

Prevention of Hypertension and Organ Damage in 2-Kidney, 1-Clip Rats by Tetradecylthioacetic Acid

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Abstract—Dietary lipids are reported to affect the blood pressure in both humans and experimental animal models with hypertension. In the present study, 2-kidney, 1-clip (2K1C) hypertensive rats were treated with the modified fatty acid tetradecylthioacetic acid (TTA) from the time of clipping or after hypertension was established. TTA treatment attenuated the development of hypertension and reduced established 2K1C hypertension. The mRNA level of renin in the clipped kidney and the plasma renin activity were markedly reduced, and the plasma angiotensin II level tended to decrease after TTA treatment. In addition, TTA reduced the mRNA level of angiotensinogen in white adipose tissue. Prevention of organ damage was demonstrated by normal urinary excretion of protein, maintained serum albumin, lower heart weight, and clearly reduced vascular, glomerular, and tubulointerstitial damage in the nonclipped kidney. Renal function was not affected as estimated by unchanged plasma creatinine. Furthermore, the serum levels of triacylglycerol and cholesterol were reduced by TTA. The serum fatty acid composition was changed, resulting in a favorable increase of oleic acid. However, the levels of all of the omega-3 fatty acids and of linoleic acid were reduced, and no change was seen in the level of arachidonic acid, but the urinary excretion of 8-iso-prostaglandin F_{2α} was declined. In conclusion, TTA attenuated the development of hypertension, reduced established hypertension, and prevented the development of organ damage in 2K1C rats, possibly by reducing the amounts of the vasoconstrictors angiotensin II and 8-iso-prostaglandin F_{2α} and by inducing a favorable increase of oleic acid in serum. (*Hypertension*. 2006;48:460-466.)

Key Words: renin-angiotensin system ■ renal disease ■ fatty acids

Elevated blood pressure is closely related to increase in cardiovascular death from events like stroke, myocardial infarction, and chronic renal failure¹ and is defined as one of the risk factors for the metabolic syndrome.^{2,3} Other risk factors include insulin resistance, hyperglycemia, and elevated serum triacylglycerol, which are conditions that are improved in rats after treatment with the modified fatty acid tetradecylthioacetic acid (TTA).⁴

The pleiotropic effects of TTA seem to be mediated through both peroxisome proliferator-activated receptor (PPAR)-dependent and PPAR-independent mechanism⁴ and include changes in the fatty acid composition of both liver and serum in rats.⁵⁻⁷ Based on these potential possibilities to change composition of the metabolic system, and because the fatty acid composition of cholesteryl ester and phospholipids in serum has been related to the blood pressure level in humans,⁸⁻¹⁰ we examined the effect of TTA on hypertension in the present study.

An inducible model of high blood pressure is the 2-kidney, 1-clip (2K1C) hypertension model, where the increased blood pressure is induced after clipping of one renal artery. This is an angiotensin II-dependent model of hypertension with increased level of plasma renin and angiotensin, and hyper-

tension is usually established 3 to 4 weeks after clipping.¹¹ Long-term 2K1C hypertension is followed by organ damage as enlarged heart and damage of the nonclipped kidney with increased urinary protein excretion and declining glomerular filtration rate.¹¹

The intention of the present study was to examine the effect of TTA on blood pressure in 2K1C hypertensive rats, a model without the other risk factors of the metabolic syndrome. Our working hypothesis was that TTA would interfere with the renin-angiotensin system in this high-renin model of hypertension and reduce the blood pressure through lowering of the plasma renin activity. Because TTA is reported to change the fatty acid composition, we investigated the relation between the fatty acid composition and 8-iso-prostaglandin (PG)F_{2α} to blood pressure in 2K1C hypertensive rats.

Methods

An expanded Methods section can be found in an online supplement (available at <http://hyper.ahajournals.org>).

Animals

The protocol was approved by the Norwegian State Board for Biological Experiments With Living Animals. Male Wistar rats

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(Møllegaard Breeding Laboratory, Ejby, Denmark), weighing 180 to 200 g at the start of the experiment, were used for establishing 2K1C hypertension.

