The structural basis that drives ligand efficacy at the serotonin 5-HT$_{1A}$ receptor

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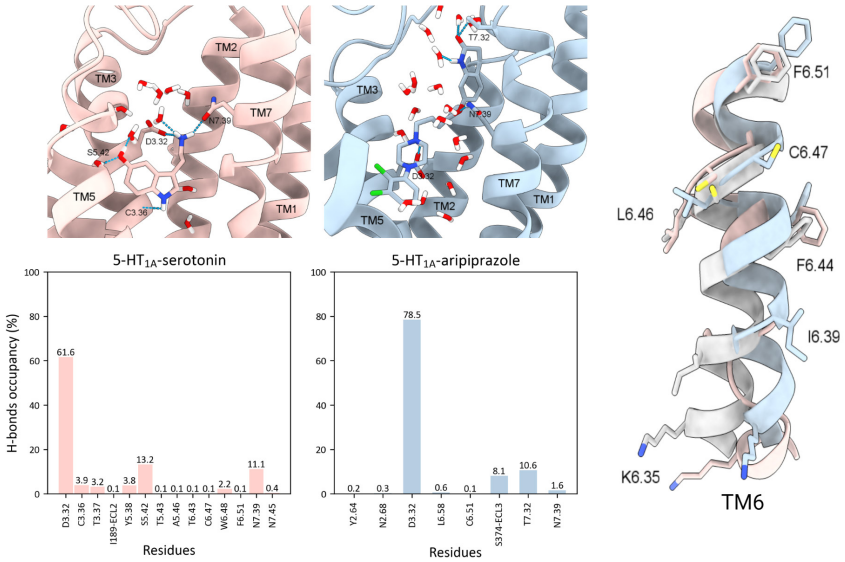
G-protein coupled receptors (GPCRs) are the largest superfamily of membrane proteins in the human genome; they modulate numerous physiological responses [1]. The 5-HT$_{1A}$ receptor, a Class A GPCR, is a member of the serotonergic receptor family, which is found in the central and peripheral nervous systems and activated by the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). Although the 5-HT$_{1A}$ receptor subtype is one of the most studied, since it is an important therapeutic target for several neuropsychiatric disorders, including anxiety, depression, and schizophrenia [2], the structural basis, which involves receptor dynamics, ligand efficacy and receptor activation, is largely unknown. Here, we use a metadynamics protocol based on the general activation index A^{100} [3] to study the activation of the 5-HT$_{1A}$ receptor. We show free-energy profiles for the serotonin receptor as binary (apo-receptor + G-protein-α-subunit and receptor + ligand) and ternary complexes with two prototypical orthosteric ligands; the full agonist serotonin and the partial agonist aripiprazole. The computed free-energy landscapes, specific interaction analysis and structural inspection suggest a combined mechanism that requires the action of both stabilizing intracellular and extracellular interactions in the receptor core for the full activation of the receptor. We have demonstrated the potential role of polar interaction networks in the receptor core as a regulator of the initial stages involved in receptor activation. In particular, our simulations have provided, on an atomistic level, direct evidence of the structural requirements that drive ligand efficacy at the 5-HT$_{1A}$ receptor. Thus, the results reported here constitute findings of remarkable value, not only for understanding the biophysical basis of signaling but also to provide the knowledge necessary to design more effective and less toxic drugs.



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