The pituitary–thyroid axis in healthy men living under subarctic climatological conditions

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Abstract

In order to evaluate the effects of climatic factors on the secretion of thyroid hormones and TSH in a high latitude population, we have taken serum and urine samples from 20 healthy men from northern Finland (67°–68° N) every 2 months for a period of 14 months. Serum free triiodothyronine (T_3) levels were lower in February than in August (3·9 vs 4·4 pmol/l, $P<0·05$) and TSH levels were higher in December than during other months (2·1 vs 1·5–1·7 mU/l, $P<0·01$). Serum total and free thyroxine (T_4), total T_3 and reverse T_3 levels and urinary T_4 levels were unchanged. Urinary T_3 levels were significantly higher in winter than in summer. Serum free T_3 correlated highly significantly with the outdoor temperature integrated backwards weekly for 7–56 days ($r=0·26$ for 1–56 days) from the day when the blood samples were taken. Serum TSH did not show any significant correlation with the thyroid hormones or with the integrated temperature of the previous days, but it did show an inverse and significant correlation ($r=-0·31$) with the ambient luminosity integrated backwards for 7 days from the day when the blood sample was taken. The gradually increasing correlation between outdoor temperatures and serum free T_3 suggests that the disposal of thyroid hormones is accelerated in winter, leading to low serum free T_3 levels and a high urinary free T_3 excretion. Since there was no correlation between thyroid hormones and serum TSH, the feedback mechanism between TSH and thyroid hormones may not be the only contributing factor, and other factors such as ambient luminosity may at least partly determine serum TSH in these conditions. Also urinary free T_3 appears to be a novel and non-invasive indicator for thyroid physiology.

Journal of Endocrinology (2001) **169,** 195–203

Introduction

Thyroid hormones are the main regulators of non-shivering thermogenesis and in some species their secretion has been shown to be activated in a cold environment. There are several previous reports which describe the seasonal variation of the pituitary–thyroid axis in humans. Japanese subjects living in unheated dwellings had higher serum total triiodothyronine (T_3) levels in winter than in summer, but subjects working outdoors showed no differences in serum T_3 or thyroxine (T_4) between summer and winter (Nagata *et al.* 1976). High serum total T_3 and T_4 levels in winter were also found in laboratory workers in the Netherlands (Smals *et al.* 1977) and the UK (Harrop *et al.* 1985). This would indicate that the pituitary–thyroid axis becomes directly activated during the cold season. Other studies have, however, led to opposite results. In healthy subjects serum total T_4 levels were similar during all seasons, but the serum thyrotrophin (TSH) response to TSH-releasing hormone (TRH) was greater in winter than in summer (Konno 1978, Harrop *et al.* 1985). In hypothyroid subjects, lower serum T_4 levels and higher serum TSH levels and TSH responses to TRH were found in winter rather than in summer (Konno & Morikawa 1982). In another study, involving large populations, the serum TSH levels of young, middle-aged and old Italian subjects were at their highest in December in the middle- and old-age classes (Simoni *et al.* 1990), but no seasonal changes were seen in younger subjects (Pasquali *et al.* 1984, Simoni *et al.* 1990). In a recent study both serum TSH and free T_3 were highest in winter in healthy Belgian subjects (Maes *et al.* 1997). Elevated TSH levels in winter may relate to decreased iodothyronine deiodination in the pituitary gland or to decreased release of somatostatin or dopamine from the hypothalamus, but the increased TSH response to TRH in winter rather suggests that there is a lack of active thyroid hormones during the cold season. Studies with subjects wintering in the Antarctic bases support this finding, for decreased serum total T_3 and T_4 and increased TSH levels were found

0022–0795/01/0169–195

after an Antarctic winter (Vining *et al.* 1983). It was also demonstrated that after Antarctic cold exposure (42 weeks) serum total and free T_4 did not change, but serum total and free T_3 decreased and the serum TSH response to TRH increased (Reed *et al.* 1986, 1988). When increased testing frequency and improved assays were used, small decreases in serum total and free T_4 and an increase in serum TSH during Antarctic residence were observed (Harford *et al.* 1993). The decrease in the serum thyroid hormone levels was likely due to an increased disposal of thyroid hormones during the cold exposure (Reed *et al.* 1990*b*).

Thus, there appears to be a discrepancy with regard to the cold-induced long-term changes in the serum levels of thyroid hormones and TSH and to the mechanisms causing these effects. Part of this discrepancy is evidently due to the fact that most studies were performed in geographical areas in which the seasonal temperature seldom goes below freezing point. Studies carried out in the Antarctic show that long-term cold exposure may initiate a cascade of events that lead to small decreases in the circulating levels of thyroid hormones, resulting in a reflex elevation of serum TSH (Harford *et al.* 1993). On the contrary, the results of a study performed on Belgian subjects suggest that the annual variation in TSH partly determines the variation in serum T_3 (Maes *et al.* 1997). Therefore we wanted to address the following questions in the present study. Are there annual changes in the levels of thyroid hormones and TSH and are there temporal correlations between these hormones and ambient temperature or luminosity in healthy males living in a circumpolar area? The subjects we chose for the study come from northern Finland, which is continuously exposed to great seasonal changes in environmental temperature and luminosity. Our results show that in winter, serum free T_3 levels are low and serum TSH levels high, the former related to low ambient temperature and the latter to low luminosity. Our findings indicate that bodily disposal of thyroid hormones increases during the cold season.

