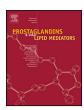


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Prostaglandins and Other Lipid Mediators



Omega-3 fatty acids and adipose tissue function in obesity and metabolic syndrome



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ABSTRACT

The n-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) have been reported to improve obesity-associated metabolic disorders including chronic inflammation, insulin resistance and dyslipidaemia. Growing evidence exits about adipose tissue as a target in mediating the beneficial effects of these marine n-3 PUFAs in adverse metabolic syndrome manifestations. Therefore, in this manuscript we focus in reviewing the current knowledge about effects of marine n-3 PUFAs on adipose tissue metabolism and secretory functions. This scope includes n-3 PUFAs actions on adipogenesis, lipogenesis and lipolysis as well as on fatty acid oxidation and mitochondrial biogenesis. The effects of n-3 PUFAs on adipose tissue glucose uptake and insulin signaling are also summarized. Moreover, the roles of peroxisome proliferator-activated receptor γ (PPAR γ) and AMPK activation in mediating n-3 PUFAs actions on adipose tissue functions are discussed. Finally, the mechanisms underlying the ability of n-3 PUFAs to prevent and/or ameliorate adipose tissue inflammation are also revised, focusing on the role of n-3 PUFAs-derived specialized proresolving lipid mediators such as resolvins, protectins and maresins.

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1. Adipose tissue dysfunction in obesity and metabolic complications

1.1. Obesity and adipose tissue

Obesity constitutes a global health problem responsible of 2.8 million deaths each year and whose prevalence has almost doubled in the last thirty years [1]. This condition, characterized by an excessive fat accumulation and accompanied by chronic low-grade inflammation, is related to metabolic diseases including type 2 diabetes, dyslipidemia, atherosclerosis or hypertension being those main components of Metabolic Syndrome (MetS) [2].

Adipose tissue plays a key role in the pathogenesis of obesity and associated complications. Three types of adipose tissue with different precursor cells, phenotype, function and regulation have been, so far, identified: (1) the energy storing white adipose tissue (WAT), (2) the energy consuming brown adipose tissue (BAT), and (3) the recently described beige/"brite" adipose tissue [3].

WAT is the main storage organ, accumulating the excess of energy in the form of triglycerides, which can be mobilized under energy deprivation conditions. In addition, WAT acts as an important endocrine organ releasing a broad range of molecules called adipokines involved in the regulation of many physiological functions including body weight (leptin), vascular metabolism (PAI-1), glucose metabolism and insulin sensitivity (adiponectin) and a number of inflammatory cytokines and chemokines (TNF- α , IL-1, IL-6, RBP-4 or MCP-1) among others [4,5]. Therefore, WAT is integrated in an overall cross-talk between different organs and tissues involved in energy homeostasis, including central nervous system (CNS), liver, skeletal muscle and pancreas due to the release of adipocytokines and the expression of receptors that facilitates two-way communications [6].

WAT is distributed around the body in different depots such as abdominal, subcutaneous or gonadal regions with different adipokine secretion profiles. It has been reported that accumulation of visceral adipose tissue (VAT) has a prominent role as a risk factor for MetS due to its location surrounding important organs such as liver, which directly receives venous blood from VAT through the portal vein. Moreover it is known to be more metabolically active than other depots with increased protein secretion [7]. In addition, in obesity VAT expandability is more limited than subcutaneous adipose tissue leading more easily to hypertrophied adipocytes [2,7].

On the other hand, BAT is known to be specialized in adaptative thermogenesis being uncoupling protein 1 (UCP1) the main responsible [8]. This thermogenic mechanism plays a key role defending against hypothermia and obesity. However, the endocrine function of such adipocytes is poorly characterized yet. Increasing evidence indicates that BAT produces factors with autocrine and paracrine actions on metabolism such as fibroblast growth factor 21 (FGF-21) or retinol binding protein 4 (RBP4) [9–11].

During the last years a new type of adipose tissue has been described and named as beige or "brite" adipose tissue. These recently discovered adipocytes have been found within some white adipose depots, but exerting similar functional and molecular characteristics as brown adipocytes. As a matter of fact, beige adipocytes have morphological characteristics of classical brown adipocytes. Thus, they are multilocular and have increased mitochondrial respiratory machinery and express inducible UCP1 having therefore thermogenic characteristics. However, it has been recently described that beige adipocytes express several beige adipocyte-specific genes that are not expressed in classical brown adipocytes such as *Tbx1*, *Tmem26* and *CD137*, among others [12,13].

1.2. Obesity and inflammation

Increased adiposity is accompanied by a low-grade chronic inflammation. In order to accumulate the excess of energy intake, a hypertrophy and hyperplasia of adipocytes take place. These hypertrophied adipocytes present an altered secretory pattern resulting in increased secretion of proinflammatory adipokines, cytokines and chemokines such as monocyte chemoattractant protein-1 (MCP-1), leptin, interleukin (IL)-6 or tumor necrosis factor (TNF)- α , and reduced production of anti-inflammatory adipokines, including adiponectin [14,15].

In addition, abundant research has demonstrated that a progressive infiltration and activation of macrophages and T cells to adipose tissue occurs in hypertrophied adipose tissue [16–19]. During obesity, the pro-inflammatory MCP-1 is secreted at high levels promoting the recruitment of macrophages to WAT [20]. Furthermore, it is recognized that a polarization of macrophages with an anti-inflammatory phenotype M2 to a M1 pro-inflammatory phenotype occurs in WAT during obesity, which also contributes to the generation of an inflammatory state [21,22]. These M1 macrophages usually are accumulated surrounding the hypertrophic necrotic adipocytes forming a crown like structure [23].

Although, initially all these inflammatory processes belong to the adipose tissue, they can finally derive in a chronic systemic inflammation [24,25], affecting different tissues such as liver and skeletal muscle, and causing metabolic disturbances including insulin resistance (IR) or non-alcoholic fatty liver disease [26–30].

Therefore, modulating the production/release of proinflammatory/anti-inflammatory molecules from adipose tissue becomes an important target to avoid or alleviate the systemic inflammation and to reduce the development of comorbidities associated with obesity such as type 2 diabetes or dyslipidemia.

2. N-3 PUFAs in obesity and related-metabolic disorders

N-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) are essential nutrients derived from marine or vegetal sources, being the most relevant those from marine origin as eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6), which can be found in oily fish including salmon, tuna, mackerel, anchovy

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