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Entitled

A COMPUTATIONAL ASSESSMENT OF THE ALLOSTERIC MODULATION OF GABA$_A$ RECEPTOR

by

Abdel Rahman Atef Ahmed Aly

Faculty Advisor

Dr. Ranjit Vijayan, Department of Biology

College of Science

Date & Venue

11:00 am

Monday, 18 April 2022

Link: https://eu.bbcollab.com/guest/9b2af65447734d51a700e03e9b7c8e29

Abstract

γ-aminobutyric acid (GABA) type A receptor (GABA$_A$R) is a pentameric ligand gated ion channel and a member of the Cys-loop superfamily. It is targeted by several clinically significant allosteric modulators. The role of individual subunits of the receptor has been very extensively studied. However, the exact molecular pathway upon which the receptor is activated remains elusive. The main objective of this study was to probe the molecular activation pathway for the orthosteric GABA and to understand how two of the most well-established positive (PAM) and negative (NAM) allosteric modulators tend to modulate the receptor. Three independent long scale molecular dynamics simulations were used to probe the early state GABA$_A$R activation pathway with GABA, in addition to the PAM, diazepam, and the NAM, methyl 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM). The study elucidated the role of α1 helices in determining the orthosteric site-wise preference. Moreover, it revealed a major role of α1 helices in controlling receptor activation through the modulation of loop 2 and B-loop. Interestingly, both diazepam and DMCM were found to modulate the receptor mainly through the α1 helices. However, the positional differences of diazepam and DMCM at the well-established unified pharmacophore model has greatly impacted their allosteric nature. These findings enhance our understanding of this complex macromolecular drug target and could facilitate the design of more efficacious allosteric modulators in the future.

Keywords: γ-aminobutyric acid, γ-aminobutyric acid type A receptor, Cys-loop superfamily, allosteric modulators, PAM, NAM, diazepam, DMCM, pharmacophore.