Title of Project： **Elucidation of mechanisms underlying glucose homeostasis mediated by inter-organ communication and development of diabetes therapies.**

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【Purpose and Background of the Research】

Metabolism in different tissues/organs is considered to be systemically regulated in a coordinated manner. In addition to humoral factors, such as hormones and cytokines, neuronal signals have recently attracted increasing attention for their roles in maintaining metabolic homeostasis at the whole-body level. We have identified several neuronal networks as being involved in inter-organ metabolic communication. A broad range of metabolic information is sent from peripheral organs/tissues and transmitted by neuronal relays consisting of vagal afferents and sympathetic efferents, resulting in cooperative metabolic regulation of functions, such as energy expenditure, pancreatic β cell mass, adaptive thermogenesis and lipid metabolism.
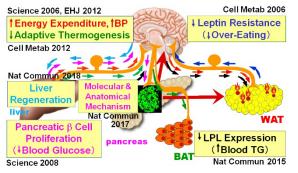

Figure. Inter-organ metabolic communications

Considering that the blood volume of an adult human is approximately 5 liters, a blood glucose concentration of 100mg/dl means that the total glucose amounts in blood is only 5 g at the whole-blood level, indicating that blood has minimal functional capacity as a glucose buffer. In particular, blood glucose levels during the fasting periods are well known to be very stable. All cells in the organs/tissues throughout the body take up and metabolize glucose as an energy source to sustain life. Moreover, since the buffering function of the blood is quite small, excesses and deficiencies of hepatic glucose release may directly induce hyper and hypo glycemia. These observations mean that hepatocytes release exactly the same amounts of glucose in total as those which are utilized throughout the body. Thus, the liver somehow knows how much glucose is consumed by remote organs in a real-time manner and continually produces and releases the right amounts of glucose. This mechanism requires great accuracy in terms of both timing and the amounts of glucose released. In this project, we aim to elucidate this mechanism.

【Research Methods】

We plan to produce inducible KO mice, in which rate-limiting enzymes catalyzing gluconeogenesis are deficient in the liver, kidney and/or small intestine and analyze metabolic phenotypes in a variety of tissues/organs. In addition, taking advantage of a new optogenetic technology which enables us to chronically activate or inactivate autonomic nerves innervating an intended tissue/organ, we aim to elucidate the inter-organ mechanism whereby the liver knows the amounts of glucose utilized throughout the body.

【Expected Research Achievements and Scientific Significance】

In this project, we aim to elucidate the fundamental mechanism which involves maintaining lives of multi-organ creatures, including human beings.

Furthermore, these exquisite mechanisms that underlie normal glucose conditions may be good targets for elucidating the causes of, and thereby novel treatments for, diabetes

【Publications Relevant to the Project】

· Uno K et al. Neuronal pathway from the liver modulates energy expenditure and systemic insulin sensitivity. Science 312: 1656-9, 2006
· Imai J et al. Regulation of Pancreatic β cell Mass by Neuronal Signals from the Liver. Science 322: 1250-4, 2008
· Yamamoto J et al. Neuronal signals regulate obesity induced β-cell proliferation by FoxM1 dependent mechanism. Nat Commun. 8: 1930, 2017
· Izumi T et al. Vagus-macrophage-hepatocyte link promotes post-injury liver regeneration and whole-body survival through hepatic FoxM1 activation. Nat Commun. 9: 5300, 2018

【Term of Project】 FY2020-2024

【Budget Allocation】 150,400 Thousand Yen

【Homepage Address and Other Contact Information】
http://www.diabetes.med.tohoku.ac.jp/