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Exercise Sensitizes the Pressure Diuresis Response: Shifting Immune Landscapes May Underlie Renal Adaptations

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Abstract

Physical activity and exercise confer health benefits through actions on several physiological systems; however, the mechanisms by which they impact renal health remain poorly understood. Studies show exercise slows age-related decline in kidney function and protects against AKI. We hypothesize that exercise triggers adaptive responses, which preserve hemodynamic balance in the kidneys under stress. We evaluated running-induced adaptations in 10–14-wk-old C57BL/6J male and female mice subjected to voluntary running or in male mice subjected to forced treadmill running. We evaluated renal perfusion with contrast-enhanced ultrasound and assessed kidney function by measuring the ability to clear a volume load. Additionally, we performed flow cytometry, cytokine array, histopathology, and bulk mRNA sequencing. We found exercise significantly increased cortical microvascular blood volume ($p=0.0085$), as indicated by increased plateau contrast signal intensity. Additionally, exercised male, but not female, mice excreted significantly more urine in the first hour after a saline bolus ($p=0.0055$). At the cellular level, we observed a significant increase in kidney resident macrophages (KRM; $CD45^+CD11b^+F4/80^{hi}$) after treadmill training in male mice. Lastly, bulk mRNA sequencing suggested treadmill training induced changes relating to water and sodium handling as well as angiogenesis and wound healing. These data suggest that exercise alters the immune landscape of the kidney, increases renal microvascular volume, and improves sensitivity of the pressure diuresis response. Future studies will test the hypothesis that macrophages cause the functional adaptations observed.

New & Noteworthy

The kidneys exhibit functional and cellular adaptations to exercise, such as increased renal cortex microvascular volume, as indicated by increased signal intensity of contrast-enhanced

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Author Contributions

SPJ, JH, YN, and SMS conceived and designed the research study. NO, EPC, KRB, YN, and SMS performed the experiments. NO, RS, CDA, KRB, PAW, YN, and SMS acquired and/or analyzed the data. SPJ and SMS interpreted results of experiments. RS and SMS prepared figures. SPJ and SMS drafted, edited, and revised the manuscript. All authors approved the final version of the manuscript.

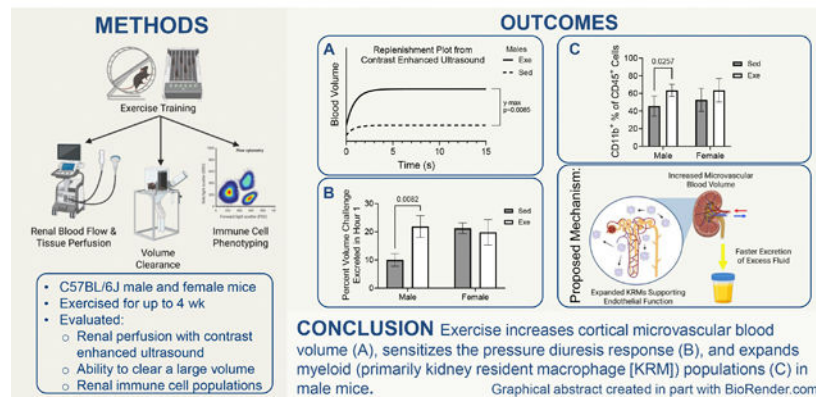
Disclosures

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ultrasound. Exercise improves efficiency of pressure diuresis in male mice, reducing time needed to excrete an isotonic volume excess. At the cellular level, exercise expands kidney resident macrophage populations and alters transcriptional pathways relating to water and sodium handling, angiogenesis, and wound healing.

Graphical Abstract

Exercise induces renal adaptations that sensitize regulation of fluid balance



Keywords

exercise; kidney resident macrophages; pressure diuresis; renal blood flow

Introduction

Physical activity and exercise promote health, while physical inactivity is the leading risk factor for development of noncommunicable diseases (1). Physical activity reduces risk of cardiovascular disease, diabetes, osteoporosis, and some cancers (1–3). Furthermore, being physically fit or active reduces risk of all-cause mortality in a dose-dependent manner (4). Hence, exercise can be used as a template for how to establish human health. Yet, how physical activity or exercise confers such benefits and mitigates the development of disease remains poorly understood.

At an organismal level, there are multiple obvious and some more imperceptible physiological changes occurring in response to exercise (5, 6). During and after exercise, chronotropic and ionotropic changes to the heart are most obvious. After prolonged training, changes in adiposity and musculature are also easily noticed. Yet, there are likely many changes that are less obvious, such as changes in kidney function. Given the enormous dynamic range in cardiac output, and that the kidney must deal with these acute excursions in blood supply to the kidney, it is reasonable to query potential changes in kidney function in response to exercise.

Acutely, exercise can be a stressful event for the kidneys. Initiation of exercise activates the sympathetic nervous system, which constricts the renal artery and increases sodium

reabsorption (7, 8). This is a necessary response as cardiac output is diverted to the working heart and skeletal muscle, and body water needs to be conserved. Despite this acute stress, data continue to emerge suggesting moderate intensity exercise may slow the age-related decline in kidney function in older adults both with and without chronic kidney disease (CKD) (9, 10). Additionally, exercise preconditioning protects in rodent models of acute kidney injury (AKI) (11–24). We wager that the acute stress of exercise on the kidney acts as a hormetic challenge that triggers adaptive responses to bolster hemodynamic resilience. The nature of such changes, however, remains enigmatic.

We reason that these adaptive responses may be mediated in part by the immune system as exercise exerts an anti-inflammatory effect (25, 26), and can influence macrophage phenotype (27). Recently, kidney resident macrophages (KRM) have gained increasing attention for their roles in regulating renal function and response to injury (28–30). Specifically, KRM protect in models of ischemic- and sepsis-induced AKI via reducing pro-inflammatory responses and promoting angiogenesis (31–33). Thus, we hypothesize that exercise influences kidney resident macrophage populations by favoring a more anti-inflammatory and pro-angiogenic subset. In this study, we evaluated functional adaptations and biological changes occurring in the kidney following different periods and forms of running. Understanding how exercise changes physiology at an organ level will help maximize its benefits and could lead to new drug targets for disease.

Materials & Methods

Forced and Voluntary Running.

All mice were maintained in AAALAC-accredited animal facilities at the University of Louisville. Mice were maintained on a 12:12 hour light-dark cycle and provided food and water *ad libitum*. All animal procedures were approved by the Institutional Animal Care and Use Committee of the University of Louisville and followed the guidelines of the American Veterinary Medical Association.

In the voluntary wheel running experiments, 14-week-old C57BL/6J male and female mice purchased from Jackson Laboratory (Stock #000664) were assigned to either voluntary wheel running (Exe) or sedentary (Sed) conditions for 4 wk. Mice were placed into individual cages with *ad libitum* access to voluntary wheels connected to a digital-analog converter and dedicated laptop for automated wheel running analysis using VitalView software. This software provides time stamped wheel movement tracking that allows for calculation of running frequency and time-of-day assessment. Sedentary controls were also individually housed.

