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Clarification of the Mechanism of Impaired Insulin Secretion Induced by Sodium Chloride Intake

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Summary

Excessive intake of sodium chloride (NaCl) is known as a risk factor for hypertension, cardiovascular disorders, renal dysfunction. However, the association between excessive NaCl intake and type 2 diabetes has not been clarified. Excessive NaCl intake is expected to cause obesity and type 2 diabetes secondarily through increased appetite and intake of soft drinks, but some reports suggest that excessive NaCl intake also affects insulin secretion itself. In the experiments, 8-week-old C57BL/6J male mice were loaded with a normal diet (NaCl concentration 0.8%) or a high-salt diet (NaCl concentration 4.0%) for 30 weeks. No differences in body weight, glucose tolerance, and the number and area of pancreatic islets were observed between the two groups. Subsequently, 8-week-old C57BL6 male mice were loaded with a high-fat diet (HFD, fat-derived calories 60%, NaCl concentration 0.4%) or a high-fat + high-salt diet (HFSD, fat-derived calories 60%, NaCl concentration 4.0%) for 30 weeks. As a result, in the HFSD diet group, although the weight gain was suppressed as compared with the HFD group, the glucose tolerance was deteriorated, and the plasma insulin level after glucose loading was significantly lower. It was shown to present with insulin deficiency. The number and area of pancreatic islets at 30 weeks were significantly lower in the HFSD group than in the HFD group. These results suggested that excessive salt intake may suppress the proliferation of pancreatic β-cells caused by ingestion of lipids. Therefore, after feeding a HFD or a HFSD for 3 to 7 days, pancreas or isolated islets were analyzed. Immunohistochemistry showed that the HFD group had a significantly higher Ki67-positive rate in pancreatic β-cells than the HFSD group. The mRNA expression of Ki67, CyB1 and CyD1 in isolated islets increased in the HFD group, whereas such an increase was not observed in the HFSD group. We confirmed that high-salt diet increased urinary catecholamine excretion in mice, suggesting that excessive salt intake activates the sympathetic nervous system. The α2 receptor is assumed to mainly express in pancreatic β cells, so the change in the Ki67-positive cell rate in pancreatic β cells after α2 blocker administration was investigated. Our mouse model fed a HFSD is considered as a model of diabetes in which obesity is mild and insulin secretion is deficient. The clarification of the pathophysiology of such a model may lead to the development of new treatments for diabetes.