Development of biosensor for real-time detection of the G-protein molecular switch

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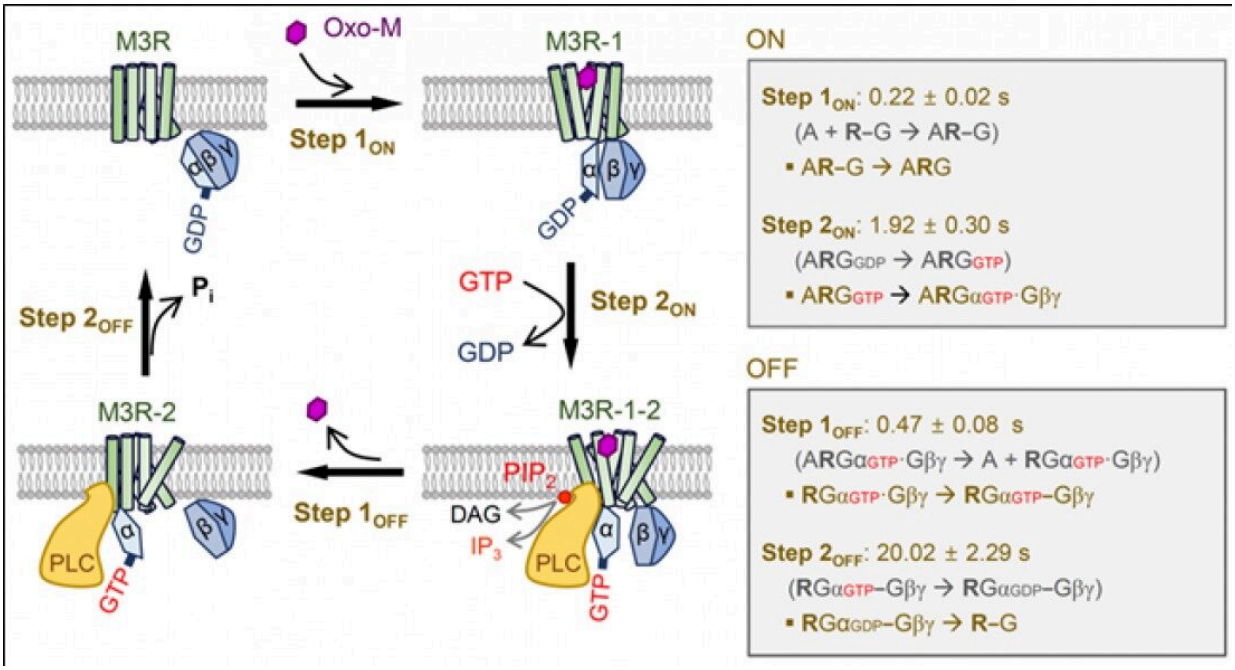

Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-36911-4

A research team led by Professor Byung-Chang Suh has investigated the real-time effect of the G-protein cycle, which acts as a switch in the body, on the structural changes in G protein-coupled receptors (GPCRs). Their study is published in the journal *Nature Communications*.

GPCRs are activated by external signals such as smell, light,

temperature, neurotransmitters, and hormones and are involved in numerous biological activities to the extent that nearly half of known drugs target GPCRs. GPCRs regulate various intracellular signaling pathways utilizing G proteins; however, the role of the reversible activation-deactivation cycle of the G protein on the structural changes in GPCRs has not yet been identified.

Professor Byung-Chang Suh's research team developed a new biosensor based on a fluorescent protein utilizing human M3 muscarinic acetylcholine receptor (hM3R), a type of GPCR. Using this biosensor, they found that a GPCR-based single receptor sensor exhibited consecutive structural conversion via the G protein cycle.

The research team also showed that G-protein activation caused a two-step change of the hM3R structure, comprising a fast step of G_q protein binding and a subsequent slow step of the physical separation of the $G\alpha_q$ and $G\beta\gamma$ subunits.

They also found that the separated active $G\alpha_q$ formed a stable complex with ligand-activated hM3R and PLCβ, a downstream signaling pathway of $G\alpha_q$.

In addition, applied research by Professor Suh's research team on the pathology of G protein-related gene mutations that cause uveal melanoma, for example, and on the pharmacology of related therapeutic drug candidates found that $G\beta\gamma$ subunits separated from $G\alpha_q$ can independently bind to hM3R, providing clues to a possible treatment of related diseases.

Professor Suh, the corresponding author, said of this study, "We confirmed the real-time communication between active GPCRs and G proteins, which had been considered separate up to this point," and that they "expect it to be of great help to future molecular and individual-

level research on diseases related to GPCRs and G protein and their treatments."

More information: Yong-Seok Kim et al, Two-step structural changes in M3 muscarinic receptor activation rely on the coupled Gq protein cycle, *Nature Communications* (2023). DOI: 10.1038/s41467-023-36911-4

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