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IMPACTO DO DIABETES INDUZIDO POR ESTREPTOZOTOCINA NA
RESPOSTA HIPERTRÓFICA DOS MÚSCULOS SÓLEO E EXTENSOR
DIGITAL LONGO (EDL)

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RESUMO

FORTES, M. A. S. Impacto do diabetes induzido por estreptozotocina na resposta hipertrófica dos músculos sóleo e extensor digital longo (EDL). 2013. 109 f. Dissertação (Mestrado em Fisiologia Humana) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2014.

O efeito da hipertrofia induzida por sobrecarga funcional no músculo extensor digital longo (EDL, de contração rápida) e sóleo (contração lenta) de ratos diabéticos induzidos por estreptozotocina foi avaliado. Ratos Wistar (8 semanas de idade) foram induzidos ao estado diabético por dose única de estreptozotocina (65mg/kg de peso corporal, i.v.) e mantidos nessa condição durante quatro semanas. Foi então realizada tenotomia do músculo gastrocnêmio ou ablação do músculo tibial anterior. Os conteúdos de Akt e S6 totais e fosforiladas foram avaliados após uma e quatro semanas de sobrecarga nos músculos EDL e sóleo. No EDL, após 7 dias de sobrecarga na pata hipertrofiada, o conteúdo de Akt total não se alterou, mas ocorreu aumento de fosfo-Akt (Thr³⁰⁸) em 2,1 vezes nos controles e em 1,5 vezes nos diabéticos. Os conteúdos de fosfo-S6 (Ser^{240/244}) e S6 total aumentaram em 2,1 vezes e 4 vezes, respectivamente no grupo diabético e em 4,8 e 3,6 vezes, respectivamente no controle, no músculo EDL após 7 dias de sobrecarga. Os aumentos induzidos pela sobrecarga nos conteúdos de fosfo-Akt, fosfo-S6 e S6 total no músculo EDL foram semelhantes entre os grupos. No músculo sóleo, os conteúdos de Akt total (em 2,7 vezes em ambos os grupos) e fosfo-Akt (em 2,2 vezes no controle e 2,6 vezes no diabético) aumentaram, após 7 dias de sobrecarga. O conteúdo de S6 total não apresentou diferença enquanto que o de fosfo-S6 aumentou em 4,7 vezes no controle e em 2,8 vezes no grupo diabético. A área da secção transversa das fibras (CSA), a massa, as forças tetânica e isotônica, absolutas e específicas, foram avaliadas nos músculos sóleo e EDL após 4 semanas de sobrecarga. Aumentos similares na massa muscular e CSA foram observados nos músculos EDL e sóleo nos animais diabéticos e controles em resposta à sobrecarga. Os animais diabéticos apresentaram aumento semelhante nas forças tetânica e força isotônica absolutas em comparação aos controles. A sobrecarga funcional aumentou a expressão do gene da FAK e reduziu de MuRF-1, Atroquina-1 e Miostatina no músculo sóleo, conforme indicado por análise em RT-PCR. A expressão do gene IGF-1 Eb se elevou devido à hipertrofia no músculo sóleo e EDL. Estes resultados são indicativos de que a deficiência de insulina por até 4 semanas não afeta de modo significativo a resposta hipertrófica induzida por sobrecarga funcional nos músculos sóleo e EDL de ratos.

Palavras-chave: Músculo esquelético. *Diabetes mellitus*. Hipertrofia muscular. mTOR. Hiperglicemia.

ABSTRACT

FORTES, M. A. S. **Impact of streptozotocin-induced diabetes in the hypertrophic response of the soleus and extensor digitoralis longus (EDL) muscles.** 2013. 109 f. Master Degree Dissertation (Human Physiology) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2014.

The effects of hypertrophy induced by functional overload on fast-twitch extensor digitoralis longus (EDL) and soleus (slow-twitch) muscles of streptozotocin-induced diabetic rats were evaluated. Male Wistar rats (8 weeks old) were rendered diabetic by a single dose of streptozotocin (65mg/kg b.w., i.v.) and maintained under this condition for four weeks. Tenotomy of the gastrocnemius muscle or tibialis anterior ablation were then performed. Contents of total and phosphorylated Akt and S6 were evaluated after one and four weeks of overload in EDL and soleus muscles. After 7 days of overload, contents of total Akt were not altered on EDL. However, phospho-Akt content was increased (Thr³⁰⁸) by 2.1 and 1.5-fold in control and diabetic animals respectively in the hypertrophied EDL muscle. Contents of phospho-S6 (Ser^{240/244}) and total S6 were increased after 7 days of overload either in the control (by 2.1 and 4-fold respectively) and diabetic (by 4.8 and 3.6-fold, respectively) groups. Increases in the contents of phospho-Akt, phospho-S6 and total S6 in the EDL muscle were similar between groups. After 7 days of overload, increases in contents of total Akt (2.7-fold in both groups) and phospho-Akt (by 2.2-fold in the control and 2.6-fold in diabetic groups) were observed in the soleus muscle. Contents of total S6 in the soleus muscle remained unchanged, whereas the content of phospho-S6 was increased by 4.7-fold in the control and by 2.8-fold in diabetic group due to overload. Fiber cross-sectional area (CSA), muscle mass, and tetanic forces were evaluated after four weeks of overload. Increases in muscle mass and CSA were observed in EDL and soleus muscles of diabetic and control rats. Diabetic animals showed similar increase in absolute tetanic force and twitch force when compared to controls. As indicated by RT-PCR, FAK gene expression was increased, whereas that of MuRF-1, Atrogin-1 and Myostatin was reduced by functional overload in the soleus muscle. Gene expression of IGF-1 Eb was increased due to hypertrophy in the soleus and EDL muscle. These results indicate that a deficiency of insulin for up to 4 weeks has no significant effect on the hypertrophic response induced by functional overload on the EDL and soleus muscles.

