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Swimming Exercise Ameliorates Hypertension-Induced Kidney Dysfunction via Alleviating Renal Interstitial Fibrosis and Apoptosis

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Keywords
Hypertension · Kidney dysfunction · Exercise · Interstitial fibrosis · Renal cell apoptosis

Abstract
Background: Hypertensive nephropathy is one of the major causes of ESRD. Exercise has been considered a nonpathological therapy for hypertension and its complications, yet mechanisms remain unclear. We sought to investigate whether periodic swimming could ameliorate hypertension-induced kidney dysfunction and its underlying mechanisms. ***Methods:*** Four-week male spontaneously hypertensive rats (SHRs) were randomly divided into the hypertension group (SHR, $n = 8$) and exercise group (SE, $n = 8$, 60 min swimming/day, 6 days per week, for 8 weeks). Wistar-Kyoto rats (WKY, $n = 8$) were served as a sedentary normotensive group. Bodyweight and blood pressure (BP) were recorded weekly. After 8-week sedentary or swimming exercise, lipids profile, BUN, and Cr were measured. The renal interstitial fibrosis was examined by the histopathological analysis using Masson's trichrome staining and hematoxylin and eosin staining. The kidney cell apoptosis was tested by TUNEL staining. The expressions of critical proteins responsible for the TGF-β1/Smad signaling of fibrosis, that is, TGF-β1, Smad2/3, and Smad7, as well as apoptosis related proteins, Bax and Bcl-2 in kidney cortex tissues were measured. ***Results:*** The 8-week swimming exercise reduced BP and bodyweight, lowered concentrations of BUN, and serum Cr, compared with SHR. Exercise remarkably inhibited hypertension-induced tubular degeneration, cellular cluster, and tubular cell swelling as well as glomerular degeneration in the kidney cortical tissues, attenuated renal interstitial fibrosis, and renal cell apoptosis. Moreover, expressions of TGF-β1, Smad2/3, and Bax were higher in the SHR than the WKY, which were significantly suppressed by the exercise. In contrast, hypertension-reduced expressions of Smad7 and Bcl-2 were enhanced by the swimming exercise. Strong correlations were found between kidney function indices, blood lipids, and key protein expressions. ***Conclusion:*** Our results demonstrate beneficial effects of the periodic swimming on ameliorating hypertension-induced kidney dysfunction highlighting the potential of swimming exercise as a nonpathological therapy for early prevention of hypertension-caused kidney diseases.

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Introduction

The prevalence of hypertension is on the rise worldwide, and hypertensive nephropathy is the second leading cause of ESRD. Accumulating evidence demonstrates associations between elevated blood pressure (BP) and risk of development or progression of several noncommunicable diseases, including CKD [1, 2]. Exercise has been considered a nonpharmacological and effective treatment to control BP [3–5] and its benefits greatly extend beyond the reduction of traditional cardiovascular risk factors [6, 7]. Several studies showed that appropriate exercise improves kidney function [8–10]. Yet, underlying mechanisms of how exercises could affect hypertension-induced kidney dysfunction remain largely unexplored [11].

The renal interstitial fibrosis, characterized by an excess deposition of the extracellular matrix, has been proposed as a common pathological hallmark of progressive CKD with diverse aetiologies [12, 13]. TGF-β is well known as a central pro-fibrotic mediator in renal fibrosis, by signaling through the downstream receptor-associated Smads, including Smad2, Smad3, and Smad7 to exert its biological activities on different types of kidney cells during renal fibrosis [14–16]. In a recent study, Huang et al. [17] found that exercise training (i.e., running for 60 min/day, 5 sessions/week, and for 12 weeks) might ameliorate renal abnormalities in hypertensive rats through the downregulation of the TGF-β and p-Smad2/3 pathway. However, these receptor-associated Smads have different or even contradictorily impacts on regulating renal fibrosis [12, 14, 16], highlighting the need to have a comprehensive understanding how exercise could influence expression of different receptor-associated Smads.

Abnormal expression of TGF-β and its family members may lead to endoplasmic reticulum stress and oxidative stress and subsequently result in renal cell injury and fibrosis that contribute to progressively renal dysfunction [18–20]. The renal cell apoptosis is an important factor in the pathogenesis of CKD, which could be induced by both excessive endoplasmic reticulum stress and oxidative stress in varying renal cell types [18, 19, 21–23] [18, 19, 21, 23]. Moreover, the renal cell apoptosis has shown strong links with the process of kidney interstitial fibrosis. Chen et al. [24] reported that treadmill running exercise (i.e., 3 times per week, for a total period of 11 weeks) ameliorated doxorubicin-induced CKD particularly through the regulation of the apoptosis pathways.

In this study, we aimed to investigate whether periodic swimming could alleviate impairment of kidney structure and function caused by hypertension, possibly via beneficial impacts on the TGF-β1/Smad signaling and renal cell apoptosis. It may provide a new perspective to understand mechanisms underlying benefits of exercise in ameliorating hypertension-induced renal damage and to optimize the early prevention for development of hypertension-caused kidney diseases.

