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Original Article

Idebenone protects the kidneys of rats with renovascular arterial hypertension by inhibiting oxidative stress and apoptosis

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Abstract

Here, the protective effect of antioxidant Idebenone (IDB) on renovascular hypertension was studied. The two-kidney one-clip (2K-1C) model of renal hypertension was established. The rats were divided into 3 groups: sham-operation group, 2K-1C renal hypertensive rats' model group and model treated with IDB group. The mean arterial blood pressure (MBP) of rats was measured and pathological condition of kidney was observed by H&E staining. The change of renal damage biomarkers (Cre, BUN, urine proteins), inflammatory factors (IL-6, IL-1β and TNF-α), oxidative stress ratio and key factors (MDA, SOD and CAT) were assessed by kits. The apoptosis key proteins (BAD, BAX, Caspase9, GSK-3β) were detected via Western blot. The 2K-1C model of renal hypertension was established. IDB reduced the MBP, Cre, BUN, urine proteins and improved the pathological condition of 2K-1C kidney. IDB restrained the inflammation factors (IL-6, IL-1β and TNF-α) and oxidative stress in kidney of renal hypertensive rats' model. Besides, IDB suppressed the expression of apoptosis key factors (BAD, BAX, Caspase9, GSK-3β) in kidney of renal hypertensive rats' model. IDB protects the kidneys of rats with renovascular arterial hypertension by inhibiting inflammation, oxidative stress, and apoptosis. These findings might provide medication guidance for IDB in renovascular arterial hypertension.

Keywords: Idebenone, Renovascular arterial hypertension, Oxidative stress, Apoptosis.

1. Introduction

Hypertension is currently one of the common chronic diseases and is one of the main risk factors for cardiovascular and cerebrovascular diseases [1]. The current global population of hypertensive individuals has exceeded 972 million with constantly increasing number [2]. Hypertension caused by renal parenchymal or renal vascular lesions, including renal artery stenosis, is called renal hypertension, which ranks first in secondary hypertension and is usually more malignant than primary hypertension [3]. Due to renal artery ischemia, it causes renal ischemia, activates the renin-angiotensin-aldosterone-system (RAAS), retention of water and sodium, contraction of peripheral arteries, and elevation of blood pressure [4]. Long-term renal artery hypertension causes intraglomerular hypertension, high perfusion, and high filtration, which accelerates glomerular arteriosclerosis and fibrosis, further exacerbating kidney damage [5,6]. Therefore, ideal drugs for treating renal hypertension should be able to effectively control blood pressure, reduce proteinuria, and protect renal function.

Idebenone (IDB) is a derivative of coenzyme Q10 (CoQ10) with the same benzene ring, which acts as a transport protein in the electron transport chain of mitochondria [7]. IDB also is an FDA-approved antioxidant used to treat neuronal oxidative stress disorders [8]. IDB can improve non-respiratory oxidation and inhibit the generation of free radicals and peroxidized lipids [9,10]. This drug belongs to the class of mitochondrial function-activating drugs that can effectively alleviate oxidative damage to cell mitochondria [11]. After medication, it can improve symptoms of ischemia [2], enhance energy metabolism [13] in patients, and prevent lipid peroxidation reactions of free radicals on mitochondrial membranes [14]. Most importantly, it was reported that IDB can inhibit the development of stroke and renal vascular lesions in hypertensive rats [15]. Nevertheless, its effect on renal hypertension remains elucidated.

At present, the two kidney one clip (2K-1C) model of renal hypertension is widely used to simulate human renal hypertension in experimental studies due to its pathological changes that are similar to human unilateral renal artery stenosis [16]. This study aimed to utilize 2K-1C renal hypertension rats' model to observe the protective effect of IDB on the kidneys. The mean arterial blood pressure (MBP), concentration of renal damage biomarkers (Cre, BUN, urine proteins), inflammatory factors (IL-6, IL-1β and TNF-α), oxidative stress ratio and key factors (MDA,

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SOD and CAT), apoptosis key proteins (BAD, BAX, Caspase9, GSK-3β) were assessed. Then pathological condition of kidney was also observed. For the first time, this study reveals the protective effect of IDB on kidney of rats with renovascular arterial hypertension.

2. Materials and methods

2.1. Animal and groups

9 SD male mice weighing 180 ± 20 g were fed and raised in an environment with a temperature of 23-26℃ and a humidity of 45-55%, with normal diet and water intake. The rats were divided into sham-operation group (sham), 2K-1C renal hypertensive rats' model group (model) and model treated with Idebenone group (model+IDB) (i.g. IDB: 0.75 g/kg/d) (N=3). All the animal experiments were approved by the Animal Care Ethics Committee of Nanping First Hospital Affiliated to Fujian Medical University. All the animals' experiments complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals.

