approximately the same rate, are termed circa rhythms: thus circadian, circannual and circalunar rhythms, according to the geophysical cycle by which they are normally entrained.

An important zeitgeber or synchroniser of the 24 hour variations in their physiological function in many animals is the change of the light-dark cycle. In man, however, although light and dark may act as a zeitgeber, other factors are probably equally if not more important.

Rhythms and sleep

The sleep-wake cycle is capable of influencing a wide variety of man's diurnal rhythms, a majority of which have a clear phase relationship to the sleep-wake cycle. The nature of the synchronisation is not a simple one-way control system but involves interactions at a number of levels. The diurnal variation in body temperature, for example, is closely tied to the timing of the sleep-wake cycle under normal circumstances. If the sleep-wake cycle is disrupted, however, the duration of sleep time will be influenced by fluctuations in body temperature and the structure of the resultant sleep may well be influenced (Aschoff, 1981). The sleep-wake cycle is one among several influences upon most cyclical parameters. Further, the control of specific rhythms may well be under more than one oscillator which can be influenced differentially by these zeitgebers.

The ultimate influence of the sleep-wake cycle on any particular rhythm is clearly dependent on a variety of interacting forces. The ways by which sleep itself may interact with a biological rhythm could, for simplicity's sake, be conceived of as falling into three basic types (see Figs 1–3).

In the first type sleep as a whole is associated with a significant alteration in a particular parameter, either increasing or decreasing it throughout sleep. When the time of sleep is shifted, the alteration in the parameter shifts to retain the same relationship to the new period of sleep. In the second type, under normal conditions, variation in the parameter bears a consistent relationship to the timing of the sleep-wake cycle. If the subject's accustomed sleep-wake cycle is suddenly altered, then initially the parameter will retain its accustomed temporal relationship and be out of phase with the new sleep-wake cycle. If the new sleep-wake cycle is maintained after a number of days, usually 5–10, the parameter will gradually shift to take up its previous relationship to the sleep-wake cycle. The third type of relationship is where the variation in the parameter is directly influenced by a particular stage of sleep. Here the occurrence of the sleep stage will directly change the parameter. A sudden shift in the timing of sleep and the occurrence of the critical sleep stage will immediately shift the influence upon the parameter.

Sleep deprivation will affect these three types of relationship in different ways. In Type I it will remove the influence of sleep from the parameter throughout the period of deprivation and the waking values will by and large persist. Type II under acute sleep deprivation will continue to vary with its accustomed temporal relationship. In Type III as in Type I sleep deprivation will totally remove the influence of the interaction between a sleep stage and the parameter.

The Type I interaction is well illustrated by prolactin secretion. The circulating levels of this hormone have

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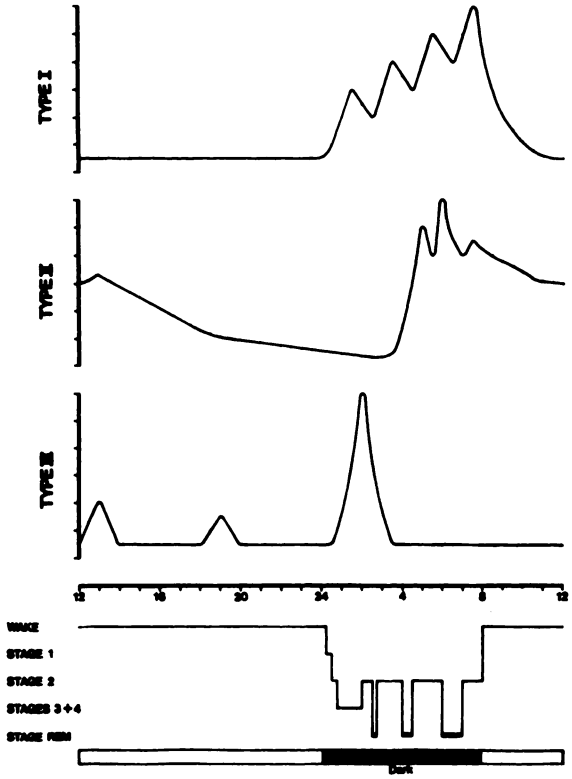


