UNIVERSIDADE FEDERAL DE MINAS GERAIS

INSTITUTO DE CIÊNCIAS BIOLÓGICAS

LABORATÓRIO DE FISIOLOGIA RENAL "PROF. FERNANDO ALZAMORA"

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS BIOLÓGICAS: FISIOLOGIA E FARMACOLOGIA

EFEITOS DO TREINAMENTO AERÓBIO MODERADO SOBRE O ESTADO REDOX, A INFLAMAÇÃO E A APOPTOSE RENAIS NA INJÚRIA RENAL AGUDA INDUZIDA PELA GENTAMICINA EM RATOS

LEDA MARIA DE CASTRO COIMBRA CAMPOS

Belo Horizonte

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Tese submetida ao Programa de Pós-Graduação em Ciências Biológicas: Fisiologia e Farmacologia, ICB/UFMG, como requisito para a obtenção do título de Doutor.

Orientadora: Profa. Dra. Maria Aparecida Ribeiro Vieira.

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Tese de Doutorado defendida e aprovada, no dia **05 de dezembro de 2017**, pela Banca Examinadora constituída pelos seguintes professores:

PROFA. DRª. ANA CRISTINA SIMÕES E SILVA
UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROF. DR. CANDIDO CELSO COIMBRA
UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROFA. DRª. GUIOMAR NASCIMENTO GOMES
UNIVERSIDADE FEDERAL DE SÃO PAULO

PROFA. DRª. LENICE KAPPES BECKER OLIVEIRA
UNIVERSIDADE FEDERAL DE OURO PRETO

PROFA. DRª. MARIA APARECIDA RIBEIRO VIEIRA
UNIVERSIDADE FEDERAL DE MINAS GERAIS
ORIENTADORA

Programa de Pós-Graduação em Ciências Biológicas - Fisiologia e Farmacologia
Instituto de Ciências Biológicas - Universidade Federal de Minas Gerais - UFMG

Belo Horizonte, 05 de dezembro de 2017

Para Giovana, filha amada

AGRADECIMENTOS

Diante das possibilidades que se abriram em minha trajetória profissional, a docência foi uma escolha. Os muitos mestres que contribuíram à minha educação são fonte de admiração e inspiração. Neste momento da vida em especial, agradeço à minha orientadora Professora Dra. Maria Aparecida Ribeiro Vieira, pela oportunidade de trabalho, pelo seu entusiasmo com a pesquisa científica e com a educação humanística e pela amizade construída.

Agradeço aos membros da banca, pela disponibilidade em avaliar este trabalho.

À Professora Dra. Rafaela Fernandes da Silva, com a qual dividimos o laboratório, pela cessão de suprimentos à pesquisa, pelas conversas esclarecedoras e encorajadoras e pela amizade. Gratidão estendida a sua aluna, Melissa Santuchi pelo auxílio nas análises de biologia molecular.

Ao Dr. Markus Berger Oliveira, do Centro de Pesquisa Experimental do Hospital de Clínicas de Porto Alegre, pelo suporte no ensaio de atividade da citrato sintase.

Ao Professor Dr. Marcelo Vidigal Caliari e seu aluno Fabrício Oliveira, do Departamento de Patologia Geral, ICB, UFMG pelo suporte à confecção das lâminas histológicas, auxílio nas análises morfométrica e imuno-histoquímica e pela cordialidade.

Ao Professor Dr. Robson Augusto Souza dos Santos e seu aluno Marcos Melo pelo auxílio nas análises ultrassonográficas e cessão de suprimentos à pesquisa quando preciso.

À Professora Dra. Adelina Martha dos Reis e sua aluna e minha amiga Gleisy Kelly Neves Gonçalves, pelo auxílio à realização dos ensaios de Western Blot e imuno-histoquímica.

Ao Professor Dr. Almir de Souza Martins e sua aluna Débora Nascimento pela cessão do primer para S26 e auxílio nas análises de expressão gênica.

Ao Professor Dr. Jorge Luiz Pesquero e sua aluna Valéria Fernandes, pelo auxílio à realização dos ensaios de atividade de enzimas antioxidantes.

À Professora Dra. Virgínia Soares Lemos e seus alunos Lucas e Josiane, pelo auxílio à realização do ensaio de FOX-2.

