IRON RESTRICTION PREVENTS RENAL TUBULOINTERSTITIAL INJURY INDUCED BY ALBUMIN OVERLOAD IN MICE

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Abstract

INTRODUCTION AND AIMS: Increased excretion of proteinuria with glomerular dysfunction binds fatty acid and causes tubulointerstitial injury due to inflammatory activation in chronic kidney disease (CKD). Others and we have clarified the preventive effects of iron restriction against diabetic nephropathy and various renal injuries. In the present study, we investigated the action of iron restriction on tubulointerstitial damage induced by excess albumin overload in mice.

METHODS: An animal model of renal tubulointerstitial injury was induced by intraperitoneal injection of excess bovine serum albumin (BSA). We divided mice into 3 groups: normal saline + normal diet (ND), BSA+ND, and BSA+low iron diet (LID).

RESULTS: BSA loading induced renal tubulointerstitial injury in mice with ND, and this change was ameliorated in mice with LID. The mRNA expression of inflammatory cytokines and extracellular matrixes was augmented in kidney of BSA-mice with ND, which was inhibited by LID. BSA-induced increase of renal superoxide production and $p22^{phox}$ expression was diminished in mice with LID. LID suppressed increased of renal macrophage infiltration induced by BSA. Moreover, mice with BSA exhibited renal inflammasomes activation, and this was inhibited by LID.

CONCLUSIONS: Iron restriction suppresses albumin overload-induced tubulointerstitial injury through inhibiting inflammation, oxidative stress and inflammasomes. These results indicate that iron restriction may be a beneficial therapeutic strategy for the management of CKD.

Introduction

・The number of patients with chronic kidney disease (CKD) has been increasing worldwide, and the presence of CKD worsens morbidity and mortality.

・Proteinuria, including albuminuria, is a biomarker for CKD, is associated with renal tubular and tubulointerstitial damage and causes further progression of kidney injury and deterioration of renal function.

(Eddy A. Nephrol Dial Transplant. 2004)

・Several studies have reported the preventive effect of iron restriction against CKD such as diabetic nephropathy or hypertensive renal failure in different experimental animal models.

(Ikeda Y, et al. *Am J Physiol Renal Physiol.* 2013, Naito Y, et al. *PLOS ONE* 2013)

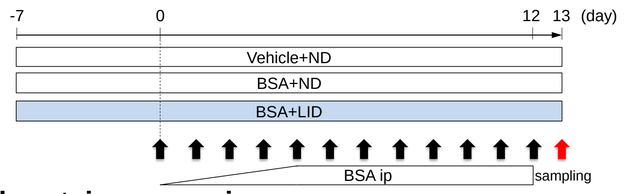
Purpose

The purpose of this study is to test the effect of iron on renal injury induced by protein overload

Methods

・Experimental animals and bovine serum albumin (BSA) treatment

The mice were randomly divided into three groups: vehicle with normal diet (ND)-fed group, BSA with ND-fed group and BSA with low iron diet (LID)-fed group. BSA of 2 mg/g body weight on the first day and was increased gradually to the maximum dose of 10 mg/g body weight on day 5, which was maintained for 7 days. Mice were given an intraperitoneal injection of BSA solution.



・mRNA expression and protein expression

mRNA and protein expression were evaluated by real-time PCR, and Western blot, respectively.

・Morphological analysis and immunohistochemistry

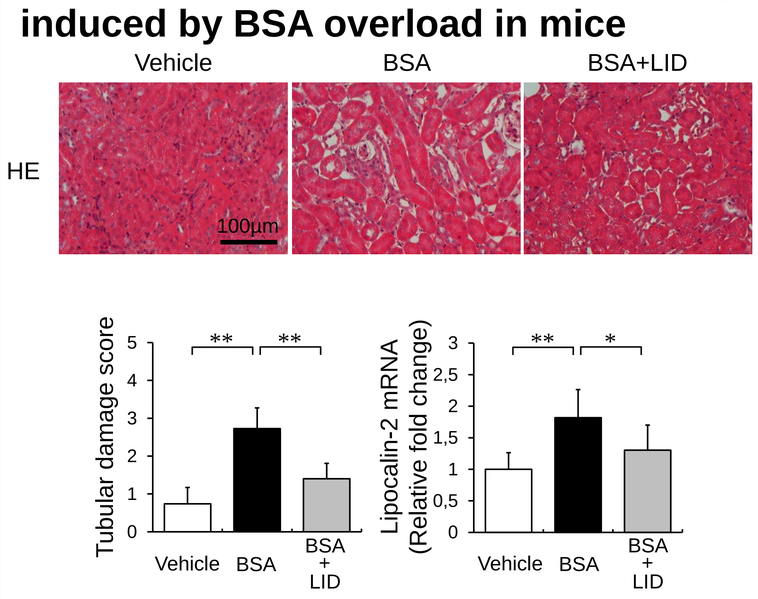
Paraffin-embedded sections were stained with hematoxylin eosin (HE) to evaluate tubular damage. Anti-F4/80 distribution was visualized to evaluate renal macrophage infiltration.

