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Adaptive changes in postprandial glucagon-like peptide-1 response and its role during the progression of diet-induced obesity and diabetic state in rats [an abstract of dissertation and a summary of dissertation review]

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Adaptive changes in postprandial glucagon-like peptide-1 response and its role during the progression of diet-induced obesity and diabetic state in rats

(食事誘導性肥満および糖尿病モデルラットにおける食後glucagon-like peptide-1分泌応答の変動とその役割)

Glucagon-like peptide-1 (GLP-1) is a gut hormone, which is produced by enteroendocrine L-cells and secreted in response to nutrient ingestion. It regulates postprandial glucose homeostasis by enhancing insulin secretion. To date, changes in postprandial GLP-1 responses under obesity, prediabetes, and diabetes are still being debated. Hence, the purposes of overall study were to clarify (1) alteration of postprandial GLP-1 secretion and (2) its role during obesity development, and (3) the potential mechanisms underlying the adaptive changes in GLP-1 responses.

Experiment 1 aimed to clarify postprandial GLP-1 response during the progression of diet-induced obesity and to determine whether dietary fat or sucrose potently impacts on adaptive changes in the postprandial GLP-1 response. Male Sprague-Dawley (SD) rats were fed a control diet, a high fat (HiFat, 30% fat) diet, a high sucrose (HiSuc, 40% sucrose) diet or a high fat and high sucrose (HFS, 30% fat and 40% sucrose) diet for 5 weeks. Meal tolerance tests (MTTs) using a standard (control) diet were conducted to assess postprandial glucose, insulin, and GLP-1 responses. Postprandial GLP-1 responses were higher in HFS and HiFat group after 2 weeks, but HiSuc group also had higher response after 4 weeks, compared to the control group. From this experiment, it was suggested that the HiFat diet rather than the HiSuc diet have a potent impact on adaptive enhancement of GLP-1 secretory responses during obesity development.

Experiment 2 aimed to clarify the role of enhanced endogenous GLP-1 secretion during glucose intolerance development. SD rats were fed a control diet or an HFS diet
with or without continuous administration of exendin-9 (Ex9, 100 µg/day), a GLP-1 receptor antagonist, for 5 weeks. Postprandial glycemic response in the HFS group was maintained similarly to the control group, whereas postprandial GLP-1 and insulin responses were increased in the HFS group. In Ex9 treated HFS group (blocking GLP-1 signal), postprandial glycemic response was higher along with a lower insulin response, compared to the HFS group without Ex9. The result suggests that the enhanced GLP-1 response during obesity development has a protective role against glucose intolerance induction.

Experiment 3 examined effects of prolonged (26 weeks) treatment with the obesogenic HFS diet on postprandial GLP-1 responses in non-diabetic Wistar rats and in diabetic Goto-Kakizaki (GK) rats. In Wistar rats, postprandial GLP-1 responses were higher or tended to be higher in the HFS group throughout the study compared to the control group. Both of GK rats showed a similar postprandial GLP-1 response, whereas the postprandial glycemic responses in HFS-fed GK rats were markedly higher, compared to GK rats fed a control diet throughout the study. GLP-1 contents (jejunum and ileum) and mRNA expression level of free fatty acid receptor 1 (Ffar1) in the jejunum were increased or mildly increased by HFS diet only in Wistar rats. These results suggest that increased intestinal fatty acid sensitivity and GLP-1 production are possibly involved in adaptive enhancement of postprandial GLP-1 response during obesity development. In addition, the failure of those adaptive changes in GK rats could be partly responsible for development of glucose intolerance.

In summary, postprandial GLP-1 response is enhanced during the progression of diet-induced obesity in rats. Fat, rather than sucrose in the diet has relatively higher impact on enhancing postprandial GLP-1 response. The enhanced GLP-1 response has a protective role against development of glucose intolerance. For the adaptive enhancement of GLP-1 response, increased fatty acid sensitivity and GLP-1 production in the small intestine may be responsible. A better understanding of GLP-1 secretion and its adaptation will lead us to design therapeutics or dietary interventions that modulate GLP-1 secretion by certain materials.