THERMOGENIC RESPONSE IN THE HYPERTHYROID AND HYPOTHYROID

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ABSTRACT

Thyroid hormone is important for facultative thermogenesis; in the absence of this hormone, the thermogenic response of brown adipose tissue, the major site of facultative thermogenesis in mammals is substantially reduced. The reduced obligatory thermogenesis in hypothyroidism is partially compensated by cutaneous vasoconstriction. Twenty hyperthyroide and 20 hypothyroide women were enrolled in the study. All the patients were evaluated for basaline thermogenic response in the first day. Next morning, all of them evaluated for thermogenic response after the mixed meal test.

Introduction

The effect of thyroid hormone on basal metabolic rate was recognized more than a century ago. In the complete absence of thyroid hormone, basal metabolic rate or resting energy expenditure could be reduced by 30% or more, a change associated with markedly reduced cold tolerance. This indicates that as much as 30% of obligatory thermogenesis depends on thyroid hormone and that this fraction of obligatory thermogenesis is essential for temperature homeostasis. In addition, thyroid hormone is important for facultative thermogenesis; in the absence of this hormone, the thermogenic response of brown adipose tissue, the major site of facultative thermogenesis in mammals is substantially reduced. The reduced obligatory thermogenesis in hypothyroidism is partially compensated by cutaneous vasoconstriction, which is perceived as cold and causes increased sympathetic stimulation of brown adipose tissue. Yet, despite showing signs of increased sympathetic stimulation in chronically hypothyroid rats, brown adipose tissue fails to produce sufficient heat to maintain body temperature, so that hypothyroid animals rapidly develop hypothermia in cold environments.

Another evidence of the importance of thyroid hormone for thermogenic function of brown adipose tissue is the abundant presence of type II 5' iodothyronine deiodinase (D2).

Materials and Methods

Patients: Twenty hyperthyroide and 20 hypothyroide women were enrolled in the study. All the patients were evaluated for basaline thermogenic response in the first day. Next morning, all of them evaluated for thermogenic response after the mixed meal test. Inclusion criteria were age range 30-50, Body Mass Index (BMI) 20-24 kg/m^2 and **hyperthyroide** or **hypothyroide** patients. Exclusion criteria were systolic blood pressure greater than 140 mmHg, diastolic blood pressure greater than 80 mmHg, euthyroid function test , obesity or drugs .

Anthropometric data and blood profiles of patients are given in **Table 1** and **Table 2** respectively in the *RESULTS*. Thermogenic response measurements were performed by direct calorimetry prior to mixed meal test

TABLE 2

Weight and thermogenic response measured by water calorimetry of each subject in the hyperthyroide and hypothyroide patients (kcal/h.kg)

Hyperthyroide			Hypothyroide		
Before mixed-meal		After mixed-meal	Before mixed-meal		After mixed-meal
Weight	Thermo. Response	Thermo. Response	Weight	Thermo. Response	Thermo. Response
67.3	1.64	1.74	61.2	1.81	1.71
50.1	1.30	1.30	63	1.68	1.58
59	1.28	1.58	62.6	1.45	1.55
58	1.58	1.78	70	1.67	1.66
56	1.51	1.61	65.3	1.76	1.56
62	1.74	1.84	65.1	1.53	1.43
66	1.57	1.60	66.1	1.77	1.67
65	1.39	1.42	65	1.50	1.60
57	1.40	1.30	65.8	1.69	1.49
60	1.31	1.71	55.2	1.75	1.55
64	1.36	1.56	60	1.79	1.69
70	1.41	1.71	55.6	1.63	1.53
70.1	1.69	1.79	57	1.84	1.74
65.7	1.78	1.78	57.5	1.69	1.64
70.1	1.57	1.77	69.2	1.53	1.53
61.8	1.72	1.82	71.3	1.86	1.71
70.1	1.79	1.71	59	1.64	1.53
65	1.60	1.89	58	1.71	1.56
59	1.52	1.79	60	1.76	1.66
68.3	1.60	1.80	59.9	1.50	1.63

TABLE 1

Average values of subject characteristics

	Hyperthyroide	Hyporthyroide
Age (year)	37± 3	36.1± 2.9
Body weight (kg)	61.75±7.1	59± 10.1
Systolic BP* (mmHg)	129.7± 11.4	125.5± 8.0
Diastolic BP (mmHg)	58.0± 12.6	61.5± 6.6
BMI (kg/m2)	23.5± 1.1	21.9± 4.8

* Blood Pressure

and after the test.