Materials and Methods

Twenty healthy Caucasian males aged 26–40 years from the counties of Sodankylä and Äkäslompolo, Kolari (67–68° N, 24–26° E) gave their informed consent for this study, which was accepted by the Ethics Committee of the Medical Faculty, University of Oulu. They were outdoor workers and their daily outdoor stays were recorded. The subjects visited a nurse's office every 2 months at 0900–1100 h. On these occasions blood and urine samples were taken and body weight was measured. A 24 h recall diet interview (Laitinen *et al.* 1996) was also taken by the nurses. Blood samples were centrifuged and stored at − 20 °C. First-voided urine in the morning of the day of the visit was measured in a graduated cylinder, acidified with 0·1 M HCl and stored in 10 ml portions at − 20 °C. Blood and urine samples were taken in April (no urine samples), June, August, October, December, February and again in April. Daily sums of solar radiation and daily mean temperature (four recordings for each) measured by the Sodankylä observatory (67° 20' N) were obtained from the Department of Aerial Sciences (Helsinki, Finland).

Serum free T_3 (Mx T_3; Abbott Diagnostics, Abbott Park, IL, USA), total T_3, free T_4 and total T_4 (Farmos Diagnostica, Turku, Finland) were measured by commercial RIA kits and TSH by a kit from Diagnostic Products, Los Angeles, CA, USA according to the manufacturers' instructions. The normal values for serum free T_3 were 3·5–7·5 pmol/l, for T_3 1·1–2·5 nmol/l, for free T_4 8–25 pmol/l, for T_4 55–140 nmol/l and for TSH 0·2–4 mU/l. The antiserum for reverse T_3 (rT_3) was purchased from UCB Bioproducts (Brussels, Belgium), code i592, and ^{125}I-rT_3 from Amersham International, Amersham, Bucks, UK, code IM 105. The sensitivity of the rT_3 assay was 0·06 nmol/l. The intra- and interassay coefficients of variation in these assays were 1–6% and 9–16% respectively. Serum albumin was measured using a Cobas Intergra Offmatic analyser (Hoffman-La Roche, Basel, Switzerland).

Urine free T_3 and T_4 were measured by kits from Farmos Diagnostica after purification by Sep-Pak cartridges (Waters, Milford, MA, USA) as follows. Two millilitres of urine were acidified by acetic acid to pH 3·5–4·0 and passed through the Sep-Pak C18 cartridge, which was then washed with 10 ml 0·1% trifluoroacetic acid (TFA). The cartridges were then eluted with 3 ml 60% acetonitrile in 0·1% TFA and the elutes were dried under vacuum. The evaporates were reconstituted with the RIA buffer and measured in T_3 and T_4 kits as above. The recovery of radioiodinated T_3 or T_4 added to urine samples was 95 ± 4 and $97 \pm 8\%$ (means ± S.D., $n=6$) respectively. Graded volumes of the Sep-Pak eluates displaced the T_3 or T_4 tracers in parallel in RIAs. The immunoreactivity of the Sep-Pak evaporates moved in reverse-phase HPLC (Bondapak C18 column (Waters), polar buffer 0·1% TFA and non-polar buffer 2-propanol, 1% gradient per minute from 10% propanol) at 12 min in the T_3 RIA and at 13 min in the T_4 RIA, corresponding to the elution positions of synthetic T_3 and T_4 respectively.

Statistical analyses

Seasonal variations in thyroid hormone and TSH levels were assessed by using ANOVA with repeated measures and Duncan's multiple range test for differences between the bimonthly means (BMDP, Los Angeles, CA, USA). Each hormone variable in an individual was proportioned to its annual mean before analyses in order to reduce the inter-individual variation.

The relationships between various thyroid hormone and TSH concentrations were assessed by using linear regression analyses and by Pearson's product moment correlation.

The relationships between the hormonal data (dependent variable) and climatic data (explanatory variable) were assessed by using multiple regression analyses. Since it was assumed that the climatic conditions that prevail at the time of blood sampling affect the hormonal levels, temperature and luminosity variables were integrated to the periods covering times 1–7, 1–14, 1–21, 1–28, 1–35, 1–42, 1–49, 1–56 and 1–63 days before the time of blood sampling. Luminosity values (solar radiation) were transformed to logarithms (base 10) for regression analyses, since retinal cells discriminate luminosity more accurately on a logarithmic than an absolute scale.

