Central Leptin Regulates Total Ceramide Content and Sterol Regulatory Element Binding Protein-1C Proteolytic Maturation in Rat White Adipose Tissue

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Obesity and type 2 diabetes are associated with insulin and leptin resistance, and increased ceramide contents in target tissues. Because the adipose tissue has become a central focus in these diseases, and leptin-induced increases in insulin sensitivity may be related to effects of leptin on lipid metabolism, we investigated herein whether central leptin was able to regulate total ceramide levels and the expression of enzymes involved in ceramide metabolism in rat white adipose tissue (WAT). After 7 d central leptin treatment, the total content of ceramides was analyzed by quantitative shotgun lipidomics mass spectrometry. The effects of leptin on the expression of several enzymes of the sphingolipid metabolism, sterol regulatory element binding protein (SREBP)-1c, and insulin-induced gene 1 (INSIG-1) in this tissue were studied. Total ceramide levels were also determined after surgical WAT denervation. Central leptin infusion significantly decreased both total ceramide content and the long-chain fatty acid ceramide species in WAT. Concomitant with these results, leptin decreased the mRNA levels of enzymes involved in *de novo* ceramide synthesis (SPT-1, LASS2, LASS4) and ceramide production from sphingomyelin (SMPD-1/2). The mRNA levels of enzymes of ceramide degradation (Asah1/2) and utilization (sphingomyelin synthase, ceramide kinase, glycosyl-ceramide synthase, GM3 synthase) were also down-regulated. Ceramide-lowering effects of central leptin were prevented by local autonomic nervous system denervation of WAT. Finally, central leptin treatment markedly increased INSIG-1 mRNA expression and impaired SREBP-1c activation in epididymal WAT. These observations indicate that *in vivo* central leptin, acting through the autonomic nervous system, regulates total ceramide levels and SREBP-1c proteolytic maturation in WAT, probably contributing to improve the overall insulin sensitivity. **(*Endocrinology* 150: 169–178, 2009)**

Leptin, an adipocyte-derived hormone, is actively involved in the control of body weight and food intake (1). Dysregulations of leptin action result in obesity, insulin resistance, and type 2 diabetes (2–4). Over-accumulation of triacylglycerides (TAGs) in lean tissues precedes the development of insulin resistance and type 2 diabetes (3). However, increased content of TAG in lean tissues may only be a marker of dysfunctional fatty acid (FA) metabolism, meanwhile more biologically active lipids, such as ceramides, which could be produced from unoxidized FAs, could be responsible for the impaired insulin signaling (4). Thus, ceramide accumulates in insulin-resistant nonadipose tissues from rodent and humans (5, 6), impairs the insulin-stimulated glucose

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Abbreviations: AUC, Area under the curve; Chol, cholesterol; ER, endoplasmic reticulum; eWAT, epididymal white adipose tissue; FA, fatty acid; INSIG-1, insulin-induced gene 1; MS/MS, Tandem mass spectrometry; PC, 1-palmitoyl-2-docosahexaenoyl-sn-glycero-3-phosphocholine; PM, plasma membrane; pSTAT3, phosphorylated signal transducer and activator of transcription-3; rWAT, retroperitoneal white adipose tissue; SCAP, sterol regulatory element binding protein cleavage-activating protein; SM, sphingomyelin; SMS, sphingomyelin synthase; SPT, serine palmitoyl transferase; SREBP, sterol regulatory element binding protein; STAT3, signal transducer and activator of transcription-3; TAG, triacylglyceride; TLC, thin-layer chromatography; TOF MS, time-of-flight mass spectrometry; WAT, white adipose tissue.