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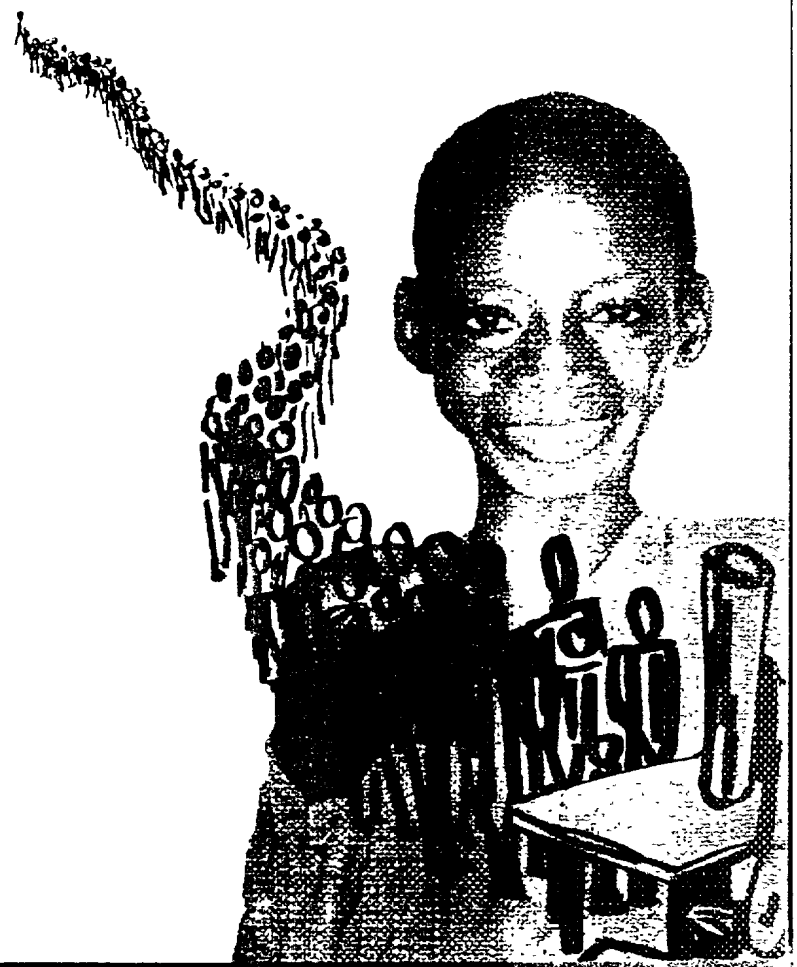

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CHAPTER 10

Hormones in human African trypanosomiasis

MW Radomski, G Brandenberger

Introduction

Humans suffering from African trypanosomiasis or sleeping sickness demonstrate major disruptions in their circadian sleep-wake distribution, with the intensity of the sleep-wake disturbances increasing with the stage of advancement of the disease [1]. Buguet et al. [1] postulated that the disruptions in the circadian sleep-wake cycle in infected humans at the stage of meningoencephalitis may be due to a disease-induced disturbance of the circadian timing system.

We undertook a series of hormonal studies on African patients with varying degrees of severity of infection to assess whether the disruptions in the circadian sleep-wake cycle extended to hormones with well-known circadian rhythms in healthy humans [2, 3]. Several hormones exhibit circadian rhythms which may be controlled by a circadian timing system synchronized to the sleep-wake cycle, or are dependent upon both of these influences [4] Three types of interactions have been described between the sleep-wake cycle and endocrine rhythms: hormones as cortisol that are relatively independent of sleep and are reflections of endogenous circadian rhythms independent of shifts in the sleep-wake cycle; those as prolactin which demonstrate sleep-dependent secretory patterns increasing during sleep even when sleep is displaced; and those as plasma renin activity (PRA) and growth hormone (GH) which are related to the internal sleep structure. To determine the extent of circadian rhythm disruptions in sleeping sickness patients, we examined the above three groups of hormones in healthy and in infected African subjects.

