Structural study of the GluA2 ligand-binding domain in complex with allosteric modulators named TDPAMs

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The ionotropic glutamate receptors (iGluRs) mediate fast synaptic neurotransmission in the central nervous system (CNS). These receptors are highly abundant in the CNS and dysfunction of the glutaminergic system has been associated with e.g. epilepsy, depression, Alzheimer's and Parkinson's disease [1]. Thus, research on iGluRs is important to understand the physiological function of the individual receptors and in the context of developing new therapeutics. The iGluRs have been divided into four subfamilies: the NMDA, kainate, AMPA and Delta receptors. They assemble as tetramers and are comprised of an extracellular region composed of the N-terminal domain and the ligand-binding domain (LBD) where glutamate binds, a transmembrane region which forms the ion channel and finally an intracellular C-terminal domain.

The AMPA receptor GluA2 is considered to be an attractive target for positive allosteric modulation for the development of pharmacological tools or cognitive enhancers. Positive allosteric modulators (PAMs) bind to the LBD dimer interface and thereby stabilize the receptor in the activated form and delay deactivation of the receptor or its entrance into the desensitized state where the ion channel is closed despite glutamate is still bound. Two new dimeric PAMs named TDPAM01 and TDPAM02 have recently been synthesized at the University of Liege, Belgium [2-3]. The potencies of these modulators are in the 1-10 nM range at the AMPA receptor GluA2.

The aim of this project has been to determine the structures of the GluA2 LBD in complex with TDPAM01 and TDPAM02, respectively, and to analyze the specific binding modes of the monomeric and dimeric PAMs to the GluA2 LBD. This information may be valuable for development of drug compounds for the treatment of glutamate related diseases or as pharmacological tool compounds.

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