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Analysis of serotonin 5-HT3 receptor and its models: identification of conformational state of the structure

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Ion channels form a major class of integral transmembrane proteins involved in the regulation of fundamental cellular processes [1]. The main function of ion channels is the selective movement of ions through the membranes. The structural and functional diversity of ion channels, as well as their participation in the vital systems of the body causes an increased interest in their study. The importance of research of channels' structures is underscored by the identification of numerous "channelopathies", caused by ion channel mutations [2]. However, the complex molecular architecture of eukaryotic ion channels, which include large non-membrane domains, is often an obstacle to structural studies by experimental methods [3]. Thus, only one atomic X-ray structure of the pentameric ligand-dependent mammalian channel of the serotonin 5-HT3 receptor (pdb id 4PIR [4]) and one Cryo-EM structure (pdb id 6BE1 [5]) are known at the present. Based on the available experimental data on this channel, the conformational state

of this channel can not be determined. In this regard, the actual task is to compare the structure of serotonin 5-HT3 receptor and its models, built by modeling homology. Structures with pdb id 2BG9 [6], 4AQ9 [7] for modeling 5-HT3 receptor closed and open conformations respectively were used as templates for modeling. The obtained models of open and closed channels of 5-HT3 receptor differ in the area of the internal threshold: the pore radius in this area is greater in open conformation models, compared with the closed conformation model and the structure of 5-HT3 receptor (4PIR). In the membrane part of the 5-HT3 receptor and the model of the closed conformation, the oxygen of the hydroxyl groups of threonine in the M2 helices form the area of the minimum radius of the pores. According to the molecular dynamics data obtained by us, hydrated sodium ions are unable to pass through this section of the channel 5-NT3 of the receptor. Thus, the data obtained suggest that the structure of the 5-HT3 receptor is more consistent with the closed conformation. The work was carried out with the financial support of the Russian Foundation for basic research, agreement № 16-34-60252.

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