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EFEITOS DO ÁCIDO PALMITOLEICO NA CAPTAÇÃO E METABOLISMO DE GLICOSE E TRIACILGLICEROL EM ADIPÓCITOS BRANCOS

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RESUMO

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Neste trabalho nós testamos a hipótese que o ácido palmitoleico, um ácido graxo que aumenta a captação de glicose e sensibilidade à insulina no músculo esquelético e fígado e suprime a esteatose hepática, modula o metabolismo de glicose e triacilglicerol (TAG) em adipócitos brancos. Para isso, células 3T3-L1 diferenciadas, tratadas com ácido palmitoleico (16:1n7, 200 µM) ou ácido palmítico (16:0, 200 µM) por 24h e adipócitos primários epididimais de camundongos C57BL6 selvagens ou deficientes para PPARα, tratados com 16:1n7 (300 mg/kg/dia) ou ácido oleico (18:1n9, 300 mg/kg/dia), via gavagem durante 10 dias, foram avaliados quanto a captação de glicose e a sua oxidação, conversão em lactato e incorporação em ácidos graxos e glicerol de TAG, bem como, a incorporação de acetato em ácidos graxos, lipólise, síntese de TAG e expressão gênica e proteica de proteínas reguladoras das vias estudadas. Nossos resultados demonstram que o tratamento com 16:1n7, mas não com 18:1n9 (*in vivo*) ou 16:0 (*in vitro*), aumenta a captação de glicose basal e estimulada por insulina e o conteúdo de GLUT4 e phosphoThr172AMPKα, sem afetar o GLUT1 ou phosphoSer473AKT. Tal aumento de GLUT4 induzido por 16:1n7 foi abolido pela inibição farmacológica da AMPK. Além disso, o 16:1n7 aumenta a conversão de glicose em lactato e CO_2 (oxidação de glicose) e diminui a síntese *de novo* de ácidos graxos *in vitro*. Corroborando com esses achados, a atividade das enzimas glicose-6-fosfato desidrogenase e ATP citrato liase também foram reduzidas pelo tratamento de células 3T3-L1 com 16:1n7. Ainda, o tratamento de células 3T3-L1 com 16:1n7, mas não com 16:0, aumentou a lipólise basal e estimulada por isoproterenol, os níveis de mRNA da lipase de triglicerídeos do adipócito (ATGL) e lipase hormônio sensível (HSL), além do conteúdo proteico da ATGL e phosphoSer660HSL. O aumento na lipólise induzido por 16:1n7, que pode ser abolido através da inibição farmacológica de PPARα, foi associado a maior atividade transcricional de PPARα *in vitro*. Ademais, 16:1n7 e 16:0 aumentaram a incorporação de ácidos graxos em TAG e a síntese de glicerol 3-fosfato a partir da glicose, sem modificar a gliceroneogênese e a expressão da gliceroquinase. Corroborando com os resultados *in vitro*, o tratamento de camundongos selvagens, mas não os deficientes em PPARα, com 16:1n7 aumentou a lipólise basal e estimulada e os níveis de mRNA da ATGL e HSL em adipócitos epididimais. Em contraste com a lipólise *in vivo*, o tratamento com 16:1n7 aumentou a incorporação de ácidos graxos em TAG e a síntese de glicerol 3-fosfato a partir da glicose, tanto em camundongos selvagens quanto em deficientes para PPARα. Em resumo, o ácido palmitoleico aumenta a captação de glicose e sua utilização pelos adipócitos brancos, um efeito que está associado com o aumento da expressão de GLUT4 e ativação da AMPK. Além disso, este ácido aumenta a lipólise e lipases em adipócitos por um mecanismo dependente de PPARα.

Palavras-chave: Metabolismo de glicose. Lipogênese. Lipólise. Ácidos graxos.

ABSTRACT

Bolsoni-Lopes A. Effects of palmitoleic acid on the uptake and metabolism of glucose and triacylglycerol in white adipocytes. [Ph. D. thesis (Human Physiology)]. São Paulo: Instituto de Ciências Biomédicas, Universidade de São Paulo; 2014.

