Thyroid Hormones Influence Serum Leptin Concentrations in the Rat

HÉCTOR F. ESCOBAR-MORREALE, FRANCISCO ESCOBAR DEL REY, AND GABRIELLA MORREALE DE ESCOBAR

Unidad de Endocrinología Molecular, Instituto de Investigaciones Biomédicas, CSIC & UAM, Arturo Duperier 4, 28029 Madrid, Spain.

ABSTRACT

Leptin, the product of the ob gene, is secreted by adipocytes and has been shown to decrease appetite and increase energy expenditure. Leptin mRNA in adipocytes correlates with body wt, and serum leptin levels correlate with body fat. Alterations in thyroid status are frequently associated with changes in body wt. To evaluate the possible influence of thyroid status on the leptin system, we have measured serum leptin concentrations in thyroidectomized rats infused either with placebo, or with different doses of T₄ (0.8 to 8.0 μg/100 g body wt per day) or T₃ (0.25 to 2.0 μg/100 g body wt per day), covering a wide range of thyroid hormone concentrations, from overt hypothyroidism to hyperthyroidism. Intact animals infused with placebo were used as euthyroid controls.

Infusion of T₄ or T₃ into thyroidectomized rats resulted in a decrease in serum leptin levels with respect to the thyroidectomized animals infused with placebo. When compared to the control group, serum leptin levels were decreased in the groups infused with the higher T₄ and T₃ doses, and tended to be elevated in the thyroidectomized animals infused with placebo. The leptin/body wt ratio was markedly increased in thyroidectomized rats infused with placebo, and decreased in the animals infused with the higher thyroid hormone doses.

In conclusion, thyroid hormones exert a negative influence on serum leptin concentrations, which is greater than expected by the changes in body wt. The precise mechanism of this influence remains to be elucidated.

LEPTIN, the product of the ob gene, is a protein secreted by adipocytes, that regulates body wt by signaling the size of the energy stores in adipose tissue (1). Administration of leptin decreases food intake and increases the resting metabolic rate and thermogenesis (2), further suggesting a role of leptin in the regulation of body wt.

Plasma leptin has been found to be highly correlated with body mass index in humans and in rodents (3). In agreement, serum leptin concentrations in humans are increased in obesity (4) and decreased in anorexia nervosa (5), reflecting the changes in body wt and fat mass.

The thyroid axis might influence leptin secretion and metabolism. Thyroid hormones increase the basal metabolic rate and increase thermogenesis, including uncoupling of oxidative phosphorylation (6). Moreover, abnormalities of thyroid function are frequently associated with changes in body wt. Finally, thyroid hormones have a permissive role in the effects of catecholamines on β-adrenergic receptors, and the stimulation β3-adrenergic receptors suppresses leptin expression in mice (7).

Thus, alterations in thyroid status might lead to compensatory changes in circulating leptin. The data available at present regarding the possible influence of thyroid status on the leptin system are confusing. On the one hand, leptin mRNA in adipocytes is increased in hypothyroid male rats, and decreases after administration of T₄ (8). On the contrary, hypothyroid patients have been reported to have decreased serum leptin levels when compared to control subjects matched for age, sex, and body mass index (9). Finally, short term hyperthyroidism in humans has no apparent effect on serum leptin concentrations (10).

To provide new insights into the relationship between thyroid hormones and leptin we have studied the plasma concentrations of the latter in thyroidectomized rats infused either with placebo, T₄ or T₃.

Materials and Methods

Young female Wistar rats of 120-150 g body wt were surgically thyroidectomized, and received 100 μCi of 131I ip one week later. After 28 days, rats with complete stasis of body wt increase were divided into groups of 5-6 animals each, and osmotic minipumps (ALZET, model. 2ML2, Palo Alto, CA) were implanted under the dorsal skin of the animals. In several separate experiments, the rats...
were infused either with placebo solution, T₄ (0.8, 0.9, 1.0, 2.0, 3.0, 4.0 and 8.0 μg / 100 g body wt • day), or T₃ (0.25, 0.50, 0.75, 1.00 and 2.00 μg / 100 g body wt • day). Non-thyroidectomized rats, matched for sex and age, and infused with placebo, served as a control euthyroid group in every experiment.

After 12-13 days of infusion the rats were bled and perfused, after being slightly anesthetized with ether. Samples of plasma and several tissues were obtained for the present and other studies. The thyroid hormone plasma and tissue concentrations of some, but not all, of the experimental groups have been previously published (11, 12).

Thyroxine, T₃ and TSH were measured as previously reported (11, 12). Serum leptin was measured by direct RIA (Linco Research Inc., St. Charles, MO, USA), with mean intra- and interassay coefficients of variation of 3.3% and 4.8%, respectively.

One-way ANOVA, and the protected least significant difference test for multiple comparisons were used, after validation of the homogeneity of variances by the Bartlett-Box F test. Logarithmic transformations usually ensured homogeneity of variances when this was not found with the raw data. Results are expressed as means±SEM. P<0.05 was considered significant in all comparisons.

