Chronic Kidney Disease. Pathophysiology, Progression & risk factors.
MP 271

Histamine Is Involved in the Pathophysiology of Heart and Kidney Dysfunctions in Mice.

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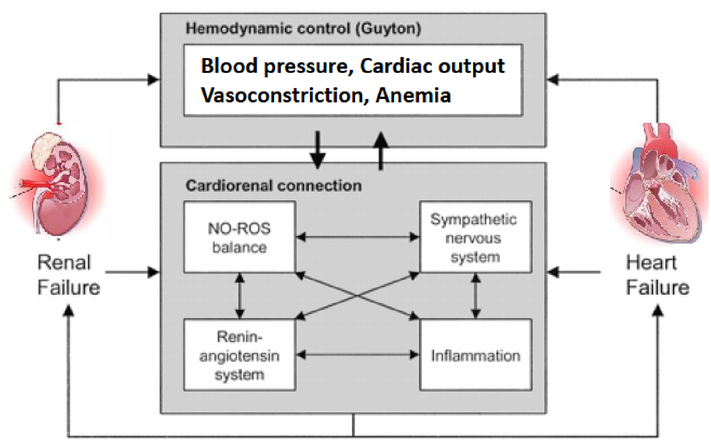
Background

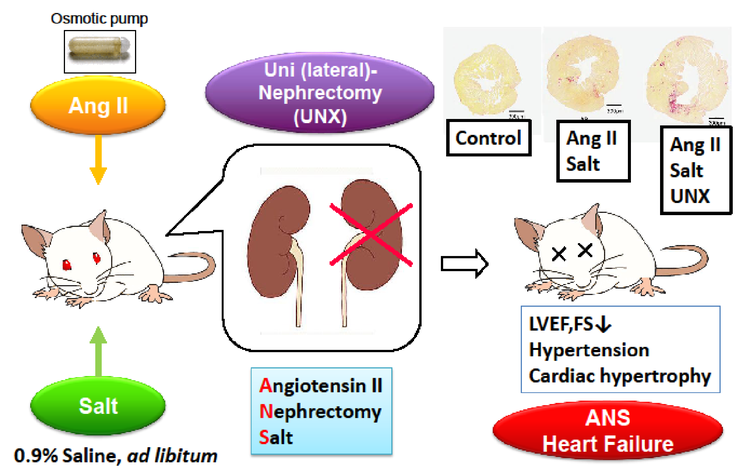
Cardiovascular disease (CVD) is one of the most important clinical issues in the world for its serious symptoms and expensive medical costs in patients. In association with this problem, chronic kidney disease is known as a high risk factor for CVD. However, the pathophysiological relationship between heart and kidney dysfunctions is still largely unknown because of lacking the detailed molecular basis. Recently, it is reported that the co-treatment of angiotensin II, nephrectomy and salt (ANS) results in hypertension-induced severe cardiac dysfunctions in mice. In this model, angiotensin II was administrated to induce hypertension, nephrectomy was treated to reduce kidney function, and salt was given to overload the body-fluid-volume. Therefore, the aim of this study is to search factors involved in the interaction between heart and kidney dysfunctions using ANS-treated mouse model as a novel pre-clinical model.

1 Cardio-renal association



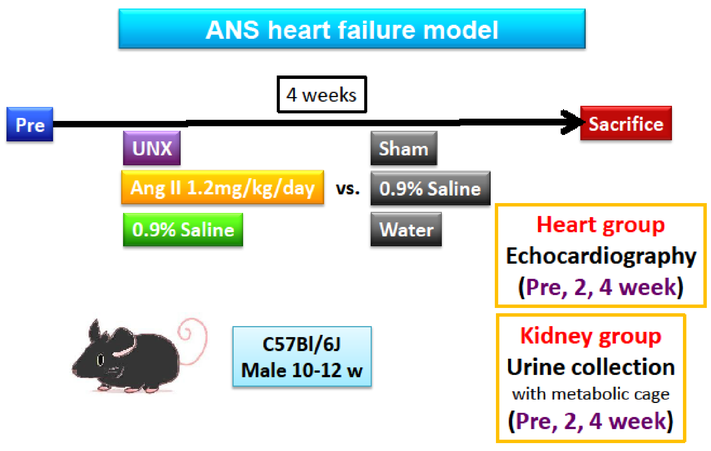
Bongartz LG *et al. Hypertension* (2004)