Results

Environmental luminosity, temperature and serum thyroid hormones and TSH

Luminosity as expressed by averaged daily sums of solar radiation varied during the summer months between 10 and 20 MJ/m^2 and decreased to almost 0 during December–February (Fig. 1, upper panel). The daily outdoor temperature was 5 to 20° in May–August and 0 to − 40 °C in December–March (Fig. 1, second panel, mean of four daily recordings). The subjects spent 8·0–9·8 h outdoors in June–October and 5·7–5·8 h in December–February (P<0·05, Table 1). There were no significant seasonal changes in body weight or caloric intake or in serum albumin levels (Table 1). Serum TSH levels were highest in December at 2·1 ± 0·1 mU/l (means ± s.e.), which was significantly higher (P<0·01) than during the other months (Fig. 1, third panel). Free T_3 levels were highest in August at 4·4 ± 0·2 pmol/l, and lowest in February at 3·9 ± 0·1 pmol/l, and this difference was statistically significant (P<0·05). Free T_4 levels were between 14 and 15 pmol/l during the whole year (P>0·05). Total T_3 and T_4 levels varied between 1·8 and 1·9 nmol/l and 82 and 85 nmol/l during the 14 month observation period and no significant differences were seen between the months (Fig. 1, lower panels). Mean bimonthly rT_3 levels varied between 0·4 and 0·7 nmol/l, and no significant changes were seen either (data not shown).

The linear regression analyses between all the hormonal parameters demonstrated that T_4 correlated significantly (P<0·01) with free T_4, T_3 and free T_3. Free T_4 correlated significantly with T_3 and free T_3 and T_3 correlated with free T_3. The regression coefficient ranged between 0·44 and 0·77 (Table 2). Urinary T_3 correlated significantly only with urinary T_4.

Several regression models containing serum or urinary thyroid hormone concentrations or TSH as dependent and integrated temperature and/or solar radiation levels as explanatory variables were constructed. As to the circulating thyroid hormones, only serum free T_3 levels correlated significantly with climatic factors, i.e. with the temperature factors integrated for 1–7 days to 1–56 days before the time when the blood sample for the measurements was taken (Table 3). The highest correlation occurred when the time factor was 1–56 days (r=0·26, Fig. 2). Interestingly, serum TSH correlated negatively (r= − 0·31) with all the solar radiation factors integrated between 1–7 and 1–56 days. The highest correlation was found when the radiation factor was 1–7 days (r= − 0·31, Table 3, Fig. 3). The temperature factors alone or combined with solar radiation did not result in a significant correlation between TSH and climatic factors. There were some sporadic correlations between TSH and temperature and urinary T_3 and solar radiance.

Urinary thyroid hormones

Urinary T_3 concentrations (Table 4) were the highest in February, 71 ± 23 pmol/l, and lowest in August, 43 ± 17 pmol/l (P<0·05). The T_3 content of the first-voided morning urine was 30 ± 11 pmol in February and 15 ± 5 pmol in August (P<0·01). There were no significant changes in urinary T_4 concentrations or in the T_4 contents of morning urines between the months. Urinary T_3 levels correlated negatively with the temperature factor integrated from 1–14 days to 1–56 days, the highest correlation coefficient (r= − 0·23, Table 3, Fig. 4) occurring when the factor was integrated for 1–28, 1–35, 1–42, 1–49 or 1–56 days. Urinary T_4 levels did not show any significant correlation between temperature or solar radiance.

Discussion

The results of the present study demonstrate that the subjects living in a circumpolar environment exhibit significant seasonal rhythmicities in serum TSH, free T_3 and in urinary T_3 but not in the levels of rT_3, T_3, T_4, free T_4 or urinary T_4. We found that TSH was highest during the cold season (December) and free T_3 in the summer (August). These findings are mostly in line with those obtained from hypothyroid patients in Japan and in healthy subjects during an Antarctic winter. Hypothyroid patients with constant T_4 replacement tended to have low serum total T_4 in winter, which points to the greater disposal of iodothyronines during cold seasons (Konno & Morikawa 1982). After a 42 week residence in the Antarctic winter, serum T_3 levels following oral administrations of T_3 were found to be lower before it, indicating that the plasma clearance rate of T_3 increased in the cold (Reed *et al.* 1990*b*). Thus, earlier findings and our present study suggest that during long-term cold exposure, such as in winter in circumpolar areas, the bodily disposal of thyroid hormones accelerates. The changes are small and are first

