Levothyroxine: A Look at Receptor Binding and Warfarin Interaction

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Abstract

This poster explores how levothyroxine binds to the thyroid hormone receptor on the molecular level through three notable points of interaction. We will also explore the interaction that can occur between levothyroxine and warfarin when binding to albumin. This interaction can increase a patient's International Normalized Ratio (INR), which measures the time it takes for blood to clot. An increased INR can lead to an increased chance of bleeding.

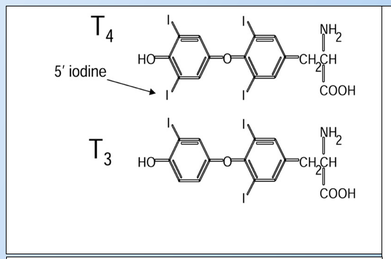

Figure 1 (above): Structures of T_4 and T_3[2]

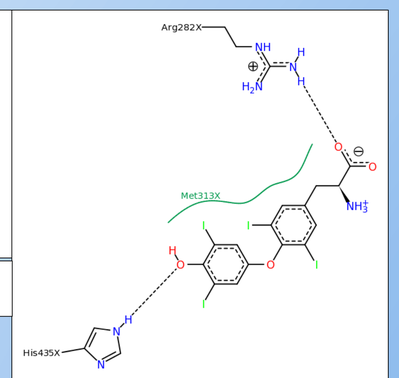

Figure 2 (above): Levothyroxine/Thyroid hormone receptor protein binding interactions[3].

Introduction

MD, an 86-year-old Caucasian male, presented to the hospital with complaints of weakness and dizziness. Upon medication reconciliation, MD has a medical history of thyroid disease and atrial arrhythmias. MD is currently taking prescription levothyroxine, warfarin, and amiodarone. Levothyroxine and warfarin both bind to albumin in the blood, which can result in higher levels of both drugs in their free drug form. We will discuss how levothyroxine binds to the thyroid hormone receptor and how levothyroxine can interfere with warfarin on the molecular level.

Thyroid disease is a disturbance in the hypothalamic-pituitary-thyroid axis that results in either an excess or depletion of thyroid hormone (TH).[1] TH comes in two forms: T_3 and T_4 for patients requiring hormone replacement (see figure 1) [1,2]. Patients with hypothyroidism may require a T_4 synthetic hormone such as levothyroxine to regulate metabolism, homeostasis, and development. While T_3 has better affinity for the thyroid hormone ligand binding domain (LBD), T_4 has a longer half-life, which makes synthesis of the T_4 precursor more attractive for once a day dosing for a patient with thyroid disease. Levothyroxine has several drug-drug interactions, and, for our purposes, we will focus on levothyroxine's interaction with warfarin and how to compensate for dual therapies[1].

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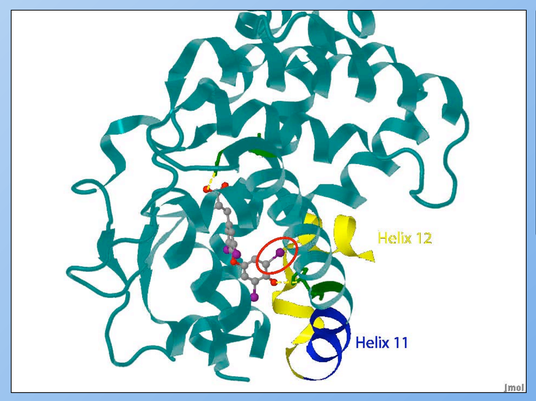

Figure 3 (left): Thyroxine bound to thyroid hormone receptor. To accommodate thyroxine in binding pocket, helix 12 (in yellow) must shift outwards as helix 11 (in blue) draws inwards. Iodine responsible for interactions is circled in red[3].

Molecular Story

Levothyroxine exerts its physiologic effects by binding to thyroid hormone receptor. Levothyroxine has four iodines (see figure 2) and is not as potent as triiodothyronine, which lacks an iodine on its distal aromatic ring. The extra iodine causes the molecule to be slightly too large for the binding pocket in the protein. Thus, Helix 12 and 11 on the protein must change their conformations to fit into the pocket (see figure 3)[2].

