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Protein-lipid nanoparticles for studying G-protein coupled receptors functional properties

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Motivation and Aim: G-protein coupled receptors (GPCRs) constitute the largest superfamily of membrane proteins in the human genome and are therapeutic targets for over 30 % of drugs on the pharmaceutical market.[1]. Structural and biophysical research of GPCRs is aimed at finding the mechanisms of ligand recognition and signaling for this protein superfamily. Such studies are extremely challenging due to the low stability of GPCRs outside their natural membrane environment. Detergent micelles and nanodiscs based on derivatives of human apolipoprotein A-1 are the most common membrane mimetic systems (MMS) and are widely used for structural studies, as well as for studying the functional activity of GPCRs and other membrane proteins by NMR, single molecules fluorescence, mass spectrometry, *etc*. Nevertheless, the choice of the optimal MMS for various applications is still an actual task [2].
Methods and Algorithms: First of all, MMS must satisfy a number of criteria such as being compatible with the procedure for isolating and purifying the protein under study, thermally stabilizing, and allowing investigation of the structural and functional properties for the protein, along with retaining protein native properties. These requirements can be met by a new generation of MMS – nanodiscs based on the lysosomal protein saposin A (Salipro®) and nanodiscs based on a synthetic diisobutylene-maleic acid copolymer (DIBMALP). In case of Salipro® and DIBMALP, the formation of stabilized in solution protein-lipid nanoparticles occurs directly from the membrane, which qualitatively distinguishes these systems from all others and makes it possible to study GPCRs in presence of lipids surrounding them in the native membrane.
Results: In this work, we performed a comparative analysis of the stability and tendency to aggregation for the human A_{2A} adenosine receptor and cysteinyl leukotriene receptors ($CysLT_1R$, $CysLT_2R$) embedded in new and classic MMS.
Conclusion: The results obtained will allow to define MMS, the most suitable for physical and chemical studies of GPCRs *in vitro*.
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References

1. Shchepinova M.M. et al. Chemical biology of noncanonical G protein-coupled receptor signaling: Toward advanced therapeutics. *Curr Opin Chem Biol.* 2020;56:98-110.
2. Majeed S. et al. Lipid membrane mimetics in functional and structural studies of integral membrane proteins. *Membranes (Basel)*. 2021;11(9):685.