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RESEARCH

Thyroid response to blocking sympathetic activity in chronic cold-exposed hunters in East Greenland: a case–control study

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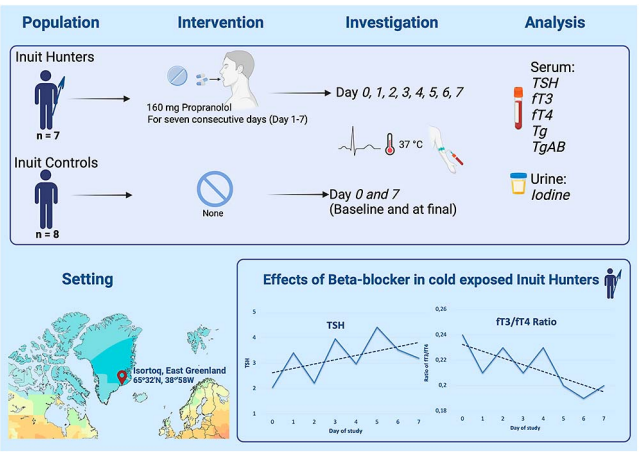
Graphical Abstract



Abstract

Background: Thyroid hormones and sympathetic stimulation are needed for activating brown adipose tissue (BAT) during cold exposure. Studies of human cold exposure have demonstrated both increased production and raised clearance of triiodothyronine (T3). Greenlandic hunters provide a unique model for evaluating metabolic effects of cold exposure.

Aim: We aimed to explore the dynamics of thyroid hormones when blocking sympathetic activity in Greenlandic hunters during winter to inspire knowledge on mechanisms of BAT activation.

Methods: We conducted a 7-day field study of Greenlandic hunters (n = 7) in East Greenland in February. The sympathetic system was blocked using a non-selective beta blocker for seven consecutive days. A group of non-hunter Greenlanders

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(*n* = 8) from the same settlement was included for parallel sampling. All participants were healthy men. Blood samples were drawn daily for measurement of TSH, thyroid hormone levels and thyroglobulin.

Results: Hunters had higher serum thyroglobulin, TSH and fT3/fT4 ratio compared to controls. Blocking the sympathetic activity was followed by changes in serum thyroglobulin and fT3 with an initial decrease and subsequent restoration of levels, while TSH and fT4 showed a gradual increase over the course of the study. The fT3/fT4 ratio showed a continuous and marked decrease.

Conclusion: We speculate that when blocking the sympathetic system, TSH increases to uphold the production of T3 needed for maintaining BAT activity. In addition, alterations of fT3/fT4 ratio support a hypothesis of adrenergic stimulation promoting T3 over T4 secretion from the thyroid via adrenergic nerve terminals in the thyroid.

Keywords: thyroid hormones; sympathetic activity; cold exposure; brown adipose tissue

Introduction

Thyroid adrenergic nerve terminals are found as a network around vessels, and the sympathetic nervous system may have a direct influence on thyroid follicular cells as numerous terminals have been demonstrated between and around thyroid follicles in the thyroid (1, 2). Thyroid adrenergic nerve terminals disappear after surgical or chemical sympathectomy (3), supporting the hypothesis of an active role in regulation of thyroid hormone secretion as they would have disappeared had they been redundant.

Sympathetic activity and thyroid hormones work together in the activation of non-shivering thermogenesis (4, 5, 6) occurring with prolonged cold exposure. We previously saw indications of raised thyroid activity, yet with low T3, among people residing in areas with chronic cold exposure, i.e., hunters living in remote areas in the Arctic (7). These findings corroborate the hypothesis of the polar T3-syndrome consisting of both raised T3 production and clearance with prolonged polar residence (8). Both T3 and sympathetic activity are required for upregulation of uncoupling protein 1 (UCP-1) responsible for the non-shivering thermogenesis in brown adipose tissue (BAT).

