T-Type calcium channel blockage ameliorates proteinuria and renal extracellular matrix accumulation in experimental diabetic rats

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Calcium channels have been shown to play an important role in the pathogenesis of diabetic nephropathy. The purpose of this study is to investigate the effect of T-type calcium channel blockers in uninephrectomized diabetic rats. Two weeks after uninephrectomy, streptozotocin (65 mg/kg) was given to male Sprague-Dawley rats to induce diabetes mellitus. In the succeeding days, four groups of animals were randomized to receive 30 mg/kg mibefradil (Mib, T-type calcium channel blocker), 30 mg/kg amlodipine (Aml, L-type calcium channel blocker), 10 mg/kg cilazapril (Cil, angiotensin converting enzyme inhibitor) or 25 mg/kg Mib + 8 mg/kg Cil (M+C), which were delivered daily by gavage (n = 6-8 for each group). At the fourth week, 24-hour urine, blood and kidney samples were collected for examinations. Renal morphometric analyses and assay for type IV collagen and laminin were performed. Untreated diabetic rats (DM) exhibited overt hyperglycemia, proteinuria and albuminuria when compared with uninephrectomized (UNx) control (17.67 ±4.9 vs 2.97 ±0.72 µg/24 hours, \( p < 0.05 \)), while Cil and M+C treated rats had significantly reduced urinary protein excretion (Cil: 5.53 ±1.45, M+C: 3.87 ±0.88 vs DM: 17.67 ±4.9 µg/24 hours; \( p < 0.05 \), respectively). Mibefradil alone also ameliorated albuminuria in DM rats (7.69 ±1.87 vs 17.67 ±4.9 µg/24 hours, \( p < 0.05 \)). Histopathological study revealed significantly less glomerular matrix, laminin, type IV collagen and proximal tubule cells (PTC) hypertrophy in the Cil and M+C groups when compared with the DM group (Collagen IV: DM 7.3 ±0.65 vs Mib 4.82 ±0.78, Cil 4.11 ±0.74, M+C 2.64 ±0.66, UNx 3.71 ±0.99, \( p < 0.05 \)). Albuminuria, glomerular matrix accumulation and collagen IV deposition were not changed in the Aml treated group. There was, however, significantly lower creatinine clearance and laminin volume in the Aml group. In conclusion, our study demonstrated that T-type calcium channel blockage reduced albuminuria and renal extracellular matrix accumulation in experimental diabetic rats, suggesting an important role for T-type calcium channel in the progression of diabetic nephropathy. Additional benefit can be achieved by combination with an angiotensin converting enzyme inhibitor. The mechanism of action, however, requires further investigation. (Hong Kong J Nephrol 2001;3(1):27-32)

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