No. 1821

Relationship between Renal and Cerebral Renin-Angiotensin System and Sodium Appetite in CKD Model Rats

Shinsuke Isobe, Takashi Matsuyama, Sayaka Ishigaki, Naro Ohashi, Hideo Yasuda

Hamamatsu University School of Medicine

Summary

(Background) Regulation of sodium intake and excretion is essential to maintain body fluid balance. The circulating renin-angiotensin system (RAS) is one of the most powerful hormones that regulates arterial pressure and sodium homeostasis. It has been confirmed that activation of the intrarenal RAS has a critical role in the pathophysiology of hypertension and renal injury independent of the circulating RAS. In normal kidney function models, a high-sodium diet causes downregulation of intrarenal RAS. However, intrarenal RAS is remarkably activated with a high-sodium diet in chronic kidney disease models. Activated intrarenal RAS in a disease models increases inappropriate sodium reabsorption and worsened renal injury.

Conversely, little is known about the regulation to control of sodium intake. Sodium restriction is a cornerstone to treat hypertension, renal failure and heart failure. However, among these morbidity patients, adherence to the sodium restriction diet is extremely low.

Sodium appetite is a behavioral drive to ingest food or fluid that contain sodium. Sodium appetite is stimulated by physiological sodium deficiency. However, when animals can available salty foods freely, they take excess amount of sodium that need to maintain fluid balance or growth. In the morbidity states, increased sodium appetite has been reported in patients on dialysis, in rat models of heart failure and spontaneous hypertensive rats, though exact mechanisms that increase the sodium appetite in these models remain incompletely understood. Activated intra-cerebral angiotensin II at the subfornical organ (SFO) and the organum vasculosum of the lamina terminal (OVLT) is known to stimulate the sodium appetite. Cao, et al reported that in CKD model rats fed high sodium diet, intra-cerebral angiotensin II including SFO is activated by intra-renal RAS activation via afferent sympathetic nerve activation.

However, little is known whether sodium appetite is increased in CKD model. Therefore, we performed to clarify that activated intra-cerebral RAS mediated CKD models increase the sodium appetite.

(Methods) All animal procedures were conducted with the approval of the Animal Committee of the Hamamatsu University School of Medicine. Six-week-old male Sprague-Dawley rats were purchased from SLC (Hamamatsu, Japan) and Kept under a 12:12h light-dark cycle. Five-sixths nephrectomy (Group Nx) or sham (Group C) operation was performed at day 0 and day 7. All rats received a normal-salt (0.4%) diet and free access to water for 2 weeks. At day 14, Group Nx and C divided to another two groups receiving a low-salt (0.04%) diet (C+LS, Nx+LS) or high-salt (4%) diet (C+HS, Nx+HS). All four groups had at libitum access to fixed sodium diet and water during day 14 to 28. For tow-bottle test, rats were given access to two-bottle of tap water including isotonic saline (0.9%) and water for 7 day. The blood pressure

(BP) was measured using non-invasive rail-cuff method before euthanasia, at day 35. Blood samples and kidneys were collected immediately.

(Results)

1. Body weight, blood pressure and serum creatinine

Body weight (BW) in group C was not heavier than group Nx at day 0 but heavier at day 35. Serum creatinine (sCr) in group Nx was significantly higher than that in group C at day 35. Systolic BP (SBP) and diastolic BP (DBP) in group Nx were higher tendency but not significantly higher than that in group C. There were no significant difference in BW, SBP, DBP and sCr between LS and HS both in group C and Nx.

2. Histological findings

Glomerular damage such as global and segmental sclerosis, and tubulointerstitial fibrosis were more increased in group Nx than that in group C. However, there were no obvious histological differences among the high and low sodium diet.

3. The intrarenal AGT and Ang II activities

We conducted quantitative evaluation by immunostaining for AGT and Ang II. Immunostaining for AGT in group C revealed slight expression in the proximal tubular cells and dramatically increased in group Nx (C+LS: 4.0 ±0.2, C+HS: 3.8 ± 0.3, Nx+LS: 8.2 ± 0.6, Nx+HS: 9.8 ± 0.8. C+LS vs Nx+LS: P = 0.03, C+HS vs Nx+HS: P = 0.02). However, there were no significant difference between LS and HS (C+LS vs C+HS: P = 0.89, Nx+LS vs Nx+HS: P = 0.76). Immunostaining for Ang II was weak and mainly seen in distal tubules in group C. In group Nx, immunostaining for Ang II was significant expression in proximal and distal tubules. Though, the degree of immunoreactivity of Ang II was significantly higher in group Nx that that in group C, but no significant change has existed between LS and HS (C+LS: 5.2 ±0.5, C+HS: 4.8 ± 0.5, Nx+LS: 13.5 ± 1.5, Nx+HS: 14.2 ± 1.3. C+LS vs Nx+LS: P = 0.042, C+HS vs Nx+HS: P = 0.03, C+LS vs C+HS: P = 0.88, Nx+LS vs Nx+HS: P = 0.66).

4. The sodium appetite

We evaluated the sodium preference score as a marker of sodium appetite. There were no significant differences in the sodium preference score between the LS and HS (C+HS: 0.17 ± 0.10, C+LS: 0.28 ± 0.17, P = 0.53, Nx+HS: 0.33 ± 0.13, Nx+LS: 0.24 ± 0.11, P = 0.62). There was also no significant difference in the sodium preference score between group C+LS and Nx+LS (C+LS vs Nx+LS: P= 0.92). The group Ns+HS showed higher tendency in that score but not statistically significant compared that score of group C+HS (C+HS vs Nx+HS: P = 0.32).