BAT is regulated via the autonomic nervous system through increased sympathetic activity (9). In addition, hypothalamic regions communicate with BAT and the thyroid gland via distinct sympathetic pathways, underscoring the importance of central nervous system regulation in adaptive thermogenesis (10, 11). Interestingly, a recent study demonstrated that cold-induced TRH release could stimulate BAT activity without detectable alterations in thyroid hormone levels (12). This suggests that TRH may activate BAT through additional pathways beyond thyroid hormone regulation.

Beta blockers influence sympathetic activation, and we speculated that thyroid activity may show a compensatory rise in thyrotropin to counterbalance the reduced sympathetic activity caused by a beta blocker in subjects with chronic cold exposure suggestive of active BAT.

This led us to perform an intervention study in a remote settlement in Arctic East Greenland during winter. A non-specific beta blocker was administered daily to assess the influence on thyroid function of blocking sympathetic activity among chronic cold-exposed hunters. In addition, we included a control group consisting of non-hunters living in the settlement to evaluate the influence of extreme cold exposure.

Materials and methods

Greenland is an Arctic environment with ambient temperatures going below −50 °C in habited parts (13). It is the world's largest island, and 1.8 of 2.2 million km^2 (2) is covered by ice. Hunting is the main occupation among Inuit in small villages in rural Greenland, and hunters have long stays outdoors also during winter (14).

Participants were recruited in the settlement Isortoq in East Greenland, positioned 65°32′N, 38°58′W, an area with ambient temperatures down to −30 °C. This settlement is situated on the coastline with the Arctic Ocean on one side and the Ice Cap on the other. The Great Ice runs down along the coastline of East Greenland and provides a lively habitat for seals, narwhals, walruses and polar bears. This is the subsistence of the hunters who hunt from small open boats on the Arctic Ocean (Fig. 1).

The settlement of Isortoq had 71 inhabitants at the time of investigation: 23 children, 26 women and 22 men. Nine of the men were subsistence hunters. One was away for medical treatment, and seven of the eight who were present participated. Eight of the remaining men were included as a control group.

The intervention group consisted of the seven subsistence hunters. All were Inuit, and six had lived their entire life

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Figure 1

A hunter on his dinghy boat in February in East Greenland illustrating the cold outdoor working conditions.

in East Greenland. The newcomer was born in South Greenland and had been a subsistence hunter in East Greenland for 15 years. They were all classified as 'Great Hunters' based on legal polar bear and narwhal catches. Subsistence hunters have an annual quota of polar bears. This was 25 in Ammassalik district in 2013. Remarkably, three of the seven hunter participants were successful in hunting polar bears during the investigation. This illustrates that they were not markedly impaired by the beta blocker intervention.

This study was approved by the Ethics Committee for Greenland (reference number 2012-20). A letter of invitation with study information was delivered to hunters. An interpreter explained the details of the investigation, and written informed consent was obtained. The investigation was performed in February of 2013.

Baseline examinations included height and weight in indoor clothing, blood pressure on the left arm, heart rate, a one-lead ECG for conduction abnormalities, otoscopy, bilateral tympanic temperature and a physical examination. An interview-based questionnaire was completed regarding ancestry, dietary habits, hunting habits, number of hours outdoors, smoking, alcohol intake, thyroid and other diseases in the participant and a family history of diseases. Daily investigations included blood pressure, heart rate, a 30-s one-lead ECG and tympanic temperature.

Tympanic temperature was measured on both sides twice daily using a Braun ThermoScan thermometer (Braun, Switzerland). One hunter was excluded from temperature calculations as he was clinically warm and had increased temperature and fatigue after he went through the ice on the Arctic Sea during polar bear hunting. In addition, his TSH and T3 were excluded from calculations.

The one-lead ECG was performed twice daily using the Daily Care ECG model RMH4.0 (BioMedical, Taiwan).

A morning spot urine sample was collected between 07:00 and 09:00 h each morning, and urine was kept frozen until analysis. A non-fasting blood sample was collected each day between 05:00 and 07:00 h in the intervention group, and at baseline and at the termination of the study in the control group. Two samples were taken 30 min apart at baseline (day 0) and at conclusion (day 7) of the study in both groups. Blood samples were taken using a minimal tourniquet, spun and separated, and serum was kept at −20 °C until analysis.