Mixed-meal test was determined after the participants had fasted overnight. The energy content of the meal was 919 kcal (3.8 MJ); 33 g (14% of energy) were derived from protein, 51 g (49% of energy) were derived from fat, and 83 g (36% of energy) were derived from carbohydrates. The meal contained 30 g of saturated fat, 15 g of monounsaturated fat, and 3 g of polyunsaturated fat.

Mean TSH level <0.02 mU/L, mean FT3 level (free T3) 14.2±0.9 pmol/ml (normal 2.75-6.42 pmol/ml) and mean FT4 level 52.7±5.1 (normal 10.2-24.4 pmol/ml) pmol/ml were measured in the hyperthyroide patients. Mean TSH level 59.6±13.7 mU/L, mean FT3 level 1.53±0.1 pmol/ml and mean level FT4 2.5±1.07 pmol/ml were found in the hypothyroide.

Direct water immersion calorimetry

The water calorimetry system used in this study consists of 2 parts; one is a thermally insulated water tank made of double layer polyester walls with polyuretane insulation

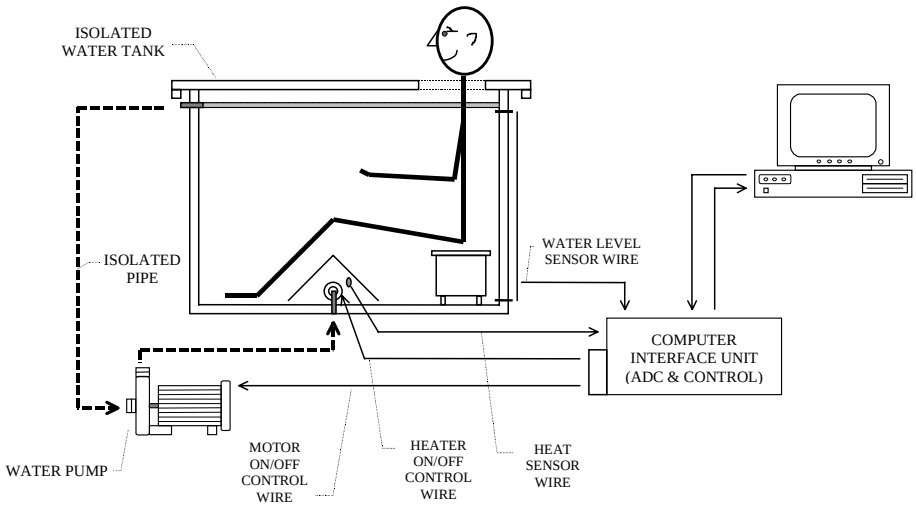

Fig. 1. Schematic diagram of water immersion calorimeter.

in between. The tank is equipped with a circulation pump, feed pump, heater, water level sensors and temperature sensors. Temperature changes are sensed and stored in the hard disk of a PC which together with its peripherals comprise the second part of the system. Temperature can be measured with an accuracy of 0.05°C. When the difference between tank water temperature and ambient temperature is 15 °C or slightly more tank temperature drifts by only 0.13 C°/hour. **Fig. 1** shows the schematic diagram of the calorimeter and its accessories.

Before a measuremnet is started tank water temperature is raised to 34°C. The patient wearing only a swimming suit is then seated in the tank on a comfortable stool so that the entire body except the head is submerged in water and stays in water for the duration of the measurement which lasts a little longer than one hour. The tank holds 360 liters of water. When the patient enters into the water a volume of water equal to the patient's body volume spills out through an outlet. This volume is measured and used to calculate the volume of the ramaining water in the tank. After the patient enters the tank, water temperature is measured every second for 60 minutes and data are stored in the hard disk of a PC. Tank water volume, patient weight and ambient temperature are also entered into the computer. A special program using these data plots the temperature of tank water versus time (**Fig. 2**) and from it calculates heat transferred from the patient to the tank water for the period of measurement. Heat transferred (Q in calories) from the patient to the water in the tank is calculated from the simple relation:

$$Q = mc\,\Delta T \quad \text{(Eq. 1)}$$

where m = mass of water in the tank (g)

c = heat capacity of water (cal/g)

ΔT = difference between the final (measured) and initial (i.e. 34°C) water temperatures in the tank.