Herein we investigated whether palmitoleic acid, a fatty acid that enhances whole body glucose disposal and suppresses hepatic steatosis, modulates glucose and triacylglycerol (TAG) metabolism in white adipocytes. For this, both differentiated 3T3-L1 cells treated with either palmitoleic acid (16:1n7**,** 200 μM) or palmitic acid (16:0, 200 μM) for 24h and primary epididimal adipocytes from wild type or PPARα knockout mice treated with 16:1n7 (300 mg/kg/day) or oleic acid (18:1n9, 300 mg/kg/day) by gavage for 10 days were evaluated for glucose uptake and its oxidation, conversion into lactate and incorporation into fatty acids and glycerol of TAG, as well as, incorporation of acetate into fatty acids, lipolysis, TAG synthesis and gene and protein expression profile. Our results demonstrate that treatment with 16:1n7, but not 18:1n9 (*in vivo*) or 16:0 (*in vitro*) acids, increases both basal and in sulin-stimulated glucose uptake and the content of GLUT4 and phosphoThr172AMPKα, without affecting GLUT1 or phosphoSer473AKT. Such increase in GLUT4 induced by 16:1n7 was prevented by pharmacological inhibition of AMPK. In addition, 16:1n7 increases glucose conversion into lactate and CO_2 (glucose oxidation), and decreases *de novo* fatty acids synthesis *in vitro*. Corroborating these findings, the activity of glucose-6-phosphate dehydrogenase and ATP-citrate liase enzymes were also decreased by treatment of 3T3-L1 cells with 16:1n7. Furthermore, treatment of 3T3-L1 cells with 16:1n7, but not 16:0, increased basal and isoproterenol-stimulated lipolysis, mRNA levels of adipose triglyceride lipase (ATGL) and hormone sensitive lipase (HSL) and protein content of ATGL and phosphoSer660HSL. Such increase in lipolysis induced by 16:1n7, which can be prevented by pharmacological inhibition of PPARα, was associated with higher rates of PPARα binding to DNA *in vitro*. In addition, both 16:1n7 and 16:0 increased fatty acid incorporation into TAG and glycerol 3-phosphate synthesis from glucose, without affecting glyceroneogenesis and glycerokinase expression. Corroborating *in vitro* findings, treatment of wild type, but not PPARα deficient mice with 16:1n7 increased epididimal adipocytes basal and stimulated lipolysis and ATGL and HSL mRNA levels. In contrast to lipolysis *in vivo*, however, 16:1n7 treatment increased fatty acid incorporation into TAG and glycerol 3-phosphate synthesis from glucose in both wild type and PPARα deficient mice. In conclusion, palmitoleic acid increases glucose uptake and utilization by white adipocytes, an effect that was associated with increase of GLUT4 expression and AMPK activation. Furthermore, palmitoleic acid increases adipocyte lipolysis and lipases by a mechanism that requires a functional PPARα.

Keywords: Glucose metabolism. Lipogenesis. Lipolysis. Fatty acids.

1 INTRODUÇÃO

O ácido palmitoleico ou ácido delta-9-cis-hexadecenóico é um ácido graxo monoinsaturado ômega 7 de dezesseis carbonos (16:1n7) sintetizado endogenamente em células como adipócitos e hepatócitos como resultado da dessaturação do ácido palmítico (16:0), processo catalisado pela enzima *estearoil-CoA-dessaturase 1* (SCD-1). Dessa forma, este ácido graxo é tido como um marcador da síntese *de novo* de ácidos graxos (1). Além da síntese endógena, o ácido palmitoleico também pode ser encontrado principalmente no óleo de semente de macadâmia (cerca de 30% do total de lipídeos) e na polpa de espinheiro-marítimo (*Hippophae rhamnoides*, entre 20 e 30%) (2).

Este ácido graxo é facilmente encontrado no plasma e tecido adiposo branco (TAB) de mamíferos e, apesar de praticamente ausente em pré-adipócitos, sua concentração aumenta acentuadamente durante a adipogênese, tornando-se o quarto ou quinto ácido graxo mais abundante que compõe os triacilgliceróis (TAG) de adipócitos humanos (variando conforme o depósito de TAB estudado) (3-5) e o mais abundante nos TAG de células 3T3-L1 (6, 7). Além disso, o ácido palmitoleico ocupa principalmente a posição *sn*2 da molécula de TAG (8, 9).

Ácidos graxos são importantes moléculas sinalizadoras celular, capazes de modular o metabolismo das células e tecidos por mecanismos distintos, que favorecem ou previnem o desenvolvimento de doenças como o diabetes tipo II, aterosclerose e obesidade (10-13). Em sua estrutura, o tamanho da cadeia carbônica e o número/posição das duplas ligações determinam suas propriedades físicas e químicas, conferindo a cada um deles funções biológicas únicas (14). Neste contexto, o ácido palmitoleico foi recentemente descrito como um hormônio lipídico, denominado lipocina, que é sintetizado e secretado por adipócitos e atua em órgãos alvos distantes modulando importantes processos metabólicos e inflamatórios de tecidos corporais como o músculo, fígado e pâncreas (1, 15).