2.2. Two kidney one clip (2K-1C) model of renal hypertension

After one week of adaptive feeding, the rats were fasted for 12 h without water, weighed, and anesthetized with 300 mg/kg chloral hydrate intraperitoneally. They were fixed in a supine position. After disinfecting the skin of rats with iodine, we cut them longitudinally along the midline of the lower abdomen. Forceps were used to remove the abdominal tissue, left kidney and left renal artery were observed, the left renal artery was bluntly separated, a 0.2 mm silver clip was inserted into the left renal artery to narrow it, and then the muscle layer and cortex of the rats were sutured layer by layer. The entire process was sterile. The surgical method of sham group was the same as above, but the left renal artery was bluntly separated without inserting a silver clip to narrow it. After the surgery, 80000 units of penicillin sodium were injected into the muscles of the hind limbs of all rats for 5 consecutive days. Before awakening, the rats should be kept warm, and after awakening, they should eat and drink freely.

2.3. Measurement of blood pressure

The blood pressure of each group of rats was measured using a non-invasive blood pressure monitor after administration, once per week, for 4 consecutive weeks. Rats were placed in a non-invasive blood pressure measuring device. After the blood pressure and heart rate lines of the rats were stabilized, the tail artery blood pressure of the rats was measured. 6 measurements of blood pressure were collected each time, and the average of the last 3 measurements to represent the blood pressure of the rats.

2.4. Biochemical tests

The creatinine (Cre) kit, blood urea nitrogen (BUN) kit and urinary protein (PRO) kit, interleukin 6 (IL-6) kit, interleukin 1β (IL-1β) kit and Tumor Necrosis Factor-alpha (TNF-α) kit, Malondialdehyde (MDA), Superoxide dismutase (SOD) and Catalase (CAT) assay kit were purchased from Nanjing Jiancheng Bioengineering Institute. The concentration of the Cre, BUN, PRO, IL-6, IL-1β, TNF-α, MDA, and activity of SOD and CAT were measured according to the instructions of detection kits.

2.5. Flow cytometry detection of ROS

DCFH-DA was diluted with serum-free culture medium at a ratio of 1:1000 to a final concentration of 10 μM. Then DCFH-DA was added to the renal tissue homogenate. The mixture was incubated in a 37℃ incubator in dark for 30 mins, and mixed upside down every 5 mins to ensure full contact between the probe and the cells. The samples were washed 3 times with serum-free culture medium. Then, the sample was detected by flow cytometry (Ex= 488 nm and Em= 525 nm).

2.6. H&E staining

The left and right kidneys of the rat were obtained and photographed, and the kidneys were quickly separated. The kidneys were fixed in 4% paraformaldehyde for 24 h and then embedded in paraffin for preservation. The 4 μm paraffin sections were dewaxed to water and stained with hematoxylin for 4 min before washing off the staining solution. After being differentiated by hydrochloric acid alcohol for 4 s, the slices were washed with water. Next, the slices were washed with water after being returned to blue with ammonia solution for 40 s. The slices were transparent with xylene and sealed with neutral gum.

2.7. TUNEL assay

Kidney samples were embedded and sliced. Then it was dewaxed with xylene and different concentrations of ethanol. Then the sample was repaired by protease K and incubated at 37℃ for 30 mins. The sample was immersed in a 3% hydrogen peroxide blocking solution and sealed at room temperature for 20 mins. An appropriate amount of biotin labeling solution was added to the sample and placed in a 37℃ incubator for 60 mins. Streptavidin HRP working solution was added to the sample and react 30 mins. DAB working solution was added. The slides were immersed in hematoxylin staining solution for 5 mins, dehydrated with anhydrous ethanol for 7 mins, dried, and sealed with neutral gum

2.8. Western blot

Approximately 30mg of renal cortex tissue was added to lysis buffer (10 mg: 1000 uL), and centrifuged before taking the supernatant to measure protein concentration. The protein was subjected to SDS-PAGE electrophoresis and then transferred to PVFD membrane, followed by washing the imprinting membrane with TBST solution. Samples were placed in a 5% skim milk powder blocking solution, diluted with primary antibody, and placed overnight at 4℃. The next day, it was placed in the secondary antibody and incubated on a shaking table at room temperature for 1 h. GAPDH was used as an internal reference protein to standardize various target bands. The antibody used in this experiment was listed as follow: Bax (Abcam, Cambridge, MA, USA, ab182733,1:2000), BAD (Proteintech, Rosemont, IL, USA, 10435-1-AP, 1:3000), GSK-3β (Proteintech, Rosemont, IL, USA, 22104-1-AP, 1:8000), caspase-9 (Proteintech, Rosemont, IL, USA, 10380-1-AP, 1:1000), GAPDH (Proteintech, Rosemont, IL, USA, 60004-1-Ig, 1:40000), HRP-conjugated Affinipure Goat Anti-Mouse IgG(H+L) (proteintech, Rosemont, IL, USA, SA00001-1). The developer solution was added and then placed in a BIO-RAD (Hercules, CA, USA) for visualization.

