© 2024 THE BIOPHYSICAL SOCIETY OF JAPAN
Vol. 21, e210011 (2024)
doi: 10.2142/biophysico.bppb-v21.0011

Biophysics and Physicobiology
https://www.jstage.jst.go.jp/browse/biophysico/

Commentary and Perspective

Holistic concepts in GPCR dynamics

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Received January 18, 2024; Accepted February 9, 2024;
Released online in J-STAGE as advance publication February 10, 2024
Edited by Haruki Nakamura

Tremendous advances in the structural biology and pharmacology of G protein coupled receptors (GPCRs), coupled with rapid advances in computational approaches, have expanded our understanding of both structural and functional aspects of GPCR dynamics and GPCR-ligand or partner protein interactions (Figure 1), providing guidance for new structure-based drug design. At the 61st Annual Meeting of the Biophysical Society of Japan in November 2023, a symposium with the title, "Holistic concepts in GPCR dynamics", was held. The goal of this symposium is to expose scientists to recent discoveries and cross-disciplinary approaches utilized to study GPCRs and provide opportunities for establishing communications that bridge complementary interests in the field of GPCRs. This session will feature speakers who have made exciting discoveries about the molecular mechanisms of GPCRs and partner proteins involved in signal transduction by utilizing spectroscopic, structural biology, single molecule observations, and computational chemistry approaches.

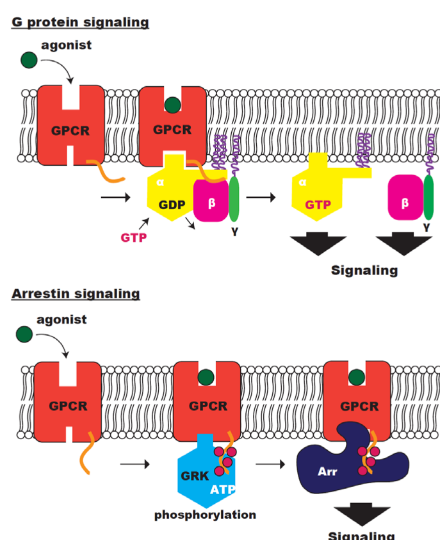

Figure 1 GPCR signaling mediated by G protein or arrestin. G protein-mediated signaling is initiated by interacting with activated GPCR following nucleotide exchange reaction between GDP and GTP. GTP-bound G protein dissociates from the GPCR as a separated α-subunit bound with GTP and βγ-dimer, both of which interact with various effectors to initiate signaling. Arrestin-mediated signaling is initiated through binding with phosphorylated GPCR at C-terminal region, resulting in physically obstructing G protein coupling to the GPCR, which causes desensitization of GPCR signaling.

Dr. Ryoji Suno (Kansai Medical University, Japan), who is one of the organizers for this symposium, reported on a study that used multiple techniques, including structural biology, infrared spectroscopy, and pharmacology, to identify

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the amino acids involved in the signaling of kappa opioid receptor (KOR) agonists. Agonists of the KOR have analgesic effects but also produce side effects such as drug aversion and sedation. It is hoped that the details of the molecular mechanism of KOR signaling will be elucidated for the development of analgesics without side effects. While other groups had already determined the structures of KOR in various agonist-bound states [1], Suno et al. successfully observed the dynamic changes in KOR upon agonist binding by infrared spectroscopy in addition to structural information. The role of these amino acids in KOR signaling will be compared with the KOR-G protein complex structure determined by Suno et al. and the previously reported inactive form [2].

Dr. Hideaki Kato (University of Tokyo, Japan) presented about dynamic recognition and activation of G proteins by the Neurotensin receptor 1 (NTSR1). NTSR1 is a class-A GPCR that can couple to multiple G protein subtypes and plays a role in various physiological functions, including the regulation of body temperature, body weight, blood pressure, and pain response. Previously, they determined the cryo-electron microscopy (cryo-EM) structures of the NTSR1-G_{i1} complex in two distinct conformations (the canonical and non-canonical states) and proposed a model for the sequential activation of G_{i1} by NTSR1 [3]. However, the mechanism by which NTSR1 recognizes and activates other G protein subtypes remains elusive. In this study, they presented cryo-EM structures of NTSR1 in complex with G_o or G_q heterotrimers. Combining this structural information with computational and functional analyses, they provided insights into the unique mechanisms that underpin G-protein recognition and activation by NTSR1.

Dr. Masataka Yanagawa (Tohoku University, Japan) presented a co-regulation of GPCR-mediated ERK signaling by G protein and β-arrestin. GPCRs convert various extracellular stimuli into intracellular signaling cascades through G proteins and β-arrestins. Previous studies have demonstrated that both G protein and β-arrestin activate the ERK signaling pathway, which regulates cell proliferation and differentiation [4]. However, it is unclear how the G protein and β-arrestin spatial-temporally control ERK signaling at living cell membrane. In this study, they showed a co-regulatory mechanism of ERK signaling by Angiotensin II type 1 receptor (AT1R), a class A GPCR, combining multi-color single-molecule imaging and NanoBiT split-luciferase assays. G_q protein activation determined GRK subtype selectivity on AT1R and subsequent β-arrestins/ERK signaling complex formation dynamics on the plasma membrane [5].