Key words: Skeletal muscle. *Diabetes mellitus*. Skeletal muscle Hypertrophy. mTOR. Hyperglycemia.

1 INTRODUÇÃO

A hipertrofia do músculo esquelético é definida como o seu aumento em diâmetro, sem acréscimo no número de fibras musculares sendo acompanhado de síntese de proteínas e força contrátil elevadas (SARTORELLI; FULCO, 2004). As condições fisiológicas que promovem crescimento do músculo esquelético do adulto, o fazem por meio do aumento da síntese de proteínas miofibrilares contráteis e diminuição da degradação de proteínas sarcoplasmáticas. O tamanho das fibras musculares é controlado por dois processos paralelos: perda ou acréscimo de mionúcleos e renovação de proteínas sarcoméricas (SANDRI et al., 2013). As vias que controlam a renovação celular e de proteínas são diferentes bem como a contribuição de cada uma para a hipertrofia muscular. As intervenções genéticas podem não ser a melhor estratégia para estimular a hipertrofia, pois genes relacionados ao ganho de massa muscular quando alterados comprometem mais a renovação celular do que a síntese de proteínas (SCHIAFFINO et al., 2013).

A insulina estimula a síntese de proteínas no músculo esquelético (SANDRI, 2008; SCHIAFFINO et al., 2013). Em estados de deficiência de insulina, como *diabetes mellitus* tipo 1, ocorre redução na síntese e aumento na degradação de proteínas, levando à perda da massa muscular esquelética (BARAZZONI et al., 2004). Animais com *diabetes mellitus* induzido por administração de estreptozotocina apresentam aumento da atividade proteolítica muscular em curto prazo (1-3 dias após a indução do diabetes) que retorna a valores semelhantes aos controles após 5 a 10 dias (PEPATO et al., 1996).

A miostatina (GDF-8 *growth/differentiation factor* - 8) é de fundamental importância na hipertrofia. Ela faz parte da família dos TGF- β (*transforming growth factor* – β) que compreendem fatores de crescimento e de diferenciação celulares (MCPHERRON et al., 1997). O aumento na expressão de miostatina em curto-prazo está associado à severidade da perda de massa muscular, sendo esta revertida pelo tratamento com insulina (CHEN et al., 2009). Após longo período de diabetes (aproximadamente 8 semanas), a expressão de

miostatina retorna ao valor dos controles (BARAZZONI et al., 2004; CHEN et al., 2009).

A hiperglicemia causa redução da massa muscular esquelética. Miotubos expostos a altas concentrações de glicose (10-25 mM) apresentam aumento na degradação e diminuição na síntese de proteínas por autofosforilação da proteína quinase R (PKR - *double-stranded-RNA-dependent protein kinase*) que fosforila a p38MAP-quinase ativando a fosfolipase A₂. A ativação desta promove liberação de ácido araquidônico dos fosfolípidos de membrana e gera espécies reativas de oxigênio (EROs) (HAYAMA et al., 2002; RUSSELL et al., 2009). As EROs causam efeitos deletérios e complicações no diabetes por modificações químicas em lipídios e proteínas (BAYNES, 1991). Causam também redução nos conteúdos de *MyoD*, miogenina e miosina de cadeia leve e inibição na formação de novas fibras musculares (GRZELKOWSKA-KOWALCZYK et al., 2013). *MyoD* é um fator de transcrição associado ao comprometimento de uma célula progenitora para o programa miogênico. A miogenina é expressa na fase terminal de diferenciação, necessária para a fusão de miócitos e formação de miotubos (BENTZINGER et al., 2012).

