Name(s)

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Project Number

S0523

Project Title

In-Silico Analysis of Angiotensin Receptor Blocker Affinity to Polymorphic Angiotensin T1 Receptor to Customize Therapy

Abstract

Objectives

Angiotensin Receptor Blockers are drugs that bind to the Angiotensin Type 1 Receptor, and are used to treat hypertensive patients.

The objective of this study is to determine if polymorphisms within the Angiotensin Type 1 Receptor (AT1R) affect Angiotensin Receptor Blocker (ARB) binding affinity; if so, personalized ARB therapy may be necessary.

Methods

A computer was used to complete the in-silico simulations. Molecular modeling programs, such as CHARMM-GUI, Amber, MOE, and Autodock, were used in conjunction with the Jupyter Notebook platform and were unmodified.

The parameters used on the wild type AT1R must result in the known median affinities using optimized parameters. Parameters include the size (grid spacing), location (grid center), and resolution (number of points) of the Autodock bounding box to be used for each ARB ligand, or drug, to dock within. The optimized parameters were proven substantially accurate for the wild type AT1R, and were applied to 103 polymorphic AT1Rs through several trials. The resultant polymorphic affinities were then compared to wild type affinities to find the fold difference.

Results

Parameters found were optimized to a mean deviation within 2 ± 2 nM of experimental values, an improvement from previous attempts. The affinities of each of the eight ARBs to each of the 103 polymorphisms were found in comparison to the wild type, ranging from substantially lower deviations from wild type affinity to no deviation.

Conclusions

These results indicate that, because binding affinities can decrease by ten-fold, certain ARBs may not bind properly to certain polymorphic AT1Rs. This suggests that particular polymorphisms render particular ARBs ineffective during treatment.

ARB therapy can be improved with personalized medicine via a tailored ARB therapy established upon a patient's AT1R sequence.

Summary Statement

By simulating polymorphisms in the Angiotensin Type 1 Receptor, resultant drug binding affinities call attention to the necessity of personalized therapy based on a patient's receptor sequence.

Help Received

I conducted research under the supervision of Dr. Bradley Andresen at Western University of Health Sciences, using Dr. Yun Luo's computational laboratory. Mr. Shane Anderson found preliminary data that I occasionally looked upon for guidance.