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

Broad Section G

Title of Project : Elucidation and application of neural mechanisms that induce hibernation-like hypometabolic state

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【Purpose and Background of the Research】

We recently found that specific excitation of a population of neurons (Q neurons) consisting of about 800 neurons expressing the gene encoding neuropeptide QRFP in a subregion of the mouse hypothalamus (anterior ventral periventricular nucleus (AVPe)) caused a significant decrease in body temperature to near ambient temperature over several days, as well as a significant decrease in oxygen consumption. In many respects, this state closely resembles that of hibernating animals. In this project, we will identify the target neurons of Q neurons and investigate their neural circuits and mechanisms of action to explore the mechanisms that induce the hibernation-like state and clarify the physiological roles of Q neurons. In addition, we are going to induce Q neurons-induced hypometabolic states (QIH) in mice to elucidate how physiological functions such as consciousness, memory, autonomic nervous system functions, and body clock are altered in the hibernation-like hypometabolic state (QIH). We also aim to identify molecules to search for small molecular weight compounds to excite Q neurons by comprehensive analysis of the Q neuron transcriptome.

【Research Methods】

Goal A. Elucidate the mechanism of QIH induction: We will identify target neurons of Q neurons in the dorsomedial hypothalamus (DMH) by TRAP2, trace their axons, and optogenetically stimulate their cell bodies or axons to reveal their effects on body temperature and metabolism. We will also use Fos mapping to identify neurons that are excited or inhibited downstream and explore downstream neural pathways. In addition, as Q neurons have subpopulations, Qe, Qi and Qh, we would like to elucidate the functional differentiation of these subpopulations. We are also going to use fiber photometry to reveal changes in the physiological activity of Q neurons to reveal changes in Q neuron activity in response to fasting and hypoxic stimuli, and changes in external temperature. On the other hand, we will perform whole-cell patch-clamp recording from Q neurons and administer various substances to the extracellular fluid to know which substances affect the activity of Q neurons. On the other hand, we will analyze the output system of Q neurons. In particular, we will conduct retrograde tracing using mice expressing Cre recombinase in sympathetic preganglionic cells to elucidate the mechanism by which Q neurons control sympathetic output.

Goal B. Elucidation of the effects of QIH on physiological and neurological functions: We are going to analyze memory, sleep, body clock, and autonomic nervous system during QIH.

Goal C. Induction of QIH in primates: We will use macaque monkeys. We are going to inject AAV-CamKII-hM3Dq to the AVPe and try to induce QIH by CNO administration. Since 80% of Q neurons are glutamatergic, expressing hM3Dq in excitatory neurons in the AVPe, and administration of CNO could induce QIH-like state. We will monitor body temperature, heart rate, EEG, and ECG. We will also try to modify and use the Qrfp promoter to express hM3Dq.

Goal D. Transcriptome analysis of Q neurons: We will conduct mononuclear RNAseq analysis to classify Q neurons by transcriptome and to elucidate their properties in more detail, and to identify genes expressed in Q neurons that are as specific as possible in Q neurons, including receptors and ion channels, which would lead to the discovery of ways to manipulate Q neurons with small molecular compounds that bound them.

【Expected Research Achievements and Scientific Significance】

QIH can induce "regulated" hypothermia, which is quite different from the drug-induced or anesthesia-induced hypometabolic state. This is a safe state that can respond to changes in the outside world, and the animal will spontaneously return to temperature without any tissue injuries and abnormalities. In addition to the discovery of a new mechanism that revolutionizes the concept of the body temperature control system, we have also shown that non-hibernating animals potentially have a mechanism to temporarily reduce their whole-body functions and drastically lower their metabolism through the function of the central nervous system. This is a unique and novel finding and is expected to provide new knowledge in many areas, from basic physiology related to body temperature control mechanisms to clinical applications in hypothermia therapy, as well as basic knowledge for the realization of artificial hibernation in near future.

【Publications Relevant to the Project】

Takahashi, T.M., et al., Nature 583, 109–114(2020) DOI:10.1038/s41586-020-2163

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