Effects of TCV-116 (Candesartan Cilexetil) on Renal Function and Oxidative Stress in Diabetic Nrf2-deficient Mice .

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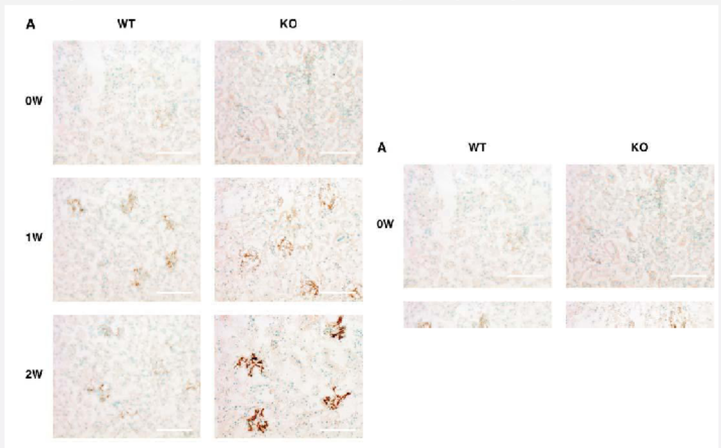
Abstract

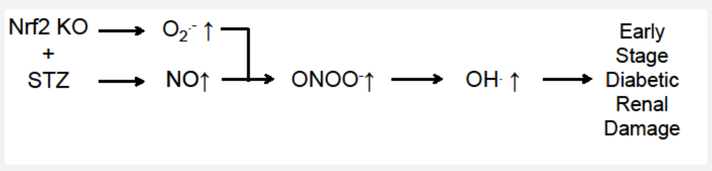
INTRODUCTION AND AIMS: Previously we have demonstrated that oxidative and nitrosative stress played a critical role in renal injury of streptozotocin-induced diabetic Nrf2-deficient (Nrf2 KO) mice. In this study we examined whether TCV- 116 (candesartan cilexetil), an Angiotensin-II-receptor blocker, ameliorates this damaging process. METHODS: 8 weeks-old Nrf2 KO and wild type mice were induced diabetes by a single intraperitoneal injection of streptozotocin (STZ). TCV-116 was given in drinking water at the dose of 5 mg/kg/day for 24 weeks from 2 weeks after diabetes development. Oxidative stress was evaluated by measuring scavenging activities against hydroxyl radical and superoxide using a newly-developed electron paramagnetic resonance (EPR)-based spin trapping method. RESULTS: Injection of STZ equally increased plasma glucose level in both wild type and Nrf2 KO mice, and TC116 made no difference on it. The survival rate of diabetic Nrf2 KO (dKO) mice was shorter than that of non-treated wild type (cWild), diabetic wild type (dWild) and non-treated Nrf2 KO (cKO) mice. TCV-116 significantly improved the survival rate of dKO mice. TCV-116 treatment also improved serum creatinine level of dKO mice at 10 weeks, but this effect was not significant at 24 weeks. Histologically, induction of diabetes induced glomerular hypertrophy and mesangial expansion both in dWild and dKO mice, and TCV-116 treatment improved the lesions in a same manner. According to nitrosative stress, urinary NOx excretions were significantly increased both in Nrf2 KO and wild type mice. TCV-116 significantly decreased urinary NOx at 10 weeks, but not significant at 24 weeks. TCV-116 also improved serum hydroxyl radical scavenging activity and serum glucose-derived AGEs (Glc-AGEs) levels at 24 weeks. No effects on superoxide scavenging activity were confirmed. CONCLUSIONS: These findings suggest that TCV-116 treatment improved survival rate and ameliorate renal failure due to reduced oxidative and nitrosative stresses in diabetic Nrf2 KO mice.

