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REVIEWS: CURRENT TOPICS

Modulation of adipose tissue inflammation by bioactive food compounds

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Abstract

Adipose tissue has an important endocrine function in the regulation of whole-body metabolism. Obesity leads to a chronic low-grade inflammation of the adipose tissue, which disrupts this endocrine function and results in metabolic derangements, such as type-2 diabetes. Dietary bioactive compounds, such as polyphenols and certain fatty acids, are known to suppress both systemic and adipose tissue inflammation and have the potential to improve these obesity-associated metabolic disorders. Mechanistically, polyphenolic compounds including non-flavonoids, such as curcumin and resveratrol, and flavonoids, such as catechins (tea-polyphenols), quercetin and isoflavones, suppress nuclear factor-κB (NF-κB) and mitogen-activated protein (MAP) kinases (MAPK) pathways while activating the 5′ adenosine monophosphate-activated protein kinase (AMPK) pathway in adipose tissue. Dietary polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), conjugated linoleic acid (CLA) and monounsaturated fatty acids (MUFA), such as oleic acid, also impart anti-inflammatory effects through several mechanisms. These include activation of AMPK and peroxisome proliferator-activated receptor gamma (PPAR-γ), as well as suppression of toll-like receptors (TLRs) and NF-κB pathway. This review discusses the major molecular mechanisms of dietary polyphenols and fatty acids, alone or in combination, which are responsible for adipose tissue-associated anti-inflammatory effects.

Keywords: Obesity; Adipose tissue; Inflammation; Phytochemicals; Polyunsaturated fatty acids; Monounsaturated fatty acids; Curcumin; Resveratrol; Quercetin; Tea polyphenols

1. Introduction

Obesity has reached epidemic proportions in the US and worldwide and is a significant economic burden [1,2]. There are multiple health consequences of obesity including type-2 diabetes, heart disease, hypertension and several forms of cancer [3,4]. While obesity and other obesity-associated co-morbid conditions are due to high caloric intake and/or reduced energy expenditure over time, their causes can be complex varying from genetic alterations, environmental factors and/or gene-environment interactions. Sedentary lifestyle and excess caloric intake due to obesigenic environmental changes coupled with genetic susceptibility likely contributed to the recent escalation of obesity rates [4,5].

Fat mass expansion in obesity occurs via adipocyte hypertrophy (increased size of adipocytes) and/or adipocyte hyperplasia (increased adipocyte number). Adipocyte hyperplasia primarily results from proliferation and subsequent differentiation of pre-adipocytes and adipose stem cells, while adipocyte hypertrophy results from excessive lipid storage within adipocytes. The latter is frequently seen in obese adipose tissue and is often associated with adipose tissue remodeling and inflammation which contributes to metabolic derangements both locally within adipose tissue and systemically [6–8]. Adipose tissue cellularity, inflammatory and metabolic functions also exhibit regional differences [9,10].

This review discusses the major molecular mechanisms of dietary polyphenols and fatty acids alone or in combination that are responsible for adipose tissue-associated anti-inflammatory effects.

2. Endocrine and inflammatory function of the adipose tissue

Adipose tissue is not simply an energy reservoir, thermal regulator, or protective padding for important organs but also a metabolically active endocrine organ. This latter endocrine function of adipose tissue contributes significantly toward overall energy homeostasis and systemic insulin sensitivity by secreting adipokines and cytokines [7,11]. In addition to adipocytes and preadipocytes, adipose tissue also contains immune cells such as macrophages and

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lymphocytes which help maintain the normal metabolic functions of the adipose tissue.

Adipose tissue from lean individuals contains small, insulin-sensitive adipocytes and predominantly alternatively activated macrophages (M2), while adipose tissue from obese individuals is characterized by large insulin-resistant adipocytes accompanied by the presence of classically activated macrophages (M1) as shown in Fig. 1 [12,13]. Adipocyte hypertrophy in obesity, coupled with adipocyte death, adipose tissue hypoxia and changes in immune cell populations alters adipokine secretory patterns [7,11]. This shift in adipokine secretory patterns from a less inflammatory environment to a predominantly pro-inflammatory profile is in part responsible for the development of insulin resistance [7]. In addition, adipose tissue produces other inflammatory hormones such as angiotensin II, steroid hormones, and chemokines that are known to play major roles in metabolic and chronic diseases [14]. Common pro-inflammatory adipo/cytokines produced by adipose tissue include tumor necrosis factor-α (TNF-α), interleukin-1 beta (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1) and resistin [14,15]. In contrast, adipose tissue can also produce anti-inflammatory cytokines such as adiponectin and interleukin-10 (IL-10) [15]. Toll-like receptors (TLRs) and nuclear factor-κB (NF-κB)-associated mechanisms have been proposed as primary molecular mechanisms mediating adipose tissue inflammation [16,17]. Adipose tissue TLRs (TLR1, 2 and 4) are cell surface receptors that are activated by several dietary stimulants including saturated fatty acids. The TLRs activate NF-κB [16], a transcription factor and potent inducer of gene transcription of several pro-inflammatory cytokines such as IL-6 and TNF-α. In addition, adipocyte differentiation increased by the phosphorylation of mitogen-activated protein kinases (MAPKs) [18] can further increase the secretion of pro-inflammatory cytokines. Recent evidence also suggests that reduced AMP-activated protein kinase (AMPK) activity is associated with adipose tissue inflammation [19]. Additionally, peroxisome proliferator–activated receptor-α (PPARα), a nuclear receptor primarily expressed in the liver, and a potent inducer of fat oxidizing genes, has also been reported to reduce adipose tissue inflammation [20].