The law of conservation of energy dictates that in a living system;

Food intake = Work done by the system + Energy stored + Heat loss

When food intake is 0 as in a fasting individual and work done is zero as in a resting individual heat generated by the body comes from the stored energy only. Under these conditions in a calorimeter such as the one described here, heat *lost* by

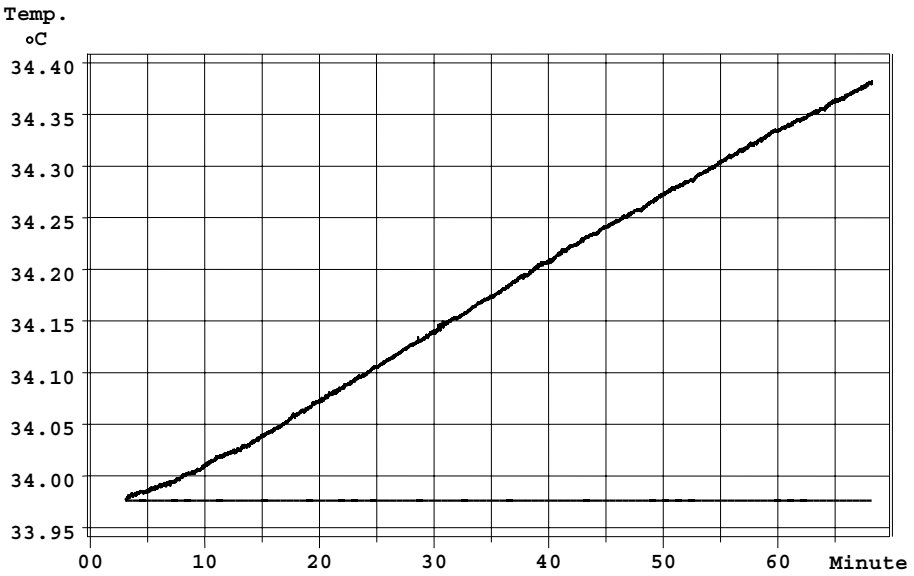

Fig. 2. Typical tank water temperature versus time graph for one patient. Heater is off, temperature rises solely due patient thermogenesis.

the patient, is nearly equal to heat *gained* by the tank water. Therefore, Q is a measure of heat generation (thermogenic response) by the subject and can be expressed in kcal per hour per unit mass of the patient (kcal/h/kg). It should be noted that Q does not include heat loss from the patient by respiration and from the skin in the head region that is outside the water. But these losses are minimal as will be explained in the subsequent paragraphs.

The above procedure is repeated for each patient. The water tank is emptied, disenfected and made ready for the next patient. Measurements are made before medication and 15 days after treatment with sibutramine.

Statistical Analysis

Mean thermogenic response, mean BMI and anthropometric parameters of patients were compared by the two tailed t-test before and after treatment with sibutramine (10 mg/day) for 15 days. A p-value >0.05 was considered significant. SPSS program version 6.1 was used for all statistical analyses. Data which were not normally distributed were analyzed by the Mann-Whitney U test.

Results and Discussion

Baseline mean thermogenic response was 1.62±0.93 kcal/kg.h in the hyperthyroide group increased to 1.74±0.24 kcal/kg.h after mixed meal. The corresponding thermogenic response measures in the placebo group were 1.53±0.01 kcal/kg.h and 1.50±0.06 kcal/kg.h respectively (**Table 2**).

Lipid level changes between the groups were statistically significant (p<00.5).

Heat production, or thermogenesis, is customarily divided into two types: obligatory and facultative. Obligatory thermogenesis can be viewed as the constitutive heat production of homeothermic species. Obligatory thermogenesis is well reflected in the so-called basal metabolic rate or the less strict but more practical *resting energy expenditure*, which are measured under conditions that eliminate the energy cost of physical activity, emotio-

TABLE 3

Blood profiles of patients

	Hyperthyroide	Hypothyroide
	N=20	N=20
Triglyceride (mg/d)	122.2± 42.8	156.8± 78.9
LDL-Cholesterol (mg/dl)	125.0± 30.7	142.7± 34.6
HDL-Cholesterol (mg/dl)	53.35± 10.8	46.0± 14.6
Fasting Blood Glucose (mg/dl)	93.9± 6.23	83.2± 7.0
Post Prandial Glucose (mg/dl)	109.4± 15.2	111.8± 18.6
SGOT (U/l)	21.0± 5.5	29.2± 5.4
SGPT (U/l)	23.4± 8.6	28.2± 11.6
Total protein (gr/dl)	7.2± 0.89	7.0± 0.4
Na (mEq/l)	145.2± 2.0	138.5± 2.9
K (mEq/l)	4.5± 0.42	4.3± 0.3
Ca (mg/dl)	9.7± 0.2	9.1± 0.6
Creatinine (mg/dl)	0.84± 0.1	0.9± 0.2
Hematocrit (%)	39.6± 3.9	37.6± 3.1
Leukocyte ($x10^3/mm^3$)	8.5± 1.9	7.7± 1.7
Platelet ($x10^3/mm^3$)	302.0± 70.2	281.8± 44.3

