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Effect of experimental hypo- and hyperthyroidism on serum adiponectin

Christina Nogueira Aragão, Luana Lopes Souza, Adriana Cabanelas, Karen Jesus Oliveira, Carmen Cabanelas Pazos-Moura*

Laboratório de Endocrinologia Molecular, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, CEP 21949 · 900 Rio de Janeiro, RJ, Brazil

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Abstract

Adiponectin, an adipocyte-derived hormone, has been shown to decrease body weight by increasing thermogenesis and lipid oxidation. Thyroid hormones have similar effects. Here we investigated if experimental hypo- and hyperthyroidism in rats would induce changes in serum adiponectin concentration. Adult rats became hypothyroid by treatment with 0.03% methimazole in the drinking water for 28 days or hyperthyroid by subcutaneous thyroxine injections (50 μg/100g body weight) for 10 days. Serum adiponectin level of hyperthyroid rats was 3.2-fold higher than that of euthyroid ones ($P < .001$), whereas that in hypothyroid rats tended to be lower (38%), but without statistical significance. Serum adiponectin had a positive correlation with serum thyroxine ($r = .81$, $P < .001$) and triiodothyronine ($r = 0.68$, $P = .03$) and a negative correlation with serum thyroid-stimulating hormone ($P = -.62$, $r = 0.015$). In addition, there was a negative correlation between serum adiponectin level and total visceral white adipose mass (= sum of inguinal, epididymal, and retroperitoneal depots; $r = -0.43$; $P = .032$), which was reduced by 40.5% in hyperthyroid ($P < .01$) but not in hypothyroid animals. A positive association between serum adiponectin level and brown adipose tissue mass was found ($r = 0.43$, $P = .03$), but not with body weight, which was reduced in both hypo- and hyperthyroid groups. Adiponectin has been reported to have an insulin-sensitizing effect. However, in hyperthyroid rats, higher serum adiponectin level was not accompanied by statistically different changes in basal serum insulin levels, blood glucose concentrations, or glucose tolerance as compared with euthyroid rats, except for a slight increase in blood glucose level at 120 minutes after glucose intraperitoneal administration ($P < .05$). Therefore, experimental hypothyroidism did not change serum adiponectin concentration, whereas hyperthyroidism induced an important elevation in the serum hormone concentration, with still unknown biological significance.

1. Introduction

Adiponectin, an adipocyte-derived protein, is an important component of the homeostatic mechanisms that regulate body weight and metabolism. Epidemiologic and experimental studies have suggested that adiponectin deficiency is linked to obesity and insulin resistance [1-5]. Adiponectin plasma concentrations are lower in obese humans than in normal-weight subjects [1,2]. Adiponectin treatment of obese rodents caused reduction in body weight along with lowering of glycemia and improvement of insulin resistance [6-8]. Mice with adiponectin deficiency developed insulin resistance, glucose intolerance, dyslipidemia, and diet-induced obesity, as well as susceptibility to vascular injury and atherosclerosis [4,5,9]. The body weight reduction effect of adiponectin has not been attributed to central action on the neuronal circuitry that regulates food intake, but rather to central and peripheral effects on energy expenditure [10]. Adiponectin has metabolic effects, such as stimulation of fatty acid oxidation, reduction in gluconeogenesis, and increase in thermogenesis [2,10-14].

Thyroid dysfunctions are associated with changes in body mass, adipose tissue metabolism, and thermogenesis and, therefore, it is reasonable to question whether thyroid dysfunctions would be accompanied by changes in adiponectin production. Clinical studies examining adiponectin circulating levels of hypo- and hyperthyroid patients are not conclusive. It has been reported that serum adiponectin concentration was higher in hyperthyroid patients before treatment than when they achieved a hypothyroid state in consequence of the treatment [15,16]. Other studies found

* Corresponding author. Tel.: +55 21 2560 8093x213; fax: +55 21 2280 8193.
E-mail address: cpazosm@biof.ufrj.br (C.C. Pazos-Moura).

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no changes in serum adiponectin concentration in thyroid dysfunctions [17,18]. However, because most thyroid dysfunctions studied are autoimmune diseases, other factors not related to alterations in thyroid hormone action may be the primary cause of modifications in adiponectin levels. In healthy subjects, among other factors, serum free thyroxine (T_4) concentration was identified as a predictive variable of serum adiponectin [19], which suggests that thyroid hormone may be one of the regulators of adiponectin secretion. However, direct evidence is lacking. Recently, in cultures of brown adipose tissue (BAT), thyroid hormone presented a small stimulatory effect on adiponectin messenger RNA expression and on hormone secretion [20], which was not found when immortalized adipocyte cells, 3T3-L1, were incubated with triiodothyronine (T_3) [21]. The aim of the present study was to determine whether thyroid state in an animal model modulates adiponectin production. As far as we know, this has not been reported yet.

