Hypertensive Nephropathy

0002
Analysis of Risk Factors in Hypertension Patients with Chronic Kidney Disease Stage 5
Li Qiu Yue, Chen Qin Kai
The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China

Objective: To analyse the risk factors for hypertension patients with chronic kidney disease stage 5 (CKDS).

Methods: Collecting 390 hypertension patients with CKDS, recording the basic information. Gender, age, primary disease, dialysis method, BMI, complications (hyperlipidemia, high uric acid, cardiac insufficiency), level of education, PTH were first examined by using univariate analysis. Univariate variables that showed statistical significance were then subjected to the multivariate analysis (logistic regression) to identify the risk factors for hypertension patients with CKDS; evaluating the level of DDD according to hypertension segmented standard.

Results: Overall hypertension control rate is 22.8%. (1) Univariate analysis showed the following variables had significant differences: >40 years old, male, diabetic nephropathy, hypertensive nephropathy, hemodialysis, hyperlipidemia, high PTH (P<0.05). (2) Logistic multivariate analysis showed that diabetic nephropathy, hyperlipidemia, high PTH were the major risk factors for hypertension patients with CKDS. (3) In hypertension segmented standard, the level of DDD was no different between 0 and 1 standard (P>0.05). DDD of 2 and 3 paragraphs were increased significantly compared with 0 and 1 paragraphs (P<0.05).

Conclusion: Overall hypertension control rate is only 22.8% in hypertension patients with CKD 5. Diabetic nephropathy, hyperlipidemia and high PTH are independent risk factors in hypertension patients with CKDS.

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0039
ACE2/Mas Double Deficiency Promotes Angiotensin II-Induced Renal Fibrosis by Enhancing the ERK1/2 MAPK-Smad3 Crosstalk Pathway
J. Ni1, X. R. Huang1, J. X. Meng2, H. Y. Lan1
1Department of Medicine and Therapeutics, Li Ka Shing Institute of Health Sciences, CUHK Shenzhen Research Institute, The Chinese University of Hong Kong, Hong Kong, China
2Medical Research Center of Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

Objective: Angiotensin II (Ang II) has been recognized as a key mediator in chronic kidney disease (CKD), particularly in hypertension-associated nephropathy. Increasing evidence shows that the angiotensin-converting enzyme 2 (ACE2)/Ang1-7/Mas receptor (Mas) axis plays a protective role in CKD by counter-regulating the pathogenic actions of the ACE/Ang II/Ang II type 1 receptor (AT1) axis. In this study, we investigated the role and underlying mechanisms of the ACE2/Ang 1-7/Mas axis in Ang II-mediated renal injury.

Methods: A mouse model of hypertension was induced in ACE2 knockout (KO), Mas KO, double ACE2/Mas KO and their littermate wild-type (WT) mice by subcutaneous infusion of Ang II (1.0 mg/kg/day) or control saline for 28 days via osmotic mini-pumps. Blood pressure, serum creatinine (Scr) and creatinine clearance (Ccr), renal fibrosis including α-SMA and collagen matrix deposition, and signaling pathways related to Ang II-mediated renal injury were examined.

Results: Deletion of ACE2 or Mas developed higher levels of blood pressure compared to WT mice, which was further increased in mice with double ACE2/Mas deletion at day 7 after Ang II infusion. Moreover, compared to single ACE2 or Mas KO mice, mice with double ACE2/Mas KO developed more severe hypertensive nephropathy as demonstrated by higher levels of Scr, a fall in Ccr, and progressive renal fibrosis with a marked accumulation of α-SMA+ myofibroblasts and collagen I matrix. Further study revealed that the development of more severe kidney injury in double ACE2/Mas KO mice was associated with enhanced AT1-dependent activation of ERK/MAP kinase-Smad3 crosstalk pathway.

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Conclusion: Double knockout of ACE2/Mas largely promotes Ang II-induced hypertensive nephropathy. Enhanced activation of AT1-dependent ERK/MAPK-Smad3 signaling may be a mechanism by which disruption of the ACE2/Ang1-7/Mas axis enhances Ang II-induced renal fibrosis.

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0044
Supplementation with Aspartic Acid Increases Renal Nitric Oxide and Attenuates Salt-sensitive Hypertension in Dahl Salt-sensitive Rats
Entai Hou, Le Wang, Fuchang Zhang, Zhongmin Tian
Xi'an Jiaotong University, Xi'an, China

Objective: NO deficiency is associated with development of salt-sensitive hypertension. NO production is limited by the capacity of the kidney to regenerate endogenous arginine through the citruline-NO pathway. High salt loading causes a deficiency in arginine availability which affects NO synthases in Dahl salt-sensitive (SS) rats. However, it is not clear why arginine in the kidney of SS rats reduced with high salt diet. Our previous research found that the activity of fumarase was lower in the kidney of SS compared with SS.13BN rats. The current study will determine whether decreased renal fumarase activity is associated with decreased endogenous arginine synthesis and whether aspartic acid supplementation has antihypertensive effects in SS rats.