Two experiments were performed. In the first experiment, TTA treatment was started either at the day of clipping or 5 weeks after clipping when the hypertension was established and compared with untreated 2K1C rats. The rats were killed 12 weeks after clipping. In the second experiment, TTA treatment was started at the day of clipping and compared with untreated 2K1C rats, and the rats were killed 6 months after clipping. The systolic blood pressure was measured by means of the tail-cuff method (UGO BASILE) in unanesthetized rats.

Real-Time Quantitative RT-PCR

Total RNA was purified from frozen tissue, and the mRNA levels of renin, angiotensinogen, PPAR α , PPAR δ , and PPAR γ were determined by relative quantification using the standard curve method and normalized to 18S rRNA.

Analysis of Vasoactive Substances and Lipids

The renin activity and the concentration of angiotensin II were measured in plasma, whereas triacylglycerol, cholesterol, albumin, and creatinine levels were measured in serum. Urine was collected for 24 hours, and the urinary excretion of 8-iso-PGF 2α and proteins were measured. The fatty acids composition in serum and liver were analyzed.

Enzyme Activities in Liver

The activities of carnitine palmitoyltransferase-II¹² and fatty acyl-coenzyme A (CoA) oxidase¹³ were measured in hepatic postnuclear fraction.

Light Microscopy

One-hundred randomly sampled glomeruli were analyzed regarding segmental or global sclerosis and podocytes with adsorption droplets and/or pseudocysts. Twenty microscopic fields were investigated for tubulointerstitial damage. Glomerular sclerosis and tubulointerstitial damage were assessed using a semiquantitative scoring system (0 to 4): grade 0 indicates no lesions, grade 1 indicates lesions in <25%, grade 2 indicates lesions in 25% to 50%, grade 3 indicates lesions in 50% to 75%, and grade 4 indicates lesions in (almost) the entire capillary tuft area/tubulointerstitial area. Atrophy in the clipped kidney was semiquantitatively graded (0 to 3): grade 0 indicates no atrophy, grade 1 indicates slight atrophy, grade 2 indicates moderate-to-marked atrophy, and grade 3 indicates global atrophy.

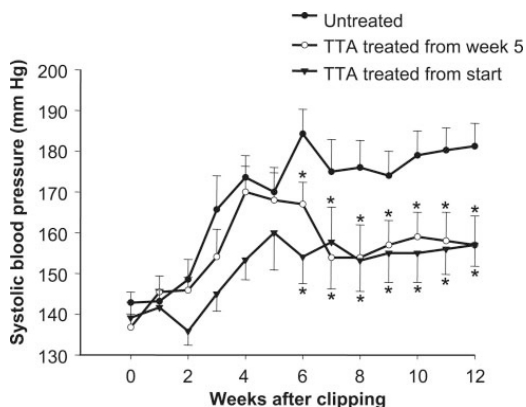


Figure 1. Changes in the systolic blood pressure in untreated and TTA-treated 2K1C rats. *Significantly different from untreated rats, $P < 0.001$.

Statistical Analysis

Data are presented as mean \pm SEM. The data were evaluated by a 2-sample variance Student's t test (2-tailed distribution).

Results

In the untreated 2K1C rats, hypertension was established 3 to 4 weeks after clipping and was stable throughout the rest of the observation period of 12 weeks (Figure 1). TTA treatment