2.9. Statistical analysis

GraphPad Prism software version 8.0 (La Jolla, CA, USA) was used to analyze data. Student's t-test was utilized to compare data from different groups. P-values < 0.05 were considered statistically significant.

3. Results

3.1. Idebenone protects the kidneys of rats with renovascular arterial hypertension

To begin with, the 2K-1C (Two-kidney one-clip) renal hypertensive rats' model was established for the following experiments (Figure 1A). After the 2K-1C model was successfully constructed, the mean arterial blood pressure (MBP) during 4 weeks was measured once a week. Before administration, compared with the sham-operation (sham) group, the MBP in the model group was significantly increased; After treatment with Idebenone (IDB) for 4 weeks, the MBP in the IDB group decreased significantly compared with model group (P < 0.001) (Figure 1B). Furthermore, the concentration of Cre, BUN and urinary protein was increased in model group vs sham group, while decreased in IDB IDB-treated group vs model group (Figure 1C).

The pathological staining (H&E staining and Masson staining) of kidneys presented that renal tissue of sham group showed normal glomerular morphology, with abundant capillary plexus enclosed in the renal capsule. The renal interstitium and tubular tissue structure in sham group were also normal. In contrast, in the model group, there was significant interstitial fibrosis of the renal units (glomeruli and tubules), with enlarged glomerular sacs and dilated tubules. The above symptoms in the IDB treatment group were significantly improved (Figure 1D). In sum, these results revealed that Idebenone protects the kidneys of rats with renovascular arterial hypertension.

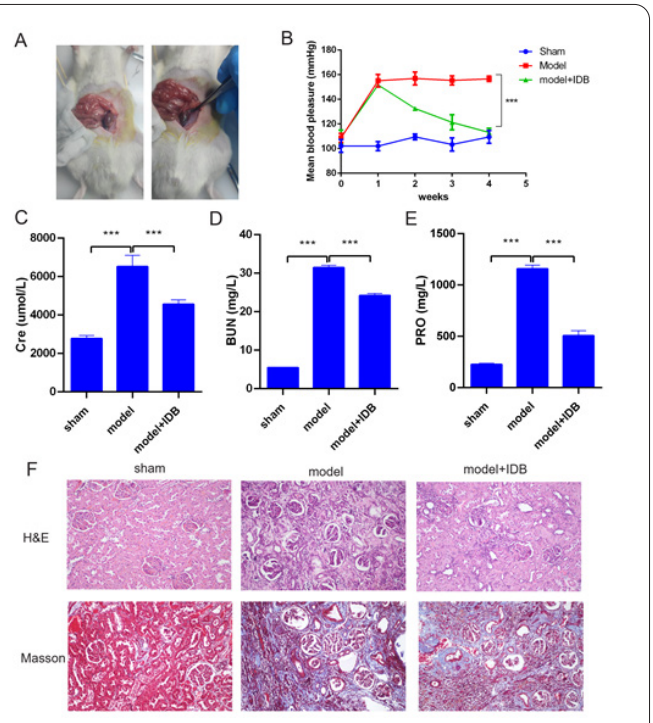

Fig. 1. Idebenone protects the kidneys of rats with renovascular arterial hypertension. (A) The representative images were taken during the process of establishing the 2K-1C (Two-kidney one-clip) renal hypertensive rats' model. (B) The change of mean arterial blood pressure during 4 weeks in sham-operation group (sham), 2K-1C renal hypertensive rats' model group (model) and model treated with Idebenone group (model+IDB). (C-E) The concentration of creatinine (Cre), blood urea nitrogen (BUN) and urinary protein (PRO) in sham, model, and model+IDB groups. (F) The pathological staining (H&E staining and Masson staining) of kidneys in sham, model, and model+IDB groups. N=3, *** P < 0.001.