In the forced treadmill running experiments, we used 10-week-old C57BL/6J male mice purchased from Jackson Laboratory (Stock #000664). Mice were divided into 4 groups: sedentary (Sed), mice subjected to pre- and post-exercise capacity tests (ECTs) with no training (24 h), mice subjected to pre- and post-ECTs with 1 wk of training (1 wk), and mice subjected to pre- and post-ECTs with 2 wk of training (2 wk). Mice were first acclimated to six-lane rodent treadmills (Columbus Instruments) 2 d prior to pre-ECT with a static 10 min warm up period (0 m/min with electric grid on 25 V, 0.34 mA, and 2 Hz) followed by a

10 min run (12 m/min). All ECTs were performed as described with established exhaustion criteria (34). All mice were group-housed for the duration of the experiment. The 1 wk and 2 wk groups were subjected to daily forced running at 70% capacity (14.4 m/min, which was the average of all mice at baseline testing) at a 5° incline for 40 min for 1 or 2 wk, respectively. 24 h mice were euthanized 24 h after the post-ECT test to discern acute responses to exercise from chronic adaptations. Sedentary mice served as controls. There is evidence from our colleagues (34) that compliance of C57BL/6J mice to the treadmill protocol may be problematic to maintain. In our present experience, we did not notice significant issues with completing the 2 wk protocol until the two-week point. Because even one week of treadmill running was problematic for our colleagues and our present experience, we reconsidered the use of the forced treadmill system for the remainder of our studies. We used the 4-week voluntary protocol because much of our prior experience with exercised mice was with the focus on cardiac muscle growth; this experience indicated that the 4-week timepoint reflected a stable period of mild cardiac hypertrophy, which did not further progress (34). Lastly, the use of the voluntary wheel model avoids disruption to light cycle inactivity in mice; the forced treadmill experiments were performed in the light cycle.

Contrast-Enhanced Ultrasound.

Renal perfusion was assessed by contrast-enhanced ultrasound (VisualSonics Vevo3100), a noninvasive imaging technique that uses a continuous intravenous infusion of inert, intravascular, lipid-shelled echogenic contrast agent (1–3 μm microbubbles) (35–39). The contrast agent was prepared in-house by sonication of a perfluorobutane-saturated aqueous suspension of distearoylphosphatidylcholine and polyoxyethylene-40-stearate (39). The contrast agent was infused at 20 $\mu\text{l}/\text{min}$ to anesthetized mice via a jugular vein catheter. The lipid-shelled contrast agent was destructed by a short (1 s) pulse of high-energy ultrasound, resulting in transient loss of signal intensity (36, 38). The subsequent time-dependent replenishment of contrast signal intensity in a 1 mm^2 region of interest in the renal cortex was used to quantify perfusion by fitting data with a single exponential function: $y = A(1 - e^{-\beta t})$, where kidney tissue plateau signal intensity (A) and the initial slope of the rise in signal intensity (β) were interpreted as the relative blood volume (rBV) and blood exchange frequency, respectively. Kidney perfusion ($\text{ml}/\text{min}/\text{g}$) was calculated as $\text{rBV} \cdot \beta / \rho$, where ρ is kidney tissue density (1.05 g/ml) (40). We simultaneously collected B- and non-linear contrast (NLC)-mode images while recording ≥ 10 burst-replenishment sequences per condition. To minimize motion-induced artifacts, we used ECG-triggered image acquisition (R peak) paired with respiration gating. For offline data analysis, we used VevoLAB software (FujiFilm VisualSonics) and MatLab to plot and fit replenishment data compiled from multiple burst-replenishment sequences.

Volume Challenge and Urinary Electrolyte Measurements.

Mice were scruffed and light pressure was applied to the bladder to void urine. Mice were then given an IP injection of 0.9% saline equal to 10% of their body weight. Mice were immediately placed in individual waste collection cages (Harvard Apparatus) coupled with recirculating water (10 L) baths for cold temperature collection/preservation (4°C) of urine and feces. Urine was collected every hour over the next 4 h. Urine was frozen at -80°C and sent to The Johns Hopkins University School of Medicine for measurement of

electrolytes. 100 μ L of urine were diluted in 200 μ L of urine diluent (Diamond diagnostics, AV-BP0344D). As a blank control, 100 μ L of molecular biology grade water was mixed with 200 μ L of urine diluent. Samples with less than 100 μ L were added with water up to 100 μ L and then correction factor was applied to the analyzer read values. The Na^+ , K^+ , and Cl^- concentration in the samples were measured using the Carelyte Plus Electrolyte Analyzer (Diamond Diagnostics).

Flow Cytometry.

Following euthanization, whole kidneys were extracted and homogenized into single cell suspensions and prepared for staining as described (41). Cells were blocked with CD16/32 (567021, BD Biosciences) and extracellularly stained with antibodies listed in Supplemental Table 1. After staining, cells were fixed and permeabilized with FoxP3/Transcription Factor Staining Buffer Set (00–5523-00, Invitrogen). Flow cytometry was conducted on a 4-laser BD LSRFortessa, collecting 1 million events per sample. Hierarchical gating was performed as depicted in Supplemental Figure 1. Fluorescence minus one (FMO) controls were used to validate gating (Supp Fig 2). Data are represented as the percentage of positively stained cells for the indicated population from the total number of CD45^+ cells observed in that sample. Resident macrophages are identified as $\text{CD45}^+\text{CD3}^-\text{CD19}^-\text{CD11b}^+\text{F4/80}^{\text{hi}}$. Infiltrating macrophages are identified as $\text{CD45}^+\text{CD3}^-\text{CD19}^-\text{CD11b}^+\text{F4/80}^{\text{lo}}$. CX3CR1 and CCR2 were used for additional phenotypic characterization of macrophages.

Clinical Chemistry.

Blood urea nitrogen (BUN) was measured in the plasma of mice using a commercially available kit from Pointe Scientific (B7552450) per the manufacturer's instructions. ELISA for neutrophil gelatinase-associated lipocalin (NGAL; DY1857, R&D Systems) was performed on mouse urine per the manufacturer's instructions. Plasma samples were sent to the University of Alabama at Birmingham O'Brien Center for Acute Kidney Injury Research Preclinical Studies of AKI Core for serum creatinine measurement via LC-MS.

Histology.

Upon euthanasia, kidney sections were fixed in 10% neutral buffered formalin and then embedded in paraffin. 5 μ m sections were cut and stained with periodic acid-Schiff stain. Glomerular and tubular size were measured by manually tracing structures at 20 $\times$ magnification in at least 8 fields of view per sample in CaseViewer software.

Cytokine Array.

