3D similarities between the binding sites of monoaminergic target proteins

Núñez-Vivanco G.

Fierro A.

Moya P.

Iturriaga-Vásquez P.

Reyes-Parada M.

The study of binding site similarities can be relevant to understand the interaction of different drugs at several molecular targets. The increasing availability of protein crystal structures and the development of novel algorithms designed to evaluate three-dimensional similarities, represent a great opportunity to explore the existence of electronic and shape features shared by clinically relevant proteins, which could assist drug design and discovery. Proteins involved in the recognition of monoaminergic neurotransmitters, such as monoamine transporters or monoamine oxidases (MAO) have been related to several psychiatric and neurological disorders such as depression or Parkinson?s disease. In this work, we evaluated the possible existence of similarities among the binding sites of the serotonin transporter (SERT), the dopamine transporter (DAT), MAO-A and MAO-B. This study was carried out using molecular simulation methodologies linked to the statistical algorithm PocketMatch, which was modified in order to obtain similarities profiles. Our results show that DAT and SERT exhibit a high degree of 3-D similarities all along the pathway that is presumably involved in the substrate transport process. Distinct differences, on the other hand, were found both at the extracellular and the intracellular ends of the transporters, which might be involved in the selective initial recognition of the corresponding substrate. Similarities were also found between the active (catalytic) site of MAO-A and the extracellular vestibule of SERT (the S2 binding site). These results suggest some degree of structural convergence for these proteins, which have different functions, tissue distribution and genetic origin, but which share the same endogenous ligand (serotonin). Beyond the functional implications, these findings are valuable for the design of both selective and non-selective ligands.