Two approaches were used in the examination of healthy and infected Africans from the Ivory Coast and the Congo. To establish whether circadian rhythms in certain hormones were disrupted as the disease progressed in severity, hourly blood samples were taken over a 24h period and analyzed for cortisol, prolactin, and GH [2, 3, 5]. To assess whether the relationship between certain hormones to the internal structure of sleep was maintained with disruptions in the sleep-wake cycle in infected

humans, blood was sampled every 10 min over 24 h and assayed for PRA prolactin and cortisol [6, 7]

Disruptions in cortisol and prolactin rhythms in sleeping sickness

Twenty-four hour patterns of plasma cortisol and prolactin were measured in 8 sleeping sickness patients (Daloa, Ivory Coast) at varying degrees of progression of the disease as well as in a control group of 6 healthy subjects of similar ethnic origin and from the same geographical area. Blood was sampled every hour over a 24h period and polysomnographic recordings were taken to monitor sleep and sleep composition in the subjects during the same period. The plasma values for cortisol, prolactin, and GH were subjected to a Z-statistical transformation and the Z-values over 24 h were tested for the presence of circadian rhythmicity by applying standard cosinor analyses.

Figure 1 shows the mean cortisol and prolactin circadian variations for the control group, the group of patients (n = 5) in the early stages of the disease, and the group (n = 3) in the late meningoencephalitic stage. The corresponding 24h variations in NREM and REM sleep are shown in the last row of the Figure. A significant periodicity in the 24h cortisol and prolactin variations were found in both the healthy group and the sick group in the early stages of the disease. These rhythms corresponded closely to the periodicity observed in the sleep parameters, cortisol increasing towards the latter half of the nocturnal and sleep period, and prolactin increasing with the onset of sleep. The advanced stage of the disease was characterized by a total disruption in cortisol, prolactin and sleep rhythms with sporadic increases distributed randomly throughout the 24h/day and independent of the nocturnal period.

Buguet et al. [1] had previously demonstrated the relationship between the disappearance of the circadian rhythm of the sleep-wake cycle and the severity of the clinical symptoms of the disease. Patients in the advanced stages of the infection in which the parasite has become established in the brain, have meninges that are infiltrated with lymphocytes, plasma cells and morular cells, and exhibit no sleep rhythms. We have found above that as the disease progresses in severity, the extent of circadian disruption in infected patients also extends to other well-known hormonal circadian rhythms as cortisol and prolactin. Whether a close temporal relationship with the disrupted rhythms in cortisol, prolactin and the sleep episodes persists in the absence of any rhythmicity could not be determined because of the infrequent hourly sampling. This question is addressed in the next section of this paper. However, the above findings indicate that the pathogenesis of this disease is related to dysfunctions of circadian pacemakers in the brain.

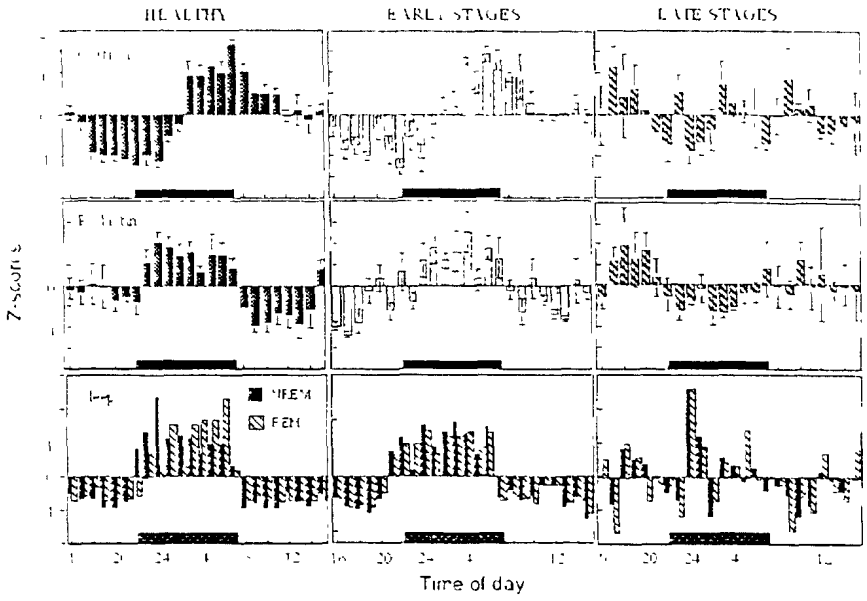

Fig. 1. Hourly variations in plasma cortisol and prolactin levels over 24 h and variations in sleep composition expressed as % NREM and REM for healthy subjects and sleeping sickness patients in the early stages and late advanced stages of the disease. The data are shown as Z-transformed scores. The dark horizontal bar on the x-axis represents the nocturnal lights-out period of the 24h/ day. The variations in the hormones and sleep stages for the healthy subjects and early-stage patients show a significant circadian rhythmicity.

