

2nd International Conference on Pharmaceutics & Novel Drug Delivery Systems

20-22 February 2012 San Francisco Airport Marriott Waterfront, USA

TITLE

Geometric Analysis of the Cavity Surrounding the Orthosteric site of AChBPs: A Way Towards the Structural Characterization of the nAChR Activation

Thérèse E Malliavin

Institut Pasteur, France

The activity of nicotinic acetylcholine receptors (nAChRs) is modulated by ligand binding in the orthosteric site, located in the extracellular domain, at the interface between subunits. The structural details of the influence of ligand binding on the opening and closing of the nAChR channels, are not fully understood, because of the lack of high-resolution structures. But, these details are of utmost importance for rational design of ligands displaying expected pharmacological properties. To better understand the relationship between ligand binding geometry and ligand function, we recently introduced (Taly et al, 2011) the use of the orthosteric cavities surrounding the ligand binding site. A systematic analysis of the orthosteric cavities observed in the acetylcholine binding proteins (AChBP), was then performed, based on hierarchical clustering of cavities and on the spherical harmonics decomposition of the cavities shapes (Buratti et al, 2011). The hierarchical clustering separates AChBP dimer structures according to the agonist and antagonist function of the ligand. The spherical harmonics decomposition reveals the appearance and disappearance of bulges on the cavities surfaces for antagonist and agonist-bound cavities. These bulges are related to various sidechain orientations of specific residues, which can thus be considered as gatekeeper residues.

Biography

Thérèse E Malliavin is graduated from Ecole Polytechnique and has completed her Ph.D at Université Paris-Sud. After a postdoctoral stay at Institute of bioorganic chemistry of the Russian Academy of Sciences (Moscow), she joined the CNRS. She is now a CNRS research fellow at the Unité de Bioinformatique Structurale, at Institut Pasteur. She has published more than 50 papers in peer-review journals, and she is serving as a referee for several international peer-review journals.