WHY DID TSH RECEPTOR MUTATIONS THAT CAUSED FRANK HYPOTHYROIDISM IN A PATIENT CAUSE ONLY SUBCLINICAL TSH RESISTANCE IN HER SIBLING?

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SUMMARY

BACKGROUND

If a high thyrotropin (TSH) level is found on screening a newborn infant, but neither a goiter nor thyroid agenesis/dysgenesis is present, about 15% of the time it will turn out to reflect a genetic defect in hormone production. Some patients with mutations in the TSH receptor (TSHR) display frank hypothyroidism, yet the same mutations cause only subclinical/compensated TSH resistance in other patients; such variable penetrance remains poorly understood. In Japan, the commonest TSHR mutation occurs in the first intracellular loop (ICL1), where a mutation at codon 450 substitutes histidine for arginine (R450H). About 1 in 300 Japanese carry this mutation, but many who carry it are not detected by newborn screening.

ICL1 is one of the regions in the TSHR that interact with the Gq heterotrimer. Gq activates pathways that promote production of H_2O_2, which is necessary for making thyroid hormone. The level of TSH required to activate the Gq path is much higher than is required to activate the Gs path, which uses cAMP to increase sodium–iodide symporter (NIS) activity and to release thyroid hormone.

METHODS

Patients previously diagnosed with congenital hypothyroidism were reevaluated years to decades later. After briefly discontinuing levothyroxine (L-T_4), their 24-hour uptake of radioactive iodine (^{123}I) was measured. Of more than 100 patients tested, 24 were found to have a ^{123}I uptake exceeding 40%. The TSH receptor alleles in those patients were sequenced.

RESULTS

A 15-year-old girl was found to have the R450H mutation on one allele and a T145I mutation on the other. She had no goiter, and after stopping her L-T_4 dose, the free thyroxine (T_4) was 0.6 ng/dl, the TSH 53.8 mU/L, the ^{123}I uptake 43%, and the perchlorate discharge test negative. The patient's 13-year-old brother had the same two mutant alleles but was clinically normal, and he had normal thyroid hormone levels and a normal ^{123}I uptake (18.5%), although his TSH was mildly elevated, at 17.7 mU/L. The gene sequences of thyroglobulin, thyroperoxidase, DUOX2 and DUOXA2, iodotyrosine deiodinase, and pendrin were normal in both siblings (expression of these proteins was not assessed). The two different TSHR mutants were then expressed separately in cultured cells. Coexpression of a reporter for assessing cAMP signaling indicated that this pathway was moderately reduced in cells expressing either mutant, as compared with the response of the normal TSHR. A reporter for assessing Gq signaling indicated that this pathway was moderately reduced in the T145I mutant, but Gq signaling was virtually absent in cells expressing the R450H mutant. These in vitro studies indicate that the predominant defect in the function of the TSHR was its coupling to the Gq pathway.

CONCLUSIONS

The elevated ^{123}I uptake in this 15-year-old girl is believed to reflect enhanced coupling of the TSHR to Gs in response to her elevated TSH level, which is in compensation for the deficit in TSHR coupling to Gq, although there was also some decrease in coupling to Gs. The authors cite the prior report of a family in which three members had subclinical congenital hypothyroidism and who had high 2-hour ^{123}I uptakes. The three patients were found to be homozygous for a mutation in the third extracellular loop of the TSHR (1). When that mutant was expressed in cultured cells, TSH produced a maximal cAMP response equal to that of cells expressing the normal TSHR. However, Gq signaling — assessed by direct measurement of phosphoinositides — was substantially reduced. Heterozygotes in that family had normal TSH levels and ^{123}I uptake.

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COMMENTARY

Defective Gq coupling should impair the generation of H_2O_2, and the increased level of TSH would be expected to increase sodium/iodide symporter activity, among other things. Some impairment in organification might have been expected, although the perchlorate discharge test was negative in the girl. However, her brother—who has the same compound heterogeneous mutations—had a normal ^{123}I uptake. The difference in sex between siblings could be an issue, although no sex difference in the ^{123}I uptake has been noted in R450H homozygotes (1,2). Indeed the thyroid defect in homozygotes does not appear very different from what is reported in heterozygotes, other than perhaps a slightly higher dose of L-T_4 being required in some cases (1). In addition, a recent Korean study used technetium-99m-pertechnetate ($^{99m}TcO_4$) uptake measurements before treatment to categorize 193 neonates with permanent congenital hypothyroidism. Of 79 whose $^{99m}TcO_4$ uptake was less than 2.5%, 13 were found to have TSHR mutations, 7 being the R450H mutation. In contrast, of 114 whose uptake was greater than 2.5%, only one had R450H, and of the 68 whose uptake was greater than 7%, none had R450H (2). However, there is a recent wrinkle to the Gq story: it now seems that before the TSH receptor can couple with Gq, the TSHR must be dimerized, and then two molecules of TSH must bind to the dimer (3). This raises the issue of how well a mutant TSHR allele can dimerize with the normal TSHR and also with itself.

Whatever the underlying cause, a recent Greek study reported that over 70% of 3- to 5-day-old infants whose TSH is between 10 and 20 mU/L will turn out to have permanent hypothyroidism when reassessed at 3 years (4). This supports the belief that newborns with mild TSH elevations who have a mutation in their TSH receptor probably should be given L-T_4 replacement, even if their thyroid hormone levels are normal (1).

— Stephen W. Spaulding

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