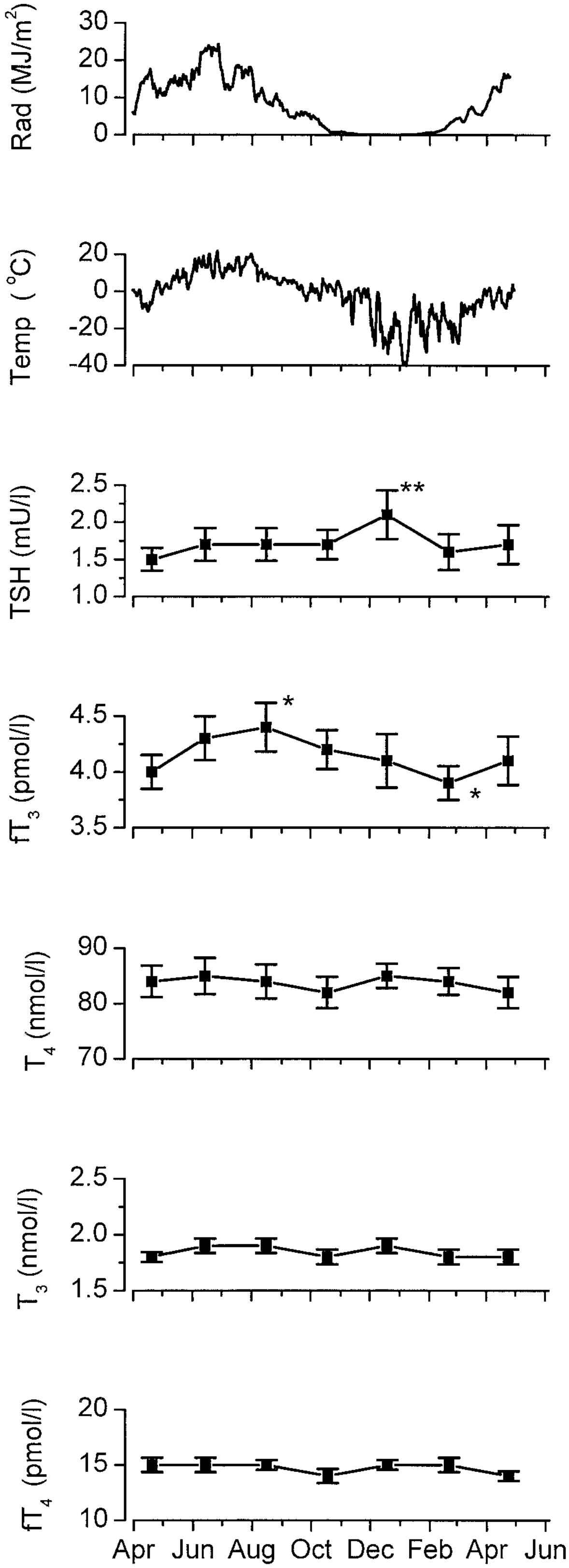

Figure 1 Seasonal luminosity (radiance, Rad), temperature (Temp), serum TSH, and free and total thyroid hormones in 20 healthy male subjects from northern Finland (67°–68° N). For luminosity daily sums and temperature daily means are given, for hormones means ± s.e. *P<0·05 between the lowest and highest value, **P<0·01 between all the other points for serum TSH.

recognisable in serum free T_3 levels (Reed *et al.* 1986, 1988, this study) and later in total serum T_3 or T_4 levels (Vining *et al.* 1983, Reed *et al.* 1986, 1988, Harford *et al.* 1993). In our present study, cold exposure during winter was less intense than that experienced in the Antarctic winter. This is probably why we found serum total T_3 and T_4 levels unchanged. One reason for the difficulty of finding decreases in serum T_4 during cold exposure might be that the T_4 pool is much greater than the T_3 pool. An increased disposal of T_3 as with T_4 has been called the 'polar T_3 syndrome' (Reed *et al.* 1990*a*,*b*).

In two European studies the relationship between ambient temperature and TSH or thyroid hormones has been studied. In older Italian subjects, elevated TSH levels were observed in winter, but the relationship between TSH and environmental temperature was not significant, indicating that temperature is not important in determining TSH levels (Simoni *et al.* 1990). In a Belgian study, serum TSH was significantly elevated in April, June and December and serum total T_3 in December (Maes *et al.* 1997). The relationship between TSH and temperature was weak but significant between serum total T_3 and temperature. There is therefore evidence from the present and earlier studies that other possibilities besides temperature may affect the TSH circannual cycle and that these may interact with the temperature effect upon thyroid hormones.

In order to study the relationships between TSH and thyroid hormones and environmental factors more closely, we first compared serum and urinary thyroid hormones and TSH with each other. Serum T_4 correlated significantly with other circulating thyroid hormone levels indicating a close (r=0·55–0·77) relationship between these hormones in their production and metabolism. Urinary T_4 correlated significantly only with urinary T_3, most possibly for the same reason. Interestingly, there was no significant correlation between TSH and thyroid hormones or between circulating and urinary thyroid hormones. This may indicate that there are other mechanisms affecting the simple feedback loop between TSH and thyroid hormones and that the kidneys eliminate thyroid hormones in a manner independent of the circulating thyroid hormone levels.

