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Taurine is Involved in Energy Metabolism in Muscles, Adipose Tissue, and the Liver

Chaoyue Wen, Fengna Li, Lingyu Zhang, Yehui Duan, Qiuping Guo, Wenlong Wang, Shanping He,* Jianzhong Li, and Yulong Yin*

Energy metabolism is a basic and general process, by which the body acquires and uses energy to maintain normal function, and taurine plays a vital role in energy metabolism. Taurine deficiency may cause a weak energy metabolism and energy metabolism dysfunction. Taurine biosynthetic ability is limited, and its supplementation in the diet can strengthen energy metabolism in muscle performance, cardiac function, liver activity, and adipose tissue. Combining taurine with other drugs may have a superior effect in energy metabolism. In many metabolic disorders, taurine, or the combination of taurine with other drugs, also functions as a repair treatment for damaged tissues, and acts as a promoter for the balance of energy metabolism. The present study discusses the potential roles of taurine in energy metabolism.

1. Introduction

Taurine (2-aminoethyl sulfonic acid) is the most abundant sulfur-containing free amino acid in excitable tissues,[1] accounting for 0.1% of the total body weight.[2] Two sources contribute to taurine levels in the body: active uptake from the diet, and the biosynthetic pathways of other sulfur amino acids such as cysteine and methionine.[3] Taurine contributes to numerous biological functions through its antioxidative, anti-inflammatory, and membrane stabilizing properties. It improves metabolic syndrome by ameliorating insulin resistance to regulate glucose metabolism.[4] Taurine as a constituent of modified uridine participates in the conjugation of mitochondrial tRNAs for leucine and lysine and plays an important role in the pathologies of mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes (MELAS) and myoclonic epilepsy and ragged-red fiber syndrome (MERRF).[5,6] Taurine also decreases plasma and liver cholesterol levels induced by a high cholesterol diet, which is involved in bile acid homeostasis.[7] Taurine is an established osmoregulator and indirect regulator of oxidative stress.[8] As a protective agent, it protects against several environmental toxins and drug-induced multiple organ injuries.[9] Previous studies were conducted to examine the physiological and pathological roles of taurine.[1,2] In this review, we summarize the role of taurine in energy metabolism in various tissues (skeletal muscle, heart, adipose tissue, and liver).

2. Endogenous Taurine Biosynthetic Enzymes

Taurine is endogenously synthesized from cysteine through the sequential actions of cysteine dioxygenase (CDO), which oxidizes cysteine to cysteinesulfinate and cysteinesulfinate decarboxylase (CSD), to catalyze the decarboxylation of cysteinesulfinate to hypotaurine, which is oxidized to taurine in mammals. However, it remains unclear whether the oxidation of hypotaurine to taurine is enzymatic reaction.[10,11] Several factors contribute to the taurine biosynthetic enzymes. Protein levels and sulfur amino acids influence the activity of CSD.[12,13] Cysteine levels are influenced by the regulation of hepatic activity.[12] Taurine can be synthesized from methionine.[14] The activities of CDO and CSD are markedly higher in the liver than in other tissues.[15]

C. Wen, W. Wang, Prof. S. He, Prof. J. Li
Laboratory of Animal Nutrition and Human Health
Hunan international joint laboratory of Animal Intestinal Ecology and Health
College of Life Science
Hunan Normal University
Changsha, Hunan, 410081, China
E-mail: hesp@hunnu.edu.cn
Prof. F. Li, L. Zhang, Dr. Y. Duan, Q. Guo, Prof. Y. Yin
Hunan Provincial Key Laboratory of Animal Nutritional Physiology and Metabolic Process
Key Laboratory of Agro-ecological Processes in Subtropical Region
Institute of Subtropical Agriculture
Chinese Academy of Sciences
Hunan Provincial Engineering Research Center for Healthy Livestock and Poultry Production
Scientific Observing and Experimental Station of Animal Nutrition and Feed Science in South-Central
Ministry of Agriculture
Changsha, 410125, China
E-mail: lifengna@isa.ac.cn
Prof. F. Li, Prof. Y. Yin
Hunan Co-Innovation Center of Animal Production Safety
CICAPS
Hunan Collaborative Innovation Center for Utilization of Botanical Functional Ingredients
Changsha, 410128, China
L. Zhang, Q. Guo
University of Chinese Academy of Sciences
Beijing, 100039, China

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However, upon treatment with excessive amounts of methionine or cysteine, CSD activity and cysteinesulfinate catabolism are not affected by sulfur amino acid supplementation.[16] It has been suggested that the activity of taurine biogenesis is limited by CSD and CDO. CDO shows low expression in the skeletal muscle and heart, but highly expressed in the liver, white adipose tissue (WAT), and brown adipose tissue (BAT). However, in obese mice, the expression of CDO in the WAT is decreased,[17] indicating that oversized adipocytes synthesize and secrete lower levels of taurine. Propargylglycine inhibits taurine synthesis in primary mouse hepatocytes.[18] Low-dose (40 mM) taurine and low-protein and sulfur amino acid-restricted diets can increase the concentration of intracellular taurine[19,20] and endogenously stimulate the taurine biosynthetic pathway.

