Molecular Determinants of Tetrahydrocannabinol Binding to the Glycine Receptor

Lautaro D. Alvarez[1] and N. R. Carina Alves[1]

[1]Universidad de Buenos Aires Facultad de Ciencias Exactas y Naturales

February 22, 2024

Abstract

The recognition of *Cannabis* as a source of new compounds suitable for medical use has attracted strong interest from the scientific community in its research, and substantial progress has accumulated regarding cannabinoids' activity; however, a thorough description of their molecular mechanisms of action remains a task to complete. Highlighting their complex pharmacology, the list of cannabinoids' interactors has vastly expanded beyond the canonical cannabinoid receptors. Among those, we have focused our study on the glycine receptor (GlyR), an ion channel involved in the modulation of nervous system responses, including, to our interest, sensitivity to peripheral pain. Here, we report the use of computational methods to investigate possible binding modes between the GlyR and Δ^{9}-tetrahydrocannabinol (THC). After obtaining a first pose for the THC binding from a biased molecular docking simulation and subsequently evaluating it by molecular dynamic simulations, we found a dynamic system with an identifiable representative binding mode characterized by the specific interaction with two transmembrane residues (Phe293 and Ser296). Complementarily, we assessed the role of membrane cholesterol in this interaction and positively established its relevance for THC binding to GlyR. Lastly, the use of restrained molecular dynamics simulations allowed us to refine the description of the binding mode and of the cholesterol effect. Altogether, our findings contribute to the current knowledge about the GlyR-THC mode of binding and propose a new starting point for future research on how cannabinoids in general, and THC in particular, modulate pain perception in view of its possible clinical applications.

Hosted file

`PSFB_Cannabinoides-GlyR.doc` available at https://authorea.com/users/499806/articles/580834-molecular-determinants-of-tetrahydrocannabinol-binding-to-the-glycine-receptor