Computational methods are also vital for understanding the complex and dynamic signaling activity regulation mechanisms by GPCRs. The group of Dr. Ayori Mitsutake (Meiji University, Japan) has recently investigated dynamics of Orexin 2 receptor (OX2R), which is one of GPCRs using molecular simulations. From simulations for wild type and several mutations without ligands, they proposed the distance between Ile 148.CA (3.46) and Tyr 364.CA (7.53) as a good indicator for distinguishing inactive and active states for Class A GPCRs [6,7]. They also investigated the structural advantages of inward movement of TM7 and outward movement of TM6 during activation to bind to a G protein. In addition, they also performed simulations with ligands to investigate the difference between inactive and active states, and presented their results.

Finally, Dr. Kota Katayama (Nagoya Institute of Technology, Japan) presented a unique approach for understanding ligand recognition and activation mechanisms in GPCRs by using Fourier-transform-infrared (FTIR) spectroscopy. GPCR signaling utilizes an allosteric coupling between the extracellular facing ligand-binding pocket and the cytoplasmic domain of the receptor that selectively interacts with the signaling transducer such as G proteins and β-arrestins. Recently, they have attempted to use FTIR spectroscopy with combining a two-liquid exchange system to study the conformational changes in muscarinic receptor (M2R) that are induced by ligand binding [8]. In addition, they also performed systematic ligand induced FTIR spectroscopy on ligands with four different efficacies [9]. These studies demonstrated the novel direct method for the quantitative evaluation of ligand efficacy on M2R. Furthermore, by performing comprehensive FTIR measurements on site-specific amino acid mutation and ligand derivatives, they have elucidated one aspect of the regulatory mechanism of M2R activation upon acetylcholine binding.

Acknowledgements

We thank all the speakers for providing meaningful talks and lively discussions that will enhance the symposium. We also thank all the attendees who worked with us to make this symposium a success.

References

[1] Che, T., Roth, B. L. Molecular basis of opioid receptor signaling. Cell 186, 5203–5219 (2023). https://doi.org/10.1016/j.cell.2023.10.029

[2] Wu, H., Wacker, D., Mileni, M., Katritch, V., Han, G. M., Vaedy, E., et al. Structure of the human κ-opioid receptor in complex with JDTic. Nature 485, 327–332 (2012). https://doi.org/10.1038/nature10939

[3] Kato, H. E., Zhang, Y., Hu, H., Suomivuori, C-M., Kadji, F. M. N., Aoki, J., et al. Conformational transitions of a neurotensin receptor 1-G_{i1} complex. Nature 572, 80–85 (2019). https://doi.org/10.1038/s41586-019-1337-6

[4] Goldsmith, Z. G., Dhanasekaran, D. N. G Protein regulation of MAPK networks. Oncogene 26, 3122–3142 (2007).

https://doi.org/10.1038/sj.onc.1210407

[5] Kawakami, K., Yanagawa, M., Hiratsuka, S., Yoshida, M., Ono, Y., Hiroshima, M., et al. Heterotrimeric Gq proteins act as a switch for GRK5/6 selectivity underlying β-arrestin transducer bias. Nat. Commun. 13, 487 (2022). https://doi.org/10.1038/s41467-022-28056-7

[6] Yokoi, S., Mitsutake, A. Molecular dynamics simulations for the determination of the characteristic structural differences between inactive and active states of wild type and mutants of the Orexin2 receptor. J. Phys. Chem. B 125, 4286–4298 (2021). https://doi.org/10.1021/acs.jpcb.0c10985

[7] Yokoi, S., Mitsutake, A. Characteristic structural difference between inactive and active states of orexin 2 receptor determined using molecular dynamics simulations. Biophys. Rev. 14, 221–231 (2021). https://doi.org/10.1007/s12551-021-00862-1

[8] Katayama, K., Suzuki, K., Suno, R., Tsujimoto, H., Iwata, S., Kobayashi, T., et al. Ligand binding-induced structural changes in the M2 muscarinic acetylcholine receptor revealed by vibrational spectroscopy. J. Phys. Chem. Lett. 10, 7270–7276 (2019). https://doi.org/10.1021/acs.jpclett.9b02942

[9] Katayama, K., Suzuki, K., Suno R., Kise, R., Tsujimoto, H., Iwata, S., et al. Vibrational spectroscopy analysis of ligand efficacy in human M_2 muscarinic acetylcholine receptor (M_2R). Commun. Biol. 4, 1321 (2021). https://doi.org/10.1038/s42003-021-02836-1

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