Next, we compared TSH and thyroid hormones with outdoor temperatures and luminosity integrated backwards weekly for 56 days from the day the blood sample was taken. There was a highly significant negative correlation between TSH and solar radiation (r= − 0·31) when the time factor was 1–7 days, indicating that approximately

Table 1 Seasonal variation of time spent outdoors, energy intake, body weight and serum albumin (means ± S.E.) in 20 healthy males

	Time of year						
	Apr	Jun	Aug	Oct	Dec	Feb	Apr
Outdoor time (h)	—	8·0 ± 0·7*	9·8 ± 0·7**	8·3 ± 0·6*	5·8 ± 0·6	5·7 ± 0·8	6·7 ± 0·8
Energy intake (kcal)	2627 ± 220	2770 ± 240	2717 ± 180	2674 ± 200	2780 ± 180	2722 ± 180	2735 ± 140
Body weight (kg)	83·2 ± 2·6	83·4 ± 2·8	83·4 ± 2·6	82·5 ± 2·6	81·4 ± 2·3	82·1 ± 2·3	83·5 ± 2·5
Serum albumin (g/l)	51 ± 0·7	52 ± 0·8	51 ± 0·8	52 ± 0·6	51 ± 0·4	53 ± 0·5	51 ± 0·6

**P*<0·05, ***P*<0·01 between any value when compared with the lowest value.

10% of the variance in TSH is explained by luminosity. Previous regression analyses have shown that only 2·9% of the variance in TSH was explained by air pressure but sunlight duration had no explanatory value (Maes *et al.* 1997). It is not known if the sunlight duration takes into account the actual radiation from the sun. The correlation between TSH and solar radiance diminished slowly with time, perhaps due to temporal autocorrelation of climatic factors. Since there was no significant correlation between TSH and temperature, we propose that the reduced luminosity in winter somehow stimulates the secretion of TSH. Another possibility is that the diurnal TSH rhythm is changed so that the night-time secretion period of TSH in winter extends into the morning, when our blood samples were taken. It has previously been observed that the diurnal rhythm of serum TSH can be shifted (phase delay) by a bright light stimulus (Allan & Czeisler 1994), but we do not know the effects of decreasing daylength on the diurnal TSH secretory pattern.

Table 2 Pearson's correlation coefficients between serum TSH and serum and urinary thyroid hormone concentrations taken bimonthly for 14 months from 20 male subjects

	TSH	fT_3	T_3	fT_4	T_4	uT_3
fT_3	− 0·18					
T_3	0·14	0·62**				
fT_4	− 0·13	0·44**	0·52**			
T_4	− 0·13	0·55**	0·67**	0·77**		
uT_3	− 0·02	− 0·05	− 0·10	− 0·02	− 0·02	
uT_4	− 0·07	− 0·01	− 0·08	− 0·10	− 0·05	0·66**

f=free, u=urinary.
***P*<0·01.

When we correlated the circulating thyroid hormones with temperature or luminosity, only free T_3 was found to show a significant correlation with temperature. The

Table 3 Pearson's correlation coefficients in the linear regression models with hormone levels as dependent and climatic factors as explanatory variables

Day factor	TSH	fT_3	T_3	fT_4	T_4	uT_3	uT_4
Solar radiance							
1–7	− 0·31***	0·05	− 0·05	− 0·04	− 0·07	− 0·11	− 0·11
1–14	− 0·31***	0·06	− 0·05	− 0·05	− 0·07	− 0·11	− 0·11
1–21	− 0·30***	0·08	− 0·04	− 0·06	− 0·08	− 0·13	− 0·12
1–28	− 0·30***	0·09	− 0·03	− 0·07	− 0·08	− 0·14	− 0·12
1–35	− 0·28**	0·11	− 0·02	− 0·07	− 0·08	− 0·15	− 0·13
1–42	− 0·27**	0·12	− 0·01	− 0·08	− 0·08	− 0·16	− 0·13
1–49	− 0·25**	0·14	0·00	− 0·09	− 0·08	− 0·17	− 0·13
1–56	− 0·22*	0·15	0·02	− 0·10	− 0·07	− 0·18*	− 0·12
Temperature							
1–7	− 0·19*	0·19*	0·02	− 0·04	− 0·03	− 0·14	− 0·14
1–14	− 0·15	0·21*	0·05	− 0·05	− 0·02	− 0·18*	− 0·15
1–21	− 0·16	0·22*	0·05	− 0·05	− 0·01	− 0·21*	− 0·16
1–28	− 0·12	0·23*	0·08	− 0·06	0·00	− 0·23*	− 0·15
1–35	− 0·10	0·24*	0·09	− 0·06	− 0·01	− 0·23*	− 0·15
1–42	− 0·10	0·24*	0·09	− 0·05	− 0·01	− 0·23*	− 0·15
1–49	− 0·07	0·24*	0·10	− 0·06	− 0·01	− 0·23*	− 0·14
1–56	− 0·07	0·26*	0·12	− 0·06	− 0·02	− 0·23*	− 0·14

Day factor is the period in days that preceded the day when the blood samples for hormonal measurements were taken and that was integrated for solar radiance or temperature for the linear regression models.
**P*<0·05, ***P*<0·01, ****P*<0·001.
f=free, u=urinary.

