Liver glutathione S-transferase expression is decreased by 3,5,3-triiodothyronine in hypothyroid but not in euthyroid mice.

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OBJECTIVE: As previously reported, the activity of liver glutathione S-transferases, an important family of enzymes for detoxification processes, is regulated by thyroid hormone levels. Here, we specifically studied glutathione S-transferase α (Gsta) gene expression in livers of mice.

METHODS: First, in wild-type (WT) mice, hypothyroidism was induced by 5 weeks of a diet containing 5-propyl-2-thiouracil plus water containing metimazole, whereas hyperthyroidism was induced by daily injections of 50 μg (100 g body weight)(-1) of 3,3',5-triiodo-L-thyronine (L-T(3)) for 15 days. Importantly, hypothyroidism induced liver Gsta mRNA (>500%) and protein levels (70%; P < 0.01), indicating an important role of baseline thyroid hormone levels to repress this gene; however, surprisingly, no differences were seen in hyperthyroid mice. To further investigate Gsta repression by T(3), we used animals expressing a naturally occurring mutation of the gene for thyroid hormone receptor (TR)-β (Δ337T), which prevents T(3) binding and causes a general resistance to thyroid hormone.

RESULTS: At baseline, homozygous animals showed increased Gsta levels (mRNA 3.5 times, protein 1.3 times) similar to those found in hypothyroid animals. After a T(3) suppression test, we found a blunted response of liver Gsta after the lower doses of T(3) in homozygous animals, as expected. However, after the highest dose of T(3), we observed a decrease in Gsta expression (80%), similar to normal animals, explained by a higher expression of TR-α1 (60%; P < 0.01) and a lower expression of Src1 (steroid coactivator receptor) in the mutant animals (50% decrease).

CONCLUSION: In summary, a decrease in Gsta expression caused by T(3) was observed only in the hypothyroid state. In addition, an essential role of TR-β1 is to mediate Gsta suppression in response to T(3) and, in the absence of a functional TR-β, there is a compensatory action of TR-α1 that depends on low levels of Src1.

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