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Structure-function of the human melatonin receptors and potential for time-resolved studies

Content

The human melatonin G protein-coupled receptors (GPCRs) MT1 and MT2 are key components in regulation of circadian rhythm and sleep patterns. Both receptors have been targeted for drug design for treatment of insomnia, cancer and in the case of MT2, type 2 diabetes. We have solved four structures of each receptor in complex with several agonists at atomic resolution. Both receptors reveal unusually compact binding pockets, where the planar ligands interact with the receptor mainly through strong aromatic stacking and two additional hydrogen bonds. Ligands were found to mainly enter through a narrow channel between transmembrane helices IV and V, connecting the ligands to the lipid bilayer. Moreover, the MT2 structure also revealed the possibility of a second entry path through the extracellular site, which was further supported by melatonin dissociation kinetic data.

We also utilized virtual ligand screening (VLS) to identify novel chemotypes with unique pharmacological profiles for both MT1 and MT2 receptors. These efforts resulted in the discovery of molecules with unique properties and efficacies also in vivo. In particular, these studies confirmed and further elucidated the importance of high-resolution structural information for drug discovery of selective compounds spanning the entire efficacy window from full agonists to antagonists.

The unusually small, and tightly sealed binding pockets of the melatonin receptors are especially suitable for structure-based drug discovery and subsequently also for design of photo-switchable ligands. In particular, we have found that very small modifications of ligand may convert them from agonists to antagonists, allowing for development of e.g. caged compounds for time-resolved studies. We will discuss different approaches to structure-guided design of novel photoswitchable ligands and alternative approaches to understanding GPCR conformational dynamics.

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