2 ANS heart failure model

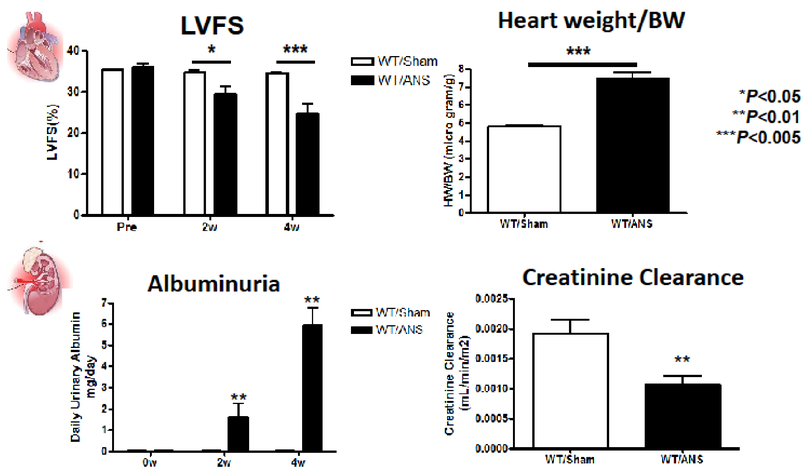


Tsukamoto *et al. Am. J. Physiol. Heart Circ. Physiol.* (2013)

3 Does ANS model show kidney disorder in addition to heart failure?

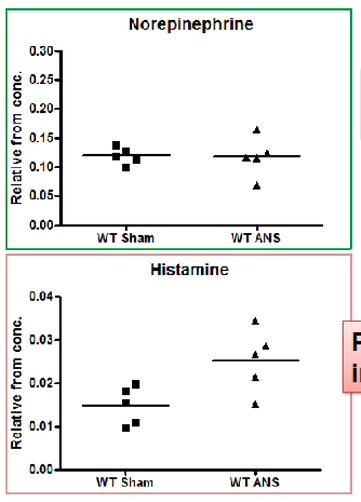


4 ANS heart failure model shows heart and kidney disorder.



5 Plasma norepinephrine level in ANS model

(analysis by LC-MS)

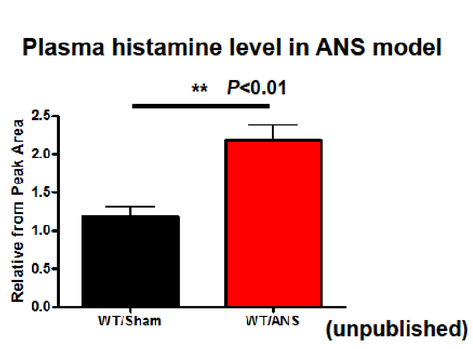


Plasma NE level is not increasing in ANS model vs. sham mice.

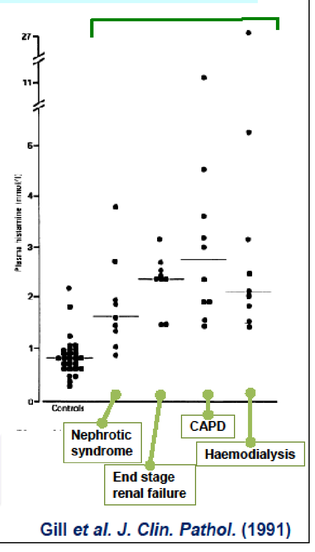
Plasma histamine level is increasing in ANS model vs. sham mice.

(unpublished)

6 Increase in plasma histamine in CKD status



(unpublished)



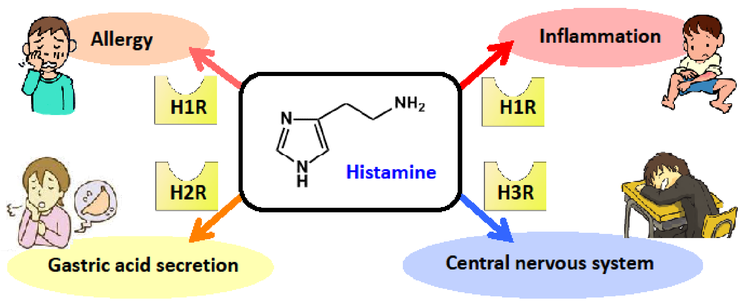
Gill *et al. J. Clin. Pathol.* (1991)

