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Commentary

Physiological Effects of Nuclear Thyroid Hormone Receptors

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DESCRIPTION

Thyroid hormones (THs) exert important physiological effects by binding to nuclear thyroid hormone receptors (TRs). The thyroid gland primarily produces thyroxine (T4), but triiodothyronine (T3) is the most active TH due to receptor affinity. The thyroid gland releases THs into the bloodstream, where they enter cells *via* the adenosine triphosphate (ATP)-dependent monocarboxylate transporters MCT8 and MCT10, as well as the organic anion transporter proteins (OATPs). Cell-specific expression of selenoenzymes deiodinases regulates the amount of T3 available for binding to nuclear receptors (DIOs). D101 and D102 catalyse the conversion of T4 to T3 in target tissues, increasing intracellular levels of the active hormone, whereas D103 inhibits hormone activity by converting T4 and T3 to the inactive metabolites reverse T3 (rT3) and T2, respectively, *via* inner ring deiodination. TRs are nuclear receptors that function as ligand-dependent transcription factors.

The primary transcripts of the TRa and TRO genes are used to generate several TR protein isoforms via promoter use or alternative splicing. TRa1, TRO1, and TRO2 are the main hormone-binding isoforms, and their relative levels of expression vary across cell types and developmental stages, implying that they may have organ-specific functions. In the case of TRO, TRO1 is more widely indicate, whereas TRO2 expression is limited to the anterior pituitary and some neural cells. 45 TRa and TRO can substitute for each other in mediating some thyroid hormone actions, but they can also mediate isoform-specific functions, according to studies with genetically modified mice. TRs are made up of several functional domains. The autonomous activation function 1 is found in the N-terminal region (A/B). It is a constitutive ligand-independent transcriptional activation domain (AF-1).

The DBD, which is composed of two zinc fingers, is the most conserved region among nuclear receptors. Four invariable cysteines coordinate with one zinc ion tetrahedrically in each zinc finger. Amino adds required for Thyroid hormone Response Element (TRE) are found at the base of the first finger in a region known as the "P box," and other residues of the second zinc finger, known as the "D box," are involved in dimerization. The DBD connects the receptors to the major groove of DNA. A hinge domain, also known as the D region, connects the DBD to the E region, which is also responsible for dimerization.

The residues in this hinge domain are required for interaction with corepressors. The LBDs are formed by 12 a helices, and the C-terminal helix (H12) contains the ligand-dependent transcriptional activation function, or AF-2, according to crystallographic analysis. TRs regulate gene transcription by forming preferential heterodimers with retinoid X receptors (RXRs) and binding to short DNA binding motifs known as thyroid hormone response elements (TREs), which are found in regulatory regions of target genes. The AGG /TTCA motif is repeated twice in TREs. They can be palindromes (Pal), Inverted Palindromes (IPs), or direct repeats separated by at least four non-conserved nucleotides (DR4).

TRs can bind to their response elements as monomers or homodimers, but heterodimerization with RXR increases DNA affinity and transcriptional activity significantly. AP-1, CREB, NF-kB-mediated transcription. The receptors in this case do not bind directly to the DNA recognition elements for these transcription factors in the target gene, but can be tethered to these binding motifs *via* protein-to-protein interactions. This type of transcriptional crosstalk between transcription factors and nuclear receptors has been shown to be essential for the regulation of many cellular functions, including nuclear receptor ligands' anti-inflammatory and anti-proliferative actions.

Finally, thyroid hormones can cause rapid non-genomic effects at the cell membrane, which can stimulate kinase pathways. These actions could be mediated by a subset of membrane-associated nuclear receptors or by the occupancy of putative membrane receptors like integrin aVB3, which binds T4 preferentially.

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