Sequential activation of the intrarenal renin–angiotensin system in the progression of hypertensive nephropathy in Goldblatt rats

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BACKGROUND

- The intrarenal renin–angiotensin system (RAS) has an important role in generating and maintaining hypertension in 2-kidney 1-clip (2K1C) rats but most studies were were focused only on the period of established hypertension. The purpose of this study was to assess how various intrarenal RAS components were contributed to hypertension not only in late time (5w; 5 week after operation) but also in early time (2w; 2 week after operation).

METHODS

- We Inserted a 2.5mm sized clip into the left renal artery or sham operated Sprague–Dawley rats, then measured systolic blood pressure (SBP) at one-week intervals. At 2 (2K1C, n=7; sham, n=5) and 5 (2K1C, n=7; sham, n=5) weeks after unilateral clipping, rats were sacrificed . At the time of sacrifice, 2w and 5w after the operation, transthoracic echocardiography was performed. Kidney tissues were prepared for molecular and pathologic analysis

RESULT

- Systolic blood pressure increased within one week after operation and left ventricular hypertrophy was occurred in 2K1C rats. At 2w, juxtaglomerular apparatus (JGA) and collecting duct (CD) renin increased in CK. The tubular angiotensin I-converting enzyme (ACE) was not changed, but peritubular ACE2 decreased in NCK and CK. At 5w, ACE and CD rein were enhanced, and ACE2 was still lessened in both kidneys of 2K1C rat. However, plasma renin activity (PRA) was not different with that of sham rat. In proximal tubule of CK, AngII type 1 receptor (AT1R) was not suppressed, but Mas receptor (MasR) was reduced; thus, the AT1R/MasR ratio was elevated. Although hypoxic change of CK could not be excluded, the JGA renin of CK and CD renin of both kidneys was highly expressed independent of time. Peritubular ACE2 changed in early time and uninhibited AT1R in proximal tubule of CK was presented in maintenance time.