2. Materials and methods

2.1. Animals

Adult male Wistar rats (289.2 ± 6.45g body weight) were kept under 12:12-hour light-dark cycle (onset at 7:00 AM) at 24°C ± 1°C and maintained on a standard diet and tap water ad libitum. All experimental protocols were approved by our institutional animal care committee.

Experiments were performed with euthyroid, hypothyroid, and hyperthyroid rats. Hypothyroidism was induced by treatment with methimazole (0.03%) in the drinking water for 28 days. Hyperthyroidism was induced by subcutaneous daily injection of 50 μg thyroxine per 100 g body weight (BW) (T_4, L-thyroxine, Sigma, St Louis, MO) for 10 days.

2.2. Effect of hypo- and hyperthyroidism on serum adiponectin

To investigate whether thyroid status interferes with serum adiponectin concentration, eu-, hypo-, and hyperthyroid rats, produced as described before, were killed by decapitation and trunk blood was collected, centrifuged to obtain serum, and stored at −20°C until assayed for adiponectin, thyroid-stimulating hormone (TSH), and thyroid hormone measurements. Retroperitoneal, inguinal, and epididymal adipose tissue, BAT, and heart were dissected and weighed.

2.3. Effect of hyperthyroidism on glucose tolerance

In another set of experiments, eu- and hyperthyroid rats obtained exactly as in the previous experiment were investigated for glucose tolerance. Rats were fasted overnight and received a single intraperitoneal injection of glucose (Merck, Rio de Janeiro, Brazil), 1.0 g/kg body weight, and tail whole-blood samples were taken at 0, 20, 40, 60, and 120 minutes after glucose administration. Blood glucose was measured by using a glucometer (MediSense Optium, Abbott Laboratories, Bedford, MA).

Eu- and hyperthyroid rats were killed by decapitation, trunk blood glucose was measured, and serum was obtained and kept at −20°C until assayed for insulin determination.

2.4. Hormone measurements

Serum adiponectin concentration was measured by radioimmunoassay using an adiponectin RIA kit produced by LINCO Research (St Charles, MO). Minimum assay detection value was 1 ng/mL. Intra-assay variation was 8.4%; all samples were run within the same assay.

TSH serum concentrations were determined by specific radioimmunoassay using reagents supplied by the National Hormone Pituitary Program, National Institutes of Health (Torrance, CA), as previously described [22], and was expressed in terms of the reference preparation (RP3). Minimum assay detection value was 0.36 ng/mL. Total T_4 and T_3 in serum samples were quantified by radioimmunoassay (T4 Mab, ICN Pharmaceuticals, Costa Mesa, CA). Sensitivity of assays were 0.76 μg/dL for T_4 and 6.7 ng/dL for T_3. Serum insulin was determined by radioimmunoassay using a commercial kit (ImmunoChem Coated Tube, MP Biomedicals, New York, NY). Limit of detection was 5μIU/mL.

In all hormone measurements, within-assay variation was less than 9%, and samples were measured within the same assay.

2.5. Statistical analyses

Data are expressed as mean ± SEM. Analysis of variance was performed to analyze data on serum adiponectin, TSH, T_3, and T_4 concentrations of eu-, hypo-, and hyperthyroid animals, whereas unpaired *t* test was used to analyze blood glucose and insulin levels of eu- and hyperthyroid rats at basal state and at each given time interval during the glucose tolerance test. Serum TSH was analyzed only after log transformation. Relations between variables were analyzed by analysis of variance and simple correlation (Pearson and Spearman tests). Levels of statistical significance were set at *P* value less than .05.

Table 1
General characteristics of euthyroid, methimazole-treated rats (hypothyroid) and T_4-treated (50 μg/100 g BW for 10 days) rats (hyperthyroid)

	Euthyroid	Hypothyroid	Hyperthyroid	*P*
T_4 (μg/dL)	4.539 ± 0.18	<2	7.491 ± 0.42[a]	<.0001
T_3 (ng/dL)	74.09 ± 3.4	<50	322.3 ± 22.6[a]	.0001
TSH (ng/mL)	2.52 ± 0.62	31.85 ± 3.23[a]	<0.36	.0001
Body weight before treatment (g)	290.1 ± 9.59	287.9 ± 11.96	289.6 ± 12.91	NS
Body weight after treatment (g)	396.3 ± 11.5	341.3 ± 12.8[a]	361.2 ± 12.2	.01
Heart weight (g)	1.13 ± 0.028	0.75 ± 0.02[a,b]	1.41 ± 0.05[a,b]	.001

NS indicates nonsignificant.
[a] Versus euthyroid rats.
[b] Versus hypothyroid or hyperthyroid rats.