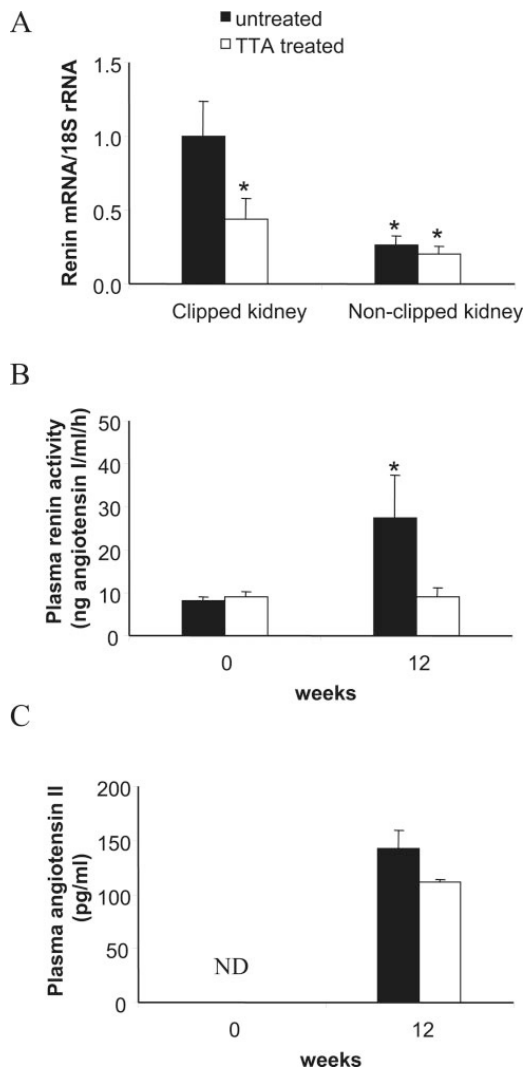


Figure 2. A, Gene expression of renin in clipped and nonclipped kidneys from untreated and TTA-treated 2K1C rats. The results are presented relative to 18S rRNA and normalized to clipped controls, arbitrary units. *Significantly different from clipped kidney in untreated rats, $P < 0.05$. B, Plasma renin activity at the time of clipping and 12 weeks after clipping in untreated and TTA-treated 2K1C rats. *Significantly different from untreated rats at the time of clipping, $P < 0.05$. C, Plasma angiotensin II level 12 weeks after clipping in untreated and TTA treated 2K1C rats. ND indicates not determined.

from the time of clipping attenuated the development of hypertension in 2K1C rats (Figure 1). Twelve weeks after clipping, the systolic blood pressure in the untreated group was 181 ± 3 mm Hg, whereas the systolic blood pressure in the TTA-treated group was 150 ± 3 mm Hg ($P < 0.001$; Figure 1). When TTA treatment was started 5 weeks after clipping, the systolic blood pressure was reduced from 168 ± 9 mm Hg to 155 ± 5 mm Hg ($P < 0.05$) within 2 weeks, which is similar to that of rats treated with TTA from the time of clipping (Figure 1).

TTA treatment reduced the renin mRNA level in the clipped kidney by $>50\%$ ($P < 0.05$), but TTA had no effect on the renin mRNA level in the nonclipped kidney, where this level is normally very low (Figure 2A). The renin mRNA level was significantly higher in the clipped kidney compared with the nonclipped kidney independent of treatment regime ($P < 0.01$; Figure 2A). The plasma renin activity at the time of clipping was equal in untreated and TTA-treated rats (Figure 2B). Twelve weeks after clipping, the plasma renin activity was markedly increased in the untreated rats but was not changed in the TTA-treated rats (Figure 2B). The plasma level of angiotensin II tended to decrease in TTA-treated rats (Figure 2C), but this was not significant ($P = 0.06$). The mRNA level of angiotensinogen, which is a precursor of angiotensin II, was reduced in epididymal white adipose tissue after TTA treatment (Figure 3A), but this level was increased in liver by TTA (Figure 3B).

Circulating fatty acids are reported to interfere with blood pressure,⁸⁻¹⁰ and it was, therefore, of interest to see how the fatty acid composition of serum was affected by TTA. TTA treatment increased the levels of palmitoleic acid, oleic acid, and icosatrienoic acid, but the levels of palmitic acid and

TABLE 1. Selected Fatty Acids (g/100 g Fatty Acids) in Serum From Untreated and TTA-Treated 2K1C Rats 3 Months After Clipping

