Abstract

The number of patients with diabetes continues to increase and has been estimated to reach 700 million persons worldwide by 2045. About 90~95% of patients with diabetes are estimated to have Type 2 diabetes mellitus (DM), which is thought to be caused by insulin resistance and/or relative insulin insufficiency. Because the pathogenesis and pathology of DM are complex and involve many genetic and/or environmental factors, there are limitations to providing a single guideline of medical treatment to all diabetic patients. This limitation has been addressed by developing several classes of anti-diabetic drugs that differ in their mechanisms of action, as well as by generating several animal models of diabetes, which differ in phenotypes. The treatment of patients with diabetes requires strict control of blood glucose concentrations, as failure of blood glucose control could seriously affect patient quality of life. Conventional major antidiabetic medicines act by stimulating endogenous insulin secretion and/or by reducing insulin resistance. However, despite treatment, some patients may develop diabetes as well as diabetic complications, such as diabetic nephropathy. Sodium glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antidiabetic drugs. Determination of their therapeutic

effects has suggested that the kidneys play roles in glycemic control. The present study describes the phenotype of diabetes with enlarged kidney (DEK) rats established in our laboratory, assesses the effects of the SGLT2 inhibitor empagliflozin on this phenotype, and analyzes the association between increased renal parenchyma and hyperglycemia in these animals. This study found that only male DEK rates developed diabetes. These rats were deficient in insulin secretion with decreases in β cell populations and enlarged kidneys, but without renal dysfunction. Examination of the enlarged kidneys of DEK rats showed that increases in the renal parenchyma were associated with increased renal tubules with luminal dilation. Because the inheritance of the phenotype of DEK rats is polygenic, as yet unidentified genetic factors responsible for these renal alterations may contribute to renal reserve capacity and resistance to the progression of diabetic nephropathy. In addition, long term empagliflozin administration eliminated chronic hyperglycemia and improved systemic metabolism as well as renal tubule function. However, these renal tubules remained dilated, with no histological improvement in response to empagliflozin. The enlarged kidneys of DEK rats had a congenitally increased number of nephrons, with the progression of renal tubular dilation and renal overgrowth

being dependent on the duration of hyperglycemia. Uninephrectomy (1/2Nx) reduced blood glucose concentrations to normal levels, suggesting that increased parenchyma in enlarged kidneys may be responsible for hyperglycemia in DEK rats. However, renal overgrowth was not prevented under normoglycemic conditions induced by empagliflozin and 1/2Nx, indicating that renal growth was independent of hyperglycemia. Taken together, these studies have shown that DEK rats are useful as a novel animal model of diabetes and suggested the potential existence of a novel pathological mechanism, in which high renal reserve capacity might contribute to the development and deterioration of diabetes.