・Renal labile ferrous iron detection

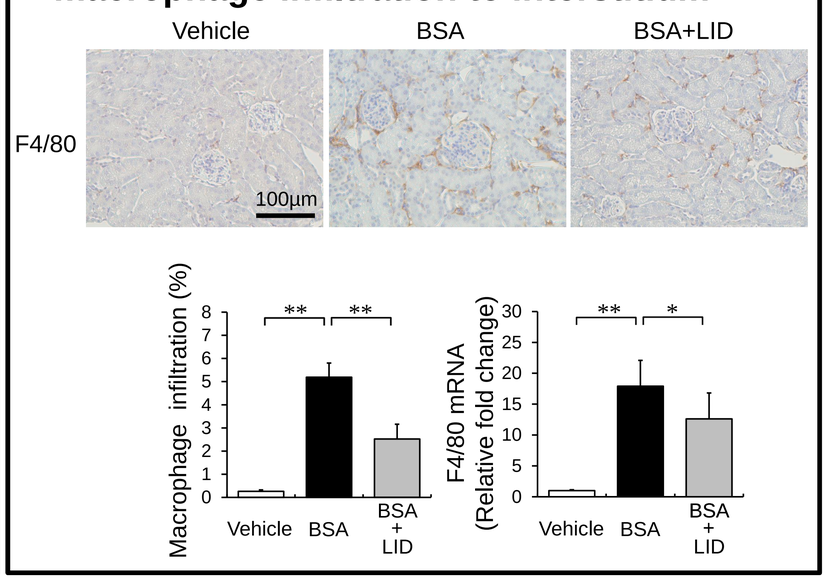
Frozen sections were stained with RhoNox-1, a ferrous iron detector.

Results

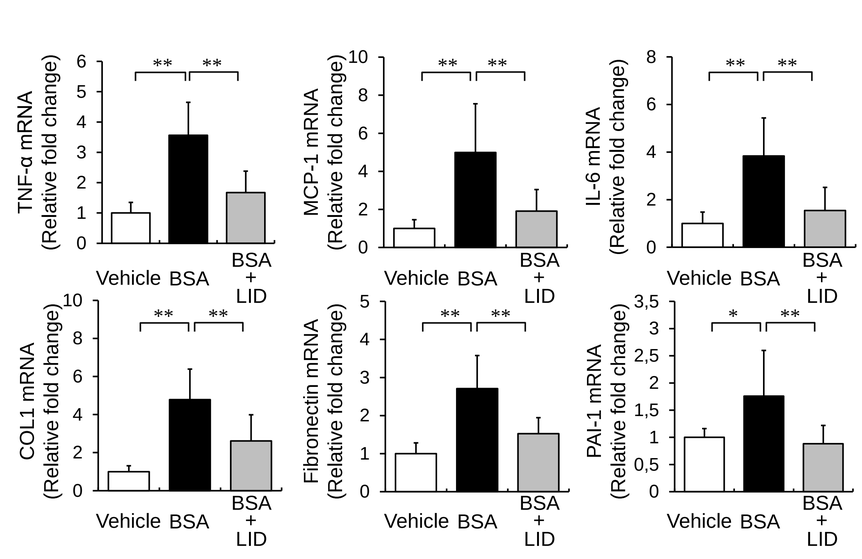
LID attenuated tubulointerstitial injury induced by BSA overload in mice



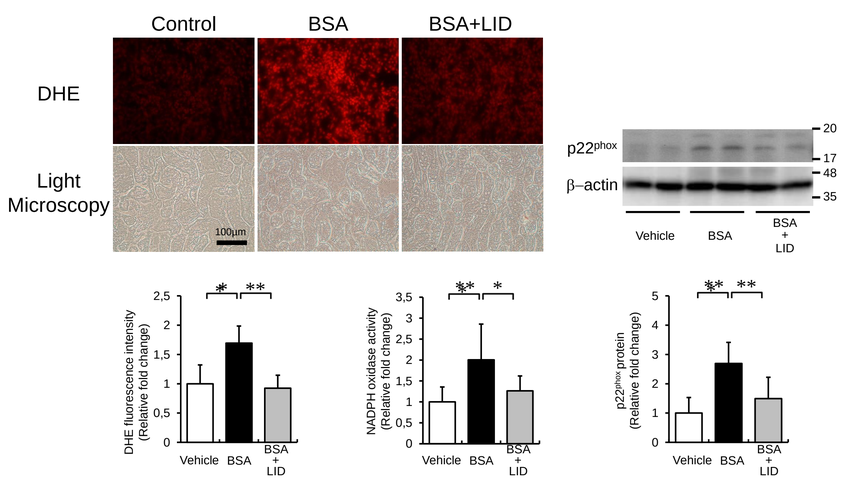
LID diminished BSA overload-induced macrophage infiltration to interstitium