Protein homogenates were prepared from renal cortex tissue using cell extraction buffer (Thermo Scientific, FNN0011) with phosphatase inhibitors (Sigma, 4906845001) and protease inhibitors (Sigma, 11836170001). Tissue was gently homogenized with a small pestle and cordless pestle motor. A Pierce BCA protein assay (Thermo Scientific, 23223 and 23224) was used to measure protein concentration, and 450 μ g of protein was sent to Eve Technologies for the Mouse Cytokine/Chemokine 44-Plex Discovery Assay[®] array.

RNA Sequencing.

Total RNA was isolated from mouse renal cortex using the Qiagen RNeasy Plus Mini kit (74134). RNA quality was evaluated using NanoDrop ONEC (Thermo Scientific), and 1.25 µg of RNA was sent to the University of Louisville Sequencing Technology Center for poly-A RNA sequencing. The TruSeq Stranded mRNA Library Prep Kit (Illumina Cat# 20020594) and TruSeq RNA CD Index Plate (Illumina Cat# 20019792) were used to generate a sequencing library. Size, purity, and semi-quantitation were performed on an Agilent Bioanalyzer 2100 system using the Agilent DNA HS Kit. Single-end sequencing was performed on an Illumina NextSeq 2000, using a P3 100 cycle cartridge with a P3 flow cell. Libraries were sequenced with a single 101 cycle read length with 2 index reads of 8bp each. FASTQ files were generated utilizing BaseSpace DRAGEN analysis Version 1.2.1.

Bioinformatics Analysis.

Analysis of RNA sequencing data was performed as previously described (42, 43). Quality control (Q.C.) of the raw sequence data was performed using FastQC (version 0.10.0) for each sequencing sample (Available: <http://www.bioinformatics.babraham.ac.uk/projects/fastqc/>). The sequences were aligned to the mm10 mouse reference genome using STAR version 2.6 (44). Differential expression of ENSEMBL protein-coding transcripts was performed using DESeq2 (45), and raw counts were obtained from the STAR-aligned bam format files using HTSeq version 0.10.0 (46). The raw counts were normalized using the Relative Log Expression (RLE) method and then filtered to exclude genes with fewer than ten counts across the samples. DESeq2 guidelines were used to identify differentially expressed genes, and all P values were adjusted for testing multiple genes (Benjamini–Hochberg procedure; $p \leq 0.05$). Functional enrichment analysis was performed using the clusterProfiler R package to identify enriched Gene Ontology biological processes and KEGG pathways for each set of differentially expressed genes (DEGs) (47). RNA-seq data were deposited in the NCBI GEO database under Accession No GSE297842.

Statistical Analysis.

Data were plotted and analyzed with GraphPad Prism. Data are presented as the mean±SEM and were analyzed with the statistical test indicated in accompanying figure legends. Significance was set at $p \leq 0.05$. P values of comparisons are indicated.

Results

Exercise increases renal cortex microvascular volume.

We performed contrast-enhanced ultrasound on mice subjected to either 4 wk of voluntary wheel running or sedentarism. Exercise trained mice had a significantly increased plateau contrast signal intensity (A) compared to sedentary controls (Fig 1A). This is indicative of an increased tissue capillary blood volume. Furthermore, the blood velocity or rate of replenishment (β) following quenching of the contrast signal was reduced in exercised mice compared to sedentary controls (Fig 1B). Overall, this amounted to a nonsignificant increase in tissue perfusion (Fig 1C–D). These results indicate that exercised mice had increased microvascular blood volume.

Exercise sensitizes the pressure diuresis response in male mice.

Following exercise training, we assessed the ability of mice to clear an isotonic volume load. We found that exercise significantly increased the fraction of the volume load excreted in the first hour after administration in male (Fig 2A) but not female mice (Fig 2C). Raw urine volume excreted after the volume challenge followed the same trend (Supp Fig 3A–B). After 4 h, the total fraction of volume challenge excreted was not significantly altered by exercise in males or females (Fig 2B&D). Lastly, we found urinary concentrations of Na^+ , K^+ , and Cl^- excreted after volume challenge to be unchanged by exercise (Fig 2E–G and Supp Fig 3C–H). Taken together, these data indicate that exercise increases the rate at which an excess volume load is excreted but does not grossly alter electrolyte balance.

Exercise expands kidney resident macrophages in male mice.

We used flow cytometry to evaluate immune cell populations in the kidney of mice subjected to both forced and voluntary exercise. In the voluntary wheel running model, we allowed male and female mice to run for 4 wk. Female mice reached peak activity within a week, while male mice reached peak activity within 2 wk (Supp Fig 4A). Mice were most active at night, with males averaging 8,037 m per night and females averaging 10,244 m per night (Supp Fig 4B). Total distance run and work done over the 4 wk period was not significantly different between sexes (Supp Fig 4C–D).

After 4 wk of voluntary wheel running, we observed no change in overall CD45^+ immune cell numbers in the kidney but observed a significant increase in the portion of CD11b^+ myeloid cells in male but not female mice (Fig 3A–B). CD3^+ T cells and CD19^+ B cells appeared to be unchanged by exercise (Fig 3C–D). The increase in myeloid cells appeared to be driven by an increase in KRM rather than bone marrow-derived macrophages (Fig 3E–F), with KRM populations predominantly expanding from tissue resident $\text{CX3CR1}^+\text{CCR2}^-$ macrophages with a minor contribution from infiltrating $\text{CX3CR1}^+\text{CCR2}^+$ macrophages (Fig 3G–H). Interestingly, we also noted that while female mice did not have an exercise-induced immune response, they had more $\text{CX3CR1}^+\text{CCR2}^-$ KRM and significantly less CD19^+ B cells than male mice under sedentary conditions (Fig 3E).

We further evaluated the effect of forced treadmill running on immune cells populations in male mice. We found that forced treadmill running also did not change overall CD45^+ immune cell numbers at any timepoint; however, 2 wk of running caused a significant increase in the portion of CD11b^+ myeloid cells (Fig 4A–B). We did not observe a change in CD19^+ B cells, but did see a significant decrease in CD3^+ T cells after 2 wk of running (Fig 4C–D). Further characterization of myeloid populations revealed that their increase was primarily a result of increased $\text{CD45}^+\text{CD3}^-\text{CD19}^-\text{CD11b}^+\text{F4/80}^{\text{hi}}$ KRM. $\text{CD45}^+\text{CD3}^-\text{CD19}^-\text{CD11b}^+\text{F4/80}^{\text{lo}}$ bone marrow-derived macrophage populations were not significantly altered (Fig 4C–F). This increase in KRM population appeared to be driven by expansion of tissue resident $\text{CX3CR1}^+\text{CCR2}^-$ macrophages with a minor contribution from infiltrating $\text{CX3CR1}^+\text{CCR2}^+$ macrophages (Fig 4G–H).