Methods: The expression of the rate-limiting enzyme involved in the citrulline-NO pathway and the content of NO were measured by biochemical analysis. The level of amino acid in kidney was analysed by GC-MS. To determine whether supplementation of SS rats with aspartic acid could increase renal arginine and attenuate salt-sensitive hypertension.

Results: The results indicated that protein expression of argininosuccinate synthase (ASS1), argininosuccinate lyase and the levels of aspartic acid, arginine and NO were significantly reduced in the kidney of SS rats compared with SS.13BN rats. Reducing fumarase expression in HK-2 cells is associated with decreased endogenous arginine synthesis and whether aspartic acid supplementation has antihypertensive effects in SS rats.

Conclusion: The reduction of fumarase activity contributes to reduced arginine synthesis and elevates the blood pressure of SS rats. Increasing delivery of aspartic acid to SS rats may be a novel way of supporting renal arginine availability.

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Mitochondria Dysfunction in Renal Medulla and Cortex Contribute to Salt-Induced Hypertension in SS Rats
Wang Zhenjun, Sun Na, He Liqin, Tian Zhongmin
Xi’an Jiaotong University, Xi’an, China

Objective: The kidney plays a critical role in the normal control of arterial blood pressure and in its elevation in salt induced hypertension. Mitochondrial dysfunction has been increasingly associated with the development of hypertension. Here, we aimed whether mitochondrial dysfunction occurs in renal medulla and cortex before hypertension and involves in the elevation of blood pressure of SS rats.

Methods: Mitochondria were isolated from renal medulla and cortex of the SS and SS.13BN rats on 0.4% NaCl diet and the ATP production rate were determined.

Results: The results showed that the activities of fumarase, isocitrate dehydrogenase, and ketoglutarate dehydrogenase were decreased in renal mitochondrial of SS rats compared with SS.13BN rats. The production rate of ATP in SS was lower than that in SS.13BN rats (0.326 ± 0.030 in SS vs. 0.439 ± 0.050 μmol ATP/min/μg protein in SS.13BN medulla), and the ATP production rate were further decreased in SS rats with a high salt diet. Meanwhile, lower levels of purine nucleotides and higher levels of amino acids, including L-alanine, L-leucine, L-valine and DL-isoleucine were observed in SS rats’ mitochondria. Further dietary intervention experiments demonstrated that exogenous ATP supplements in the water significantly attenuated hypertension (126 ± 2 mmHg ATP vs. 136 ± 3 mmHg in SS rats after 10 days).

Conclusion: Those data indicated dysfunction of mitochondria in renal medulla and cortex in SS rats. And current research suggests that the decreased of renal mitochondrial energy metabolism may contribute to salt-induced hypertension in SS rats.

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0058
Reduction of Polyamine Depletion Protects Against Renal Tubulointerstitial Fibrosis Induced by Hypertensive Nephropathy
Rong Li, Arthur C. K. Chung, Hui Y. Lan
1Hong Kong Baptist University, Kowloon Tong, Hong Kong
2Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong
3Department of Nephrology, First People’s Hospital of Yunnan Province, Yunnan, China

Hypertensive nephropathy is the leading cause of chronic kidney disease, second to diabetic nephropathy. Angiotensin II (AngII) induces tubulointerstitial fibrosis, a hallmark of hypertensive nephropathy. Our laboratory previously reported that suppressing Azin1 via a Smad3-dependent miR-433 pathway not only depletes cellular polyamine levels but also forms a positive-feedback loop of TGF-β1 signaling. This study aimed to investigate the role of polyamines in AngII-mediated hypertensive nephropathy. Results from in vitro studies demonstrated that treatment of AngII on rat epithelial cells, NRK52E, depleted the cellular polyamine levels and regulated expression of Azin1, antizyme and miR-433. Depletion of polyamine enhanced AngII-induced expression of pro-fibrotic genes and activation of TGF-β1 signaling while treatment with polyamine abolished such effects. The reduction of polyamine depletion by overexpressing Azin1 and suppressing either antizyme or miR-433 inhibited AngII-induced fibrosis and activation of TGF-β1 signaling. These findings were further validated in a mouse model of hypertensive nephropathy. At four weeks after nephrectomy, the renal polyamine depletion was positively correlated with miR-433 expression but negatively correlated with Azin1. Restoring Azin1 expression or suppressing miR-433 in remnant kidneys was capable of reducing the renal polyamine depletion, blocking renal interstitial fibrosis, and inhibiting TGF-β1/Smad 3 signaling. In addition, the reciprocal renal expression of miR-433 and Azin1 was observed in patients with hypertensive nephropathy. In conclusion, regulating cellular polyamine levels via Azin1 and miR-433 is a new pathway for AngII to induce renal fibrosis and demonstrates a protective role of polyamines in renal injury.

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