Materials and Methods

Animal Experiments

Four-week male Wistar-Kyoto rats (WKY, $n = 8$) and spontaneously hypertensive rats (SHRs, $n = 16$) were purchased from Beijing Vital River Laboratory Animal Technology Co. Ltd. (the license number: SCXK [Beijing] 2016-0006, MHC Haplotype: RT1k). SHR is the most widely studied animal model of hypertension [25–27]. All rats were housed under constant room temperature (22°C ± 1°C), humidity (60 ± 5%), and 12-h dark/light cycles, with free access to tap water and standard rat chow (Xietong shenwu, Jiangsu, China). The production standard of the standard chow refers to the standard of Jackson experiment of USA. The contents of nutrients are provided in the online suppl. Table 1 (see www.karger.com/doi/10.1159/000514680 for all online suppl. material).

Exercise Training Protocol

SHRs were randomly divided into the hypertension group ($n = 8$) and exercise group (SE, $n = 8$). Exercise training was performed in the animal tank with heated water (30 ± 1°C) for 9 weeks. The first week consisted of an adaptation period, initiated with 10 min of continuous swimming training on the first day. Swimming time was increased daily until reached to 60 min at the end of the protocol. The formal training began from the second week, and the exercise duration was kept constant (60 min/day, 6 days/week). It was maintained until the end of the training period, which lasted 8 weeks. To avoid the occurrence of acute exercise-related errors, animals rested for 48 h before being sacrificed for all additional procedures.

Assessments of Bodyweight, Blood Pressure, and Heart Rate

After 1-week adaptive feeding, bodyweight (BW) of each rat was measured weekly. Systolic (SBP)/diastolic blood pressure, mean arterial pressure (MAP), and the heart rate (HR) were evaluated in conscious rats before the training period. We applied an indirect tail-cuff method for BP analysis, conditioned to the procedure with cuff inflation-deflation cycles until the end of the exercise training protocol, using the CODA™ mouse rat tail-cuff system (Kent Scientific Corporation, Torrington, CT, USA).

Blood Collection and Biochemical Parameters Analyses

Rats were anesthetized with pentobarbital sodium and sacrificed by decapitation. Blood samples were collected from the abdominal aorta and put into water bath (37°C) for 30 min. The serum was obtained by centrifugation (12,000 *g*, 20 min) and stored under −80°C until analyses. Concentrations of BUN, serum Cr (SCr), total cholesterol (TC), total triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol

Table 1. Effects of swimming exercise on blood lipids and renal function indices in SHRs

	TC, mmol/L	TG, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	SCr, mmol/L	BUN, mmol/L
WKY	1.86±0.11	0.54±0.02[a]	0.78±0.10	0.61±0.04[a]	37.39±1.58[a]	3.56±0.19[a]
SHR	1.93±0.04	0.62±0.23[b]	0.90±0.20	0.96±0.08[b]	71.88±2.23[c]	7.04±0.26[c]
SE	1.77±0.07	0.63±0.03[b]	0.73±0.12	0.68±0.08[a]	61.25±2.07[b]	5.87±0.29[b]

Different letters indicate significances. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SCr, serum Cr; SE, SHR exercise group; SHRs, spontaneously hypertensive rats; TC, total cholesterol; TG, total triglycerides; WKY, Wistar-Kyoto rats.

(LDL-C) were assayed with the corresponding kits provided by Nanjing Jiancheng Bioengineering Institute (Nanjing, China) following the manufacturer's instruction.

Tissue Collection

After euthanization, kidneys were immediately divided into 2 parts: one part was stored in 10% formaldehyde for histopathological analysis; the other part was frozen with liquid nitrogen and was stored at −80°C.

Histologic Analysis

Kidney tissues were fixed by immersion with 10% formaldehyde at 4°C for 24 h and processed for paraffin embedding. After dehydration and embedding, tissues were sliced into 5-μm paraffin sections for hematoxylin and eosin staining and Masson staining. The renal cortex and medulla were not separated during the dissection. This procedure could protect the kidney morphology as much as possible during the dehydration and embedding process, which is beneficial to histopathological experiments [28]. Finally, all sections were visualized using an Olympus light microscope (CX31, Tokyo, Japan). Selected portions were randomly scanned, and quantitative analysis was performed using an Image-Pro Plus (Media Cybernetics, Rockville, MD, USA) analysis system at ×400 magnification.

TUNEL Staining

A terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling (TUNEL) reaction was carried out according to the manufacturer's instruction. Paraffin-embedded sections were cut to 5-μm thicknesses, followed by conventional dewaxing and rehydration. Prior to the test with TUNEL Apoptosis Assay Kit (Seven Sea Biotech Company, Guangzhou, China), sections were incubated with Proteinase K to increase permeability. Subsequently, they were scanned randomly and visualized using an Olympus inverted fluorescence microscope (IX73, Tokyo, Japan) in the darkroom.