Aim of this study

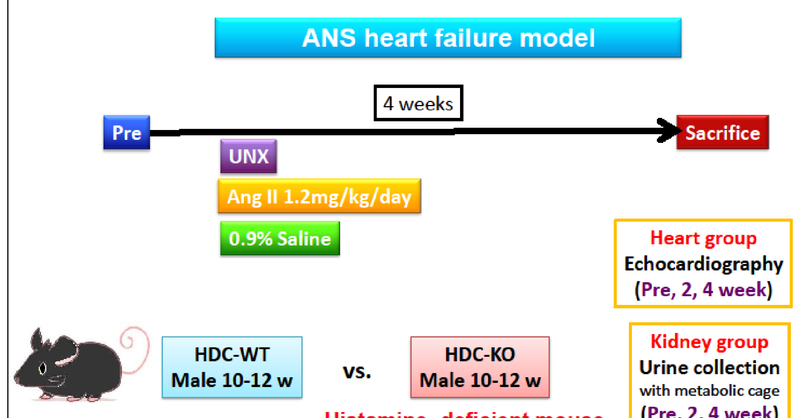
➢ To reveal the involvement of histamine in cardio-renal association using ANS model

7 What is histamine?

- Histamine is synthesized from L-histidine by histidine decarboxylase (HDC).
- Histamine has various bioactivities by connecting with histamine receptors.
- 4 types of histamine receptors as GPCR are discovered.

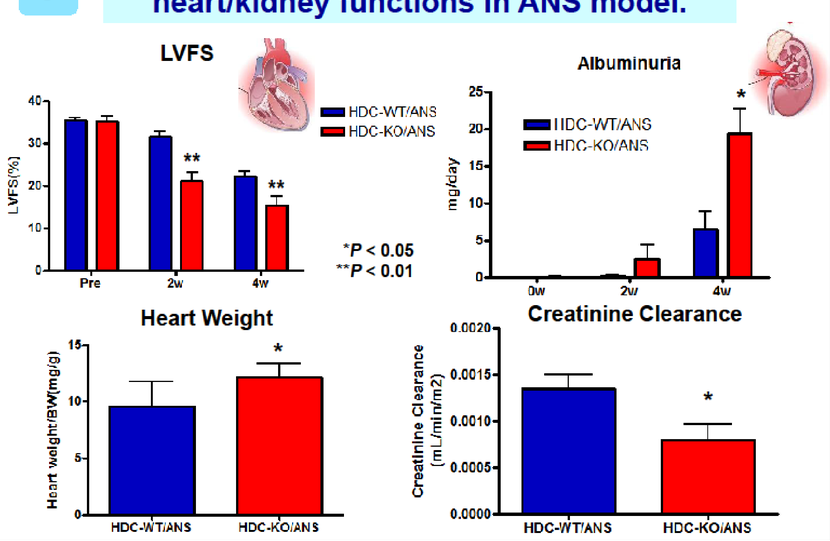


8 Whether does histamine ameliorate or deteriorate heart/kidney functions in ANS model?

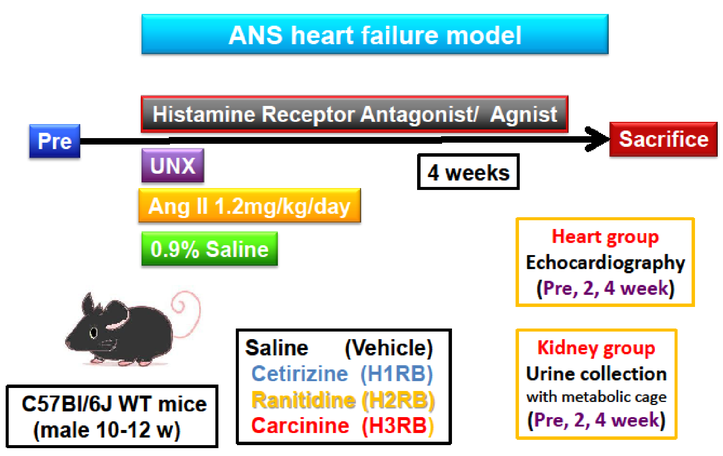


Histamine- deficient mouse
(Ohtsu H *et al.* *FEBS Lett.*, 2001)

