Tissue kallikrein deficiency and renovascular hypertension in the mouse

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TK activity is inversely correlated with BP in man (27) and in strains of hypertensive rats (1, 26). It has been suggested that genetically high urinary kallikrein excretion may protect against essential hypertension in humans (8). It has also been suggested that reduced expression of the TK gene (klk1) may contribute to salt-sensitive hypertension in Dahl rats (21). However, mice with a disrupted TK gene display normal BP (29), suggesting that TK does not play an important role in regulating BP under normal conditions. This finding does not exclude the possibility that TK may influence the development of secondary forms of hypertension. In rats with two-kidneys, one-clip (2K1C) renovascular hypertension, renal TK gene expression has been reported to be unaltered during the onset of hypertension, and then to decrease during the chronic phase of established hypertension, with a reduction in both urinary and vascular TK activity (15, 31). TK synthesis and secretion are reduced in the clipped kidney, but remain unaltered in the contralateral kidney (19). Whereas hypertension induced by clipping a renal artery is clearly renin- and angiotensin-dependent, observations referred to above, suggest that TK activity may protect against kidney dysfunction and excessive elevation of BP. In this context, we tested this hypothesis in TK-deficient mice in which the gene encoding for TK had been disrupted (29, 42). These mice exhibit extremely low levels of kallikrein in the kidney (29).

MATERIALS AND METHODS

Mice. TK+/+ and TK−/− mice were generated in our laboratory as previously described (29, 42). The mouse mutants had been back-crossed in a C57BL/6 genetic background (Charles River, L’Arbresle, France) for over 10 generations before obtaining the wild-type TK+/+ and homozygous mutant TK−/− littermates used in our experiments by heterozygous crossing. Mice were housed in an air-conditioned room with a 12:12-h light-dark cycle (8:00 PM–8:00 AM; 8:00 AM–8:00 PM) cycle, and received standard mouse chow (AO4; Scientific Animal Food and Engineering, Augy, France) and tap water ad libitum. All the experimental procedures were performed in accordance with the European regulations for the care and use of laboratory animals (L 358–86/609/EEC). All procedures in this study were approved by the university Animal Care and Use Committee.

2KIC hypertension. Adult male mice were anesthetized by isoflurane inhalation (3% in an oxygen stream). The left kidney was exposed through a small flank incision and externalized. The left renal artery was isolated from the renal vein and connective tissue. A U-shaped silver clip (3 × 2 × 1 mm with a 2-mm-long cleft and 120-μm internal gap; Excidell) was placed near the aorta, around the renal artery for partial occlusion (44). Two groups of mice underwent clipping of the left renal artery: 2KIC-TK+/+ (n = 31) and 2KIC-TK−/− (n = 32). Control mice underwent a sham procedure (n = 44; TK+/+; n = 32; TK−/−; n = 12). Sham procedures were performed as described above (incision, isolation of the renal artery), except for the clipping of the left renal artery. In addition, 10 TK+/+ and 10

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TK−/− mice underwent left renal artery clipping and were used for telemetric measurement of BP before and up to 24 days after surgery. BP. BP was followed by two different methods. First, systolic BP (SBP) was measured by tail cuff plethysmography in trained conscious mice (11, 29) using a model BP2000 Visitech (Biosbe, Chaville, France). Measurement was performed 4 wk after clipping, in the animals used for noninvasive and invasive hemodynamic determinations (sham, n = 38; 2K1C-TK+/+, n = 26; 2K1C-TK−/−, n = 26). An additional set of experiments was devoted to analyze the evolution of SBP 3, 8, 15, 21, and 28 days after clipping (sham, n = 6; 2K1C-TK+/+, n = 5; 2K1C-TK−/−, n = 6). BP was also measured telemetrically. The mice were anesthetized with isoflurane (5% in an oxygen stream). The BP radiotelemetry probe (model TA11PA-C10; Data Sciences International, St Paul, MN) was implanted. The catheter of the telemeter was inserted into the left common carotid artery, and the body of the probe was positioned in the right flank (4). The mice received amoxicillin (20 mg/kg ip Clamoxyl; SmithKlineBeecham, Nanterre, France), and ketoprofen (5 mg/kg ip Profenid; Aventis, Paris, France) just after surgery. After a 2-wk recovery period, each individual mouse cage was placed on the top of a radio-receiver (model RPC-1; Data Sciences, St Paul, MN) for monitoring BP, heart rate (HR), and spontaneous locomotor activity in conscious, freely moving animals. The telemetry BP signal was digitized at 1,000 Hz. The experimental data were collected continuously in real time, stored on the local hard disk, and analyzed using the Data Sciences acquisition system and the Dataquest ART analysis software. BP, HR, and locomotor activity were recorded daily, continuously over 4 h (10:00 AM–2:00 PM) under basal conditions before clipping and up to 24 days after inducing renovascular hypertension.

