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SHORT COMMUNICATION

Variations in thyroid function and sleep in healthy young men

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Summary

1. The total serum thyroxine, tri-iodothyronine resin uptake, total plasma protein concentration and the free thyroxine index (FTI) were determined repeatedly, at 07.15, 13.00 and 22.30 hours over 4 days, in six healthy young men.

2. There was a significant diurnal variation in the total serum thyroxine concentration but this reflected changes in the binding capacity of serum proteins and in the total plasma protein concentration which could be explained by changes of posture. The FTI, and presumably therefore the free thyroxine concentration, varied very little with the time of day.

3. The FTI varied significantly from day to day in three of the six subjects, presumably as a result of changes in thyroxine secretion because the serum binding capacity did not vary.

4. The subjects' sleep at night was assessed by electro-encephalogram. . On days when the FTI was highest for a particular subject his sleep was more fragmented by spontaneous awakenings, the amount of rapid-eye-movement sleep was reduced and that of delta-wave sleep was increased, implying that variations in thyroid function over a period of a few days in healthy subjects can be of physiological significance. The cause of these variations is uncertain.

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Introduction

The thyroid function of healthy subjects is usually considered to be constant, at least over a period of a few days, whereas there is a known circadian rhythm in the rate of secretion of thyroid hormones (Nicoloff, 1970), in the plasma concentration of thyrotrophin (Patel, Alford & Burger, 1972) and in the total serum thyroxine (T_4) concentration (De Costre, Buhler, De Groot & Refetoff, 1971). However, much of the variation in total T_4 results from postural changes in the concentration of plasma proteins, which bind thyroid hormones (De Costre *et al.*, 1971). Slower variations in thyroid function, from day to day, have received little attention (Danowski, Hedenberg & Freeman, 1949).

We have made repeated measurements of the free thyroxine index (FTI) in healthy young men to determine if this measure of thyroid function varies over a period of 4 days. The FTI[2] is the product of the total serum T_4 concentration and the tri-iodothyronine resin uptake (T_3RU), a measure of the serum binding capacity, and is highly correlated with direct measurements of the free serum T_4 concentration (Clark & Horn, 1965; Stein & Price, 1972). Because the FTI makes allowance for

[2] Abbreviations: FTI, free thyroxine index; T_4, serum thyroxine; T_3RU, tri-iodothyronine resin uptake.

variations in serum binding capacity it should not be affected by changes of posture.

In order to ascertain if there are physiologically significant variations in FTI from day to day in healthy subjects, we have related the FTI each night to objective measurements of the subject's level of sleep. Clinical hypo- or hyper-thyroidism is known to influence sleep (Kales, Heuser, Jacobson, Kales, Hanley, Zweizig & Paulson, 1967; Dunleavy, Oswald, Brown & Strong, 1974). Do smaller variations in thyroid function, within the normal range, between different subjects and within the same subject from day to day, also relate to the level of sleep?

Methods

Six healthy male medical students, aged 21–24 years, volunteered to sleep in the laboratory on 4 consecutive nights, although going about their usual activities during the day. No medication, drugs or alcohol were permitted.

Venous blood was collected just before going to bed at night (at approx. 22.30 hours), upon waking up but while still lying in bed in the morning (07.15 hours) and, in three subjects, in the middle of the day (13.00 hours). Total serum T_4, T_3RU and total plasma proteins were assayed in duplicate. All samples from a particular subject were assayed together and assays were repeated if duplicates differed by more than 10%. Total T_4 was assayed with a commercial kit (Tetralute, Ames Co.), and T_3RU by a modification of the method of Taylor, Winikoff & Davies (1964). The coefficient of variation for FTI determinations was 0·04.

All-night recordings of the electroenecephalogram and of eye movements enabled the pattern of sleep and wakefulness to be measured objectively in terms of the usual stages of sleep (Johns, 1971). The analysis of sleep recordings, the FTI determinations and the plasma protein assays were performed without knowledge of the other results.

The statistical significance of differences in the total T_4, T_3RU, FTI and plasma proteins at different times of the day was tested by the paired *t*-tests. Variations from day to day were tested by two-way analysis of variance (day and time of day effects) in each subject. Relationships between the FTI and the level of sleep each night were determined by analysis of covariance within and between subjects (Snedecor & Cochran, 1967).

Results

Diurnal variations

There were highly significant diurnal variations in the total T_4 and total protein concentrations and in T_3RU, amounting to approximately 12% of the mean value for each day (Table 1). Total T_4 and total protein concentrations were lowest in the morning (before getting out of bed), increased to a maximum in the middle of the day and then often fell slightly, but not significantly, at night. Diurnal variation of T_3RU was similar, but the lowest values (i.e. the highest binding capacity) occurred in the middle of the day when total T_4 was highest. These variations were observed in all subjects. In contrast, the FTI did not vary significantly with the time of day.

Variations from day to day

Analysis of variance within each subject showed that there were statistically significant ($P<0·05$) variations in FTI from day to day in three (subjects A, D and E) of the six subjects. Over the 4 days period the mean FTI for each day varied by 0·7 in subjects D, E and F and by 1·0 in subject A, less in subjects B and C. Variations in FTI arose from changes in total T_4 rather than in the serum binding capacity. Only subject B showed a significant change in T_3RU and in total protein concentration from day to day but his FTI did not vary.

The FTI at night was related significantly to the characteristics of the ensuing sleep, analysis of covariance within subjects (removing the effect of differences between subjects) showing that a high FTI in a particular subject was associated with sleep more disturbed by awakenings ($P<0·05$), a decrease in the amount of rapid-eye-movement (REM) sleep, and an increase in delta-wave sleep ($P<0·01$), when compared with observations on other nights.

