Cryo-EM structure of the MT1-Gi signaling complex

Hiroyuki H Okamoto1 Hirotake Miyauchi1 Asuka Inoue2 Francesco Raimondi3
Hirokazu Tsujimoto4 Tsukasa Kusakizako1 Wataru Shihoya1 Keitaro Yamashita5
Ryoji Suno6 Norimichi Nomura4 Takuya Kobayashi6 So Iwata4,7
Tomohiro Nishizawa8 Osamu Nureki1

1 Department of Biological Sciences, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan
2 Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3, Aoba, Aramaki, Aoba-ku, Sendai, Miyagi, 980-8578, Japan
3 Laboratorio di Biologia Bio@SNS, Scuola Normale Superiore, Piazza dei Cavalieri, 7-56126, Pisa, Italy
4 Department of Cell Biology, Graduate School of Medicine, Kyoto University, Kyoto, 606-8541, Japan
5 MRC Laboratory of Molecular Biology, Francis Crick Avenue, Cambridge, CB2 0QH, UK.
6 Department of Medical Chemistry, Kansai Medical University, Hirakata 573-1010, Japan
7 RIKEN SPring-8 Center, Sayo, Hyogo, 679-5148, Japan
8 Graduate School of Medical Life Science, Yokohama City University, Yokohama, Japan.

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Melatonin (N-acetyl-5-methoxytryptamine) activates melatonin receptors (MT1 and MT2), which are one of the Gi-coupled class A GPCRs and transduce inhibitory signaling by inhibiting the adenylyl cyclase (AC). Melatonin thus induces our sleep and modulates our circadian rhythm, and melatonin receptors have long been regarded as an important therapeutic target for insomnia. Although melatonin itself serves as a sleep-inducing supplement, its property is not enough to use clinically, because it is rapidly cleared from our body. Therefore, a lot of melatonin analogs with prolonged release properties have been developed so far, such as ramelteon, agomelatine, tasimelteon.

Recently reported crystal structures of ligand-bound MT1 and MT2 elucidated the structural basis of ligand entry and recognition, but the molecular mechanism of the ligand-induced MT1 structural change that would lead to Gi-coupling remains unclear.

Here we report the cryo-EM structure of the MT1-Gi signaling complex at 3.3 Å resolution. The structure reveals the receptor activation mechanism, in which the ligand-induced conformational changes are propagated to the G-protein coupling interface. As compared to other Gi-coupled receptors, MT1 exhibits a large outward movement of TM6, which is considered to be a specific feature of Gi-coupled receptors. The structural comparison among the Gi- and Gs-complexes demonstrated the conformational diversity of the C-terminal entry of the G protein, suggesting the loose and variable interactions at the helix end. These notions, together with our biochemical and computational analyses, highlight the different binding modes of Ga1 and provide the basis for the selectivity of G-protein signaling.