The well-known temporal relationship between SWS and GH persists in many conditions of disrupted sleep. We examined the hourly levels of GH in our subjects above and compared them to the occurrence of SWS episodes. We hoped that the sleeping sickness model of circadian disruption might shed further light on the association of plasma levels of GH and the occurrence of SWS. A strong correlation between plasma GH levels and the occurrence of SWS (applying a lag time of 16 min as in Holl et al. [8]) was found in all three groups of subjects indicating that this association persists in even the most severely ill patients, despite the absence of any circadian rhythmicity in GH or SWS [5]. Although dissociations between sleep and GH secretion have been described in the literature, sleep and stimulation of GH secretion are regarded as outputs of a common central nervous system mechanism [9, 10] with hypothalamic GHRH being the likely factor for synchronizing GH secretion and SWS [11]. The fact that the association between GH levels and the occurrence of SWS persisted even under conditions of severe disruptions of the sleep-wake cycle in our sleeping sickness patients suggests that the trypanosomiasis-induced disruption in the synchronization of endogenous rhythms does not impact on the

hypothalamopituitary axis, but perhaps on mechanisms activating GHRH

Pulsatile hormone release in relation to the internal sleep structure in sleeping sickness

Pulsatile hormone secretion appears to be a common characteristic of several endocrine systems and, through frequent blood sampling (every 10 min), some well-defined ultradian rhythms have been identified with periodicities of about 90-100 min similar to that of the REM-NREM sleep cycles, suggesting that both processes could be temporally linked [12]. Cortisol, little influenced by sleep and rather controlled by an internal oscillator, exhibits a temporal association with slow wave sleep which invariably occurs during the descending phases of the secretory pulse [13]. Prolactin is strongly influenced by sleep, increasing during sleep even when this is displaced, and REM sleep onset is associated with a low secretory rate of prolactin [14]. Renin, a key enzyme of the renin-angiotensin system, is related to a specific stage of sleep with nocturnal oscillations in PRA mirroring changes in the NREM-REM sleep cycle, such that PRA can be considered as a biological marker of sleep stage alternation [15, 16]. The sleeping sickness model provided an opportunity to further test this association between hormone pulses and sleep stages under conditions of disrupted REM-NREM sleep cycles in sick patients.

As well as examining the same subjects in the previous section, an additional 6 patients from the Congo were also included. Continuous withdrawal of small quantities of blood via a catheter occurred over 24 h and analysis of cortisol, prolactin and PRA every 10 min. These analyses were then compared to polysomnographic recordings of sleep and the temporal relationship of the pulses of these hormones to sleep stages examined [7].

In sleeping sickness patients, the temporal organisation of cortisol pulses within the 24h period differed widely. The 24h profiles were characterized by a succession of pulses with a reduced circadian amplitude and a shorter quiescent period, as compared to healthy subjects. However, despite these alterations, the previously described relationship between cortisol and SWS episodes was preserved. SWS remained associated with the declining phases of cortisol pulses even in the most severely ill patients (Fig. 2). Sleep-wake episodes in sleeping sickness patients were fragmented throughout the 24h period in association with attenuated nocturnal prolactin levels and higher daytime levels. Prolactin release remained pulsatile with the same number of pulses per 24 h in both groups. The relationship between prolactin pulses and sleep stages [14] was maintained with REM sleep onset beginning in the non-ascending