Western Blotting

Frozen kidney cortex tissues (approximately 50 mg at −80°C) were homogenized with 1 mL of Pro-PREP lysis buffer and 1 mL protease inhibitor (Beyotime Company, Shanghai, China) in a homogenizer (Proteintech, China). The homogenate was centrifuged at 12,000 *g* for 20 min at 4°C, and the supernatant was collected as tissue sample protein, and the concentrate was determined using a bicinchoninic acid assay kit (Proteintech, China). Then, the sample was heated at 100°C for 10 min before loading and separated on precast 10% SDS-PAGE to electrophoresis. Twenty μg total protein was loaded into a single well of a 10–12% polyacrylamide gel for electrophoretic separation and subsequently transferred onto a polyvinylidene difluoride membrane (Millipore, German). The nonspecific binding to the membrane was blocked with 5% nonfat milk in TBS buffer for 1 h at room temperature. The membranes were then incubated for 16 h at 4°C with primary antibody: rabbit monoclonal anti-Smad2/3 antibody (Abcam, ab202445, 1:1,000), rabbit monoclonal antibody anti-Smad7 antibody (Bioss, bs-0566R, 1:500), rabbit polyclonal anti-TGF/β1 (Bioss, bs-0086R, 1:500) antibody, rabbit monoclone anti-GAPDH antibody (Abcam, ab181602, 1:1,000), Bcl-2 (Bioss, bsm-33411M), and Bax (Bioss, bs-0127R). After washing in TBST buffer for 5 times, the membranes were incubated for 1 h at room temperature with the HRP conjugated secondary antibody (Bioss, bs-0566R, bs40295G, 1:10,000) in blocking buffer containing 5% nonfat milk. The PVDF membranes were then washed with TBST buffer for 5 times, and SuperSignal West Femto Maximum Sensitivity Substrate (Thermo Fisher Scientific, Waltham, MA, USA) was used to detect the bands in a darkroom. The integrated optical density was measured by scanner. The sum of the integrated optical density was obtained, and the mean value calculated. Levels of TGF-β1, Smad-2/3, and Smad-7 were analyzed by Image-Pro Plus.

Statistics

Data are expressed as mean ± standard error of mean and analyzed using GraphPad prism 6.0 (GraphPad software, San Diego, CA, USA). Data were analyzed by using Student's *t* test for comparison of 2 groups and by one-way ANOVA for multiple groups. A p value <0.05 was considered significant. Spearman rank correlations between BW, BP, HR, BUN and SCr, blood lipids, and key proteins were computed. Heat map was drawn using MetaboAnalyst (www.metaboanalyst.ca).

Results

Effects of Swimming on Bodyweight, Blood Pressure, Heart Rate, and Blood Parameters

No significant difference in BW was observed between groups during the period 1–7 weeks ($p > 0.05$, shown in Fig. 1). In the eighth week, SHR showed significantly high-