O tratamento com concentração elevada de glicose (10-25 mM) leva à ativação da apoptose em miotubos murinos mediada por caspases 3 e 8 sendo acompanhada de ativação do sistema ubiquitina-proteassoma (RUSSELL et al., 2009). Este é um mecanismo importante da perda de massa muscular esquelética no estado diabético (RUSSELL et al., 2009).

O modelo de sobrecarga funcional por ablação da musculatura sinergista é a abordagem experimental mais utilizada para o estudo dos mecanismos envolvidos na hipertrofia do músculo esquelético (ROSENBLATT; PARRY, 1992; PHELAN; GONYEA, 1996; BODINE et al., 2001; ISHIDO et al., 2006; PATURI et al., 2010; KATTA et al., 2010). A hipertrofia dos músculos extensor digital longo (EDL) e sóleo é induzida por ablação do tibial anterior e tenotomia do gastrocnêmio, respectivamente (BODINE; BAAR, 2012; BOOTH; THOMASON, 1991). A hipertrofia por sobrecarga funcional está associada à ativação da via de sinalização da mTOR. Rosenblatt e Parry (1992) demonstraram que ativação, proliferação e fusão de células tronco musculares são essenciais para a hipertrofia compensatória após ablação sinergista. O

tratamento com rapamicina atenua mas não inibe a hipertrofia muscular induzida por sobrecarga funcional após ablação sinérgica (BODINE et al., 2001). Além desse fator, o envelhecimento e a ativação da AMP-quinase estão associados ao menor crescimento da massa muscular induzido por sobrecarga funcional (RIVAS et al., 2011; THOMSON; GORDON, 2005).

Pouco se sabe sobre o efeito do *diabetes mellitus* nas adaptações ou respostas da massa muscular esquelética ao exercício resistido e sobrecarga funcional. Paturi e colaboradores (2010) demonstraram que a hipertrofia por sobrecarga funcional no músculo sóleo de ratos Zucker (obesos e com resistência à insulina) é menor comparada a dos animais controles. Há menor ativação da via de sinalização da mTOR (SITNICK; BODINE; RUTLEDGE, 2009) caracterizada por menor fosforilação de p70S6-quinase e aumento de TSC1/TSC2 (hamartina/tuberina) no músculo sóleo de animais obesos submetidos à hipertrofia (PATURI et al., 2010). Menor ativação da via da mTOR também foi demonstrada por Katta e colaboradores (2010) no músculo sóleo de ratos Zucker com hipertrofia induzida por sobrecarga funcional (KATTA et al., 2010). Não há evidências do efeito do estado diabético sobre a hipertrofia do músculo extensor digital longo (EDL) que apresenta predominância de fibras musculares brancas. Em experimentos realizados pelo nosso grupo verificou-se que o músculo EDL de animais com diabetes induzido por estreptozotocina apresenta maior perda de massa quando comparado ao sóleo. Houve diminuição do número total de células-tronco musculares no músculo EDL de ratos diabéticos e diminuição das capacidades proliferativa e de fusão dessas durante a miogênese *in vitro* que não foi revertida pelo tratamento com insulina (3U/dia). Quando submetidos à lesão muscular por injeção de cardiotoxina, os animais controles recuperaram espontaneamente a força muscular ao contrário dos diabéticos que continuaram com a função comprometida. Animais diabéticos induzidos por estreptozotocina também apresentaram aumento da fosforilação de AMP-quinase (AMPK) com efeito negativo sobre a hipertrofia muscular por reduzir a ativação das proteínas da via da mTOR: Akt em Ser⁴⁷³, mTOR em Ser²⁴⁴, *ribosomal protein S6 kinase* em Thr³⁸⁹ e *eukaryotic initiation factor (eIF4E)-binding protein* em Thr³⁷ (BOLSTER et al., 2002; THOMSON; GORDON, 2005).

7 CONCLUSÃO

A sobrecarga funcional causou hipertrofia semelhante nos músculos sóleo e EDL nos animais controles e diabéticos, com aumento das forças tetânica e isotônica, absolutas e específicas. O músculo EDL hipertrofiado se tornou mais resistente à fadiga nos animais diabéticos, mas não houve mudança nos controles. O músculo sóleo hipertrofiado se tornou menos resistente à fadiga nos animais diabéticos e mais resistente nos controles. A ativação das vias de síntese (fosfo-Akt e fosfo-S6) persistiu por até 30 dias no músculo vermelho. O aumento no conteúdo de mRNA de IGF-1 Eb foi mais pronunciado no músculo sóleo do que no EDL devido à sobrecarga funcional. A expressão de mRNA da FAK aumentou no músculo sóleo nos dois grupos, mas no EDL se elevou somente no grupo controle. A hipertrofia causou aumento na expressão de Ankrd2 no EDL dos diabéticos e redução no sóleo dos controles. Os músculos dos animais diabéticos sofrem alterações fenotípicas semelhantes porém com o envolvimento de vias moleculares distintas.

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