Selectivity of dopamine D_1 and D_2 receptor agonists

A combined computational approach

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Akademisk avhandling för filosofie doktorsexamen i kemi, inriktning läkemedelskemi, som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras fredagen den 16 november, 2012, kl. 9.00 i KA-salen, Institutionen för kemi och molekylärbiologi, Kemigården 4, Göteborg.

ISBN: 978-91-628-8572-4

Abstract

Dopamine (DA) is an endogenous neurotransmitter acting in the central nervous system. DA plays a key role in many vital brain functions such as behavior, cognition, motor activity, learning, and reward. Dopamine receptors belong to the rhodopsin like family of G-protein coupled receptors (GPCRs). There are five subtypes of DA receptors (D_1-D_5), which are further divided into two main families based on sequence similarities and their coupling to intracellular signaling (D_1- and D_2-like receptors). Dopamine agonists mimic the effects of the natural neurotransmitter and it has been found that selective dopamine D_2 or D_1 and mixed D_1/D_2 agonists are useful in the treatment of Parkinson disease. As D_2 (but not D_1) agonists have shown undesirable dyskinetic effects it is of highest interest to understand the reasons behind D_1/D_2 agonist selectivity.

This thesis is focused on the identification of structural features that determine the selectivity of D_1 and D_2 receptor agonists for their respective receptors. Selective pharmacophore models were developed for both receptors. The models were built by using projected pharmacophoric features that represent the main agonist interaction sites in the receptor, and excluded volumes where no heavy atoms are permitted. The sets of D_1 and D_2 ligands used for modeling were carefully selected from published sources and consist of structurally diverse, conformationally rigid full agonists as active ligands together with structurally related inactives.

3D receptor models in their agonist bound state were also generated for dopamine D_1 and D_2, in order to get improved insight into agonist binding. The constructed D_1 and D_2 agonist pharmacophore models were superimposed into their corresponding receptor model. The arrangement of pharmacophoric features were in agreement with the position of the agonist key interacting amino acids in the binding site, with exception of one hydrogen bond accepting/donating feature in the D_2 model and the positioning of the excluded volumes in both models. Both pharmacophore models were refined to better reflect the shape of the binding pocket and had similar pharmacophore hit rate when screening the test sets of dopamine ligands. Several key factors for D_1/D_2 agonist selectivity were identified.

In addition, a semi-empirical method to model transmembrane proteins with focus on the ligand binding site has been developed. The method was evaluated by generating a β_1-adrenergic receptor model which had an RMSD of 1.6 Å for all heavy atoms in the binding site relative the crystal structure. A D_2 receptor model with an agonist present was constructed, but this model was unable to discriminate actives from inactives in a docking study.

Keywords: dopamine, agonists, GPCRs, pharmacophore modeling, protein structure modeling, agonist selectivity