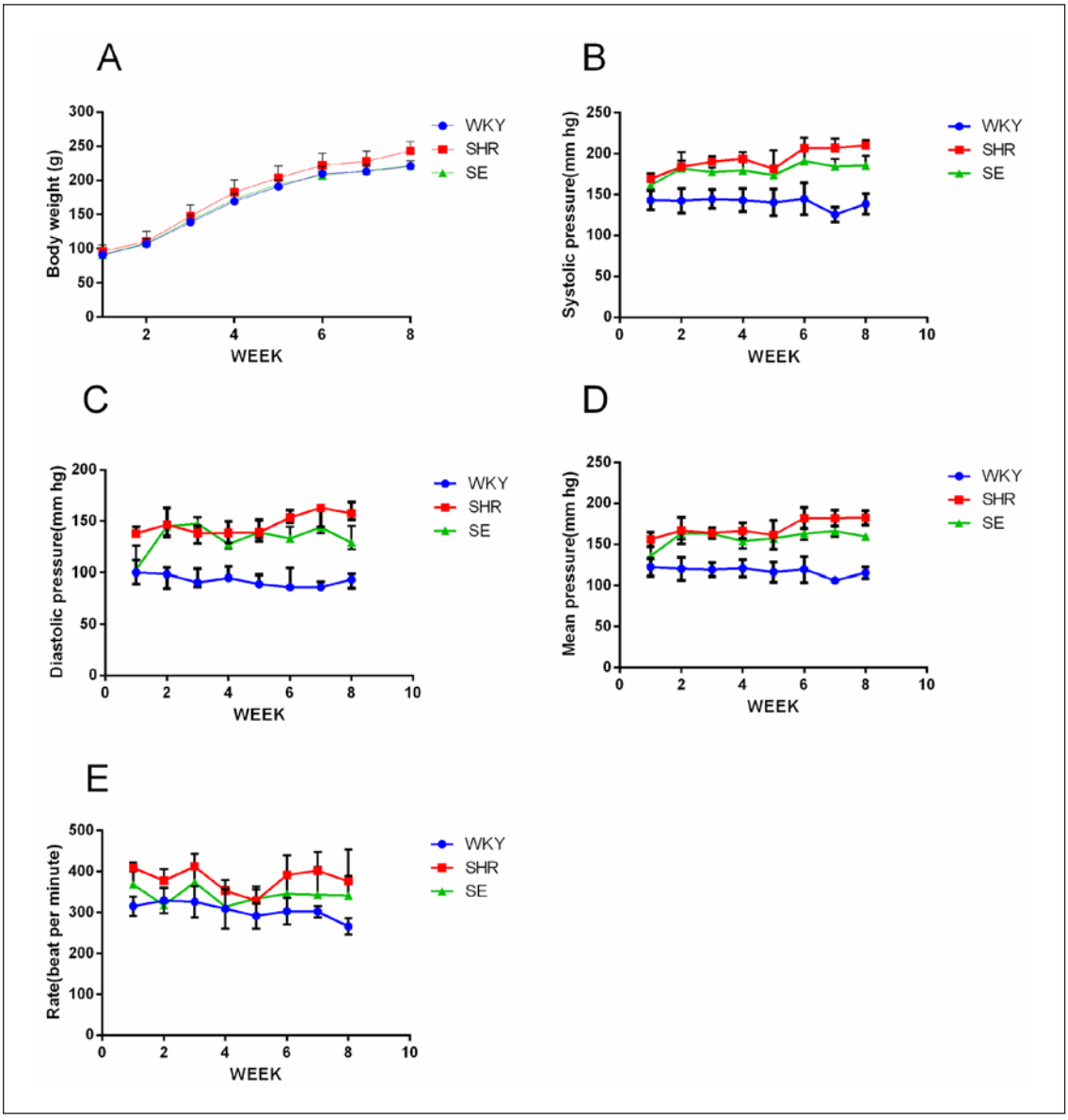

Fig. 1. Effects of swimming exercise on the BW and BP in SHRs. Changes in BW (**A**), SBP (**B**), DBP (**C**), MBP (**D**), and HR (**E**) in each group during the exercise period. Data are presented with mean ± SEM (n = 8). BW, body-weight; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blod pressure; HR, heart rate; SHRs, spontaneously hypertensive rats; SE, SHR exercise group; WKY, Wistar-Kyoto rats.

er BW than WKY and SE. Blood pressure in general were higher in the SHR group than in the WKY group ($p < 0.01$). Swimming exercise reduced SBP, diastolic blood pressure, and MAP, and significant differences were seen at week 7–8 for SBP and week 6–8 for MAP between the SE group and the SHR group ($p < 0.05$). HR was lower after 8 weeks of swimming (342.0 ± 7.514 beats/min) than the SHR group (381.2 ± 10.21 beats/min ($p < 0.01$).

SHR had significantly higher levels of BUN and SCr than the WKY group ($p < 0.05$, Table 1). The swimming exercise substantially reduced levels of BUN and SCr compared with the SHR group. The serum TG and LDL-C in the SHR group were raised to 0.62 and 0.96 mmol/L compared with the 0.54 and 0.61 mmol/L in the WKY. Swimming exercise ameliorated the level of LDL-C to 0.68 mmol/L ($p < 0.05$, Table 1).