3. Results

As depicted in Table 1, the pharmacologic induction of hypo- and hyperthyroidism was effective. Hypothyroid rats presented serum T_4 and T_3 levels below detectable values, whereas serum TSH was significantly increased (12.6-fold, $P < .001$). Hyperthyroid rats, as compared with euthyroid rats, exhibited 1.7- and 4.4-fold higher serum T_4 and T_3 levels, respectively, whereas TSH was suppressed to undetectable levels.

As expected, thyroid status affected body composition. Both hypo- and hyperthyroid rats presented lower body weight than euthyroid ones, but the difference was significant only for hypothyroid group ($P < .01$). Heart weight was decreased by 33.4% in hypothyroid rats ($P < .001$ vs euthyroid and hyperthyroid groups), whereas it was increased 1.3-fold in hyperthyroid animals ($P < .001$ vs euthyroid and hypothyroid groups). As shown in Fig. 1, retroperitoneal and inguinal white adipose mass (WAT) were significantly reduced in hyperthyroid rats (47.7% and 36.1% reduction; $P < .01$ and $P < .05$, respectively), whereas epididymal fat mass was equally reduced in both hyper- and hypothyroid groups (22.3% and 25.4% reduction, respectively; $P < .05$). Total visceral WAT, as calculated by the sum of the 3 fat depots, was reduced by 40.5% in hyperthyroid animals ($P < .01$), whereas it did not change significantly with hypothyroidism. BAT mass of hyperthyroid rats was 1.7-fold higher than that of euthyroid ones and remained unchanged in hypothyroid animals.

Serum adiponectin level (Fig. 2) was significantly increased in the hyperthyroid group, which exhibited 3.2-fold higher values than the euthyroid group ($P < .001$). Although there was a strong trend to lower serum adiponectin levels in hypothyroid animals compared with euthyroid ones (38% lower), the difference did not reach statistical significance.

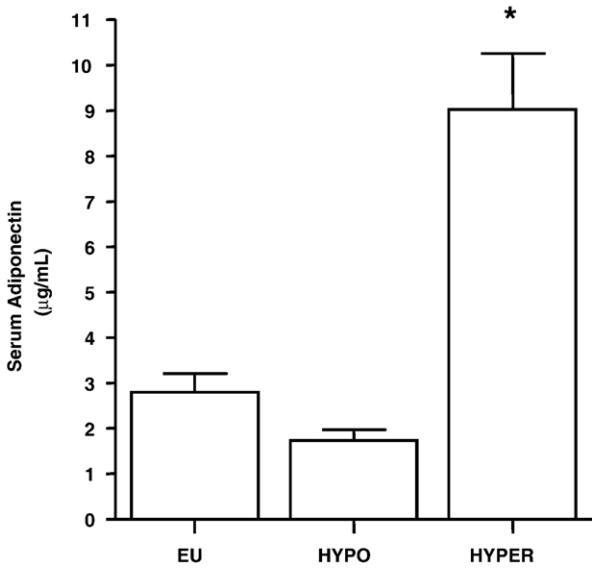

Fig. 1. Fat depot mass of normal euthyroid rats (EU), methimazole-treated rats (HYPO), and T_4-treated (50 μg/100 g BW for 10 days) rats (HYPER). $^{\#}P < .001$; $^{*}P < .05$.

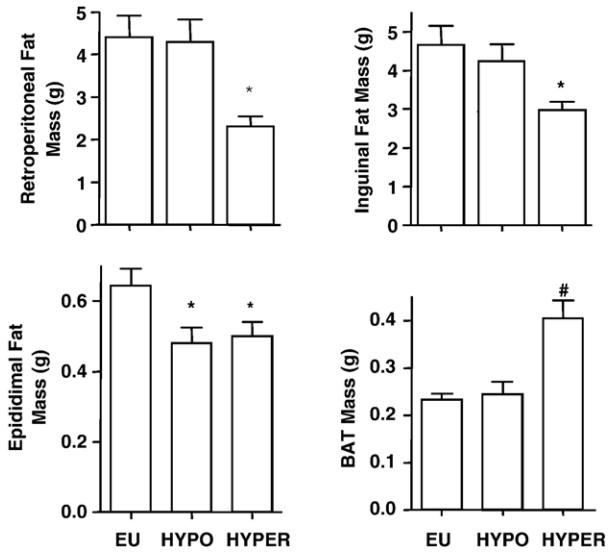

Fig. 2. Serum adiponectin levels of normal euthyroid rats (EU), methimazole-treated rats (HYPO), and T_4-treated (50 μg/100 g BW for 10 days) rats (HYPER). $^{*}P < .001$.

