

Salt Intake Influences the Circadian Rhythm of Intrarenal Renin-Angiotensin System and Renal Damage

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Summary

(Background) Chronic kidney disease (CKD) is a risk factor for end-stage renal failure and cardiovascular disease (CVD). It has been clarified that activation of the intrarenal renin-angiotensin system (RAS) plays a critical role in the pathophysiology of CKD and hypertension, independent of the circulating RAS that exhibits a circadian rhythm. Urinary angiotensinogen (AGT) is reported to be a useful biomarker that reflects intrarenal RAS activity and CKD severity.

Not only high blood pressure (BP) levels but also disruptions of diurnal BP variation are risk factors for renal damage. Moreover, intrarenal RAS activation and the disruption of diurnal BP variation are closely related.

A high-sodium diet is significantly and positively associated with BP elevation. On the other hand, increase of intrarenal angiotensin II (Ang II) levels by a high-sodium diet causes renal damage independent of BP elevation in disease models as well as clinical studies. However, little is known regarding whether intrarenal RAS circadian rhythm exists or if sodium intake influences the intrarenal RAS circadian rhythm, the disruption of diurnal BP and renal damage.

(Methods) We investigated the circadian rhythm of urinary AGT in healthy individuals and CKD patients classified according to circadian BP rhythms.

(Results) BP values were higher during the day than during the night in healthy individuals and CKD patients. Urinary AGT levels were not different between the day and night in healthy individuals, but were significantly higher in the daytime in CKD patients. Furthermore, in CKD patients showing a riser pattern that is classified as night-to-day ratio of systolic BP > 1.00, the circadian rhythm of urinary AGT disappeared because these levels did not decrease during the night compared with those in the day. Circadian fluctuation of albuminuria and proteinuria occurred parallel to that of the urinary AGT levels. Urinary AGT levels were significantly and positively correlated with the degree of hypertension, and urinary AGT fluctuations were correlated with diurnal BP changes.

(Conclusions) These data indicate that the circadian rhythm of intrarenal RAS activation may lead to renal damage and hypertension, which are associated with diurnal BP variation.

According to this study, when renal damage exists, the intrarenal RAS is inappropriately activated, leading to sodium retention. Consequently, sodium excretion is disturbed during the daytime, and renal damage and nighttime sodium retention activates the intrarenal RAS in CKD-riser patients.

(Perspectives) We are now constructing diseased models, collecting kidney samples and investigating the circadian rhythm of intrarenal RAS. In addition, we are recruiting CKD patients with different conditions of salt loading to investigate the influence of sodium accumulation.