HISTONE ACETYLATION IN EACH SEGMENT OF THE KIDNEY AFTER TRANSIENT SALT LOADING IN MICE AND THE SIGNIFICANCE FOR THE ONSET OF PERSISTENT HYPERTENSION

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SP044
June 4 2017
54th ERA-EDTA
Madrid

Introduction and aims

- The role of salt intake in the development of hypertension is familiar, but the mechanism has not been revealed.
- We have previously found out that the medial hypertrophy of renal arteriole induced by transient salt loading causes sustained elevation of blood pressure in spontaneous hypertensive rat (SHR) even after the salt loading had quitted [Oguchi H et al. Hypertension 2014] (Fig1).
- Epigenetic modification of gene expression has attracted attention as a possible mechanism for sustained effects of transient stimuli (Fig2).
- The present study investigated the significance of histone acetylation in each segment of the kidney in the induction of hypertension after transient salt loading.

Fig1. Medial hypertrophy of renal arterioles induced by transient salt loading

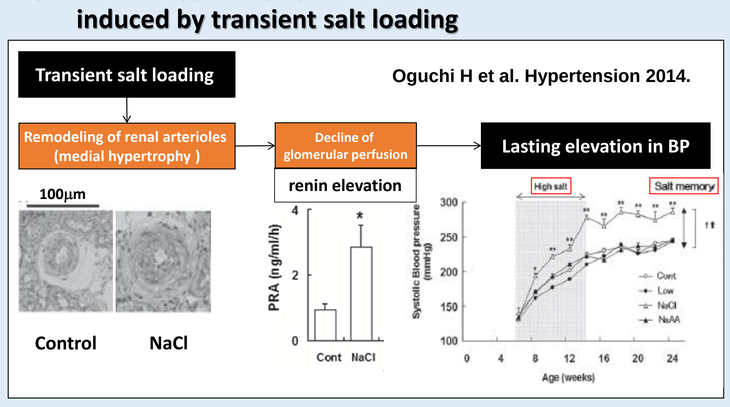
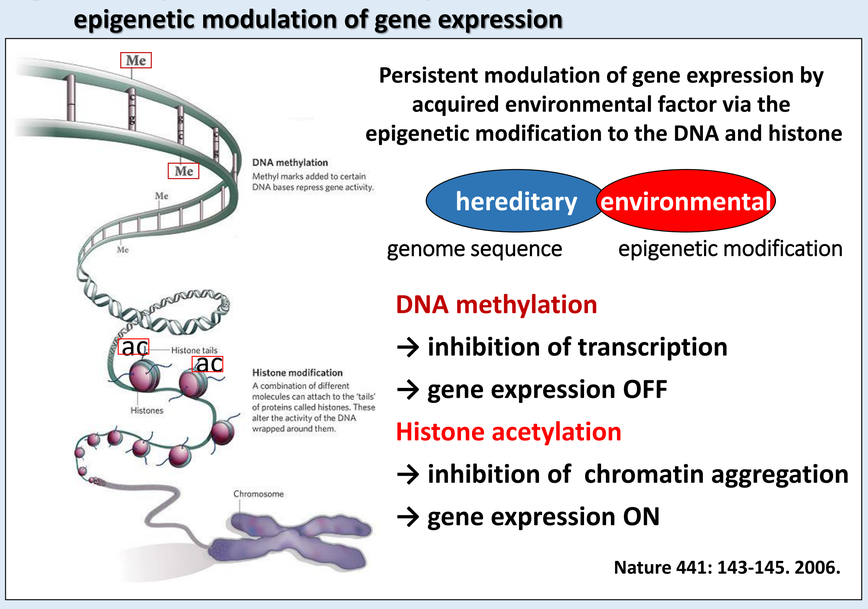


Fig2. Memory of transient stimuli by epigenetic modulation of gene expression



Methods

- C57bl6 mice were implanted deoxycorticosterone acetate (DOCA) pellets and given drinking water containing 1% NaCl for 2 weeks to induce salt-induced hypertension (Fig3).
- Blood pressure was measured by tail-cuff method during and after transient salt loading.
- Histological examinations of the kidney were performed. The degree of histone acetylation was assessed by immunostaining of acetylated H3 and H4 in each segment of the kidney including renal arterioles, segmental arteries, glomeruli and proximal tubules.
- Gene expressions were examined in the whole kidney and the arterioles collected by laser capture microdissection (LCM) (Fig4).