The intervention consisted of 160 mg of the beta blocker propranolol in a slow-release formulation. The dose of 160 mg was a viable daily dose accepted by the ethics committee to be administered to healthy subjects with a slow release to ensure stable drug levels and provide an adequate blockade of the sympathetic nervous system while avoiding nonlinear accumulation (15). The first dose was split in two to provide a test dose, and one hunter was given only 80 mg daily due to a resting morning heart rate below 40. Blood pressure, heart rate, one-lead ECG, temperature and weight were measured twice daily for the duration of the study.

Participants came in for observed intake of the beta blocker between 07:00 and 09:00 AM. A physical workup was performed, and the urine samples were collected. Participants came in again between 05:00 and 07:00 PM for measurement of blood pressure, heart rate, ECG, temperature, weight and blood sampling.

The control group was matched for gender and residence. Controls underwent similar baseline investigations. Two blood samples and a urine sample were collected at baseline and at conclusion of the study using identical techniques. No beta blocker was given to this group. They lived in the same settlement, but they were not hunters by trade.

Assay

Iodine concentration in urine was determined by the ceri/arsen method after alkaline ashing as described in detail previously (16). The analytical sensitivity was 2 mg/L, and the iodine laboratory is certified by the US Centers for Disease Control and Prevention's program for Ensuring the Quality of Urinary Iodine Procedures (EQUIP).

We measured thyroglobulin antibodies (TGAb), thyroglobulin (Tg), thyrotropin (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) in serum. Serum TSH, fT3 and fT4 were analysed with LUMItest (BRAHMS, Germany) as previously described (7).

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Table 1 Demographic characteristics of participants. None of the numeric differences were statistically significant. Data are presented as *n* or as median (IQR).

	Controls	Hunters	Total	*P*
All Inuit, *n*	8	7	15	
Age (years)	41 (32–47)	46 (40–61)	41 (36–49)	0.27
Height (cm)	168.8 (160.5–174.5)	161.0 (157.5–171.0)	166.0 (159.5–172.0)	0.35
Weight (kg)	77.5 (67.8–95.8)	73.0 (69.0–90.0)	75.0 (68.0–90.0)	1.00
BMI (kg/m^2)	31.95 (24.5–32.6)	29.2 (24.6–35.2)	31.4 (24.6–33.2)	0.73
Body temperature (°C)	36.6 (36.2–37)	36.7 (36.6–36.8)	36.4 (36.0–36.8)	0.95
Urinary iodine (μg/L)	109.5 (70.5–175.5)	117.4 (95.0–176.0)	116.0 (88.0–176.0)	0.25

The functional sensitivity of the TSH assay was 0.01 mU/L. Reference intervals were 0.3–4.5 mU/L for TSH, 3.6–6.9 pmol/L for fT3 and 9.8–20.4 pmol/L for fT4.

TGAb were measured using Dynotest RIA (BRAHMS Diagnostica, Germany) with a detection limit of 30 kU/L. Serum Tg was measured using an immunofluorescent assay (hTg KRYPTOR, BRAHMS) with a functional assay sensitivity below 0.8 ng/mL (information by the manufacturer). The inter-assay CV for samples with average Tg concentrations of 3.3 and 50.5 mg/L was 5.6 and 2.8%.

All samples from one individual were measured in the same run to account for between-assay variation.

Statistical analysis

Frequencies were described by medians and percentiles. Non-parametric tests were used to compare pre- and post-intervention levels due to non-normal data distribution. The Wilcoxon signed-rank test and Friedman's test were used for comparison of changes with time in the same individuals. The Mann–Whitney *U* test and Kruskal–Wallis test were used to compare medians between individuals. A *P*-value below 0.05 was considered statistically significant.

