Contribution ID : **182** Type : **Poster Presentation**

A Computational Study of the MOR1–PKR Interaction

Opioids are one of the most commonly used group of drugs in pathological pain treatment due to their remarkable analgesic effect. The main target for opioids is the transmembrane receptor μ-opioid receptor 1 (MOR1), which belongs to the G protein-coupled receptor superfamily (GPCR). Several kinases, such as G protein-coupled receptor kinases, cyclic AMP-dependent protein kinase, protein kinase C, and mitogen-activated protein kinases, interact with opioid receptors, modulating their activity. We investigated the potential interaction between the MOR1 and the double-stranded RNA-activated protein kinase (PKR), which participates in different cellular processes, including immune responses, cell growth control, and responses to cellular stress. To obtain more details on this interaction, this work aims to apply a set of computational chemistry methods to formulate a hypothesis regarding the mechanism of interaction between MOR1 and PKR. Different approaches on protein-protein docking were employed to generate a diverse set of putative complexes, including affinity-based or artificial intelligence (AI) methods. Molecular dynamics (MD) simulations were performed for each suggested complex to collect data and allow further validation. Resulting trajectories revealed stable and unstable complexes, providing key information on residues importance for the interaction. Stability of complexes was determined by parameters such as distance, root mean square deviation (RMSD) and contact mapping. The importance of PKR self-phosphorylation was also observed in this study. Once characterized, the remaining complexes will undergo experimental validation and serve as base for identifying future drug candidates. However, the impact of this study is not limited to the experimental field: the ensemble of states generated in this study will support supervised machine learning models for complex validation, which might be extended to other kinases on the future. This work is funded by Sao Paulo Research Agency (FAPESP), grants 2023/07855-3 and 2024/09222-0.

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