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Review article

The physiological and pathophysiological roles of taurine in adipose tissue in relation to obesity

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ABSTRACT

Obesity is caused by an imbalance between energy intake and energy expenditure. It is established that obesity is a state of low-grade chronic inflammation, which is characterized by enlarged hypertrophied adipocytes, increased infiltration by macrophages and marked changes in the secretion of adipokines and free fatty acids. The effects of taurine on the pathogenesis of obesity have been reported in animals and humans. Although the mechanisms underlying the anti-obesity action of taurine remain to be defined, taurine seems to ameliorate obesity through stimulation of energy expenditure, modulation of lipid metabolism, anorexic effect, anti-inflammatory and anti-oxidative effects. Recent studies revealed that taurine supplementation reduces the infiltration of macrophages and modulates the polarization of adipose tissue macrophages in high-fat diet-induced obese mice. In addition, taurine downregulates the production of pro-inflammatory cytokines by adipocytes, suggesting that taurine plays an anti-inflammatory role in adipose tissue. This article reviews the effects and mechanisms of taurine on the development of obesity, focusing on the role of taurine in white adipose tissue.

1. Introduction

The prevalence of overweight and obesity and their associated metabolic disorders are considered a major threat to the health of the global population. Although energy balance is tightly regulated, excess nutrition and a sedentary lifestyle induce excessive lipid accumulation in adipose and peripheral tissues. Obesity is associated with various chronic diseases, particularly cardiovascular diseases, type 2 diabetes, hypertension, sleep apnea, certain types of cancer and osteoarthritis [1]. For many years, adipose tissue was considered an inert energy storage organ that accumulates and stores triglycerides. However, recent research has shown that adipocyte tissue itself is an endocrine organ capable of secreting bioactive mediators called adipokines, affecting various metabolic and immunologic activities [2,3]. It is now well established that the obese state is a chronic inflammatory condition, characterized by macrophage infiltration and increased production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and monocyte chemoattractant protein (MCP)-1 [4,5].

Taurine is one of the most abundant free amino acids in mammals. Intracellular concentrations of taurine reach the millimolar range, often up to 20–50 mM [6], in contrast to other free amino acids, which exist at micromolar concentrations. Taurine is considered a basic regulator of cell homeostasis. It is endogenously synthesized from cysteine and it is also obtained by the diet. Cellular taurine results from the concerted operation of synthesis, influx and efflux. In addition to its well-known role in the conjugation of bile acid, recent energetic studies have unveiled the diverse physiological and pharmacological effects of taurine. These effects are attributed to osmoregulation, anti-oxidation, anti-inflammation, Ca^{2+} modulation, cell membrane stabilization and neuromodulation [7]. Taurine transporter-deficient mice were generated, and an analysis of their phenotype revealed impairment of various physiological functions, suggesting the crucial role of taurine in maintaining physiological homeostasis [8].

A number of studies have shown that taurine alleviates obesity in genetically and high-fat diet-induced animal models of obesity [9–11]. Although the mechanisms responsible for the anti-obesity effect of taurine remain to be elucidated, taurine appears to have multiple sites of action. We showed that taurine supplementation attenuates the progression of obesity and insulin resistance in mice fed a high-fat diet [11]. These effects of taurine are closely associated with the suppression of adipocyte inflammation. This article reviews the effects and mechanisms of taurine on the development of obesity in animals and humans, with a particular focus on the role of taurine in adipose tissues.

2. Anti-obesity effects of taurine

2.1. Animal study

The anti-obesity effects of taurine have been examined in mice, rats

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and *Caenorhabditis elegans* (*C. elegans*). High-fat diet-induced models are the most popular for evaluating the anti-obesity effects in animals. Eighteen-week-supplementation of dietary taurine (5%) suppressed increases in adipocyte size, body fat, and body weight in C57BL/6J mice fed a high-fat diet [10]. This was accompanied by improved insulin resistance and resting oxygen consumption. Fourteen weeks' supplementation of 5% (w/w) dietary taurine reduced the body weight gain and weight of the white adipose tissue in C57BL/6J mice fed a high-fat diet [11]. The effects of taurine were associated with amelioration of inflammation in adipose tissue, suppression of macrophage infiltration and inhibition of pro-inflammatory adipokine production. In weaned C57BL/6J mice fed a high-fat diet, taurine prevented obesity and improved glucose tolerance, which was associated with increased phosphorylation of AMP-activated protein kinase (p-AMPK) in the liver [12]. In addition, the effects of taurine on obesity were examined in *C. elegans* [13]. The total triglyceride content was reduced in *C. elegans* cultured in high-fat media by taurine treatment, whereas the effect of taurine was not seen in *C. elegans* cultured in normal media. Taurine seems to suppress cellular lipid accumulation by stimulating mobility and modulating the lipid metabolism.

The anti-obesity effects of taurine were also demonstrated in genetically obese mice. A twenty-week-supplementation of taurine (0.5% and 1% in drinking water) in genetically obese/hyperglycemic KK mice was shown to reduce body weight gain and abdominal fat pads compared with control KK mice [9]. Similarly, taurine has been reported to exert anti-obesity effects in genetically obese/hyperglycemic KKAy mice [10].