Results

The participants in the intervention group did not differ markedly from the control group (Table 1). None showed signs of chronic disease at the physical examination. Urinary iodine excretion was similar between groups. Blood pressure was unaltered during intervention, while heart rate decreased by 18% following beta blocker. Body temperature decreased numerically from 36.7 to 36.2 following intervention (P = 0.07).

Table 2 lists blood pressures, pulse and body temperature and details the test results for thyroid function and Tg. Controls had similar thyroid parameters at the baseline and final sampling one week apart. Hunters and controls had similar parameters at baseline, although Tg was numerically higher among hunters. Figure 2 illustrates the overall difference between hunters and controls in Tg, TSH and fT3/fT4 ratio. Among hunters, serum TSH, fT4 and fT3/fT4 ratio differed following the intervention with the beta blocker, while serum Tg and fT3 did not (Fig. 2).

Figure 3 illustrates the changes in serum Tg, TSH, fT3 and fT4 among hunters over seven days of intervention against controls. Tg (lower graph) showed an initial numeric decrease with a subsequent recovery to the initial level (P = 0.09). Tg remained high compared to the control group throughout the study period (P = 0.001).

Table 2 Physical and biochemical findings among hunters and controls living in a remote settlement in East Greenland. All values are presented as median (IQR).

	Controls		Hunters		*P* values	
	Baseline	End	Baseline	End	[A]	[B]
TSH (mIU/L)	1.76 (1.36–1.90)	1.79 (1.34–2.20)	1.78 (1.40–2.78)	3.09 (2.71–5.14)	0.020	0.028
TG (ng/mL)	12.0 (9.4–17.9)	11.7 (10.2–16.0)	18.4 (13.2–19.5)	18.3 (15.2–20.9)	0.037	NS
fT3 (pg/mL)	3.47 (3.03–3.74)	3.15 (2.60–3.65)	3.26 (2.68–3.44)	2.93 (2.78–3.21)	0.063	NS
fT4 (pmol/L)	13.3 (12.5–14.9)	13.8 (12.4–14.7)	12.4 (11.9–14.2)	14.2 (13.3–15.0)	NS	0.028
fT3/fT4 ratio	0.26 (0.24–0.28)	0.24 (0.22–0.26)	0.24 (0.21–0.27)	0.19 (0.18–0.22)	0.073	0.018
Body temperature (°C)	36.6 (36.2–37.0)	36.8 (36.6–37.0)	36.7 (36.6–36.8)	36.2 (35.5–36.6)	0.008	0.075
Systolic BP (mmHG)	127.5 (120–130)	130.0 (122–140)	120.0 (115–142)	120.0 (117–130)	NS	NS
Diastolic BP (mmHG)	80.0 (72–80)	85.0 (80–87)*	80.0 (75–82)	80.0 (77–85)	NS	NS
Heart rate (bpm)	77.0 (72–84)	72.0 (68–75)	83.0 (73–94)	67.8 (62–70)	0.027	0.047

[A]Mann–Whitney test for values among hunters and controls at the termination of the study period. [B]Paired test (Wilcoxon signed-rank test) among hunters comparing baseline and post-intervention.
**P*-values significant for paired baseline and end values for controls.

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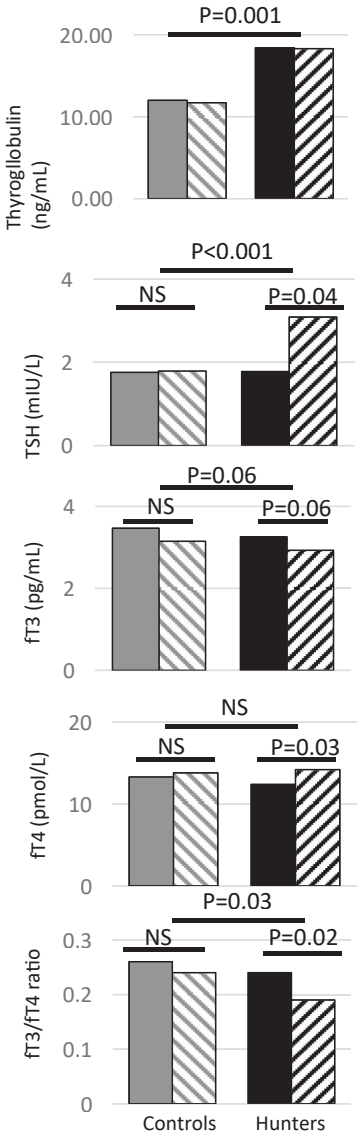