Fatty Acid	Untreated	TTA-Treated
Palmitic acid (16:0)	22.98 ± 0.60	22.34 ± 0.48
Stearic acid (18:0)	7.71 ± 0.25	7.11 ± 0.21
Palmitoleic acid (16:1n-9)	0.46 ± 0.02	$0.66 \pm 0.03^*$
Oleic acid (18:1n-9)	13.32 ± 0.24	$24.22 \pm 1.21^*$
Icosatrienoic acid (20:3n-9)	0.22 ± 0.06	$2.16 \pm 0.05^*$
Linoleic acid (18:2n-6)	21.59 ± 1.15	$12.85 \pm 1.15^*$
γ -Linolenic acid (18:3n-6)	0.39 ± 0.06	$0.61 \pm 0.08^*$
Dihomo- γ -linolenic acid (20:3n-6)	0.49 ± 0.05	$1.12 \pm 0.03^*$
Arachidonic acid (20:4n-6)	20.47 ± 0.54	18.58 ± 0.89
α -Linolenic acid (18:3n-3)	0.66 ± 0.05	$0.28 \pm 0.05^*$
Eicosapentaenoic acid (20:5n-3)	0.37 ± 0.03	$0.19 \pm 0.02^*$
Docosapentaenoic acid (22:5n-3)	0.59 ± 0.06	$0.12 \pm 0.01^*$
Docosahexaenoic acid (22:6n-3)	2.06 ± 0.08	$0.68 \pm 0.06^*$
TTA	ND	1.79 ± 0.16
TTA:1n-8	ND	2.06 ± 0.24

ND indicates not detected.

*Significantly different from untreated rats, $P < 0.05$.

stearic acid were unchanged in serum (Table 1). In addition, the level of linoleic acid and all of the omega-3 polyunsaturated fatty acids (PUFAs) were reduced after TTA treatment (Table 1).

The isoprostane 8-iso-PGF 2α is formed nonenzymatically from the attack of a superoxide radical on esterified arachidonic acid. Although the level of arachidonic acid in serum was not affected (Table 1), the urinary excretion of 8-iso-PGF 2α was significantly decreased after TTA treatment (Figure 4).

The effect of TTA on the fatty acid composition in liver was similar to that seen in serum (data not shown). TTA and its $\Delta 9$ desaturated metabolite TTA:1n-8 were recovered in both serum (Table 1) and liver (data not shown) of TTA-treated rats.

TTA treatment significantly reduced the serum levels of triacylglycerol and cholesterol (Table 2). Concomitant with this, the activities of carnitine palmitoyltransferase-II and fatty acyl-CoA oxidase were increased (Table 2), suggesting that TTA increased the capacity for fatty acid oxidation. However, TTA did not significantly change the mRNA levels of PPAR α , PPAR δ , or PPAR γ in clipped or nonclipped kidneys (data not shown).

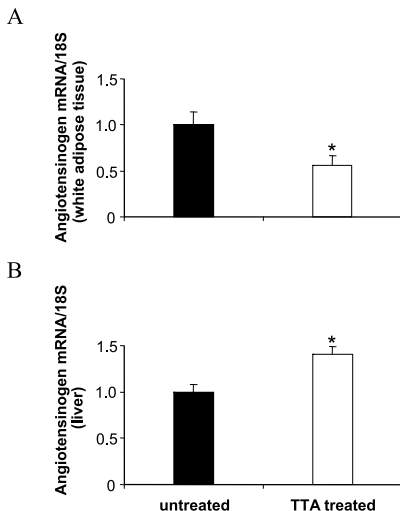


Figure 3. Gene expression of angiotensinogen in epididymal white adipose tissue (A) and liver (B) from untreated and TTA-treated 2K1C rats 12 weeks after clipping. The results are presented relative to 18S rRNA and normalized to untreated rats, arbitrary units. *Significantly different from untreated rats, $P < 0.05$.

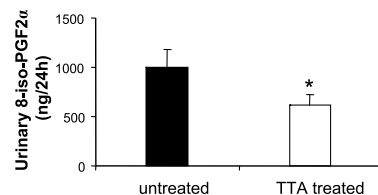


Figure 4. Excretion of 8-iso-PGF 2α in urine from untreated and TTA-treated 2K1C rats measured 12 weeks after clipping. *Significantly different from untreated rats, $P < 0.05$.