nal distress, temperature adaptation, and food processing. If obligatory thermogenesis becomes insufficient to maintain body temperature, the body activates heat-conserving mechanisms (cutaneous vasoconstriction, piloerection) and recruits additional thermogenic mechanisms. These latter mechanisms constitute what is called adaptive thermogenesis. Skeletal muscle shivering is the most immediate thermogenic response to a cold environment. If cold is sustained, this form of adaptive thermogenesis is rapidly replaced by the so-called nonshivering facultative thermogenesis, or simply facultative thermogenesis.

It has recently been reported that resting energy expenditure, a good measure of obligatory thermogenesis, is remarkably responsive to thyroid hormone around the euthyroid state in humans. In athyroic patients who maintained a euthyroid state by taking exogenous thyroxine (T_4), minimal changes in daily dose allowing the free T_4 concentration in serum to stay within the normal range, were associated with clearly detectable changes in resting energy expenditure. However, no changes were detected in measures of thyroid hormone action used clinically, such as levels of low-density lipoprotein cholesterol, sex hormone–binding protein, or angiotensin-converting enzyme. Yet thyroid-stimulating hormone, the most sensitive marker of thyroid hormone action, correlated inversely and closely with resting energy expenditure. For a maximal excursion of thyroid-stimulating hormone between 0.05 and 10 mU/L induced by a change in l-thyroxine dose, resting energy expenditure changed by 15% ($r = 0.82$; $P < 0.001$). Such levels of thyroid-stimulating hormone are well within those seen in subclinical thyroid dysfunction. Moreover, it has been subsequently reported that spontaneous fluctuations in free T_4 concentration in lean normal men are also associated with significant changes in resting energy expenditure.

Thyroid hormone is necessary for both forms of thermogenesis and has the potential to stimulate both. In hyperthyroidism, the two effects would be additive, creating the risk for hyperthermia. Even so, hyperthermia is rarely a manifestation of hyperthyroidism in the so-called thyroid or thyrotoxic storm. As mentioned earlier, there is evidence in rodents that hyperthyroidism is associated with reduced brown adipose tissue facultative thermogenesis. Hyperthyroidism decreases sympathetic stimulation of tissues, probably acting at a central level. Thyroid hormone also rapidly reduces the expression of $ß_3$-adrenergic receptors in brown adipose tissue. These changes may explain the reduced UCP activation and synthesis responses to cold in thyrotoxic rats The hyperthermia of thyroid storm might result from failure of these or similar mechanisms which prevent activation of facultative thermogenesis in human hyperthyroidism. Type II 5'-iodothyronine

deiodinase is present in human muscle and thermogenesis in humans may depend on T_3 locally generated by this enzyme. The inhibition of D2, suppression of the sympathetic activity or both could be impaired in the thyrotoxic storm. This view is consistent with the clinical features of the thyrotoxic storm, such as its proximity to stressful situations and its alleviation by sympathetic blockade. Hyperthyroidism is evidently associated with an increase in metabolic rate and an acceleration of practically all the metabolic pathways with a consequent increase in ATP turnover and heat production. For all three macronutrients, namely proteins, carbohydrates and lipids, both anabolic and catabolic pathways are accelerated. The contribution of this accelerated metabolic cycling however accounts for a small percentage of the thermogenic effect of thyroid hormone althogether, probably not more than 15%.

In hypothyroidism, obligatory thermogenesis is reduced and stimulation of brown adipose tissue is increased. Although this tissue shows signs of adrenergic stimulation such as hyperplasia and increased protein content, lack of T_3 in brown adipose tissue drastically limits its thermogenic response to sympathetic stimulation. The reduced obligatory thermogenesis is compensated by heat-saving mechanisms and shivering which are effective only in a narrow temperature range. Thyroidectomized (Tx) rats however, present hypothermia and die rapidly when placed in the cold despite increased norepinephrine (NE) turnover in several tissues. Even exogenous administration of large amounts of NE will not restore the thermal response or core temperature in Tx rats. However, cold- or NE-induced facultative thermogenesis are rapidly restored upon administration of subphysiological doses of T_4, reinforcing the key role of thyroid hormones in the triggering and maintenance of cold-induced thermogenesis.

In summary, we suggest that diet induced thermogenetic response in hyperthyroidism is higher than that in hypothyroidism.

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