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A comprehensive structural study on AT1 Receptor Variants: Towards the Design of Potent Biased Agonists

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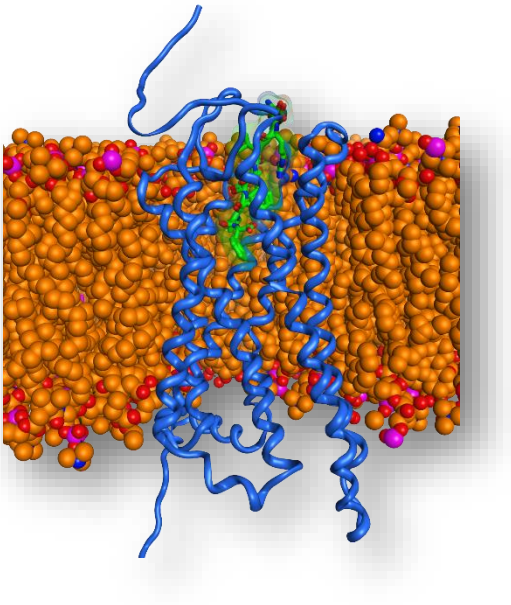
The angiotensin II type 1 receptor (AT_1R) is a crucial component of the renin-angiotensin system (RAS), which plays a significant role in regulating blood pressure, and cardiovascular health [1]. Biased agonism is an emerging concept that activates specific signaling pathways of G protein-coupled receptors (GPCRs). It involves selectively targeting the receptor with a ligand that stimulates one pathway while inhibiting others, leading to more precise treatments with fewer side effects. To gain a deeper understanding of GPCR functional selectivity at a molecular level, this study focuses on the use of AT_1R mutants and biased agonists. The activation of the AT_1R by different agonists leads to different signaling pathways which is known as functional selectivity [2]. Understanding this mechanism can help to develop more effective and targeted treatments for hypertension and other cardiovascular diseases. To assess the activation of Gq and the recruitment of β-arrestin in response to the stimulation of AT_1R with angiotensin II (AngII), [Sar^1Ile8], AngII [Sar^1LBpa^8]AngII, and [Sar^1DBpa^8]AngII ligands, we opted to substitute position $W253^{6.48}$, also referred to as the rotamer toggle switch, with alanine (W253A-AT_1R). The activation of G_q and recruitment of β-arrestin were quantified using BRET-based biosensors. Our results indicate that the mutant W253A-AT_1R was able to activate Gq and recruit β-arrestin when stimulated with AngII. However, upon stimulation with [Sar^1Ile^8]AngII or [Sar^1DBpa^8]AngII, which are β-arrestin-biased ligands on AT_1R, W253A-AT_1R mutant failed to recruit β-arrestin. Interestingly, [Sar^1LBpa^8]AngII could activate β-arrestin in the W253A-AT_1R mutant background.



This study proposes significant interactions exist between the mutant W253A-AT_1R and specific determinants of the different peptide ligands, which are involved in stabilizing the receptor in a conformation capable of recognizing β-arrestin. To investigate the structural dynamics of the native AT_1R and W253A-AT_1R mutant receptor, we utilized molecular dynamics (MD) simulations. Our study incorporated interactions with the native endogenous ligand and the three modified peptides. Our simulations revealed distinct conformational landscapes for each receptor-ligand pairing, with particular emphasis on regions of flexibility and interaction. Significantly, these unique conformational tendencies, lead to a better understanding of the molecular determinants responsible for selecting a given biased pathway. This information provides opportunities to design biased agonists with great therapeutic promise, as they may offer the potential for enhanced efficacy and reduced side effects.

References:

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