Figure 1. Blood pressure and renin between sham-operated and 2K1C

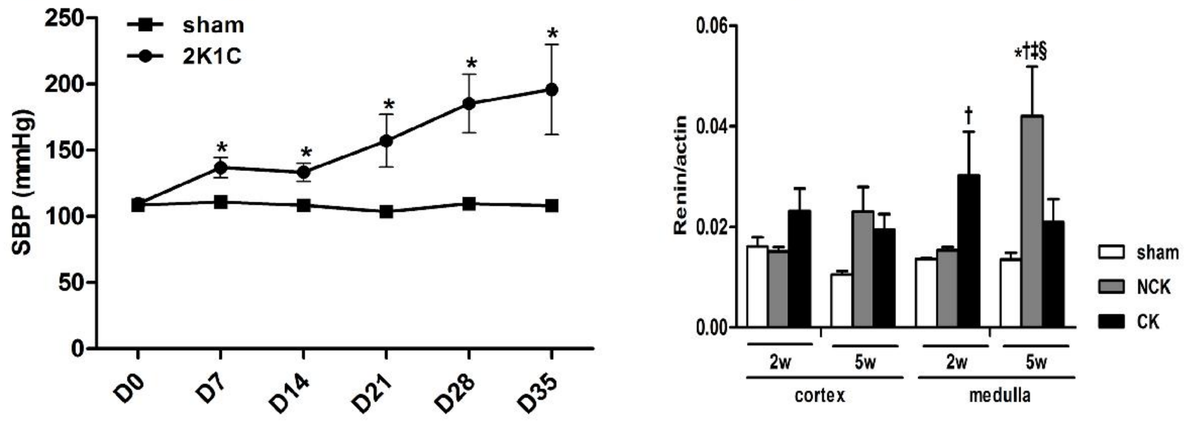


Figure 2. ACE and ACE2 expression in the kidney of shame-operated and 2K1C rats

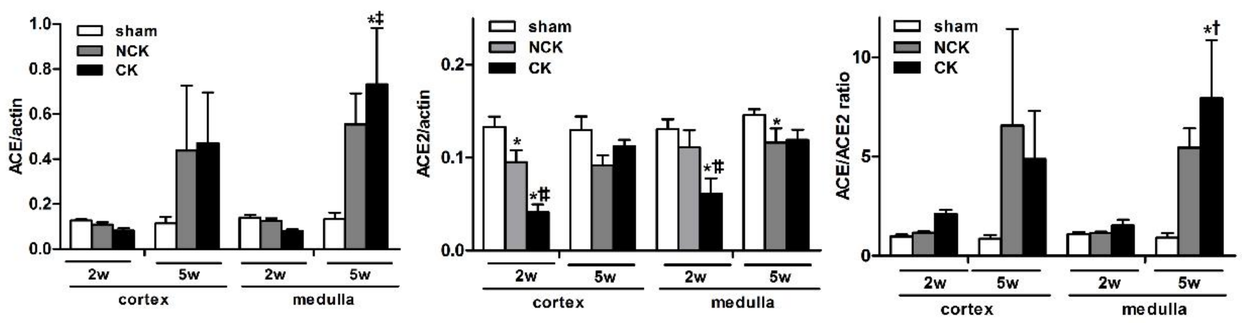


Figure 3. AT1R and Mas R expression in the kidneys of shame operated and 2K1c rats