3. Models of Taurine Deficiency

Many factors affect the concentration of taurine: biosynthetic enzymes and taurine transporter (TauT) activities,[21] volume-sensitive flux pathways,[22] liver diseases,[23] age,[24] and diet[25–28] (high-fat diet (HFD),[25] high-arginine diet,[26] high/low-protein diet,[27,28] and ethanol-containing diet[29]). Taurine levels are also related to motion.[30] TauT mediates the uptake of taurine from the extracellular space into the cell, thus maintaining high intracellular levels of taurine. To examine the pathophysiological role of taurine, models of taurine deficiency were developed by knocking out the TauT gene,[31–34] nutritional depletion, an inhibitor of taurine intake, such as guanidinoethane sulfonate,[35] or β-alanine,[36–38] and carbon tetrachloride (CCL_4),[39] which time-dependently significantly decreases taurine (86%) in the liver.[37] Mitochondrial taurine content decreased by 60% after supplementation with β-alanine.[38] Therefore, depletion of TauT, or supplementation with structural analogs can cause severe deficiency.

4. Energy Metabolism in Taurine Deficiency

Considering the role of taurine in maintaining physiological homeostasis, taurine depletion may cause an imbalance in energy metabolism in the skeletal muscle, heart, liver, and adipose tissue (**Figure 1**).

4.1. Abnormalities in Skeletal Muscle Function in Taurine Deficiency

Taurine depletion accelerates histological functional defects.[34,40] Taurine transporter knockout (TauTKO) mice exhibit low body weight[31,32,41] and decreased skeletal muscle mass.[31] Histological disorders were observed in TauTKO mice,[40] reduced myofibrillar cross-sectional area (CSA) of the tibial anterior muscle in mutant mice, ultrastructural abnormalities, filament fragmentation,[41] and a larger number of irregularly appearing muscle fibrils.[34] Muscle performance, such as peak twitch force, force output were observed to be significantly decreased,[35] indicating that the level of taurine in vivo plays a role in converting extensor digitorum longus muscle (EDL) from a powerful pattern to an endurance pattern. Some diseases can also cause the loss of taurine to accelerate the body's disturbance. In Duchenne muscular dystrophy (DMD) patients, the urinary excretion of taurine was increased, the dystrophin gene contained a defect, resulting in the replacement of skeletal muscle with nonfunctional fibrotic tissue.[42–44]

Muscle intolerance has been found to be related to impaired energy metabolism.[45] Adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) regulates and senses energy expenditure and has been associated with controlling skeletal muscle weight by inhibiting the activity of the mammalian target of rapamycin complex 1 and increases protein degradation by regulating the ubiquitin-proteasome and autophagy pathways.[45] AMPK activation leads to increased fatty acid oxidation, preventing it from accumulating in muscle cells as lipid fractions.[46] The peroxisome proliferator-activated receptor α (PPARα) gene is involved in the transcriptional activation of fatty acid oxidation;[47] the levels of PPARα and its transcriptional targets are reduced

Chaoyue Wen, bachelor of agriculture, received his B. Agr. from the College of Veterinary Medicine, Hunan Agricultural University in 2016. He is an MSc. candidate in the College of Life Science, Hunan Normal University. His research interests include the regulation of oxidative stress and animal health, taurine, molecular nutrition and meat quality.

Fengna Li, received her Ph.D. from China Agricultural University in 2009. She is currently Professor in the Animal Nutrition Department, Institute of Subtropical Agriculture, Chinese Academy of Sciences, China. She is a member of the Animal Nutrition Branch of the Chinese Association of Animal Science and Veterinary Medicine. Current research interests include: development and regulation of skeletal muscle and adipose tissues; swine nutrition and physiology.

Shanping He, received his Ph.D. in biotechnology from Peking University in 2011. He had received his postdoctoral training in the Department of Molecular Microbiology and Immunology at the University of Southern California, Los Angeles, CA, from 2011 to 2016. He is a Professor in the School of Life Sciences at Hunan Normal University, Changsha, Hunan. His research interests include nutritional regulation of intestinal innate immunity, molecular mechanisms of nutrient-sensing pathways, and development of new feed additives.

