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THYROID HORMONE RESPONSE TO PROLONGED COLD EXPOSURE IN MAN

By C. J. EASTMAN, R. P. EKINS, I. M. LEITH and E. S. WILLIAMS

From the Institute of Nuclear Medicine, the Middlesex Hospital Medical School, London W1N 7RL

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SUMMARY

1. Four men, of ages varying from 23 to 28 years, living at Halley Bay, Antarctica (75° 31′ S, 26° 39′ W), were exposed to a mean air temperature of 6·6° C.

2. The concentration of serum triiodothyronine (T_3) rose significantly by the second day, remained raised, and returned to pre-exposure levels within 2 days of return to a normal environment.

3. The concentration of serum thyroxine (T_4) rose more slowly than did the T_3, reaching a maximum in 3–4 days and also returning to normal within 2 days of return to a normal environment.

4. There was a wide individual variation in the change of concentration of serum cortisol.

INTRODUCTION

Metabolic adaptation to cold is well recognized in animals, especially in small mammals and birds (Whitton, 1970; Chaffee & Roberts, 1971). It is believed that this process involves increased circulating levels of catecholamines and thyroid hormones. In man, however, acclimatization to cold has been difficult to demonstrate, due in part to man's success in avoiding cold stress by behavioural and insulative mechanisms, so that there is usually an inadequate stimulus for cold acclimatization to occur (Edholm & Lewis, 1964). Nevertheless, there is some evidence that man exhibits certain metabolic adaptations during prolonged cold exposure, as illustrated by the increased sensitivity to noradrenaline displayed by Australian men in the Antarctic (Budd & Warhaft, 1966). In addition, increased thyroid hormone turnover (Bass, 1960; Ingbar & Bass, 1967) and elevated serum thyrotrophin (TSH) levels (Raud & Odell, 1969) have been measured in normal men during prolonged cold exposure in the Arctic. However, this evidence has not been corroborated by other studies

which have failed to show any significant changes in serum protein bound iodine (PBI) (Ingbar, Kleeman, Quinn & Bass, 1954; Wilson, 1966; Wilson, Hedner, Laurell, Nosslin, Rerup & Rosengren, 1970; Suzuki, Tonoue, Matsuzaki & Yamamoto, 1967).

In this paper we report the results of a study to evaluate the effect of prolonged cold exposure on circulating thyroid hormone concentrations in man.

METHODS

Four men living at Halley Bay, Antarctica (75° 31′ S, 26° 39′ W) spent 4 days in a cold room where the mean air temperature was 6·6° C. Food and drink were cold and taken *ad libitum*. Activity was restricted to sitting, standing or walking about the room. Each day three of the subjects spent 45 min at +15° C when blood was taken in the Physiology Laboratory. The fourth subject spent 125 min in the laboratory each day.

The subjects were healthy men of European descent, aged between 23 and 28 yr. One subject was in his second consecutive year in the Antarctic while the other subjects had arrived in Antarctica 4 months before the experiment. None of the subjects had previously visited the Antarctic but one had spent a short time in Arctic Canada in 1967. Another had spent 2 days in a cold room (+4° C) in the U.K. in 1969.

Test cold exposure

A room measuring 40 × 18 × 7·5 ft. was used for cold exposure lasting for 4 days during May 1970. Mean air temperature was 6·6° C and wind speed was negligible. The mean relative humidity was 54·5 %. Time was mostly spent sitting or lying. The room was left for washing and blood collection only; one subject also left the room to centrifuge blood specimens. Clothing consisted of a thin shirt and pair of trousers, underpants, a pair of woollen socks, and felt slippers. Each person had a single blanket for sleeping at night, though in practice two subjects sometimes used these during the day as well.

Blood samples were withdrawn by venepuncture at 0, 6, 12, 24, 48, 72 and 96 hr during the cold exposure, and at 2 and 7 days after leaving the cold. Blood sampling was between 10 and 10.30 a.m. except at 6 hr (4 p.m.) and 12 hr (10 p.m.) on the first day. Samples were centrifuged within 24 hr at 2000 rev/min for 20 min and serum separated into plain tubes. Serum samples were then stored in darkness, deep-frozen for nearly 2 yr before serum estimations were done in the U.K.