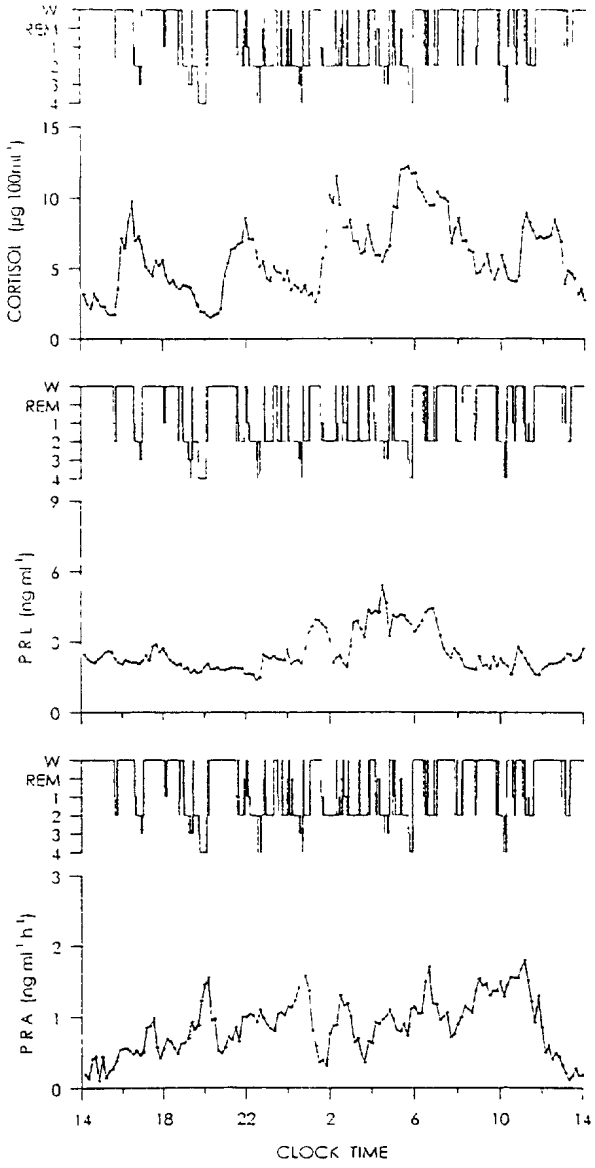

Fig 2. Individual 24h cortisol, prolactin and plasma renin activity (PRA) profiles in one patient with sleeping sickness illustrating the relationship between hormone pulses and sleep stages. As in healthy subjects, slow wave sleep occurs in the descending phases of cortisol pulses (*top panel*), the onset of REM sleep occurs in the descending phases of prolactin pulses (*middle panel*). SWS occurs in the ascending phases of PRA oscillations (*bottom panel*)

portions of the pulses in both healthy subjects and patients, despite the disruptions in the rhythms of both sleep and prolactin in the latter group (Fig 2)

A significant rhythm in PRA was observed in healthy subjects with increases during nocturnal sleep, and it was not evident in the patients The mean levels of PRA showed a general ascending trend over 24 h in sleeping sickness which was not related to any trend in sleep quality Pulse analysis of the individual profiles revealed that in healthy subjects the number of oscillations was significantly greater when asleep rather than awake in contrast to the sleeping sickness patients where oscillations in PRA were distributed throughout the 24h period The previously described relationship between oscillations in PRA and alternations in internal sleep structure [15, 16] was observed in both healthy subjects and patients, with increasing levels of PRA occurring during SWS episodes and decreasing levels during REM sleep In the 6 patients studied, 32 of 33 SWS episodes recorded were linked to significant increases in PRA, and 40 of 42 REM sleep episodes occurred when PRA was declining [7] Thus, the normal relationship between PRA and sleep structure is preserved in sleeping sickness (Fig 2)

Conclusions

The two approaches described above demonstrate that there are profound disruptions in the circadian rhythms of cortisol, prolactin, GH and PRA in human African trypanosomiasis. These studies of the sleeping sickness disease model have confirmed that 24h variations in prolactin, GH and PRA are not circadian in nature but are principally related to sleep Despite the disorganization of the 24h rhythms, the relationship between hormonal pulses and internal sleep structure found in healthy subjects was preserved in sleeping sickness. The SWS episodes remained associated with increases in GH and decreases in cortisol, and REM sleep onset with the non-ascending phases of prolactin pulses. Similarly, the association between PRA oscillations and NREM-REM sleep cycles, when long enough, persisted in all patients.

Buguet et al. [1] demonstrated that the disappearance of the circadian variation of the sleep-wake cycle was related to the severity of clinical progression of the disease Our findings demonstrate that disruptions in the mechanisms controlling the sleep-wake cycle also extend to other circadian rhythms supporting the hypothesis that the networks of the biological clock are altered in the course of the disease. Such disappearances of circadian rhythms have been observed in animals after lesions of the suprachiasmatic nucleus [17] and dysregulation of gene expression in the suprachiasmatic nucleus has been shown in trypanosome-infected rat brains [18]

Thus, the pathogenesis of the disease, particularly in its advanced state, appears to be related to dysfunctions of the circadian pacemaker. However, the temporal relationship between pulsatile hormone release and specific sleep stages remains persistent, emphasizing the strength of the processes coupling hormonal release and the internal sleep structure and its independence of the circadian timing system.

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