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Deciphering the "elixir of life": Dynamic perspectives into the allosteric modulation of mitochondrial ATP synthase by J147, a novel drug in the treatment of Alzheimer's disease

The discovery of J147 represented a significant milestone in the treatment of age-related disorders, which was further augmented by the recent identification of mitochondrial ATP synthase as the therapeutic target. However, the underlying molecular events associated with the modulatory activity of J147 has remained unresolved till date. Herein, we present, for the first time, a dynamical approach to investigate the allosteric regulation of mATP synthase by J147, using a reliable human αγβ protein model. The highlight of our findings is the existence of the J147-bound protein in distinct structural associations at different MD simulation periods coupled with concurrent open ↔ close transitions of the β catalytic and α allosteric (ATP5A) sites as defined by Cα distances (d), TriCα (Θ) and dihedral (ϕ) angular parameters. Firstly, there was an initial pairing of the αγ subunits away from the β subunit followed by the formation of the 'non-catalytic' αβ pair at a distance from the γ subunit. Interestingly, J147-induced structural arrangements were accompanied by the systematic transition of the β catalytic site from a closed to an open state while there was a concurrent transition of the allosteric site from an open αE conformation to a closed state. Consequentially, J147 reduced the structural activity of the whole αγβ complex while the unbound system exhibited high atomistic deviations and structural flexibility. Furthermore, J147 exhibited favourable binding at the allosteric site of mATP synthase with considerable electrostatic energy contributions from Gln215, Gly217, Thr219, Asp312, Asp313, Glu371 and Arg406. These findings provide details on the possible effects of J147 on mitochondrial bioenergetics, which could facilitate the structure-based design of novel small-molecule modulators of mATP synthase in the management of Alzheimer's disease and other neurodegenerative disorders.

Supported Student

Primary authors: Mr IWUCHUKWU EMMANUEL, Iwuchukwu (University of Kwazulu-Natal); Mr CLEMENT , Agoni (University of Kwazulu-Natal); Prof. PROF MAHMOUD E.S. , Soliman (University of Kwazulu-Natal)

Co-author: Dr FISAYO A., Olotu (University of Kwazulu-Natal)

Presenter: Mr IWUCHUKWU EMMANUEL, Iwuchukwu (University of Kwazulu-Natal)

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