3.2. Idebenone restrains the inflammation and oxidative stress in kidney of renal hypertensive rats' model.

In the next step, the underlying mechanism of Idebenone was further investigated. The concentration of inflammatory factors was measured. The concentration of IL-6, IL-1β and TNF-α was enhanced in model group vs. sham group, while lessened in model+IDB group vs model group (P<0.001) (Figure 2). These evidences indicated that IDB restrained the inflammation in kidney of renal hypertensive rats' model. Besides, the ROS was detected to enhanced in in model group vs. sham group, while reduced in model+IDB group vs model group (P<0.001) (Figure 3A). At the same time, the products of intracellular lipid peroxidation-MDA were also increased in model group vs. sham group, while reduced in model+IDB group vs model group (P<0.001) (Figure 3B). In contrast, the SOD and CAT were presented higher-activity in model group vs. sham group, while showed lower-activity in IDB treated group vs. model group (Figure 3C-3D). These results indicated that Idebenone restrains the oxidative stress in

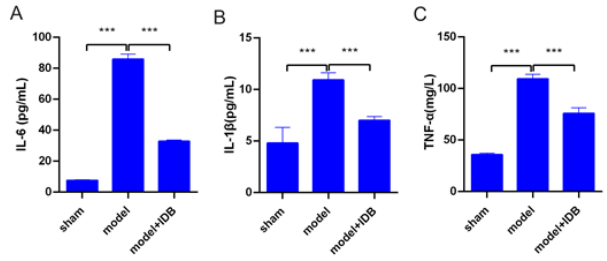

Fig. 2. The Idebenone suppresses the inflammation in kidney of renal hypertensive rats' model. (A-C) The concentration of IL-6, IL-1β and TNF-α in sham-operation group (sham), 2K-1C renal hypertensive rats' model group (model) and model treated with Idebenone group (model+IDB). N=3, *** P < 0.001.

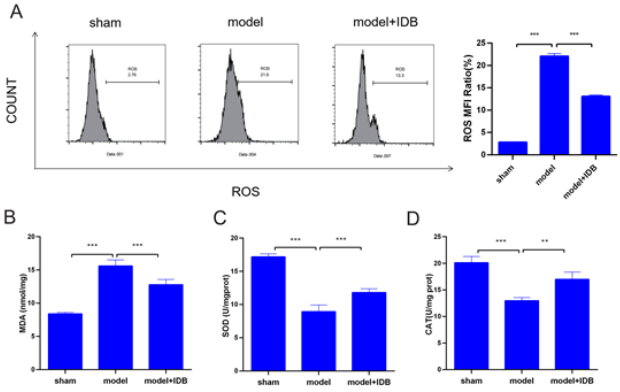

Fig. 3. The Idebenone restrains the oxidative stress in kidney of renal hypertensive rats' model. (A) The ROS (reactive oxygen species) ratio (%) in sham, model, and model+IDB groups. (B-D) The concentration of MDA (Malondialdehyde), SOD (Superoxide dismutase) and CAT (Catalase) in sham-operation group (sham), 2K-1C renal hypertensive rats' model group (model) and model treated with Idebenone group (model+IDB). N=3, ** P < 0.01, *** P < 0.001.

kidney of renal hypertensive rats' model.

3.3. The Idebenone represses the apoptosis in kidney of renal hypertensive rats' model.

Oxidative stress can induce cell apoptosis through various pathways. Since the ROS was detected to be accumulated in model group vs. sham group, we also explored the effect of IDB on apoptosis rate of in kidney of renal hypertensive rats' model. As seen in Figure 4A, the TUNEL assay showed that apoptosis was highest in model group, and the apoptosis rate in IDB treated group was improved. In addition, the protein expression level of apoptosis key factors (BAD, BAX, Caspase9, GSK-3β) was enhanced in model group compared with sham group, while decreased in model+IDB treatment group compared with model group (Figure 4B). These results indicated that Idebenone represses the apoptosis in kidney of renal hypertensive rats' model.

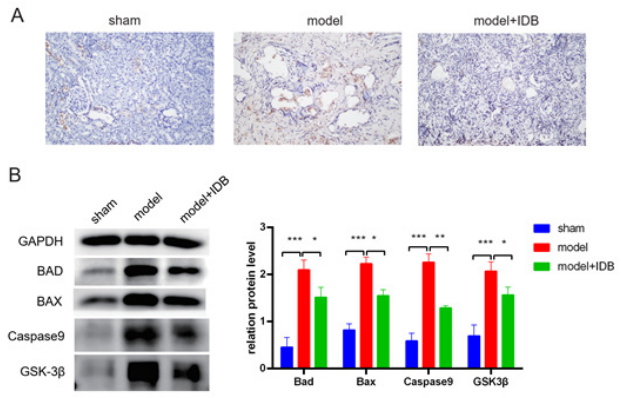

Fig. 3. Idebenone represses the apoptosis in kidney of renal hypertensive rats' model. (A) The apoptosis condition was detected by TUNEL assay. (B) The western blot was utilized to measure the expression of BAD, BAX, Caspase9, GSK-3β and GAPDH in sham, model, and model+IDB groups. The relative protein level was calculated as protein/GAPDH. N=3, * $P < 0.05$, *** $P < 0.001$.

