The Structural studies of dopamine and some antagonist complexed mosquito Dopamine Receptor: A new target for insecticide development

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Vector borne diseases pose as one of the major threats to human life; accounting for more than 17% of deaths from infectious diseases worldwide. The studies of mosquito vectors (particularly Aedes, Anopheles and Culex) are crucial for developing insecticides due to their involvement in transmitting diseases to humans. Acetylcholinesterase (ACE) is a well-known insecticide target that has been exploited for more than two decades for vector control. However recently reported insecticide resistance in Anopheles and Culex mosquitos necessitates identification of novel targets for drug development and new mechanisms of drug administration. The Dopamine receptors (DAR), a vital GPCR in brain and central nervous system of mosquitos could be an important insecticide target. Recently, some antagonists for DAR have been suggested that show promising pharmacological properties and may function as potential insecticide to control Aedes and Culex mosquito vectors. However, in spite of these studies at present, there are no solved structures by crystallographic or NMR or computational methods that depict the 3D-coordinate positions of mosquito DAR. So, in the present study we have performed molecular modeling of dopamine receptor (Fig. 1) from different mosquito species (Anopheles stephensi, Anopheles gambiae, Aedes aegypti and Culex quinquefasciatus) followed by molecular docking with dopamine (substrate) and few reported antagonist molecules [1]. Molecular Dynamics Simulation studies have been performed to understand the dynamic nature of the ligand complexed dopamine receptor. At the active site of the protein, one Aspartic acid residue along with two other conserved water molecules are found to play important role in stabilizing the protonated amino terminal of dopamine. The catechol ring hydroxyls are stabilized by two Serine residues through direct and conserve water mediated hydrogen bond interactions. The study will aid for development of new insecticide molecules.

Figure 1. Representative modelled structure of DAR from Anopheles stephensi, Anopheles gambiae, Aedes aegypti and Culex quinquefasciatus


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