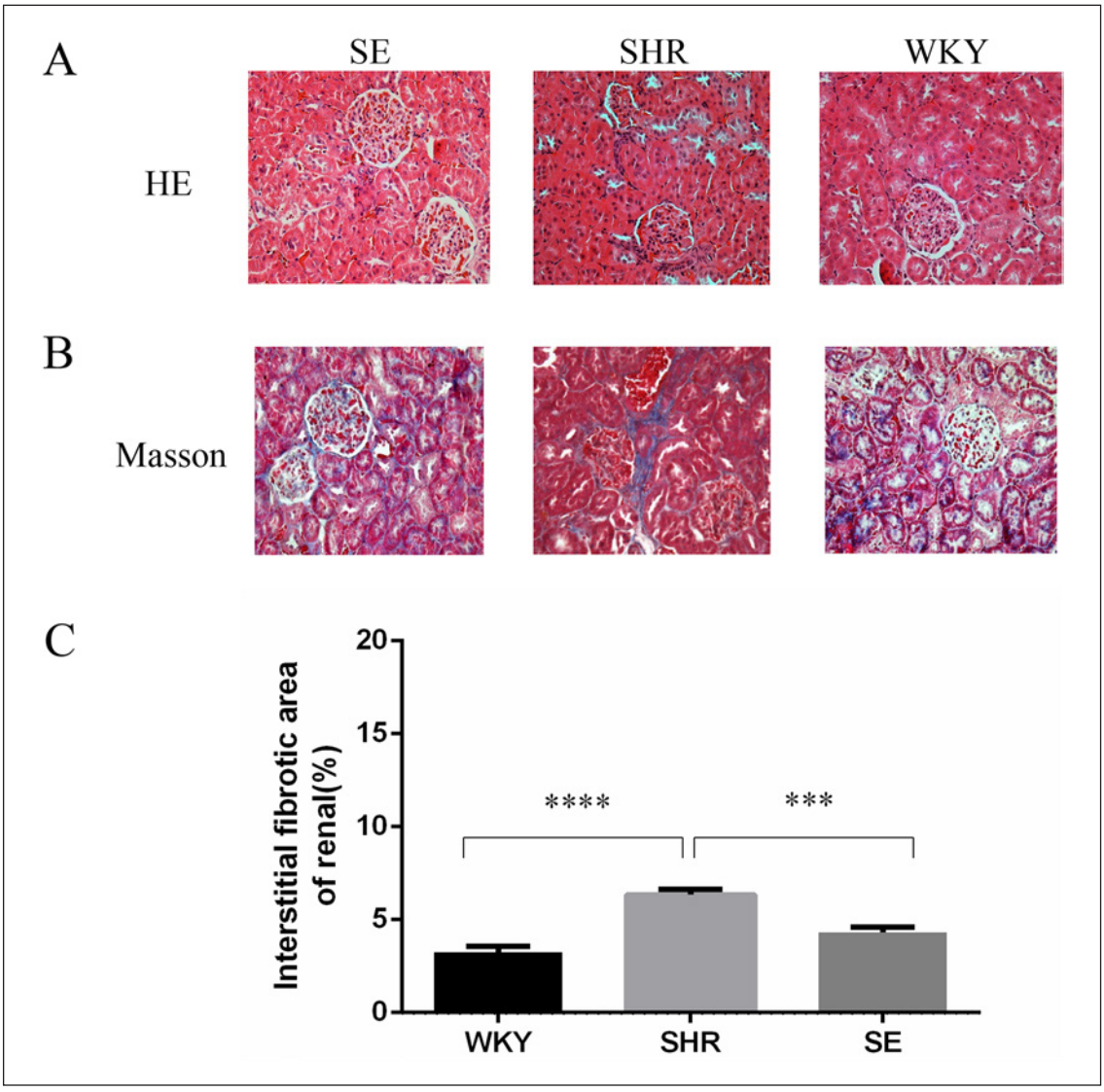

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Fig. 2. Effects of swimming exercise on the renal interstitial fibrosis examined by using hematoxylin and eosin staining (**A**) and Masson's trichrome staining (**B**), as well as on the area of interstitial fibrosis (**C**). ***$p < 0.001$. ****$p < 0.0001$. SHRs, spontaneously hypertensive rats; SE, SHR exercise group; WKY, Wistar-Kyoto rats.

Effects of Swimming on Pathologic Changes of Renal Tissues

Results from hematoxylin and eosin staining showed that there were prominent degenerative changes with tubular degeneration, cellular cluster, and tubular cell swelling as well as glomerular degeneration in the kidney cortical tissues in the SHR group (shown in Fig. 2A). The swimming exercise decreased cellular cluster, and there was no obviously structural lesion in the SE group. The kidney tissue fibrosis which comes from the histopathologic evaluation was assessed for the SHR, WKY, and SE groups by using Masson's trichrome analysis. The renal cortex in the SHR group exhibited a larger area of fibrosis than the WKY group, which was significantly suppressed by swimming exercise ($p < 0.01$, shown in Fig. 2B, C).

Effects of Swimming on Expressions of Proteins Related with TGF-β1/Smad Signaling

The expressions of pro-fibrosis factors, including TGF-β1, Smad2/3, and p-Smad2/3, were higher in the SHR group than the WKY group (shown in Fig. 3, $p < 0.01$), while Smad7 was lower in the SHR group. Signifi-