Aos colegas do Laboratório de Fisiologia Renal “Prof. Fernando Alzamora”: Esdras, Mariana, Roberta, André, Gabriela, Fernando, Melissa, Mário, Miriane, Ildernandes, Ana Carolina, Bruno e Fernanda. Um grupo de pessoas íntegras, de convivência harmoniosa e muito amistosa, com o qual tive grande prazer em trabalhar. Construí com muitos laços sinceros de amizade e respeito que levarei para sempre.

Aos colegas de outros laboratórios: Carolina Campos, Letícia Cordeiro, Tatiane Almeida e Tatiane Barreto pela amizade e auxílio nos experimentos.

A Universidade Federal de Minas Gerais (UFMG) e ao Programa de Pós-Graduação em Ciências Biológicas: Fisiologia e Farmacologia (PGFisFar) do ICB, UFMG pelo ensino e pesquisa de qualidade.

Aos professores e funcionários do Departamento de Fisiologia e Biofísica e PGFisFar, em especial ao Zezé, a Simone, a Cintya e ao Rodner pela disposição para ajudar sempre que necessário.

Ao Programa Multicêntrico de Pós-graduação em Ciências Fisiológicas, pelo acesso aos centros de referência em pesquisa na Fisiologia, como a UFMG.

Às agências de fomento CNPq, CAPES E FAPEMIG pelo suporte financeiro.

Aos meus pais, pelo amor e esforço para garantir a mim o acesso a educação de qualidade.

A minha irmã, familiares e amigos, de longa data e recém-chegados, pelo apoio e encorajamento.

Ao Eric, meu esposo, por possibilitar que eu renunciasse à minha carreira profissional já conquistada para investir nesse sonho/desafio, pela parceria na vida e no amor, e à nossa filha Giovana, a quem dedico este trabalho.

“Curto e hábil é o caminho da especulação, mas não conduz a nenhuma parte; longo e penoso é o caminho da experiência, mas nos leva a conhecer a verdade.”

Galeno (129 – 200)

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ACSM	Colégio Americano de Medicina Esportiva (do inglês, *American College of Sports Medicine*)
ADH	Hormônio antidiurético (do inglês, *antidiuretic hormone*)
ANOVA	Análise de variância (do inglês, *analysis of variance*)
ATP	Adenosina trifosfato
Bax	Proteína X associada a Bcl-2 (do inglês, *Bcl-2-associated X protein*)
Bcl2	Linfoma de células B 2 (do inglês, *B-cell lymphoma 2*)
Bid	Agonista do domínio de interação BH3 (do inglês, Bcl-2 homology 3 interacting-domain death agonist)
Casp-3	Caspase 3
Casp-8	Caspase 8
Casp-9	Caspase 9
CH_2O	*Clearance* de água livre
Cosm	*Clearance* osmolar
CS	Enzima citrato sintase
Ct	*Cycle threshold*
DNA	Ácido desoxirribonucleico
DRC	Doença renal crônica
ELISA	Ensaio imunoenzimático (do inglês, *enzyme linked immunosorbent assay*)
EPM	Erro padrão da média
ERO	Espécies reativas de oxigênio
FC	Frequência cardíaca
Fe2+	Íon ferroso
Fe3+	Íon férrico
FOX2	Esnaio de oxidação ferrosa do xilenol orange, versão 2 (do inglês, *ferrous oxidation in xylenol orange version 2*)
FTG	*Feedback* túbulo-glomerular
FU	Fluxo urinário

GAPDH	gliceraldeído 3-fosfato desidrogenase (do inglês, *glyceraldehyde-3-phosphate dehydrogenase*)
GM	Gentamicina
H_2O_2	Peróxido de hidrogênio
IκB	Inibidor de kappa B
IL-10	Interleucina 10
IL-1β	Interleucina 1 beta
IL-6	Interleucina 6
IRA	Injúria renal aguda
K^+	Potássio
KEAP1	Repressor citoplasmático do Nrf2 (do inglês, *Kelch-like ECH-associated protein 1)*
mRNA	RNA mensageiro
Na^+	Sódio
NFκB	Fator de transcrição nuclear kappa B (do inglês, *nuclear factor kappa-light-chain-enhancer of activated B cells*)
NO	Óxido nítrico (do inglês, *nitric oxide*)
Nrf2	Fator nuclear eritróide 2 relacionado ao fator 2 (do inglês, *nuclear factor erythroid-2-related factor 2*)
NT	Não-treinado
NTA	Necrose tubular aguda
$O_2^{\cdot-}$	Ânion superóxido
PAD	Pressão arterial diastólica
PAM	Pressão arterial média
PAS	Pressão arterial sistólica
PBS	Solução tampão fosfato salino
PGC1-α	Receptor ativado por proliferador de peroxissoma gama coativador 1-alfa (do inglês, *peroxisome proliferator-activated receptor gamma coativator 1-alpha*)
PPARα	Receptor ativado por proliferador de peroxissoma alfa (do inglês, *peroxisome proliferator-activated receptor alpha*)
PVS	Pico da velocidade sistólica
qPCR	Reação em cadeira de polimerase quantitativa em tempo real
RFG	Ritmo de filtração glomerular