Cardiac function and renal and coronary blood flows. Cardiac function and renal and coronary blood flows parameters were measured 4 wk after clipping in mice (sham, n = 19; 2K1C-TK+/+, n = 12; 2K1C-TK−/−, n = 14) anesthetized with pentobarbital (60 mg/kg ip). Catheters were placed in the left femoral artery and in the left ventricle (LV) via the right carotid artery. The maximum and minimum rates of rise of LV pressure (dP/dtmax and dP/dtmin) were continuously visualized and recorded on a personal computer using a model MP100 system (Biopac Systems, Cerom, Paris, France). Renal (clipped and nonclipped kidneys) and coronary blood flows were determined according to the reference blood sample technique using the fluorescent microsphere method (38).

Cardiac remodeling. Transthoracic two-dimensional echocardiographic measurements were performed under light anesthesia (70 mg/kg ketamine and 10 mg/kg xylazine ip) using a digital ultrasound device (Sequoia 512; Acuson, Mountain View, CA) equipped with a specifically designed 13–15 MHz short-focus linear array probe (model 15L8) (36, 39). Two-dimensional images were obtained with M-mode cursor positioned perpendicular to the interventricular septum and the posterior wall of the LV at the tip of the mitral valve leaflets. End diastolic (EDD) and systolic (ESD) LV diameter, and the interventricular septum (S) and posterior (P) wall thicknesses were measured in diastole using the American Society of Echocardiography leading edge method (39). From these parameters, the fractional shortening (FS; %) and LV mass (LVM; g) were calculated as: FS = [(EDD − ESD)/EDD] × 100 and LVM = [(S + EDD + P − EDD) × 1.055]. All measurements were averaged for three consecutive cardiac cycles and analyzed by a single observer who was unaware of the status of the animals. At death, 4 wk after clipping, LV and right ventricle weights were determined gravimetrically in all animals.

Renin. Four weeks after clipping, blood samples from the retroorbital plexus were collected into heparinized Eppendorf tubes from the mice under ketamine-xylazine anesthesia after the echocardiographic measurements. The plasma renin concentration (PRC) was determined by radioimmunoassay of ANG I generated after incubating the plasma for 1 h at pH 8.5 in the presence of an excess of rat angiotensinogen (28). Renal renin immunostaining was performed in sham (TK+/+) and n = 14 and TK−/−, n = 9, 2K1C-TK+/+ (n = 15) and 2K1C-TK−/− (n = 17) mice as previously described (35). Sections (5 μm) from formalin-fixed paraffin-embedded kidneys were deparaffinized, incubated in 1% hydrogen peroxide, and blocked with 3% normal goat serum in PBS pH 7.6. The primary antibody (18) (polyclonal rabbit antiserum) detects mouse salivary gland and renal renin, and detection was carried out using biotinylated anti-rabbit IgG, avidin peroxidase complex (Vectastain Elite ABC kit, Vector Laboratories) with 3,3′-diaminobenzidine (Sigma) in 0.1% hydrogen peroxide. The intensity of immunostaining localized in the juxtaglomerular apparatus was analyzed by optical microscopy, and scored from 0 (no labeling) to 5 (strong labeling). Total renin staining per section was expressed as the mean labeling index (35).