Discussion

We agree with De Costre *et al.* (1971) that there is a circadian rhythm in the total serum T_4 but not in the free T_4 concentration, which we measured indirectly by means of the FTI. Postural changes, with haemodilution when supine and haemoconcentration when erect, can explain most of our diurnal variation in total T_4, plasma proteins and

TABLE 1. *Total serum thyroxine (T_4), tri-iodothyroxine resin uptake (T_3RU), total plasma protein concentration and free thyroxine index (FTI) measured two or three times per day for 4 days in six subjects*

The mean values of differences between different times of the day (22.30, 07.15 and 13.00 hours) are shown with their statistical significance, tested by two-tailed *t*-tests for paired observations.

Subject	Day no.	Total T_4 (nmol/l)			T_3RU (%)			Total proteins (g/100 ml)			FTI		
		22.30	07.15	13.00	22.30	07.15	13.00	22.30	07.15	13.00	22.30	07.15	13.00
A	1	90	85	—	89·3	101·9	—	7·0	6·5	—	4·1	4·4	—
	2	89	84	—	92·7	104·7	—	6·5	7·8	—	4·2	4·4	—
	3	94	85	—	96·9	114·0	—	7·9	7·2	—	4·7	4·8	—
	4	85	75	—	90·6	98·2	—	7·7	6·9	—	3·9	3·7	—
B	1	75	67	—	91·5	99·9	—	8·5	8·5	—	3·5	3·4	—
	2	67	57	—	98·8	104·2	—	8·2	8·1	—	3·4	3·0	—
	3	70	66	—	98·8	106·2	—	8·0	7·3	—	3·5	3·5	—
	4	57	63	—	102·2	105·4	—	7·1	7·1	—	3·0	3·4	—
C	1	101	99	—	96·4	107·0	—	7·8	6·8	—	4·9	5·4	—
	2	105	95	—	95·4	102·2	—	8·8	6·8	—	5·1	4·9	—
	3	107	105	—	93·4	97·7	—	8·7	6·9	—	5·0	5·2	—
	4	95	105	—	91·0	103·8	—	8·0	7·0	—	4·4	5·5	—
D	1	111	103	103	90·4	95·3	90·2	8·6	7·8	9·4	5·1	5·0	4·7
	2	93	88	93	97·6	97·3	92·8	8·2	7·1	8·8	4·6	4·3	4·4
	3	89	84	94	91·5	97·3	92·3	8·4	6·8	8·8	4·1	4·1	4·4
	4	90	81	90	92·1	100·7	93·2	8·1	7·2	8·9	4·2	4·1	4·3
E	1	89	88	101	90·5	97·4	87·7	7·1	6·7	7·5	4·1	4·3	4·5
	2	97	92	105	93·4	95·1	84·1	7·0	6·9	8·3	4·6	4·4	4·5
	3	111	97	117	88·6	92·0	86·0	6·6	7·2	7·8	5·0	4·5	5·1
	4	112	97	108	94·6	97·3	89·0	7·3	7·2	7·4	5·4	4·8	4·9
F	1	101	90	89	92·9	96·3	88·7	8·7	8·2	8·6	4·7	4·4	4·0
	2	90	79	89	91·6	101·5	89·3	8·9	7·7	8·4	4·2	4·1	4·0
	3	84	71	76	89·7	100·2	91·8	8·5	7·5	8·2	3·8	3·6	3·6
	4	79	88	97	92·8	96·8	95·2	8·4	7·7	8·3	3·7	4·3	4·7
Overall mean		90·9	85·2	96·8	93·45	100·52	90·03	7·92	7·29	8·37	4·30	4·31	4·43

Mean of differences between times of day	T_4	T_3RU	Total protein	FTI
22.30–07.15 hours	−6·5 ($P<0·001$)	+7·07 ($P<0·001$)	−0·63 ($P<0·0001$)	+0·01 ($P>0·8$)
07.15–13.00 hours	+9·5 ($P<0·001$)	−7·24 ($P<0·001$)	+1·03 ($P<0·001$)	+0·10 ($P>0·2$)
13.00–22.30 hours	−2·4 ($P>0·1$)	+3·22 ($P<0·05$)	−0·49 ($P>0·05$, $P<0·10$)	+0·04 ($P>0·6$)

T_3RU, as the morning blood samples were taken before the subjects arose from bed whereas the later samples were taken after standing or sitting for several hours. However, there was a slight fall both in total T_4 and in total plasma protein, and a corresponding increase in T_3RU, between 13.00 and 22.30 hours that cannot readily be explained by postural changes. Only the increase in T_3RU late in the day was statistically significant, but these results are consistent with reports that part of the diurnal variation in the plasma protein concentration is independent of postural change (Renbourn, 1947; De Costre *et al.*, 1971).

In three subjects the FTI varied by 16–20% of their mean values over 4 days. Since it was the total T_4 concentration rather than the binding capacity of serum proteins which brought about this change, it appears that the secretion rate of thyroid hormones varied from day to day. The cause of this variation in healthy young men is uncertain. The physiological significance of this variation is suggested by our finding that changes in FTI were paralleled by changes in the objective characteristics of sleep. Thyroid function varied with the amount of delta-wave sleep in a manner similar to that reported for thyroid disease (Dunleavy *et al.*, 1974). Details of this relationship and its causal nature are being investigated further.

We conclude that accurate assessment of a subject's mean level of thyroid function requires several measurements to be made over a few days. Changes of posture do not affect the FTI but do affect the total serum T_4 and the serum binding capacity.

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