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Clarification of the Mechanism Controlling Beta Cell Volume via the Autonomic Nervous System in Response to Sodium Chloride Intake

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Summary

In studies conducted among Japanese, an association between excessive salt intake and an increased risk of developing diabetes has been suggested; however, the underlying mechanisms remain insufficiently elucidated. A recent characteristic of dietary habits among the Japanese population includes excessive intake of both fat and salt. We previously reported that a high-fat, high-sodium chloride diet in a mouse model induces impaired glucose tolerance accompanied by impaired insulin secretion. In the course of exploring effective therapeutic strategies for this mouse model, it was confirmed that insulin secretion was improved by treatment with an SGLT2 inhibitor. It has been reported that excessive salt intake activates the sympathetic nervous system. Based on this, it was hypothesized that in this pathological condition, the high-fat, high-sodium chloride diet activates the sympathetic nervous system, and that suppression of this activation by the SGLT2 inhibitor contributed to its therapeutic effect. Thus, the involvement of the sympathetic nervous system was investigated. Eight-week-old male C57BL/6 mice were divided into groups receiving a normal diet, a high-fat diet, or a high-fat, high-sodium chloride diet, and their pancreata were analyzed using immunohistochemistry. Sympathetic nerve terminals were labeled with tyrosine hydroxylase (TH) and parasympathetic nerve terminals with choline acetyltransferase (ChAT) to examine the distribution of nerve fibers. Additionally, the high-fat, high-salt diet group was subdivided, with one subgroup receiving the SGLT2 inhibitor dapagliflozin, and urinary norepinephrine levels and TH-positive areas in pancreatic islets were compared. Dapagliflozin led to a reduction in urinary norepinephrine excretion and a decrease in the TH-positive area within the islets. In the high-fat, high-sodium chloride diet group, the TH-positive areas within the islets were significantly increased, and there was also a trend toward an increase in ChAT-positive areas. The number of α-cells remained unchanged. These findings suggest that excessive sodium chloride intake activates the sympathetic nervous system, thereby suppressing β-cell proliferation and insulin secretion. They also indicate that the sympathetic inhibitory effects of SGLT2 inhibitors may contribute to the restoration of insulin secretory function. Overall, these insights are expected to contribute to understanding the pathophysiology specific to Asians, who characteristically exhibit mild insulin resistance and impaired insulin secretion, as well as to underscore the importance of limiting excessive salt intake and to propose new therapeutic approaches for type 2 diabetes.