To identify the functional phenotype of these macrophages, we assessed cytokine levels in renal cortex tissue. We found that 2 wk of exercise significantly increased tissue levels

of M-CSF and decreased expression of MIP-1 α and IL-1 α (Fig 5A–C). While increased M-CSF levels could support expansion of macrophage populations, decreases in MIP-1 α and IL-1 α suggest these populations may be more anti-inflammatory in nature. Additionally, we observed a significant increase in the proangiogenic cytokine eotaxin-1 (CCL11) after 2 wk of exercise (Fig 5D). We observed fluctuations in four other interleukins at different timepoints of exercise (Supp Fig 5A–D).

Lastly, in both forced and voluntary exercise experiments, there was a low-level increase in monocyte and neutrophil populations in the kidney of male but not female mice (Supp Fig 6A–F). Taken together, these data indicate that exercise triggers endogenous expansion of KRM and limited recruitment of infiltrating monocytes in male mice. Although females did not appear to have this exercise-induced immune response, they had higher baseline levels of KRM.

Exercise alters renal transcriptional pathways related to fluid handling and endothelial cell function.

Following 24 h, 1 wk, and 2 wk of forced treadmill running, we isolated RNA from renal cortex tissue for bulk mRNA sequencing (Table 1). Following 2 wk of exercise we found 24 differentially expressed genes compared to sedentary controls (Table 2). Cluster profiling revealed these genes fell into GO pathways related to water and ion homeostasis as well as angiogenesis and wound healing (Fig 6A). Notably, transcripts of all the subunits of epithelial sodium channel (ENaC; subunit genes: *Scnn1a*, *Scnn1b*, and *Scnn1g*) were increased after 2 wk of forced treadmill running (Fig 6B–D). We did not identify any differentially expressed genes after 1 wk of forced treadmill running. Mice assessed 24 h after an exhaustive bout of exercise had 54 differentially expressed genes compared to sedentary controls (Table 1). These genes fell into pathways relating to stress responses (Supp Fig 7A). We also observed a non-significant increase in *Lcn2* and *Havcr1* expression at this timepoint that was absent after 2 wk of running (Supp Fig 7B–C). These data indicate that exercise does induce an acute stress response in the kidney, but with training this response is suppressed, and adaptive changes occur.

Moderate intensity exercise does not induce kidney injury.

We assessed serum creatinine, blood urea nitrogen (BUN), and urinary NGAL after both forced treadmill and voluntary wheel running. We did not observe an increase in any of these markers with exercise, except for a mild increase in BUN in female mice after 4 wk of voluntary wheel running (Supp Fig 8A–E). Additionally, we did not observe any gross histological changes, and glomerular size was preserved (Supp Fig 8F–I).

Discussion

In this study, we examined how exercise training impacted renal perfusion, volume clearance, and immune cell populations in C57BL/6J male and female mice. Using contrast enhanced ultrasound, we found that exercised male mice had increased microvascular volume in the renal cortex, as indicated by increased plateau contrast signal intensity. Additionally, exercised male, but not female, mice excreted a significantly greater portion

of a volume load in the first hour after administration. We posit these functional adaptations may be mediated by exercise-induced changes in the renal immune landscape. We found that exercise expands kidney resident macrophages in male but not female mice. Additionally, our data from cytokine array suggest that the expanded macrophages have an anti-inflammatory and pro-angiogenic phenotype that would bolster resilience against AKI.

While many studies have evaluated how exercise preconditioning can mitigate development of AKI in rodent models (11–24), they do not evaluate how exercise alters baseline function or structure of the kidney. Our data suggest that exercise induces vascular remodeling in the kidney that sensitizes control of body fluid balance. The concept of pressure diuresis, whereby an increase in pressure above the “set point” induces a diuretic response, has long been known (48, 49). For this process to occur, renal perfusion pressures must be adequately maintained, necessitating maintenance of renal microvasculature. Based on our data, we propose that exercise induces angiogenic processes that support microvascular maintenance and improves efficiency of the pressure diuresis response.

Our data suggest that exercise-responsive KRM s could be partial mediators of these functional adaptations. As initiation of exercise is known to reduce renal blood flow (8, 50), we propose that this serves as a quasi-ischemic trigger causing tubule cells to produce M-CSF. M-CSF is known to promote macrophage polarization and repair processes in response to ischemic insults in the kidney (51). Furthermore, subsets of kidney resident macrophages have been shown to have proangiogenic properties and protect peritubular capillaries in response to ischemia (31). Lastly, we observed a significant increase in eotaxin-1 (CCL11) expression in the kidney after exercise. We propose this could be a novel mediator of angiogenesis in the kidney as it has been shown to have angiogenic activity in other organs (52, 53).

Additionally, our study identified CD3⁺ T cells as potential mediators of exercise-induced adaptations. We observed a significant decrease in CD3⁺ T cells in male mice after forced treadmill running, although they were not significantly altered with voluntary wheel running. T cells have been shown to be important regulators of sodium and fluid handling (54–56). Further analysis of T cell subsets would be needed to explore this potential relationship further.

Unexpectedly, we observed an increase in mRNA expression of *Scnn1a*, *Scnn1b*, and *Scnn1g* following 2 wk of exercise. These findings align with data from the MoTrPAC group, where 2 wk of exercise training increased *Scnn1g* and *Scnn1b* expression (57) (<https://motrpac-data.org/>). These genes make up the subunits that form the epithelial sodium channel (ENaC), which is known to play an important role in Na⁺ and fluid balance. We hypothesize that the increased expression of the ENaC subunits is an adaptive response to aid the sodium and water reabsorption acutely induced by exercise; however, increased activity of ENaC is associated with hypertension (58–60) and exercise regimens reduce blood pressure. Additional studies are needed to identify how steady-state activity of ENaC is affected by exercise training, as activity of the transporter is regulated by a plethora of factors. It is also notable that there were no significant changes in DEGs at 1 wk, which

may reflect intrinsic variability and/or the possibility that 1 wk is a transitional timepoint of changes in expression that are not significant until 2 wk.

The differences between the sexes were another notable observation. There are multiple differences between males and females, and their responses to physiologic and pathologic stimuli often differ. The present study offers additional support for intrinsic differences between males and females in terms of their kidney-centric responses to exercise. Yet, this should not be interpreted to indicate that females do not respond favorably to exercise. Instead, it could be that kidneys from females may already exhibit the level of ‘adaptation’ we assessed in kidneys from males, which creates the illusion of them being refractory to our proposed benefits we observed in males. One should recall our finding that kidneys from exercised female mice may have more KRMs, but this was not an *a priori* endpoint for which we were powered; however, there were significantly fewer B cells at baseline in kidneys from female mice compared to male mice. We could also hypothesize that the sex-dependent response to exercise could be due to differences in hemodynamic function, which is known to be impacted by sex hormones (61). It should also be noted that total work performed was not different between males and females. A study designed to determine sex differences—which ours was not—would be required to definitively answer such questions.

