Birmingham Medical Research Expeditionary Society 1977 Expedition: Thyroid function and acute mountain sickness

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Summary

In a study of 17 subjects plasma-thyroxine-binding globulin and plasma thyroxine concentrations rose during a high altitude trek. An early and sustained rise in plasma reverse triiodothyronine occurred independently of changes in plasma thyroxine and was probably related to physical exertion. Similar changes in thyroid function were found in subjects most affected and least affected by acute mountain sickness.

Introduction

Thyroid function is an important determinant of oxygen consumption and might be expected to alter in response to the hypoxia of high altitude. Studies in normal subjects above 3000 m have shown rises in total serum thyroxine (Surks, Beckwith and Chidsey, 1967; Kotchen *et al.*, 1973). The finding of normal serum thyroid stimulating hormone levels, both basally and in response to thyrotrophin releasing hormone (Rastogi *et al.*, 1977) suggests that the rise in serum thyroxine is not due to increased pituitary drive. Measurements of serum thyroxine-binding capacity at high altitude have been conflicting; a rise being found by Surks (1966) and no change by Rastogi *et al.* (1977).

Thyroid function has not previously been studied in acute mountain sickness (AMS) so the opportunity was taken of measuring daily basal serum thyroid hormone levels during a high altitude trek and related the findings to the development of AMS. In addition to thyroxine (T_4) and triiodothyronine (T_3), plasma 3,3',5'-triiodothyronine - reverse T_3 (rT_3) and thyroxine binding globulin (TBG) were measured by specific immunoassays.

Methods

Plasma was taken daily from 17 healthy fasting male subjects on the first 13 days of a high altitude trek. Plasma T_4 and T_3 were measured by specific radio-immunoassays with normal reference range of 60-160 nmol/l and 1.6-3.4 nmol/l respectively (Black *et al.*, 1975). Plasma rT_3 was measured as described by Griffiths, Black and Hoffenberg (1976)

with a normal reference range of 0.4-0.9 nmol/l and plasma TBG by rocket immune electrophoresis (Bradwell *et al.*, 1976) with a reference range of 6-16 mg/l for normal males. The significance of changes compared with baseline on day 1 or 2 has been assessed using Student's paired *t*-test.

Results

Plasma T_4 levels rose at an altitude ≥ 3505 m without any significant change in plasma T_3 (Table 1). In the earlier part of the trek plasma T_3 tended to fall. There was a highly significant rise in rT_3 well above the normal range on the second day. This raised level was maintained throughout the trek with a tendency to increase further at high altitude (Fig. 1). Plasma TBG rose with increasing altitude

FIG. 1. Plasma rT_3 (mean $\pm$ s.e. mean) $n=17$ except where stated. The dotted lines indicate the upper and lower limits of the normal range. The levels on days 2-12 inclusive were significantly higher than on day 1 ($P < 0.001$). The levels on days 4, 5 and 6 were significantly lower than on day 2 ($P < 0.01$, < 0.05 , < 0.001 respectively) and on days 11 and 13 were significantly higher than on day 2 ($P < 0.01$ and < 0.05 respectively). Comparison was made using the paired *t*-test.

TABLE 1. Plasma thyroid hormones, thyroxine-binding globulin (TBG) and albumin levels. Mean values: s.e. mean in parentheses

Day	1	2	3	4	5	6	7	8	9	10	11	12	13
Altitude (metres)	884	1458	1494	2835	1189	2012	2586	2713	3505	3505	4115	5029	5029
T ₄ nmol/l	92 (7.5)	97 (5.3)	95 (5.0)	96 (6.3)	94 (6.3)	93 (4.4)	97 (6.3)	97 (6.0)	95 (7.3)	104 ^a (7.0)	110 ^b (7.3)	112 ^b (7.7)	116 ^c (7.0)
T ₃ nmol/l	2.80 (0.15)	2.50 ^a (0.12)	2.40 (0.15)	2.41 ^b (0.15)	2.36 ^b (0.13)	2.45 ^b (0.13)	2.42 ^a (0.13)	2.56 (0.14)	2.43 ^b (0.12)	2.53 (0.16)	2.84 (0.18)	2.63 (0.12)	2.65 (0.13)
rT ₃ nmol/l	0.71 (0.08)	2.27 ^c (0.11)	2.30 ^c (0.14)	1.89 ^c (0.17)	2.0 ^c (0.11)	1.9 ^c (0.11)	2.29 ^c (0.09)	2.14 ^c (0.10)	2.09 ^c (0.12)	2.31 ^c (0.11)	2.74 ^c (0.13)	2.49 ^c (0.12)	2.67 ^c (0.15)
TBG mg/l	8.6 (0.54)	9.2 (0.50)	9.3 (0.46)	9.2 (0.48)	9.5 (0.51)	9.6 ^a (0.39)	10.0 ^a (0.43)	10.0 ^a (0.54)	10.1 ^b (0.59)	10.8 ^a (0.52)	11.4 ^c (0.56)	12.1 ^c (0.55)	11.8 ^c (0.54)
Albumin g/l	36.2 (0.66)	36.5 (0.33)	37.1 (0.70)	37.2 (0.75)	34.2 ^a (0.49)	34.5 ^a (0.53)	34.0 ^b (0.46)	34.5 ^b (0.54)	36.0 (0.61)	35.7 (0.62)	37.1 (0.75)	37.7 (0.54)	37.0 (0.55)

