PhD 10

Allosteric modulation of the human GABA B receptor

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Ɣ-aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the central nervous system (CNS), and dysregulation of the GABAergic system is related to brain disorders such as depression. The GABA B receptor is a heterodimeric class C G-protein coupled receptor (GPCR) consisting of two subunits (B1 and B2) of 7-transmembrane spanning sequences. GPCRs are targets for more than 1/3 of marketed drugs. Most of these drugs are regular orthosteric GPCR regulators. The orthosteric binding site is well conserved among GPCRs families and orthosteric drugs may lack selectivity.

Allosteric modulators (AMs) are drugs with higher specificity than regular orthosteric drugs and hence may trigger fewer side effects. In family C GPCRs, the allosteric binding pocket is located in the transmembrane domain at a similar location as the family A GPCRs orthosteric binding pocket. GABA B2 subunit contains the allosteric binding site while GABA B1 subunit contains the extracellular orthosteric binding site. No experimental structures of GABA B receptor are available, hence by using the technique of homology modeling we have generated several hundred models of GABA B2 subunit using templates from different GPCR families. A database consisting of 74 known allosteric binders and 2536 decoys was generated and used to evaluate the GABA B2 models. The evaluation indicated that the constructed GABA B2 models can be used as tools in structure-based virtual ligand screening for new allosteric GABA B modulators.