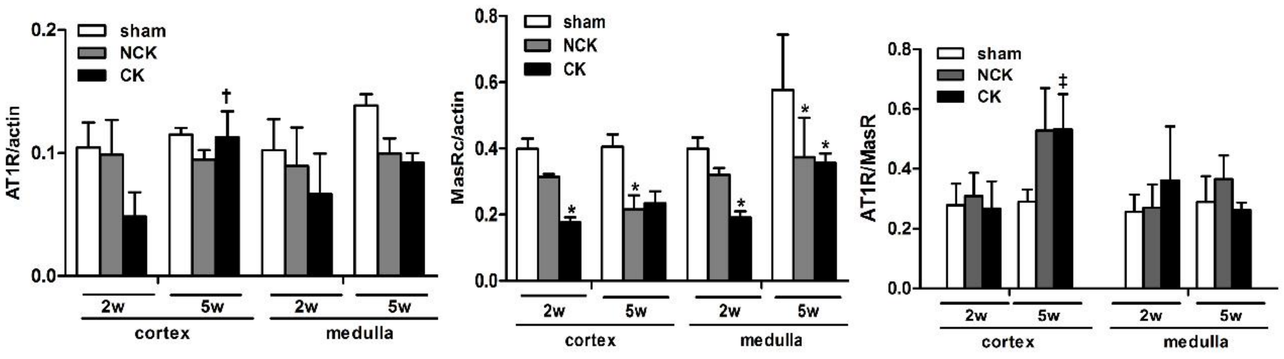


Figure 4. Immunohistochemistry findings for renin in sham-operated and 2K1C rats

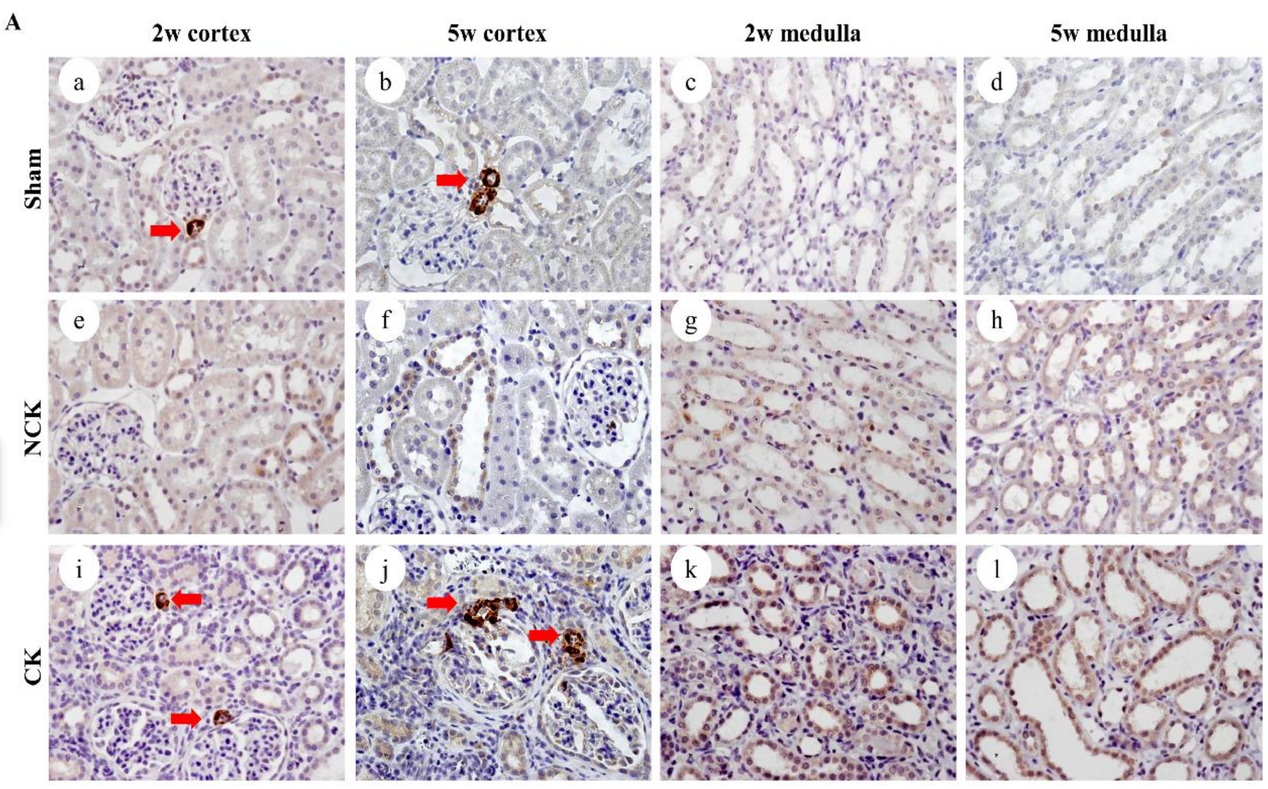


Figure 5. Immunohistochemistry findings for ACE in sham-operated and 2K1C rats

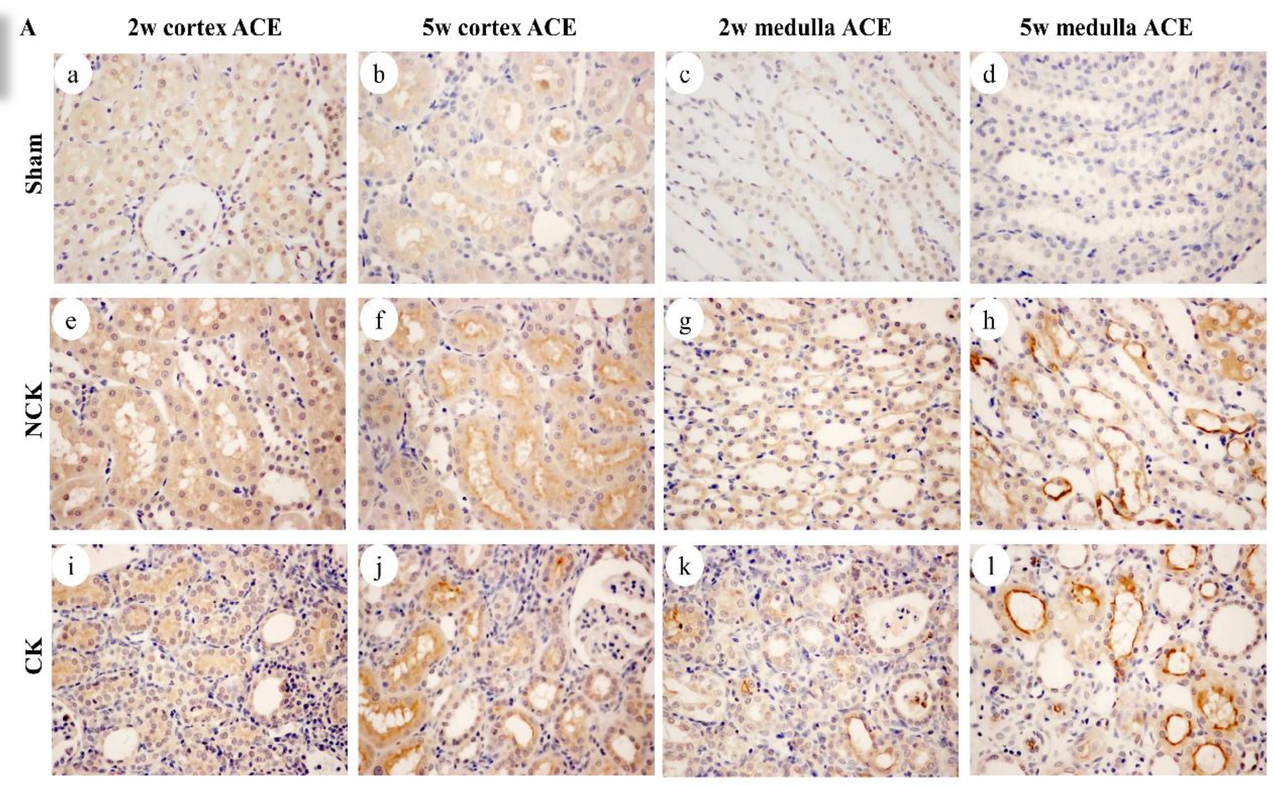
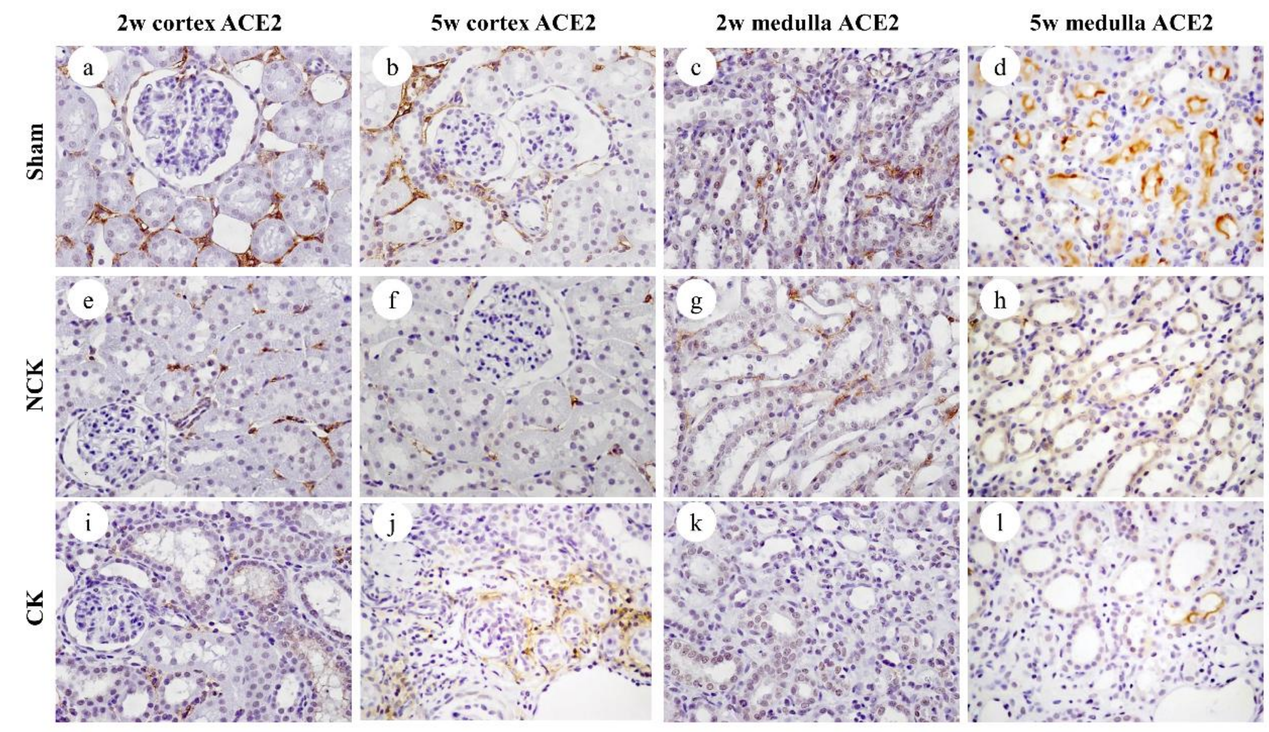


Figure6. Immunohistochemistry findings for ACE2 in sham-operated and 2K1C rats



CONCLUSION

- Our results indicate that intral RAS is conducted independent of systemic RAS and changes depending on time, tissue, and side of 2KIC rat kidneys.
- In 2K1C rat, attenuated ACE2 seems to contribute to initiating hypertension while up-regulated ACE in combination with un-suppressed AT1R may have a key role in maintaining hypertension.

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