Fig3. Methods: DOCA-salt hypertension model mice

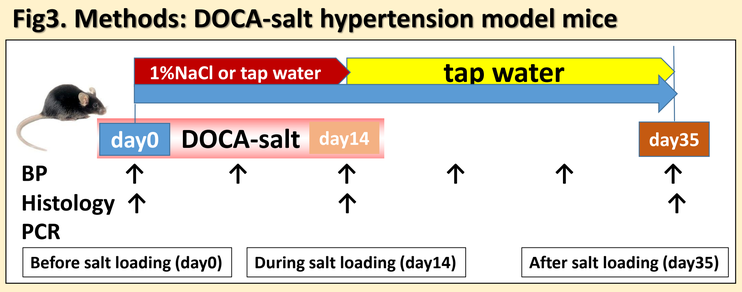
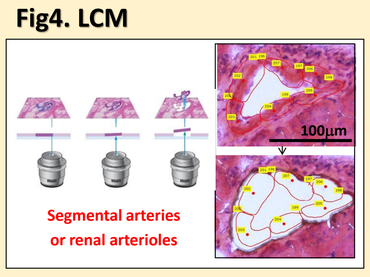


Fig4. LCM



Results

- Transient salt loading caused elevation in blood pressure during the loading period in mice, and they remained even after stopping salt loading associated with persistent medial hypertrophy of renal arterioles (Fig5↓).
- In the media of renal arterioles, histone acetylation was enhanced during salt loading, and the enhanced histone acetylation persisted even after stopping salt loading. In the tubules, enhanced histone acetylation by the salt loading returned to the initial level after its termination (Fig6→).
- Real time PCR in the whole kidney revealed that the gene expressions of CGN5, CBP and p300, which are HATs, were elevated; and conversely, those of Sirt1, Sirt3, HDAC1 and HDAC5, which are HDACs, were decreased during salt loading (Fig7).
- The gene expression of MMP-2 in the renal arterioles collected by LCM increased during salt loading, and did not decline after the termination of salt loading (Fig8).

Fig6. Immunostaining of histone H3 acetylation (H3Ac)

