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Towards high resolution GABAA receptor modular structure

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Abstract

Type A gamma-butyric acid (GABAA) receptor is the main inhibitory neurotransmitter receptor family in the brain. Previous studies including those by us have associated GABAA receptor structural and functional variations with neuropsychiatric disorders such as schizophrenia. Differential expressions of alternative splicing isoforms of GABAA receptor beta- 2 subunit different in electrophysiology properties have been found in a developmental stage and disease status dependent manner. High resolution structural information is required to provide in-depth knowledge about the mechanisms of associated neuropsychiatric disorders and a foundation for structure-based drug development. To enable detailed structural studies, we have previous established a platform for hyper expression and purification of recombinant GABAA receptor proteins. By systematic deletions coupled with secondary structure integrate analysis, two consecutive beta-rich structural domains spanning the entirety of the extracellular region and a part of the potential transmembrane portion of the receptor protein have been identified. In addition, through site-directed Ala substitution of all non-Ala amino acid residues within the second of the two domains, secondary structure determinant and benzodiazepine binding site residues have been identified. A beta-sandwich type of domain structure has been implicated from our series of studies, which represents a discrepancy with the current structure model of neurotransmitter-gated channel receptors. As a critical step in resolving the recombinant GABAA receptor protein structure at atomic level, we have recently achieved in sample preparation for Cryo-electro microscopic analysis.

This will lead to high resolution structure for a important family of neurotransmitter receptors pivotal in schizophrenia and comorbid disorders and pave the way to new therapeutics for neuropsychiatric diseases. Recent Publications 1. Zhiwen Xu, Shisong Fang, Haifeng Shi, Hoiming Li, Jiun-Ming Wu, Hueih-Min Chen, Yiqun Deng, Yinglei Liao, Hui Zheng, Huaimin Zhu, Shui Ying Tsang and Hong Xue (2005). Topology characterization of a benzodiazepine-binding-rich domain of the GABAA receptor α1 subunit. Protein Science 14: 2622 – 2637. 2. Haifeng Shi, Shui Ying Tsang, Man Kit Tse, Zhiwen Xu and Hong Xue (2003). Recombinant extracellular domain of the three major subunits of GABAA receptor show comparable secondary structure and benzodiazepine binding properties. Protein Sci. 12:2642-2646. 3. Jun Hang, Haifeng Shi, Dongyang Li, Yinglei Liao, Dejun Lian, Yazhong Xiao, and Hong Xue (2000). Ligand binding and structural properties of segments of GABAA receptor α1 subunit overexpressed in Escherichia coli. J. Biol. Chem. 275: 18818-18823. 4. Xue, H, H Zheng, HM Li, A Kitmitto, H Zhu, P Lee and A Holzenburg (2000). A fragment of recombinant GABAA receptor α1 subunit forming rosette-like homo-oligomers. J. Mol. Biol. 296: 739-742. 5. Xue, H, J Hang, R Chu, Y Xiao, H Li, P Lee, and H Zheng (1999). Delineation of a membraneproximal β-rich domain in GABAA receptor by progressive deletions. J. Mol. Biol. 285:55-61.

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