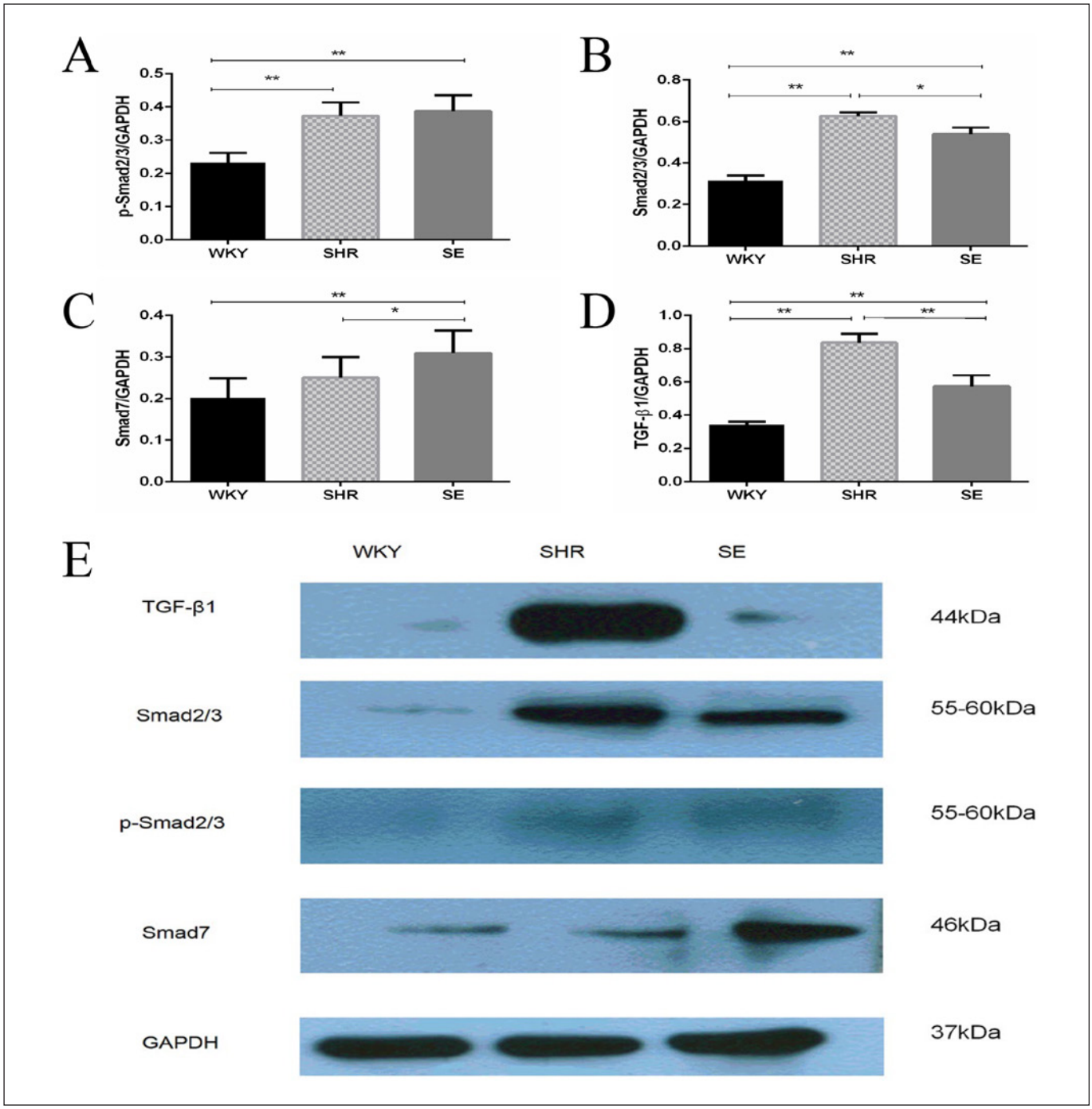

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Fig. 3. Effects of swimming on expressions of proteins related with TGF-β1/Smad signaling. p-Smad 2/3 (**A**); Smad 2/3 (**B**); Smad 7 (**C**); TGF-β1 (**D**). **E** Western blot of protein expressions. SHRs, spontaneously hypertensive rats; SE, SHR exercise group; WKY, Wistar-Kyoto rats.

cant reductions of TGF-β1 and Smad2/3 were observed in the SE group compared with the SHR group. On the contrary, Smad7 was elevated after swimming compared with the SHR group ($p < 0.05$).

Effects of Swimming on Renal Tubular Cell Apoptosis

Results from TUNEL staining of DNA damage showed that less apoptosis in the kidney tissue of the WKY group was observed than in the SHR group (shown in Fig. 4).

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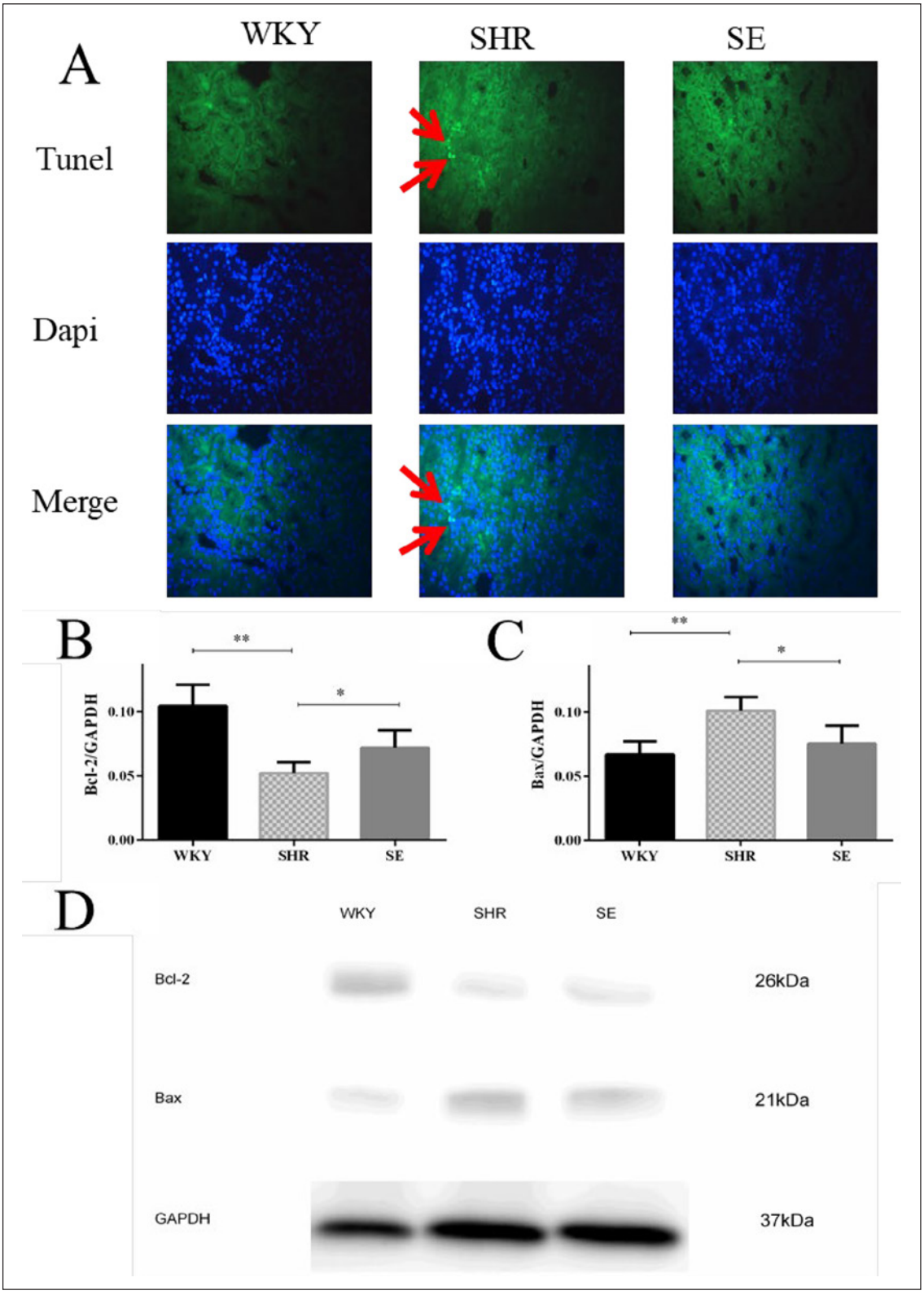

