No. 1630

Both Low Salt Diet and Renin-Angiotensin System Blockeres Increase Melatonin Secretion

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Summary

(Background) Activation of the intrarenal renin-angiotensin system (RAS) plays a critical role in the pathophysiology of chronic kidney disease (CKD) and hypertension. The circadian rhythm of intrarenal RAS activation leads to renal damage and hypertension, which are associated with diurnal blood pressure (BP) variation. In addition, salt loading develops renal damage due to activation of intrarenal RAS, independent of BP elevation.

Melatonin is a hormone regulating the circadian rhythm, and has multiple functions such as anti-oxidant and anti-adrenergic effects and enhancement of nitric oxide bioavailability. We have clarified that nocturnal melatonin concentrations are lower in CKD patients, and that impaired nighttime melatonin secretion may be associated with nighttime intrarenal RAS activation and renal damage in CKD patients.

However, the associations among salt loading, melatonin secretion and renal damage have not been clear. Therefore, this study was performed to clarify whether salt restriction ameliorates melatonin secretion and salt loading suppresses it melatonin secretion more significantly.

(Methods) We recruited 32 CKD patients without RAS blockers [12 men and 20 women, age: 50.3±15.7 years and estimated glomerular filtration rate (eGFR) 63.7±21.1 ml/min/1.73m^2]. After CKD patients consumed a standard diet (10 g/day of salt), the data were collected. Then, low salt diet (6 g/day of salt) was fed and the data were collected again. Daytime (6:00 am to 9:00 pm) and nighttime (9:00 pm to 6:00 am) urine collection were conducted to evaluate urinary excretion of 6-sulfatoxymelatonin (aMT6s), a main metabolite of melatonin, albumin and protein, and angiotensinogen (AGT), a surrogate marker of intrarenal RAS activation, respectively. We divided the daytime and nighttime for 24-h ambulatory BP monitoring using sleep and waking times. Blood samples were drawn at 9:00 pm and 6:00 am on the following day.

(Results) Although no significant differences of urinary aMT6s excretion levels were found between standard and low salt diets, urinary aMT6s excretion levels during low salt diet tended to be increased compared with those during a standard diet. When only the patients whose eGFR was less than 60ml/min/1.73m^2 were analyzed, urinary aMT6s excretion levels during a low salt diet was significantly higher than those during a standard diet in daytime ($p=0.023$) and tended to be increased in nighttime ($p=0.082$).

Urinary aMT6s excretion levels during a standard diet was significantly and negatively correlated with urinary albumin or protein excretion levels in both daytime and nighttime. No significant correlations were found between urinary aMT6s excretion levels and the levels of urinary AGT excretion, blood pressure, renal function, and plasma AngII during a standard diet. On the other hand, there were no significant associations

between urinary aMT6s excretion levels and other parameters during a low salt diet.

Multiple regression analyses revealed that the levels of urinary albumin in nighttime or protein in daytime were significantly and negatively associated with urinary aMT6s levels during a standard diet, when age, gender and BMI were adjusted. On the other hand, no significant associations were observed between urinary aMT6s levels and other parameters in daytime and nighttime during a low salt diet by multiple regression analyses.

(Conclusions) It is possible that salt loading induces renal damage via decrease of melatonin secretion independent of intrarenal RAS activation.

(Perspectives) We will continue to recruit the patients with careful attention to the amount of salt intake. In addition, we will perform the animal study by using CKD model animals that were fed with normal, high or low salt diet and caused by various degrees of renal damage.