Figure 2

Median thyroglobulin, thyrotropin (TSH), free T3, free T4 in serum and fT3/fT4 ratio among hunters exposed to cold by trade (black bar) prior to (full bars) and after 7 days (striped bars) of daily beta blockage with propranolol 160 mg and controls (grey bar) having indoor occupation and living in the same settlement in East Greenland.

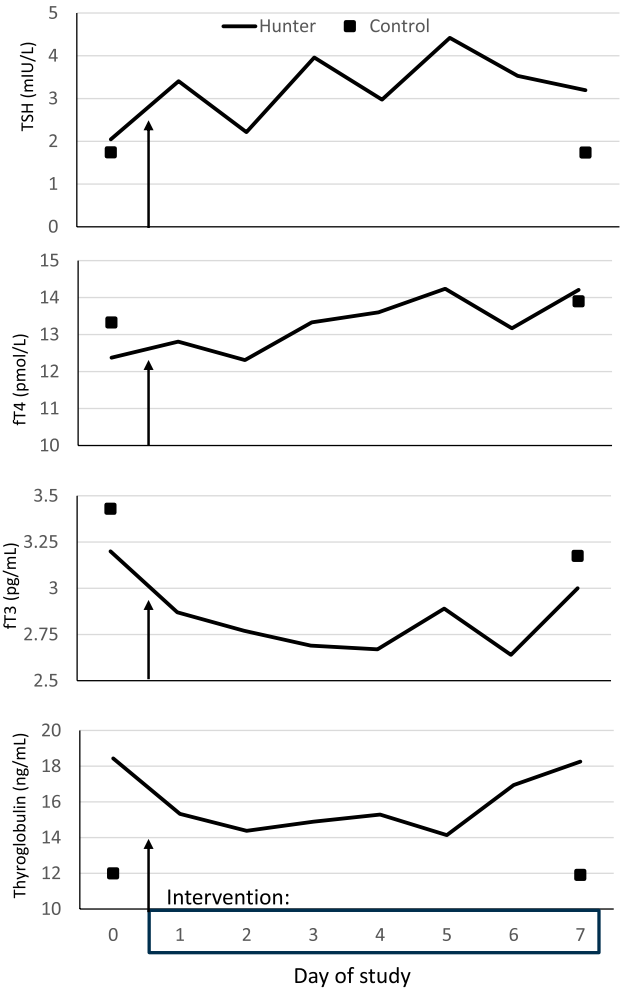

Figure 3

Thyroglobulin, thyrotropin (TSH), free T3 and free T4 levels (median) in serum among hunters (solid line) receiving a non-specific beta-blocker (intervention) and controls (squared dots) without intervention. All lived in the same settlement in East Greenland and were investigated in winter.

TSH showed an increasing trend during the first five days of intervention (P = 0.005) with a rise from 2.04 mIU/L, a peak at 4.42 on day-5, followed by a decrease to 3.19 mIU/L. TSH was markedly higher among hunters compared to the control group (P < 0.001). Overall, changes were not statistically significant until day-3 of the intervention when TSH, fT4 and fT3/fT4 ratio were markedly different from baseline values (P = 0.036/0.014/0.002, respectively).

Hunters had lower fT3 than controls with a numeric decrease following intervention. In parallel, the rise in fT4 with intervention among hunters was statistically significant (P = 0.03). Similarly, fT3/fT4 ratio showed a marked and continuous decrease during the intervention (P = 0.018) (Fig. 4) (Table 2).

