Alternative splicing of thyroid hormone receptor alpha transcripts during health and disease

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Summary
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Thyroid hormone receptors (TRs) mediate the effects of thyroid hormone on gene expression. TRs are transcribed from two different genes and this thesis deals with the receptors that are derived from the c-erbAα (thyroid hormone receptor alpha) gene. The thyroid hormone receptor alpha gene is transcribed into a pre-mRNA transcript that is alternatively spliced and gives rise to TRα1 and TRα2. TRα1 is a functional receptor that binds T3 whereas TRα2 cannot bind T3 and has a dominant negative activity over the other TRs. The splicing process of TRα transcripts may be regulated during physiological or pathological conditions which might change the balance in TRα1 to TRα2 thereby possibly influencing thyroid hormone sensitivity.

Chapter 1 describes the gene structure and function of the different TRα isoforms. Furthermore this chapter reviews the general and alternative splicing of pre-mRNA transcripts. Splicing proteins such as SF2 and hnRNP A1 play opposite roles in the selection of alternative 5'splice sites. Furthermore Rev-erbA mRNA transcripts, which are derived from the opposite strand of the c-erbAα gene are partly complementary to TRα2 mRNA transcripts and could interfere with the splicing process of TRα.

In chapter 2 the effects of thyroid hormone on the alternative splicing of TRα transcripts in HepG2 cells is studied. The endogenous TRα transcription in HepG2 cells is not affected by thyroid hormone but the balance between TRα1 and TRα2 is altered. High concentrations of thyroid hormone in the medium of HepG2 cells (either by supplementation of T3 or incubation with sera from hyperthyroid patients) results in a shift of the splicing direction towards TRα2. A low TRα1: TRα2 ratio may indicate a lower sensitivity to thyroid hormone which would help cells to maintain euthyroidism in a hyperthyroid environment. The mechanism of this effect of thyroid hormone on the splicing is unknown and no relationship with the expression of well-known splicing factors such as SF2 and hnRNP A1 was found. The expression of Rev-ErbA was also not associated to the TRα1: TRα2 ratio.

In chapter 3 the TRα mRNA expression was studied in human liver biopsies of critically ill patients who had died at the ICU. A change in the balance in TRα1 to TRα2 was associated with age and severity of disease. Patients with a higher age, more severe illness (as measured by APACHE II) or who had needed more interventions (as measured by the TISS score) had a higher TRα1: TRα2 ratio. Moreover patients who had needed renal replacement therapy or inotrope treatment also had an increased TRα1:
TRα2 ratio. In the light of low serum thyroid hormone levels a compensatory increase in the TRα1: TRα2 ratio might help to increase the thyroid hormone sensitivity in liver. Treatment with thyroid hormones or glucocorticoids did not alter TRα expression or the balance between TRα1 and TRα2. Strict glycemic control of patients by intensive insulin treatment also had no effect on TRα expression or the TRα1: TRα2 ratio. No relationship between the TRα1: TRα2 ratio with the splicing factors SF2 and hnRNP A1 was found.

Chapter 4 describes the changes in TRα mRNA expression in the hypothalamus-pituitary-thyroid axis (HPT-axis) during acute illness in a mouse model of LPS induced illness. LPS induces nonthyroidal illness as was confirmed by low serum T3 levels. In addition LPS induces a decrease in both TRα mRNA levels in liver, thyroid and pituitary (in the latter only TRα1). Moreover the TRα1:TRα2 ratio decreases in the liver and pituitary indicating that in addition to decreased transcription, the regulation of the splicing direction towards TRα2 might help to decrease thyroid hormone sensitivity in tissues. Rev-ErbA mRNA expression showed a concomitant decrease with the TRs indicating that the TRα locus may have a concordant transcriptional regulation but that Rev-ErbA is not associated with changes in the splicing of the TRα transcripts. In the hypothalamus no changes in the TRα mRNA expression were observed. The absolute levels of the splicing factor SF2 could be related to the TRα1:TRα2 ratio in tissues but changes in the TRα1: TRα2 ratio were not preceded by changes in SF2 excluding a role for SF2 in the splicing direction of TRα transcripts.

Chapter 5 deals with the effect of the PPARγ co-activator 1 (PGC-1) on the alternative splicing of TRα transcripts. PGC-1 was discovered as a transcriptional co-activator but also has certain motifs characteristic of splicing factors which enable PGC-1 to associate with splicing factors and alter RNA processing of a minigene. We demonstrate that PGC-1 can alter the splicing direction of endogenously expressed TRα transcripts in HepG2 cells towards TRα2. PGC-1 showed a similar effect on the splicing direction of a TRα minigene containing only the last 4 exons and introns of the TRα gene. Deletion of the RNA processing domain attenuated the effect of PGC-1 on the endogenously expressed TRα transcripts whereas expression of only the RNA processing domain had an opposite effect on the splicing direction favouring TRα1. These data suggest that PGC-1 is involved in the RNA processing of TRα transcripts probably via its RNA processing domain.
Summary

From this thesis it can be concluded that the alternative splicing of TRα transcripts is a regulated process and that the direction of the splicing can change as a result of pathological conditions.