

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

Biological Sciences (Agricultural Sciences)



Title of Project : Analysis on Molecular Nutritional Functions of Bile Acids as a Feeding Signal, and Regulation of Metabolic Response to Feeding by Food Factors

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Research Area : Agricultural Chemistry, Food Sciences

Keyword : Bile acids, Feeding signal, TGR5, FGF15/19

【Purpose and Background of the Research】

Physiological events that induce the most dramatic metabolic changes in humans are fasting and refeeding. Insulin secretion is induced by rise in blood glucose in response to feeding. It is convinced that insulin resistance caused by reduced sensitivity of insulin receptors associated with high serum insulin levels leads to the onset of multiple diseases including metabolic syndrome. Despite insulin resistance hepatic fatty acid and triglyceride synthesis induced by insulin action remains elevated, thereby causing fatty liver and lipid metabolism disorder. Recent studies have revealed that several types of signals delivered by bile acids secreted from the gallbladder in response to feeding stimulation function as regulatory factors to orchestrate metabolic responses to feeding like insulin does. These findings, therefore, imply that adjusting unhealthy metabolic responses to feeding which are caused by out-of-control insulin actions resulting from obesity or overeating, by bile acids is strongly desired. For this purpose the molecular basis of the feeding responsive pathway controlled by bile acids needs to be fully understood. The molecular basis will provide a new approach to improve metabolic disorders by adjusting metabolic responses to feeding through actions of food factors. The aim of this project is to elucidate the mechanism of bile acid-dependent metabolic response to feeding, and to show a new concept on bile acid functions and importance of the bile acid-dependent feeding signal pathway as a novel target for functional food factors.

【Research Methods】

The molecular basis on the relationship between alteration in metabolic responses to feeding and reduced feeding signals resulted from inhibition of bile acid uptake through its intestinal transporter is analyzed by multiple methods. Food factors that interact with bile acids or directly hinder the activity of their transporter are examined on the

molecular mechanism for their mode of actions and regulation of metabolic responses to feeding. The regulatory mechanism of metabolic response to feeding through the bile acid receptor TGR5 in the small or large intestine and liver is investigated *in vivo* or *in vitro*. The mode of action of FGF15/19, a mediator of bile acid signals, as well as their receptor is examined at a molecular level. These studies will elucidate the molecular nutritional basis of ameliorating effects on metabolic response to feeding by reduced bile acid-dependent feeding signals, leading to novel food science researches from the perspective of exploring functional food factors with the capacity to exert ameliorating effect on metabolic response to feeding.

【Expected Research Achievements and Scientific Significance】

There is significant value to verify the new role of bile acids as a feeding signal so as to improve disorders of metabolic response to feeding. Findings confirmed in the current project are thought to lead to innovation by exploring functional food factors with the capacity to reduce metabolic responses to feeding.

【Publications Relevant to the Project】

- Shimizu M, Li J, Maruyama R, Inoue J, and Sato R (2013) FGF19 (fibroblast growth factor 19) as a novel target gene for activating transcription factor 4 in response to endoplasmic reticulum stress. *Biochem. J.* 450, 221-229.
- Irisawa M, Inoue J, Ozawa N, Mori K, and Sato R (2009) The sterol-sensing ER membrane protein TRC8 hampers ER-to-Golgi transport of SREBP-2/SCAP and reduces SREBP-2 cleavage. *J. Biol. Chem.* 284, 28995-29004.

【Term of Project】 FY2015-2019

【Budget Allocation】 147,700 Thousand Yen

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