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.

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).

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.
- 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.
- 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.

Levothyroxine is interesting because it is the fourth most prescribed drug in America. 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.

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.

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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