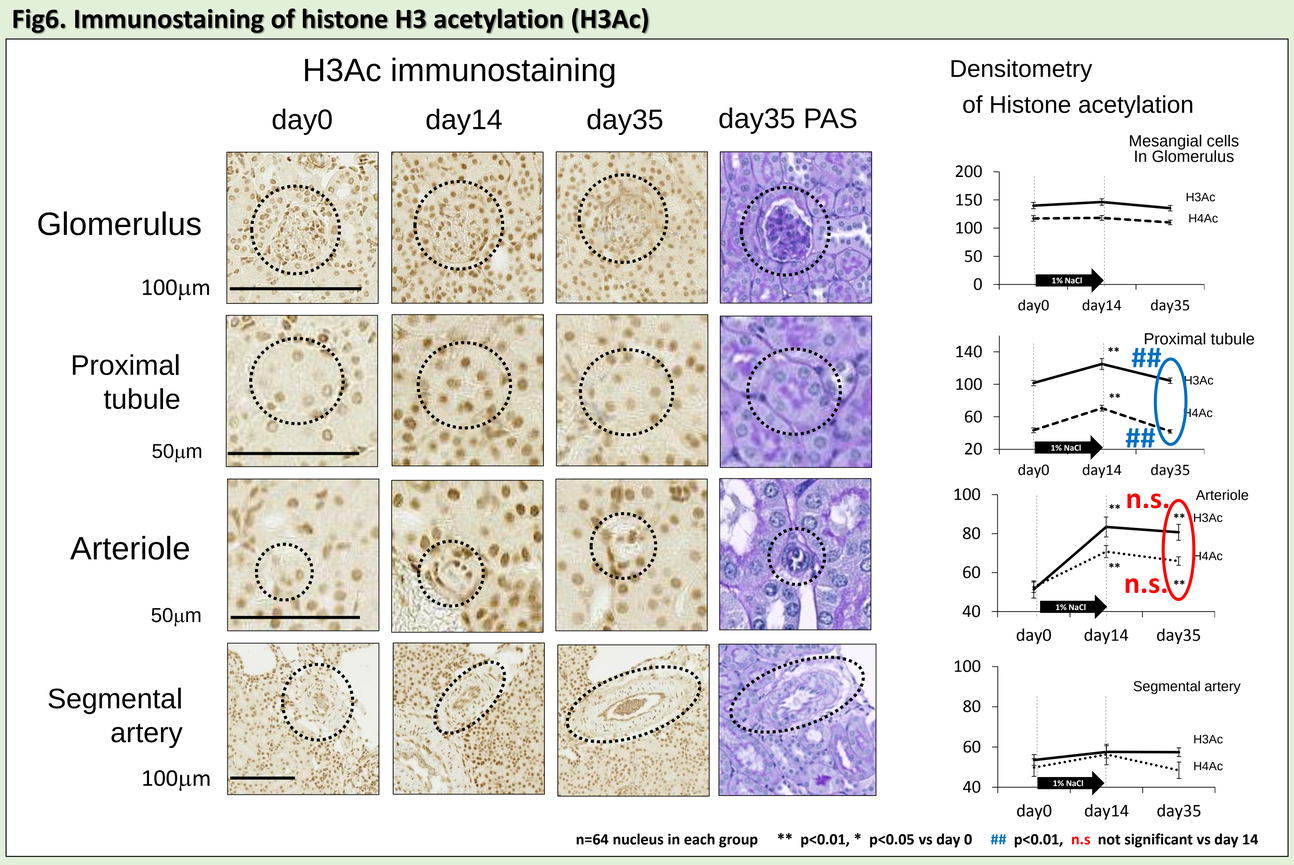


Fig5. Results: DOCA-salt hypertension model mice

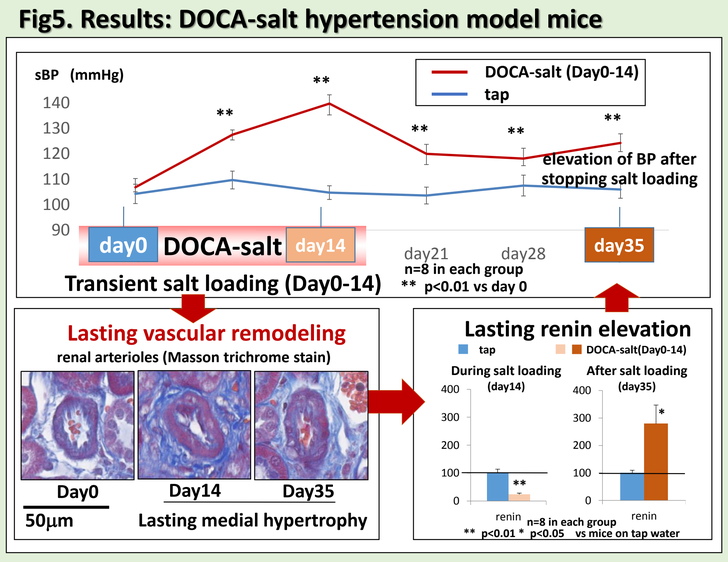


Fig7. Gene expression in the whole kidney (real time PCR)