RNA	Ácido ribonucleico
RT-PCR	Reação em cadeia de polimerase com transcrição reversa
SAL	Solução salina
SOD	Superóxido dismutase
T	Treinado
TA	Temperatura ambiente
TAE	Tecido adiposo epididimal
TAMes	Tecido adiposo mesentérico
TAR	Tecido adiposo retroperitoneal
TBS	Tampão tris salino (do inglês, *tris-buffered saline*)
TEMP	Teste de esforço máximo progressivo
TGF-β	Fator de crescimento transformante (do inglês, *transforming growth factor-beta*),
TNF-α	Fator de necrose tumoral alfa (do inglês, *tumor necrosis factor*)
UA	Unidades arbitrárias
UTI	Unidade de terapia intensiva
VDF	Velocidade diastólica final
VE	Ventrículo esquerdo
VMC	Velocidade média do ciclo
$VO_{2máx}$	Consumo máximo de oxigênio

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RESUMO

O treinamento aeróbio vem se consolidando como um agente terapêutico em diversas doenças, inclusive em doenças renais. No entanto, os mecanismos que evidenciam o papel renoprotetor do treinamento ainda não estão bem elucidados. Além disso, são escassos os estudos que verificam se indivíduos que treinam apresentam alguma proteção renal, caso sejam acometidos de injúria renal aguda (IRA), em relação a indivíduos não-treinados. O presente estudo tem como objetivo avaliar os efeitos do treinamento instituído previamente à IRA induzida por gentamicina (GM) sobre a função, morfologia, estado redox, inflamação e apoptose renais. Ratos Wistar machos foram submetidos a um protocolo de treinamento aeróbio moderado durante 8 semanas, antes do tratamento com GM (80 mg / kg / dia / 5 dias) ou NaCl a 0,9% (solução salina). Então, os ratos foram divididos em 4 grupos: grupos não-treinado e treinado tratados com solução salina (NT-SAL e T-SAL) e grupos não-treinado e treinado tratados com gentamicina (NT-GM e T-GM) (n = 5 - 7). A pressão arterial e freqüência cardíaca foram medidas antes e após o treinamento. Ultrassonografia com Doppler das artérias renais e ecocardiografia foram realizadas ao final do tratamento. Amostras de urina, sangue e tecidos foram coletadas para investigações bioquímicas e histológicas (CEUA / UFMG, protocolo nº 46/2014). Os ratos treinados apresentaram melhores desempenho físico e adaptação oxidativa muscular comparados aos ratos não-treinados. Não foram detectadas modificações na pressão arterial, função cardíaca, perfusão renal e metabolismo energético renal (por expressão gênica de PPAR-α e PGC1-α) atribuídas ao treinamento. O treinamento prévio à IRA pela GM, atenuou o aumento da creatinina plasmática e da proteinúria, atenuou a queda do ritmo de filtração glomerular e na osmolalidade urinária, diminuiu a gravidade do dano no tecido renal, aumentou o nível de hidroperóxidos urinários e a expressão protéica de Nrf2 (fator de transcrição relacionado à resposta anti-oxidante), impediu a redução da atividade da catalase, atenuou os níveis de TNF-α, IL-1β, IL-6, inibiu a expressão protéica do NFκB (fator de transcrição relacionado à inflamação) e evitou o aumento da expressão de caspase 8 e Bax no tecido renal. Concluímos que o treinamento aeróbio prévio à IRA induzida pela GM atenuou os danos morfofuncionais renais, por reduzir a inflamação e a expressão de fatores pró-apoptóticos. É possível que o aumento na produção de espécies reativas de oxigênio pelo treinamento induza maior expressão de Nrf2, que pode exercer um papel central na renoproteção mediada pelo treinamento, por inibir o NFkB e assim reduzir a sinalização pró-inflamatória e pró-apoptótica nos rins.

