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Pendant-bearing glucose-neopentyl glycol (P-GNG) amphiphiles for membrane protein manipulation: Importance of detergent pendant chain for protein stabilization

Hyoung Eun Bae[a], Cristina Cecchetti[b], Yang Du[c], Satoshi Katsube[d], Jonas S. Mortensen[e], Weijiao Huang[c], Shahid Rehan[f,g], Ho Jin Lee[a], Claus J. Loland[e], Lan Guan[d], Brian K. Kobilka[c], Bernadette Byrne[b], Pil Seok Chae[a,*]

[a] Department of Bionanotechnology, Hanyang University, Ansan, 15588 (Korea)
[b] Department of Life Sciences, Imperial College London, London, SW7 2AZ (UK)
[c] Department of Molecular and Cellular Physiology, Stanford University, CA 94305 (USA)
[d] Department of Cell Physiology and Molecular Biophysics, Center for Membrane Protein Research, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, TX 79430 (USA)
[e] Department of Neuroscience, University of Copenhagen, Copenhagen, DK-2200 (Denmark)
[f] Institute of Biotechnology, University of Helsinki, Helsinki (Finland)
[g] HiLIFE, University of Helsinki, Helsinki (Finland)

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ABSTRACT

Glucoside detergents are successfully used for membrane protein crystallization mainly because of their ability to form small protein-detergent complexes. In a previous study, we introduced glucose neopentyl glycol (GNG) amphiphiles with a branched diglucoside structure that has facilitated high resolution crystallographic structure determination of several membrane proteins. Like other glucoside detergents, however, these GNGs were less successful than DDM in stabilizing membrane proteins, limiting their wide use in protein structural study. As a strategy to improve GNG efficacy for protein stabilization, we introduced two different alkyl chains (i.e., main and pendant chains) into the GNG scaffold while maintaining the branched diglucoside head group. Of these pendant-bearing GNGs (P-GNGs), three detergents (GNG-2,14, GNG-3,13 and GNG-3,14) were not only notably better than both DDM (a gold standard detergent) and the previously described GNGs at stabilizing all six membrane proteins tested here, but were also as efficient as DDM at membrane protein extraction. The results suggest that the C14 main chain of the P-GNGs is highly compatible with the hydrophobic widths of membrane proteins, while the C2/C3 pendant chain is effective at strengthening detergent hydrophobic interactions. Based on the marked effect on protein stability and solubility, these glucoside detergents hold significant potential for membrane protein structural study. Furthermore, the independent roles of the detergent two alkyl chains first introduced in this study have shed light on new amphiphile design for membrane protein study.

Statement of significance

Detergent efficacy for protein stabilization tends to be protein-specific, thus it is challenging to find a detergent that is effective at stabilizing multiple membrane proteins. By incorporating a pendant chain into our previous GNG scaffold, we prepared pendant chain-bearing GNGs (P-GNGs) and identified three P-GNGs that were highly effective at stabilizing all membrane proteins tested here including two GPCRs. In addition, the new detergents were as efficient as DDM at extracting membrane proteins, enabling use of these detergents over the multiple steps of protein isolation. The key difference between the P-GNGs and other glucoside detergents, the presence of a pendant chain, is likely to be responsible for their markedly enhanced protein stabilization behavior.

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* Corresponding author.
E-mail address: pchae@hanyang.ac.kr (P.S. Chae).

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