Renal Sympathetic Nervous System Hyperactivity in Early Streptozotocin-Induced Diabetic Kidney Disease

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Aims: We assessed the role of renal sympathetic nervous system in the deterioration of renal hemodynamic and excretory functions in rats with streptozotocin (STZ)-induced diabetic kidney disease (DKD). Methods: Male Sprague–Dawley (SD) rats were induced with diabetes mellitus (DM) using STZ (35 mg/kg, i.p.). The acute studies were conducted on denervated anesthetized rats 7 days after STZ administration. Two sets of experiments were performed: clearance experiments in which six 20-min urine and plasma collections were carried out to measure kidney function parameters, and hemodynamic experiments in which the renal nerves were electrically stimulated and responses in renal vasoconstriction (EVR) and renal blood flow (RRF) were recorded. Results: Renal denervation in STZ-induced diabetic rats produced higher fractional excretion of sodium (FE\textsubscript{Na}) but lower plasma sodium (P\textsubscript{Na}), glomerular filtration rate (GFR), and plasma creatinine (P\textsubscript{Cr}) (all P < 0.05 vs. innervated diabetic rats). In innervated diabetic rats, renal nerve stimulation (RNS) caused significant attenuation in the renal vasoconstrictor responses (all P < 0.05 vs. innervated control). Renal denervation in diabetic rats significantly blunted these responses (all P < 0.05 vs. innervated diabetic rats); however, they were significantly higher (all P < 0.05) while compared to denervated control counterparts. Conclusions: The data demonstrate an early role for the renal sympathetic innervation in the pathogenesis of DKD. If the kidney is prevented from renal sympathetic nerve actions renal functional parameters are markedly improved. The data further suggest an early enhancement in renal sensitivity to intrarenal NE upon the removal of renal sympathetic tone in STZ-induced diabetic rats. Neurourol Urodyn. 9999:1–9, 2010. © 2010 Wiley-Liss, Inc.

Key words: diabetic kidney disease; renal denervation; renal nerve stimulation; renal sympathetic nerve; streptozotocin

INTRODUCTION

Diabetic kidney disease (DKD) develops in approximately one-third of all patients with diabetes. Among the major morbidity and mortality factors confronted by diabetic patients is an increased risk of developing diabetic nephropathy that often perpetuates to end-stage renal disease (ESRD). A long-standing question pertaining to the occurrence of ESKD concerns the mechanisms involved in this pathological process. A wealth of data has been generated on possible mechanisms by which diabetes and its ancillary metabolic, hemodynamic, growth, and glomerular cell injury-related alterations may modulate the progression of diabetic nephropathy. Hyperglycemia, which is a major pathogenic factor in the development of diabetic nephropathy, but elevated plasma glucose levels alone is not completely responsible for renal injury.

The early stages of DKD induced by streptozotocin (STZ) are characterized by renal hemodynamic changes leading to a wide range of glomerular filtration rate (GFR) from normal to high values in humans and in animals. A recent investigation from our laboratory has shown that early renal functional and hemodynamic responses to acute-stage type 1 diabetes mellitus (DM) by STZ exhibit a range of physiological and biochemical maladaptive changes mainly characterized by the likely existence of prenal acute renal dysfunction, such as glomerular hyperperfusion, hypotonic urinary flow, and sustained elevations in plasma sodium (P\textsubscript{Na}) and plasma creatinine (P\textsubscript{Cr}). Of particular interest is the hemodynamic phenotype in early diabetic which is characterized by glomerular hyperfiltration, a likely prerequisite for progressive diabetic nephropathy. Hyperglycemia does not rely upon accumulation of NaCl in the body, because GFR can increase relentlessly in early diabetes, notwithstanding a decline in extracellular volume. Glomerular hyperfiltration has been correlated with abnormalities of the glomerulus and podglomerular vessels, although specific mechanisms have not been fully delineated. It has been proposed that in recent-onset DM there is increased proximal tubular reabsorption. Accordingly, more of the glomerular filtrate is reabsorbed and less reaches the macula densa at the end of Henle's loop. This causes GFR to increase through the normal physiologic action of the tubuloglomerular feedback (TGF) system.