Urinary parameters. Four weeks after clipping, randomly selected mice (sham-TK+/+, n = 10; sham-TK−/−, n = 9; 2K1C-TK+/+, n = 13; 2K1C-TK−/−, n = 12) were housed individually in metabolic cages for 24-h urine collection for urinary sodium, potassium, chloride, and calcium assays (Konenlab version 6.0.7). Urinary kallikrein activity was assessed by quantifying generation of p-nitroanilide with a spectrophotometer at 405 nm (model 3550; Bio-Rad Hercules, CA) after incubating the urine with the substrate S 2266 (H-D-Val-Leu-Arg-pNA; Chromogenix-Instrumentation Laboratory, Milan, Italy) (22).

Statistical analysis. Results are expressed as means ± SE. The means were compared by one-way ANOVA followed by post hoc analysis using the JMP software system (SAS Institute, Cary, NC). Telemetric data were analyzed by two-way ANOVA (Surgery/Genotype) for paired values. The level of statistical significance was fixed at P < 0.05.

RESULTS

Under basal conditions, before clipping, there was no difference between TK+/+ and TK−/− mice for any of the parameters evaluated, including renal and cardiac morphology and function, BP, HR, PRC, with the exception of the urinary kallikrein activity, which was not detectable in TK−/− mice. Consequently, the sham mice of both genotypes were pooled for any of the urinary kallikrein activity.

Renal characteristics of 2K1C mice. In 2K1C-TK+/+ mice, 4 wk after clipping, a major decrease in the left renal blood flow was observed (−90%, when expressed in ml/min vs. sham, P < 0.001, Fig. 1A; −68%, when expressed per gram of tissue vs. sham, P < 0.001), whereas the right renal blood flow was increased [+19%, when expressed in ml/min vs. sham, P < 0.001, Fig. 1A; −8%, when expressed per gram of tissue vs. sham, not significant (NS)]. The sum of ipsilateral and contralateral renal blood flow (both kidneys) was not significantly different from that of the sham animals (6.75 ± 0.66 ml/min−1g−1 vs. sham 8.02 ± 0.60, NS). The left-clipped kidney became atrophic (−65% vs. sham, P < 0.001, Fig. 1, B and C), whereas the contralateral unclipped kidney developed hypertrophy (+32% vs. sham, P < 0.001). Urinary Na+/K+ was unchanged (Table 1).

In 2K1C-TK−/− mice, clipping the left renal artery also led to a marked fall in left renal blood flow (−93%, when expressed in ml/min, Fig. 1A; −61%, when expressed per gram of tissue vs. sham, P < 0.001), whereas the right renal blood flow increased (+17%, when expressed in ml/min vs. sham, P < 0.001, Fig. 1A; −2%, when expressed per gram of tissue: vs. sham, NS). Total, right plus left, renal blood flow remained unchanged compared with sham (7.37 ± 1.04 vs. sham 8.02 ± 0.60 ml/min−1g−1, NS). The left kidney became atrophic (−66%, P < 0.001 vs. sham), and the right kidney developed...
compensatory hypertrophy (±30%, P < 0.001 vs. sham, NS vs. 2K1C-TK/+), Fig. 1B). There was no significant difference between 2K1C-TK/− and 2K1C-TK/+ mice regarding ipsilateral, contralateral, and total renal blood flow, ipsilateral and contralateral kidney weight, or urinary parameters (Fig. 1, Table 1).

Histological analysis revealed no change in the contralateral kidney, whereas the clipped kidney displayed chronic ischemia in both genotypes (data not shown). The ratios of right kidney weight to left kidney weight did not significantly differ among the two clipped groups or among the two sham groups (data not shown).