Background

1. Angiotensin-II-receptor blocker (ARB) is currently regarded as the first-line choice drug in the treatment of diabetic nephropathy.
2. Nrf2 is a transcription factor which plays important roles in oxidative stress-related reactions.
3. We have reported the reno-protective effect of Nrf2 and involvements of NO-hydroxyl radical system in mice diabetic nephropathy model. (Yoh



STZ-treated Nrf2 KO mice increased glomerular 8-nitroguanosine.
Genes to Cells 13;1159-70, 2008



Proposed ROS role in early stage of diabetic nephropathy.
Genes to Cells 13;1159-70, 2008

Aim of This Study

- In this study, we examined whether TCV-116 (candesartan cilexetil), and Angiotensin-II-receptor blocker, ameliorates the progression of diabetic nephropathy, oxidative and nitrosative stresses in diabetic Nrf2 KO mice.

Conclusion

- TCV-116 may improve the pathophysiology of diabetic nephropathy through Nrf2-dependent mechanisms.

Acknowledgement

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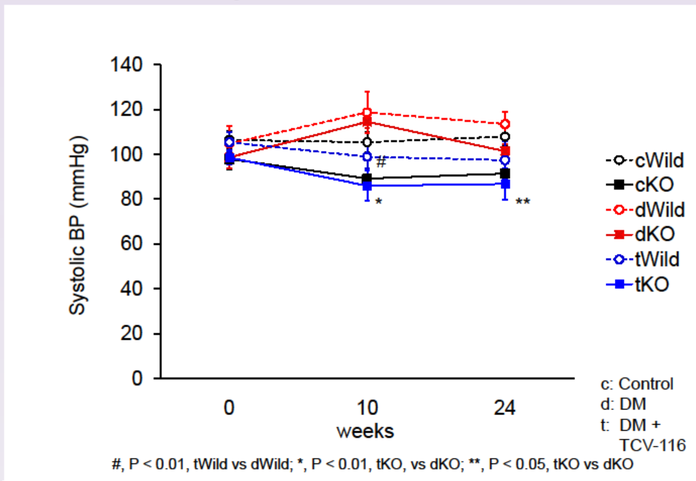
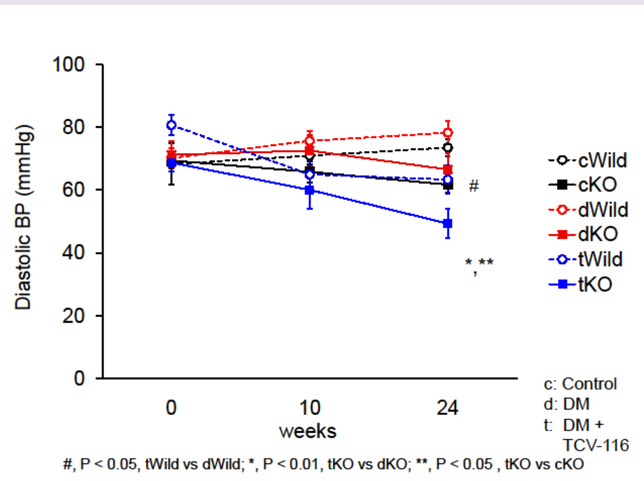
Results

Systolic Blood Pressure



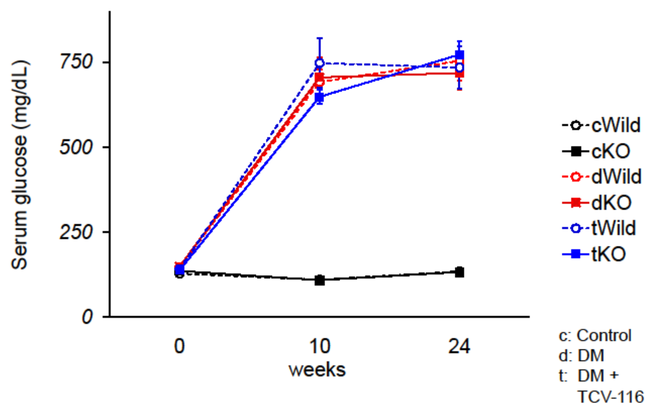
TCV-116 decreased SBP of diabetic Nrf2 KO mice.