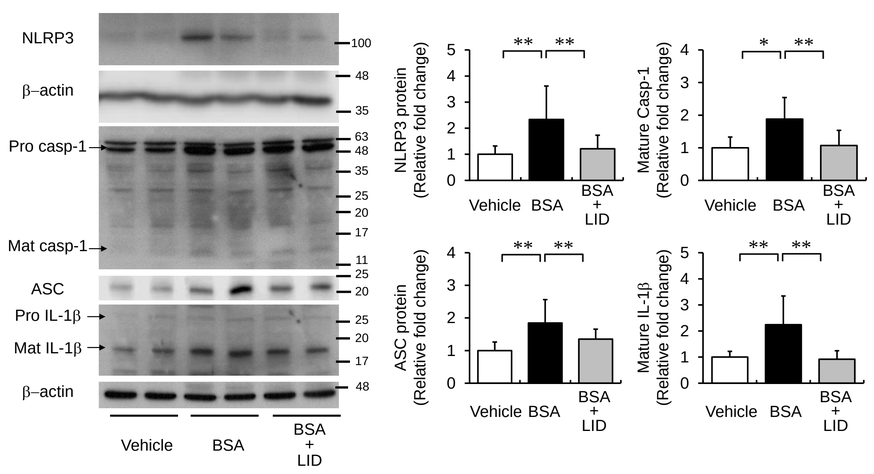
LID decreased BSA overload-induced mRNA upregulation of inflammation and fibrosis-related genes



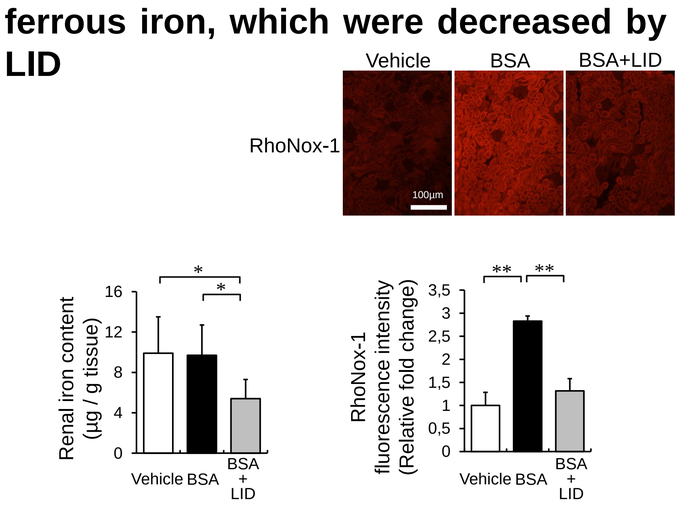
LID inhibited superoxide production, NADPH oxidase activity, and $p22^{phox}$ expression



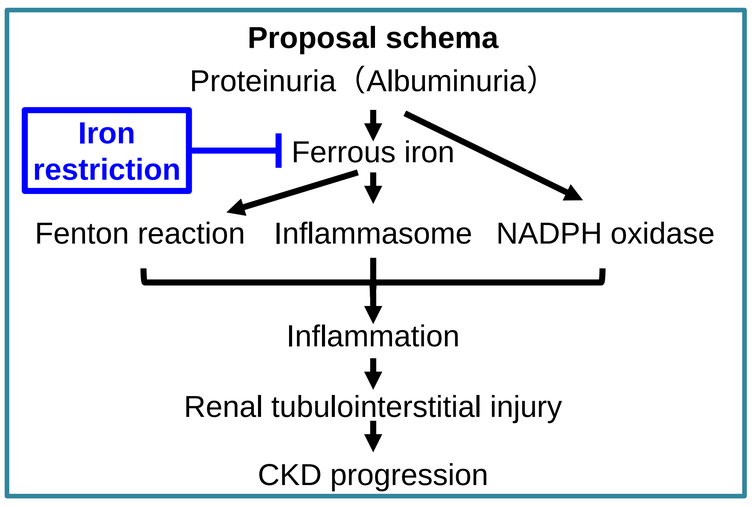
LID abolished NLRP3-inflammasome activation induced by BSA overload in the kidney



BSA overload did not change renal iron content, but augmented labile ferrous iron, which were decreased by LID



Proposal schema



Conclusion

Iron restriction protects against protein overload-induced tubulointerstitial injury by inhibiting oxidative stress and inflammation, indicating that iron restriction is a potential therapeutic strategy for CKD.

The authors have no conflict of interest to disclose with respect to this presentation.

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