4. Discussion

Renovascular arterial hypertension is a secondary hypertension caused by renal parenchymal or renal artery lesions[4]. Elevated blood pressure progressively worsens renal function, making it difficult to control blood pressure and leading to poor patient prognosis [17]. 2K-1C is a mature model that simulates human renal hypertension [18]. IDE is synthesized from a derivative of coenzyme Q10 [19]. Compared with coenzyme Q10, IDE has the characteristics of being more stable, less prone to oxidation, and stronger penetration [20]. In this experiment, 2K-1C model was chosen to observe the protective effect of IDB on the kidneys of renal hypertension. Besides, the influence of IDB on inflammation, oxidative stress and apoptosis were also investigated.

At present, the 2K-1C model is widely used due to its pathological changes (fibrosis and atrophy of the kidney on the side with arterial stenosis, and compensatory hypertrophy of the opposite kidney) that are similar to human unilateral renal artery stenosis [21]. In this hypertension model, RAAS is activated, and due to the narrowing of the renal artery, the blood flow perfusion of the occluded side of the kidney is reduced, resulting in an increase in plasma renin activity and angiotensin II (Ang II) levels [22]. This model constricts blood vessels, stimulates the secretion of aldosterone by the adrenergic cortex, and thus increases hypertension [18]. Therefore, in this study, we successfully established 2K-lC rats model to observe the protective effect of IDB on renal hypertension-induced renal injury.

Furthermore, if IDE has a protective effect on renal injury in 2K-1C rats, what is its underlying mechanism? IDE is a novel brain metabolism and psychiatric symptom improver, structurally similar to coenzyme Q10, with good antioxidant activity (approximately 100 times that of enzyme Q10) [23]. IDE is an FDA-approved antioxidant used in addition to treating neuronal oxidative stress disorders [8]. In addition to Parkinson's disease [24], it is also used to study the relationship between a certain disease and oxidative stress, providing new treatment ideas for some traditional diseases. IDB can improve non-respiratory oxidation and inhibit the generation of free radicals and peroxidized lipids [10]. This drug can effectively alleviate oxidative damage to cell mitochondria [25]. In our results, we found that the IDE can significantly repress the oxidative stress (MDA, SOD and CAT) of kidney in 2K-1C rats.

Oxidative stress affects some renal structures, such as glomeruli, tubules, and blood vessels [26], inducing inflammatory cells and pro-inflammatory cytokines (e.g. TNF-α) recruitment, leading to inflammation stage and later fibrosis damage to renal function [27,28]. IDB was reported to repress the inflammation in murine lupus [13], liver injury [29], and murine molitis [30]. Our results confirmed that IDB reduced the inflammation (IL-6, IL-1β and TNF-α) of kidney in rats with renovascular arterial hypertension. Apoptosis refers to the autonomous and orderly cell death controlled by genes in order to maintain the homeostasis of the internal environment [31]. Previous studies have confirmed that ROS can cause various forms of cell damage, including apoptosis [32]. Preclinical studies have shown that IDB can reduce cell apoptosis after oxidative stress injury [33,34]. Our results for the first time to reveal that IDB reduced the apoptosis key protein (BAD, BAX, Caspase9, GSK-3β) of kidney, which suggests the protective role of IDB in rats with renovascular arterial hypertension.

5. Conclusions

In sum, this study utilized the 2K-1C model to observe that IDB plays a protective role on the kidneys of renal hypertension. Besides, for the first time to learned that the IDB restrains the inflammation, oxidative stress, and apoptosis of kidneys of renal hypertension in rats. These findings might provide medication guidance of IDB in renovascular arterial hypertension.

Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

All the animal experiments were approved by the Animal Care Ethics Committee of Nanping First Hospital Affiliated to Fujian Medical University.

Informed consent
The authors declare that no patients were used in this study.

Availability of data and material
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions
Jinsen He, Lixin Huang and Linqi Lu designed the study and performed the experiments, Jinsen He and Lixin Huang collected the data, Linqi Lu analyzed the data, Jinsen He, Lixin Huang and Linqi Lu prepared the manuscript. All authors read and approved the final manuscript.

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