Molecular Mechanisms of $GABA_A$ Receptor Allosteric Modulation by pH Level.

Connections between neurons and glial cells in nervous system are called synapses. Synapses are making connections between e.g. sensory neurons, receiving the stimuli and projection neurons which are transmitting information about red signal them to the brain. Mechanism of their work will than strongly affect how the nervous system functions. Two types of synapses can be distinguished – electrical, in which signal is transmitted almost directly via gap junctions and chemical ones, in which cells are separated by synaptic clefts. Special molecule, called neurotransmitter is necessary to move the signal trough this cleft. Neurotransmitters are small molecules, secreted by presynaptic cell and received by receptors at postsynaptic cells. Gamma aminobutyric acid (GABA) is the most important neurotransmitter for inhibitory signals transmission and a postsynaptic receptor responsible for its sensing is called $GABA_A$ receptor ($GABA_AR$). $GABA_AR$ itself is a big protein, made of five subunits within each three domains are present: extracellular domain (ECD), transmembrane domain (TMD) and intracellular domain (ICD). The goal of the project is to investigate molecular interactions between GABA and $GABA_AR$ at various pH (acidic/neutral/basic) levels. Neurotransmitter binding sites are located at the ECD at the interface of neighboring subunits. In the project both computational simulations and electrophysiological recordings will be performed. Structural models of $GABA_AR$ will be constructed and neurotransmitter molecules will be docked to them. A structural templates for model construction experimental (x-ray crystallography and cryo-electron microscopy) structures of similar proteins will be used. Obtained by this method systems will be put in motion using molecular dynamics simulations, a computational technique simulating protein movement on the basis of quantum calculations and empirical corrections. Computational results will be used to design electrophysiological experiments. The goal of the computations will be to design mutated receptors not prone to modulation by pH. Wild type receptors' and mutated ones', in regions investigate at previous step, kinetics will be compared. This in vivo observation will allow to validate results of the simulations and will deliver new insights about investigated process. All results of performed experiments will be a valuable input to the current state of knowledge about receptors in nervous system. Analysis of presented interactions will allow to better understand physiological phenomena both in healthy organisms and during clinical treatment e.g. during depression therapy, because $GABA_AR$ is a target of multiple drugs, including benzodiazepines.