Investigation of the binding mechanism and molecular nature of human Sigma 1 receptor Ligands

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The Human Sigma 1 Receptor (hS1-R) is an enigmatic endoplasmic reticulum resident transmembrane protein. hS1-R is implicated in neuroprotection and neuroplasticity, therefore it is considered a potential therapeutic target to cure neurodegenerative diseases, like amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, Huntington's disease. Despite Kruse and coworkers solved the X-ray structures of hS1-R bound to agonists and antagonists [1], the molecular mechanisms of hS1-R activation remain unclear. In particular, two of the most important features required to fully understand hS1-R function, namely the receptor endogenous ligand(s) and the molecular mechanism of ligand access to the binding site, have not yet been unequivocally determined.
To shed light on the nature of the endogenous hS1-R ligand(s), we used a combination of computational virtual screening (VS), electron density maps fitting and fluorescence titration assay to measure ligand binding to hS1-R in vitro. We found that the molecules with steroid-motif were the ligands with the highest affinity for the receptor, and that among them 16,17-didehydroprogesterone was shown by fluorescence titration to bind HS1-R, with significantly higher affinity than the prototypic hS1-R ligand pridopidine in the same assay [2].
To investigate the molecular mechanism of the ligand access to the binding site, we performed all atoms MD simulations of hS1-R embedded in a lipid bilayer. The MD trajectories suggested that ligands access the binding site through a cavity, opening on the protein surface in contact with the membrane. Furthermore, we started to investigate the structure of hS1-R in solution by Cryogenic Electron Microscopy (Cryo-EM) to shed light on the molecular mechanism of protein polymerization/depolymerization induced by antagonists/agonists.

References:
1: Schmidt HR et al. (2016) Nature 532, 527-30.
2: Pascarella G, Antonelli L, et al. (2023) Int J Mol Sci. 24, 6367.