To evaluate the role of TTA in the prevention of organ damage induced by hypertension, 2K1C rats were treated with TTA for 6 months from the time of clipping. At the end of this long-term study, the systolic blood pressure was 213 ± 6 mm Hg in the untreated rats and 168 ± 8 mm Hg in the TTA-treated rats ($P < 0.001$). The urinary protein excretion was increased >5 -fold (175 ± 40 versus 29 ± 4 mg/24 h⁻¹; $P < 0.01$) during the experiment (Figure 5A), accompanied by decreased serum albumin level (34 ± 1.2 versus 46 ± 2 gL⁻¹; $P < 0.01$; Figure 5B). However, serum creatinine was unchanged at the end of the experiment (Figure 5C). The urinary protein excretion (Figure 5A), serum albumin level (Figure 5B), and serum creatinine (Figure 5C) were not affected during the experiment in the TTA-treated rats. The body weight and the heart weight were significantly lower in the TTA-treated rats, whereas TTA treatment did not affect the kidney weights (Table 3).

TTA-treated rats clearly developed less morphological damage in the nonclipped kidney 6 months after clipping compared with untreated rats (Figure 6). There were only minor arterial and arteriolar changes in the nonclipped kidney in TTA-treated rats in contrast to marked vascular wall changes with media hypertrophy, intima proliferation, hyalinosis, and fibrinoid necrosis in untreated rats. Hypertension-associated glomerular changes in the nonclipped kidney (adsorption droplets, pseudocysts, segmental, and global sclerosis; Figure 7) as well as tubulointerstitial damage were significantly reduced in TTA-treated rats (Table 4). There was no significant difference in the atrophy score of the clipped kidney in untreated and TTA-treated rats (Table 4).

Discussion

Elevated blood pressure is closely related to increase in cardiovascular death from events like stroke, myocardial infarction, and chronic renal failure.¹ In the present study, we wanted to examine the effect of TTA on secondary hypertension induced by clipping of one renal artery to see whether TTA could interfere with the renin-angiotensin system, the lipid metabolism, and development of hypertension.

In the present article, we show for the first time that TTA attenuated the development of hypertension in 2K1C when TTA was given from the day of clipping, and, in addition, TTA reduced the blood pressure when hypertension was established. In agreement with previous findings, 12 weeks after clipping, the clipped kidney contained a higher level of

TABLE 2. Serum Lipids and the Hepatic Mitochondrial and Peroxisomal β -Oxidation Capacities in Untreated and TTA-Treated 2K1C Rats 3 Months After Clipping

Lipids and Enzymes	Untreated	TTA-Treated
Serum lipids, mmol/L		
Triacylglycerol	2.04 ± 0.27	$0.70 \pm 0.12^*$
Cholesterol	3.11 ± 0.51	$1.35 \pm 0.12^*$
Enzyme activities, nmol/mg protein per min		
Carnitine palmitoyl-transferase II	3.84 ± 0.33	$16.82 \pm 1.23^*$
Fatty acyl-CoA oxidase	12.2 ± 0.9	$144.1 \pm 4.9^*$

*Significantly different from untreated rats, $P < 0.05$.