^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.001$ paired t test comparison with levels on day one.

FIG. 2. Plasma TBG/albumin (mean ± s.e. mean) $n = 17$ except where stated. Significant elevation was found after day 5 ($P < 0.05$) with the greatest rise at high altitude on days 11, 12 and 13 ($P < 0.001$) on paired t -testing compared with day 1.

(Table 1) and when corrected for changes in albumin the rise was first seen the day after reaching 2835 m (Fig. 2). The rise in TBG was greater than the rise in T₄. On correcting plasma T₄ for changes in plasma TBG it was found that plasma T₄ tended to fall with increasing altitude (Fig. 3).

The 5 subjects most affected by AMS did not differ significantly from the 5 subjects least affected (Table 2). The plasma T₃ levels tended to be higher in those most affected but the elevation of plasma T₃ seen on day 11 in the affected group was due to one subject immediately before descent, leaving 4 subjects for analysis on days 12 and 13.

FIG. 3. Plasma T₄/TBG ratio (mean ± s.e. mean) $n = 17$ except where stated. The ratio on days 7 and 12 was significantly lowered on paired t -testing in comparison with day 1 ($P < 0.05$).

TABLE 2. Plasma thyroid hormones, thyroxine-binding globulin (TBG) and albumin levels in acute mountain sickness

Day	8	9	10	11	12	13
T ₄ nmol/l						
*	95	95	108	106	108	116
†	93	93	92	99	105	106
T ₃ nmol/l						
*	2.76	2.44	2.78	3.16	2.58	2.26
†	2.13	2.19	2.14	2.47	2.31	2.49
rT ₃ nmol/l						
*	2.18	2.16	2.10	2.64	2.63	2.71
†	2.24	2.12	2.42	2.72	2.46	2.73
TBG mg/l						
*	9.7	9.7	11.3	11.6	11.6	11.0
†	10.3	10.0	10.1	11.4	11.0	11.3
TBG/albumin						
*	0.278	0.280	0.320	0.308	0.326	0.308
†	0.265	0.268	0.265	0.310	0.288	0.302
T ₄ /TBG						
*	10.35	9.92	9.7	9.3	9.25	10.5
†	9.34	9.86	9.04	8.86	9.58	9.3

Mean of the 5 most affected* and the 5 least affected† by acute mountain sickness.

Discussion

The changes found during this trek might be due to the effect of exertion, stress, changes in environmental temperature in addition to the effect of high altitude. Physical exertion is the most likely explanation of the striking elevation in rT₃ which was seen so early in the trek. The data suggest that plasma T₄ is not effectively increased so that the rise in rT₃ must be due to a switch of deiodination from T₃ to rT₃ or to decreased metabolic clearance of rT₃ as, for example, found in cirrhosis (Chopra, 1976). An inverse relationship of rT₃ and T₃ has been found in a variety of acute and chronic illnesses (Nicod *et al.*, 1976), postoperatively (Burr *et al.*, 1975) and in starvation (Palmblad *et al.*, 1977).

Alterations in plasma volume are insufficient to account for all the change in plasma TBG concentration and indeed tend to obscure the rise. On correcting TBG for changes in plasma albumin the rise in TBG is more apparent and correlates well with increasing altitude. Albumin (mol. wt approx. 66 500) was chosen for comparison having a similar molecular weight to TBG (approx. 57 000). The rise in TBG was similar in timing and extent to the changes found in haptoglobin and orosomucoid in the same samples (Bradwell, 1979). The continuing rise of these proteins throughout the trek may be due to the effect of either altitude or stress. The rise in plasma TBG was more than sufficient to explain the rise in plasma T₄ and it would seem unlikely that there was a significant increase in free thyroxine as reported by Surks (1966). Indeed Rastogi *et al.*

(1977) found that urinary T₄ excretion fell at high altitude; the failure to find a rise in TBG at altitude by those authors may be due to their indirect method of measurement rather than to the different altitude (3700 m) studied.

The present results suggest that the adaptation of thyroid function to high altitude is not disturbed in subjects prone to AMS.

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