Topic: LIPID METABOLISM IN HYPOTHYROIDISM: EXPERIMENTAL STUDY OF APO-RECEPTORS

Title: Distinct dysregulation of lipid metabolism by unliganded thyroid hormone receptors isoforms.

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Background: Thyroid hormone receptors (TRs) play critical roles in energy homeostasis.

Objective: To understand the role of TRs in lipid homeostasis in vivo, the authors adopted the loss-of-function experimental approach by creating knock-in mutant mice with targeted mutation in the TRα gene (TRα1PV mouse) or TRβ gene (TRβPV mouse). This approach was based on the “PV” mutation, which had previously been identified in a patient with RTH, and shown to exhibit potent dominant-negative activity on TREs.

Results: The results showed that, in contrast to TRα1PV mouse, TRβPV mice exhibited no significant reduction in white adipose tissues but had significant increases in serum free fatty acids and total triglycerides. Moreover, the liver of TRβPV mice was markedly increased and displayed excess lipid accumulation, while the liver mass of TRα1PV mouse was decreased. Thus, apo-TRβ and apo-TRα1 exerted distinct abnormalities in lipid metabolism. Further biochemical analyses indicated that increased lipogenic enzyme expression, activated Pparaγ signaling, and decreased fatty acid β-oxidation activity contributed to the adipogenic steatosis and lipid accumulation in the liver of the TRβPV mice. In contrast, the expression of lipogenic enzymes and Pparaγ was decreased in the liver of the TRα1PV mice.

Conclusions: These results indicate that apo-TRβ and apo-TRα1 had different effects on lipid metabolism and that both TR isoforms contribute to the pathogenesis of lipid metabolism in hypothyroidism.

COMMENT

Thyroid hormone receptors (TRs) are present as four isoforms, derived from TRα & TRβ genes by alternative splicing. TRs regulate transcription of T3-target genes by binding to thyroid hormone response elements (TREs) in the promoter region of specific genes. Each TR isoform has unique developmental and tissue-specific expression and, in addition, gene transcription modulated by TRs requires a host of corepressors and coactivators.

TRs are ligand-dependent transcription factors, first requiring the binding of T3 to exert their effects on TREs. Apo-TRs are the unliganded forms of these receptors and, therefore, in circumstances such as severe hypothyroidism for instance, TRs function as apo-receptors.

Studies of genetically engineered mice lacking individual TR isoforms (or all TRs) have shown that TR isoforms mediate different metabolic processes. TRα1 is a major regulator of body temperature, while TRβ plays a major role in regulating cholesterol metabolism. With mice lacking all TRs, this maximal TR deficient condition yields a pattern that is surprisingly less severe than the phenotype.
observed in congenital hypothyroidism, highlighting the critical role of apo-TRs in the pathogenesis of hypothyroidism.

In the present study, the authors created knock-in mice mutants, harbouring specifically a targeted mutation in the TRα gene (TRα1PV mouse) or TRβ gene (TRβPV mouse) to address the question of how apo-receptors may influence lipid metabolism. The study showed that TRβPV mice exhibited no significant reduction in white adipose tissues (inguinal, epididymal, peri-renal, and interscapular fat tissues) but had significant increases in serum free fatty acids and total triglycerides. Moreover, the TRβPV mice developed enlarged fatty liver, with a 33% mass increase and excess lipid accumulation. In contrast, the liver mass of TRα1PV mice was decreased by 23% with paucity of lipids.

These results indicate that apo-TRβ and apo-TRα1 exert distinct abnormalities in lipid metabolism and the authors concluded by speculating that both TR isoforms may contribute to the pathogenesis of lipid metabolic alterations such as observed in hypothyroidism.  

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**See Figures below**