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Combined *in silico* and experimental approach to identify the peptide mimetic of the nanobody that stabilize functional conformational state of the beta2 adrenergic receptor (β2AR)

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Abstract:
Stabilization of specific G-protein coupled receptor (GPCR) conformation is achieved by ligand binding to orthosteric or allosteric sites on a GPCRs. A crucial unresolved issue in GPCRs activation/signaling is the role of receptor structural conformations in G protein/effector protein selection. One of the possible approaches to get comprehensive depiction of GPCRs activation dynamics are molecular simulations and recently described nanobody-derived intrabodies. Monomeric single-domain antibody (nanobody) from the Camelid family was found to allosterically bind to and stabilizes distinct conformational states of the β2AR. By applying informational spectrum method (ISM), a virtual spectroscopy method for investigation of the protein-protein interactions, we have designed peptide mimetic of the nanobody related to the β2AR (nanobody derived peptide, NDP). Further, interaction between NDP and the ligand-bound β2AR active conformation have been studied by protein-peptide docking, molecular dynamics simulations and metadynamics calculations of free energy binding. Finally, the affinity of selected NDPs towards agonist-activated β2AR was also studied by microscale thermophoresis (MST) and by bioluminescence resonance energy transfer (BRET) based β-arrestin 2 recruitment assay. MST data predicted micromolar range interaction of selected NDPs with the β2AR, while the preliminary β-arrestin 2 recruitment results suggest prospective further modification and optimization of NDPs toward effective modulators of the β2AR.

Keywords:
bioinformatics, informational spectrum method, molecular dynamics simulations, nanobody derived peptides, protein-protein interactions

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