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SLEEP AND THYROID FUNCTION: FURTHER STUDIES IN HEALTHY YOUNG MEN*

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HEALTHY adults differ widely in the amount or proportion of delta-wave sleep (stages 3 and 4) which they obtain at night—the sleep in which high amplitude, low frequency waves (delta-waves) dominate the electroencephalogram. The frequent temporal association between growth hormone secretion and delta-wave sleep has led some investigators to believe that this particular kind of sleep is especially important for anabolism and physical restoration after the exertion and catabolism of the day [1].

However, the functions of sleep, particularly of delta-wave sleep, in relation to the activities of wakefulness, remain uncertain [2]. The results of several investigations have been inconsistent in their attempts to relate energy expenditure during the day to the amount of delta-wave sleep at night [3–7]. Delta-wave sleep is reported to vary also with isocaloric changes in diet [8], and to be increased by fasting for several days [9] and after sleep deprivation [10]. Delta-wave sleep is decreased in old age [11], in some psychiatric and medical illnesses [12], and with the use of some hypnotic drugs [13].

In addition, the level of thyroid function may be important. Delta-wave sleep is reported to be reduced in hypothyroidism, increasing as the patients recover with replacement therapy [14]. In some thyrotoxic patients the proportions of delta-wave sleep and the plasma levels of growth hormone are increased and slowly decline after the patients become euthyroid [15]. However, the distinguishing characteristic of other thyrotoxic patients' sleep has been difficulty in falling asleep initially and restlessness with frequent body movements during sleep, but not an increase in delta-wave sleep [6]. In a preliminary investigation, Johns *et al.* [17, 18] reported that differences in the thyroid function of normal subjects, as assessed by the Free Thyroxine Index (FTI), were positively related to the amount of delta-wave sleep and negatively related to the proportion of rapid-eye-movement (REM) sleep at night. The more direct effects of the level of thyroid function on sleep have been studied in rats injected either with thyroxine to make them hyperthyroid, or with propyl-thiouracil to make them hypothyroid [16]. With hyperthyroidism, the rats' sleep became more fragmented by periods of wakefulness, delta-wave sleep was decreased rather than increased, and the percentage of REM-sleep was increased; consequently the REM–NREM sleep cycles became shorter. Hypothyroidism had the opposite effects on REM sleep and sleep-cycle length.

Thus, the level of thyroid function has not been related consistently to the characteristics of sleep under different circumstances. The present investigation was intended to elucidate some of these previous inconsistencies.

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METHODS

Subjects

The experimental subjects were 15 healthy, male university students aged 20–22 yr, who were paid volunteers, selected without detailed knowledge of their sleep habits or thyroid function, but with their informed consent. Their diet and usual daily routines were unchanged except that they slept in the sleep laboratory for 3 consecutive nights each, at about the same times as they would have slept at home. One subject was studied for a second time using the same methods when he was febrile, suffering from infectious mononucleosis, and a third time a year later when he was quite well.

Sleep recordings

All-night recordings were made of the electroencephalogram (EEG), electrooculogram and electrocardiogram (ECG). Sleep stages were scored visually in 40-second periods using standardized criteria [19]. The first night in the laboratory was an adaptation night and the sleep results were discarded. Sleep latency was measured from the time when lights were put out until the appearance of the first spindle in the EEG of stage 2 sleep. Sleep efficiency was calculated from the total duration of sleep as a percentage of the time available for sleep each night. The length of REM-NREM sleep cycles was the average interval, in minutes, between the onset of the first 3 consecutive REM-sleep periods each night. The heart rate was calculated from the time taken by 20 consecutive R-waves in the ECG and was measured about once every 3 min during the night. For the purposes of this experiment, the mean heart rate for a particular night's sleep was the average of all such measurements after sleep onset until the first REM period, and then during each period of NREM sleep in the next 3 sleep cycles. This covered $5\frac{1}{2}$–$7\frac{1}{2}$ hr from sleep onset in different subjects.

Blood samples

Venous blood samples were collected each morning soon after the subjects awoke and before they got out of bed. Serum was frozen and assays were performed later in duplicate for the total serum thyroxine (T_4) and triiodothyronine (T_3) uptake (Thyopac-4 and Thyopac-3 kits respectively, manufactured by Radiochemical Centre, Amersham, Bucks.) The mean Free Thyroxine Index (T_4/T_3 uptake) over the 3-day period was calculated for each subject. The FTI is closely related to absolute measurements of the free thyroxine concentration in serum and makes allowances for differences in the protein binding capacity of each subject [20].

Statistical methods

The sleep latencies were log-normally distributed and were normalized by transformation to natural logarithms. Thus, geometric means were calculated for the sleep latencies within and between subjects whereas arithmetric means were used for all other variables. Two-way analysis of variance (2 nights and 15 subjects) was performed for each variable. Sleep latency was the only variable to show significant differences between nights ($p < 0{\cdot}05$). It was the differences between subjects, based on the results for the second and third nights, which were of primary concern here. Product–moment correlation coefficients were calculated between the means for the FTI and for each sleep variable and heart rate in turn.