ABSTRACT

Aerobic exercise has been increasingly used as a therapeutic agent in several diseases, including kidney disorders. However, the mechanisms playing a renoprotective role in physical exercise are still unclear. Additionally, there are few studies targeted at investigating whether trained individuals are powered with some renal protection in case they develop acute kidney injury (AKI). In the present study it was evaluated the effects of training prior to gentamicin (GM)-induced AKI on renal function, morphology, redox status, inflammation and apoptosis in rats. Male Wistar rats were submitted to a moderate aerobic training protocol for 8 weeks prior to treatment with GM (80mg/kg/day/5 days) or 0.9% NaCl (saline) (CEUA/UFMG, protocol #46/2014). Rats were divided into 4 groups: not trained and trained rats treated with saline (NT-SAL and T-SAL groups), not trained and trained rats treated with GM (NT-GM and T-GM groups) (n = 5-7). Blood pressure and heart rate were measured before and after training. Doppler ultrasonography of renal arteries and echocardiography were performed at the end of treatments. Samples of urine, blood and tissues were collected for biochemical and histological studies. Trained rats exhibited higher physical performance and muscular oxidative adaptation than not trained rats. Training did not induce any change in blood pressure, cardiac function, renal perfusion and renal energetic metabolism (gene expression of PPAR-α and PGC1-α). Training prior to GM-induced AKI attenuated the increase in plasma creatinine, proteinuria and the reduction in glomerular filtration rate and urinary osmolality. Training also decreased the severity of renal tissue damage, increased the level of urinary hydroperoxides and expression of Nrf2 (transcription factor related to the anti-oxidant response), prevented the reduction of catalase activity, attenuated the increse in renal levels of TNF-α, IL-1β, IL-6, inhibited expression of NFκB (transcription factor related to inflammation) and prevented the expression increase of renal caspase 8 and Bax. It was concluded that aerobic training prior to AKI induced by GM has attenuated renal morphofunctional damage by reducing inflammation and expression of pro-apoptotic factors. It is possible that increased production of reactive oxygen species by training induces a higher expression of Nrf2, which may play a central role in training-mediated renoprotection, by inhibiting NFκB and thereby reducing proinflammatory and pro-apoptotic signaling in the kidneys.

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9. ANEXO

APROVAÇÃO DA COMISSÃO DE ÉTICA NO USO DE ANIMAIS

UNIVERSIDADE FEDERAL DE MINAS GERAIS

CEUA
COMISSÃO DE ÉTICA NO USO DE ANIMAIS

UFMG

CERTIFICADO

Certificamos que o Protocolo nº. 46 / 2014, relativo ao projeto intitulado "Efeitos do treinamento aeróbio sobre o estado redox, a inflamação e a apoptose renais na injúria renal aguda induzida pela gentamicina", que tem como responsável MARIA APARECIDA RIBEIRO VIEIRA, está de acordo com os Princípios Éticos da Experimentação Animal, adotados pela Comissão de Ética no Uso de Animais (CEUA/UFMG), tendo sido aprovado na reunião de 19/05/2014. Este certificado espira-se em 19/05/2019.

CERTIFICATE

We hereby certify that the Protocol nº. 46 / 2014, related to the Project entilted "Effects of aerobic training on renal redox state, inflammation and apoptosis in gentamicin-induced acute kidney injury ", under the supervision of MARIA APARECIDA RIBEIRO VIEIRA, is in agreement with the Ethical Principles in Animal Experimentation, adopted by the Ethics Committee in Animal Experimentation (CEUA/UFMG), and was approved in 19/05/2014. This certificates expires in 19/05/2019.

Adriane da Costa Val Costa-Val
Coordenador(a) da CEUA/UFMG
Belo Horizonte, 19/05/2014.

Atenciosamente.

Sistema CEUA-UFMG
https://www.ufmg.br/bioetica/cetea/ceua/

Universidade Federal de Minas Gerais
Avenida Antônio Carlos, 6627 – Campus Pampulha
Unidade Administrativa II – 2º Andar, Sala 2005
31270-901 – Belo Horizonte, MG – Brasil