Laboratory methods

After ethanol extraction of thyroxine from the serum total serum thyroxine (T_4) concentration was measured by a saturation analysis technique, employing thyroxine binding globulin (TBG) as the binding agent. The sensitivity, precision and reproducibility of this assay has been reported previously (Ekins, Williams & Ellis, 1969). Triiodothyronine (T_3) resin uptake was measured using Thyopac 3 Kits (Amersham IM 62). The free thyroxine index (FT4I) was calculated from the T_3 resin uptake and serum T_4 results by dividing the serum concentration of T_4 in ng/ml. by the T_3 resin uptake derived from the Thyopac 3 result. This ratio is proportional to the free T_4 concentration. Total serum triiodothyronine (T_3) concentration was measured in whole serum by a radioimmunoassay method using a specific T_3 antibody and employing 8-anilino-1-naphthalene-sulphonic acid to

inhibit T_3 binding to TBG. The sensitivity of this assay is in the region of 100 pg T_3/ml. of serum and the within assay precision, expressed as 95 % confidence limits for replicate estimations at 1000 pg/ml. and 2000 pg/ml., was ± 60 and ± 100 pg/ml. respectively. The normal range of serum T_3 in healthy, euthyroid adults resident in London is 850–1600 pg/ml. Serum cortisol concentration was measured by a modified protein binding technique (Piyasena, 1972). Serum osmolality was measured by a depression of the freezing point method, using the Advanced Osmometer (Model 63–31). To exclude interassay error all samples for estimation of a specific parameter were included in a single assay. All hormone assay results were corrected for haemoconcentration although this correction was small, the haemoconcentration ranging from zero to 4 %.

Statistical analysis

The *t* test was used to determine the significance of the difference of mean values of hormone concentrations in the cold as compared with corresponding mean values before cold exposure. Ratcliffe (1968) has shown that for the *t* values obtained in this analysis and with a sample size of four even marked deviations from a normal distribution would have negligible effect upon the corresponding values.

RESULTS

The results are set out in Table 1.

Serum T_4 concentration

Each subject exhibited an increase in serum T_4 concentration during the period of cold exposure with peak values being observed on the third day in one subject and on the fourth day in the other three subjects. The mean serum T_4 level on day 4 represented a 24 % increase in serum T_4 concentration over the mean pre-exposure level. This rise in serum T_4 was statistically significant ($P < 0{\cdot}025$). Serum T_4 levels declined to control values in each subject within 48 hr of removal to a warm environment and remained relatively constant over the next 6 days. FT4I values paralleled total serum T_4 estimations in each subject, indicating that the rise in total serum T_4 was accompanied by a similar rise in serum 'free' T_4.

Serum T_3 concentration

A rise in serum T_3 concentration occurred in each subject and preceded the rise in serum T_4 concentration. The mean maximum increase in serum T_3, occurring on the second day of cold exposure, represented a rise in serum T_3 of 14 % above the mean control value. This increase in serum T_3 was statistically significant ($P < 0{\cdot}025$). Serum T_3 concentration declined to pre-exposure levels in each subject within 48 hr of removal to a warm environment.

TABLE 1. Serum assay results

Subject	Serum constituent	Date and time: Exposure to cold — 25 v. 70 10.00	25 v. 70 16.00	25 v. 70 22.00	26 v. 70 10.00	27 v. 70 10.00	28 v. 70 10.00	29 v. 70 10.00	31 v. 70 10.00	5 vi. 70 10.00
M.V.	Total T_4 ng/ml.	70·9	63·6	76·9	70·1	69·1	77·5	92·5	77·0	64·7
	Total T_3 pg/ml.	1370	1390	1485	1561	1586	1670	1720	1566	1740
	Free T_4 index	72·9	60·8	78·2	70·7	69·1	77·5	91·8	77·4	68·0
	Cortisol μg/ 100 ml.	8·5	—	—	5·6	5·8	12·5	15·0	11·1	15·0
S.B.	Total T_4 ng/ml.	85·5	90·0	93·6	88·0	89·6	100·1	114·9	86·9	93·9
	Total T_3 pg/ml.	1720	1703	1752	1787	1776	1830	1730	1580	1790
	Free T_4 index	85·2	90·4	94·1	88·5	86·6	100·4	112·5	93·8	94·1
	Cortisol μg/ 100 ml.	10·25	—	—	6·9	13·5	15·8	11·0	15·5	11·0
C.W.	Total T_4 ng/ml.	85·1	97·0	112·3	97·4	106·7	113·2	109·4	86·2	86·5
	Total T_3 pg/ml.	1540	1780	1639	1647	1880	1748	1624	1510	1580
	Free T_4 index	78·0	86·5	115·0	92·0	98·7	105·5	100·2	81·6	82·6
	Cortisol μg/ 100 ml.	10·8	—	—	6·6	7·8	8·4	8·9	8·3	8·0
I.L.	Total T_4 ng/ml.	98·9	108·7	88·8	95·0	95·3	93·8	103·8	79·6	82·1
	Total T_3 pg/ml.	1620	1693	1465	1680	1897	1704	1980	1455	1316
	Free T_4 index	98·3	101·2	81·6	89·6	87·9	89·1	97·1	83·0	89·2
	Cortisol μg/ 100 ml.	12·5	—	—	15·8	14·9	11·7	10·1	13·1	11·6

