Rationale

Due to the increasing incidence, obesity and related complications (such as type 2 diabetes, hypertension and hyperlipidemia) constitute a major medical and socioeconomic problem. Treatment of obesity and associated complications is challenging because the availability of noninvasive and effective therapies is limited. Therefore, there is a need for the development of novel therapeutic strategies. When we asses the health risk of the obese person, not only the amount of adipose tissue but also its distribution is important. In adults, the distribution of adipose tissue differs between men and women and is regulated by sex steroids, especially estrogens. Estrogens have an influence on adipocyte growth but also control lipid synthesis, glucose homeostasis and inflammatory activity of adipose tissue. Lack of estrogens in menopausal women results in unfavourable changes in body composition and increases the risk of metabolic complications. These can be partially reversed by the hormone replacement therapy. Therefore, understanding the role of estrogens in the regulation of adipose tissue function might provide novel therapeutic applications in obesity and related diseases. However, before proteins involved in estrogen synthesis and action become targets for therapy, their role in the development of human obesity should be clearly defined. Till now, the role of estrogens in the development of obesity has been studied in cell cultures and animal models.

Description of the research to be carried out

The main goal of this project is to measure the concentration of estrogens and their precursors in adipose tissues in normal-weight and obese individuals before and after weight loss by the liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Next, using the real-time polymerase chain reaction (RT-PCR) we aim to measure in the same tissues the expression of genes involved in local estrogen synthesis and genes of estrogen receptors to understand mechanisms responsible for the obesity-related changes in estrogen action in adipose tissue. Since epigenetic modifications, play an important role in regulating gene expression in adipose tissue we aim to investigate if two epigenetic mechanisms (methylation of CpG islands in the regulatory regions and microRNA (miRNA) interference) can be responsible for the observed differences in expression of genes involved in estrogen synthesis and action.

Reasons for choosing the research topic

Understanding how sex steroids, enzymes involved in their synthesis and their receptors contribute to adipose tissue development and metabolism promises to yield novel therapeutic applications in managing obesity and its complications. Finding that epigenetic mechanism are involved in regulation of genes related to estrogen synthesis and action in adipose tissue will help to assess whether estrogen-targeted therapeutic strategies based on miRNA interference or modification of methylation profile will succeed in the treatment of obesity.

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