Significance of histone acetylation in vascular remodeling of renal arterioles induced by DOCA-salt loading in mice.

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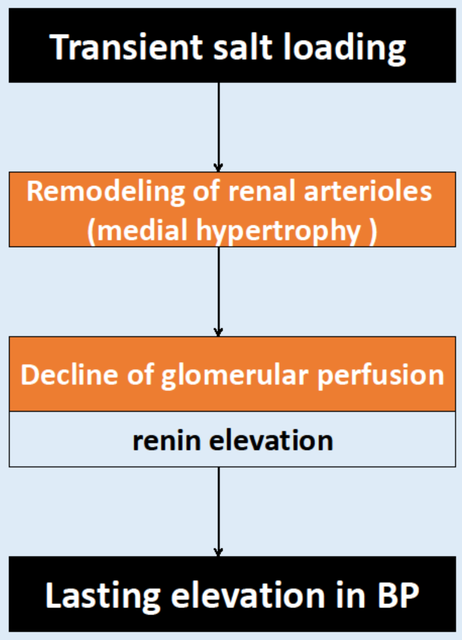
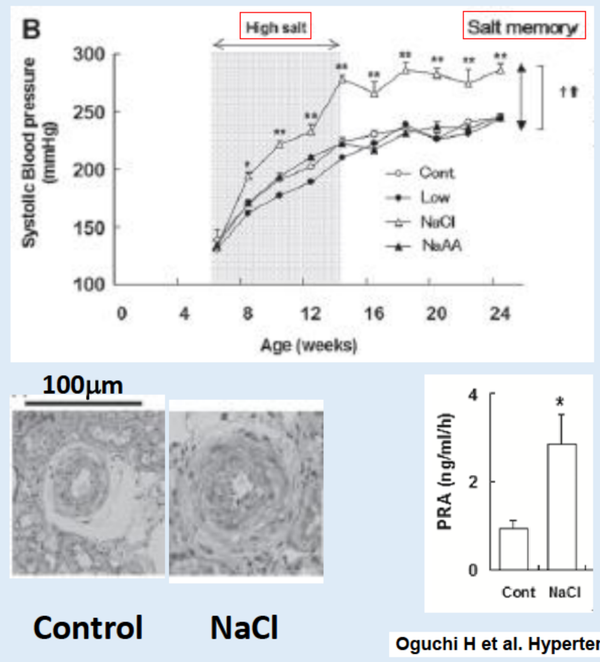
Introduction

▸ The role of salt intake in the development of hypertension is prominent, but the mechanism has not been fully elucidated.

▸ Our previous report showed that the medial hypertrophy of renal arterioles caused lasting elevation in blood pressure (BP) after transient salt loading in spontaneous hypertensive rat (SHR) [Oguchi et al. Hypertension 2014].

▸ The present study investigated the significance of epigenetic regulation of the gene expression which is relevant to the medial hypertrophy after transient salt loading.