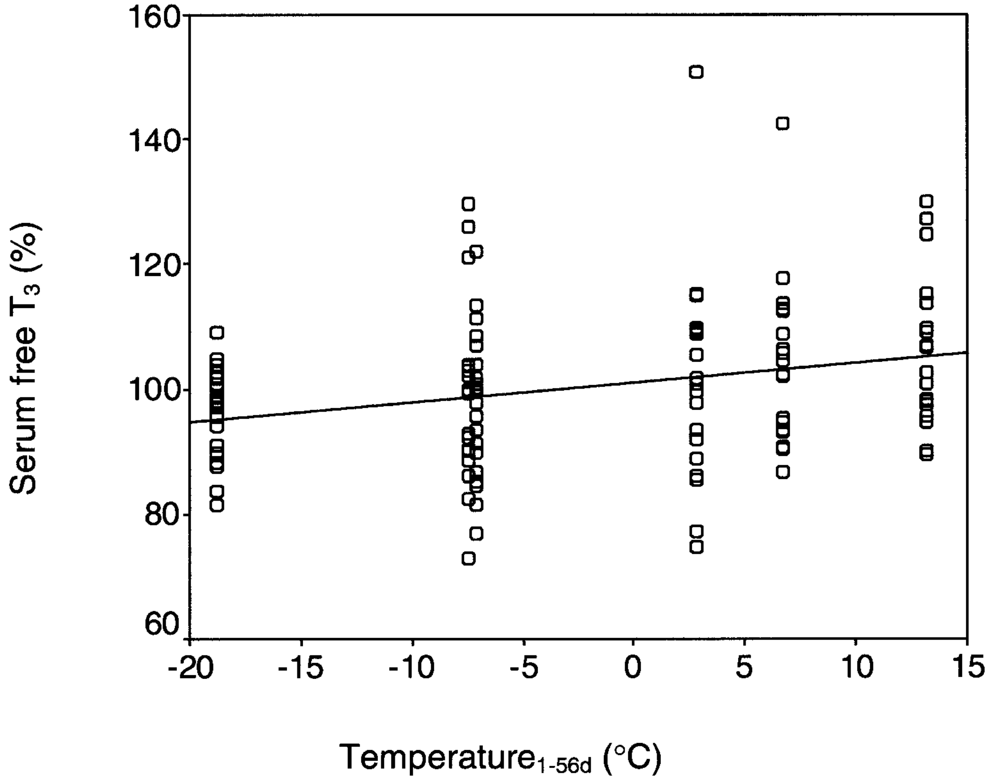

Figure 2 Bimonthly mean serum free T_3 (per cent of the annual mean) as a function of ambient temperature integrated back for 56 days from the day of blood sampling for the T_3 measurements in 20 male subjects. There is a significant positive correlation between serum free T_3 and ambient temperature (r=0·26, P<0·05).

correlation was best (r=0·26), when the temperature factor was 1–56 days, explaining approximately 7% of the variance in free T_3. In an earlier study an increase in serum total T_3 during winter, and therefore a highly significant negative correlation between total T_3 and temperature, had been reported (Maes *et al.* 1997). The negative correlation is difficult to understand, because in the majority of the studies dealing with seasonal changes in the secretion of thyroid hormones there are rather decreases in the levels of free or total T_3 during winter (Vining *et al.* 1983, Reed *et al.* 1986, 1990*a*,*b*, Harford *et al.* 1993, this study). We interpret our results so that at the end of winter the tissue uptake/metabolic degradation of T_3 gradually exceeds its production rate and leads to decreased levels of free T_3. The increased tissue uptake may also explain the increased urinary secretion of T_3 which we observed in late winter.

In the Belgian subjects an inverse relationship between serum total T_3 and ambient temperature of the preceding week was observed that was partly determined by TSH (Maes *et al.* 1997). These findings are difficult to reconcile, since we observed neither seasonal changes in serum total T_3 nor any relationships between TSH and thyroid hormones. An experimental study in which healthy subjects were repeatedly exposed to cold air and in which free T_3 was found to be decreased with no changes in other thyroid hormone or TSH levels (Hesslink *et al.* 1992) supports our present observation. We point out that other seasonal changes in outdoor activities, luminosity, caloric intake, body weight or serum albumin do not explain our findings, since we did not find any significant changes in these parameters during our study.

There are some indirect findings supporting increased TSH secretion during the cold season. Ultrasonically measured thyroid volumes were found to be 23% greater in winter than in summer, even though serum TSH and thyroid hormones were not significantly changed in healthy subjects from Denmark (Hegedus *et al.* 1987). The same authors then concluded that the seasonal variation in thyroid size should be taken into account, for example in goitre treatment.