Discussion

Subjects with extreme chronic cold exposure had higher Tg, TSH and fT3/fT4 ratio compared to our control group comprising of residents in the Arctic settlement (Fig. 2). FT4 differed only upon administration of a beta blocker (intervention), while fT3 tended to differ both between controls and hunters, and with intervention. Thus, blocking the sympathetic activity was followed by changes in Tg and fT3 with an initial decrease and subsequent restoration of levels, while TSH and fT4

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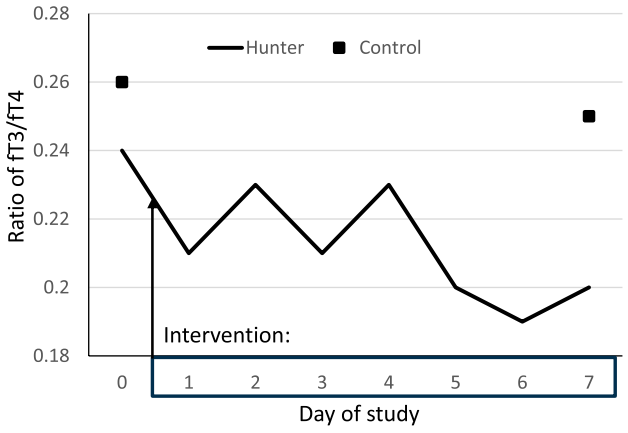

Figure 4

Ratio of fT3/fT4 among hunters receiving intervention (solid line) and controls living in the same settlement in East Greenland (squared dots). The intervention consisted of a non-specific beta-blocker from day-1 through day-7.

showed a gradual increase over the course of the study. Moreover, fT3/fT4 ratio showed a continuous and marked shift towards lower fT3 relative to fT4.

Propranolol has been shown to affect thyroid hormone levels, not only through its impact on sympathetic outflow but also via direct hepatic effects, as propranolol can inhibit the conversion of T4 to T3 in isolated rat liver cells (17). This points to an alternative pathway by which beta-blockers may influence thyroid hormone metabolism. Such a direct effect on hepatic thyroid hormone metabolism must be taken into account when interpreting changes in circulating hormone levels following beta-adrenergic blockade in humans.

Tg in serum is associated with the synthesis and secretion of thyroid hormones, and elevated Tg levels suggest increased thyroid hormone production irrespective of cause (18). Thus, it may be a sensitive marker of thyroid gland activity, and measurement of Tg was included in the present study. While serum Tg may be used to describe iodine nutrition in populations with iodine deficiency (19), hunters in Greenland are not iodine deficient, and we thus used Tg as an indirect marker of changes in thyroid gland activity, both evaluated by differences in occupation as a measure of cold exposure and following blocking of sympathetic activity in hunters. Notably, we found that Tg was around 50% higher among hunters with extreme cold exposure compared to residents of the settlement, while urinary iodine concentration was around 115 μg/L in both groups. The difference in Tg corroborates the previous findings among subjects adapted to chronic cold exposure in Greenland. The previous report used two different ways to classify cold exposure, i.e. cold exposure evaluated from residence and based on occupation. Findings were similar with both comparisons, showing progressively higher Tg with increasing chronic cold exposure (7). Hence, thyroid activity was raised with extreme and chronic cold exposure.

Interestingly, the higher thyroid activity associated with a slightly lower fT3 among hunters compared to controls, as fT3 showed a decreasing trend in parallel with the reduced thyroid activity during intervention. The recovery of thyroid activity by day-7 also saw a parallel rise in fT3. The raised turnover of T3 was suggested with the polar T3-syndrome (8), and the need for T3 production makes serum fT3 dependent on even slight changes in the production rate. Thus, even a minor decrease in thyroid activity would be followed by a decrease in fT3 in serum, as seen in the present study, with a parallel restoration of fT3 with recovery of thyroid activity. The parallel changes in fT3 and thyroid activity are further supported by the previous finding of differences in T3 and Tg in serum with chronic cold exposure mentioned above (7). The present study adds that blocking sympathetic activity is followed by alterations in thyroid function, supporting the hypothesis of high T3 turnover with extreme chronic cold exposure.

