News Release

Title

Inhibition of inflammasome activation by ketone body prevents against chronic kidney disease

~It shed light on the elucidation of mechanism and development of therapy in obesity-related chronic kidney disease~

Key Points

- Adipokine, adipolin, which is downregulated by obesity, protects against chronic kidney disease.
- Adipolin protects against renal injury by reducing inflammasome activation via HMGCS2-dependent ketone body production.
- Adipolin could be a novel therapeutic target of obesity-related chronic kidney disease.

Summary

In this study, associate professor Koji Ohashi, professor Noriyuki Ouchi in Department of Molecular Medicine and Cardiology, Nagoya University Graduate School of Medicine and post graduate student Lixin Fang and professor Toyoaki Murohara in Department of Cardiology, Nagoya University Graduate School of Medicine, demonstrated the role of adipolin in obesity-related chronic kidney disease (CKD).

Although CKD is a major health problem worldwide, its underlining mechanism is incompletely understood. We previously identified adipolin as a circulating adipokine which has beneficial effects on obesity-related cardio-metabolic disorders. Because obesity is a crucial risk factor for CKD, we investigated the role of adipolin in the development of CKD. Adipolin-deficiency exacerbated urinary albumin excretion, inflammatory response and oxidative stress in injured kidney after 5/6 nephrectomy operation through inflammasome activation. Adipolin positively regulated the production of ketone body, β-hydroxybutyrate (BHB) and expression of a main catalytic enzyme producing BHB, HMGCS2 in the remnant kidney of mice after subtotal nephrectomy. Treatment of cultured proximal tubular cells with adipolin led to PPARα-dependent induction of HMGCS2 expression, thereby contributing to reduction of inflammasome activation and apoptosis. Furthermore, systemic administration of adipolin to wild-type mice with subtotal nephrectomy ameliorated urinary albumin excretion, renal apoptosis and inflammasome activation, and these renal protective effects of adipolin were diminished in PPARα deficient mice. These data suggest that adipolin protects against renal

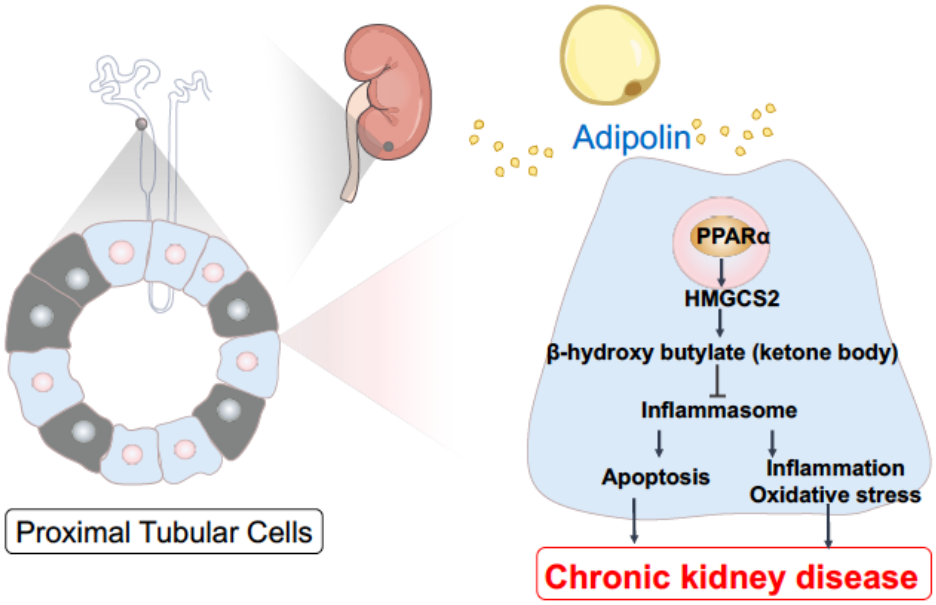
injury by reducing renal inflammasome activation through its ability to induce HMGCS2-dependent ketone body production via activation of PPARα.

Research Background

Although CKD is a major health problem worldwide, its underlining mechanism is incompletely understood. We previously identified adipolin as a circulating adipokine which has beneficial effects on cardio-metabolic diseases. Here, we investigated the role of adipolin in the development of CKD.

Research Results

Adipolin knockout (APL-KO) mice exhibited exacerbated urinary albumin excretion, tubulointerstitial fibrosis, inflammatory response and oxidative stress of injured kidneys compared with wild-type (WT) mice after subtotal nephrectomy through inflammasome activation. Adipolin increased the production of ketone body, β-hydroxybutyrate (BHB) and expression of a main catalytic enzyme producing BHB, HMGCS2 in the remnant kidney after subtotal nephrectomy. Treatment of cultured proximal tubular cells with adipolin led to PPARα-dependent induction of HMGCS2 expression, thereby contributing to reduction of inflammasome activation. Furthermore, systemic administration of adipolin to WT mice with subtotal nephrectomy ameliorated urinary albumin excretion and inflammasome activation, and these renal protective effects of adipolin were diminished under conditions of PPARα-deficiency.



The mechanism of protective effect of adipolin against chronic kidney disease

Research Summary and Future Perspective

Adipolin protects against renal injury by reducing renal inflammasome activation through its ability to induce HMGCS2-dependent ketone body production via activation of PPARα.

We aim to identify adipolin receptor and lead to drug identification of obesity-related CKD.

In addition, inflammasome inhibition will be a novel therapeutic target of CKD. Furthermore, increase in ketone body production by new drug or diet could be a novel therapeutic target of CKD.

Publication

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