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**ESPÉCIES REATIVAS DE OXIGÊNIO COMO
SINALIZADORES DAS RESPOSTAS METABÓLICAS
MEDIADAS POR CONTRAÇÃO NO MÚSCULO
ESQUELÉTICO**

Dissertação apresentada ao Programa de Pós-Graduação em Fisiologia Humana do Instituto de Ciências Biomédicas da Universidade de São Paulo, para obtenção do Título de Mestre em Fisiologia Humana.

Área de Concentração: Fisiologia Humana

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RESUMO

PINHEIRO, C.H.J. **Espécies reativas de oxigênio como sinalizadores das respostas metabólicas mediadas por contração no músculo esquelético**. 2008. 141 f. Dissertação (Mestrado em Fisiologia Humana) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2008.

O objetivo deste estudo foi avaliar os efeitos da remoção intracelular de peróxido de hidrogênio (H_2O_2), induzida por tratamento com N-Acetilcisteína (NAC), nas respostas metabólicas mediadas por contrações moderadas produzidas por eletroestimulação, durante 30 e 120 minutos, em células musculares esqueléticas mantidas em cultura primária. Os seguintes parâmetros foram avaliados: produção de espécies reativas de oxigênio; translocação do transportador de glicose 4 (GLUT-4); captação de 2- desoxiglicose (2-DG); oxidação de palmitato; atividade máxima de enzimas glicolíticas (hexoquinase – HK e fosfofrutoquinase - PFK-1) e do ciclo de Krebs (citrato sintase - CS); produção de lactato; expressão dos genes GLUT-4, HKII, PFK-1, CS e carnitina palmitoil transferase 1 (CPT-1); e conteúdo das proteínas GLUT-4 e CPT-1. Os efeitos do tratamento com H_2O_2 (500 nM), por 30 e 120 min, também foram avaliados. O tratamento com NAC (800 μ M), por 24 horas, promoveu maior remoção do H_2O_2 produzido em condições basais e durante contrações. Em condições basais, o antioxidante diminuiu a expressão dos genes GLUT-4, PFK-1, atividade da PFK-1, produção de lactato, e aumentou a expressão dos genes CS e CPT-1, oxidação de palmitato e a atividade da CS. Não houve qualquer efeito na captação basal de 2-DG e na expressão da HKII e atividade da HK. A maior remoção intracelular do H_2O_2 durante contrações diminuiu a translocação de GLUT-4, captação de 2-DG, atividade da HK e da PFK-1, produção de lactato e expressão transiente dos genes GLUT-4, HKII e PFK-1. O H_2O_2 aumentou a captação de glicose, atividade da HK e da PFK, produção de lactato e expressão dos genes GLUT-4, HKII e PFK-1. Esses efeitos foram abolidos por NAC. A contração aumentou a atividade e expressão gênica da CS, expressão e conteúdo de CPT-1 e oxidação de palmitato. Entretanto, não houve efeito pelo tratamento com NAC. O H_2O_2 aumentou a oxidação de palmitato, no entanto, o mesmo efeito foi abolido por NAC e quando da diminuição da concentração intracelular de glutathione (GSH) pelo tratamento com L-Butionina sulfoximina (BSO) a 1 mM por 1 hora. O aumento transiente de H_2O_2 está envolvido na maior captação de glicose, ativação de enzimas glicolíticas, produção de lactato e expressão de genes relacionados à regulação do metabolismo de glicose em células musculares esqueléticas em contração. A sinalização redox, portanto, regula o metabolismo de glicose e ácidos graxos em células musculares esqueléticas.

Palavras-chave: Músculo Esquelético. Metabolismo Celular. Espécies Reativas de Oxigênio. Metabolismo de Carbohidratos. Metabolismo de Gordura. Contração Muscular.

ABSTRACT

PINHEIRO, C.H.J. **Reactive oxygen species as signaling molecules of contraction-mediated metabolic responses in skeletal muscle.** 2008. 141 f. Master Degree Thesis (Human Physiology) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2008.

