COMPARATIVE ANALYSIS OF THE STRUCTURE OF THE CHANNEL DOMAIN OF PENTAMERIC LIGAND-GATED ION CHANNELS

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The members of Cys-loop ligand-gated ion channel proteins superfamily display important physiological functions, and their mutations may lead to a development of various pathologies. One of them is a 5-HT3 receptor which represents an integral peptide in a synaptic membranes. Three-dimensional structure of 5-HT3 receptor is currently unknown due to its difficult extraction and purification for different experimental methods. Molecular modeling remains the only approach for studying of the 5-HT3 receptor structure, which is needed for understanding of its role in neurophysiological processes and predicting specific ligands that may serve as drugs during different neurological diseases. In this work I present a model of the 5-HT3 receptor constructed by homology with nicotinic acetylcholine receptor, and discuss the amino acid sequence responsible for the selective ion transmission.

To create a molecular model of the 5-HT3 receptor the MODELLER software was applied. An available structure of the nicotinic acetylcholine receptor was used as a template. To study ion migration through the 5-HT3 receptor (stirred molecular dynamics) and characteristics of the close interaction between an ion and amino acid substitutions of the 5-HT3 channel (Constraint force) the GROMACS software was used.

The created model of the 5-HT3 receptor has shown the abundance of negative charges in the extracellular domain of the receptor, that obviously direct the cations migration. The dynamics of Na+ and Cs+ cations migration has been irregular because ions movement arrest has been observed in rings with negative charged amino acids GLU 272, ASP 293. It was shown that the steric factor in the region of residue THR 279 has an influence on Cs+ transmission. The energy profile analysis has demonstrated the presence of energy minimum in a region that is 2 nm apart from the mouth of the channel. Seemingly, it is the region of negative charged amino acids GLU 272, ASP 293 that take part in a cation hydrate coat reorganization.The structure of the channel domain of the serotonin 5-HT3 receptor as a universal functional unit of the ligand-gated ion channels was discussed.

Data obtained in silico from the molecular model of 5-HT3 receptor gives deeper understanding of its functioning and may be useful in neurophysiological and pharmacological studies.