Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION FOUNDED 1923

WHAT IS THE ROLE OF DEIODINASE TYPE 2 POLYMORPHISM FOR THE REGULATION OF THE SET POINT BETWEEN SERUM TSH AND FT_4?

Hoftijzer HC, Heemstra KA, Visser TJ, le Cessie S, Peeters RP, Corssmit EP, Smit JW. **The type 2 deiodinase ORFa-Gly3Asp polymorphism (rs12885300) influences the set point of the hypothalamus-pituitary-thyroid axis in patients treated for differentiated thyroid carcinoma.** J Clin Endocrinol Metab 2011;96:E1527-E1533. Epub June 29, 2011.

SUMMARY

BACKGROUND

It is believed that each individual has a specific set point that controls thyroid function and that the genetic background underlying this setting is of crucial importance. Even before the genetic era, evidence emerged that a human being has a much narrower range of free thyroxine (T_4) and thyrotropin (TSH) variations than defined by the reference range, indicating a remarkable stability of thyroid function in a healthy individual (1,2). Some known factors are race and obesity. The activating and inactivating metabolism of thyroxine is certainly another possible factor. As for the deiodinases, several polymorphisms have been described with the possibility for differences in their activities, a question raised by several research groups. For instance, in young and healthy subjects (but not in elderly ones) with the polymorphic variant D2-ORFa-Asp (rs12885300), lower free T_4 levels despite normal TSH values have been described (3). Since thyroid function can be affected by many environmental situations in normal subjects, it is difficult to isolate the effect of genetic differences in the deiodinase structure from such confounding effects. In the present study, this problem was avoided by studying patients who had undergone thyroidectomy and radioactive iodine ablation.

METHODS AND RESULTS

The investigators studied 151 consecutive thyroid cancer patients. Only cured patients were included; patients taking interfering drugs (e.g., dopamine and derivatives, amiodarone, and steroids) were excluded. The observation period lasted from 1992 to 2007, yielding a large number of serum TSH and thyroxine levels. For each individual a mean of 12 measurements was evaluated (with a large range, from 4 to 32). The average (±SD) therapeutic dose of thyroxine was 2.18±0.97 μg/kg, a rather high dose. For comparison of the set point of the hypothalamic–pituitary–thyroid axis, the correlation between the natural logarithm of TSH and free T_4 was calculated. Genotyping was performed in 2007. Four polymorphisms were studied, three of which did not show any significant difference for serum free T_4 and TSH as compared with the wild-type values. For the polymorphism of interest, D2-rs12885300 (D2-ORFa-Gly3Asp), 70 patients with wild-type (Gly/Gly), 64 heterozygotes (Gly/Asp), and 13 homozygotes (Asp/Asp) were studied. Interestingly, there were significant differences between homozygotes and the wild-type and heterozygote groups. Expressed in clinical terms, for a free T_4 level of 10 pmol/L, serum wild-type TSH would be 5.64 mU/L, while the homozygote TSH would be 13.46 mU/L. For a free T_4 of 20 pmol/L, the difference in the corresponding values is less pronounced, 0.225 and 0.42 mU/L.

CONCLUSIONS

In completely athyroid yet otherwise healthy patients, the homozygote variant of D2-rs12885300 changes the set point of the hypothalamic–pituitary–thyroid axis, suggesting a reduced negative feedback of T_4 in these subjects. No deductions on possible alterations of thyroid hormone metabolism could be made, since only a few serum triiodothyronine (T_3) and reverse T_3 values were available.

continued on next page

COMMENTARY

It is remarkable that in this particular clinical setting such differences in the set point of the hypothalamic–pituitary–thyroid axis could be identified. The results clearly indicate a crucial role of deiodinases in the central control of TSH. The clinical consequences are not to be neglected, as exemplified above for serum TSH concentrations corresponding to free T_4 levels of either 10 or 20 pmol/L. These results are comforting for the clinician who often finds considerable differences in the amount of thyroxine needed to suppress serum TSH. Nevertheless, they do not explain the large interindividual differences seen in normal subjects, for whom many additional parameters can influence the ratio between serum TSH and free T_4. This fact is well documented in earlier works (1). To what extent, the genetic background really affects the clinical data in normal subjects remains uncertain.

— Albert G. Burger, MD

References

1. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: A clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab 2002;87:1068-1072.
2. Meier CA, Maisey MN, Lowry A, Muller J, Smith MA. Interindividual differences in the pituitary-thyroid axis influence the interpretation of thyroid function tests. Clin Endocrinol (Oxf) 1993;39:101-107.
3. Peeters RP, van den Beld AW, Attalki H, Toor H, de Rijke YB, Kuiper GG, Lamberts SW, Janssen JA, Uitterlinden AG, Visser TJ. A new polymorphism in the type II deiodinase gene is associated with circulating thyroid hormone parameters. Am J Physiol Endocrinol Metab 2005;289:E75-E81.