FIG 1

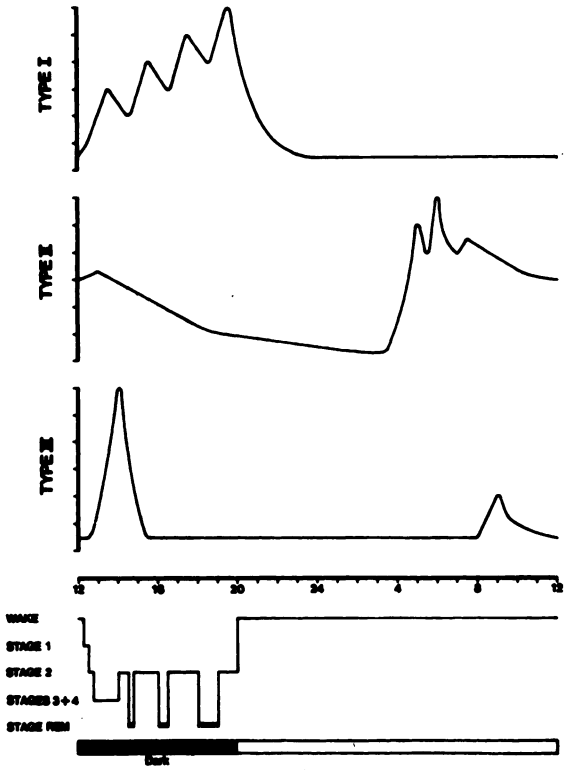


FIG 2

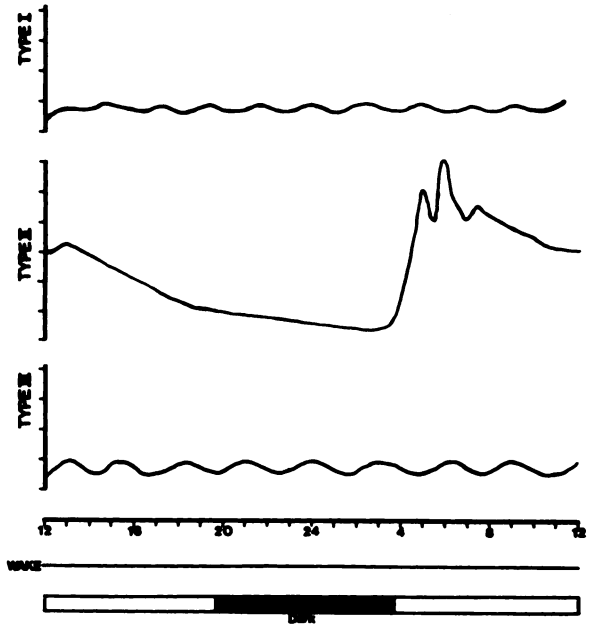


FIG 3

FIGS 1–3.—These figures represent schematically three types of interaction between sleep and the daily fluctuations in an endocrine or related parameter. In Fig 1, the changes occurring during the subject's accustomed sleep-wake pattern are represented. In Fig 2, the effects of acute sleep reversal on the parameters are represented, and in Fig 3, the effects of total sleep deprivation through the 24 hours are shown. In Type I, exemplified by *prolactin*, a change occurs with sleep as a whole, which alters when sleep time is altered, and is abolished by sleep deprivation. In Type II interactions, *as in ACTH*, a constant relationship obtains between the habitual time of sleep and an alteration in the parameter but sudden changes in sleep time by acute reversal or deprivation have little discernible effect on the parameter. If, however, the alteration in timing of sleep were maintained for a matter of days or weeks, the relationship between time of sleep and the change in the parameter would be gradually re-established. In Type III relationships, *as with growth hormone*, the alterations are connected to the presence of a particular stage of sleep, in the case illustrated to slow wave sleep stages 3 and 4. A shift in timing of the sleep stage immediately shifts the related change in the parameter, and the absence of sleep removes the influence.

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been reported to show a consistent rise during the period of sleep (Sassin *et al,* 1972). The levels begin to rise at sleep onset and fall on waking to reach basal daytime values an hour or two later. Acute sleep reversal is reported to produce an immediate shift in the time of the rise to coincide with the new period of sleep (Parker *et al*, 1973).

Cortisol and its trophic hormone ACTH are an example of the Type II relationship, showing a rhythm with peak concentrations at or about the normal time of waking, and a trough in the early hours of the morning soon after sleep onset (Krieger, 1979). This pattern of secretion has a remarkably constant relationship to the sleep-wake cycle in normal subjects under standard conditions. In our own laboratory, correlations of better than 0.9 are obtained between the rhythms in different individuals. Inverting or altering the sleep-wake cycle is reported to produce increasing disruption of the previously established pattern with a gradual re-establishing of the rhythm in relationship to the timing of the new sleep time (Weitzman *et al,* 1975).