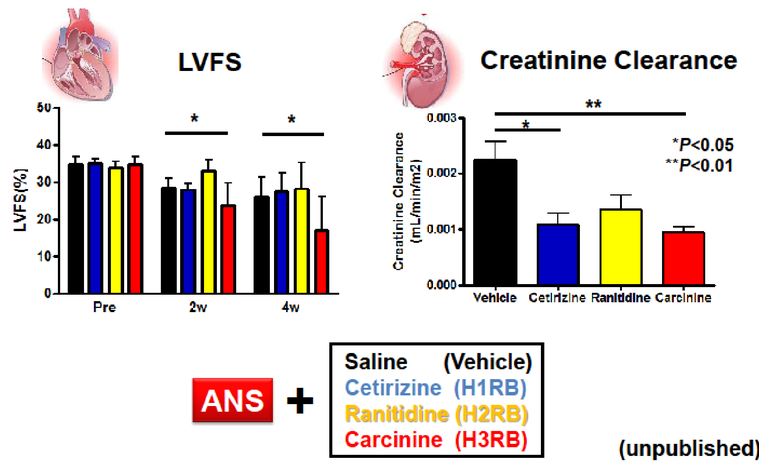
9 The lacking of histamine deteriorated heart/kidney functions in ANS model.



10 Histamine receptor blockade in ANS model

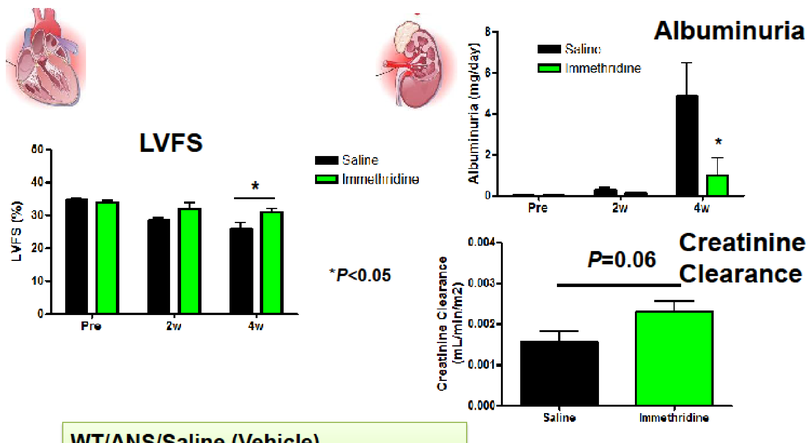


11 Deterioration of heart/kidney functions in ANS model with histamine H3 receptor antagonist



(unpublished)

12 Preservation of heart/kidney functions in ANS model with histamine H3 receptor agonist.



WT/ANS/Saline (Vehicle)
WT/ ANS/ Immethridine (H3R agonist)

(unpublished)

13 Results

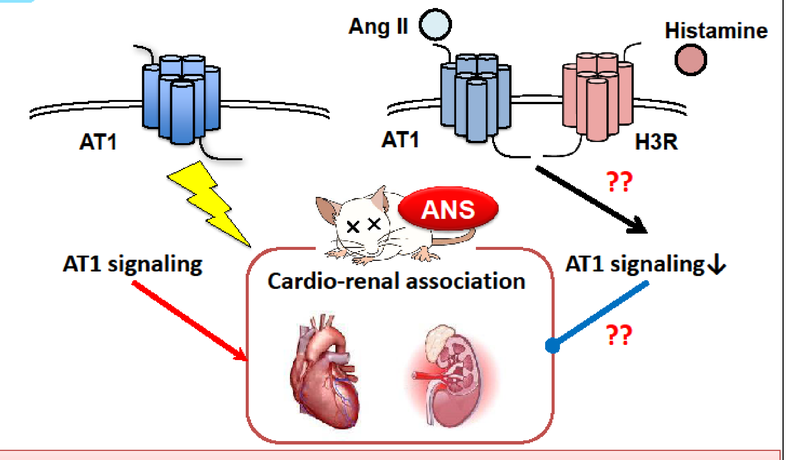
➢ ANS model exhibits deterioration of kidney function in addition to heart failure.

➢ The plasma histamine level in ANS model mouse was significantly higher than that in sham mouse.

➢ The lacking of histamine decreased heart and kidney functions in ANS model mouse.

➢ Cardiac and renal functions in ANS model were exacerbated by H3 receptor antagonist, and ameliorated by H3 receptor agonist.

14 Hypothesis



Histamine potentially has a protective role on cardio-renal association via the interaction of histamine-H3 and AT1 receptors in ANS model.

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