We acknowledge there are limitations of this study. First, we did not assess baseline hydration status of mice before the acute volume challenge. All mice had unrestricted access to water throughout the training period, but we did not track water intake. Our conclusions assume that all mice were adequately hydrated at the time of volume challenge. Second, we were unable to normalize contrast signal in kidney tissue to a whole blood signal within the same animal, as we have done in similar studies in the heart (39). Batch to batch variation of the contrast agent could affect signal intensity; however, contrast-enhanced ultrasound measurements were performed over a series of days, decreasing the likelihood that our findings were due to this variation. Third, our assessment of immune cell subtypes suffered from limited statistical power and relatively superficial immunophenotyping panel.

Collectively, our data suggest that the vascular benefits of exercise extend to the kidneys. This benefit may occur through a favorable shift in the KRM population. The result is the ability to more efficiently clear a volume load. Over the course of a lifetime, physical activity may antagonize the development of hypertension through these mechanisms. Future studies will more fully detail the changes in renal vascular density and perfusion in response to exercise conditioning. In addition, we will address the factors regulating the infiltration/expansion of the exercise-induced KRM population. Such insights will develop these new ideas related to the ability of exercise to improve health through changing the structure and function of the kidney.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability.

The bulk RNA sequencing data used in this study are available in the NCBI GEO database (GSE297842). Any additional information is available upon request to the corresponding author.

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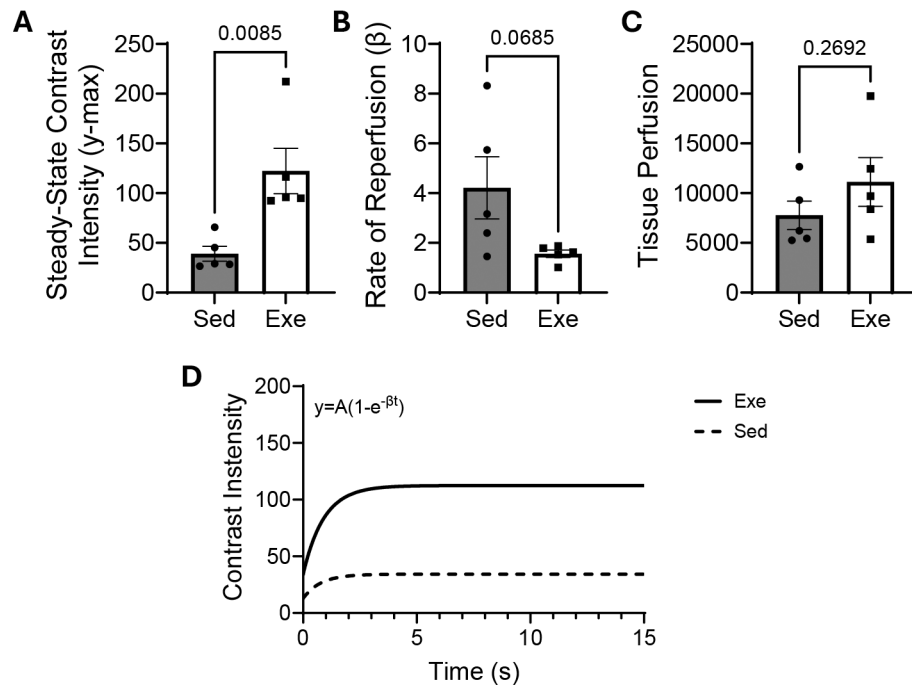


Figure 1. Exercise increases renal cortex microvascular volume.

Following 4 wk of voluntary wheel running, mice were subjected to contrast-enhanced ultrasound to evaluate renal tissue perfusion. Replenishment intensity plots were recorded and data were fit with single exponential association. (A) Steady-state contrast intensity y-max values of the replenishment plots. (B) Rate of reperfusion (β value) based on the slope of the growth phase of the replenishment plots. (C) Tissue perfusion calculated as $y=A(1-e^{-\beta t})$ where A =y-max and β =initial slope of the rise in replenishment plot signal intensity. (D) Compiled replenishment plots from sedentary and exercised mice. All data are represented as the mean $\pm$ SEM with n=5 per group (all male). Data were analyzed with an unpaired Students t-test. Significance was set at $p\leq 0.05$. Sed, sedentary; Exe, exercise.