Serum cortisol

Serum cortisol concentrations, corrected for haemoconcentration, are included as these represent an index of individual response to the 'stress' of the experimental conditions.

DISCUSSION

This study has demonstrated significant increases in the circulating concentration of thyroid hormones in normal adult males during prolonged cold exposure in the Antarctic. In addition, the rise in serum T_3 and T_4 accompanying cold exposure was followed by a prompt decline to pre-exposure levels on removal to a warm environment. These findings suggest that prolonged cold exposure is a potent stimulus to increased circulating thyroid hormone levels in man. However, it is not clear from these studies whether the rises in serum T_3 and T_4 represent increased production rates of both hormones in response to cold exposure, or whether they are secondary to other cold induced metabolic clearance rates.

The rise in serum T_4 concentration is unlikely to be secondary to a rise in thyroid hormone binding proteins, as estimations of the free thyroxine index revealed significant increases in the unbound or free thyroxine level in each subject during cold exposure. Also, serum osmolality changes (in the cold) were insignificant.

The demonstration of different time courses for the serum responses of T_3 and T_4 during cold exposure was a notable feature of this study. The rise in serum T_3 in each subject reached a mean peak level after 2 days and thence remained relatively constant over the ensuing two days of cold exposure. By contrast, serum T_4 levels rise more slowly reaching a mean peak level on the fourth day of cold exposure. It is interesting that the time course of the rise in serum T_3 in this study parallels the time course in the rise in serum TSH, reported by Raud & Odell (1969), in men exposed to prolonged cold in the Arctic.

In cold acclimatized animals, mechanisms known to affect T_4 secretion include the secretion rate and metabolic clearance rate of T_4, in addition to the dietary bulk and intake of iodine and the faecal and biliary losses of T_4 (Chaffee & Roberts, 1971). The increased T_4 secretion rate (Bauman & Turner, 1967) and fractional turnover rate (Hillier, 1968) displayed by certain cold acclimatized animals suggest that increased thyroid hormone secretion and peripheral utilization are involved in the acclimatization process.

We have shown that the adult human is capable of responding in terms of raised concentrations of circulating T_3 and T_4 to prolonged exposure

to a low environmental temperature. The response is delayed, needing two or more days to develop, in contrast to the rapid rise in circulating TSH concentration when neonates are exposed to a cold stress (Fisher & Odell, 1969). This delay might be a factor in the recorded lack of a pituitary-thyroid response in earlier experiments. The adrenal response to cold stress is probably related to the degree of stress and not to temperature *per se* and the results recorded here are consistent with this, showing a marked individual variation. Where normal body temperature is not maintained the adrenal appears to respond submaximally (Woolf & Hollander, 1971).

As pointed out in the introduction, man uses his intellect to adapt to low environmental temperature and physiological mechanisms are rarely called upon. It is, nevertheless, important to study the effect of cold stress upon the thyroid in view of the gland's central role in maintaining basal metabolism, and the possibility of body temperature being fundamental among the complex factors influencing the feed-back control of the thyroid. Such work is of practical importance in spite of Héroux's (1970) criticism that cold chamber studies are artificial and pathological. Accidental hypothermia is also pathological, and an understanding of the sequence of failures which leads to this state could assist in its clinical management as well as its prevention.

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