Human α7 nicotinic receptor in active and inactive conformations: a molecular dynamics study

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Nicotinic acetylcholine receptors, belonging to the Cys-loop superfamily of ligand-gated ion channels (LGICs), are membrane proteins present in neurons and at neuromuscular junctions. They are responsible for signal transmission, and their function is regulated by neurotransmitters, agonists, and antagonists drugs. A detailed knowledge of their conformational transition in response to ligand binding is critical to understanding the basis of ligand-receptor interaction, in view of new pharmacological approaches to control receptor activity. However, the scarcity of experimentally derived structures of human channels makes this perspective extremely challenging. To contribute overcoming this issue, we built, via homology modeling, and assessed, via molecular dynamics, an all-atom structural model of the human homopentameric α7 nicotinic receptor, presenting both active and nonconductive states. We characterize here the open active state [1] and three different nonconductive conformations, a putative desensitized [2], a closed-locked and an apo conformational state [3].
The active and desensitized states are obtained for the receptor bound to the agonist epibatidine, while the locked state is obtained for the receptor bound to its natural antagonist α-conotoxin ImI. The apo-resting state is obtained from the spontaneous relaxation of the open, agonist-bound α7 structure after ligand removal. We carefully compare our structures with available experimental data and computational models of other eukaryotic LGICs, identifying key discriminators among states, and providing a quite complete structural characterization of the conformational landscape of the human α7 receptor.
Our detailed benchmarks could help in discriminating among conformations found in experiments or in simulations of LGICs.

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