Thus, obesity is characterized by a chronic low-grade inflammation, primarily due to an imbalance between production/secretion of pro-inflammatory cytokines vs. anti-inflammatory cytokines [21]. Such an imbalance has been associated with several metabolic disorders including type-2 diabetes and cardiovascular disease risk factors [22,23]. This imbalance can be restored, at least in part, through weight loss, energy restriction and nutrient dense diets [24,25]. Moreover, both human and animal studies provide evidence to support the assertion that the use of dietary bioactive compounds can increase thermogenesis and energy expenditure, providing additional benefits in preventing/limiting obesity.

3. Dietary interventions to reduce adipose tissue inflammation and insulin resistance

In addition to total energy intake, the composition of a diet can also affect the metabolic and endocrine functions and overall energy balance [11,26]. Indeed, most health recommendations emphasize diets rich in fruits and vegetables, which have higher nutrient density and lower caloric density, for prevention of chronic diseases [26]. Such diets would provide significant amounts of bioactive components, with known beneficial effects due in part to their anti-inflammatory properties [27].

Since adipose tissue inflammation is causally linked to the pathogenesis of insulin resistance and several chronic diseases, dietary interventions targeted at improving adipose tissue inflammation could be a useful strategy for improving the overall metabolic profile.

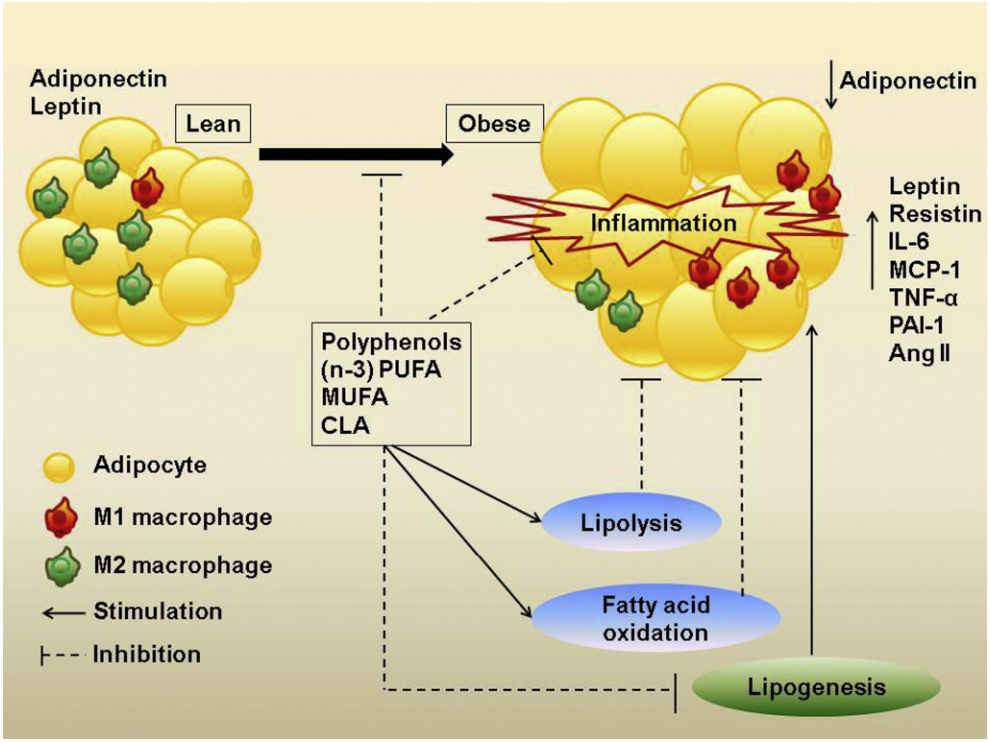

Fig. 1. Effects of polyphenols, (n-3) PUFA, MUFA and CLA on adipose tissue function. Obesity leads to adipocyte hypertrophy and increased secretion of pro-inflammatory adipokines and reduced secretion of anti-inflammatory adipokines from the adipose tissue, giving rise to a chronic low-grade inflammation. This is also characterized by an increase in M1:M2 macrophage ratio. Polyphenols, (n-3) PUFA — mainly EPA and DHA, MUFA and CLA promote loss of adiposity via increasing lipolysis and fatty acid oxidation and inhibiting lipogenesis. EPA, DHA, MUFA and *cis*-9,*trans*-11-CLA also exhibit anti-inflammatory properties.