Allosteric modulation of the human GABAB receptor

Thibaud Freyd,[a] Dawid Warszycki,[b] Mari Gabrielsen,[a] Stefan Mordalski,[b] Andrzej J.Bojarski,[b] Ingebrigt Sylte[a]

[a]Department of Medicinal Biology, UiT The Arctic University of Norway, N-9037 Tromsø, Norway

[b]Institute of Pharmacology, Polish Academy of Sciences, 12 Smetna Street, 31-343 Krakow, Poland

[c]National Medicines Institute, 30/34 Chełmska Street, 00-725 Warsaw, Poland

e-mail: thibaud.freyg@uit.no

□-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. The $GABA_B$ receptor is a heterodimeric class C G-protein coupled receptor (GPCR) consisting of two subunits (gabr1 and gabr2). GPCRs are targets for more than 1/3 of marketed drugs. Most of these drugs are orthosteric drugs. But due to the conservation of the orthosteric binding site among GPCRs family they may lack selectivity.
Allosteric modulators (AMs) have higher specificity than regular orthosteric drugs and hence may trigger fewer side effects. For $GABA_B$ receptor, the allosteric binding pocket is located in the transmembrane domain of gabr2 while gabr1 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 gabr2 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 gabr2 models. The evaluation indicated that the constructed gabr2 models can be used as tools in structure-based virtual ligand screening for new allosteric $GABA_B$ modulators.

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