Diastolic Blood Pressure



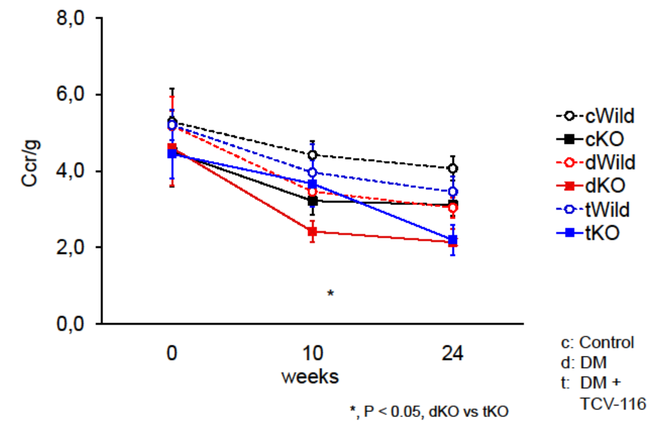
TCV-116 decreased DBP of diabetic Nrf2 KO mice.

Serum Glucose Level



No significant differences among diabetic mice.

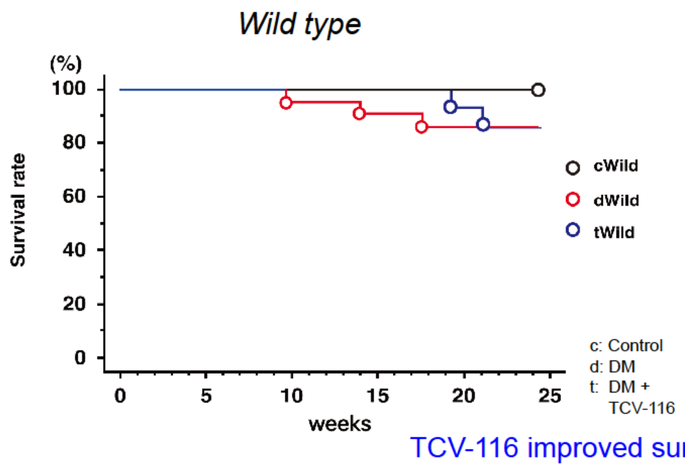
Renal Function



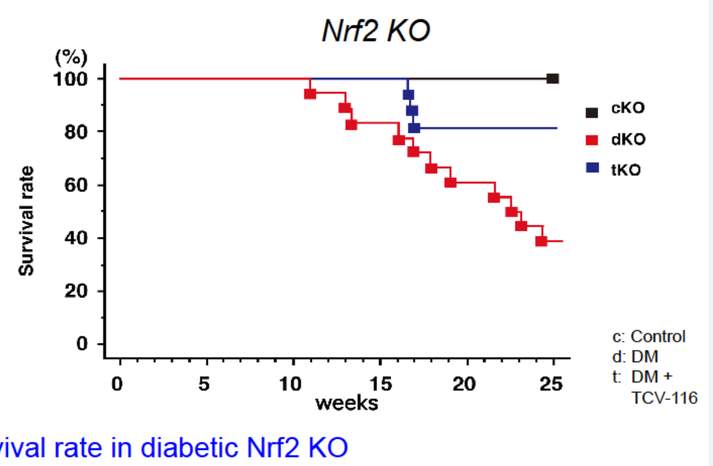
TCV-116 improved Ccr at 10 wks.