Table 1. Biological parameters in the 3 groups measured 4 wk after left renal artery clipping or sham surgery

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>2K1C-TK/+</th>
<th>2K1C-TK/−</th>
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</thead>
<tbody>
<tr>
<td>No. Mice</td>
<td>19</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>33 ± 1</td>
<td>32 ± 1</td>
<td>31 ± 1</td>
</tr>
<tr>
<td>Diuresis, ml/24 h</td>
<td>1.0 ± 0.1</td>
<td>1.4 ± 0.2</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Calcium, mol/mol creatinine</td>
<td>0.26 ± 0.02</td>
<td>0.28 ± 0.04</td>
<td>0.30 ± 0.10</td>
</tr>
<tr>
<td>Chloride, mol/mol creatinine</td>
<td>35.4 ± 1.7</td>
<td>33.7 ± 1.9</td>
<td>34.1 ± 1.9</td>
</tr>
<tr>
<td>Potassium, mol/mol creatinine</td>
<td>22.4 ± 0.9</td>
<td>24.7 ± 1.9</td>
<td>25.4 ± 1.31</td>
</tr>
<tr>
<td>Sodium, mol/mol creatinine</td>
<td>26.1 ± 1.4</td>
<td>25.7 ± 2.4</td>
<td>24.2 ± 2.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. Results are not statistically different for sham, 2K1C-TK/+ and 2K1C-TK/−.
nine). As expected, no urinary kallikrein activity was detected in either of the TK−/− groups.

**BP in 2K1C mice.** Telemetric measurements showed that under basal conditions, there was no significant differences between the 24-h profiles of BP, HR, and locomotor activity of sham-TK+/+ and sham-TK−/− mice under a 12:12-h light-dark cycle (Fig. 4). In 2K1C-TK+/+ mice, hypertension developed immediately after clipping. SBP increased significantly the first day after clipping (+24% vs. the day before clipping, P < 0.05) (Fig. 5). In 2K1C-TK−/− mice, hypertension also occurred soon after clipping (+20% 1 day after clipping vs. the day before clipping, P < 0.05) (Fig. 5), but did not significantly differ from that observed in 2K1C-TK+/+ mice. During the first week after clipping, SBP of both 2K1C-TK+/+ and 2K1C-TK−/− mice was significantly higher than the corresponding basal value measured in each group before clipping. Thereafter, SBP remained elevated in all clipped mice but tended to decrease over time. There was no significant difference between genotypes. HR was not affected by clipping, and there was no difference between genotypes (Fig. 5). Telemetric measurements were also performed in two sham-operated mice. There was no difference in SBP, HR, and locomotor activity before and after surgery (data not shown).

SBP was also evaluated by plethysmography in another dedicated experiment with three groups of mice (Fig. 6). The results document a lack of effect on BP of sham procedure, a significant rise in SBP in clipped mice with no effect of genotype.

**Cardiac remodeling in 2K1C mice.** In both genotypes, a similar increase in septal wall thickness (roughly +20% vs. sham, P < 0.001) and posterior wall thickness (roughly +14% vs. sham, P < 0.001) developed, whereas end-diastolic diam-

Fig. 4. Profiles over 24 h in systolic blood pressure (SBP; A), heart rate (HR; B), and activity (C) under a 12:12-h light-dark (8:00 AM–8:00 PM; 8:00 PM–8:00 AM) schedule in TK+/+ (n = 10) and TK−/− (n = 10) mice instrumented with a telemetric system under basal condition. AU, arbitrary units.

Fig. 5. SBP (A) and HR (B) recorded daily between 10:00 AM and 2:00 PM in conscious mice (telemetry) before (0) and after left renal artery clipping in TK+/+ and TK−/− mice. Data are means ± SE; bpm, beats/min. n = 8–10 per group. *P < 0.01 vs. corresponding basal condition before clipping (0), not significant between genotype.

Fig. 6. SBP measured in trained conscious mice before (0) and 3, 8, 15, 21, and 28 days after clipping in TK+/+ (n = 5) and TK−/− (n = 6) mice (plethysmography). *P < 0.05 vs. sham (n = 6).
eter was not altered (Fig. 7). The LV mass-to-body weight ratio obtained from echocardiographic measurements was also higher in both 2K1C groups than in the sham animals. These results were confirmed by measuring gravimetrically the LV weight-to-body weight ratio at death in the same animals (2K1C-TK+/+, 4.145 ± 0.161, +24%; 2K1C-TK−/−, 3.910 ± 0.124, +17%, NS; both P < 0.05 vs. sham, 3.350 ± 0.061 mg/g). The same results were obtained in the groups of mice used for SBP measurement by plethysmography at regular intervals after clipping (2K1C-TK+/+, 3.993 ± 0.088, +13%; 2K1C-TK−/−, 4.013 ± 0.154 +14%, NS; both P < 0.05 vs. sham, 3.520 ± 0.142). These data show that clipping the left renal artery had led to similar concentric LV hypertrophy in both genotypes. Histological analysis of LV confirmed the presence of moderate interstitial and pericoronary fibrosis in both 2K1C groups (not shown), but LV morphology did not differ in TK+/+ and TK−/− animals.

