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## Inter-organ proteomic analysis reveals insights into the molecular mechanisms underlying the anti-diabetic effects of *cis*-9, *trans*-11 conjugated linoleic acid in *ob/ob* mice

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The major stereo-isomer of conjugated linoleic acid (CLA) in meat, *cis*-9 *trans*-11 CLA, exerts potent anti-diabetic effects in animal models of insulin resistance, such as the *ob/ob* mice, by improving insulin and lipid metabolism and decreasing obesity-induced inflammation<sup>(1)</sup>. The aim was to further explore the effects of CLA on molecular biomarkers of the metabolic syndrome using a proteomic approach.

Male *ob/ob* mice (eight per group) received a *cis*-9 *trans*-11 CLA-rich diet which comprised either a high beef-derived CLA or a synthetic CLA diet, or a control diet for 28 d. Diets were substituted with 36% (w/w) either high- or low-CLA freeze-dried beef and comprised 52% energy derived from fat. Both CLA-rich diets contained 0.6% (w/w) *cis*-9 *trans*-11 CLA. Fasting plasma biomarkers of insulin sensitivity were measured and changes in protein expression in skeletal muscle, hepatic and epididymal adipose tissues were determined using two-dimensional gel electrophoresis and MS<sup>(2)</sup>.

The CLA-fed mice were equally protected from the metabolic syndrome compared with the control, as shown by significant decreases of 30–50% in plasma insulin ( $P < 0.05$ ), glucose ( $P < 0.05$ ), NEFA ( $P < 0.05$ ), TAG ( $P < 0.05$ ) and IL-6 ( $P < 0.05$ ) and an increase of 34% in plasma adiponectin ( $P < 0.05$ ). Proteomic analysis indicated that 134, ninety-two and forty-three proteins, including post-translationally modified isoforms, were significantly altered ( $P < 0.05$ ) in the skeletal muscle, hepatic and adipose tissues respectively of CLA-fed mice. The majority of these proteins were involved in cellular and oxidative stress, cytoskeletal integrity, glucose and lipid metabolism, membrane signalling and vesicular transport.

Decreased glyceroneogenesis and increased  $\beta$ -oxidation in the adipose tissue of CLA-fed mice may partly underlie their improved metabolic profile. Unexpectedly, key gluconeogenic enzymes were increased alongside an increased flux through the tricarboxylic acid cycle in their liver, which may indicate a complex coordination between hepatic gluconeogenesis and energy metabolism. Moreover, multiple positional variants of key regulatory glycogenolytic enzymes were up regulated in their skeletal muscle, with a concurrent decrease in  $\beta$ -oxidation. A host of cytoskeletal proteins were differentially modulated across all tissues and may reflect altered cytoskeletal re-organisation in these mice.

The biochemical interplay between these proteins will be further studied, using systems biology tools, to elucidate the molecular changes in proteomic signatures that may explain the systemic anti-diabetic effects observed following supplementation with CLA.

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1. Moloney F, Toomey S, Noone E *et al.* (2007) *Diabetes* **56**, 574–582.
2. de Roos B, Duivenvoorden I, Rucklidge G *et al.* (2005) *FASEB J* **19**, 813–815.