Predictive *in silico* screening to determine vector-mediated transport properties for the blood-brain barrier choline transporter

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Abstract

An attempt to analyze vector-mediated transport properties for the blood-brain barrier choline transporter (BBBCHT) was made to assess and improve drug delivery to the central nervous system. The molecular docking methods were applied to determine energetic profiles (ΔG) and correlate them to the experimental binding modes. We report strong correlation of ΔG values with number of heavy atoms in the molecule. The molecular docking methods were able to predict almost all active compounds except for those with low number of heavy atoms, which limits rotational degrees of freedom. Knowledge gained from this study is useful to better understand the BBBCHT as well as can be used in medicinal chemistry programs targeting this transporter.

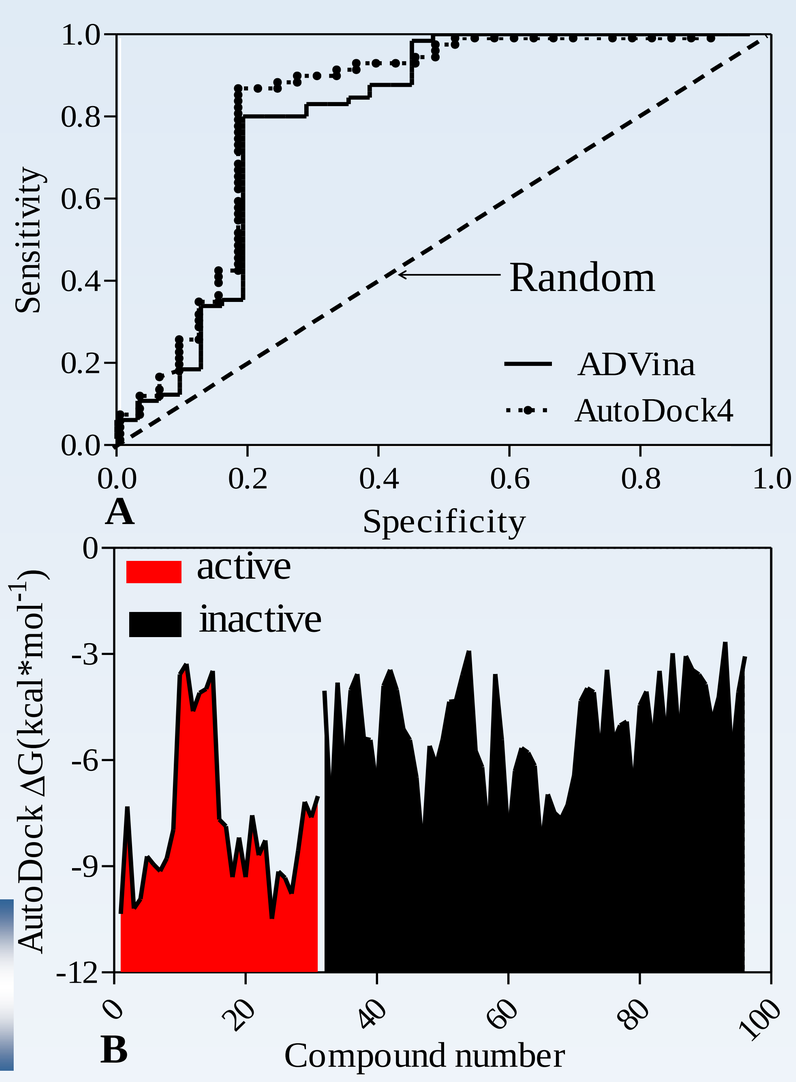
Objectives

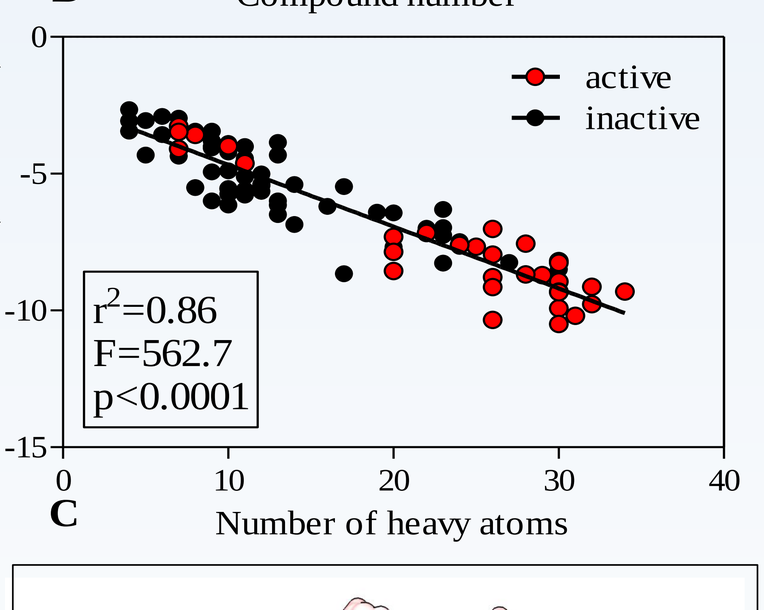
- *In silico* screening of molecular database.
- Predict compound affinity the BBBCHT molecule.
- Compare the AutoDock4 and AutoDock Vina performances (Receiver Operating Characteristic curve).
- Determine the BBBCHT binding site.
- Correlate predicted and experimental binding modes.

