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Theoretical Investigation of Interaction Between the Set of Ligands and α7 Nicotinic Acetylcholine Receptor

Theoretical investigation of interaction between the set of ligands and α_7 nicotinic acetylcholine receptor

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ABSTRACT

Nicotinic acetylcholine receptors (nAChRs) are neuron receptor proteins that provide a transmission of nerve impulse through the synapses. They are composed of a pentametric assembly of five homologous subunits (5 α_7 subunits for α_7nAChR, for example), oriented around the central pore. These receptors might be found in the chemical synapses of central and peripheral nervous system, and also in the neuromuscular synapses. Transmembrane domain of the one of such receptors constitutes ion channel. The conductive properties of ion channel strongly depend on the receptor conformation changes in the response of binding with some molecule, f.e. acetylcholine. Investigation of interaction between ligands and acetylcholine receptor is important for drug design. In this work we investigate theoretically the interaction between the set of different ligands (such as vanillin, thymoquinone, etc.) and the nicotinic acetylcholine receptor (primarily with subunit of the α_7nAChR) by different methods and packages (AutodockVina, GROMACS, KVAZAR, HARLEM, VMD). We calculate interaction energy between different ligands in the subunit using molecular dynamics. On the base of obtained calculation results and using molecular docking we found an optimal location of different ligands in the subunit.

Keywords: acetylcholine receptors, ligands, optimal location, transmembrane domain, ion channel, molecular dynamics, molecular docking, homologous subunits.

1. INTRODUCTION

The α_7 nicotinic acetylcholine receptor (nAChR) is the one of the most abundant receptors in human brain, playing an important role in learning, memory and cognition functions.[1] It is also located in a spleen, lymphocytes of lymph nodes, where activation yields post- and presynaptic excitation by increased permeability of potassium ions.[2] And it's a reason why the α_7 nAChR is the actual target to regulate processes impaired in neurological disorders, schizophrenia[3,4] and the target of general anesthetics. Also α_7 nAChR is the primary receptor mediating the cholinergic anti-inflammatory pathway and the treatment with a selective agonist of this receptor significantly decreases the neuroinflammation and neuronal damage resulting from cardiac arrest.[5]

This receptor contains five pseudosymmetric subunits arranged around the central pore. Each subunit contains a signature sequence of 13 residues bordered by cysteines that form a disulfide-bonded loop at the junction of extracellular and pore domains.[6] The state of the one subunit can significantly influence on whole receptor state: ions flow through the pore depends on conformational state of subunit which in turn depends on binding with the ligand.

Due to known model of transmembrane subunit (Fig. 1) it was determined to use solution state NMR.[1] It is possible to model some processes in the subunit with different mathematical modeling methods, tools, packages before experimental investigations. The molecular docking is the well-known method for drug-design purposes.

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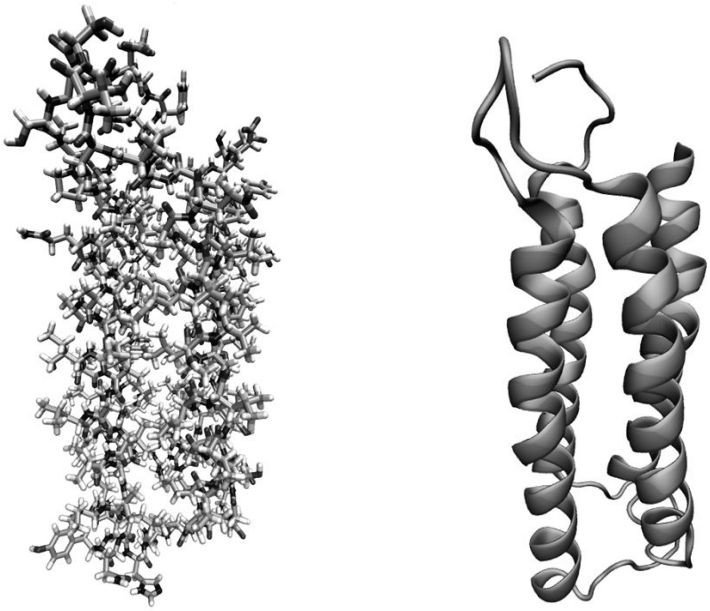

Fig. 1. Atomistic model of α_7 nicotinic acetylcholine receptor subunit and its secondary structure.

