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O efeito da deleção do SOCS3 em células responsivas à leptina em diferentes condições experimentais

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RESUMO

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Diversos estudos buscam estratégias que aumentem a sensibilidade à leptina, como uma possível alternativa para o tratamento da obesidade. No entanto, neste contexto, a maioria das pesquisas limita-se em investigar somente os aspectos relacionados com o balanço energético. Poucos estudos averiguaram as demais variáveis fisiológicas moduladas pela leptina. Portanto, no presente trabalho investigamos os efeitos do aumento da sensibilidade à leptina sobre a ingestão alimentar e o balanço energético, mas também sobre a modulação da homeostase glicêmica, a capacidade cardiovascular e o impacto que a sensibilidade à leptina causa na taxa de mortalidade em longo prazo. Para tanto, considerando a participação das proteínas supressoras do sinal de citocinas (SOCS) na inibição da sinalização da leptina, camundongos com deleção do gene SOCS3 em células que expressam o receptor de leptina (LepR SOCS3 KO) foram submetidos, inicialmente, à obesidade induzida pela dieta. Como resultado, observamos que a deleção condicional do SOCS3 não foi capaz de prevenir o ganho de peso induzido pela dieta. Todavia, essa manipulação aumentou a sensibilidade à ação da insulina. A seguir, outro grupode animais controle e LepR SOCS3 KO foram submetidos a protocolo de restrição alimentar e, na sequência, acompanhamos o consumo de ração e a recuperação de peso no período de realimentação. Constatamos que a ausência do SOCS3 em células responsivas à leptina promoveu redução da hiperfagia alimentar e menor ganho de peso no período de realimentação; no entanto, foi observado comprometimento nos mecanismos de controle da glicemia durante o período de restrição alimentar, particularmente, através da modulação no sistema nervoso simpático. Para elucidar possíveis efeitos colaterais ocasionados pelo aumento a sensibilidade à leptina, grupos de animais foram utilizados para analisar a capacidade cardiovascular, por meio do teste de esforço em esteira. Animais LepR SOCS3 KO apresentaram menor desempenho no teste Constatamos que a taxa de mortalidade foi de quase 80% no grupo LepR SOCS3 KO, ao longo de 16 meses, enquanto que, no grupo controle, os animais permaneceram quase todos vivos durante esse período de acompanhamento. Nossos resultados ajudam a entender o efeito da leptina no balanço energético e no controle glicêmico durante a obesidade e após um período de restrição alimentar. Por fim, nossos dados apontam possíveis efeitos colaterais de futuras estratégias que visam aumentar a sensibilidade à leptina como alternativa para o tratamento da obesidade.

Palavras-chave: Leptina. Obesidade. Gliconeogênese. Emagrecimento.

ABSTRACT

PEDROSO, J. A. B. The effect of SOCS3 deletion from leptin responsive cells in different experimental conditions. 2016. 98 p. PhD. thesis (Human Physiology) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2016.

Several studies have investigated strategies that increase leptin sensibility as a future alternatives to treat obesity. However, these studies investigated only changes in energy balance and only few assessed other potential effects of leptin. We investigated the effect of increasing leptin sensitivity on energy balance and weight control, but also in glucose homeostasis, cardiovascular performance and long-term mortality rate. For this purpose, we produced mice lacking SOCS3 only in leptin receptor-expressing cells (LepR SOCS3 KO mice). Initially, mice received high-fat diet to induce obesity. Inactivation of SOCS3 only in LepR-expressing cells protected against leptin resistance induced by diet-induced obesity (DIO), but did not prevent weight gain. However, LepR SOCS3 KO mice were protected from insulin resistance induced by DIO. Next, we investigated whether SOCS3 modulates post-restriction hyperphagia and weight regain. Control and LepR SOCS3 KO mice were subjected to a 48 hours fasting, followed by refeeding. LepR SOCS3 KO mice showed attenuated food intake and weight regain after a 48 h fasting. Post-restriction hyperleptinemia was also prevented in LepR SOCS3 KO mice. Remarkably, LepR SOCS3 KO mice showed impaired glucose control during fasting, leading to hypoglycemia. To investigate the mechanisms of action, we showed that increased leptin sensibility modulates the sympathetic nervous system and can be harmful to glucose homeostasis during fasting. To elucidate possible long-term side effects of leptin sensibility, we performed a maximal aerobic test in treadmill. LepR SOCS3 KO showed a lower aerobic performance in the test. This result indicates that leptin sensibility modulates cardiac function. Finally, mortality rate was over 80% during 16 months follow-up period in LepR SOCS3 KO, while control group remained alive during the same period. In conclusion, our results help to understand the effects of leptin to prevent obesity, but also highlight possible side effects from strategies that increase leptin sensitivity.

Keywords: Leptin. Obesity. Gluconeogenesis.

INTRODUÇÃO

O aumento da incidência da obesidade, acompanhado pela dificuldade em manter a massa corporal reduzida, sugere a ação de importantes mecanismos moleculares envolvidos na regulação do balanço energético. Neste contexto, a leptina, hormônio produzido pelo tecido adiposo, tem ganhado cada vez mais atenção, devido seu potente efeito na modulação do consumo alimentar e do gasto energético.

