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Review

Leucine in Obesity: Therapeutic Prospects

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Obesity develops from an imbalance of energy homeostasis and is associated with chronic low-grade inflammation in white adipose tissues (WAT). Inflammation is involved in the pathophysiology of many obesity-induced disorders including insulin resistance and diabetes. Increasing evidence has shown that dietary leucine supplementation positively affects the parameters associated with obesity and obesity-related metabolic disorders. The beneficial effects include increased loss of body weight, reduced WAT inflammation, improved lipid and glucose metabolism, enhanced mitochondrial function, and preserved lean body mass. Although these beneficial effects have not been clearly established, dietary leucine supplementation, either alone or as part of a therapeutic regimen, may be a good nutritional tool in the prevention and management of obesity and obesity-induced metabolic disorders.

Trends

Obesity is not an exclusively adipocyte disease, but also involves other cell types that reside in WAT. In most obese subjects, obesity is accompanied by low-grade inflammation of WAT resulting from chronic activation of the innate immune system, which can subsequently result in insulin resistance, impaired glucose tolerance, and even diabetes.

Leucine regulates appetite and satiety, energy expenditure, lipid and glucose metabolism, insulin sensitivity, chronic inflammation, browning of WAT, and other metabolic processes.

leucine supplementation is associated with obesity and related metabolic disorders, and the use of dietary leucine supplementation has been extensively explored for therapeutic intervention of obesity and obesity-induced metabolic dysfunction.

Obesity

Obesity develops from an imbalance between energy intake and energy expenditure, increases the risk to develop insulin resistance and diabetes, and is a major public health concern [1,2]. Approaches for reducing the current obesity epidemic are becoming a primary focus of human healthcare. Traditionally, strategies for treating obesity have mainly focused on dietary and lifestyle modifications such as caloric restriction and increasing physical activity [3,4]. However, recent years have witnessed growing interest in the use of branched-chain amino acids (BCAAs), especially leucine, in obese subjects [5,6]. In this regard, the use of dietary leucine supplementation has been extensively explored for therapeutic intervention of obesity and obesity-induced metabolic dysfunction [7–9]. Leucine supplementation has been shown to block high-fat diet (HFD)-induced obesity, hyperglycemia, and dyslipidemia in animal and human models. Although the underlying mechanisms are not fully understood, it has been suggested that the mammalian target of the rapamycin (mTOR) pathway and the sirtuin 1 (SIRT1)–AMP-activated protein kinase (AMPK)–peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1α (PGC-1α) axis is involved [5]. In this review we will discuss current understanding of the association between obesity and obesity-related metabolic disorders, the effects of dietary leucine on alleviating obesity and the metabolic syndrome, and relevant signaling mechanisms.

Adipose Tissue and Obesity-Induced Metabolic Dysfunction

Obesity is strongly related to excess accumulation of WAT owing to increased food intake and decreased energy expenditure [10,11]. Obesity is a health problem of epidemic proportions that affects not only developed countries but people worldwide [12]. A better understanding of the complex pathogenesis of inflammation, insulin resistance, and type 2 diabetes mellitus (T2DM) in obesity is therefore of major importance to improve preventive and therapeutic strategies.

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Adipose Tissue Composition and Function

Adipose tissue is made up of various cell types, including pre-adipocytes, adipocytes (mainly white or brown), macrophages, fibroblasts, and blood vessels [12]. WAT contains large unilocular lipid droplets and is an active endocrine organ, producing and secreting a wide range of inflammatory molecules (e.g., tumor necrosis factor-α, TNF-α; interleukin-6, IL-6) [13]. By contrast, brown adipose tissue (BAT) contains multiloculated adipocytes that contain large numbers of mitochondria, and is mainly involved in thermogenesis [14]. Importantly, in addition to the two major types of fat (white and brown), another subtype of adipose tissue [so-called 'beige/brite (brown in white) fat] has been found [15]. Similarly to BAT, beige fat can dissipate chemical energy into heat (thermogenesis) through uncoupling respiration [16]. The mechanisms that increase the brown-like phenotype in WAT should offer an intriguing strategy for the treatment of metabolic disease [17].

Adipose tissue was originally considered to be merely an energy storage site. It stores free fatty acids (FFAs) from the blood after food intake and releases FFAs under conditions of energy stress to ensure a status of sufficient energy [2]. However, this classical perception has been replaced in recent years by the notion that adipose tissue plays a crucial role in lipid and glucose metabolism, and produces a wide range of hormones and cytokines. These hormones and cytokines are mainly implicated in inflammation (e.g., TNF-α; IL-6), lipid metabolism (e.g., cholesteryl ester transfer protein), glucose metabolism (e.g., adiponectin, resistin), feeding behavior (leptin), and coagulation (plasminogen activator inhibitor-1) [9,18–20]. Therefore, both adipocytes and macrophages can secrete cytokines, influencing the metabolism and function of many organs and tissues including the brain, liver, muscles, and vasculature [13]. An in-depth discussion of most adipokines is beyond the scope of this review; interested readers can refer to [21] for further reading.

Adipose Tissue Dysfunction, Obesity, and Inflammation

Obesity in most, but not all, subjects results from an imbalance of energy homeostasis [22]. In obese subjects, environmental and genetic factors give rise to a chronic positive energy balance and elevated storage of energy as fat that results in weight gain. With the gain of body weight, adipose tissue correspondingly changes its size, distribution, cellular composition, and function [21]. Meanwhile, obesity results in the infiltration of adipose tissue by macrophages [23]. As adipose tissue expands, increasingly enlarged adipocytes release increased levels of (saturated) FFAs. Saturated FFAs stimulate the already present macrophages in adipose tissue and bind to macrophage toll-like receptor-4 (TLR-4), leading to the activation of nuclear factor-κB (NF-κB) and subsequently the production of proinflammatory cytokines such as TNF-α [24,25]. In turn, macrophage-derived TNF-α activates adipocytes, further stimulating lipolysis and increasing the expression levels of various genes [IL-6, intracellular adhesion molecule-1 (ICAM-1), and macrophage chemoattractant protein-1 (MCP-1)] [26–28]. ICAM-1 and MCP-1 further attract monocytes/macrophages into adipose tissue [29,30]. The local paracrine loop between adipocyte-derived FFAs and macrophage-derived TNF-α forms a gradual vicious cycle (Figure 1), presumably resulting in a proinflammatory state of both adipocytes and macrophages [2]. The subsequently increased production of adipokines and inflammatory cytokines (e.g., leptin, TNF-α, and IL-6) and the decreased production of adiponectin [31], in association with the inability of adipose tissue to store the surplus FFAs [32], can be regarded to reflect adipose tissue dysfunction [12]. Taken together, obesity significantly affects adipocyte biology and may result in adipose tissue dysfunction and inflammation, and obesity-induced inflammation is characterized by the increased cytokine/chemokine expression and macrophage infiltration [33].

Insulin Resistance and T2DM

Insulin resistance, a characteristic feature of obesity-induced metabolic dysfunction, is defined as a reduced response to insulin in adipose tissue, muscle, and liver [34,35]. Although it is not