Methods

All molecular compounds (96 molecules) were retrieved from the PubChem BioAssay database; among them 32.29% were active and 67.71% inactive substances. The BBBCHT homology model was build using the i-Tasser server (Zhang *et al*., 2008). The PROCHECK software was implemented for stereochemical validation of the protein structure to investigate the dihedral angles in a Ramachandran plot. Flexible molecular docking was performed with the AutoDock4 (Raccon v1.0) (Morris *et al*., 2009) and AutoDock Vina (iDOCK) docking engines (Trott and Olsen, 2010). The PyRx software was used to optimize and minimize the dataset, add Gasteiger parcial charges, set up rotational bonds, merge all non-polar atoms, and convert SDF files into PDBQT format. The summarize_results4.py script from the MGLTools was used to analyzed the results.

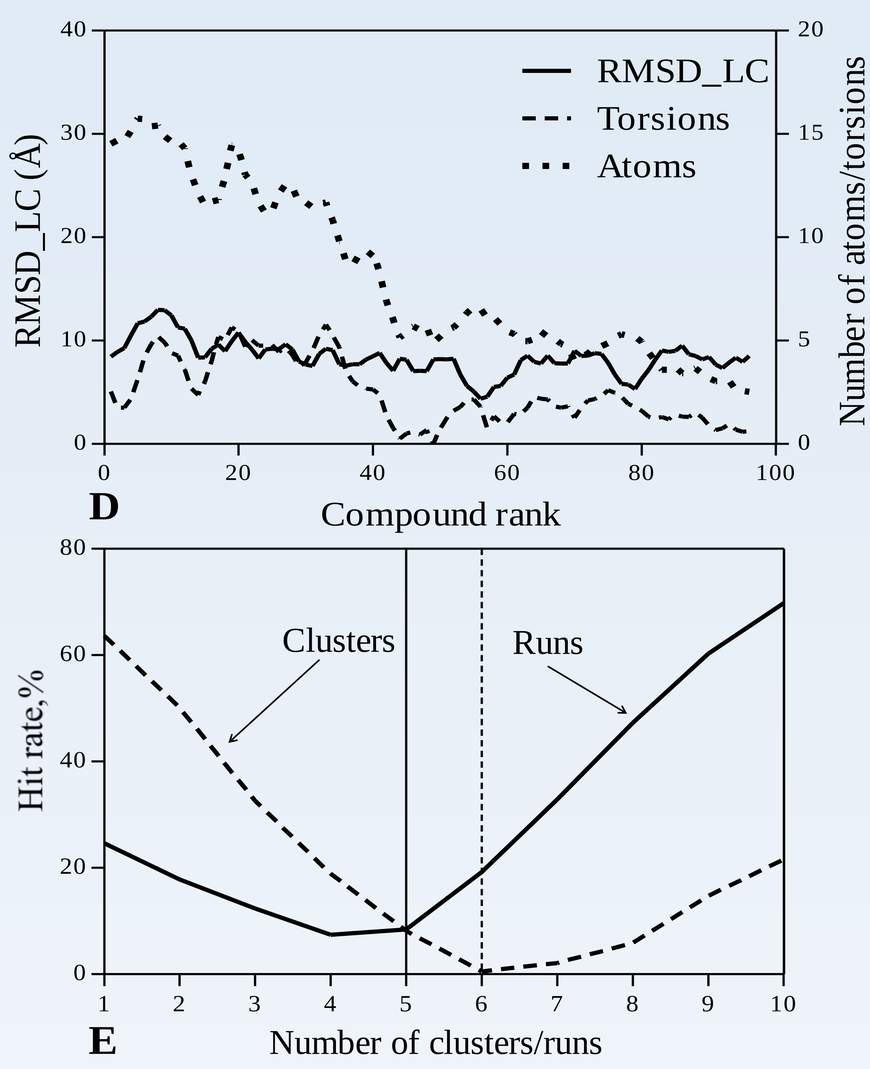
Results





Rigid-flexible docking of the active compounds into the binding site of the BBBCHT molecule. The molecular surface is divided by the frontal plane to visualize a binding channel of the protein. Red and blue colors are depicted for negative and positive electrostatic potentials; while zero potential is in white.

Clustering



Conclusion

The ROC curve shows that AutoDock4 achieved an AUC of 0.82, whereas the AUC for the ADVina is 0.80. They indicate that AutoDock4 outperforms slightly the Vina method (**Fig. A**).

Five active compounds were predicted as inactive due to a low number of heavy atoms (**Fig. B, C**)

The RMSD difference between the lowest energy conformation in the largest cluster and reference molecule (RMSD_LC) was decreasing while the compound ranking was increasing (**Fig. D**).

Number of clusters/runs goes down before the threshold is reached representing the similar pattern: number of clusters/runs increased with an increase of compound hit rate and vice versa (**Fig. E**).

References

Zhang *et al*., 2008, BMC Bioinform., 2008; 9:40.

Trott and Olsen, 2010, J. Comp. Chem., 2010; 31(2):455-461.

Morris *et al*., 2009, J. Chem. Inf Model., 2009; 51 (10):2528–2537.