CANDESARTAN AMELIORATES THE FUNCTIONAL RENAL DISORDER IN DIABETIC NEPHROPATY INDUCED BY STREPTOZOTOCIN

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Summary

Background

Diabetic nephropathy (DN) occurs in approximately 40% of patients with diabetes mellitus, and is the most common cause of end-stage renal disease. The mechanisms of DN are not very clear more recently, but the renin-angiotensin system (RAS) plays an important role. It has been known that rennin-angiotensin system blockers have a renal protective effect. The present study was undertaken to evaluate the effects of the candesartan on functional renal tests in streptozotocin (STZ) induced DN in rats.

Methods

DM was induced by a single intraperitoneal injection (ip) injection of STZ (60 mg/kg). In order to develop DN the animals were left in diabetic condition during 4 weeks. The DM rats were randomly assigned to the two experimental groups (STZ and STZ+CAN). To estimate the symptoms and signs of DN, the STZ group of rats was left without treatment. For assessment of the effects of the AT1 antagonist, candesartan (CAN) (5 mg/kg/day) was administered from week 4 to week 12. Renal function was assessed by determination of serum creatinine, blood urea nitrogen (BUN) test, 24-hour urine volume and urine albumin.

Results

The administration of STZ have caused diabetes mellitus (DM) with symptoms and signs of DN including poor general condition, body weight loss, as well as abnormalities of serum and urinary renal function tests. In STZ group of rats, these symptoms have been more distinctly 8 and 12 weeks after administration of STZ.

Conclusion

The candesartan treatment, although not completely but to a great extent ameliorates the functional renal disorder induced by STZ and may be used as a first line drug in preventing DN.

Key words: Streptozotocin, Candesartan, Diabetic Nephropathy, Rats.

Introduction

❖Diabetic nephropathy (DN) is one of the most serious problems in nephrology, as **40%** of the cases of end stage renal disease (ESRD) are **due to this entity**.

❖It has been shown that the **renin-angiotensin system (RAS)** plays an important role during the development of DN.

❖The renal protective effect of some AT1 receptor blockers (ARB) have been demonstrated in animal models of diabete mellitus (DM), and **some clinical trials have shown that ARB are more effective than traditional antihypertensive therapies in reducing renal failure progression** in patients with type 2 DM.

❖Candesartan (CAN) is a *relatively new*, potent and selective, long-acting, effective angiotensin II type 1 receptor blocker which **binds tightly to** and **dissociates slowly** from the AT1 receptor.

❖Candesartan with its flexible dosage regimen therefore appears to **offer an effective and well-tolerated alternative** to other established agents in the treatment of a wide range of hypertensive patients.

Material and Methods

Results

Table 1 Changes in 24-hour urine volume in each experimental group during the study

24-hours urine volume (ml)				
	0-Day	4-Weeks	8-Weeks	12-Weeks
Control				
X	8.86	9.11	7.71	8.75
SD	1.35	2.15	2.29	1.83
Min	7.00	6.00	4.00	6.00
Max	11.00	12.00	11.00	11.00
STZ				
X	7.86	16.89^a	20.57^a	21.29^a
SD	1.95	3.59	4.39	6.73
Min	6.00	12.00	15.00	14.00
Max	12.00	24.00	28.00	35.00
STZ+CAN				
N				
X	8.29	18.25^{a,b}	17.88^{a,b}	17.14^{a,b}
SD	2.21	3.20	4.19	5.81
Min	6.00	13.00	13.00	9.00
Max	12.00	23.00	24.00	27.00

^a<0.05 vs Control ^b>0.05 vs STZ

❖The administration of STZ have caused DM with distinct symptoms and signs of DN including poor general condition, body weight loss, as well as abnormalities of serum and urinary renal function tests.

Table 2 Effects of candesartan treatment on serum creatinine and BUN in rats with STZ induced DN

Serum creatinine (μmol/L)					BUN (mmol/L)			
	Weeks of the treatment				Weeks of the treatment			
	0	4	8	12	0	4	8	12
Control								
X	37.44	37.89	36.81	38.11	7.67	7.79	8.01	7.96
SD	3.18	3.78	3.53	3.37	1.90	1.75	1.45	1.85
Min	30.10	31.01	30.3	31.0	4.30	5.30	5.40	5.20
Max	41.9	46.05	44.2	43.5	11.50	10.30	10.60	11.60
STZ								
X	39.58	42.49	94.09^a	148.32^a	8.03	28.41^a	32.48^a	34.05^a
SD	5.43	7.37	41.63	67.91	1.79	12.48	16.45	20.63
Min	30.5	35.25	35.7	57.3	4.50	8.70	11.95	12.90
Max	49.6	58.14	158.3	253.8	11.20	53.50	77.60	85.40
STZ+CAN								
X	37.31	43.27	54.82^{a,b}	61.18^{a,b}	7.69	29.73^a	22.07^{a,b}	20.08^{a,b}
SD	4.27	9.12	18.95	19.18	2.05	10.92	9.53	8.30
Min	32.15	32.51	28.9	32.3	4.90	11.50	9.15	8.45
Max	45.3	61.22	95.9	94.7	12.20	43.70	44.16	39.60

^a<0.05 vs Control ^b<0.05 vs STZ

❖ In diabetic rats, significant increased values of serum creatinine and BUN, accompanied by increased diuresis, proteinuria, albuminuria and decreased clearance of creatinine (as a measure of glomerular filtration rate) of the experimental animals have been manifested 4 weeks after, and even more distinctly 8 and 12 weeks after administering STZ. The candesartan treatment resulted in significant improvement of all symptoms and signs of diabetic nephropathy significantly lowering the values of BUN and serum creatinine, albuminuria, proteinuria, glomerular filtration rate and diuresis.

Figure 1 Effects of candesartan on urinary albumin levels

➤ The obtained results regarding albuminuria confirms the importance of this parameter in detecting DN induced by STZ as well as the therapeutic effects of candesartan.

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Conclusion

❑Based on the obtained results from this study it can undoubtedly be concluded that:
✓ **candesartan** although not completely but **to a great extent ameliorates** the functional renal disorder induced by STZ
and
✓ may be used as a **first line drug as ACE inhibitors** in preventing DN.

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