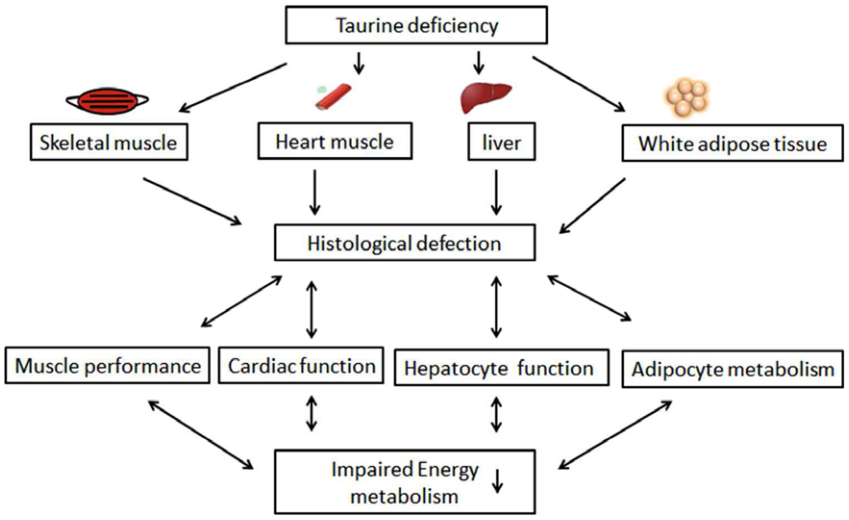

Figure 1. Taurine deficiency creates a vicious circle promoting the imbalance of energy metabolism. Taurine deficiency cause tissue histological defection and then affects its function, finally induce compromised energy metabolism (vicious circle).

in the skeletal muscle of TauTKO.[33] Genes involved in the oxidation of long-chain fatty acids (glutathione peroxidase 3 and carnitine palmitoyl transferase 2) are downregulated in TauTKO mice.[33] Additionally, these genes are regulated by PPARα and AMPK, whose subunit AMPKβ2 has been found to be downregulated in TauTKO skeletal muscle, which is associated with its protein content.[33] Acetyl CoA carboxylase is regulated by AMPK,[48] and it is an enzyme that indirectly regulates the transport of long chain fatty acids into the mitochondria for β-oxidation. Fatty acid metabolism is significantly depressed, shifting energy metabolism in favor of anaerobic metabolism.[33] These findings indicate that taurine plays a crucial role in regulating energy metabolism in skeletal muscle.

4.2. Abnormalities of Cardiac Muscle Function in Taurine Deficiency

It has been reported that a taurine-deficient heart is energy starved.[38] ^{1}H NMR spectroscopy revealed nearly complete depletion of cardiac taurine in TauTKO mice.[34] Electron microscopy showed remarkable cardiac myofibrillar fragmentation, mitochondrial disruption, and swelling of the outer mitochondrial membrane.[31] Taurine depletion induces cardiomyopathy with cardiac atrophy, a lower body weight concomitant with a reduction in heart weight[31] and heart failure.[38] A decrease in complex 1 activity caused by cardiac taurine deficiency exceeds the inhibition of oxidative metabolism.[49] Treatment with β-alanine disturbed the synthesis of mitochondrial proteins,[50] reduced electron transport as the activity of respiratory chain complexes I and III decreased by 50–65%, and decreased oxygen consumption (VO_2) by 30%,[49] thereby affecting the capacity of the mitochondria to synthesize ATP. This suggests that taurine deficiency is related to a decrease in the integrity of the electron transport chain. Glycolysis is superior to lactate for nicotinamide adenine dinucleotide (NADH) production. When the citric acid cycle is impaired, oxidation of endogenous fatty acids and exogenous acetate in the taurine depleted heart is decreased.[38] Additionally, three acyl-CoA dehydrogenase enzymes, which are important for the c-oxidation of fatty acids, show optimal activity in a taurine buffer.[51] The expression of fatty acid metabolism-related genes, such as muscle-type carnitine palmitoyl transferase-1 (mCPT-1) and PPARα, are decreased in the taurine-depleted heart[38] and increase pyruvate dehydrogenase activity by downregulating its dephosphorylation.[52] These results suggest that fatty acid metabolism is reduced under taurine-deficient conditions.

4.3. Abnormal Adipose Tissue Function in Taurine Deficiency

Taurine depletion cause an imbalance in the metabolism of adipocytes. TauTKO mice exhibit less abdominal fat mass when fed a normal diet.[32] One study reported an increased rate of blood glucose disposal after intraperitoneal glucose injection, despite diminished serum insulin levels,[32] indicating reduced energy metabolism in adipose tissue. Additionally, a higher rate of blood glucose disposal was observed during exercise.[33] However, the blood lactate level was remarkably increased by more than threefold during exercise, but remained unaltered in wild-type mice,[33] suggesting competition between fatty acids and glucose metabolism.

