Usage Report for Fiscal Year 2019

Project Title:

Protein-Ligand and Protein-Lipid Interaction

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1. Background and purpose

The most important border in the biological world, biological membranes, provide an essential barrier towards the outside world. Membranes protect the function of life within its boundaries and separate different areas within a cell to give rise to specialized cellular compartments. While biological membranes are crowded with proteins, their main constituents are a wide variety of lipids.

To allow the exchange of nutrients and information between the interior and the surrounding environment, a barrier or wall requires windows and doors. In a cellular context, this task is conducted by proteins, embedded in the lipid membranes of cells, such as receptors to convey signals or transporters, capable to transport nutrients or ions across this barrier.

Lyso-phosphatidyl-β-D-glucoside (lyso-PtdGlc) derived from glial produced phosphatidyl-β-D-glucoside has been demonstrated to act as the first identified lipid derived regulator of central projections in nociceptive (pain) sensory afferents during embryonic development. This lyso-PtdGlc associated patterning is mediated by G-protein coupled receptor 55 (GPR55). GPR55 has originally been deorphanized as a cannabinoid receptor, but has later been described as lysophospholipid-responsive receptor. GPR55 upregulation has been reported in a variety of cancers, while GPR55 knock out mice show abnormal responses to inflammation and mechanical stimuli, suggesting a role of GPR55 in neuropathic pain and inflammatory processes. Furthermore, GPR55 has been linked to a variety of physiological and pathological processes, such as synaptic transmission, obesity, bone development and gastrointestinal functions. To-date no x-ray crystallographic structure for GPR55 has been reported.

2. Usage status and calculation methods

Quantum mechanics (QM) simulations utilizing the Gaussian 09 software package have been performed. Molecular dynamics simulations were performed utilizing the NAMD software package and results were visualized with VMD.

2. Results

To characterize lysolipid-GPR55 interaction and more specifically the ligand binding pocket, we established synthetic access to lyso-PtdGlc and prepared a variety of synthetic lyso-PtdGlc analogues. The biological activity of our synthetic analogues was evaluated using our previously developed functional assay, based on primary cultured DRG sensory neurons endogenously expressing GPR55. To overcome the lack of structural information of GPR55, we established and validated a GPR55 homology model and performed molecular dynamics (MD) simulations of GPR55 in the presence of natural and synthetic lysolipid ligands.

3. Conclusion

The results of our MD simulation were in good agreement with our biological assay results, providing novel insight into the ligand binding pocket specifics and highlight the conformational differences as well as preference of GPR55 for gluco- over inositol-configured head groups.

4. Schedule and prospect for the future including aims for the next usage term

Specifics of the lipid-lipid and lipid-protein interaction at atomistic levels are still not well understood and thus remain under investigation.

For example, preferred conformation of lyso-phospholipids in solution state, micelle arrangement or solublized with methyl-β-cyclodextrine are still not well understood. To gain a more complete atomistic understanding of this lipid conformation, we will probe lyso-phospholipid conformation by MD simulation in different solution states and correlate our results with experimental observation such as nuclear magnetic resonance spectroscopy.

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Fiscal Year 2019 List of Publications Resulting from the Use of the supercomputer

[Oral presentation]

1. “Synthetic Access to Mycotoxin Fumonisin B1 Analogues and Visualisation of Intracellular Trafficking”; P. Greimel
   Institute for Organic Chemistry, Graz University of Technology, December 6th, **2019**.
2. “Recent Progress: Solving the Native Structure of BMP and Probing the Ligand Binding Pocket of GPR 55”; P.Greimel
   SFB Seminar Series at the University of Graz, December 5th, **2019**.

[Poster presentation]

1. “G Protein-Coupled Receptor 55: Probing the Ligand Binding Pocket”; Adam T. Guy, Koki Kano, Yukishige Ito, Hiroyuki Kamiguchi, Ichiro Matsuo and Peter Greimel; Eurocab XX, June 30th – July 4th , **2019**.
2. “Ligand Binding Pocket of G Protein-Coupled Receptor 55”; Adam T. Guy, Koki Kano, Yukishige Ito, Hiroyuki Kamiguchi, Ichiro Matsuo and Peter Greimel; 60th International Conference on the Bioscience of Lipids, June 17th - 21th, **2019**.