Studies of thyroid hormone receptor and its mutations

Paulo C. T. de Souza*[1] (PG), Leandro Martínez[1] (PQ), Igor Polikarpov[2] (PQ), Munir Salomão Skaf[1] (PQ) (paulocts@gmail.com)

[1] *Instituto de Química, Universidade Estadual de Campinas*
[2] *Instituto de Física de São Carlos, Universidade de São Paulo*

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Introduction

Thyroid hormone receptors (TRs) belong to a superfamily composed of 48 different proteins that have the function of regulating gene transcription. Hormonal regulation by TRs and their ligand (T3) occurs in all organs and metabolic paths, where their action influences cellular differentiation, development, oxygen consumption, the regulation of body temperature, cardiac frequency and also carbohydrate, protein and lipid metabolism. Therefore, they are important targets for drug development[1].

TRs are composed of three domains: an N-terminal domain, a DNA binding domain (DBD), and a ligand binding domain (LBD). The LBD is situated in the C-terminal region and, apart from recognizing hormones selectively, it controls dimerization, the interaction with co-regulator proteins and the inhibition of transcription.

Many experimental[2] and theoretical[3] studies have been made in order to clarify the molecular mechanisms involved in the biological functions of these receptors. This project is situated in this context, that is, it aims to investigate, through molecular dynamics (MD), the influence of 40 different mutations, most of them related to the resistance to thyroid hormone (RTH) syndrome disease, in the structural, dynamical and energetic properties of the LDB.

Results e Discussion

The more general results from 4 ns MD simulations indicate a set of common changes caused by mutations. Most of the mutants causes structural and dynamical changes in the LBD of TR, especially in the region in which the mutation is placed and in the binding pocket. These changes cause loss of hydrophilic interactions and hydrophobic contacts with the natural ligand T3, especially in the region surrounding the β-hairpin.

These effects may be associated with structural instability of the LBDs and the loss of affinity for the hormone, shown experimentally.

Figure 1 shows the average structure of L428R (exchange of a leucine by an arginine at position 428 of the primary sequence), an example of one of the mutants studied. The experiments showed low affinity and lost of dimerization function to this mutant[4]. The color scale is related to the mobility difference between mutant and native TR. The mutant has induced increased mobility (red color) and lost of secondary structure in the mutation region (Figure 1a), that includes the dimerization surface (helices H8 and H11). Another important fact is high mobility in the region around β-hairpin and ligand (Figure 1a). This region is involved in ligand dissociation path[2], thus this result provides insights into the reasons for the low ligand affinity to this mutant.

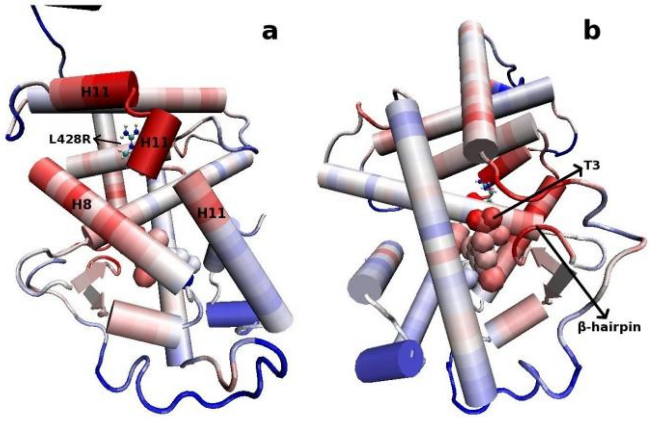

Figure 1. Comparison between the mobility of the L428R mutant and the wild-type TRβ.

Conclusions

Molecular dynamics simulations show changes in structure, mobility and interactions of TR mutants related with RTH syndrome that explain the lost of functions and the low affinity.

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