4.4. Abnormal Liver Function in Taurine Deficiency

Taurine is a nutritional amino acid, and depletion of intracellular taurine levels often progresses into severe hepatic dysfunction. Hepatocyte destruction and apoptosis are markers of liver pathology in TauT-deficient mice. The loss of hepatocytes is thought to stimulate hepatocyte proliferation. In TauTKO mice, hepatic glycogen is significantly lower under running conditions than under resting conditions.[33] TauTKO triggers chronic liver diseases, including hepatitis, liver fibrosis, and mitochondria

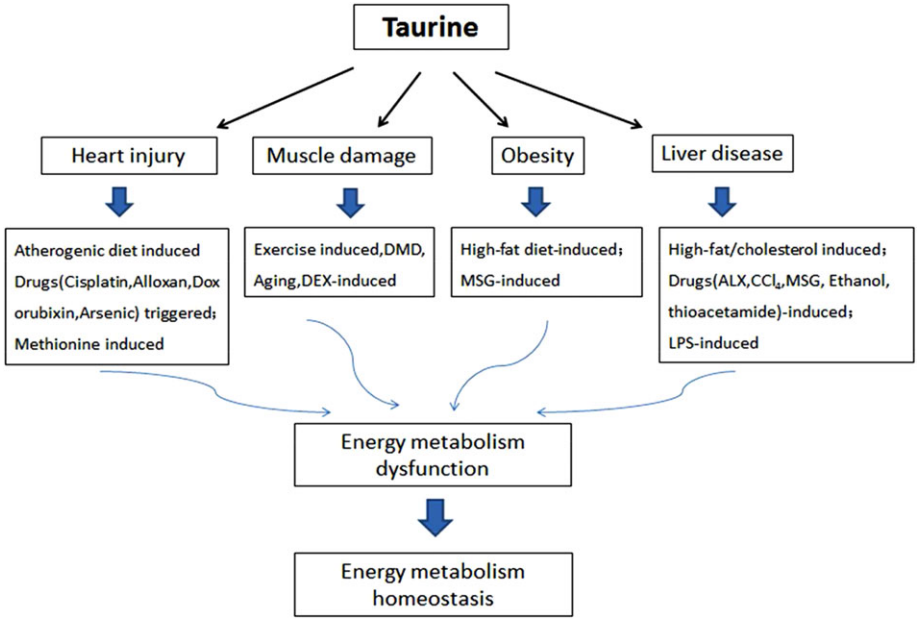

Figure 2. Taurine rebuilds energy metabolism homeostasis in drug- or diet-induced energy expenditure dysfunction, in various tissues.

dysfunction, as well as significantly lowers the respiratory control ratio in isolated mitochondria.[53] In TauTKO mice, taurine content varies across different cells; there is nearly complete depletion of taurine in Kupffer and sinusoidal endothelial cells but not in parenchymal cells.[53]

5. Energy Metabolism for Taurine Single Use

Taurine supplementation partly restores the dysfunction of energy expenditure under pathological conditions (**Figure 2**) and strengthens muscle performance under normal conditions.

5.1. Energy Metabolism in Muscle

5.1.1. Energy Metabolism and Taurine Supplementation in Muscle-Related Diseases

Research has shown that taurine is conducive to muscle recovery after damage[54] and is required for normal contractile function in skeletal muscle.[55] Many studies showed that increasing dietary taurine is a useful measure for DMD.[44,56,57] Skeletal muscle mass is regulated by catabolic and anabolic processes, which determine muscle weight and muscle fibers diameters.[58,59] Taurine appears to have no effect on muscle weight or fiber CSA.[30] However, it does affect muscle function under pathological conditions.[30,35] An increased taurine content was shown to improve muscle strength and function both in vivo and ex vivo. For instance, it significantly increases EDL fiber length and specific force and decreases protein thiol oxidation.[56] Taurine plays an important role in controlling ion channels in the skeletal muscle.[60] As shown by Huxtable, high levels of taurine promote calcium homeostasis by promoting active re-uptake by the endoplasmic reticulum.[61] Taurine attenuates the atrophic process by restoring the expression of atrophy-associated genes.[30] Dexmedetomidine-induced muscle atrophy in C2C12 myocytes is ameliorated by taurine supplementation and the expression of TauT has been shown to be upregulated during myogenesis in C2C12 cells.[62]Additionally, TauT participates in the regeneration of muscle fibers in patients.[63] Thus, TauT expression may be a cytoprotective mechanism for controlling the myogenic program and disease management.

