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Cryo-EM structure of the MT_1-G_i signaling complex

Hiroyuki H Okamoto[1] **Hirotake Miyauchi**[1] **Asuka Inoue**[2] **Francesco Raimondi**[3] **Hirokazu Tsujimoto**[4] **Tsukasa Kusakizako**[1] **Wataru Shihoya**[1] **Keitaro Yamashita**[5] **Ryoji Suno**[6] **Norimichi Nomura**[4] **Takuya Kobayashi**[6] **So Iwata**[4,7] **Tomohiro Nishizawa**[8] **Osamu Nureki**[1]

[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 (MT_1 and MT_2), which are one of the G_i-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 an 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 MT_1 and MT_2 elucidated the structural basis of ligand entry and recognition, but the molecular mechanism of the ligand-induced MT_1 structural change that would lead to G_i-coupling remains unclear.

Here we report the cryo-EM structure of the MT_1-G_i 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 G_i-coupled receptors, MT_1 exhibits a large outward movement of TM6, which is considered to be a specific feature of G_s-coupled receptors. The structural comparison among the G_i- and G_s-complexes demonstrated the conformational diversity of the C-terminal entry of the G_i 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 $G\alpha_i$ and provide the basis for the selectivity of G-protein signaling.