The change in TSH among hunters following intervention suggests that stimulation of thyroid activity does not depend solely on TSH. Thus, the present study demonstrated a gradual rise in TSH following blocking of the sympathetic activity, which suggests that TSH works to compensate for the dampened stimulation of thyroid activity via the sympathetic system. The parallel rise in fT4 supports this finding, emphasising the importance of the interplay between sympathetic and thyroid activity.

The ratio of fT3 to fT4 showed a distinct decline with the intervention, and this ratio was unaltered in the control group. The majority of T3 is produced in peripheral tissues, where deiodinases convert T4 to T3, and type II deiodinase activity is raised in response to sympathetic activity. The presence of adrenergic nerve terminals both around vessels and between and around follicles in the thyroid (20) is a puzzling and noteworthy observation, and the function of these adrenergic nerve terminals (21) merits further attention. It remains to be disclosed if the change in T3 relative to T4 following blocking of the sympathetic activity with a compensatory rise in TSH is due to reduced sympathetic activity affecting only the deiodinase activity, or if the stimulation via the adrenergic nerve terminals in the thyroid habitually favours a secretion of T3 over T4 to meet the physiological demands of adrenergic activity, which was restricted due to intervention. One of these activities is the activation of UCP-1 in BAT, which is highly needed with the extreme cold exposure in the participants in the present study.

The thermogenic process is dependent on T3 and adrenergic activation of brown adipocytes. The identification of active BAT in human adults (22, 23) has attracted considerable attention because of the

possibility of turning body fat into body heat without the necessity of physical exercise and hence oppose the global obesity epidemic. This has caused a renewed interest in mechanisms for activating UCP-1 and BAT. The metabolic activity of BAT as shown by 18F-FDG uptake using positron emission tomography is effectively reduced by pre-scan preparation with propranolol (24) in support of the intervention of the present study.

Our study provides indications of the mechanism and need for the adrenergic innervation of the thyroid gland. This leads to a hypothesis of adrenergic stimulation promoting T3 over T4 secretion from the thyroid in addition to activating type-II deiodinase activity in peripheral tissues, under normal conditions.

A limitation of the present study was the lack of direct study of the kinetics of thyroid hormone metabolism. In addition, while the design of a field study in the remote settlement allowed us to gather valuable data in a unique population, the low number of inhabitants in the settlement limited the sample size and hence the sensitivity of detecting effects and the generalisability of our findings. The relatively short duration of the study may be a limitation, as additional effects of propranolol on sympathetic regulation and thyroid hormones may evolve over a longer period.

However, the people included were all born and had lived their entire life in the Arctic. Moreover, they were Inuit who show genetic adaptation to the extreme cold of the Arctic (25, 26). In addition, the intervention was based on the finding of adrenergic nerve terminals in the thyroid, as supported by raised serum T3 concentrations following beta-receptor stimulation (27). Finally, participants were investigated while maintaining their usual activities with three hunters catching polar bears during the course of the study.

In conclusion, thyroid activity was raised in subjects with extreme and chronic cold exposure. Blocking the sympathetic activity caused an initial decrease in circulating fT3 in parallel with decreasing thyroid activity, followed by restoration of fT3 levels along with thyroid gland activity. Interestingly, fT3/fT4 ratio showed a continuous and marked shift towards lower fT3 relative to fT4. These alterations in thyroid function support a hypothesis of adrenergic stimulation promoting T3 over T4 secretion from the thyroid via the adrenergic nerve terminals in the thyroid.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work.

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Author contribution statement

MMJ analysed and interpreted the data with hypothesis construction and wrote the manuscript. CA interpreted the data and reviewed the manuscript. HCFS designed the data collection and reviewed the manuscript. SLA interpreted the data and reviewed the manuscript. SA conceived and designed the study, raised funds, performed data collection and interpretation, was involved in the discussion of data, provided assistance in writing the manuscript and edited the manuscript.

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