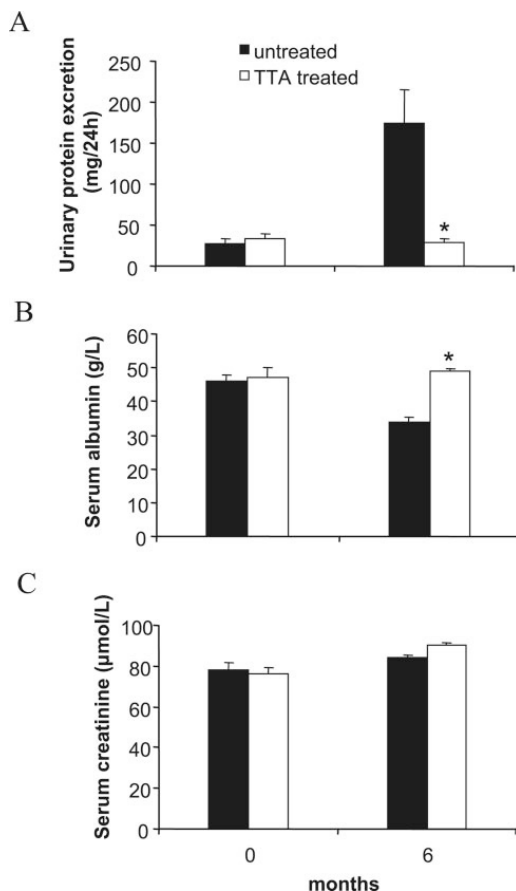


Figure 5. Urinary excretion of protein (A), serum albumin (B), and serum creatinine (C) in untreated and TTA-treated 2K1C rats at the time of clipping and 6 months after clipping. *Significantly different from untreated rats at the time of killing, $P < 0.01$.

renin mRNA than the nonclipped kidney, as shown previously.¹⁴ In addition, TTA treatment had no effect on the renin mRNA level in the nonclipped kidney, but markedly reduced this level in the clipped kidney. This was accompanied by reduced plasma renin activity and a strong tendency to decrease the plasma angiotensin II level by TTA. Thus, regulation of the renin-angiotensin system seems to be important for the effect of TTA on

TABLE 3. The Weight of the Body, Heart, and Kidneys in Untreated and TTA-Treated 2K1C Rats 6 Months After Clipping

Body and Organ Weight	Untreated	TTA-treated
Body weight, g	525 ± 14	$475 \pm 12^*$
Heart weight, g	1.8 ± 0.09	$1.6 \pm 0.06^*$
Kidney weight, g		
Nonclipped	2.5 ± 0.12	2.4 ± 0.19
Clipped	1.2 ± 0.17	1.0 ± 0.10

*Significantly different from untreated rats, $P < 0.05$.

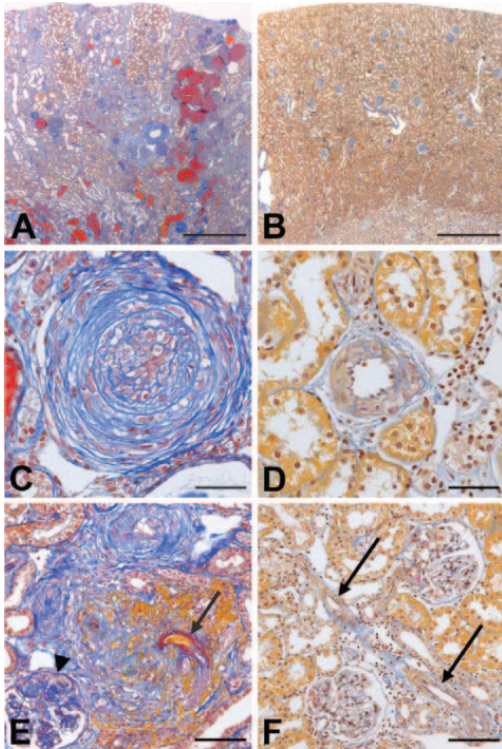


Figure 6. Histological changes in the nonclipped kidney in untreated (A, C, and E) and TTA-treated (B, D, and F) 2K1C rats, 6 months after clipping (trichrome acid fuchsin orange-G). A and B, Overview showing pronounced tubulointerstitial damage with tubular dilation, cast formation and interstitial fibrosis in A (scale bar, 1 mm). C and D, Marked arterial wall changes with media hypertrophy and intimaproliferation in C. Normal artery of the same size in D (scale bar, 50 μ m). E and F, Arteriole with fibrinoid necrosis (\rightarrow), glomerulus with segmental sclerosis (\blacktriangle) in E, normal arterioles (\rightarrow) and glomeruli with minor changes in F (scale bar, 100 μ m).

blood pressure by reducing the production of angiotensin II, which is the main vasoconstrictor in 2K1C hypertension. Activation of PPAR γ has been reported to decrease the expression of the angiotensin-II type I receptor,^{15,16} but although TTA is a pan-PPAR ligand,⁴ no change was seen in the mRNA level of PPAR γ in clipped or nonclipped kidneys after TTA treatment.