5.1.2. Energy Metabolism and Taurine Supplementation in Exercise-Induced Injury

Previous studies showed that taurine has beneficial effects on high frequency stimulation.[64] Dietary taurine significantly increases taurine concentrations in the plasma and muscle.[64–67] Taurine supplementation under endurance exercise decreased the levels of plasma creatinine and triglycerides (TG) and demonstrated that dogs undergoing endurance exercise may benefit from taurine supplementation by minimizing oxidation and maintaining taurine status.[67] It also decreases the content of the cytosolic enzyme lactate dehydrogenase (LDH) and creatine kinase (CK),[66] which are markers of muscle damage and oxidative stress. Glutamine content was increased by dietary taurine after prolonged exercise.[68] As reviewed by Xiao et al., glutamate is deaminated by glutamate dehydrogenase to generate α-ketoglutarate (AKG), and AKG participates in the tricarboxylic acid cycle for ATP generation.[69] This suggests that taurine is beneficial for recovery after exercise. Taurine affects the closed state of the ATP-sensitive K+ channel after exercise, thus affecting the intracellular content of ATP.[70] It has been reported that 30 min of eccentric exercise (ECC) per week can improve the quality of life.[71] Continuous taurine supplementation can reduce delayed onset muscle soreness (DOMS) but not CK activity after high-intensity ECC in healthy young men.[72] Researchers

showed that urinary taurine is significantly correlated with muscle activity,[73] suggesting the potential effectiveness of urinary taurine in valuating muscle injury. These results support the therapeutic potential of taurine and its ability to promote normal muscle function.

5.1.3. Energy Metabolism in Normal Muscle

Taurine regulates protein synthesis in the mitochondria by elevating electron transport chain activity and preventing the mitochondria from generating excessive superoxide.[49] Supplementation with 5% taurine in drinking water for 12 months increased the activation of AMPK and reduced total AMPK protein content in the gastrocnemius (GAST) muscle of ob mice, alleviated glucose tolerance and insulin sensitivity in ob mice, and increased the respiratory exchange ratio during the sleep phase,[74] suggesting increased carbohydrate (rather than fat) oxidation. AMPK also increases fatty acid utilization and prevents TG deposition.[75]Based on these data, long-term taurine supplementation has a beneficial effect on glucose tolerance. Taurine was found to attenuate glucose administration and induce an increase in blood glucose post-exercise, as blood glucose status is mostly influenced by glucose uptake into the skeletal muscle. These results suggest that taurine enhances skeletal muscle glucose uptake.

5.2. Energy Metabolism in Heart-Related Disease

Taurine has potent beneficial effects on different physiological conditions, such as ischemic insult, diabetes, and oxidative stress.[76–78] Under pathological conditions, the requirement for taurine is higher, and 2.5% taurine administration inhibited myocardial apoptosis during consumption of an atherogenic diet.[79] Taurine reverses methionine-induced cardiac dysfunction by reducing mitochondrial structural damage and maintaining the integrity of cristae.[80] In ischemia, taurine depletion favors the activation of K^+-ATP channels and slows the decrease in intracellular ATP.[81] Taurine may pharmacologically inhibit the activation of matrix metalloproteinase-2, which is a major gelatinase under oxidative stress conditions in the rabbit heart.[78] Long-term treatment with taurine in a diet ameliorated mitochondria protein oxidation levels.[82] Doxorubicin-induced cardiac oxidative stress suppressed body growth and heart development, while increasing reactive oxygen species (ROS) generation, intracellular Ca^{2+}, and disturbing mitochondrial membrane potential;[83] taurine may also prevent intracellular calcium overload.[84] Taurine also restored cardiac dysfunction by decreasing LDH and uric acid (a serum marker of cardiac disorder).[85] Thus, taurine can ameliorate mitochondrial dysfunction induced by various types of stress.

5.3. Energy Metabolism in Obesity

Adipose tissue is not only an energy store but also an endocrine organ that synthesizes and releases adipokines, such as adiponectin and leptin, both of which play vital roles in food intake, energy expenditure, and glucose homeostasis regulation.[86–88] Obesity is characterized by excessive accumulation of fat, resulting from an imbalance between energy intake and energy expenditure and is thought to be a condition of chronic inflammation and oxidative stress. There is considerable evidence linking mitochondrial dysfunction with metabolic diseases, including obesity (**Table 1**).

