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A protein replacement Reduces Dysregulation of Lipid Metabolism in Liver and Adipose Tissue in Ceruloplasmin-Deficient Mice

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Abstract

Ceruloplasmin is a ferroxidase associated with iron homeostasis; The liver stores iron, which is necessary for the production of the soluble protein secreted into the bloodstream, as one consequence of its absence. Adipose tissue also secretes ceruloplasmin, but little is known about how it works in adipocytes. We hypothesized that the interaction between iron and lipids might be mediated by ceruloplasmin. To determine whether ceruloplasmin replacement was successful, we examined iron/lipid dysmetabolism in the liver and adipose tissue of the CpKO mouse model of aceruloplasminemia. Steatosis, iron deposition in the liver, and fat accumulation in the adipose tissue were observed in CpKO mice. Iron homeostasis was unaffected in CpKO mice's adipose tissue. On the other hand, the behavior of adiponectin and leptin was distinct from that of the wild-type. CpKO mice's liver and adipose tissue showed an increase in macrophage infiltration, indicating tissue inflammation. Ceruloplasmin reduced liver iron accumulation and steatosis in CpKO mice without normalizing the expression of iron homeostasis-related proteins. Protein replacement reduced serum triglycerides, partially restored adipokines, and limited macrophage infiltration in both the adipose and hepatic tissues of CpKO mice. A correlation between iron and lipid dysmetabolism in mice lacking ceruloplasmin suggests that the anti-inflammatory function of ceruloplasmin in adipose tissue may be more important to iron homeostasis than iron homeostasis. Additionally, these findings suggest that ceruloplasmin replacement therapy might be useful throughout the body.

Keywords: Steatosis; Adipose tissue; Adipokines; Enzyme replacement therapy; Iron Homeostasis; Infiltrating macrophages; Inflammation

Introduction

Extracellular multi-copper ferroxidase ceruloplasmin (Cp) is responsible for both the promotion of oxidized iron incorporation onto transferrin (Tf) and the membrane stabilization of the iron exporter ferroportin (Fpn). In addition to this significant physiological function, Cp has been linked to a number of other less well-defined functions. Copper transport, anti-inflammatory and anti-oxidant properties, nitric oxide and amine oxidase, and anti-inflammatory and anti-inflammatory properties are among the functions that Cp performs. In contrast, CpKO mice and humans lack Cp ferroxidase activity, which outcomes in decreased Tf saturation **[1-3]**, iron-restricted erythropoiesis, and iron accumulation in the liver, pancreas, retina, and brain. A wide range of tissues contain both the membrane-bound and secreted forms of Cp. As the secreted form enters the bloodstream, the majority of the systemic expression of Cp is controlled by the liver, which is the primary regulator of iron metabolism. A number of different kinds of cells, including adipocytes, express and release Cp as an adipokine. Adipokines, iron homeostasis-related proteins, and feedback mechanisms regulate the interaction between hepatocytes and adipocytes **[4-7]**. Hepcidin is made by the liver. Hepcidin is controlled by adipokines like adiponectin and leptin, which are made by adipose tissue and can be affected by iron levels. Although Cp is secreted by both the liver and adipose tissue and counteracts the function of hepcidin in the regulation of Fpn, little research has been done on its role in the interaction between hepatocytes and adipocytes and in the pathogenic mechanisms of Acp. Iron metabolism's dysfunctional interaction with lipid metabolism **[8,9].**

Discussion

This work demonstrates that lack of Cp fosters lipid dysmetabolism in adipose tissue and liver that underline the cross-talk between iron and lipid homeostasis. Lipid dysmetabolism in the CpKO model was evidenced by overweight mice (but not overt obesity) due to adipose tissue accumulation and by slight adipocyte hypertrophy at 10 months of age. Noteworthy was the observation that in these animals, the adipose tissue showed features of inflammation, inferred by macrophage infiltration and by altered profiles of the adipokines, namely a decrease in adiponectin and increased leptin levels as compared to WT mice. Conversely, the lack of Cp expression seems to be less critical for iron homeostasis in adipose tissue. Indeed, CpKO adipocytes did not show iron accumulation or alteration of iron homeostasis-related proteins, which is in line with a previous report **[10]**. Moreover, the adipose tissue of CpKO mice responds to iron homeostasis imbalance induced by Cp administration by modulating the expression of iron-related proteins as WT mice. This further confirms the activity/functionality of the purified Cp delivered intraperitoneally. Thus, a compensatory mechanism for Cp ferroxidase activity in the CpKO mice might occur in adipocytes due to hephaestin ferroxidase activity indeed, iron accumulation in adipocytes was reported only when both molecules were absent.

Our observations and the Cp expression level in the pgAT of WT mice, which is much higher than in the liver, suggest an important role for Cp in the metabolism of adipose tissue in addition to or alternative to cellular iron homeostasis. Cp itself has been defined as adipokine secreted by the adipocytes thus, it is conceivable that it might contribute

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to the control of the network of other adipokines released, for example, a metal ions-regulated mechanism. Indeed, Cp is one of the Cu and Zn plasma carriers, and the level of these ions affect lipid metabolism, for example, via zinc-related Our outcomes show that Cp is important in pgAT to maintain the physiological levels of adiponectin and leptin, which are essential for the maintenance of energy homeostasis, favoring adipogenesis and lipolysis, respectively, in the adipocytes.

Conclusion

In addition to iron homeostasis, the lack of Cp also dysregulates lipid metabolism, likely due to its potential anti-inflammatory role. This work underlines the cross-talk between liver and adipose tissue in Acp, which in turn suggests that adipocytes may also contribute to the pathology. Moreover, the Cp replacement was efficacious at the systemic level in ameliorating iron and lipid dysmetabolism in the liver and adipose tissue.

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