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Fig. 4. Effects of swimming exercise on renal tubular cell apoptosis. **A** TUNEL staining of renal tubular cell apoptosis. The red arrows indicate the apoptotic cells. Effects of swimming on expressions of Bcl-2 (**B**) and Bax (**C**). **D** Western blot of protein expressions. SHRs, spontaneously hypertensive rats; SE, SHR exercise group; WKY, Wistar-Kyoto rats.

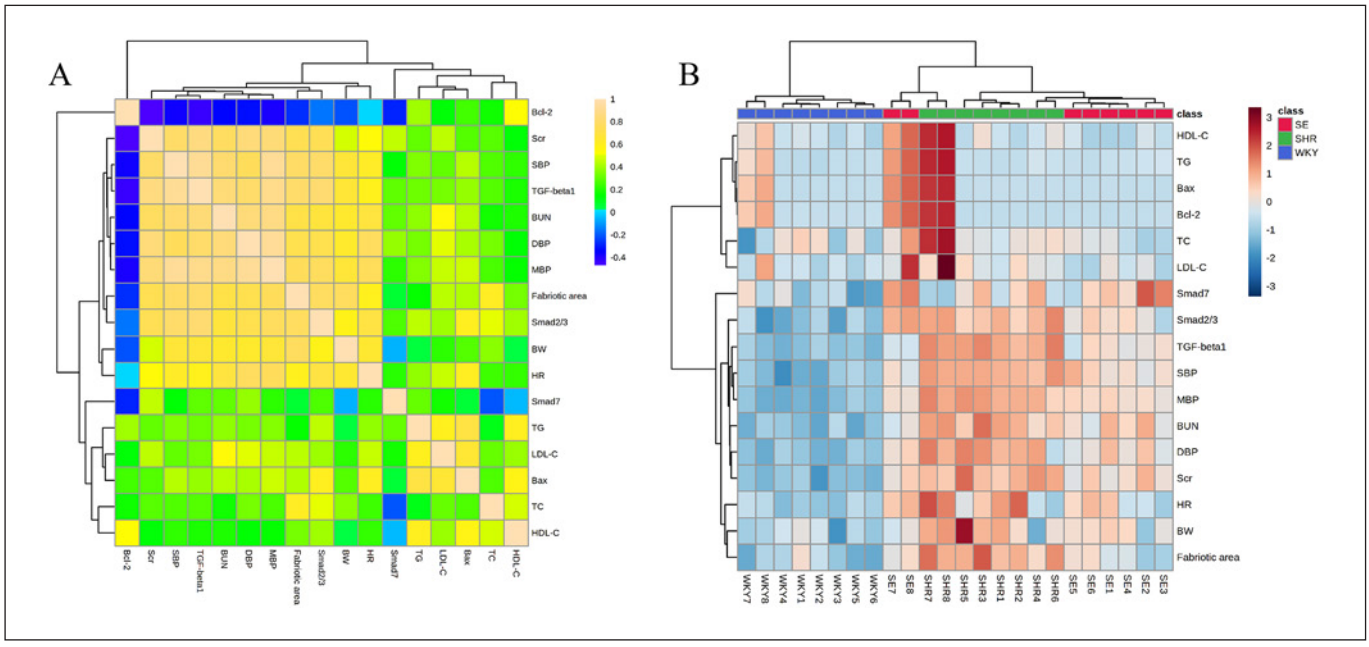

Fig. 5. Correlations between BW, BP, HR, BUN and SCr, blood lipids, and key proteins (**A**) and their clusters discriminating spontaneously hypertensive rats (SHR, $n = 8$), SHR exercise group (SE, $n = 8$), and the Wistar-Kyoto rats (WKY, $n = 8$) (**B**). BW, bodyweight; BP, blood pressure; HR, heart rate; SCr, serum Cr; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, total triglycerides; MBP, mean blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Swimming alleviated apoptosis which was consistent with the Bax and Bcl-2 results. Specifically, we observed that swimming elevated the expression of Bcl-2 while inhibited the expression of Bax (shown in Fig. 4).

Correlations

Benefits of swimming exercise on BP control and kidney protection were accomplished by the swimming-induced favorable regulation of TGF-β1/Smad signaling as well as the pro-apototic and apoptotic parameters, that is, Bcl-2 and Bax expressions (shown in Fig. 5B). Significant correlations between BW, BP, HR, BUN, and SCr, blood lipids, and key proteins were observed (shown in Fig. 5A).

