Direct renin inhibition is not enough to prevent reactive oxygen species generation and vascular dysfunction in renovascular hypertension


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INTRODUCTION
Introduction

Renin-angiotensin-aldosterone system

- Angiotensinogen → Angiotensin I → Angiotensin II
- Liver
- Lungs
- Kidney
- Surface of pulmonary and renal endothelium: ACE
- Adrenal gland: cortex
- Arteriole
- Pituitary gland: posterior lobe
- Collecting duct: H₂O reabsorption
- Sympathetic activity
- Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion: H₂O retention
- Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.

Legend:
- Blue: Secretion from an organ
- Plus: Stimulatory signal
- Minus: Inhibitory signal
- Dashed: Reaction
- Dotted: Active transport
- Dashed-dotted: Passive transport

https://upload.wikimedia.org/wikipedia/commons/3/36/Renin-angiotensin-aldosterone_system.svg
Introduction

Losartan

Angiotensinogen → Angiotensin I → Angiotensin II

ARBs

AT_1 Receptor

AT_2 Receptor

Hypertension, Vasoconstriction, Vascular growth

Renin, ACE

Vasodilation, Natriuresis
no previous study has examined the effects of the direct renin inhibitor aliskiren associated with the AT1 receptor antagonist losartan on the functional alterations induced by two-kidney, one-clip (2K1C) hypertension
Introduction

Objective

To compared the effects of long term administration of aliskiren, losartan, or the combination of these drugs on vascular dysfunction found in 2K1C hypertension, which is associated with Ang II-stimulated reactive oxygen species generation.
Methods
Methods

Male Wistar rat
Weighing 180–200 g

(n=10/group)

Sham group

2K1C group

water
Losartan 10 mg/kg
Aliskiren 50 mg/kg
ALK/LOS

water
Losartan 10 mg/kg
Aliskiren 50 mg/kg
ALK/LOS
Parameter measurements

vascular reactivity to phenylephrine, acetylcholine and sodium nitroprusside

Blood pressure → Tail – cuff method

Angiotensin peptides Quantification → HPLC

Immunofluorescence to assess aortic Ang II levels
Parameter measurements

Plasma nitrite concentration

Assessment of vascular [NAD(P)H] oxidase activity and reactive oxygen species generation
RESULTS
Fig. 1 Systolic blood pressure (mmHg) measured by tail-cuff method.
**RESULTS**

**Fig. 2** Endothelial-dependent and endothelial-independent vasorelaxation induced by Ach and Nps in rat aortic rings.
**Fig. 3** Effects of different antihypertensive effects on plasma concentrations of Ang I, II and aortic angiotensin II in 2K1C rats
**Fig. 4** Effects of treatment with aliskiren and losartan on vascular reactive oxygen species production in 2K1C rats

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200μm

(B)

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DHE fluorescent intensity (Arbitrary units)
**Fig. 5** Effects of treatment with aliskiren and losartan on vascular [NAD(P)H] generation in 2K1C rats in the aortic rings.
**Fig. 6** Effects of treatment with aliskiren and losartan on plasma nitrite concentrations
**Discussion**

- **Kidney**
  - Stenosis
  - $\uparrow$ Renin
  - $\uparrow$ Angiotensin II
  - $\downarrow$ Aldosterone

  **Vasoconstriction**
  - $\uparrow$ Blood Volume
  - Hypertension

  **Adrenal Cortex**
**Conclusion**

- **Aliskiren** are not associated with prevention of hypertension-induced vascular oxidative stress and endothelial dysfunction.

- **Losartan** lowers blood pressure and promotes vascular antioxidant effects that may result in improved vascular function.

Suggest that direct renin inhibition is not enough to prevent reactive oxygen species generation and vascular dysfunction in hypertension.
ACKNOWLEDGEMENT

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Thank you for your attention