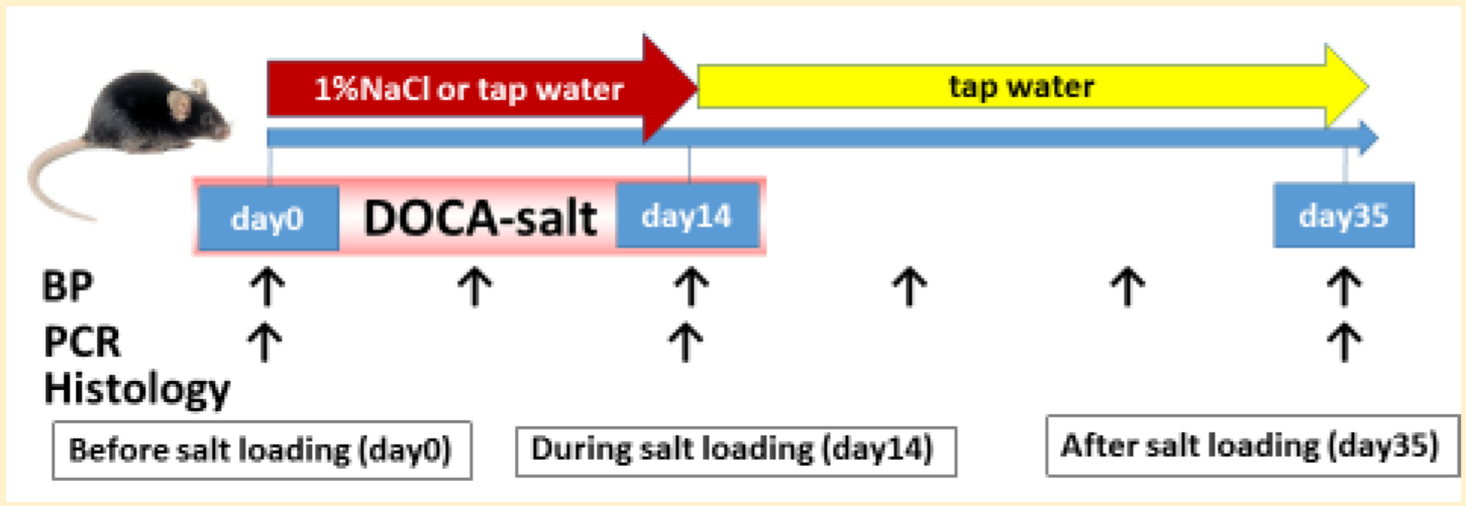


Oguchi H et al. Hypertension 2014.

Methods

▸ Male 6 week old C57bl6 mice were implanted deoxycorticosterone acetate (DOCA) pellets and given drinking water containing 1% NaCl for 2 weeks as a mouse model of salt-induced hypertension.

1. The BP was measured by a tail-cuff method during and after the transient salt loading.
2. Histological examination was performed on the kidney.
3. Gene expressions in the kidney such as matrix metalloproteinases (MMPs), which promote the medial hypertrophy, were quantified.



Results

▸ Transient salt loading caused elevation in BP during the loading period. BP after stopping salt loading was also significantly higher than that before salt loading.

▸ Salt loading caused medial hypertrophy of renal arterioles, and it remained after stopping salt loading, as to cause lasting renin elevation.

▸ Real time PCR revealed that MMP2, MMP9 were increased during the salt loading and Sirt1, Sirt3, HDAC1, HDAC5, which are histone deacetylases, were decreased. Histone H3K9 and H4K16 acetylations in the MMP2 gene were enhanced by the salt loading.