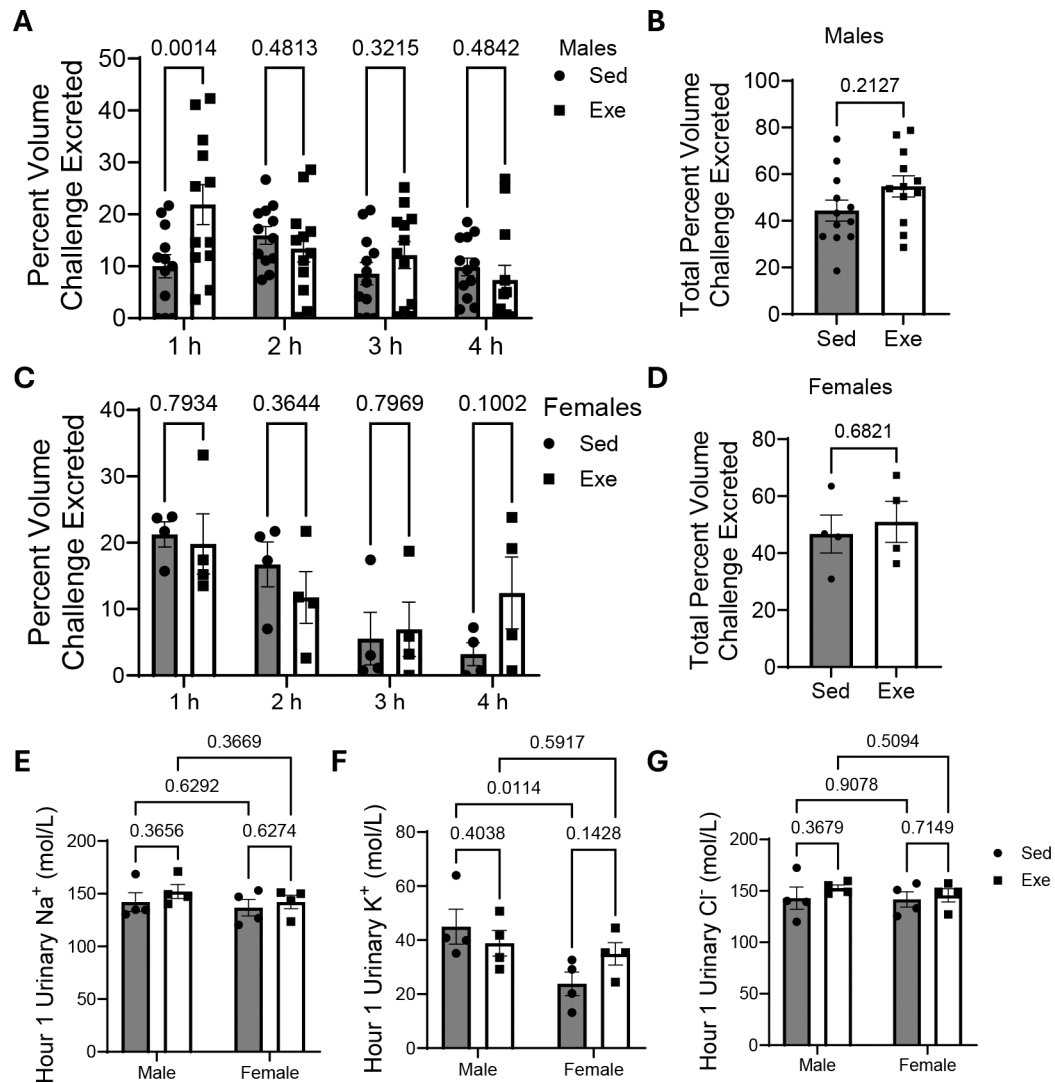


Figure 2. Exercise sensitizes the pressure diuresis response in males.

Mice were administered an IP injection of 0.9% saline equal to 10% of their body weight. Total urine output was collected hourly over the next 4 h. (A) Percent of volume challenge excreted by hour in males (n=12). (B) Total percent of volume challenge excreted at the end of 4 h in males (n=12). (C) Percent of volume challenge excreted by hour in females (n=4). (D) Total percent of volume challenge excreted at the end of 4 h in females (n=4). (E–G) Concentration of urinary sodium, potassium, and chloride ions excreted in urine in the first hour after volume challenge (n=4). All data are represented as the mean±SEM. Data were analyzed with multiple or single unpaired Student's t-tests with indicated comparisons (A–D) or two-way ANOVA with Tukey's post test (E–G). Significance was set at $p \leq 0.05$. Sed, sedentary; Exe, exercise.

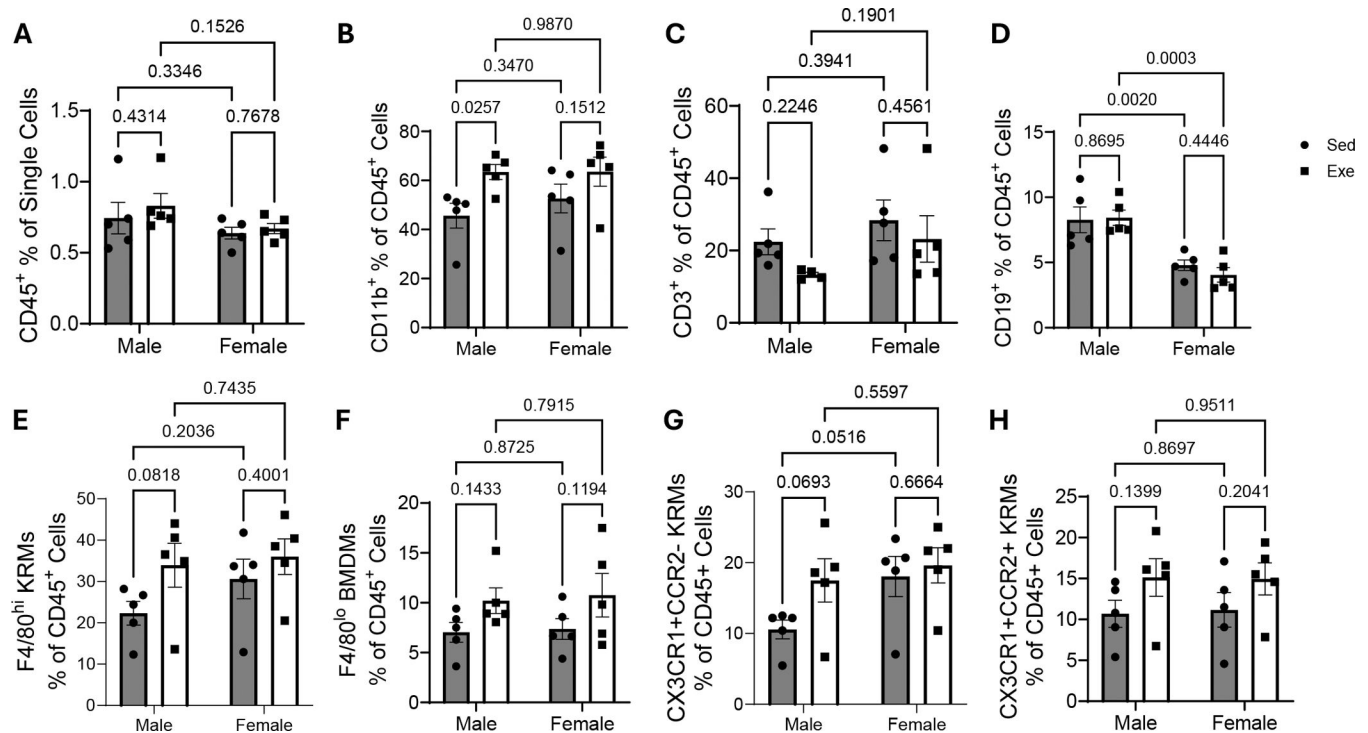


Figure 3. Exercise expands myeloid populations in male but not female mice.

Following 4 wk of voluntary wheel running, whole kidneys were homogenized into a single-cell suspension for flow cytometric analysis of immune cells. (A) CD45⁺ total immune cells presented as a percentage of positively labeled cells from the total number of single cells counted. Hierarchical gating was performed to identify (B) CD11b⁺ myeloid cells, (C) CD3⁺ T cells, (D) CD19⁺ B Cells, (E) F4/80^{hi} KRM, (F) F4/80^{lo} bone marrow-derived macrophages, (G) CX3CR1⁺CCR2⁻ KRM, and (H) CX3CR1⁺CCR2⁺ KRM. Data are presented as the percentage of positively labeled cells from the total number of CD45⁺ counted for each sample. All data are represented as the mean±SEM with n=5 per group. Data were analyzed with a two-way ANOVA with a Tukey's post test. Significance was set at p≤0.05. Sed, sedentary; Exe, exercise.