Apesar de a leptina ser classicamente considerada como um potente hormônio anorexígeno (FRIEDMAN; HALAAS, 1998; HALAAS et al., 1995) em animais e humanos obesos sua ação na promoção do apetite e da perda de peso é reduzida, indicando, portanto, que a obesidade é marcada por uma resistência à leptina (HALAAS et al., 1997; ZHANG; SCARPACE, 2006). Nessa temática, diversos estudos demonstraram que um grupo de proteínas, conhecidas como supressores do sinal de citocinas (SOCS), tem papel essencial na resistência da ação da leptina. Comprova essa conclusão o fato de a obesidade ser marcada pelo aumento da concentração plasmática de leptina e, ao mesmo tempo, pelo aumento da expressão de SOCS3 no núcleo arqueado do hipotálamo de roedores (KROL; SPEAKMAN, 2007). Da mesma forma, em camundongos, a superexpressão de SOCS3 em neurônios pró-opiomelanocortina (POMC) promoveu obesidade, resistência à leptina e intolerância glicose (REED et al., 2010). Destacando, portanto, a importante participação do SOCS3 na redução aos efeitos da ação da leptina, e consequentemente, na predisposição à obesidade.

Baseando-se nisso, terapias que aumentem a ação da leptina, como por exemplo, através de inibidores do SOCS3, apresentam-se como futuras estratégias terapêuticas no combate contra a obesidade, conforme demonstrado em animais deficientes de SOCS3 no cérebro ou somente em neurônios POMC, uma vez que estes apresentam atenuação da obesidade induzida por dieta (KIEVIT et al., 2006; MORI et al., 2004). Da mesma forma, sugere-se que o aumento da sensibilidade à leptina seja interessante também em prevenir o reganho de peso, uma vez que a administração deste hormônio é capaz de reduzir a hiperfagia alimentar após período de restrição calórica (HAMBLY et al., 2012).

Contudo, a ação fisiológica da leptina não deve ser limitada somente ao balanço energético. Já é bem estabelecida sua influência na modulação do eixo tiroidiano, na puberdade, na fertilidade, além promover modulação no sistema nervoso autonômico, bem como na imunidade (FAROOQI; O'RAHILLY, 2014). Além disso, estudos demonstram o efeito da leptina no aumento da pressão sistólica e a associação entre o nível de leptina plasmática com problemas cardiovasculares (BELTOWSKI et al., 2004; MARTIN et al., 2008). Portanto, apesar de terapias que aumentem a ação da leptina serem consideradas futuras alternativas no tratamento da obesidade e no combate ao reganho de peso, não é claro se, no longo prazo, este fenômeno pode causar alguma disfunção, comprometendo a integridade do organismo. Por isso, torna-se necessário investigar o efeito do aumento na sensibilidade à leptina, não só no balanço energético, mas também em outros aspectos fisiológicos regulados por este hormônio.

No presente trabalho, foram produzidos camundongos deficientes da proteína SOCS3, apenas em células que expressam o receptor da leptina (LepR), e avaliado o efeito do aumento da sensibilidade à leptina, em diferentes aspectos fisiológicos (balanço energético, gliconeogênese e sistema cardiovascular) de animais submetidos à obesidade induzida por dieta e também no reganho de peso durante o período de recuperação nutricional. Nossos dados ajudam a entender o efeito da leptina, não só no balanço energético, mas também sua potente ação no controle da homeostase glicêmica e alterações no sistema cardiovascular como consequência da alteração do funcionamento do sistema nervoso simpático.

CONCLUSÃO

Baseados em nossos resultados, podemos concluir que a ablação do gene SOCS3 em células que expressam o LepR não atenua o ganho de peso, mas promove melhora na sensibilidade à insulina durante a obesidade induzida pela dieta.

Também podemos aferir que o aumento da sensibilidade à leptina preveniu o ganho de peso após período de restrição alimentar. Entretanto, a deleção parcial do gene SOCS3 comprometeu a capacidade dos animais em manter a glicemia, particularmente por meio do sistema nervoso simpático.

Além disso, como possíveis efeitos colaterais relacionados ao aumento da sensibilidade à leptina em longo prazo, encontramos que a ablação do gene SOCS3 em células que expressam LepR promoveu menor capacidade cardiovascular e aumento de taxa de mortalidade ao longo do envelhecimento.

Assim, mais pesquisas devem ser desenvolvidas para elucidar não só os benefícios do aumento da sensibilidade à leptina no tratamento da obesidade e no reganho de peso, mas também os possíveis efeitos colaterais que esta estratégia terapêutica pode causar.

Os resultados da presente tese resultaram nas publicações dos seguintes artigos científicos:

PEDROSO, J. A., et al. Inactivation of SOCS3 in leptin receptor-expressing cells protects mice from diet-induced insulin resistance but does not prevent obesity. **Molecular Metabolism**, v. 3, n. 6, p. 608-618, 2014.

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