Cardiac function in 2K1C mice. Coronary blood flow expressed per gram of tissue, tended to be lower than in sham mice in the 2K1C-TK+/+ and 2K1C-TK−/− groups, but the three experimental groups did not differ statistically (Table 2). Left ventricular functional parameters evaluated 4 wk after clipping noninvasively by echocardiography (FS) or invasively by dP/dt max and dP/dt min determination, showed no difference from sham animals (Table 2). There was no significant difference between the genotypes.

DISCUSSION

In this study, we observed that clipping a renal artery in mice led to activation of the renin-angiotensin system (RAS) without affecting TK urinary activity. Rapid-onset moderate hypertension developed with concentric LV hypertrophy. The lack of TK in TK−/− mice did not modify the degree of RAS activation, since PRC and renal renin labeling were the same in 2K1C-TK−/− and 2K1C-TK+/+ mice. Following clipping, the kinetics of the onset of hypertension in 2K1C-TK−/− mice was similar to that in their wild-type littermates. No significant differences were observed between the two genotypes regarding cardiac and renal morphology and function at up to 4 wk. These findings suggest that TK does not play any physiologically significant role in 2K1C renovascular hypertension in the mouse.

Table 2. Cardiac functional parameters in the 3 groups measured 4 wk after left renal artery clipping or sham surgery evaluated by left ventricular catheterization or echocardiography

<table>
<thead>
<tr>
<th></th>
<th>SHAM</th>
<th>2K1C-TK+/+</th>
<th>2K1C-TK−/−</th>
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<tbody>
<tr>
<td>Cardiac output, ml·min⁻¹·g⁻¹</td>
<td>6.4±0.7</td>
<td>5.5±0.6</td>
<td>4.7±0.4</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>46±1</td>
<td>46±2</td>
<td>49±1</td>
</tr>
<tr>
<td>dP/dt_max, mmHg/s</td>
<td>2179±77</td>
<td>2159±85</td>
<td>2158±53</td>
</tr>
<tr>
<td>dP/dt_min, mmHg/s</td>
<td>−2490±70</td>
<td>−2472±95</td>
<td>−2441±42</td>
</tr>
</tbody>
</table>

Values are means ± SE. Results are not statistically different for sham, 2K1C-TK+/+ and 2K1C-TK−/−. dP/dt_max and dP/dt_min, maximum and minimum first-degree differential of the left ventricular pressure.

Under our experimental conditions, hypertension developed rapidly then BP reached a plateau. A moderate elevation of BP (10–20%) in this mouse experimental model has also been reported by other authors (2, 17, 23, 25, 32, 44), but in a few studies, a greater increase in BP (~50%) has been observed (11, 20, 22, 24). It is now established that the elevation of BP is less marked in 2K1C mice than in 2K1C rats (24). In addition, glomerulosclerosis, which usually occurs in the unclipped kidney of rats exposed to high BP (16), was not observed in mice, probably as a consequence of the lower BP level induced in mice, and/or the known resistance of C57BL/6 mice to the development of glomerulosclerosis (30). Some studies of the kinetics of renovascular hypertension development in mice have shown that hypertension occurred very early after clipping, as in our study, and then the BP stabilized (14, 16, 44) or even decreased (17). In other studies, a sustained increase in BP over several weeks was observed (10, 11, 25). Different degrees of reduction in renal blood flow and activation of the RAS, and/or the use of different methods to measure BP could account for the minor discrepancies between these studies. In the present study, we evaluated BP by two different methods. Both documented the lack of effect of TK gene inactivation.