The purpose of this study was to evaluate the effects of the removal of intracellular hydrogen peroxide (H_2O_2), induced by treatment with N-Acetylcysteine (NAC), on moderate contraction-mediated metabolic responses in primary culture of skeletal muscle cells. The contractions were induced by electrostimulation during 30 and 120 minutes. The following parameters were evaluated: production of reactive oxygen species (ROS); translocation of glucose transporter 4 (GLUT-4); uptake of 2-deoxyglucose (2-DG); oxidation of palmitate; activities of glycolytic enzymes (hexokinase – HK and phosphofructokinase - PFK-1) and of TCA cycle (citrate synthase - CS); production of lactate; expression of GLUT-4, HKII, PFK-1, CS and carnitine palmitoyl transferase 1 (CPT-1) and protein levels of GLUT - 4 and CPT-1. The effects of treatment with H_2O_2 (500 nM), for 30 and 120 min, were also investigated. Treatment with NAC (800 μ M) promoted great removal of the H_2O_2 produced in baseline conditions and during muscle contractions. In baseline conditions, the antioxidant decreased expression of GLUT-4, PFK-1, activity of PFK-1, and production of lactate, and increased expression of CPT-1 and CS, oxidation of palmitate and CS activity. There was no effect on basal uptake of 2-DG and gene expression and activity of HK. The removal of intracellular H_2O_2 during muscle contractions decreased the translocation of GLUT-4, uptake of 2-DG, activities of HK and PFK-1, production of lactate and transient expression of GLUT-4, HKII and PFK-1. H_2O_2 increased glucose uptake, and the activities of glycolytic enzymes (HK and PFK-1), production of lactate and transient expression of GLUT-4, HKII and PFK-1. These effects of H_2O_2 were abolished by NAC treatment. Muscle contraction increased activity and gene expression of CS, expression of CPT-1 and oxidation of palmitate. The antioxidant did not cause effect in contraction-induced changes in β -oxidation of fatty acids. H_2O_2 induced increase of palmitate oxidation. However, this effect was not observed in NAC-treated cells and when the intracellular concentration of glutathione (GSH) was lowered by treatment with L-Butionine sulfoximine (BSO) to 1 mM for 1 hour. The contraction-induced transient increase of H_2O_2 levels is involved in the increases of glucose uptake, activation of glycolytic enzymes, lactate production, and expression of genes associated to regulation of glucose metabolism in skeletal muscle cells. The redox signalling, therefore, regulates the metabolism of glucose and fatty acids in skeletal muscle cells.

Key words: Skeletal Muscle. Cell Metabolism. Reactive Oxygen Species. Metabolism of Carbohydrate. Metabolism of Fat. Muscle Contraction.

1 INTRODUÇÃO

A contração é um potente estímulo fisiológico que induz alterações bioquímicas, metabólicas e moleculares no músculo esquelético. Demonstra-se que, mesmo na ausência de estímulos hormonais, somente a atividade contrátil é capaz de aumentar o transporte de glicose, a atividade de enzimas glicolíticas e oxidativas, a oxidação de ácidos graxos e a transcrição de genes relacionados à regulação do metabolismo, defesa antioxidante e neoangiogênese (WILLIAMS e NEUFER, 1996; PATTWELL *et al.*, 2004; GUSTAFSSON *et al.*, 2005; SILVEIRA *et al.*, 2006; WALSH *et al.*, 2006; WALSH *et al.*, 2008). Uma única sessão de exercício/contração induz aumento transiente na transcrição dos genes do transportador de glicose 4 (GLUT-4) (NEUFER e DOHM, 1993; KRANIOU *et al.*, 2000), hexoquinase II (HKII) (O'DOHERTY *et al.*, 1994), coativador 1 alfa do receptor ativado por proliferadores de peroxissoma (PGC-1 α) (SILVEIRA *et al.*, 2006), proteína desacopladora mitocondrial 3 (UCP3) (TSUBOYAMA-KASAOKA *et al.*, 1998; PILEGAARD *et al.*, 2000), lipase de lipoproteínas (LPL) (SEIP *et al.*, 1997; HAMILTON *et al.*, 1998), piruvato desidrogenase quinase 4 (PDK4) (PILEGAARD *et al.*, 2000), óxido nítrico sintase induzível (iNOS) (GOMEZ-CABRERA *et al.*, 2005), fator de crescimento endotelial vascular (VEGF) (GUSTAFSSON *et al.*, 2005), heme oxigenase 1 (HO-1) (ESSIG *et al.*, 1997), carnitina palmitoil transferase 1b (CPT-1b) (PILEGAARD *et al.*, 2000) e citrato sintase (CS) (NEUFER e DOHM, 1993).

Paralelamente a essas respostas metabólicas e moleculares, durante a contração no músculo esquelético, observa-se aumento na produção de espécies reativas de oxigênio (EROs) (SILVEIRA *et al.*, 2003). As EROs possuem baixo peso molecular, curta meia-vida e alta reatividade com compostos orgânicos. O radical ânion superóxido ($O_2^{\bullet -}$) é gerado pela redução incompleta do oxigênio molecular (O_2), principalmente na cadeia respiratória mitocondrial e por oxidases. Espontaneamente, o $O_2^{\bullet -}$ pode sofrer dismutação, reação auto-redox, e originar peróxido de hidrogênio (H_2O_2). Na presença de íons metálicos, o H_2O_2 é transformado em radical hidroxil ($OH^{\bullet}$) que é altamente reativo e possui alto potencial para causar danos na célula. Ao longo da evolução, as células desenvolveram sistemas de defesa antioxidante. A superóxido dismutase (SOD), presente na mitocôndria e no citoplasma celular, catalisa a conversão de $O_2^{\bullet -}$ à H_2O_2 . Já, o H_2O_2 formado é convertido em água pela catalase (CAT) e pela glutational peroxidase (GPX-1). Através dessas reações redox, as defesas antioxidantes previnem a formação de $OH^{\bullet}$ e protegem a célula de danos oxidativos em lipídeos de membrana, proteínas reguladoras e ácidos nucleicos. Condições patológicas como doenças neurodegenerativas, câncer, insuficiência cardíaca, hipertensão arterial, obesidade e diabetes envolvem um desequilíbrio redox que se

caracteriza, em parte, por deficiência nas defesas antioxidantes associada a uma maior produção de EROs.

