【Grant-in-Aid for Transformative Research Areas（B)】

Section II

Title of Project： Multi-scale platform for untangling physiological complexity

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【Purpose of the Research Project】

In this research project, we aim to establish a multi-scale platform for untangling physiological complexity that functions as a "sensor" to collect integrated information across scales from molecules to individuals.

The conventional drug discovery research relies on a probabilistic approach based on empirical rules, in which we examine a large number of molecules as “input”, but with only a limited number of “output” measurements, thereby wasting multi-dimensional information. In the field of AI/digital drug discovery, quality of training data is critical for success, yet such high-quality data are generally not available. Furthermore, from such low-dimensional information, it is challenging to untangle complex biological phenomena in a digital manner, which is an obstacle to an efficient drug development program.

In order to establish a series of integrated platforms that efficiently acquire high-dimensional information at each scale of molecules, cells, and individuals and link it to drug discovery, we combine highly unique analytical technologies in the scale of molecular (A01: R. Suno/Kansai Medical University, D. Fujita/Kyoto University), cellular (A02: A. Inoue/Tohoku University), and individuals (A03: K. Sakurai/University of Tsukuba), and unique molecules (A04: T. Saitoh/University of Tsukuba). In this Transformative Research Areas (B) period, we will focus on G protein-coupled receptors (GPCR), which are targeted by 30% of commercially available drugs, and in particular opioid receptors, with technological development and proof of concept.

【Content of the Research Project】

1. Identification of signal factors corresponding to physiological effects and acquisition of protein complex structure

We will characterize ligand with different physiological effects for their intracellular signal comprehensively to identify the dominant signaling factors (transducers) associated with the effects. Then, we will conduct a structural analysis of the ternary complex of the identified transducer, ligand, and GPCR to understand the binding mode corresponding to the physiological effect at an atomic level. In order to achieve rapid protein complex structure analysis, we will challenge new structural stabilization methods using protein inclusion technology with a chemical cage.

2. Elucidation of brain regions and neural circuits that responsible for ligand-induced physiological effects

We will explore the candidate brain regions and neural circuits responsible for ligand-induced physiological outputs with anatomical methods. Afterward, CANE technology, a neural activity-dependent labeling and manipulation system, confirms the causal relationship between ligand-induced neural activities and physiological phenotypes.

3. Discovery of ligands that selectively induce physiological effects

A morphinan-based focused library will be constructed and applied for the structure-signal relationship study with the intracellular signal comprehensive analysis. With the precise structural data obtained by structural analysis, we will also conduct a molecular dynamics simulation study to elucidate how ligand-GPCR-transducer complexes selectively transmit the corresponding cell signaling. By integration of simulations, structure-signal relationship information, and structural analysis data, we will offer a role model for a rational design of drugs that induce a specific physiological effect.

【Expected Research Achievements and Scientific Significance】

Our project will obtain comprehensive and high-quality physiological information on opioid receptors, in which structures link to signals, neural circuits, and individual effects. We expect that the further collaboration of our results with informatic science will open a new door to replicate physiological effects in a digital space and predict drug effects, which leads to creating a new field "reverse drug discovery" in which drugs are designed from desired effects.

【Key Words】
G protein-coupled receptors (GPCRs), opioids, Cryo-EM SPA, supramolecular cage, intracellular signaling, neuroscience, reverse drug discovery

【Term of Project】 FY2021-2023
【Budget Allocation】 105,000 Thousand Yen
【Homepage Address and Other Contact Information】
TBA