2K1C renovascular hypertension is typically a model of renin-dependent hypertension, but it has been suggested that the kallikrein kinin system may have an antihypertensive effect in this model. The study was based on the hypothesis that

![Fig. 7. Morphological cardiac parameters measured or calculated by echocardiography in the 3 groups 4 wk after left renal artery clipping. Data are means ± SE, n = 26–38/group. *P < 0.01, **P < 0.001 vs. sham.](http://ajpregu.physiology.org/10.220.33.1/chunk1.png)
before renal atrophy occurs, kallikreins and kinins, present in the ipsilateral kidney may have influenced renal hemodynamics and protected against renal ischemic damage in the early phase of renovascular disease, thus resulting in delayed hypertension. This is the reason why we followed BP on the first days after clipping; Also, in the contralateral kidney that undergoes compensatory hypertrophy, kallikrein synthesis remains unaltered (19) and could have influenced renal function and BP. Finally kallikrein is present in capacitance and resistance arteries and is involved in the control of vascular tone (7, 29). The development of renovascular hypertension has been reported to be accelerated in B2-deficient (B2−/−) mice (25) and hypertension to be aggravated (11), despite similar plasma renin activity and tissue gene expression of RAS components. In contrast, Duka et al. (14) have reported that 2K1C B2−/− mice displayed the same increase in BP as their wild-type littermates.

In our study, hypertension developed with similar kinetics and magnitude in TK+/+ and TK−/− mice after clipping. We especially focused on the early period after clipping, where renin secretion is activated and trophicity of the kidney is not yet altered, especially in the distal tubule where kallikrein is synthesized. Kallikrein deficiency did not potentiate the hypertensive effect of renin secretion. Cardiac hypertrophy was the same in both genotype groups, confirming that cardiac afterload has been similar during the follow-up period. Some studies have suggested that kinins have a direct inhibitory action on LV hypertrophy, the development of which was not related to their hemodynamic effects (12, 13, 43, 45). However, no exacerbation of cardiac hypertrophy was reported in 2K1C mice lacking the B1 or the B2 receptor (11, 14, 25). As in these studies, we found that the LV hypertrophy that developed after clipping was not influenced by the absence of TK and kinins. It is interesting to note that the pathogenesis of hypertensive remodeling seems to be different from postischemic heart remodeling, as far as TK and kinin involvement is concerned. TK deficiency indeed exaggerates cardiac remodeling and decreases survival after myocardial infarction (36, 37). The difference is, however, not surprising, as the development of cardiac remodeling is strongly influenced by underlying myocardial disease and peripheral hemodynamic status, which are very different among the two models. Renal renin synthesis and secretion are causally linked to hypertension in 2K1C mice. These parameters were not altered in TK−/− mice. The reduction in renal blood flow in the clipped kidney was very similar in wild-type and TK-deficient mice. These observations do not support the hypothesis that TK or kinins have a role in renal renin secretion and activation (5, 40, 41), at least under conditions of strong hemodynamic stimulation. Finally, the observation that ipsilateral and contralateral kidney morphology was not influenced by TK deficiency suggests that TK and kinins play no role in bilateral renal remodeling secondary to chronic unilateral ischemia.

Perspectives and Significance

The study shows that TK deficiency does not play any detectable role in 2K1C renovascular hypertension in mice. While TK and kinins influence cardiac remodeling in other experimental settings, they do not seem to exert any counter-regulatory influence on cardiac hypertrophy in 2K1C hypertensive mice. Kallikrein remains abundant in the contralateral kidney, but does not play any role in compensatory hypertrophy. These negative findings were obtained in an experimental model in which BP elevation and cardiac hypertrophy are secondary to a major stimulation of renin secretion and high ANG II production. In fact, they should not be extrapolated to other forms of hypertension involving different pathogenic mechanisms, as supported by the observation of a hypertensive effect of TK deficiency during chronic aldosterone administration, a situation where, contrary to 2K1C hypertension, kallikrein synthesis is increased and renin secretion is suppressed (unpublished results).

GRANTS

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