Fig1. Systolic blood pressure

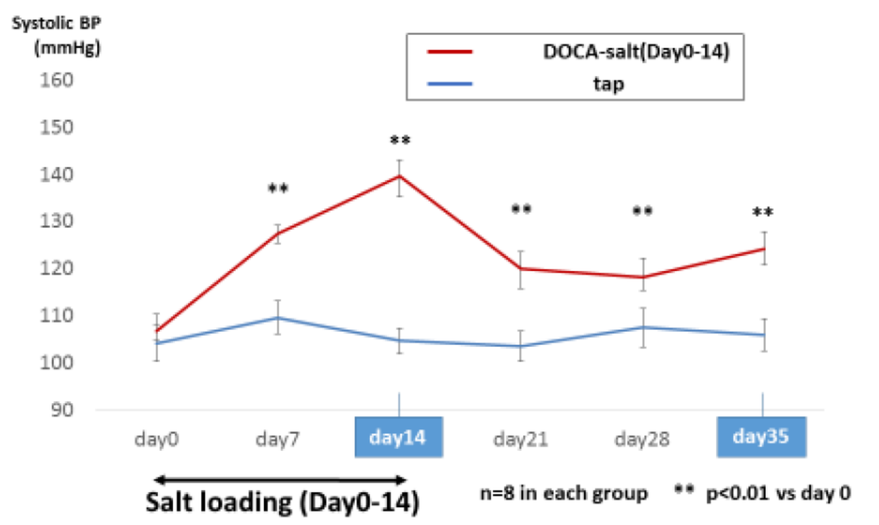


Fig2. Masson trichrome stain

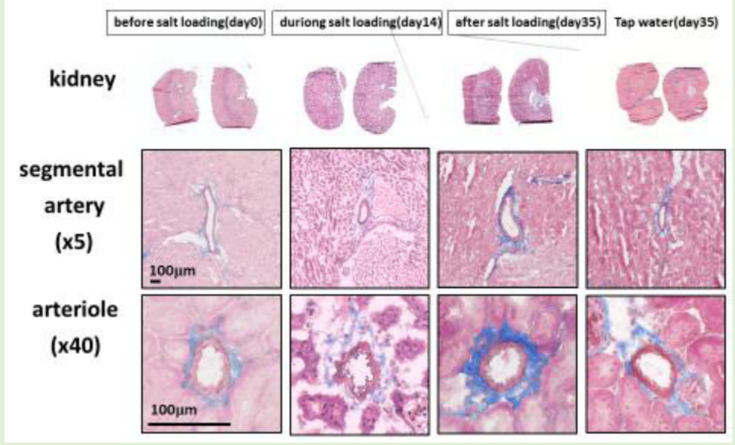


Fig3. Gene expression (real time PCR)

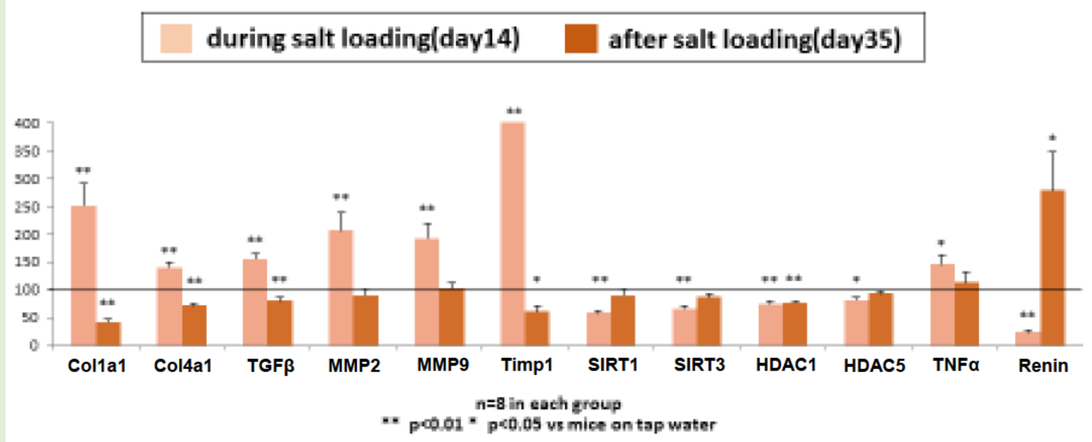
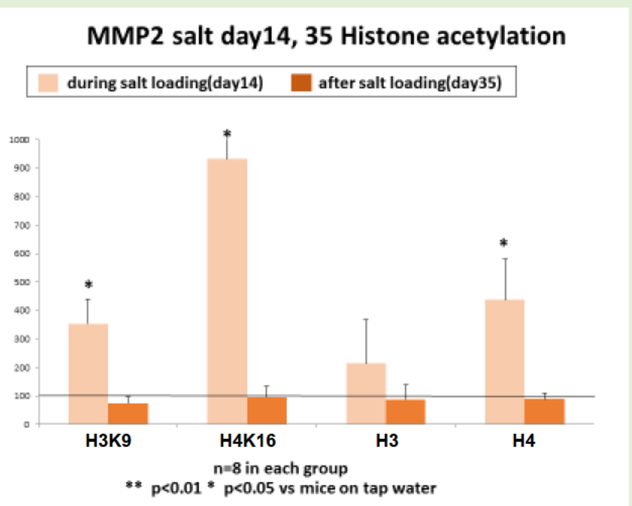


Fig4. Gene expression (real time PCR)

category	gene	during salt loading (Day14)	after salt loading (Day35)
Regulation BP	Renin	↓↓↓	↑↑
inflammation promoting factor	TNFα	↑	→
medial hypertrophy promoting factor	MMP2 MMP9	↑↑↑	→
adventitia fibrosis promoting factor	TGFβ Col1a1 Col4a1 Timp1	↑↑↑	↓↓
epigenetic regulation	Sirt1 Sirt3	↓↓↓	→
	HDAC1 HDAC5	↓↓	↓

Fig5. MMP2 Histone acetylation (chromatin immune precipitation assay)



Conclusion

▸ We assume that the lasting medial hypertrophy and renin elevation after stopping salt loading were caused by the increased expression of MMPs along with histone acetylations by the salt loading.

▸ Decreased expressions of Sirts and HDACs were suggested to be involved in the enhancement of the histone acetylations by the salt loading.

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