An example of Type III is provided by growth hormone. The episodic secretion of growth hormone is covered by changes within the CNS linked to sleep and more specifically to a particular stage of sleep, slow wave sleep (Quabbe, 1977). A nocturnal surge in growth hormone occurs immediately following the onset of the first slow wave sleep of the night. If sleep onset is delayed then the surge in growth hormone is delayed until such time as sleep is allowed and slow wave sleep supervenes (Takahashi *et al,* 1968). When the sleep rhythm is inverted, the growth hormone immediately shifts to maintain its relationship to slow wave sleep (Weitzman *et al,* 1975). If sleep is prevented for a time, slow wave sleep will obviously not occur and the triggering of the nocturnal surge in growth hormone will likewise not occur.

Thus in prolactin, a rise in circulating levels is tied to the occurrence of sleep and when sleep shifts, so immediately does the peak in prolactin. ACTH and cortisol are entrained to sleep and though under conditions of a constant sleep-wake cycle a very predictable temporal relationship obtains between sleep and these hormones, when a shift in the timing of sleep occurs, it is several days before this relationship is re-established. A surge in growth hormone is triggered by the first slow wave sleep stage of sleep. The changing of the timing of slow wave sleep immediately shifts the peak in growth hormone. Here it is a particular stage of sleep, not merely sleep itself, which is the critical factor.

These three simplified forms of interaction between sleep and a diurnally fluctuating parameter, can be further illustrated by the examples of noradrenaline, plasma renin activity and β-Lipotrophin with the structurally related met-enkephalin.

Noradrenaline

The fluctuations in plasma noradrenaline were investigated in normal volunteers sampled through the 24 hours (Mullen *et al*, 1981). The circulating level of noradrenaline is often assumed to reflect sympathetic nervous system activity (Lake *et al,* 1976) and noradrenaline and the other catecholamines have considerable interest as possible indicators of psychological and emotional stress. A diurnal rhythm in noradrenaline production, with lower levels during sleep, has been inferred from urinary excretion of catecholamines and their metabolites (Akerstedt and Levi, 1978) and recent studies on blood levels employing the sensitive radioenzymatic assays appeared to confirm this (Maling *et al*, 1979; Prinz *et al*, 1979; Saar and Gordon, 1979). In addition to this diurnal rhythm, an ultradian variation has been reported with a periodicity in the region of 100 minutes, which is hypothesized to relate to the basic rest-activity cycle (Levin *et al*, 1979).

Ten normal volunteers were studied, seven sleeping as was normal for them between approximately 23.00 hours and 07.00 hours, while two had their sleep onset delayed by 12 hours, and one subject was totally sleep-deprived. Noradrenaline was measured by a radioenzymatic assay (Henry *et al*, 1975).

Noradrenaline levels in those subjects on a normal sleep-wake cycle showed significantly lower values during sleep, with a mean difference of 168 pg/ml which was significant by a two tailed t-test at the 0.01 level. To test for rhythms both curve fitting (Rubin and Poland, 1976) and the more rigorous cosinor analysis (Halberg *et al*, 1972) were employed, which suggested a diurnal rhythm in plasma noradrenaline, with lower levels throughout the period of sleep. In those subjects whose sleep onset was delayed, there was a suggestion that the decrease in circulating noradrenaline levels was similarly delayed. In the sleep deprived subject, the levels remained elevated throughout the 24 hours. No evidence for the ultradian rhythm reported by Levin and his colleagues was found in our data when it was subjected to a spectral analysis.

These results supported the presence of a diurnal rhythm in noradrenaline with lower levels associated to the period of sleep. Changes of sleep stage did not directly influence levels, though because of the very low levels in sleep as a whole real changes between sleep stages could have been obscured at the sensitivity of our assay. The trough during sleep appeared to shift immediately the time of sleep was altered and to be lost during sleep deprivation. On the face of it, therefore,

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noradrenaline appeared like prolactin to have the first type of relationship to sleep.

β-Lipotrophin and Met-enkephalin

The discovery of the naturally occurring opioid peptides (Hughes *et al*, 1975) opened up fascinating research questions for biological psychiatry, both in the field of addiction and mental illness. The opioid peptides met-enkephalin and β-endorphin have a structural relationship to the pituitary hormone β-lipotrophin (β-LPH) and this in turn derives together with ACTH from a common precursor, pro-opiocortin (Mains *et al*, 1977). In conjunction with Professor Lesley Rees and her group at St Bartholomew's Hospital, studies have been performed on fluctuations through the 24 hours of met-enkephalin, β-lipotrophin, ACTH, and β-endorphin. It was hoped by studying the covariation of these hormones in detail under resting physiological conditions to obtain information about potential interactions and shared control mechanisms. Further, as both the enkephalins and endorphins are potentially psychoactive, it was hypothesized that the changes in cerebral activity occurring during sleep might have some association with fluctuations in these compounds.