High-fat diet-induced obesity models are the most popular for estimating anti-obesity effects in animals. Taurine ameliorates obesity through multiple mechanisms. One study showed that during adipogenic differentiation of 3T3-L1 cells, the protein levels of CDO and CSD were significantly increased, after 10 days of adipocyte differentiation, a sixfold increase in CDO mRNA was observed,[17] further accompanied by increased production of taurine.[11] Some researchers found that the levels of plasma taurine were decreased in obese human subjects and animals,[17,97] indicating that obesity is a taurine-deficient condition. The protein levels of CDO and blood taurine were decreased in an HFD in the parametrial WAT but not in the liver or in BAT,[17] suggesting that CDO in the WAT regulates plasma taurine levels and that large adipocytes synthesize and secrete lower levels of taurine. To investigate the potential anti-obesity effects of taurine, energy expenditure was measured. Peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) is a powerful regulator of energy expenditure in adipose tissues. Taurine treatment prevents excessive weight gain and hyperplasia.[96] In a taurine-supplemented diet, the WAT was reduced and BAT weight was increased. These changes in adipose levels were related to upregulation of PGC-1α expression,[86] suggesting that taurine stimulates energy expenditure. Adipocytes secrete various molecules, such as adiponectin.[98] Adiponectin levels are decreased in obese patients and rats.[99,100] The taurine-supplemented group exhibited a significant increase in plasma adiponectin, and restored adiponectin mRNA in adipose tissue compared to in obese rats.[29,97,100] Supplementation with 3% taurine in drinking water for 8 weeks significantly decreased serum total cholesterol (TC) compared to in obese women on an HFD,[100] suggesting that taurine reverses obesity by increasing adiponectin levels. In worms, taurine reduced fat deposition by modulating lipid accumulation and stimulating mobility, without affecting lipid biosynthesis or food intake.[101] The anti-obesity effects of taurine were also tested in obese trained rats.[102] Several studies showed that serum taurine concentrations were lower under obese conditions than under control treatment and that the adiponectin level is increased by taurine supplementation,[97] suggesting that taurine can improve insulin sensitivity and lipid peroxidation.[97] Taurine ameliorates HFD-induced obesity reducing fat depots and plasma insulin levels in a dose-dependent manner, significantly limiting the increase in fasting blood glucose level and increased taurine concentrations in the WATs, possibly normalizing calorie intake, and decreasing visceral fat on an HFD + 0.7% taurine.[91,95,96] The serum levels of TG, TC, and non-high-density lipoprotein cholesterol (HDL-C) were significantly decreased by 0.35 or 0.7% taurine supplementation on a HFD compared to control treatment.[95] Furthermore, the effect of supplemented taurine for 12 weeks was superior to that after only 6 weeks of treatment.[103] Taurine increases lipolysis in adipocytes in two manners: by stimulating cyclic adenosine

Table 1. Summary of the effects of dietary taurine on lipid and glucose metabolism in obese animals.

Experimental model and subjects	Taurine treatment	Response[a)]	References
Male Wistar rats	5% Taurine for 14 d	Cholesteryl ester ↓fatty acid oxidation↑	[89]
Genetically type 2 diabetic/pbese KK-Ay mice	Fish oil (7%)+ taurine via drinking water (4%) for 4 weeks	WAT weight↓; fatty acid oxidation↑; hyperglycemia and hyperinsulinemia improved	[90]
HFD-induced obese C57BL/6J mice	Taurine via drinking water (5%) for 14 weeks	Subcutaneous, epididymal, mesenteric, Retroperitoneal WAT↓;	[91]
MSG-induced obese male Wistar rats	Taurine via drinking water (2.5%) for 100 d	Retroperitoneal fat pad, perigonadal fat pad, insulin level↓;	[92]
MSG-induced obese male Wistar rats	Taurine via drinking water (2.5%) for 70 d	Retroperitoneal, periepididymal fat pad, NEFA, TG↓;	[93]
HFD-induced obese C57BL/6J mice	Taurine via drinking water (2.5%) for 18 weeks	Body fat,parametrial WAT, adipocytes size↓; resting energy expenditure↑	[17]
MSG-induced obese male Wistar rats	Taurine via drinking water (2.5%) for 100 d	Body weight, retroperitoneal fat pad, lee index, perigonadal fat pad, liver TG↓; lipid oxidation↑	[94]
High-fat/cholesterol diet-induced NAFL male hamster	Taurine via drinking water (0.7%) for 4 weeks	Weight gain, visceral fat, liver TG and TC↓; energy expenditure↑	[95]
Chronic ethanol-induced hepatic steatosis rats	Taurine via drinking water (30 g/L) for 4 weeks	Fatty acid oxidation↑; adiponectin levels↓	[29]
HFD-induced obese weaned male C57BL/6J mice	Taurine via drinking water (5%) for 8 weeks	Liver glucose control↑; body weight, periepididymal fat pad, retroperitoneal fat pad↓	[96]

[a)] Symbols:↑ increase; ↓ decrease.