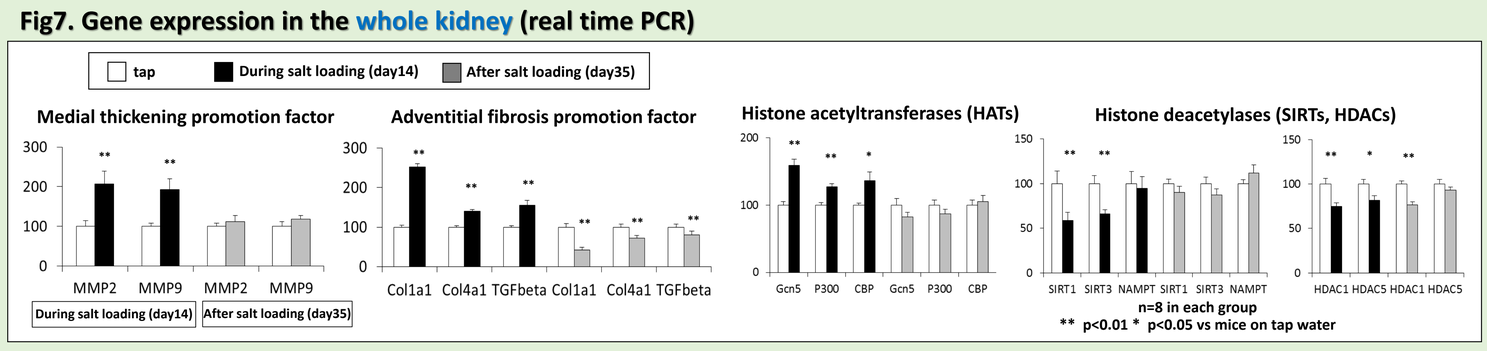
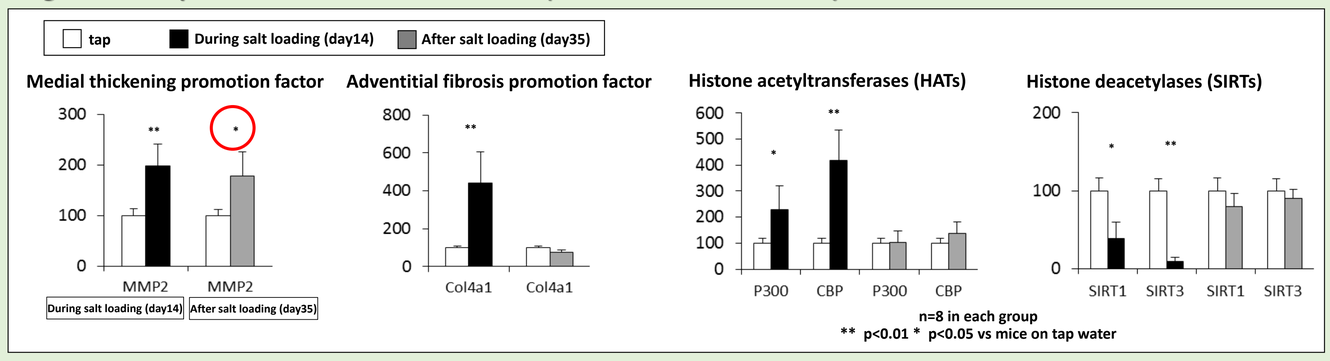


Fig8. Gene expression in the renal arterioles (real time PCR after LCM)



Conclusions

- The lasting medial hypertrophy along with sustained histone hyper-acetylation and elevation in MMP-2 expression in the renal arterioles were suggested to contribute to sustained elevation of blood pressure after transient salt loading.
- Increased expressions of HATs and decreased expressions of SIRTs during salt loading would be involved in the enhancement of histone acetylation.

Fig9. Conclusions

Whole kidney	During salt (Day14)	After salt (Day35)
HATs	↑↑	→
SIRTs, HDACs	↓↓	→
Immunostaining H3Ac,H4Ac	↑↑	→
Medial thickening promotion factor MMP2,9	↑↑↑	→
Adventitial fibrosis promotion factor Col1a1, Col4a1	↑↑↑	↓↓
H3 and H4 acetylation in the promoter region of MMP-2	↑	→
Renin	↓↓↓	↑

Renal arterioles	During salt (Day14)	After salt (Day35)
HATs	↑↑	→
SIRTs	↓↓	→
Immunostaining H3Ac,H4Ac	↑↑	↑↑
Medial thickening promotion factor MMP2	↑↑	↑
Adventitial fibrosis promotion factor Col4a1	↑↑↑	→
medial hypertrophy	↑↑	↑↑
sBP	↑↑	↑

54 ERA
44--SP
Experimental hypertension
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DOI: 10.3252/pso.eu.54ERA.2017
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