Estudos *in vitro* e *in vivo* (roedores e humanos) encontraram que o ácido palmitoleico possui ações importantes no músculo esquelético e fígado aumentando a captação de glicose e a sensibilidade à insulina, bem como reduzindo a esteatose hepática, respectivamente (1, 16-18). Mais especificamente, estudos verificaram que células musculares esqueléticas tratadas com ácido palmitoleico apresentam

aumento na captação de glicose, maior conteúdo proteico de transportadores de glicose 1 e 4 (GLUTs) na membrana celular e aumento na fosforilação da AKT, do receptor de insulina (IR) e dos substratos do receptor de insulina 1 - 2 (IRS), além de aumento na oxidação de glicose (1, 17, 19). Interessantemente, Dimopoulos et al. (2006) demonstraram que o tratamento com ácido palmitoleico bloqueou os efeitos deletérios do ácido palmítico no metabolismo da glicose e sensibilidade à insulina em células musculares L6 (17).

Já no tecido hepático, o tratamento com ácido palmitoleico também aumentou a fosforilação da AKT, IR e IRS 1, além de inibir a síntese *de novo* de ácidos graxos, esteatose hepática e a ativação do promotor e expressão gênica da SCD-1 (1). Esse último achado indica a existência de um sistema de retroalimentação negativa no qual o ácido palmitoleico inibe a expressão de SCD-1 e assim a sua formação a partir do ácido palmítico neste tecido.

Corroborando estes estudos, camundongos diabéticos tratados com ácido palmitoleico (300 mg/kg) por quatro semanas apresentaram uma atenuação da hiperglicemia, hipertrigliceridemia e melhora na sensibilidade à insulina. Além disso, houve redução na expressão gênica das enzimas lipogênicas *ácido graxo sintase* (FAS), SREBP-1 e SCD-1 no fígado e dos mediadores pró-inflamatórios - fator de necrose tumoral alfa (TNF-α) e resistina no TAB (16). Efeitos similares foram também encontrados após tratamento de adipócitos bovinos com concentrações crescentes de ácido palmitoleico (50-300 μM), como evidenciado pela redução na expressão gênica da FAS e SCD-1 e aumento na expressão da enzima *carnitina palmitoil-transferase* 1A (CPT1), que transporta ácidos graxos para a mitocôndria para serem oxidados (20). Além dos efeitos no metabolismo de glicose e lipídeos, o tratamento com 16:1n7 também produziu efeitos citoprotetores, protegendo células beta pancreáticas da morte induzida por ácido palmítico (15, 21).

Em estudos clínicos também se observam efeitos do ácido palmitoleico na homeostase metabólica de humanos. Hiraoka-Yamamoto et al. (2004) relataram que mulheres japonesas jovens com dieta rica em óleo de macadâmia têm o peso corporal, índice de massa corpórea e concentrações séricas de colesterol total e de LDL significativamente diminuídos (22). Interessantemente, o acúmulo de gordura glúteo-femural em humanos é inversamente associado a riscos cardiovasculares, efeito este, que é parcialmente justificado pelo grande acúmulo e liberação de ácido

palmitoleico por este tecido (5). Além disso, a concentração plasmática deste ácido graxo foi inversamente associada com o risco de câncer (23, 24). Contudo, no plasma de crianças e adultos obesos são detectadas concentrações elevadas de ácido palmitoleico e esses sujeitos também apresentam aumento da atividade da SCD-1 (25, 26).

Apesar de todos estes efeitos metabólicos importantes no fígado, músculo esquelético e células beta pancreáticas, ainda não foi demonstrado se o ácido palmitoleico também modula o metabolismo e funcionamento do TAB, um órgão fundamental para o controle da homeostase energética corporal. No presente estudo, portanto, nós testamos a hipótese de que o ácido palmitoleico é um importante modulador do metabolismo de glicose e triacilglicerol de adipócitos brancos. Para isto, utilizando experimentos *in vitro* e *in vivo* com células 3T3-L1 diferenciadas e adipócitos primários de murinos, nós investigamos, em dois estudos distintos, os efeitos e mecanismos de ação do ácido palmitoleico na captação e utilização de glicose (Estudo I) e no metabolismo do TAG (Estudo II) em adipócitos brancos.

7 CONCLUSÃO

Nossos dados sugerem fortemente que o ácido palmitoleico atua como uma importante molécula sinalizadora capaz de modular o metabolismo da glicose e do TAG em adipócitos brancos. Resumidamente, o tratamento de adipócitos com ácido palmitoleico, diferentemente do ácido palmítico ou oleico, induziu um aumento no conteúdo de GLUT4, na captação e utilização da glicose. Estes efeitos estão, ao menos em parte, associados com ativação da AMPK no tecido adiposo. O ácido palmitoleico também promoveu aumento da lipólise e do conteúdo das lipases ATGL e HSL através de um mecanismo dependente de PPARα. O aumento na lipólise está associado a um aumento concomitante da reesterificação de ácidos graxos a TAG, sugerindo um aumento no ciclo TAG-ácido graxo. Assim, podemos concluir que este ácido parece acelerar o metabolismo celular de adipócitos promovendo a ativação das vias de produção de energia.

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