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Direktor: Prof. Dr. H.-J. Seitz

Molecular Mechanisms of Action of Thyroid Hormone: The Liver Fatty Acid Binding Protein as a Model

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Alexander Iwen
aus Hamburg

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Prüfungsausschuss, der Vorsitzende: Prof. Dr. H.J. Seitz

Prüfungsausschuss: 2. Gutachter: PD Dr. W. Hampe

Prüfungsausschuss: 3. Gutachter: Prof. Dr. F. Rinninger

Abstract

The thyroid hormone (T3) has a profound influence on normal development and metabolic balance. Hyperthyroid individuals have a markedly elevated basal energy expenditure, which includes an increased hepatic fatty acid (FA) turnover. Conversely, a decrease of T3 has the reverse effect. At least two genomic mechanisms of molecular action have been postulated, (i) a direct one and (ii) an indirect one, working via intermediary factors. Unlike direct T3 effects, which can be adequately explained by T3 response elements (TREs) in promoter regions of T3 responsive genes, mechanisms of indirect effects are still elusive. A characteristic of indirect T3 effects is a latency period of 12 to 48 hours before an elevation of the target gene mRNA concentration can be observed in response to T3 in vivo.

The aim of this thesis was to investigate mechanisms by which indirect effects of T3 are mediated. Microarray analysis, conducted earlier in our laboratory, revealed a latency period in the case of liver fatty acid binding protein (LFABP) gene expression in rats. LFABP, an important hepatic FA transport protein, was therefore chosen as a model gene.

Northern hybridisation confirmed the microarray results. Sequence analysis of the human and rat LFABP promoters revealed a putative TRE in the human promoter, but not in the rat sequence. Transient transfection experiments did not show an effect of T3 and thyroid hormone receptor on either rat or human LFABP promoter regions, thus a T3 effect via a TRE does not appear to be likely. Putative peroxisome proliferator response elements (PPREs) were found by sequence analysis of the promoters, and confirmed through electrophoretic mobility shift assays. Transient transfections showed a clear response of the rat LFABP promoter region to clofibric acid, a peroxisome proliferator, and peroxisome proliferator activated receptor alpha (PPARα), thus verifying an active PPRE in the rat LFABP promoter. Rat PPARα itself was not positively regulated by T3 in vivo.

Given the fact that rat PPARγ co-activator 1 (PGC-1) shows a direct response to T3 in vivo and is known to interact with PPARα, the following working hypothesis was created: T3 increases PGC-1 gene expression. The synthesis of the protein is time consuming, which explains the latency period. PGC-1 then interacts with PPARα, which is bound to the PPRE in the LFABP promoter region, and increases LFABP gene activity. This mechanism offers an attractive explanation for the latency period of indirect T3 effects.