XLVIII Reunión Anual de la Sociedad Argentina de Biofísica

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SAB
XLVIII

27 al 29 de noviembre de 2019
Universidad Nacional de San Luis

XLVIII Reunión Anual de la Sociedad Argentina de Biofísica / compilado por Sebastián Andujar ...
[et al.]. - 1a ed . - Buenos Aires : SAB - Sociedad Argentina de Biofísica, 2019.
Libro digital, PDF

Archivo Digital: descarga
ISBN 978-987-27591-7-9

1. Biofísica. 2. Investigación. I. Andujar, Sebastián, comp.
CDD 570

Diagramación y Edición

M. Soledad Celej, Juan Pablo Acierno

Diseño de Tapa y Logo

Comité Organizador

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Juan Pablo Acierno

Sociedad Argentina de Biofísica

Member of the International Union for Pure and Applied Biophysics

XLVIII Reunión Anual SAB

27-29 Noviembre 2019

San Luis, Argentina

XLVIII Annual Meeting SAB

27-29 November 2019

San Luis, Argentina

Effect of gabaergic phenols on the dynamic and structure of lipid bilayers: a molecular dynamic simulation approach

Miguel V[a], Villarreal M[b], García DA[a]

a - IIBYT (CONICET-UNC), Departamento de Química, Cátedra de Química Biológica, Facultad de Ciencias Exactas, Físicas y Naturales, Universidad Nacional de Córdoba

b - Instituto de Investigaciones en Físico-Química de Córdoba, Consejo Nacional de Investigaciones Científicas y Técnicas, Departamento de Química Teórica y Computacional, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. $GABA_A$ receptors are activated by GABA and modulated by a wide variety of recognized drugs, including anesthetics and benzodiazepines. GABAergic phenols (GP) like propofol, thymol, chlorothymol, carvacrol and eugenol are positive allosteric modulators of R-$GABA_A$. These GP are lipophilic, therefore their anesthetic activity could be the combined result of their specific interaction with the receptor, as well as nonspecific interactions with the receptor lipidic environment. We used molecular dynamic (MD) simulations to contribute to a description of the molecular events that occur at the membrane as part of the mechanism of general anesthesia. Previous MD simulations indicated that GP interacts with the polar interface of phospholipid bilayer. The presence of GP in a DPPC bilayer has an ordering effect on lipid acyl chains for carbons near the interface. We have now determined GP orientation in the bilayer by defining a set of molecular axes. We have calculated the correlation of the experimental membrane partition coefficients obtained by the IAM–HPLC method (log k_{IAM-W}), with ΔG of partition obtained in biased MD and obtained a value of 0.935. Potential of mean force (PMF) calculations using umbrella sampling were used to characterize the forces that drive propofol partition into the bilayer. This analysis showed that propofol partition is mainly enthalpic driven at the polar region and entropic driven at the hydrocarbon chains. We calculated the GP-water, GP-GP and GP-DPPC non-bonding interactions. We found attractive Lennard-Jones (LJ) interactions between phenol and DPPC, while GP-GP LJ forces were found to be nearly zero. Finally, we determined the first hydration shell for PRF. While in the aquose phase PRF has ~35 water molecules, at the lipid phase there is an average of ~5 water molecules, except at translocations, were water molecules drop to cero. These results confirm that all the GP studied interact with membranes, and exert some alteration of the receptor lipid environment. Thus, it is possible that anesthetic activity of GPs could be the combined result of their interaction with specific receptor proteins (GABA-Rs) but also with the surrounding lipid molecules.

Acknowldegments

This work was supported by grants from SECyT-UNC, FONCYT-MinCyT and CONICET.