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MUTATION-DEPENDENT REMODELING OF THIAMETHOXAM BINDING TO INSECT NICOTINIC ACETYLCHOLINE RECEPTORS ASSESSED BY DOCKING AND MOLECULAR DYNAMICS SIMULATIONS

Background/Aim. Nicotinic acetylcholine receptors (nAChRs) are major molecular targets of neonicotinoid insecticides, while point mutations in their subunits may affect ligand binding and insecticide sensitivity. This study is aimed to develop models and to evaluate how selected mutations in $\alpha 1\beta 1$ and $\alpha 2\beta 1$ receptor complexes of *D. melanogaster* nAChRs alter thiamethoxam binding. **Methods.** $\alpha 1\beta 1$ and $\alpha 2\beta 1$ receptor complexes were modeled using AlphaFold-Multimer, followed by thiamethoxam docking with AutoDock Vina. The wild-type and mutant complexes were analyzed by 100 ns molecular dynamics (MD) simulations in GROMACS using structural stability, flexibility, contact, hydrogen bonding, solvent exposure, principal component analysis (PCA), and free energy landscape (FEL) metrics. **Results.** Docking placed thiamethoxam at the α/β interface corresponding to the ligand-binding region of nAChRs. MD simulations showed that wild-type $\alpha 1\beta 1$ and $\alpha 2\beta 1$ complexes differed in ligand stability, persistence of protein-ligand contacts, and local mobility of residues surrounding the binding pocket. In the $\alpha 1\beta 1$ system, K197A, K197H, and V116F mutations modified the interaction pattern of thiamethoxam by changing the balance between persistent contacts, hydrogen bonds, and ligand solvent exposure. These changes indicate that the residues located near binding interface contribute to direct ligand recognition and stabilization of the local pocket environment. In the $\alpha 2\beta 1$ system, the R54Q mutation affected the dynamic behavior of the receptor-ligand complex and changed the conformational sampling of the binding interface compared with the wild type. PCA and FEL analysis further suggests that mutations can shift the dominant conformational states of receptor-ligand complexes, rather than produce only local side-chain effects. Together, the results support a model in which mutation-dependent changes in thiamethoxam binding arise from combined effects on contact networks, hydrogen bonding, pocket exposure, and α/β -interface dynamics. **Conclusions.** K197A, K197H, and V116F mutations in $\alpha 1\beta 1$ and R54Q mutation in $\alpha 2\beta 1$ nAChR models reshape the structural and dynamic environment of thiamethoxam binding. The combined docking and MD workflow identifies interaction patterns that may contribute to altered neonicotinoid sensitivity and provides a basis for further experimental validation of insecticide resistance mechanisms.

Keywords: nicotinic acetylcholine receptor, thiamethoxam, neonicotinoids, molecular docking, molecular dynamics, insecticide resistance, *Drosophila melanogaster*.

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