monophosphate (cAMP)-dependent protein kinase A (PKA) catalytic activity and by favoring PKA activation through the action of cAMP and inhibiting the H_2O_2 pool increase.[104] Taurine chloramine produced by macrophages may inhibit the differentiation of preadipocytes into adipocytes.[105] Further studies showed that taurine chloramine modulates the expression of adipokines by inhibiting the signal transducer and activator of transcription 3 signaling pathway,[106] demonstrating its potential applications in obesity-related diseases. In mono sodium glutamate (MSG)-induced obese rats, the mass of BAT in the taurine-treated group was higher compared to that in the model group. In contrast, the mass of WAT was significantly lower.[107] Compared to the control treatment, the expression of PGC-1α in the WAT and BAT were higher following taurine treatment and more significantly upregulated in the BAT.[107] PGC-1α was shown to switch cells from an energy store to energy expenditure types, which involves mitochondrial biogenesis and adaptive thermogenesis.

5.4. Energy Metabolism in Liver-Related Diseases

Nonalcoholic steatohepatitis (NASH), also known as hepatic steatosis, is associated with obesity, abnormal metabolism of free fatty acids, mitochondrial dysfunction, and oxidative stress, and is increasingly recognized as a precursor of severe liver disease. Liver damage can lead to taurine deficiency, which may result in diminished antioxidant defense, upregulation of inflammatory cytokines, and mitochondrial dysfunction. HFD-induced NASH is a good model for evaluating human conditions.[108] Taurine supplementation in drinking water or by subcutaneous injection remarkably decreased the liver weight and liver index in the treatment group compared to the high-fat/cholesterol group.[95,109] Taurine treatment significantly decreased the hepatic levels of malondialdehyde, the product of lipid peroxidation, and significantly increased hepatic superoxide dismutase activities.[29,95,109] Taurine prevents ethanol-induced oxidative stress and alleviates the expression of TNF-α and steatosis, accelerates the reduction in hepatic steatosis, and attenuates the decrease in PPARα and carnitine palmitoyltransferase 1α.[29] Activation of AMPK was shown to increase fatty acid oxidation, reduce TG and cholesterol synthesis, and reverse fatty liver. Taurine supplementation normalized liver glucose output and decreased liver glycogen content on an HFD.[96] Taurine restored thioacetamide-induced liver mitochondrial function by reducing mitochondrial ROS and inhibiting mitochondrial swell by restoring mitochondrial ATP.[110] Taurine supplementation upregulated the expression of low-density lipoprotein receptor, PPARα, and uncoupling protein 2 were upregulated in high-fat/cholesterol +0.35%/0.7% taurine hamster. Additionally, a previous research study showed a tendency toward low fatty acid synthase gene expression and increased energy expenditure.[95] It also improved liver antioxidant ability,[95] suggesting that taurine plays a protective role in the development of hepatic steatosis. In MSG-induced obesity, the damaged liver structure appeared to be alleviated by low-dose taurine.[107] The liver X receptor α promotes liver lipogenesis and hyperlipidemia by inducing sterol regulatory element-binding protein 1c (a critical transcription factor that promotes liver lipogenesis), without inducing the synthesis of fatty acids.[111] In hepatocytes, taurine stimulated liver X receptor α activation, and significantly induced Insig-2a levels as well as delayed nuclear translocation of the SREBP-1 protein, resulting in a dose-dependent reduction in cellular lipid levels, without inducing the expression of fatty acid synthesis genes. Oil Red O staining showed a remarkable reduction in cellular lipid accumulation in hepatocytes supplemented with taurine.[112]

Taurine also ameliorates CCL_4-induced hepatic damage, including histological damage. Diminished fibrotic infiltrations in both the pericentral and periportal regions and bridging fibrosis were observed to be completely formed. These findings were confirmed by immunohistochemical staining.[113] Previous research showed that excessive dietary taurine supplementation has adverse effects on growth performance and hepatic histopathology.[114] Taurine may be an accessible marker in the plasma and urine of hepatic damage caused by paracetamol.[115] These findings indicate that taurine is efficacious for preventing liver injury under different conditions.

6. Taurine's Combined Use

High-dose taurine supplementation can be toxic.[114] Numerous studies have shown that compared to monotherapy, combined therapy is more effective because of its synergistic effects and reduced side effects, which is a promising approach for using lower doses.

