**Topic:** T₃ REGULATES THE BIOACTIVITY OF THYROID’S REGULATOR: TSH

**Title:** Evidence for thyroid hormone as a positive regulator of serum thyrotropin bioactivity.

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**Reference:** Journal of Clinical Endocrinology & Metabolism 92: 3108-3113, 2007

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**SUMMARY**

**Context:** The regulation of TSH bioactivity in humans is not completely understood.

**Objective:** Aim of study was to investigate the role of serum thyroid hormones in regulating the bioactivity of TSH.

**Design:** The bioactivity and glycosylation of TSH were determined in vitro in 9 patients (6 females and 3 males; age: 41.3 yrs) with primary hypothyroidism before and after l-T4 replacement, as well as in 11 age- and sex- comparable controls (7 females and 4 males; age: 37.6 yrs), and finally in 2 thyroidectomized patients with TSH-secreting adenomas during and after l-T4 withdrawal.

**Methods:** *In vitro* TSH bioactivity was measured by a sensitive and specific bioassay based on the generation of cyclic AMP by CHO cells transfected with the human TSH receptor (in JP-26 cells obtained from Gilbert Vassart in Brussels). The glycosylation of TSH was measured by concanavalin A lectin and ricin column affinity chromatography.

**Results:** *In vitro* TSH bioactivity in hypothyroid patients was low as compared with controls (0.48 ± 0.1 versus 1.10 ± 0.2; \(P=0.004\)) and increased during l-T4 treatment (from 0.48 ± 0.1 to 0.80 ± 0.1; \(P=0.01\)). A strong significant positive correlation was found between the absolute increments of serum TSH bioactivity and T₃ during l-T4 replacement (\(r = 0.80; \ P=0.004\)). The degree of sialylation was elevated in hypothyroid patients before treatment (47 ± 2% versus 29 ± 4%; \(P=0.002\)) and decreased significantly after l-T4 (from 47 ± 2% to 33 ± 4%; \(P=0.02\)). The mannose content of serum TSH in hypothyroid patients was similar to controls and did not change during l-T4. *In vitro* TSH bioactivity also decreased in patients with TSH-secreting adenomas during l-T4 withdrawal.

**Conclusions:** These results indicate that serum thyroid hormone level is a positive regulator of TSH bioactivity.

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**COMMENT**

The bioactivity of serum TSH is classically investigated by determining the B/I ratio of TSH, i.e. the ratio between bioactive (B) TSH and immunoassayable (I) TSH. This method was refined by the group of Paolo Beck-Peccoz and allowed these authors to show (Persani et al., JCEM 83:2486, 1998) that the bioactivity of serum TSH was reduced in hypothyroid patients and increased after l-T4 administration. Mature TSH is a glycoprotein hormone containing complex bi- & tri-antennary carbohydrate structures, with terminal sulfate & sialic acid residues. With affinity chromatography (concanavalin A), the degree of TSH sialylation can be determined. In the JCEM 1998 article alluded to above, the authors showed that circulating TSH was...
more heavily sialylated in hypothyroid patients, compared to normal. In the present work, not only were these earlier results confirmed but, in addition, the authors were able to show that serum TSH bioactivity was directly correlated to serum T_{3} concentrations and their rapid and marked changes after l-T4 administration in hypothyroid patients. The correlation was surprisingly strong (r = 0.80), but one should remember that the study was carried out in severely hypothyroid patients, with a mean TSH of 136 µU/ml and a mean serum free T_{4} & total T_{3} (before treatment) of 2.7 pmol/L and 0.5 nmol/L, respectively.

What does it all mean and what do we learn from this interesting study? First, the data confirmed the notion that the biological properties of circulating isoforms of serum TSH vary in pathological states and that the high TSH levels characteristic of primary hypothyroidism may represent an adaptive mechanism aiming at adjusting temporarily the thyroid stimulating activity of TSH (longer half-life with reduced bioactivity). Thus, primary hypothyroidism is associated with the secretion of highly sialylated TSH with a reduced intrinsic biological activity. Second, the study of TSH bioactivity in patients with rapidly changing thyroid hormone levels (after l-T4 administration) provides an assessment of the role of hypothalamic TRH in these processes, suggesting that the role of high TRH is probably relatively minor compared to that of thyroid hormones. Third, we should keep in mind that in clinical practice our reasoning on thyroid function tests is often based on absolute serum TSH levels but does not take into account possible variations in TSH bioactivity. In the present study for instance, the authors found a negative correlation in the normal controls between TSH bioactivity and age (between 28 and 52 years). Fourth and finally, a “finalistic” interpretation of present data remains difficult. In a clinical state with “low thyroid hormone/high TRH” (i.e. primary hypothyroidism), it is understandable that “nature” has favoured elevated TSH levels in order to help restore more normal thyroid hormone levels (this is the basis for a physiologic feed-back mechanism of a “thyrostat”). However, why “nature” would have favoured at the same time the presence of a less bioactive TSH with a prolonged half-life is difficult to comprehend, although the notion that the resulting secretion product of TSH action (namely, thyroid hormones produced by the thyroid) somehow regulates positively its own regulator has something appealing, albeit still mysterious.

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See Figures below