MOLECULAR DYNAMIC SIMULATIONS OF GABERGIC CICLIC KETONES: Interaction with membranes and their contrast with experimental results

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The GABAA receptor (GABA-R) is the main inhibitory receptor of the Central Nervous System. It possesses binding sites for drugs other than the neurotransmitter GABA, including benzodiazepines, barbiturates, and the convulsing picrotoxine, which behave as allosteric modulators or channel blockers. The study of this last binding site is especially relevant since it constitutes the target of widely used neurotoxic organochlorine pesticides with agricultural importance. Our group has studied some highly lipophilic cyclic ketones demonstrating their ability to inhibit the GABA-R activity. Many lipophilic compounds that regulate GABAA-R function may change the physical properties of the lipid bilayer. In the present work, we show Molecular Dynamics (MD) Simulation studies of the interaction of cyclic ketones with gabaergic activity, using a model bilayer of 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (dpPC). Free diffusion MD simulations of dpPC in presence of the different ketones were used to analyze their interaction with a bilayer. These studies revealed a looser packing in the hydrocarbon chains of the dpPC in presence of these ketones. Additionally, we obtained spatially resolved free energy profiles of ketones partition into dpPC bilayers based on umbrella sampling. These profiles allowed us to determine the most probable ketones-dpPC interaction site. MD simulations results were contrasted with experimental data and agreements were found. Fluorescence anisotropy studies with different probes (DPH and TMA-DPH) indicated that all compounds were able to increase the membrane fluidity in a concentration dependent manner, and their effects were evidenced at different depth of the bilayer. Considering that the functions of proteins in the membrane might be altered as a result of the bilayer properties like elasticity, fluidity, thinning, etc., it is expected that GABAA-R could be also modulated not only by the specific ligand recognition, but also by changes in the physical state of the membrane.
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