Hypertension is one of the complications in obesity, and the adipose angiotensinogen gene expression has been shown to play a role in both adipose tissue development and hypertension of obese patients,¹⁷⁻¹⁹ representing a link between obesity and hypertension. The increased activities of carnitine palmitoyltransferase-II and fatty acyl-CoA oxidase in liver of TTA-treated 2K1C rats suggested that both the mitochondrial and the peroxisomal β -oxidation were increased, and this was accompanied by reduced serum triacylglycerol, as demonstrated previously in normotensive rats.²⁰ The increased β -oxidation of fatty acids by TTA could lead to lowered amounts of the adipose tissue, as we have found previously,²¹ a finding that may contribute to reduced

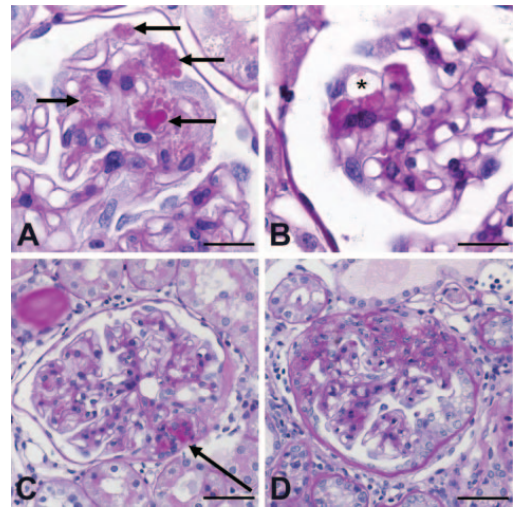


Figure 7. Hypertension-associated glomerular changes in non-clipped kidney from untreated 2K1C rats, 6 months after clipping. A, Adsorption droplets in podocytes (\rightarrow). B, Podocyte with adsorption droplets and a pseudocyst (*). C, A minor (\rightarrow) and (D) a major focus of segmental sclerosis (periodic acid Schiff reaction, scale bar, 20 μ m in A and B and 50 μ m in C and D).

production of angiotensinogen.²² Interestingly, TTA seemed to have a tissue-specific effect on the gene expression of angiotensinogen, because the mRNA level of angiotensinogen was reduced in white adipose tissue and increased in liver. This is in line with findings by others showing that high-fat feeding differently affects the mRNA level of angiotensinogen in adipose tissue and liver of mice.²³ Because fat surrounds many of the muscular arteries, changes in adipose angiotensinogen mRNA level and, thus, the production of angiotensin II might affect the systemic vascular resistance.²⁴

Olive oil contains a high amount of oleic acid and is reported to decrease blood pressure in humans.²⁵⁻²⁷ Here we show that the attenuation of hypertension after TTA treatment is accompanied by increased levels of oleic acid and its metabolites palmitoleic acid and icosatrienoic acid, probably because of increased $\Delta 9$ desaturase activity.²⁸ An elevated level of palmitic acid⁹ and a reduced level of stearic acid⁸ in serum cholesteryl esters are associated with higher risk of

TABLE 4. Quantitative and Semiquantitative Evaluation of Morphologic Changes in Nonclipped and Clipped Kidney in Untreated and TTA-Treated 2K1C Rats 6 Months After Clipping

Morphologic Changes	Untreated	TTA-Treated
Nonclipped kidney		
Adsorption droplets, % glomeruli	16.66 \pm 3.81	5.54 \pm 1.87*
Pseudocysts, % glomeruli	9.17 \pm 2.50	2.20 \pm 1.01*
Segmental sclerosis, mean score	0.94 \pm 0.31	0.04 \pm 0.01*
Tubulointerstitial damage, mean score	1.70 \pm 0.47	0.22 \pm 0.09*
Clipped kidney		
Atrophy, score	1.60 \pm 0.31	1.33 \pm 0.41

*Significantly different from untreated rats, $P < 0.05$.

hypertension; however, in the present study, no change was seen in the serum levels of these fatty acids.