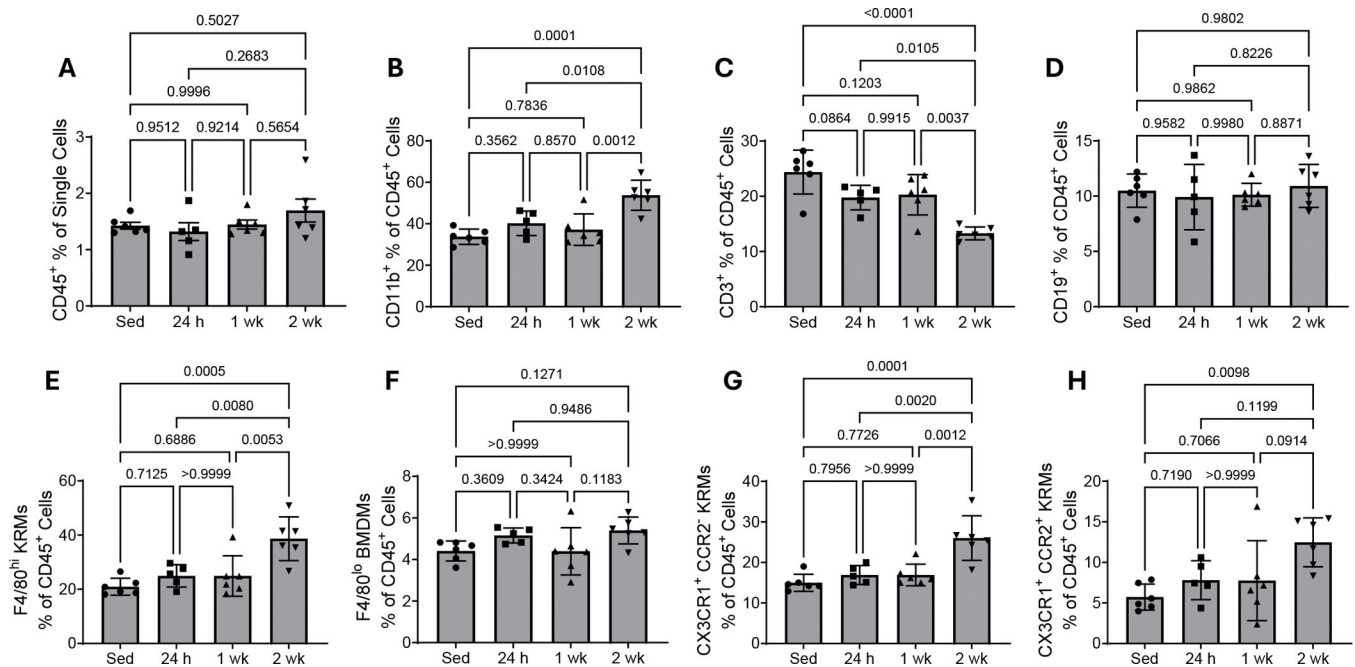


Figure 4. Exercise expands kidney resident macrophage (KRM) populations.

Following 24 h, 1 wk, and 2 wk of forced treadmill running, whole kidneys were homogenized into a single-cell suspension for flow cytometric analysis of immune cells. (A) CD45⁺ total immune cells presented as a percentage of positively labeled cells from the total number of single cells counted. Hierarchical gating was performed to identify (B) CD11b⁺ myeloid cells, (C) CD3⁺ T Cells, (D) CD19⁺ B Cells, (E) F4/80^{hi} KRM, (F) F4/80^{lo} bone marrow-derived macrophages, (G) CX3CR1⁺CCR2⁻ KRM, and (H) CX3CR1⁺CCR2⁺ KRM. Data are presented as the percentage of positively labeled cells from the total number of CD45⁺ counted for each sample. All data are represented as the mean±SEM with n=6 per group (all males). Data were analyzed with a one-way ANOVA with a Tukey's post test. Significance was set at p≤0.05. Sed, sedentary.

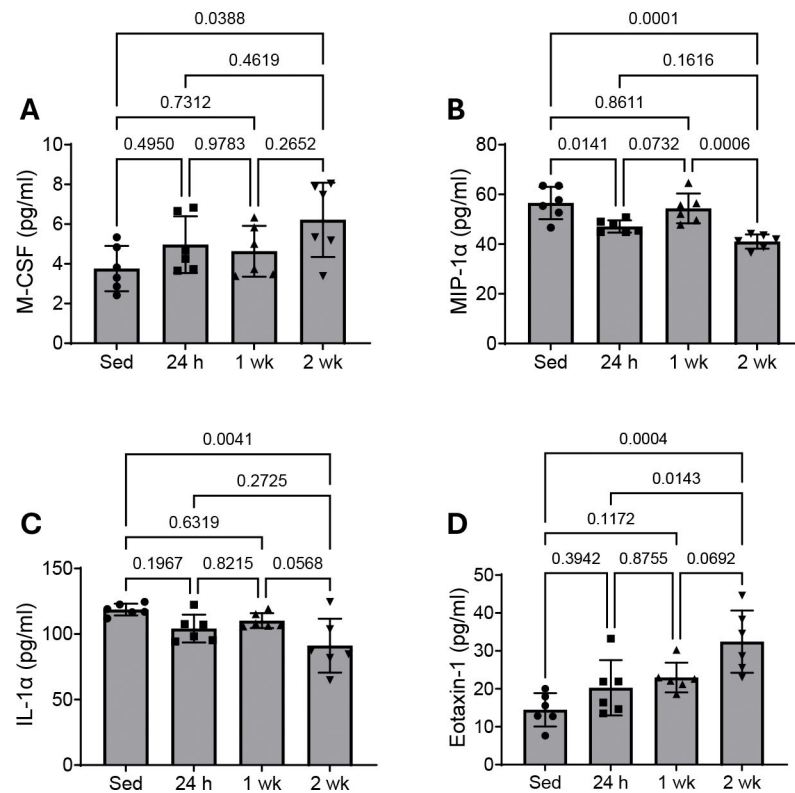


Figure 5. Exercise alters cytokine expression in the renal cortex.

Following 24 h, 1 wk, and 2 wk of forced treadmill running, protein homogenates were prepared from pieces of renal cortex tissue and sent to Eve Technologies for cytokine/chemokine array. (A) M-CSF, (B) MIP-1α, (C) IL-1α, and (D) Eotaxin-1 (CCL11) levels were significantly altered at 2 wk compared to sedentary conditions. Data are represented as the mean±SEM with n=6 per group (all males). Data were analyzed with a one-way ANOVA with a Tukey's post test. Significance was set at $p \leq 0.05$. Sed, sedentary.

