【Grant-in-Aid for Scientific Research (S)】

Chronomedical innovation based on circadian biology

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Project Information	Project Number : 22H04987　　Project Period (FY) : 2022-2026 Keywords : Circadian clock, Sleep, GPCR, Dry eye, Alzheimer-type dementia

Purpose and Background of the Research

● Outline of the Research

Can diseases be cured by reactivating the body clock rhythm? As one of the breakthroughs, we have found this year that evaporative dry-eye disease, an illness of unknown etiology, can be treated by reactivating the rhythm of local enzyme activity in the eye, which has been attenuated by aging (Sasaki et al., Nat Aging 2022). Using this as a stepping stone, this study aims to create chronomedical innovations, based on circadian clock biology. Under the slogan of "Cure Disease by Controlling Time", we will not only bring a new perspective to the conventional concept of disease and drug discovery, but also conduct fundamental research to propose new treatments and/or drugs for disease groups for which treatment satisfaction is still low.

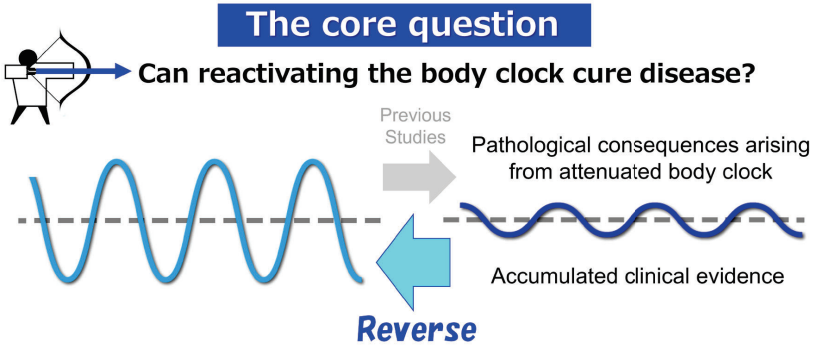

Figure 1. The core question of this research

● Research background: A paradigm shift in our understanding of circadian clock-related diseases

One of the most important conceptual changes brought about by the analysis of circadian-clock-deficient mice is that abnormalities in the circadian clock are linked not only to sleep arousal disorders, but also to a broad range of common diseases such as high blood pressure, obesity, and cancer. Conversely, however, despite these clinical important findings, the current chronobiology still does not have a unified answer to the fundamental question in the opposite direction: "Can various diseases be reversed by correcting the biological clock?"

● Proposed plan

Can correcting biological clock function cure disease? This year, the principal investigator found that age-related evaporative dry eye, for which there has been no effective treatment, can be treated by a method that normalizes the enzymatic activity rhythm in the eye (Nat Aging 2022). This is a world-leading achievement in providing an answer to the above question through a basic biological approach that makes use of clinical findings. Using this achievement as a stepping stone, this research project will create chronomedical innovations, based on cutting-edge basic research in chronobiology. Specifically, we will (1) verify the drug discovery potential based on the mechanism of G-protein coupled receptor (GPCR) action in the central clock in the brain, (2) clarify the sleep-wake mechanism based on the regulator of G-protein signaling (RGS), and (3) build evidence using clinical information and samples to promote drug discovery for age-associated dry eye disease, cancer, and Alzheimer's disease. Through these studies, we will open up new modalities and options for understanding diseases and developing treatments from the new perspective of the biological clock.

Expected Research Achievements

Toward the major goal of chronomedicine, this project will conduct basic research to create new drugs and chronotherapies for diseases with extremely high medical needs. The development of rhythm-regulating drugs targeting the suprachiasmatic nucleus (SCN), the locus of the master clock in the brain in mammals, is essential for the creation of new drugs for the treatment of insomnia and other diseases. To address this issue, we have previously identified orphan GPCRs Gpr176 and Gpr19 that regulate the SCN (Sci Rep 2021; Nat Commun 2016) and searched for their ligands. Using these preliminary data, this study will create central rhythm regulator that targets the central clock. In addition, this study will also develop a treatment for insomnia based on sleep-wake timing dysfunction in humans. In order to find regulators that work in humans, understanding the central clock G-protein signaling that causes sleep rhythm disorders in humans is necessary. The principal investigator has analyzed RGS16, a G-protein signaling regulator most strongly correlated with early morning arousal in humans (IJMS 2020; Nat Commun 2011), and will use this as a basis for research aimed at reverse translation using the human chronotype as a starting point. In parallel, in this study, we will also focus on treating age-associated dry eye, cancer, and Alzheimer's disease. Making use of the data already obtained, i.e., 1) improvement of age-related dry eye disease via 3β-HSD enzyme activity rhythm by NAD^+ (Nat Aging 2022), 2) cell cycle disorders caused by the clock protein Per2 abnormality (Nat Commun 2019; Nat Commun 2017), and (3) identification of the calcitonin receptor Calcr, which regulates napping (Genes Dev 2018), we push forward basic research that will create new drugs and therapeutic options from the perspective of chronobiology.

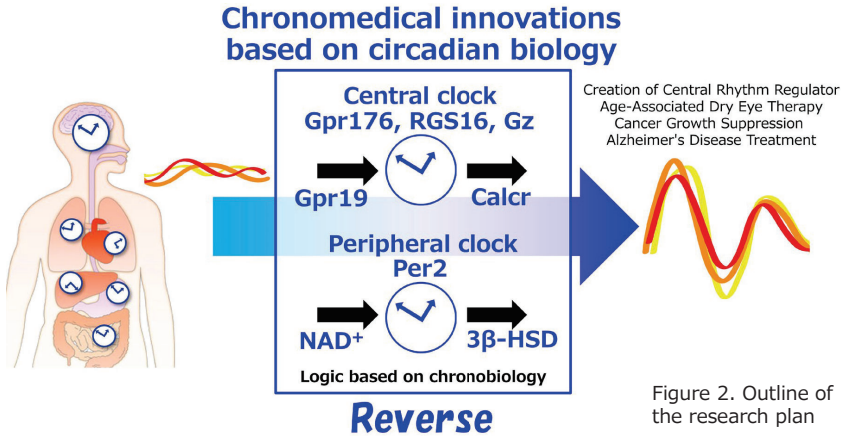

Figure 2. Outline of the research plan

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