Dietary supplementation with omega-3 PUFAs, such as eicosapentaenoic acid and docosahexaenoic acid, lowers blood pressure and prevents the development of hypertension,^{29–32} possibly because of the ability of omega-3 PUFAs to replace and, thus, reduce the cellular membrane levels of arachidonic acid.³³ Despite the attenuation of 2K1C hypertension by TTA treatment, the level of all of the omega-3 acids in serum was reduced, probably as a result of the increased mitochondrial and peroxisomal β -oxidation.¹²

Reduced serum linoleic acid is observed in patients and experimental animal models with hypertension,^{9,10} whereas a high level of dihomo- γ -linolenic acid and arachidonic acid in serum cholesteryl esters has been shown to be associated with increased risk of hypertension.^{8,9} In the present experiment, TTA decreased the level of linoleic acid and increased the level of dihomo- γ -linolenic acid, whereas no change was seen in the level of arachidonic acid. Linoleic acid is the essential precursor of the longer omega-6 PUFAs, and arachidonic acid can be synthesized from linoleic acid via γ -linolenic acid and dihomo- γ -linolenic acid in liver. The biosynthesis of arachidonic acid is catalyzed by $\Delta 5$ and $\Delta 6$ desaturases, and we have found previously that TTA increases the level of arachidonic acid in normotensive rats³⁴ and upregulates the gene expression of these desaturases in rat liver (O.G. Gudbrandsen, T.H. Røst, R.K. Berge, unpublished data, 2006). Because the rate-determining desaturases and intermediates are increased, it may be reasonable to assume that the generation of arachidonic acid was increased. However, because no change was seen in arachidonic acid in serum or liver, the conversion of arachidonic acid to other compounds, such as prostaglandins, may be increased by TTA in the present experiment.

The isoprostane 8-iso-PGF₂ α is produced by free-radical peroxidation of esterified arachidonic acid and is an extremely potent renal vasoconstrictor.^{35,36} In the present study, the attenuation of hypertension in 2K1C by TTA was associated with reduced excretion of 8-iso-PGF₂ α in urine, whereas the level of arachidonic acid in serum and liver was unchanged. The lack of correlation between 8-iso-PGF₂ α and arachidonic acid may be explained by changes in the peroxisomal β -oxidation capacity, because 8-iso-PGF₂ α can be oxidized by peroxisomes.³⁷ Because the peroxisomal β -oxidation activity was enhanced by TTA, TTA may protect 2K1C rats from the vasoconstrictive effect of 8-iso-PGF₂ α by increasing the peroxisomal β -oxidation.

A blood pressure-lowering drug should also reduce or inhibit development of organ damage. Six months after clipping, TTA treatment not only attenuated hypertension but also abolished proteinuria, in contrast to untreated 2K1C rats, which developed heavy proteinuria and a decline in serum albumin. TTA also protected the heart, because the heart weight was lower than in untreated rats. Most important, the morphological changes were markedly attenuated during TTA treatment in the nonclipped kidney, whereas the clipped kidney was protected by the clip and showed similar changes in untreated and TTA-treated rats.

Perspectives

We have shown previously that TTA improve several risk factors of the metabolic syndrome, such as insulin resistance, hyperglycemia, and hyperlipidemia, in rats. In the present study, we show for the first time that TTA also prevented the development of hypertension and organ damage in rats. This effect seems to be mediated through the renin-angiotensin system, which plays a major role in human types of hypertension. The combination of lipid-lowering effect and blood pressure reduction makes TTA a promising drug, because high lipid levels and high blood pressure are major challenges in clinical practice. A further perspective will be to examine the effect of TTA in genetic hypertension where the renin-angiotensin system is less upregulated than in renal hypertension. Because the blood pressure-lowering effect of TTA seems to be mediated at least partly via the renin-angiotensin system, further studies on the effect of TTA in rat models with normal renin levels, such as the spontaneously hypertensive rats, will be performed.

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Disclosures

None.

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