Discussion

Early implementation of protective interventions aiming to ameliorate the decline in renal function prior to reaching end-stage renal failure holds great potential to decrease the incidence of CKD, thereby reducing morbidity, mortality, and improving quality of life [29–31]. Our study reveals beneficial effects of 8-week swimming exercise on BP control, improving kidney function, alleviating renal interstitial fibrosis, and cell apoptosis in hypertensive rats. Strong correlations between benefits of swimming on kidney protection, favorable regulation of TGF-β1/Smad signaling as well as the pro-apoptotic and apoptotic parameters, that is, Bcl-2 and Bax expressions, were observed. Our results provide compelling evidence on the protective effects of swimming exercise as a non-invasive and effective therapy on the development of CKD caused by hypertension.

Persistent hypertension is often coupled with multiple target organ damages [32]. A worldwide epidemic of CKD exists, and hypertensive nephropathy is a vital cause for ESRD globally. Previous studies have suggested that aggressive control of high BP, BW, and blood lipids, obtained through an appropriate therapeutic intervention, represents the key strategy to achieve a satisfactory prevention or management of the hypertension-induced kidney dysfunction [33]. Of note, our results showed that BW, BP, HR, and blood lipids, in particular, TG and LDL-C were effectively reduced by swimming exercise in hypertensive rats, which were associated with the exercise-induced reduction of BUN and SCr. Circulating levels of BUN and SCr have been validated as the reliable and easily accessible biologic marker for detecting kidney injury [34, 35].

Moreover, we found hypertensive rats suffered renal interstitial fibrosis, indicated by deleterious changes with tubular degeneration, cellular cluster, and tubular cell swelling as well as glomerular degeneration in the kidney tissues, consisting with previous studies [11, 36]. Although the mechanisms involving the pathogenesis of hypertensive renal fibrosis are not fully understood, TGF-β has been demonstrated as a central pro-fibrotic mediator in renal fibrosis. Specifically, Smad2 and Smad3 are the key molecules mediating TGF-β1 activity leading to renal fibrosis [12]. On the contrary, Smad7 is the inhibitor of TGF-β1/Smad signaling, and the enrichment of Smad7 has been suggested as a therapeutic agent for renal fibrosis in kidney diseases. We observed the 8-week swimming exercise successfully decreased cellular cluster, suppressed area of renal fibrosis, and beneficially regulated expressions of Smad2, Smad3, and Smad7. These findings highlight that swimming exercise could be effective for early prevention and management of hypertensive nephropathy through the suppression of renal fibrosis via regulating the TGF-β1/Smad signaling.

Besides, hypertension has been associated with endothelial dysfunction, altered contractility, vascular remodeling, and oxidative stress. Both excessive endoplasmic reticulum stress and oxidative stress may contribute to renal apoptosis. In line with previous studies [37], our results have shown strong links between renal cell apoptosis and interstitial fibrosis in the kidney lesion, and under the condition of the injury, the functional cell transition from a normal morphology to an apoptotic or fibrotic phenotype could be activated. Most interestingly, we found that exercise reversed hypertension-induced elevation in the Bax/Bcl-2 ratio, while increasing Bcl-2 levels in the kidney, supporting the protective effects of swimming exercise against increased apoptosis [15, 24, 38–40].

It should be noted that the pathogenesis of hypertension-induced kidney disease is complex and may include several molecule alterations that have not been fully elucidated. Although exercise has shown benefits in alleviating hypertension-induced kidney dysfunction, underlying mechanisms remain largely unexplored. Except for the TGFβ/Smad signaling pathway and renal cell apoptosis, 2 essential and pathological hallmarks of progressive CKD that we particularly investigated in this study, the renin-angiotensin-aldosterone system has also been closely related to hypertensive nephropathy and cardiovascular diseases and plays an important role in regulating BP [41–43]. Exercise may act as an inhibitor of the renin-angiotensin-aldosterone system significantly and has shown to reduce circulating AngII levels in SHR models [43]. Comprehensive analyses of molecule alterations are warranted aiming to improve understanding of beneficial effects of exercise on hypertension-induced kidney diseases.

Conclusion

The 8-week swimming exercise beneficially reduced BP, BW, HR, and biologic markers for kidney injury, that is, BUN and SCr, in hypertensive rats. Consistently, swimming exercise remarkably ameliorated tubular disorder, hypertension-induced renal interstitial fibrosis, and renal cell apoptosis, partly via favorably regulating the TGF-β1/Smad signaling and Bcl-2 family protein expressions that were largely involved in the mitochondrial apoptotic pathway. Our findings suggest that swimming exercise holds great promise to be an antihypertensive and renal protective treatment prior to reaching severe hypertension-induced renal failure.

Statement of Ethics

All animals care and experimental procedures were approved by the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Pub. No. 85-23, Revised 1996) and complied with guidelines for ethical care of experimental animals of the Institutional Animal Care and Use Committee of Shaanxi Normal University (No. 202016002).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: Z.K.R., D.Y.C., and S.L.; methodology: J.Z., H.H., H.M., Y.T., and D.Y.C.; software: J.Z., H.M., Y.T., and D.Y.C.; formal analysis: J.Z., H.H., H.M., and D.Y.C.; investigation: D.Y.C., S.L., J.Z., H.H., and H.M.; writing – original draft preparation: D.Y.C. and S.L.; writing – review and editing: D.Y.C., S.L., Y.T., and Z.K.R.; visualization: D.Y.C. and S.L.; supervision: S.L. and Z.K.R.; project administration: Z.K.R.; funding acquisition: Z.K.R. and S.L. All authors have read and agreed to the published version of the manuscript.

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