Cell Metabolism
Previews

In and Out: Adipose Tissue Lipid Turnover in Obesity and Dyslipidemia

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Adipose tissue is the main site of storage and mobilization of lipid. In a recent study published in *Nature*, Arner et al. (2011) report that high storage and low removal of adipose triglycerides promotes obesity, whereas low storage and low removal favor the development of dyslipidemia in humans.

Adipose tissue fat cells have the unique capacity to accumulate large amounts of energy-rich triglycerides in specialized lipid droplets. Body fat mass is the result of the balance between storage and removal of fat cell triglycerides. When food calories are supplied in excess, fat mass increases, whereas in situations of energy demand such as fasting, triglycerides from adipose tissue are hydrolyzed into fatty acids (lipolysis) with subsequent fatty acid oxidation. In a study recently published in *Nature*, Peter Arner, Kirsti Spalding, and collaborators determined the age of lipids in human subcutaneous adipose tissue (Arner et al., 2011). The method uses the temporary enrichment of ^{14}C in the atmosphere during aboveground nuclear bomb tests between 1955 and 1963. After cessation of the tests, ^{14}C levels exponentially decreased as $^{14}CO_2$ was incorporated into organic compounds during plant photosynthesis. Because humans eat plants or animals having eaten plants, the ^{14}C concentration in the human body parallels that in the atmosphere. The incorporation of atmospheric ^{14}C into adipose tissue lipid was determined to estimate lipid age, which reflects the irreversible removal of lipids from fat stores in lipolysis followed by fatty acid oxidation and/or ectopic deposition in nonadipose tissues, e.g., in skeletal muscle and liver. From lipid age and total fat mass, the authors calculated the net lipid storage, which represents the amount of lipid stored in adipose tissue each year and reflects fat incorporation from exogenous sources (e.g., derived from food) and endogenous synthesis (e.g., de novo synthesis of fatty acids from glucose) subtracted from the irreversible removal of lipids.

Mean adipocyte lipid age was 1.6 years. As mean fat cell age was previously shown to be 9.5 years, this implies that during the life span of an adipocyte, triglycerides are replaced six times on average (Spalding et al., 2008). Spalding and colleagues also found that lipid age was inversely correlated with adipocyte lipolysis stimulated by various molecules, indicating that lipolysis is an important determinant of lipid removal. Although stimulated lipolysis rate correlated with fat cell size (Reynisdottir et al., 1997), lipid age was similar in fat depots with small or large adipocytes. This observation suggests an exchange of fatty acids within adipose tissue between adipocytes of different sizes and metabolic capacities. Indeed, fatty acid esterification is coupled to lipolysis in fat cells (Bezaire et al., 2009). The lack of variation in lipid age over the years does not preclude short-term changes in the dynamics of lipid turnover such as the "last in, first out" replacement of fatty acids in triglycerides (Ekstedt and Olivecrona, 1970) or selective release of fatty acids according to molecular structure (Raclot et al., 1997). Given the documented difference in fat metabolism according to gender (Blaak, 2001), it is also puzzling that no difference in lipid storage and removal was observed between men and women, again highlighting the tight long-term control of adipose lipid turnover. The nature of the genetic and epigenetic mechanisms determining this control remains elusive.

In pathological conditions, however, disturbances in the dynamics of adipose tissue lipids were observed (Arner et al., 2011). Obesity was characterized by increased lipid storage and decreased lipid removal (Figure 1). In familial combined hyperlipidemia (FCHL), a hereditary lipid disorder predisposing to premature coronary heart disease, both triglyceride storage and lipid removal rates were low. This defect in lipid storage induces a routing of fatty acids to the liver, where fatty acid overflow contributes to the mixed dyslipidemia characteristic of this condition. Moreover, ectopic deposition of lipids in liver and skeletal muscle may favor the development of insulin resistance through lipotoxic mechanisms (Samuel et al., 2010). Indeed, lipodystrophic patients that have a defect of triglyceride storage in adipose tissue resulting in lipid accumulation elsewhere in the body develop severe insulin resistance. At the other end of the spectrum, increased capacity to store fat with low net mobilization leads to expansion of fat mass and may also be viewed as a way to do a safe deposit of lipids into a harmless compartment. According to the adipose tissue expandability hypothesis, as long as an individual has the capacity to store fat in adipose tissue, there is no ectopic deposition of lipids and resulting metabolic complications (Virtue and Vidal-Puig, 2008). In the obese population, Spalding and colleagues found that lipid storage capacity was correlated to body mass index, but not to HOMA-IR, an index of insulin resistance. Lipid age, on the other hand, was correlated to HOMA-IR, but not to body mass index. The data suggest a complex

interplay between determinants of adipose lipid turnover, fat mass, and insulin sensitivity.

Metabolic complications are also related to the distribution of fat in different anatomical locations. Prospective studies have shown that an excess of visceral fat is associated with increased mortality and risk for diabetes and cardiovascular complications (Wajchenberg, 2000). It will be of interest to compare lipid storage and lipid age in visceral and subcutaneous fat and to determine whether the putative differences between the two fat depots vary according to fat mass. Another intriguing observation is the fact that storage and removal of adipose lipids proved constant during adulthood. This is also the case for fat cell number and turnover rate (Spalding et al., 2008). Therefore, in individuals with early-onset obesity, the higher number of adipocytes is set during childhood and adolescence. The metabolism of adipocytes is also fixed during that period, with increased capacity for storing lipids and decreased capacity for mobilizing lipids. Identification of the genetic and environmental factors determining the number and metabolism of fat cells may help in designing novel therapeutic strategies to prevent the development of obesity and related complications.

The article by Arner et al. contains seminal data on the dynamics of adipose tissue lipid turnover. It reveals that fatty acid metabolism in this tissue is tightly controlled during adulthood and identifies defects in this metabolism in two common metabolic disorders, obesity and FCHL. The study provides a theoretical framework for future work on lipid metabolism in the context of impaired glucose metabolism and insulin resistance.

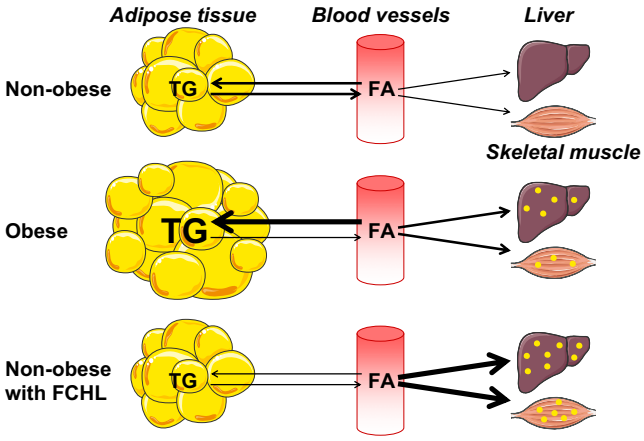

Figure 1. Lipid Turnover in Adipose Tissue of Nonobese, Obese, and Nonobese-with-FCHL Individuals

Increased lipid storage and decreased lipid removal favors the expansion of fat mass in obesity. If the capacity of storage is exceeded, there is ectopic lipid deposition in other organs, which favors metabolic complications leading to diabetes and cardiovascular diseases. In familial combined hyperlipidemia (FCHL), both triglyceride storage and lipid removal rates are low. FAs (fatty acids) are shunted to skeletal muscle and liver, promoting dyslipidemia and insulin resistance.

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