［課程―２］

審査の結果の要旨

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The mPGES-1 and PGE2 are considered to contribute to the progression of chronic kidney disease. In the present study, to clarify this hypothesis I used young-aged rats undergoing renal mass reduction and high salt-induced salt-sensitive hypertension model and obtained following results.

1. Sprague-Dawley rats uninephrectomized at the young age of 3 weeks old plus a high salt loading for two and four weeks showed increased mean arterial blood pressure and urinary protein level which was a suitable model for study salt-sensitive hypertension-induced chronic kidney disease (CKD).
2. Treatment by antioxidant SOD mimetic, tempol or mineralocorticoid receptor blocker eplerenone, ameliorated kidney dysfunction. Tempol protected kidney dysfunction independent from blood pressure changes. However, eplerenone reversed renal damages partly due to blood pressure lowering effect.
3. The histological studies showed severe glomerulosclerosis and tubulointerstitial injury in uninephrectomized high salt loaded group concomitant with the fibrosis marker Col1a1 and Col3a1 mRNA expression. Both tempol and eplerenone treatment group returned the level to normal.
4. Prostaglandin D2 level was not affected by high salt loading. Urinary PGE2, PGE2 synthase mPGES-1 mRNA and protein expression levels increased in two and four weeks high salt loaded group. The antioxidant SOD mimetic, tempol suppressed the level to normal, suggested that oxidative stress plays an important role to induce PGE2 generation in young-aged CKD model.
5. The precursor cyclooxygenase (COX) plays an indispensable role in the formation of prostaglandins, the COX1 level was not changed by high salt loading, COX2 showed biphasic fashion in the different period of high salt loading. On the other hand, the chronic high salt administration may influence production of other prostaglandins. In the present study, excretion levels of other prostaglandins such as PGI2, PGF2, and TXA2 were not examined, which a waits for future investigation.

6. Uninephrectomized high salt loaded group increased oxidative stress marker 8-isoprostanesis level, and tempol showed a superior antioxidant effect together with reduced the level of PGE2 and mPGE-1 expression in comparison with eplerenone.

This dissertation showed that high salt-loaded uninephrectomized model of chronic kidney disease, the antioxidant tempol reversed ROS-induced renal damages by reducing mPGES-1 derived PGE2 expression independent from the hemodynamic stress of hypertension. In this research, for the first time, I examined the effect of salt loading on young-aged uninephrecomized rats for a short period of two weeks causing salt-sensitive-hypertension, and investigated the important role of PGE2 in renal damage. Considering that the present study contributes to the understanding of the pathogenesis of chronic kidney disease to some extent, this dissertation is worthwhile to grant the degree.