Measurements of urinary thyroid hormone concentrations have been used for the evaluation of thyroid activity. Previous methods utilised untreated urine samples or simple extractions (Rastogi & Sawhney 1976). In our experience untreated or extracted urine samples did not give reliable results and we adopted a reverse-phase Sep-Pak cartridge method for the purification of urine

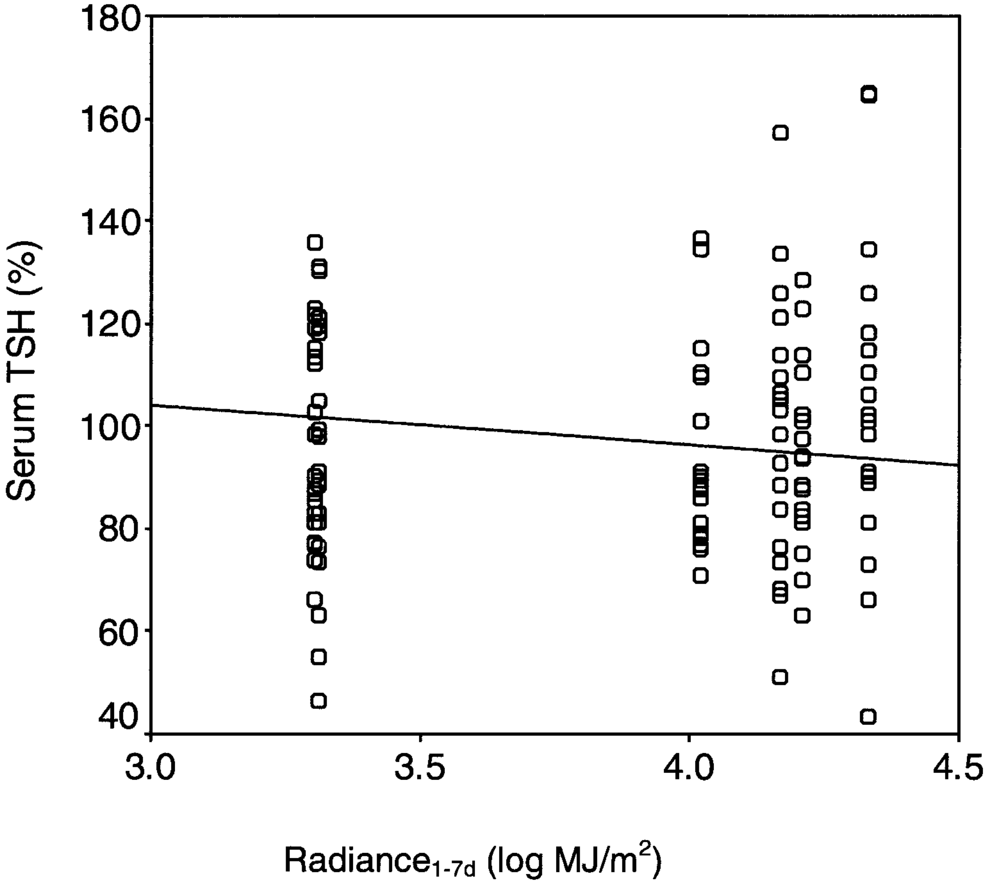

Figure 3 Bimonthly mean TSH (per cent of the annual mean) as a function of luminosity (solar radiance) integrated back for 7 days from the day of blood sampling for TSH measurements in 20 male subjects. There is a significant inverse correlation between the parameters ($r = -0{\cdot}31$, $P<0{\cdot}001$).

samples for thyroid hormone RIAs. The recovery of the method was good, and the T_3 and T_4 immunoreactivities of the Sep-Pak eluates moved in HPLC as synthetic T_3 and T_4 respectively. By using this method we obtained urine T_3 concentrations of 40–70 pmol/l and 350–470 pmol/l for T_4. These values were approximately one-tenth of those presented earlier (Rastogi & Sawhney 1976). Taking the improved purification method into account, our urinary T_3 and T_4 values most probably present 'true' urinary free thyroid hormone levels. Serum free T_3 levels and urinary T_3 levels showed opposite trends in our study. Moreover, urinary T_3 correlated significantly with temperature ($r = -0{\cdot}23$, when the time factor was more than 4 weeks) indicating that approximately 5% of the variance in the urinary T_3 is explained by temperature. These findings may be related to an increased uptake of T_3 in the kidneys as we discussed before, and also to the increased formation of T_3 from T_4 in the kidneys, as we

Table 4 Seasonal variation of urinary T_3 and T_4 in 20 healthy men (means ± S.D.)