A group of six subjects was studied through the 24 hours; β-LPH was measured, together in two cases with ACTH (Mullen *et al*, 1979). A clear diurnal rhythm in plasma immunoreactive LPH was found with a trough occuring soon after midnight and a peak at about the time of waking. In the subjects where both LPH and ACTH were estimated, the fluctuations in the two compounds showed a very close and highly significant correlation throughout the 24 hours. Such a close correspondence between the two suggested a common control mechanism in their release, which is perhaps not surprising in view of their derivation from a common precursor, their storage in the same cells of the anterior pituitary (Moriarty, 1973) and their concomitant release following acute stress (Krieger *et al*, 1977).

Plasma met-enkephalin levels were studied in a group of volunteers in whom further samples were also obtained for LPH and β-endorphin (Shanks *et al*, 1981). No regular rhythm was discernible through 24 hours in the circulating met-enkephalin levels, nor was there any evidence for an association between the changes of the sleep-wake cycle and fluctuations in the met-enkephalin. The β-endorphin estimations, though far more limited, in contrast did appear to vary together with LPH. The LPH, like ACTH and cortisol, has a clear and reproducible diurnal rhythm. The dissociation between plasma levels of met-enkephalin and those of the ACTH/LPH/β-endorphin group of peptides strongly suggests that the control mechanisms for the secretion of met-enkephalin are quite different. The plasma met-enkephalin measured in this study probably does not originate from the pituitary with the ACTH/LPH/β-endorphin peptides but from the adrenals, so separate control mechanisms are perhaps not to be wondered at.

The lipotrophin, and probably the β-endorphin, appear to share the same characteristic rhythmic fluctuation through the 24 hours as ACTH and cortisol. The relationship of both to sleep is identical to that of ACTH and cortisol and is an example of the Type II relationship.

Plasma renin activity

Renin, which is produced predominantly in the kidney, has its main biological activity in the renin-angiotensin system (Peart, 1978). The major source of plasma renin activity is undoubtedly the kidney though renin-like activity has been described within the brain (Reid, 1976). A role for renin has been sought in the causation or maintenance of some forms of hypertension. A primary defect in the renin-aldosterone system has also been postulated to exist in bipolar manic-depressive psychosis (Hullin *et al*, 1977).

The factors involved in the control of renin release in man under physiological conditions are not fully understood. In animals, direct stimulation of the central nervous system has been shown to influence renin release via the β-adrenergic innervation to the kidney. To test directly for such an effect in man would be difficult. However, the changes associated with sleep represent profound shifts in CNS activity, and by monitoring any accompanying alterations in plasma renin activity interactions between changes in the CNS and changes in renin release might be discernible.

A study was undertaken in the changes of plasma renin activity through the 24 hours and with changes in the sleep-wake cycle (Mullen *et al*, 1980). Nine normal volunteers were studied, two of whom were subjected to an acute sleep reversal procedure. Plasma renin activity varied widely through the 24 hours but no consistent diurnal rhythm or ultradian rhythms were observed. The changes in plasma renin activity during sleep did, however, show an association with changes in the stage of sleep. A significant decrease in plasma renin activity was noted to occur at the onset of a REM phase. In the nine subjects, 26 measurements occurred in REM, all but two of which showed a drop compared to the level in the preceding sleep stage (two tailed t-test $P < 0.001$). The mean decrease in plasma renin activity accompanying REM was 407 pg per ml per hour. It was possible to calculate from our data the rate of decrease in plasma renin activity following REM onset, which suggested that 50 per cent of the activity would disappear after 33 minutes, with a standard

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error of 8 minutes. This is a close approximation to the best available estimate for the half-life of plasma renin activity itself and suggests that REM onset is associated with a cessation in renin release. The sleep reversal procedures confirmed that REM was associated with a decrease in plasma renin activity, whatever time of night or day the sleep stage occurred.