Results

Serum leptin concentrations

The plasma leptin concentrations of the thyroidectomized rats infused with placebo, T₄ or T₃, as compared to placebo-infused intact control animals, are shown in Fig. 1. The infusion of T₄ resulted in a decrease in serum leptin levels as compared to those of the placebo-infused thyroidectomized animals, with the unexplained exception of the group infused with 1.0 μg T₄ / 100 g body wt • day. A decrease was also found in the animals infused with T₃ at doses above 0.25 μg T₃ / 100 g body wt • day.

When compared to the control group, leptin concentrations in the placebo infused thyroidectomized rats were found to be the same. Serum leptin was decreased with respect to controls in all the groups infused with T₄ or T₃, with the exception of the groups infused with 1.0 μg T₄ / 100 g body wt • day and 0.25 μg T₃ / 100 g body wt • day.

However, marked differences in body wt were present between the groups (P<0.0001 by one-way ANOVA), the control group having the highest wt, and the thyroidectomized rats on placebo showing the lowest. We therefore evaluated the leptin/wt ratios, which are also shown in Fig. 1. Thyroidectomized rats infused with placebo had a marked increase in the leptin/wt ratio as compared to the control group. Infusion of T₄ or T₃ resulted in a progressive decrease in the leptin/wt ratio, which was similar to that of controls in all the groups infused with T₄ or T₃, with the exception of the groups infused with 3.0 and 4.0 μg T₄ / 100 g body wt • day, and the groups infused with 1.0 and 2.0 μg T₃, 100 g body wt • day, in which the leptin/wt ratio was reduced.

Serum thyroid hormone concentrations

The thyroidectomized animals infused with placebo were severely hypothyroid, with decreased plasma T₄ and T₃, and increased plasma TSH (Fig. 2). The groups infused with 0.8 and 0.9 μg T₄ / 100 g body wt • day, and the group infused with 0.25 μg T₃ / 100 g body wt • day, were hypothyroid, with low T₄ and T₃, and elevated TSH. The group infused with 1.0 μg T₄ / 100 g body wt • day had normal T₃, and a slight increase in T₄ and TSH. The remaining groups were biochemically hyperthyroid: the groups infused with 2.0 to 8.0 μg T₄ / 100 g body wt • day had elevated T₄ and T₃, with decreased TSH, and the groups infused with 0.5-2.0 μg T₃ / 100 g body wt • day had elevated T₃ and decreased TSH, whereas T₄ was very low, as T₄ was not infused.
Discussion

Our data show an effect of changes in thyroid status on serum leptin concentrations. Serum leptin concentrations of thyroidectomized rats were decreased by subcutaneous infusions of both T₄ or T₃. Serum leptin concentrations, however, were not different in hypothyroid animals when compared to controls.

Thyroidectomized animals on placebo had a much lower wt than controls. Their wt increased with the infusion of thyroid hormone, but control body wt was not reached. Hypothyroidism in young rats is characterized by growth retardation, with the resultant stasis of both body wt, and length, increase. Thus, the difference in body wt which we have observed between hypothyroid animals and controls was not totally dependent on a decrease in fat mass. When the difference in body wt was taken into consideration, hypothyroid animals had an elevated serum leptin relative to their wt. The leptin/wt ratio normalized, and even decreased, when T₄ or T₃ were infused. This result further suggests that thyroid hormones exert an inhibitory influence on serum leptin concentrations.

Our results are in agreement with a previous study in which hypothyroid rats showed increased leptin mRNA levels, and increased leptin secretion, acutely reversed by administration of supraphysiological doses of T₄ (8). Our data confirm these results, and further suggest that the inhibitory effects of thyroid hormone on serum leptin might be a physiological phenomenon:

1) The inverse relationship between leptin and thyroid hormones is maintained over a wide range of thyroid hormone levels, from severe hypothyroidism to hyperthyroidism.

2) The inhibitory effects of thyroid hormone on serum leptin occurs during chronic administration [12-13 days is equivalent to approximately 7 months in humans (11)], in addition to the acute effect described by Fain et al (8).

3) Both T₄ and T₃ have inhibitory effects on serum leptin.

Our experimental design does not offer any explanation regarding the mechanism underlying the inhibitory effect of thyroid hormone on serum leptin, but it seem plausible that leptin might decrease to avoid excessive catabolism when excess thyroid hormone is present, as both leptin and thyroid hormone increase the metabolic rate.

Although there is very little information at present, the relationship between leptin and thyroid hormones appears to be different in the rat and in humans. To date, the only published studies have shown no effect on serum leptin of short-term T₃-induced hyperthyroidism in normal volunteers (10). Moreover, decreased leptin levels have been described in hypothyroid patients, suggesting a stimulatory role of thyroid hormone on leptin levels in humans (9). Thus, the inhibitory effect of thyroid hormone on leptin does not seem to occur in humans and, in fact, thyroid hormone has been postulated to be a permissive factor for leptin secretion (9).

In conclusion, thyroid hormones exert an inhibitory effect on circulating leptin concentrations in the rat. The mechanisms underlying this effect remain to be elucidated.

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