The binding of levothyroxine to the thyroid hormone receptor has three main points of interaction (see figure 2).

- The carboxylic acid on the levothyroxine molecule forms a hydrogen bond to arginine 282 on the protein[2].
- The two phenol rings, and iodines of levothyroxine interact with the methionine313x amino acid on the receptor. Both of these regions are polar and interact via van der Waals forces[2].
- The alcohol on levothyroxine and the histidine435x of the receptor. The two hydrogen bonds are much stronger than the van der Waals forces and this accounts for most of the binding energy[2].

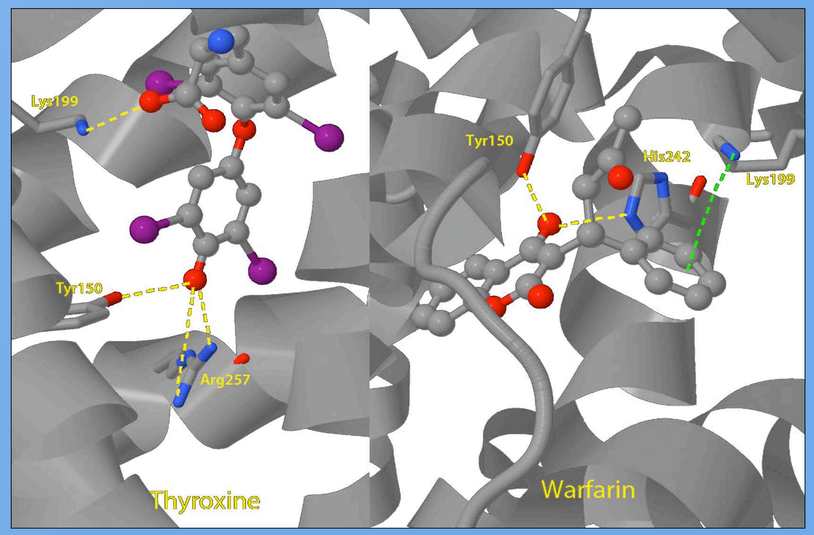

Figure 4: Thyroxine and warfarin bound to albumin, using same exposed amino acids in binding site. The hydrogen bonds are shown in yellow and the pi-cation interaction is shown in green[4,5].

Molecular Story Continued

The major interaction between levothyroxine and warfarin is due to the two molecules occupying the same binding site on human serum albumin (see figure 4). When levothyroxine displaces warfarin on the albumin protein the effect of warfarin on the body is enhanced, leading to an increased INR[2]. Warfarin is much more sensitive to this process than levothyroxine as it only has one potential binding site on albumin, while levothyroxine has six total potential binding sites[6,7].

Levothyroxine is interesting because it is the fourth most prescribed drug in America[2]. Pharmacists are especially interested in this drug-protein interaction because it is often their responsibility to monitor and change a patient's warfarin dose to meet their INR goals.

Future Work

Over the past 100 years levothyroxine has proven its place in therapy for hypothyroidism. The future of this medication could focus on the addition of other natural thyroid products, such as T3, to make the product safer and more closely mimic that natural physiology. Addition of a long-acting triiodothyronine could have the potential to improve patient outcome over monotherapy. Future studies would need to be conducted in order to determine if this would translate into a biochemical advantage of any clinical significance.

Further work also has the possibility of looking at specific genetic biomarkers and tailoring therapy accordingly. Recently some companies have offered genetic testing to determine specific genotypes on genes that are expressed in people with specific disease states. Prophylactic treatment might be possible in preventing this disease all together. Screening for patients at high risk might help identify these patients and prevent the disease before it starts.

Summary

The interaction between levothyroxine and warfarin is potentially very significant. The binding of levothyroxine to albumin increases the amount of warfarin in the serum, since levothyroxine has a higher affinity for its active site on albumin. This can have devastating consequences for the patient. It is, however, possible to address this problem through addition of a long-acting triiodothyronine. It could also be possible to make it routine to perform genetic studies on patients to identify their risk of developing hypothyroidism and treating them prophylactically.

References

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