

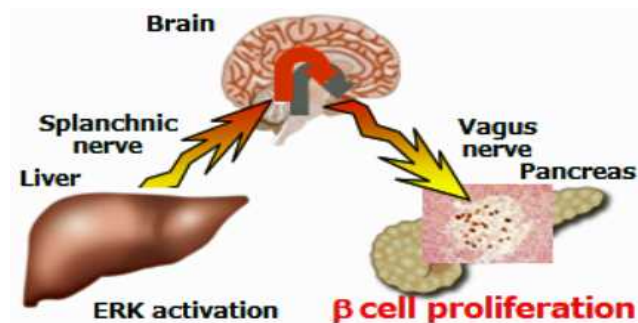
Elucidation of homeostatic mechanisms by inter-organ communication and development of therapeutic and diagnostic methods

Progress until FY2022

1. Outline of the project

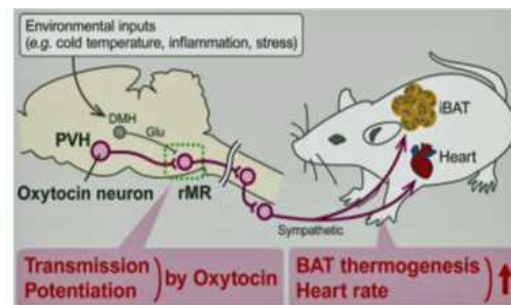
This R&D theme is responsible for the project's themes of (i) elucidating the inter-organ network mechanisms (See figure below) that maintain metabolic and circulatory homeostasis, and (ii) developing new prevention, diagnosis, and treatment methods for diabetes and its co-morbidities based on these mechanisms.

To achieve this goal, we are tackling this challenging theme by conducting detailed analyses to elucidate the molecules involved in the signaling of afferent, central, and efferent nerves connecting organs and their regulatory mechanisms. With the idea of developing preventive, diagnostic, and therapeutic methods for diabetes using inter-organ networks through the nervous system, which is completely different from conventional methods, we are working on this project using single cell RNA sequencing, optogenetics, fMRI, artificial nerve connections, plasma lipidomics, and other techniques.



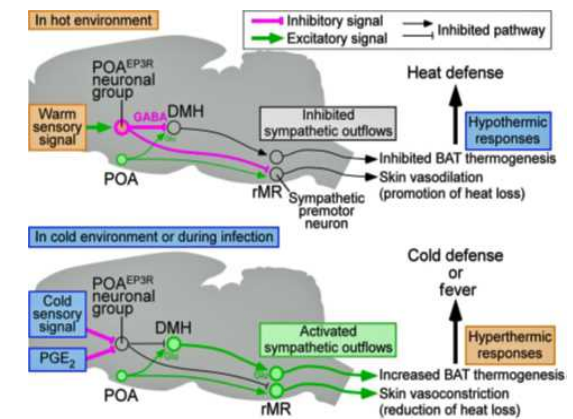
2. Outcome so far

- (1) Vagus nerve stimulation of the pancreas leads to proliferation of pancreatic β cells and suppresses the onset of diabetes in model mice (lower left figure)
- (2) Successful single-cell RNA sequencing of ganglia
- (3) Discovery of the oxytocin nervous system in the hypothalamus, which is linked from emotion to heat metabolism (lower figure)
- (4) Identification of master EP3 neurons that regulate energy metabolism (right figure)
- (5) Simultaneous measurement of vagal and sympathetic activity in rats
- (6) Establishment of fMRI method to measure activity of human hypothalamus brainstem system and discovery of activity during muscle exertion
- (7) Transient control of heart rate and blood pressure by magnetic stimulation of the thoracic spinal cord
- (8) Discovery of neural signals from intestinal bacteria and the intestinal tract that regulate sugar preference



Press Release with Nagoya University and JST (2022.9.21)

In the above, (1) is an important finding for POC when considering human applications. (3) will lead to the



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development of a new treatment for obesity caused by dysfunction of oxytocin neurons. (4) will lead to the development of techniques for obesity prevention and therapeutic intervention in the pre-symptomatic stage.

3. Future plans

In the future, to verify the results of vagus nerve stimulation obtained in mice, we will try to perform vagus nerve stimulation in monkeys and analysis of glucose metabolism in epilepsy patients with implanted human vagus nerve stimulators. This will lead to the development of methods to prevent and treat diabetes using vagus nerve stimulation.

In addition, we will search for receptors and ligands to elucidate the molecular mechanisms of afferent nerve signaling involved in the inter-organ network. This will lead to the development of prevention and treatment of diabetes and its co-morbidities by controlling the inter-organ network.