RESULTS

The mean results for each subject, and for subject 15 when febrile, are shown in Table 1. There were statistically significant differences between subjects in terms of their thyroid function, the delay before falling asleep initially, the percentages of stage 1, stage 2 and delta-wave sleep (stages 3 and 4), the total duration of sleep, the number of times each subject was awake or drowsy (in stage 1) per hr of sleep, and the heart rate during sleep. Delta-wave sleep was reported as a percentage of the total sleep as well as an absolute number of min per night, and the differences between subjects were significant with both methods. A large subject × night interaction for the percentage of REM sleep meant that for this variable the differences between subjects were not significant; similarly, with sleep efficiency and the length of REM–NREM sleep cycles. The average amounts of delta-wave sleep in different subjects varied between 62 and 137 min per night; the total duration of sleep varied between 333 and 493 min. The overall means for the sleep results were very similar to those reported for other healthy young adults [21]. The mean heart rate during sleep varied between 47 and 65 beats per min in different subjects.

The FTI values covered much of the normal range which is 0.60–1.50. Indeed, the lowest value would be considered abnormal if there had been other signs or symptoms of thyroid insufficiency.

Relationships between sleep and thyroid function

None of the correlation coefficients between the FTI and each of the other variables was statistically

significant, even at the 0.1 probability level (13 degrees of freedom). Although not statistically significant, the amount of delta-wave sleep was negatively correlated with FTI ($r = -0.274$) rather than positively correlated as in the previous investigation [17]. Differences in thyroid function were unrelated also to the degree of fragmentation of sleep by periods of wakefulness or drowsiness ($r = -0.038$), or to the heart rate ($r = 0.069$). Since the percentage of REM-sleep and the length of REM–RNEM cycles did not differ significantly between subjects it is less surprising that they, too, were unrelated to thyroid function.

Effects of fever

When subject 15 was febrile with infectious mononucleosis he took 1.0 g of paracetamol three times daily on the second and third days of the experiment. Nevertheless, his oral temperature was at least 38°C, both at night and in the morning, he had a moderate tachycardia and his FTI was increased. His average temperature when well was 36.2° at bed-time and 35.9°C in the morning. In comparison with his healthy state, his sleep with the fever was of similar duration but was more frequently interrupted by wakefulness or drowsiness, and both REM sleep and delta-wave sleep were reduced whereas stage 2 was increased. This subject had the most delta-wave sleep of all when he was well. To confirm that this was a long-term characteristic of his sleep he was studied a third time when well a year later. His sleep then was very similar to that recorded previously when he was well and included an average of 128 min of delta-wave sleep per night.

DISCUSSION

The results do not support the conclusions from an earlier investigation in healthy young men in whom the FTI was related positively to the amount of delta-wave sleep and negatively to the percentage of REM sleep each night [17]. Nor was it confirmed that the level of thyroid function was related to the average length of REM–NREM sleep cycles [18]. The reason for these inconsistencies in the results of similar investigations is unclear. The visual scoring of stages 3 and 4 sleep is subject to error, but this is unlikely to be so large as to explain the substantial differences between subjects which continue across nights. In the earlier investigation the sleep stages were analysed by an automatic, analogue EEG analyser [22] which was probably more reliable than the visual scoring methods used in the other investigations.

There were only 6 subjects in the earlier investigation (compared with 15 here) and the relationship between sleep and FTI was derived from differences between subjects as well as within the same subject from day to day. The FTI was measured just before going to bed at night and may have been influenced by the activities of the day, more than was the case with the FTI measured after the night's sleep and before getting out of bed, as in the present study. However, the FTI did not vary consistently with the time of day in the earlier investigation. Much of the relationship between sleep and FTI was based on changes in both variables from day to day in only 3 of the 6 subjects. Why such changes should occur in some subjects but not in others remains unclear, but they do suggest the existence of some unknown factor which can influence both sleep and thyroid function, perhaps indirectly.

The inconsistency of the relationship between sleep and thyroid function, within the normal range and beyond it [14–16], makes it unlikely that sleep varies simply in relation to changes in metabolic rate. Hypermetabolism induced artificially by injecting thyroxine into rats for several days [16] or by injecting pyrogens into humans [23] is usually associated with sleep which is fragmented by periods of wakefulness or drowsiness and which includes less REM sleep, less delta-wave sleep and more stage 2 sleep than normal. Fever which occurred during the natural course of infectious disease in one subject of the present investigation had similar effects. The rebound in delta-wave sleep which might be expected subsequently during recovery sleep [10] did not occur after fever induced in humans [23].