Survival Rates

Wild type

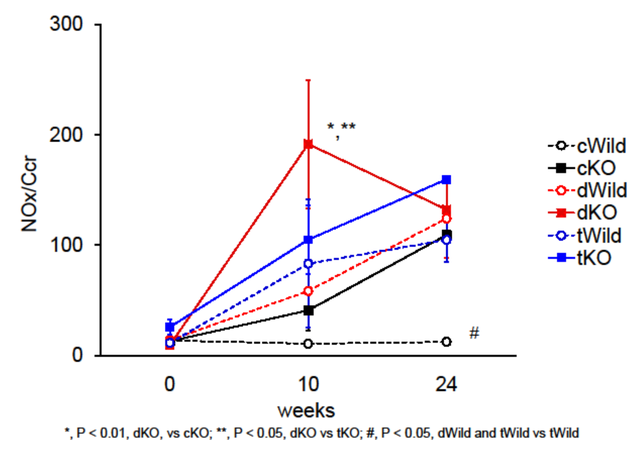


Nrf2 KO



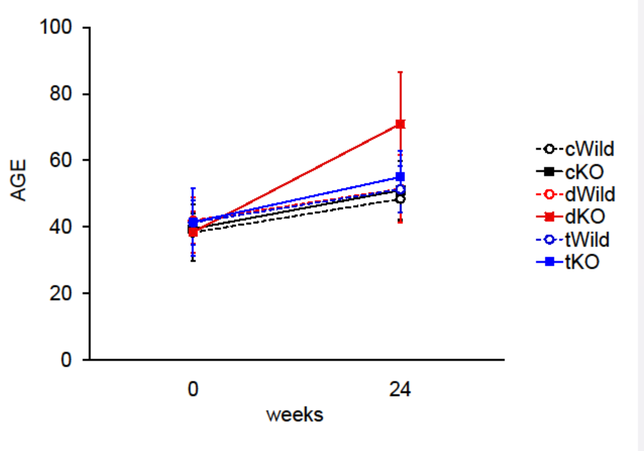
TCV-116 improved survival rate in diabetic Nrf2 KO mice.

Urinary Nox



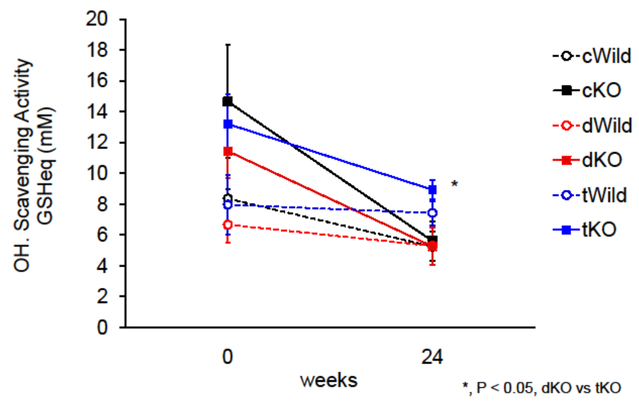
TCV-116 decreased urinary NOx at 10 wks.

Glc-AGE



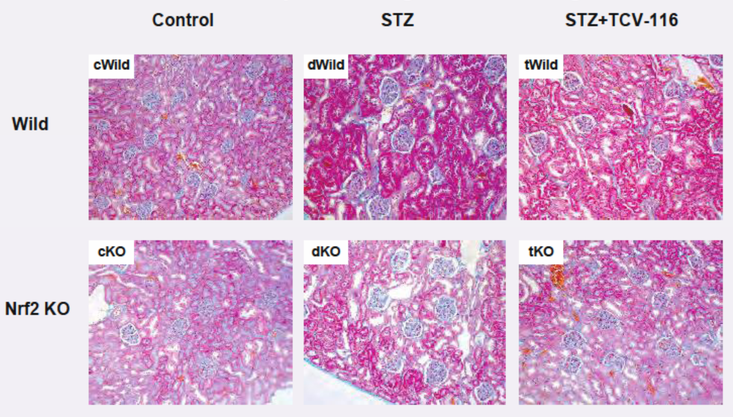
TCV-116 decreased AGE at 24 wks.

OH· Scavenging Activity



TCV-116 increased ·OH scavenging activity at 24 wks.

Histopathological Changes



TCV-116 improved diabetic changes including glomerular hypertrophy and mesangial expansion at 24 wks.

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