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Review

Role of bioactive lipid mediators in obese adipose tissue inflammation and endocrine dysfunction

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ABSTRACT

White adipose tissue is recognized as an active endocrine organ implicated in the maintenance of metabolic homeostasis. However, adipose tissue function, which has a crucial role in the development of obesity-related comorbidities including insulin resistance and non-alcoholic fatty liver disease, is dysregulated in obese individuals. This review explores the physiological functions and molecular actions of bioactive lipids biosynthesized in adipose tissue including sphingolipids and phospholipids, and in particular fatty acids derived from phospholipids of the cell membrane. Special emphasis is given to polyunsaturated fatty acids of the omega-6 and omega-3 families and their conversion to bioactive lipid mediators through the cyclooxygenase and lipoxygenase pathways. The participation of omega-3-derived lipid autacoids in the resolution of adipose tissue inflammation and in the prevention of obesity-associated hepatic complications is also thoroughly discussed.

Contents

Abbreviations: BAT, brown adipose tissue; COX, cyclooxygenase; CYP, cytochrome P450; DHA, docosahexaenoic acid; EDPs, epoxydocosapentaenoic acids; EEQs, epoxyeicosatetraenoic acids; EETs, epoxyeicosatrienoic acids; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; FFA, free fatty acid; HFD, high-fat diet; HSL, hormone sensitive lipase; IL, interleukin; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LD, lipid droplet; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PG, prostaglandin; PUFA, polyunsaturated fatty acids; sEH, soluble epoxide hydrolase; TAG, triacylglycerides; TNFα, tumor necrosis factor α; WAT, white adipose tissue.

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1. Introduction

White adipose tissue is now well recognized as a highly active metabolic tissue and an important endocrine organ that plays a major role in balancing the homeostasis of our body. Unfortunately, this balance is lost in obese individuals in whom the excessive expansion of adipose tissue gives rise to a chronic state of "low-grade" inflammation. This unresolved inflammation of adipose tissue in obesity is deleterious and leads to many pathological sequelae including insulin resistance and type 2 diabetes, hypertension, dyslipidemia and non-alcoholic fatty liver disease (NAFLD).

Bioactive lipids play a major role in the inflammatory process. Among the different lipid mediators, polyunsaturated fatty acids and especially the essential omega-6 arachidonic acid are the prime precursors for the biosynthesis of inflammatory mediators, generically known as eicosanoids (from the Greek *eicosa* = twenty; for 20-carbon fatty acid derivatives). Arachidonic acid is primarily found esterified in the 2-acyl position of phospholipids in all mammalian cell membranes. The intracellular levels of unesterified arachidonic acid are remarkably low and in its free form this fatty acid is readily available as a substrate for the intracellular biosynthesis of eicosanoids. With the exception of lipoxins, the majority of eicosanoids have pro-inflammatory properties. In contrast, another family of essential polyunsaturated fatty acids, the omega-3 family, is linked to the biosynthesis of lipid mediators with anti-inflammatory properties. Among the different lipid mediators generated from the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), resolvins, protectins and maresins have attracted much attention in recent years because they act as 'braking signals' of the persistent vicious cycle leading to unremitting inflammation. An important aspect of these endogenous omega-3-derived lipid autacoids is their critical role in the dynamic resolution of tissue inflammation.

The aim of this review is to highlight the role of bioactive lipids as key protagonists of the intracellular and intercellular communication networks in white adipose tissue (WAT). Special emphasis is placed on the novel opportunities offered by omega-3-derived lipid mediators to prevent the "low-grade" state of mild inflammation present in adipose tissue of obese individuals. This review also covers different aspects of adipose tissue physiology and pathophysiology, including the metabolic consequences of adipose tissue expansion in obese subjects, the structural and storage lipid composition of adipose tissue and a detailed enumeration of the principal and most common bioactive lipids present in adipose tissue and their biosynthesis and actions on adipocytes and other insulin-sensitive cells.

2. Expansion of adipose tissue in obesity: metabolic consequences

WAT is an anatomical term for loose connective tissue composed of adipocytes or fat cells. Adipocytes are nucleated cells comprising a characteristic unilocular lipid droplet mainly composed of triglycerides (TAG) and cholesterol esters, which occupy most of the cell, and a thin rim of cytoplasm displaced to the periphery (Redinger, 2009). The physical adaptability and the storage capacity of adipocytes are key components of their function. Indeed, during times in which energy intake is higher than the metabolic demand, adipocytes can expand nearly 1000-fold in volume and 10-fold in diameter in order to store the excess of fuel as TAG (Redinger, 2009). In contrast, in periods of food restriction or in periods demanding more energy expenditure, adipose tissue serves, via lipolysis, as the major source of energy. Under starving conditions, lipolysis is an essential mechanism whereby rate-limiting enzymes such as hormone-sensitive lipase (HSL) and monoacylglycerol lipase (MAGL) catalyze the hydrolysis of TAG to release free fatty acids (FFA) into the circulation (Carmen and Victor, 2006). Circulating FFA are subsequently taken up via the fatty acid binding protein (FABP) and fatty acid translocase (FAT/CD36) by metabolically active and insulin-sensitive tissues (primarily skeletal muscle and liver). These tissues use FFA as substrates for the generation of the high-energy nucleotide adenosine triphosphate (ATP) (Redinger, 2009).

The expansion of WAT occurring in obese individuals leads to prevailing high levels of hypoxia and chronic inflammation in this tissue. This inflammation is described as "metainflammation" and is characterized by a "low-grade", "long-term" inflammatory response triggered by nutrients and metabolic surplus (Hotamisligil, 2006). It involves the rise in pro-inflammatory cytokines (i.e. tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1β, monocyte chemoattractant protein-1 (MCP-1)) and adipokines (i.e. leptin and resistin) (Ouchi et al., 2011). In parallel, a reduction in anti-inflammatory and insulin-sensitizing adipokine adiponectin signals the onset of metabolic dysfunction in obese individuals (Ouchi et al., 2011). Among the metabolic consequences of this persistent state of inflammation insulin resistance leading to type-2 diabetes and hepatic steatosis leading to NAFLD are the most clinically relevant (Hotamisligil, 2006; Ouchi et al., 2011).

2.1. Insulin resistance and type 2 diabetes

Insulin resistance is one of the most important sequelae of obesity. Insulin resistance is defined as a reduced response of target tissues, such as the skeletal muscle, liver, and adipose tissue, to insulin, compared with subjects with normal glucose tolerance without a family history of diabetes (DeFronzo and Tripathy, 2009). Although skeletal muscle is the predominant site of insulin-mediated glucose uptake in the postprandial state, adipose tissue plays a major role in the development of peripheral insulin resistance. In fact, in obese subjects, the degree of insulin resistance is directly correlated with the serum levels of pro-inflammatory adipokines (i.e. TNFα, IL-6, and MCP-1) (Ouchi et al., 2011; de Luca and Olefsky, 2008). In parallel to the heightened secretion of inflammatory adipokines, there is an activation of the c-jun-N-terminal kinase (JNK) and inhibitor of κ kinase (IKK) pathways and their downstream signaling cascades by stress sensors through classical receptor-mediated mechanisms (Shoelson et al., 2006).