TABLE 1.—THE FREE THYROXINE INDEX, MEAN CHARACTERISTICS OF SLEEP AND HEART RATE IN EACH SUBJECT. THE OVERALL MEANS, THE STATISTICAL SIGNIFICANCE OF DIFFERENCES BETWEEN SUBJECTS (ANALYSIS OF VARIANCE) AND THE RESULTS FOR SUBJECT 15 WHEN FEBRILE ARE AT THE BOTTOM. GEOMETRIC MEANS WERE CALCULATED FOR SLEEP LATENCY, ARITHMETRIC MEANS FOR OTHER VARIABLES

Subject No.	FTI	Sleep latency (min)	Sleep in stage— 1 (%)	2 (%)	3 + 4 (%)	REM (%)	3 + 4 (min)	Total sleep (min)	Awake + stage 1 (times/hr)	Sleep efficiency (%)	REM–NREM cycle length (min)	Heart rate (b/min)
1	0.83	78	1.1	44.9	35.0	19.0	115	333	0.59	75.8	115	65.4
2	0.91	12	1.7	59.1	19.4	19.8	85	435	0.55	95.7	128	58.2
3	0.99	8	0.8	54.0	14.7	30.5	62	418	0.00	90.8	102	52.4
4	0.97	13	1.5	46.3	25.6	26.6	114	444	1.08	91.7	87	52.5
5	0.97	14	1.6	49.7	18.7	30.2	91	486	0.62	95.0	112	54.8
6	0.78	10	1.5	57.5	16.7	24.3	82	493	0.49	97.3	82	56.5
7	0.73	6	1.3	53.2	18.5	27.0	84	454	0.93	95.9	98	46.7
8	0.88	33	1.5	54.3	20.7	23.5	98	474	0.49	90.0	109	54.1
9	1.12	15	3.9	55.2	13.2	27.7	65	493	1.16	93.7	96	52.9
10	1.21	13	3.4	53.8	20.1	22.8	89	441	1.43	94.0	88	58.1
11	0.95	15	1.5	48.7	23.0	26.8	100	435	0.91	95.5	88	53.2
12	0.48	8	2.3	56.6	20.8	20.4	87	415	1.59	94.4	92	53.9
13	0.77	10	2.5	57.9	19.6	20.0	93	472	1.79	95.5	104	47.4
14	0.73	29	0.8	54.1	20.8	24.4	95	458	0.34	89.6	87	56.6
15	0.72	7	1.2	44.2	29.3	25.3	137	467	0.39	98.1	113	59.6
Overall means	0.87	13	1.8	52.6	21.1	24.6	92.9	447.9	0.82	92.9	99.8	54.8
Signif. of differences between Ss	< 0.001	< 0.01	< 0.01	< 0.05	< 0.01	N.S.	< 0.01	< 0.01	< 0.01	N.S.	N.S.	< 0.001
15, febrile	0.85	9	4.2	55.5	23.9	16.4	109	454	1.26	93.6	99	78.4

It may be that the differences in thyroid function which we have measured at rest in the morning did not closely reflect differences in the subjects' general metabolic rate which was not measured. The lack of a significant relationship between their sleeping heart rates and thyroid function would be consistent with that contention. However, differences in heart rate were not without significance from the point of view of the subjects' sleep. The higher the heart rate after going to bed at night the longer the subject took to fall asleep, as reported previously for the same subjects. [24].

The subjects' diet and levels of energy expenditure during the day were not accurately assessed. However, it was considered unlikely that they would be a major cause of the consistent differences between the subjects' sleep. Experimental manipulation of diet and exercise in healthy young adults [3–8] has produced changes in delta-wave sleep (and even then not consistently) which were relatively small in comparison to the large differences occurring naturally between subjects of similar age. It has been suggested also that a high visual load during the day increases delta-wave sleep at night [25], but further investigation of this point is required before it could be invoked to explain consistent differences between normal subjects.

Although detailed results have not been presented here, factor analysis of the variables used to describe the present subjects' sleep confirmed an earlier finding among different subjects that the amount of delta-wave sleep on a particular night is not closely related to other characteristics of sleep such as the delay before its initial onset, the total amount of sleep obtained, its subjective quality, its fragmentation by periods of wakefulness, and the proportion of REM sleep [26]. More experimental work will be required before it could safely be said that the functions of the various stages of sleep and their relationship to wakefulness are understood [2].

SUMMARY

The results of previous investigations, although sometimes inconsistent with one another, suggest that variations in thyroid function, even within the normal range, influence the characteristics of sleep at night. Fifteen healthy young men each slept for 3 consecutive nights in the sleep laboratory where continuous recordings of the electroencephalogram, electrooculogram and electrocardiogram enabled the stages of sleep and the sleeping heart rate to be measured. The average Free Thyroxine Index (FTI) was determined for each subject from venous blood collected each morning. There were highly significant differences between subjects for the FTI, heart rate and several parameters of sleep. However, none of correlations between the FTI and the other variables in turn even approached statistical significance. In particular, differences in the amounts of delta-wave sleep obtained at night by normal subjects do not directly reflect differences in their level of thyroid function and probably not in their general metabolic rate.

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