The administration of monosodium glutamate (MSG) to rodents during the neonatal period leads to the development of obesity, glucose intolerance, and insulin resistance by disturbing the regulation of food intake and energy expenditure [14,15]. The anti-obesity effects of taurine have been examined in this obese model. Taurine supplementation (2.5% in drinking water) for 70 days reduced fat accumulation in the retroperitoneal and periepididymal fat pads and decreased lipid levels in the plasma and liver in MSG-induced Wistar rats [16]. Other researchers have also reported the anti-obesity effects of taurine (2.5% in drinking water) in a similar MSG-induced rat model [17]. Taurine supplementation to male Wistar rats for 100 days did not alter the pro-inflammatory cytokine content in adipose tissue, but normalized circulating TNF-α and IL-4 concentrations. In another experiment using MSG-induced rats, 3 months' treatment with taurine (2.5% taurine in drinking water) decreased body fat accumulation and triglyceride level of serum and liver [18]. The effect of taurine in the liver was accompanied by upregulation of mRNA expression of carbohydrate response element-binding protein (ChREBP), microsomal triglyceride transfer protein (MTP), peroxisome proliferator-activated receptor (PPAR)-α, acyl-CoA oxidase (ACO) and carnitine palmitoyltransferase (CPT)-1α, suggesting stimulation of hepatic lipid efflux and fatty acid β-oxidation. The combined supplementation of fish oil and taurine (4% in diet) for 4 weeks has been shown to prevent the development of obesity and hyperglycemia more effectively in obese/hyperglycemic KKAy mice than when used separately [19]. In genetically obese/hyperglycemic ob/ob mice, where taurine (5% in drinking water) was administered to mice from weaning until 90 day of age, taurine ameliorated glucose homeostasis but did not affect obesity [20].

Recent studies have demonstrated that the circadian rhythms and metabolism are tightly regulated in both adipose tissue and the peripheral metabolic organs. A high-fat diet disrupts the 24 h pattern of the circulating levels of hormones and the behavioral and molecular circadian rhythms in rodents [21]. It has been shown that taurine prevented the development of obesity in mice fed a high-fat diet, which was accompanied by the normalization of the gene and protein expression of clock genes in beta-cells [22].

2.2. Human study

In contrast to animal studies, far less data are available on the anti-obesity effects of taurine in humans. The anti-obesity effect of taurine has been demonstrated in a double-blind randomized trial of 30 overweight or obese college students [23]. The body weight and plasma triglyceride level of the taurine-treated group was significantly lower than in the placebo group after 7-week oral administration of taurine (3 g/day). In a randomized double-blind placebo-controlled study in 16 obese women and 8 non-obese women, 8-week supplementation of taurine (3 g/day) increased the plasma taurine (+97%) and adiponectin (+12%) and reduced the levels of the inflammatory marker C-reactive protein (CRP) (−29%) and the lipid peroxidation marker, thiobarbituric acid reactive substances (TBARS) (−20%) [24]. However, taurine had no significant effect on body weight.

Epidemiological studies have suggested the anti-obesity effect of taurine. The CARDIAC Study was conducted in 61 populations of 25 countries across the world [25]. Twenty-four-hour urinary samples were collected and analyzed for taurine, creatinine and other nutrients. The urinary taurine content was used as a marker of dietary taurine intake. The results showed that 24-h-urinary excretion of taurine was inversely related to mortality due to coronary heart disease. In addition, subjects with a higher urinary taurine content had a significantly lower body mass index (BMI), systolic and diastolic blood pressure and plasma total cholesterol than those with lower urinary taurine content [26]. These findings indicate that a constant intake of dietary taurine reduces the risk of metabolic diseases, including obesity, diabetes, hyperlipidemia, and hypertension, which may lead to decreased mortality from cardiovascular diseases. It is expected that people who consume more fish have higher body taurine levels than meat eaters or vegetarians [27]. The effectiveness of taurine in humans may therefore depend on the dose or duration of treatment and the type of patients selected.

3. Anti-obesity mechanisms of taurine

Taurine has been shown to modulate the metabolism of lipids and glucose, enhance energy expenditure, suppress inflammation and inhibit appetite. In addition, taurine seems to have multiple points of action, including adipose tissue, liver, muscle and the central nervous system. The direct effect of taurine on adipose tissue is considered to be the most important for the pathogenesis of obesity. Therefore, this section will focus on adipose tissue as a target organ with a discussion of the possible role that taurine plays.

3.1. Taurine synthesis in adipose tissue

It is well known that the content and synthetic activity of taurine is higher in the liver and kidney, than in other organs, as taurine is used for bile acid conjugation in the liver, and it protects the kidney from severe osmotic changes. An exhaustive study in rat tissue revealed unexpectedly high levels of enzyme expression and activity responsible for taurine synthesis in the epididymal and perirenal white adipose tissues [28]. The mRNA expression of cysteine dioxygenase (CDO) and cysteine sulfinic acid decarboxylase (CSAD), rate-limiting enzymes in taurine biosynthesis, was comparable to that observed in the liver and kidney. Similar findings were obtained in the white adipose tissue of C57BL/6J mice [10]. The CDO mRNA level was high in parametrial and retroperitoneal white adipose tissues. Of note, the CDO mRNA expression of adipose tissue was markedly lower in obese C57BL/6J mice fed a high-fat diet and genetically obese KKAy mice than in their non-obese counterparts, accompanied by a decrease in the blood taurine level. These findings suggest that white adipose tissues are the major source of taurine in the body, and the blood taurine level is reduced during the development of obesity in parallel with decreased taurine synthesis in adipose tissues. Indeed, reduced plasma taurine levels have also been