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General Summary

Physicians should practice patient-oriented medicine based on the concept of evidence-based medicine, which consists of research evidence, clinical expertise, and patients' preferences. To accomplish this goal, we encourage the members of our staff to do basic and clinical research. Areas of research include diabetes, metabolism, and endocrinology.

Research Activities

Epidemiology and evidence-based medicine

Several clinical trials of the treatment of type 2 diabetes using continuous glucose monitoring (CGM) are under way. The relationship between glucose fluctuation and diabetic complications is also studied with the data from CGM.

A nationwide epidemiologic study of mortality in approximately 3,500 patients with type 1 diabetes was started in 1986 and has continued to provide much information about the prognosis of Japanese children with type 1 diabetes. A population-based study of childhood obesity and insulin resistance as well as diabetes in elderly and genetic factors has also continued in Niigata Prefecture.

Molecular diabetology

Objective: Spontaneous hypoglycemia occurs owing to several causes with different patterns of hypoglycemia and hormone responsiveness. The aim of this study was to identify gene mutations in a family with spontaneous hypoglycemia by focusing on candidate genes and evaluating metabolism and hormone status.

Methods: The metabolic state was observed with CGM during the starvation test in the proband. Genomic DNA from peripheral blood was sequenced directly to identify gene mutations.

Results: The proband was a 34-year-old woman who was admitted to our university hospital because of severe hypoglycemia and metabolic acidosis associated with diarrhea and loss of appetite. She had had hypoglycemia-like episodes, especially when fasting, since the age of 1 year. In the starvation test, CGM clearly demonstrated no hypoglycemia until 29 hours. However, once hypoglycemia occurred at 29 hours, it persisted even after the induction of glucagon and the suppression of insulin secretion. These findings

strongly suggest that a glyconeogenic enzyme is inactive. Therefore, we focused on key glyconeogenic enzymes, including fructose-1,6-bisphatase (FBP1), phosphoenolpyruvate carboxykinase 1, and pyruvate kinase. The sequencing of these enzymes revealed that the proband and her brother, who had similar hypoglycemia-like episodes, share the same mutant genotype of compound heterozygosity for *FBP1* (G164S/F194S), in which homozygotes of each allele had been reported as a responsible mutation for the phenotype.
Conclusion: Observation of hypoglycemia with CGM and hormone responsiveness in a patient with hypoglycemia permitted a focus on candidate genes and enabled identification of *FBP1* mutations.

Insulin resistance and obesity
A series of basic research studies of insulin resistance were performed in Otsuka Long-Evans Tokushima Fatty rats. The effects of a new oral hypoglycemic agent (a dipeptidyl peptidase IV inhibitor) on insulin resistance were investigated.

Dietary therapy
A highly monounsaturated enteral formula more effectively suppressed postprandial hyperglycemia without causing exaggerated insulin secretion compared with a high-carbohydrate enteral formula in patients with type 2 diabetes and healthy subjects. In patients with type 2 diabetes receiving tube feeding with a highly monounsaturated eternal formula was shown with CGM to suppress postprandial hyperglycemia and to reduce 24-hour glycemic variations to greater extents compared with a high-carbohydrate eternal formula, even if carbohydrate nutrients had been adjusted for a low glycemic index.

Diabetic Vascular Complications
Diabetic complications are major sources of morbidity and mortality in patients with diabetes and an economic burden on societies worldwide. A greater understanding of the molecular targets that regulate both microangiopathy and macroangiopathy could lead to novel therapeutic strategies against diabetic complications. The Rho GTPases and their downstream effectors, Rho-associated kinases (ROCKs), have been implicated as regulators of the actin cytoskeleton. Because changes in the actin cytoskeleton are associated with vascular function, recent studies have revealed that ROCKs play a pivotal role in cardiovascular diseases, such as atherosclerosis, and in vascular remodeling. Accumulating evidence from animal models of diabetes shows that ROCK activity is increased in the kidney, retina, and vessels. Studies using pharmacological inhibition and genetic deletion of ROCKs have demonstrated that ROCK inhibition suppresses diabetic nephropathy by attenuating the excessive production of extracellular matrix induced by diabetes and slows the development of glomerular sclerosis and interstitial fibrosis. Given this background, we investigated the mechanism by which Rho-kinase promotes diabetic nephropathy. It is known that the diabetic kidney is exposed to hypoxic conditions. We found that ROCKs regulate the expression and function of hypoxia-inducible factor 1a, thereby inducing glomerulosclerosis under diabetic conditions.
Furthermore, we reported for the first time that Rho-kinase regulates endoplasmic reticulum stress-mediated endothelial function.

Finally, we found that fasudil (a Rho-kinase inhibitor) attenuates the progression of diabetic neuropathy in rats with streptozotocin-induced diabetes.

Endocrinology

To identify and isolate stem-like cells in human pituitary adenomas, we focused on the expression of CD133, which is a tumor stem cell marker in brain tumors, and examined the differences between CD133-positive cells and CD133-negative cells indicating stem properties.

The 12-lipoxygenase pathway may play a role in the pathogenesis of diabetic cardiomyopathy. Therefore, the role of the 12-lipoxygenase pathway in cardiomyopathy was examined in a rat model of diabetic cardiomyopathy and in an *in-vitro* study with a primary cardiomocyte culture system.

Previous studies have shown that the secretion of adrenocorticotropic hormone is increased in the hearts of patients with hypertension, indicating that adrenocorticotropic hormone may be involved in the pathophysiology of cardiovascular diseases. Recently, pro-opiomelanocortin messenger RNA has been shown to be expressed in the murine heart. Therefore, we designed a study using HL-1 cardiomyocytes to clarify the pathophysiological role of pro-opiomelanocortin.

In patients with hyperaldosteronism, Ca blockers (type T and type N) reduce levels of aldosterone.

In patients with hypertension and type 2 diabetes, fluctuations of glucose and systolic blood pressure were found to be related and to be associated with the development of arteriosclerosis.

Publications

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Reviews and Books

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