Clinical THYROIDOLOGY



T₃ Stimulates Hepatic Fatty Acid β -Oxidation by Inducing Lipophagy

Sinha RA, You SH, Zhou J, Siddique MM, Bay BH, Zhu X, Privalsky ML, Cheng SY, Stevens RD, Summers SA, Newgard CB, Lazar MA, Yen PM. Thyroid hormone stimulates hepatic lipid catabolism via activation of autophagy. J Clin Invest 2012;122:2428-38. Epub June 11, 2012.

SUMMARY • • • • • • • • • • • • • •

Background

In the liver, physiological mobilization and metabolism of free fatty acids is a crucial step in intracellular energy transfer. Autophagy is an essential cellular degradation process of proteins and organelles. Recently, it was shown that autophagy is also involved in the transfer of lipid droplets to mitochondria—a process termed "lipophagy." It is probably a major pathway of lipid mobilization. For more than 100 years, thyroid hormones were known to stimulate basal metabolic rate. Several hypotheses have been proposed to explain the mechanisms underlying this phenomenon. Yet, a satisfactory explanation is still missing. The authors of the present article provide important new information by demonstrating that the induction of lipophagy is under the control of thyroid hormones.

Methods and Results

In vitro studies were performed with hepatic cell cultures (HepG2 cells) transfected with functional T_3 receptors. In the present studies, an easily identifiable form of LC3 (i.e., LC3 conjugated to phosphatidylethanolamine (LC3-II) was studied. LC3-II is a critical component of autophagosomes. An increase in LC3-II indicates increased autophagy and is the most common marker of autophagy. Low concentrations of T_3 , similar to those encountered in vivo, are able

to stimulate synthesis of LC3. More refined studies indicated that autophagic clearance was simultaneously increased, and therefore the net LC3-II production was even greater. In further studies, the authors confirmed increased autophagosomes and lipophagy by using fluorescence techniques and electron microscopy. Morphologic evidence confirmed the increased number of autophagosomes and lipophagosomes within autolysosomes and lipid droplets. Using a knockin mouse model expressing a mutant T₃ receptor known to confer resistance to thyroid hormone, the authors elegantly demonstrated that T₃-mediated autophagy required a fully functional T₃ receptor. In addition, they showed that lipophagy is tightly coupled with β -oxidation. Metabolomic analysis confirmed that there was an increased flux of fatty acid metabolites in the liver of T₃-treated mice as compared with mice with hypothyroidism.

Conclusions

One of the mechanisms whereby thyroid hormones participate in the control of energy expenditure is the activation of β -oxidation of fatty acids. The present finding that T_3 is specifically promoting lipophagy is consistent with its key role as an important regulator of the delivery of fatty acids to mitochondria. The data provide support for a novel mechanism that increases fat energy expenditure.

ANALYSIS AND COMMENTARY • • • • • •

Practicing physicians are often confronted with questions from patients concerning the mechanism of thyroid hormone action. The standard answer is an increase in metabolic rate or, in other words, of oxygen consumption in a quiet state. This remains a very elusive answer. Increased metabolic rate during hyperthyroidism requires mobilization of lipids and carbohydrates. For instance, the muscle glycogen stores are rapidly depleted. In this article, we find an answer to the question of how increased hepatic lipid oxidation is controlled by thyroid hormones. This is certainly a remarkable addition to our knowledge, even though it is only one piece of a puzzle.

continued on next page

T_3 Stimulates Hepatic Fatty Acid β -Oxidation by Inducing Lipophagy

roid liver is more sensitive to fatty degeneration (1). The new discovery of T_3 -regulated lipophagy raises many questions that will stimulate clinical research.

Albert G. Burger MD I would like to thank Professor Paul Yen for his help.

Sinha RA, et al.

REFERENCE

1. Chung GE, Kim D, Kim W, Yim JY, Park MJ, Kim YJ, Yoon JH, Lee HS. Non-alcoholic fatty liver disease across the spectrum of hypothyroidism. J Hepatol 2012. 57:150-6. Epub March 14, 2012.

We invite you to join the ATA!

Are You Intrigued by the Study of the Thyroid? You Belong in the ATA!

- ATA members are leaders in thyroidology who promote excellence and innovation in clinical care, research, education, and public policy.
- Join us as we advance our understanding of the causes and improve the clinical management of thyroid diseases in this era of rapid pace biomedical discovery.
- A close-knit, collegial group of physicians and scientists, the ATA is dedicated to the reseach and treatment of thyroid diseases. ATA's rich history dates back to 1923 and its members are respected worldwide as leaders in thyroidology.
- The ATA encourages you to apply for membership. We want you to experience the wealth of knowledge and enjoy the benefits of being active in this highly specialized and regarded society. The ATA looks forward to having you as a member!