As depicted in Fig. 3, serum adiponectin concentration had a positive correlation with serum concentrations of T_4 ($r = 0.81$, $P < .001$) and T_3 ($r = 0.68$, $P = .03$) and negative association with serum TSH ($r = -0.52$, $P = .015$). In addition, there was a negative correlation between serum adiponectin concentration and total WAT, calculated as the sum of 3 depots (inguinal, epididymal, and retroperitoneal; $r = -0.43$; $P = .032$). A positive association of serum adiponectin level and BAT mass was found ($r = 0.43$, $P = .03$). However, there was no correlation between serum adiponectin level and body weight ($r = -0.15$).

Serum insulin and blood glucose concentrations of euthyroid and hyperthyroid rats did not show statistically significant differences (serum glucose: 121 ± 4.2 and 132 ± 7.6 mg/dL for the eu- and hyperthyroid groups, respectively; serum insulin: 14.7 ± 2.8 and 16.7 ± 2.0 μIU/mL for the eu- and hyperthyroid groups, respectively). The homeostasis model assessment index, calculated as the product of glucose (millimoles per liter) and insulin (microinternational units per milliliter) was similar between groups (116.2 ± 32 vs 125 ± 20). In addition, glucose tolerance seems not importantly altered in the hyperthyroid group. Blood glucose level was similar between groups at 0, 20, 40, and 60 minutes after glucose administration, although at 0 (baseline) and 120 minutes after glucose intraperitoneal administration, blood glucose level tended to be slightly higher in the hyperthyroid group, reaching statistical significance ($P < .05$) at 120 minutes.

4. Discussion

The present article shows that circulating levels of adiponectin are elevated in experimental hyperthyroidism

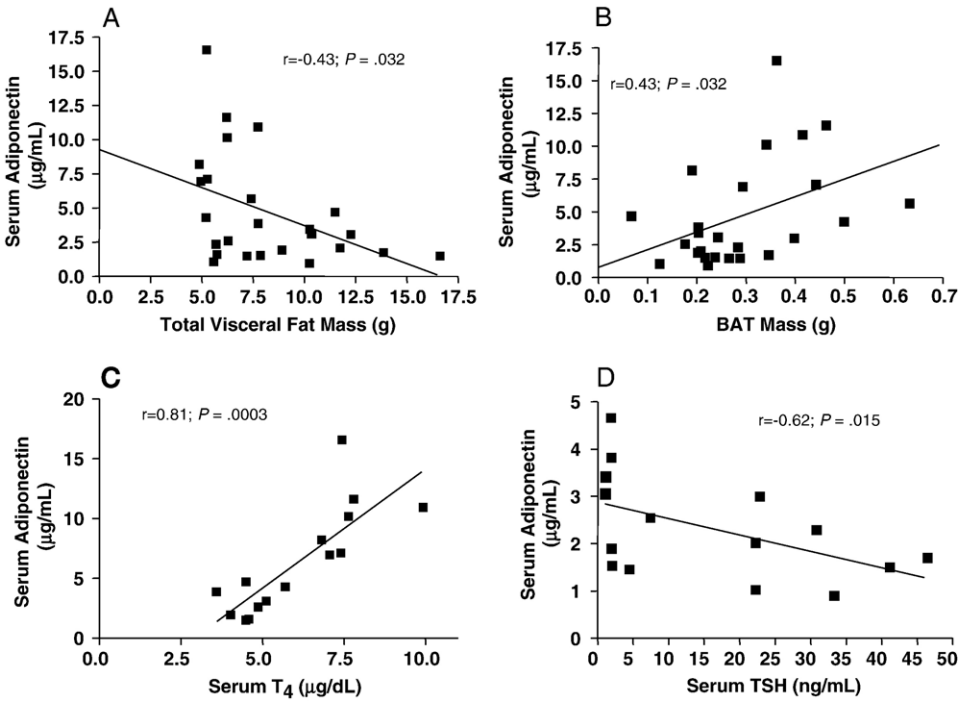

Fig. 3. Relation between serum adiponectin levels and (A) total visceral fat mass (sum of inguinal, epididymal, and retroperitoneal pads), (B) BAT mass of eu-, hypo-, and hyperthyroid rats, (C) serum T_4 of eu- and hyperthyroid rats, and (D) serum TSH of eu- and hypothyroid rats.