2. COMPUTATIONAL METHOD

Molecular docking is the method that predicts preferred orientation of a ligand to a biomacromolecular target, when they bound to each other to form a stable compound. There are a lot of packages for such purpose. One of such packages is the AutoDock Vina. It uses genetic algorithm to reach a minimum of energy and the general functional form of the conformation-dependent part of the scoring function:

$$c = \sum_{i<j} f_{t_i t_j}(r_{ij}), \tag{1}$$

where summation goes over all pair of atoms that can move relative to each other, excluding interactions between atoms, separated by more than 3 consecutive covalent bonds, r_{ij} is an interatomic distance, t_i and t_j are the types of atoms *i* and *j*, $f_{t_i t_j}$ - symmetric set of interaction functions for distance r_{ij}.[7] *c* is the sum of intermolecular and intramolecular parts. The interaction functions can be written in the next form:

$$f_{t_i t_j}(r_{ij}) = h_{t_i t_j}(d_{ij}), \tag{2}$$

where $d_{ij} = r_{ij} - R_{t_i} - R_{tj}$, R_{t_i} and R_{t_j} are the van der Waals radii for atoms *i* and *j* accordingly. $h_{t_i t_j}(d_{ij})$ is a weighted sum of steric interactions, hydrophobic interactions of hydrophobic atoms and hydrogen bonding, where it is applicable.

The optimization algorithm attempts to find global minimum of *c* value and other low-scoring conformations, which it then ranks. The predicted free energy of binding is calculated from the intermolecular part of the lowest-scoring conformation.[7]

3. RESULTS AND DISCUSSION

The set of ligands we used to work included following molecules: carvacrol, carveol, thymoquinone, vanillin, eugenol, thymol, carvone, pulegone, imenthone, isomenthone (some molecules models are shown on Fig. 2). We used AutoDick Vina and AutoDock Tools to operate with models of α_7 nicotinic acetylcholine receptor subunit and the models of the

ligands. The AutoDock Tools was used to prepare initial file for calculations and to analyze the results. Also VMD [8] and the graphical part of program package for molecular dynamic simulation KVAZAR [9, 10] were used for visualization.

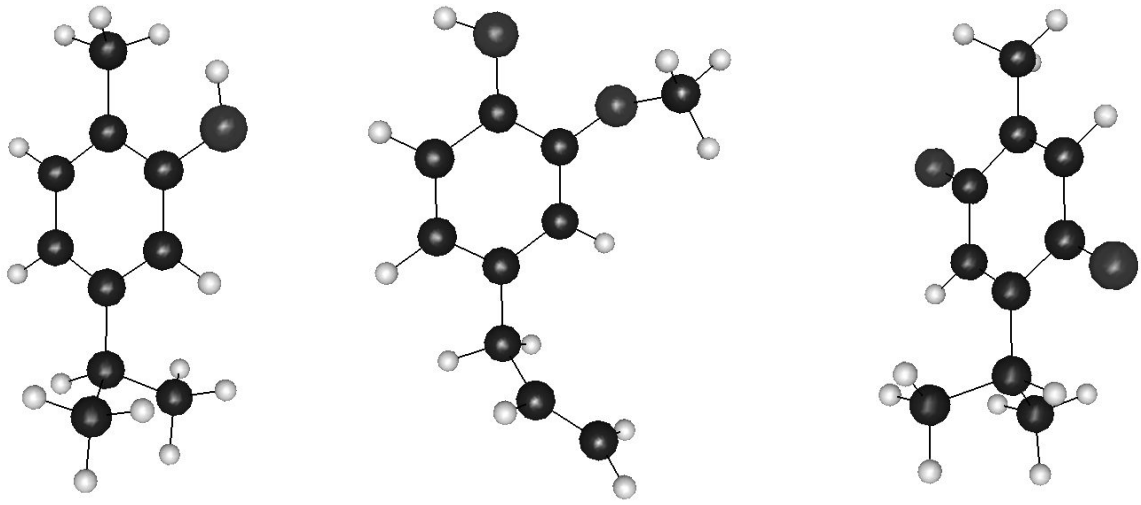

Fig. 2. PDB-models of carvarcol, eugenol, thymoquinone.

In the result of study the interaction and binding energies of ligands and transmembrane subunit of α_7 of nicotinic acetylcholine receptor were found. The highest interaction energy was occurred for thymoquinone and was about -7 eV. The lowest interaction energy was occurred for vanillin: -5.7 eV. Interaction energy for all other ligands was between -6.4 and -6.9 eV. The interaction energy for all ligands in the set is shown in the Fig. 3.