The association between REM onset and the drop in renin release could indicate that changes in cerebral activity are capable of influencing renin release from the kidney. Alternatively, the association might depend on some intervening variable such as changes in the blood pressure. In animal experiments the effects of CNS stimulation on renin release have been demonstrated to be directly mediated by the sympathetic innervation to the kidneys. To test whether a similar mechanism is operative in man, a study was undertaken on a volunteer who had previously undergone bilateral nephrectomy and renal transplantation, on the assumption that his transplanted kidney, though functional, would be effectively denervated. A 15 minute sampling schedule was adopted. The subject had three episodes of REM in which measurements were obtained but in none of them did the type of drop in renin occur found in our normal subjects (Mullen and Lightman, unpublished observation). This gives a degree of support to the hypothesis that it is a direct effect of the changes in CNS activity accompanying REM that is responsible for inhibition of renin release.

The association of changes in plasma renin activity with REM would appear to be an example of the third type of association described earlier. It is similar to the association between growth hormone and slow wave sleep but it differs in one important regard: for growth hormone slow wave sleep is the single most important determinant of its daily release but for renin REM sleep is a modifier of its release. This is probably of more theoretical than practical import.

Conclusions

Sleep is capable of interacting with endocrine and related parameters to alter the pattern of secretion. In some cases, the timing of sleep is the single most important factor in determining the secretory pattern.

The rhythmic changes which characterise much biological function are in animals largely tied to enviromental changes. In man, the timing of some of these biological rhythms may be in part or even primarily dependent not on the immutable changes in our natural environment, but on the partly controllable pattern of our sleep-wake cycle.

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References

AKERSTEDT, T. & LEVI, L. (1978) Circadian rhythms in the secretion of cortisol, adrenaline and noradrenaline. *European Journal of Clinical Investigation*, **8**, 57–8.

ASCHOFF, J. (1979) Circadian rhythms: general features and endocrinological aspects. In *Endocrine Rhythms* (ed. D. T. Krieger). New York: Raven Press.

—— (1981) Circadian Rhythms: Interference with and dependence on work-rest schedules. In *Biological Rhythms, Sleep and Shift Work*, (eds. L. C. Johnson, D. I. Tepas, W. P. Colquhoun, M. J. Collisan). Lancaster: MTP Press.

HALBERG, F., JOHNSON, E. A., NELSON, W., RUNGE, W. & SOTHERN, R. (1972) Autorhythmometry—procedures for physiological self-measurement and their analysis. *Physiology Teacher*, **1**, (4), 1–11.

HENRY, D. P., STARMAN, B. J., JOHNSON, B. G. & WILLIAMS, R. H. (1975) A sensitive radioenzymatic assay for norepinephrine in tissues and plasma. *Life Sciences*, **16**, 375–84.

HUGHES, J., SMITH, T. W., KOSTERLITZ, H. W., FORTHERGILL, L. A., MORGAN, B. A. & MORRIS, H. R. (1975) Identification of two related pentapeptides from brain with potent agonist activity. *Nature*, **258**, 577–9.

HULLIN, R. P., JERRAM, T. C., LEE, M. R., LEVELL, M. J. & TYRER, S. P. (1977) Renin and aldosterone relationships in manic depressive psychosis. *British Journal of Psychiatry*, **131**, 575–81.

KRIEGER, D. T. (1979) Rhythms in CRF, ACTH and corticosteroids. In *Endocrine Rhythms* (ed. D. T. Krieger). New York: Raven Press.

—— LIOTTA, A. & LI, C. H. (1977) Human plasma immunoreactive β lipotrophin: correlation with basal and stimulated plasma ACTH concentrations. *Life Sciences*, **21**, 1771–6.

LAKE, C. R., ZIEGLER, M. G. & KOPIN, I. J. (1976) Use of plasma norepinephrine for evaluation of sympathetic neuronal function in man. *Life Sciences*, **18**, 1315–26.

LEVIN, B. E., RAPPAPORT, M. & NATELSON, B. H. (1979) Ultradian variations of plasma noradrenaline in humans. *Life Sciences*, **25**, 621–8.

MAINS, R. E., Eipper, B. A. & LING, N. (1977) Common precursor to corticotrophins and endorphins. *Proceedings of the National Academy of Sciences of the USA*, USA 74, 3014–18.

MALING, T. J. B., DOLLERY, C. T. & HAMILTON, C. A. (1979) Clonidine and sympathetic activity during sleep. *Clinical Science*, **57**, (6), 509–14.

MORIARTY, G. C. (1973) Adenohypophysis; ultrastructural cytochemistry: a review. *Journal of Histochemistry and Cytochemistry*, **21**, 855–94.

MULLEN, P. E., JAMES, V. H. T., LIGHTMAN, S. L., LINSELL, C. & PEART, W. S. (1980) A relationship between plasma renin activity and the rapid eye movement phase of sleep in man. *Journal of Clinical Endocrinology and Metabolism*, **50**, 466–9.

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