Os primeiros estudos sobre a geração de EROs e estresse oxidativo durante o exercício físico foram realizados entre 1970 e início de 1980. Os trabalhos seguintes buscaram compreender a natureza e as fontes geradoras dessas espécies, assim como os fatores que influenciam sua produção, no músculo esquelético. Atualmente, está bem estabelecido que o exercício extenuante e contrações intensas induzem estresse oxidativo no músculo esquelético. Isso ocorre porque a produção de EROs está intensificada e supera a capacidade antioxidante da fibra muscular. Concomitantemente, as fibras musculares produzem EROs continuamente em baixas concentrações no repouso sendo que a atividade contrátil eleva de forma significativa essa produção. O $O_2^{\bullet -}$ é gerado principalmente pelos complexos I e III da cadeia respiratória mitocondrial e também por oxidases no músculo esquelético durante o exercício físico. Dentre as principais enzimas geradoras de EROs, destacam-se o complexo NADPH oxidase, presente no sarcolema, e a xantina oxidase (XO) presente no endotélio. Diante das evidências científicas de que o exercício físico induz estresse oxidativo, por quê praticar atividade física, se a produção de radicais livres se eleva? Uma das respostas está no efeito da contração na expressão gênica e atividade das enzimas antioxidantes. Com o treinamento físico, o potencial antioxidante aumenta na fibra muscular. Por outro lado, alguns autores demonstraram que quando em concentrações baixas as EROs podem atuar como sinalizadores por um mecanismo denominado de sinalização redox. Tal mecanismo envolve oxidações reversíveis de grupos tióis em proteínas específicas (enzimas e fatores de transcrição gênica) sendo a reversibilidade dessas reações atribuída à substâncias redutoras de tióis incluindo a glutathione reduzida (GSH), tioredoxina, glutarredoxina e peroxirredoxina.

Durante contrações intensas e exercício extenuante, concentrações altas de EROs estão associadas ao declínio da função muscular. Isso se deve a oxidações irreversíveis em grupos tióis de proteínas contráteis e na bomba de Ca^{2+} do retículo sarcoplasmático (SERCA) levando ao desenvolvimento da fadiga e queda do desempenho do músculo esquelético. Já, durante contrações moderadas, a produção de EROs se eleva sendo também acompanhada do aumento na expressão gênica e atividade de enzimas antioxidantes o que reduz o estresse oxidativo. Dessa maneira é possível que, em concentrações baixas/moderadas as EROs possam atuar como sinalizadores no músculo esquelético em contração.

7 CONCLUSÕES

O metabolismo de glicose e ácidos graxos em células musculares esqueléticas é regulado por alterações no estado redox. Em condições basais, o tratamento com o antioxidante NAC reduziu a expressão dos genes GLUT-4 e PFK-1, ao passo que aumentou a de CS e CPT-1. O NAC também diminuiu a atividade da PFK, produção de lactato, e aumentou a atividade da citrato sintase e oxidação de ácidos graxos, porém não teve qualquer efeito sobre o transporte de glicose e atividade da hexoquinase.

Em células submetidas à contração por 30 minutos, a presença do antioxidante reduziu a captação de glicose, conteúdo de GLUT-4 no sarcolema, atividade da hexoquinase e fosfofrutoquinase e a produção de lactato. A expressão transiente dos genes GLUT-4, HKII e PFK-1 também foi inibida pelo tratamento com NAC. O tratamento com H_2O_2 promoveu aumento no transporte de glicose, nas atividades da hexoquinase e fosfrutoquinase, produção de lactato e expressão transiente dos genes GLUT-4, HKII e PFK-1.

Durante contrações por 120 minutos, onde o consumo de ácidos graxos está favorecido, a presença do antioxidante NAC não teve qualquer efeito na atividade da citrato sintase e oxidação de ácidos graxos de cadeia longa. Também não houve efeito na expressão gênica de CS e CPT-1. O tratamento com H_2O_2 resultou em aumento na oxidação de ácidos graxos e esse efeito foi abolido pela diminuição na concentração intracelular de GSH induzida pelo tratamento com BSO. Visto que o aumento na expressão de genes da β -oxidação de ácidos graxos é demonstrado no período de recuperação do exercício (onde a síntese de antioxidantes está estimulada e a produção de EROs é reduzida) as evidências obtidas no presente estudo sugerem que o conteúdo de tióis pode ter um papel importante nesses mecanismos de regulação.

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