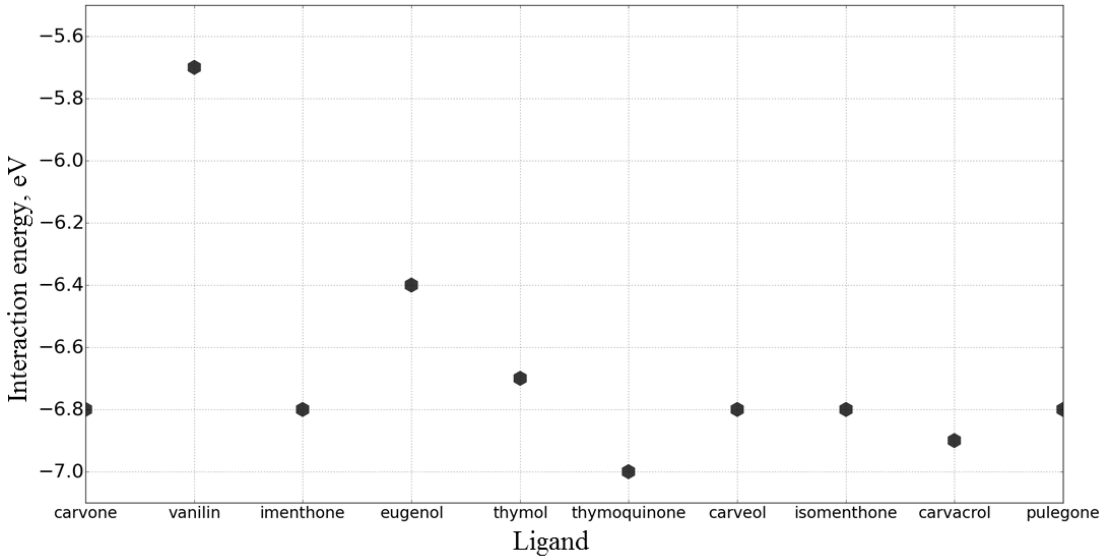

Fig. 3. Interaction energy between ligands and the subunit of the α7nAChR.

The optimal location of ligands set and subunit to each other was also found. As example we show the interposition of the transmembrane subunit with the karvakrol ligand (Fig. 4). It's seen that the karvalol strongly interacts with transmembrame' amino acids of cysteine, phenylalanine, serine and valine.

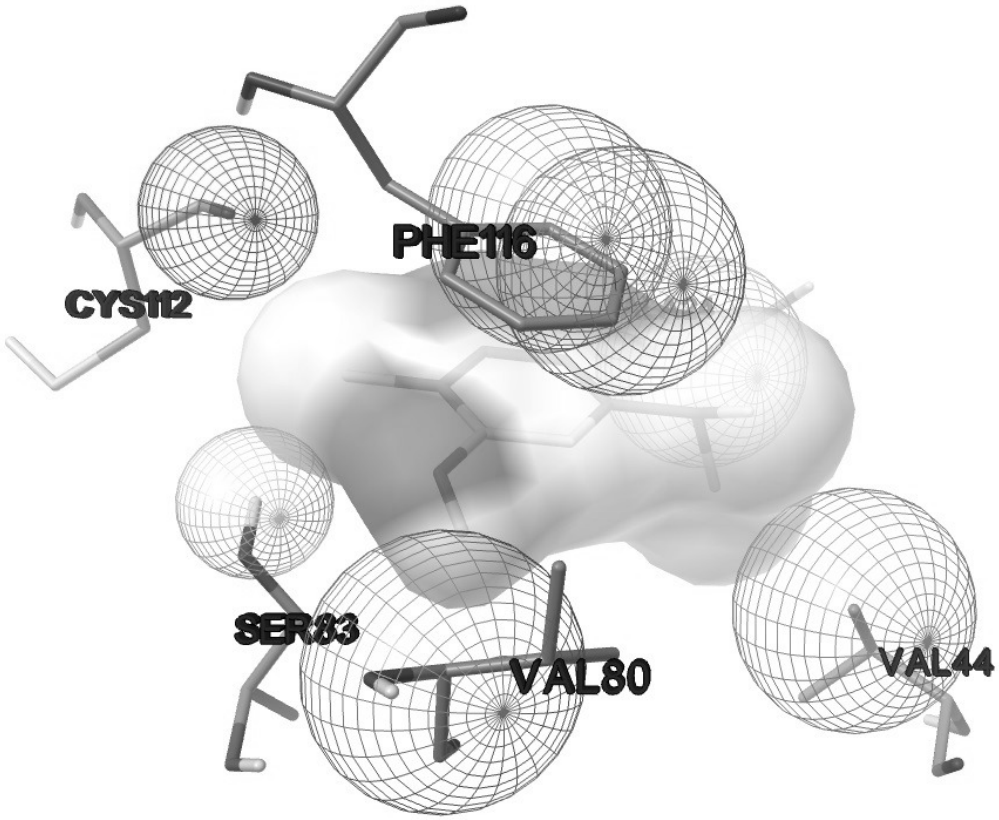

Fig. 4. The interposition of the transmembrane subunit subunit of α_7 of nicotinic acetylcholine receptor with the karvakrol ligand. The spheres note the radius of van der Waals interaction of amini acids.

4. CONCLUSION

Within the theoretical study the interaction between the set of different ligands (such as vanillin, thymoquinone, etc.) and the nicotinic acetylcholine receptor (primarily with subunit of the α7nAChR) was studied by molecular docking method and different packages (AutodockVina, GROMACS, KVAZAR, HARLEM, VMD). The interaction and binding energies as well as the interposition of ligands' set with the the α7nAChR subunit were found. The obtained results allow us to predict such biophysical features as conductance of ion channels in receptors of human's cell that can be applied during the drug design of anesthetics.

5. ACKNOWLEDGMENTS

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