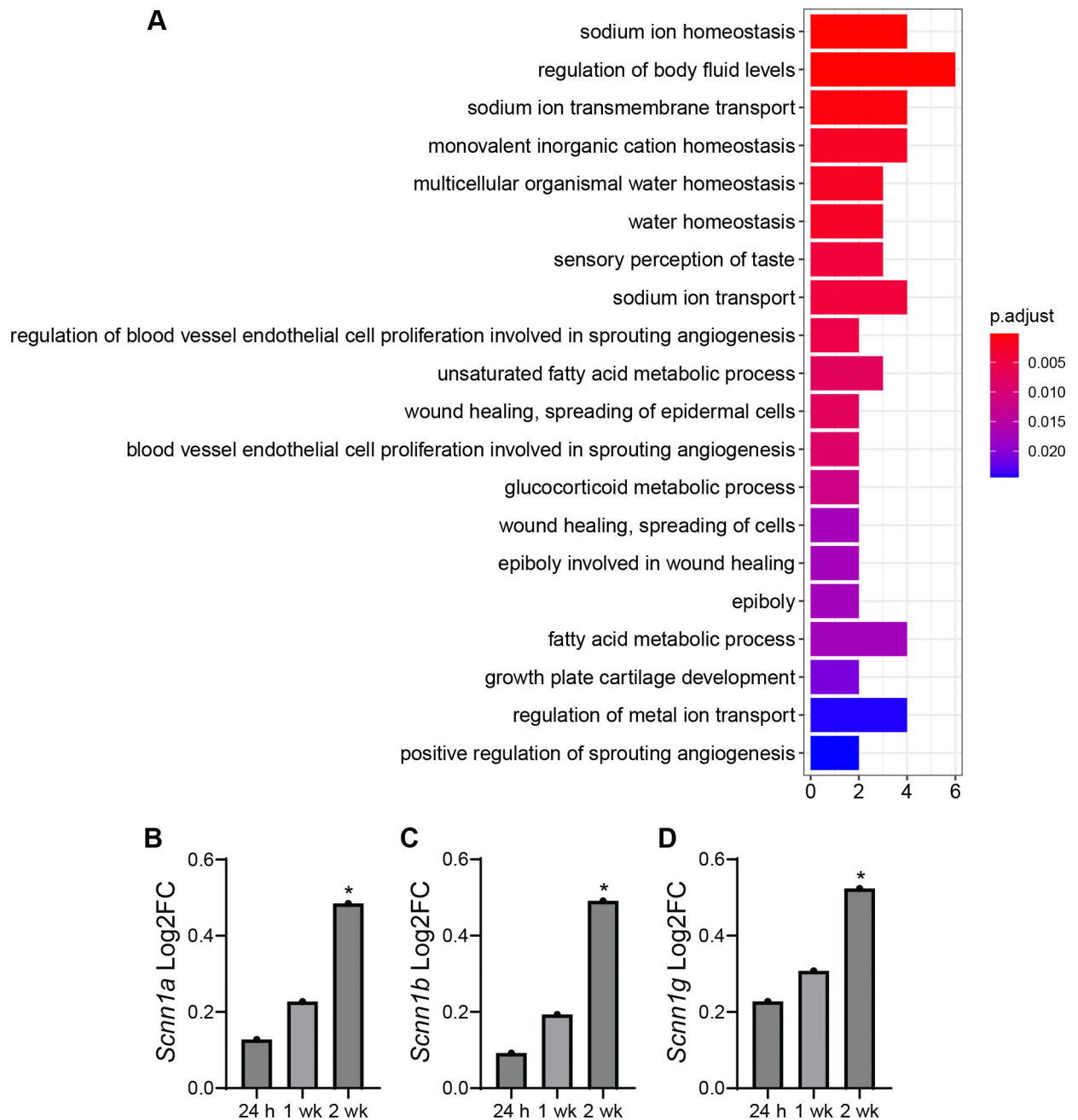


Figure 6. Exercise alters renal transcriptional pathways related to fluid handling and endothelial cell function.

(A) Cluster profiler of GO pathways associated with differentially expressed genes in 2 wk exercised vs sedentary control male mice. (B–D) Log2FC of sodium channel epithelial 1 subunits relative to sedentary controls (n=4 per group). *=significantly different from sedentary controls ($p \leq 0.05$, $q \leq 0.05$).

Table 1.

Number of differentially expressed genes (DEGs) in the renal cortex following forced treadmill running.

Comparison	DEGs ($p \leq 0.05$; $q \leq 0.05$; $ \log_2FC \geq 0$)
2 wk vs Sed	24 (17 $\uparrow$, 7 $\downarrow$)
1 wk vs Sed	0 (0 $\uparrow$, 0 $\downarrow$)
24 h vs Sed	54 (34 $\uparrow$, 20 $\downarrow$)

Sed, sedentary

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Table 2. Differentially expressed genes ($p \leq 0.05$; $q \leq 0.05$; $|\log_2FC| \geq 0$) in the renal cortex following 2 wk of forced treadmill running compared to sedentary controls.

GENE SYMBOL DESCRIPTION	$\log_2FC$ (2 wk vs Sed)	p value	q value
Mmp13 matrix metalloproteinase 13	-0.9927161	1.20079124821137e-06	0.00286217
Cd209a CD209a antigen	-0.9297285	1.39594701818255e-06	0.00291142
Lipo2 lipase, member O2	-0.8140514	7.0608930313063e-05	0.04908792
Gm48281 predicted gene, 48281	-0.7427619	6.96859514127292e-05	0.04908792
Aplnr apelin receptor	-0.7362014	5.64340856981446e-06	0.00784669
Hsd11b1 hydroxysteroid 11-beta dehydrogenase 1	-0.6776846	6.75441427702162e-07	0.00217947
Bn19 butyrophilin-like 9	-0.55668	1.38923571537246e-05	0.01545293
Ptges prostaglandin E synthase	0.46447018	5.08743500694678e-05	0.04460685
Plekhd1 pleckstrin homology domain containing, family D (with coiled-coil domains) member 1	0.47365306	5.34693992151293e-05	0.04460685
Scnn1a sodium channel, nonvoltage-gated 1 alpha	0.48453738	4.4861074845423e-05	0.04402983
Scnn1b sodium channel, nonvoltage-gated 1 beta	0.49149907	6.94103162908644e-05	0.04908792
Gata2 GATA binding protein 2	0.49430821	8.68718810324816e-06	0.01114967
Il17re interleukin 17 receptor E	0.50633934	4.12959029246292e-06	0.00691373
Scnn1g sodium channel, nonvoltage-gated 1 gamma	0.5237748	4.76150421875476e-06	0.00722234
Hsd11b2 hydroxysteroid 11-beta dehydrogenase 2	0.52392481	4.88116923935426e-05	0.04460685
Cyp2d12 cytochrome P450, family 2, subfamily d, polypeptide 12	0.56069828	5.6857870368824e-05	0.04517493
Scd2 stearoyl-Coenzyme A desaturase 2	0.56812931	2.71001376924377e-07	0.00150722
Slc8a1 solute carrier family 8 (sodium/calcium exchanger), member 1	0.69592878	2.78640942581597e-05	0.02905703
Phactr1 phosphatase and actin regulator 1	0.72335467	1.76377395602284e-07	0.00147143
Foxi1 forkhead box I1	0.72459442	3.08250155682238e-08	0.00051432
Clu clusterin	0.73163776	1.03711154770606e-05	0.01236015
Stc1 stanniocalcin 1	0.74051396	4.14368240692022e-06	0.00691373
Acnat2 acyl-coenzyme A amino acid N-acyltransferase 2	0.75070466	3.62522018487204e-07	0.00151217
Cyp4a14 cytochrome P450, family 4, subfamily a, polypeptide 14	0.9283281	7.83746695460502e-07	0.00217947

Sed, sedentary