	Time of year					
	Jun	Aug	Oct	Dec	Feb	Apr
Urinary T_3 (pmol/l)	62 ± 15	43 ± 14	52 ± 10	64 ± 15	71 ± 23*	46 ± 9
T_3 content (pmol)	21 ± 7	15 ± 6	23 ± 6	26 ± 9	30 ± 11**	21 ± 9
Urinary T_4 (pmol/l)	407 ± 65	352 ± 73	388 ± 91	478 ± 94	414 ± 72	365 ± 79
T_4 content (pmol)	155 ± 55	142 ± 54	178 ± 74	195 ± 58	176 ± 57	183 ± 81

*$P>0{\cdot}05$, **$P<0{\cdot}01$ between the highest and lowest value.

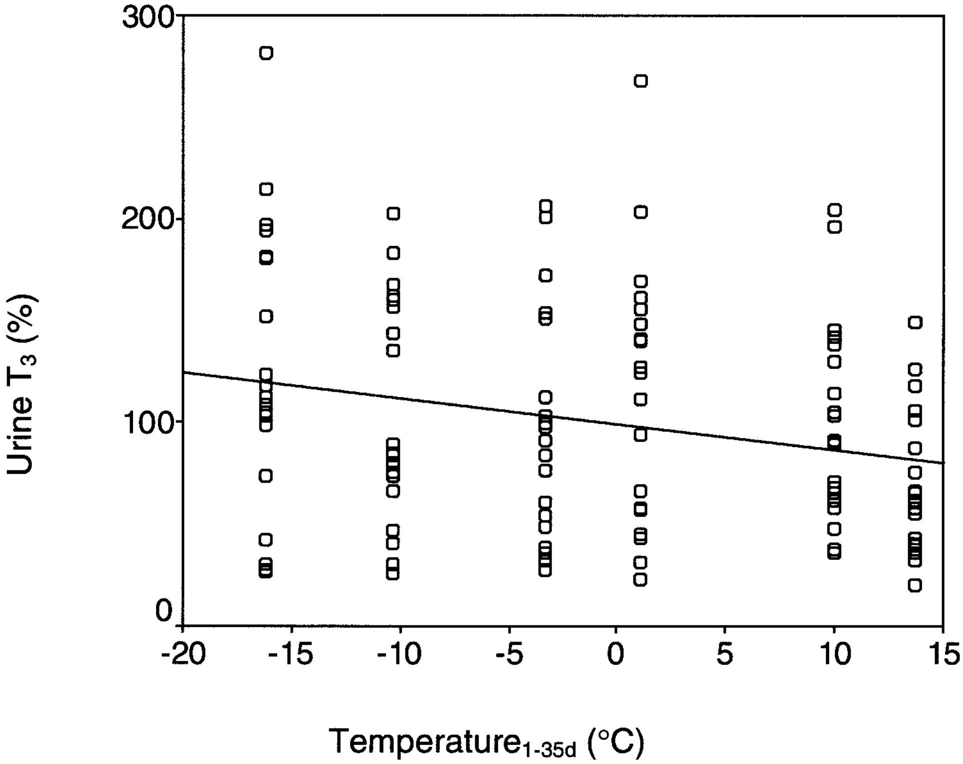

Figure 4 Bimonthly mean urinary T_3 (per cent of the annual mean) as function of the ambient temperature integrated back for 35 days from the day of blood sampling in 20 male subjects. There is a significant inverse correlation between the parameters ($r= -0{\cdot}23$, $P<0{\cdot}05$).

found a significant correlation between urinary T_3 and T_4. In healthy human males the daily production of T_3 is reported to be 78–113 nmol/m^2 (Reed *et al.* 1990*b*) and the urinary content of free T_3, about 0·1 nmol, is only a small fraction of it. In spite of this, the urinary excretion of free T_3 represents a novel and non-invasive indicator for studies in thyroid physiology.

The results of our study suggest that decreasing ambient temperature in winter gradually increases the disposal of thyroid hormones, seen in falling serum free T_3 levels, which reach the minimum at the end of winter. Serum TSH levels increase also in December and may be associated with reduced ambient luminosity. According to our present results the association between serum TSH with free T_3 is not clear, since low free T_3 and high TSH levels did not occur at the same time. In this climate the cold exposure may not have been intense enough to cause changes in serum T_3 as well as in free or total T_4. The urinary free T_3 showed opposite seasonal curves to serum free T_3 levels and this may indicate increased disposal of T_3 during cold exposures.

Increased metabolic clearance of thyroid hormones during the cold season has several clinical consequences. As presented above, the substitution doses of thyroid hormones could be increased in winter (Konno & Morikawa 1982). This may be advantageous also in goitre patients (Hegedus *et al.* 1987). Decreased thyroid hormones tend to increase blood lipid levels (Harford *et al.* 1993) and minimal thyroid dysfunction is often associated with increased levels of low density lipoprotein cholesterol (Staub 1998), established risk factors for cardiovascular diseases. More studies are, however, required to screen populations living in circumpolar areas to determine who could benefit from a substitution with thyroid hormones in winter.

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Received 7 November 2000
Accepted 8 December 2000