in rats. Previously, clinical studies had suggested that the thyroid state may be one determinant of adiponectin secretion [16,15], although others could not confirm this observation [17,18]. However, it is difficult to make conclusive remarks in studies with patients because of many intervening factors besides lack or excess of thyroid hormone action. Our study reinforces the possibility that excess of thyroid hormones causes an increase in circulating adiponectin. Although it did not reach statistical significance, hypothyroidism seems to induce a decrease in serum adiponectin concentration. Therefore, it is possible that thyroid hormones are in vivo regulators of adiponectin secretion. This hypothesis is reinforced by studies in euthyroid subjects, where serum T_4 was found to be associated with higher levels of adiponectin [19]. In addition, another study [23] showed that in euthyroid, healthy obese women there was an inverse correlation between plasma TSH and adiponectin levels, which we also found in the present study.

The precise mechanism leading to increased serum adiponectin level in hyperthyroid animals cannot be elucidated by the present study. The first possible mechanism to be considered is related to T_4-induced decrease in visceral fat mass. Negative association of serum adiponectin with body mass and adiposity has been clearly demonstrated in humans and animal models [1,3,24,25], although this is more evident in the context of obesity. Some authors could not observe changes in adiponectin levels in lean subjects that had lost weight after dieting [26]. Moreover, in anorexia nervosa, despite the significant decrease in adipose mass, adiponectin has been found increased, unaltered, or even decreased [27-31]. Therefore, it seems that other factors besides adiposity affect adiponectin production. In the present article, changes in body weight did not seem to be a determinant factor because hypo- and hyperthyroid animals presented reduced body weight, and only hyperthyroid animals had higher serum adiponectin levels. Therefore, although the higher adiponectin level can be related to the reduction in visceral fat presented in hyperthyroid rats, the possibility of a direct T_4 action on adiponectin expression must be considered. The effect of T_4 on adiponectin production of primary white adipocytes is unknown, although in the adipocyte cell line 3T3-L1 [21] T_3 was not able to modify adiponectin messenger RNA expression. However, in brown adipocyte cultures, incubation with T_4 resulted in a modest increase in the secretion and expression of adiponectin [20]. It is interesting to note that BAT is enlarged in hyperthyroid rats and there was a positive correlation between BAT mass and serum adiponectin level. Thus, it raises the possibility that BAT may be one contributing source of adiponectin in hyperthyroid rats. In any case, the magnitude of adiponectin increment ant the strong positive correlation between serum adiponectin and T_4 reinforce the hypothesis that T_4 may be one important direct or indirect in vivo regulator of circulating concentrations of adiponectin. Further studies will be necessary to clarify the precise mechanisms involved.

Decreased plasma adiponectin concentration observed in obese patients and in diabetic patients has been associated with insulin resistance [1,3], which can be ameliorated by

reduction in body weight concomitant to increase in adiponectin production [2,4,7]. In addition, experimental studies had supported the insulin-sensitizing effect of adiponectin [2,8,9,11-14]. However, not in all situations is there a positive association between increasing plasma levels of adiponectin and higher insulin sensitivity. Abassi and coworkers [32] showed that circulating adiponectin concentrations did not change in association with enhanced insulin sensitivity after moderate weight loss in insulin-resistant, obese individuals. Another study [33] could not find such a relation in lean subjects, but only in obese subjects. Therefore, the modulation of insulin action by adiponectin is complex and probably has many intervening factors. The present article suggests that thyroid hormone status is one of these factors, as the higher adiponectin concentration of hyperthyroid rats was not accompanied by higher insulin sensitivity.

The biological meaning of increased adiponectin levels in the hyperthyroid state is unknown. Adiponectin administration to rodents reduces body weight and fat mass as well as increases adrenergic activity and thermogenesis [6,10]. These alterations are present in hyperthyroidism, which raises the question of whether the higher levels of adiponectin in hyperthyroidism are, to some extent, contributing to the effects of thyroid hormone excess. On the other hand, the higher adiponectin levels could represent a compensatory mechanism that counteracts the effect of hyperthyroidism in the direction of insulin resistance [34,35].

In conclusion, in rats, thyroid hormone excess, but not deficiency, modified serum concentrations of adiponectin. The important elevation of serum adiponectin concentrations in the hyperthyroid state may have a biological relevance, which remains to be clarified.

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