6.1. Combined Use of Taurine with Other Drugs in Muscle Disease

Branched-chain amino acids (BCAAs) are abundant in the skeletal muscle and help to inhibit protein breakdown.[116] Combined supplementation of taurine (2.0 g)–BCAA (3.2 g) attenuate eccentric elbow flexor exercise-induced DOMS and muscle damage, which is a sign of lower LDH levels.[117] Glucocorticoids are the only drugs clinically used in DMD, but are dangerous because of their considerable side effects. A single dose of α-methyl-prednisolone (PDN) or taurine in vivo significantly increased forelimb strength. A visible synergistic effect caused by the combined use of PDN and taurine was observed. Additionally, PDN plus taurine increased taurine concentrations in fast-twitch muscle on mdx mice.[118] In parallel, the overactivity of voltage-independent cation channels was reduced in dystrophic myofibrils.[118] PDN plus taurine completely restored the mechanical threshold (an index of calcium homeostasis in EDL myofibrils), and the effect was greater than that of PDN alone.[118]

6.2. Combined use of Taurine with Other Drugs in Normal Muscle

A physiological dose of dietary taurine combined with caffeine significantly increased muscle power output and time to fatigue, but there was no difference compared to the effect of caffeine alone,[119] suggesting that larger amounts of taurine are needed to derive a significant ergogenic benefit. The combination of taurine and fish oil improved the GLUT4 distribution in the plasma membrane of muscle tissue, reduced serum free fatty acids, and increased the activity of acyl-CoA oxidase (ACO),[90] which is the rate-limiting enzyme of peroxisomal β-oxidation. Taurine modulates glucose homeostasis by regulating the expression of pancreas duodenum homeobox-1 genes and increasing insulin-mediated tyrosine phosphorylation of the insulin receptor in skeletal muscle.[120]

6.3. Combined Use of Taurine with Other Drugs in Adipose Tissue

n-3 PUFAs, such as eicosapentaenoic acid and docosahexaenoic acid, are functional compounds abundant in seafood. It is widely known that n-3 PUFAs decrease plasma lipid levels. Fish oil containing n-3 PUFAs and the combination of fish oil and taurine are considered advantageous for preventing obesity. Dietary fish oil +4% taurine for 4 weeks significantly prevented the gain of WAT and blood glucose in KK-Ay mice, and this effect was enhanced compared to that after soybean oil treatment alone.[90] The mice fed fish oil +2% taurine exhibited a significant increase in the levels of ACO.[90] These data suggest that a combination of fish oil and taurine has a high potential to ameliorate adipose metabolism in obese mice. It has been reported that BCAAs, particularly leucine supplementation, alter the body fat condition and promote energy metabolism, including fatty acid oxidation and glucose uptake.[121–123] The potential combined effect of taurine with BCAA in the treatment of obesity require further analysis.

6.4. The Use of Tauroursodeoxy Cholic Acid

Bile acids are excreted in mammalian bile mainly glycine or taurine conjugates. Tauroursodeoxycholic acid (TUDCA) is considered as an essential regulator of energy metabolism in obesity.[87] Following therapy with TUDCA, liver, and muscle insulin sensitivity increased by ≈30% and insulin signaling was increased in the muscle but not the adipose tissue in obese subjects.[124] TUDCA protects against contractile dysfunction and intracellular Ca^{2+} mishandling and these effects may be related to TUDCA-ameliorated cardiac endoplasmic reticulum stress (ERS) in obesity. Treatment with TUDCA induced a decrease in body weight gain, reversed ERS, and improved glycolipid metabolism disorder by restoring defective hepatic autophagy.[125] Additional studies are needed to explore the specific cellular mechanisms in obese people with insulin resistance.

6.5. Combined Use of Taurine with Other Drugs in Liver Disease

Liver fibrosis is a wound-healing process, which can lead to subsequent development of cirrhosis and eventually to hepatocellular carcinoma, with negative consequences on energy metabolism. In arsenic-induced oxidative stress, taurine supplementation significantly decreased hepatic oxidative injury. The combination of taurine and dimercaptosuccinate had a greater effect in improving the antioxidant status in the liver.[126] The CCL_4 model group exhibited some cellular damage, portal inflammation, severe centrilobular necrosis, and excessive deposition of collagen. Combined therapy with taurine, epigallocatechin gallate, and genistein alleviated histopathologic damage in liver fibrosis.[127] During the early stages of liver injury, an

adaptive metabolic shift occurs: energy is generated mainly from oxidative phosphorylation during glycolysis homeostasis, leading to mitochondrial dysfunction.[128] Mitochondrial dysfunction not only cause energy deficiency, but also elevates ROS to critically high levels in cells. Thioredoxin 1 (Txn1) interacts with numerous proteins involved in several cellular processes, including energy metabolism and several biosynthetic pathways, it was upregulated in the combined therapy group compared with the model group.[127] These findings show that the upregulated interaction of Txn1 in the glycolysis pathway increases energy metabolism and prevents ROS generation in hepatocytes. Tea polyphenols (TPs) are natural antioxidants and recent studies demonstrated that TPs alleviate fatty liver disease.[129] Combination treatment with taurine and TPs alleviates serum biochemical parameters, such as alanine transaminase and aspartate transaminase, improves histological examination in NASH, and has synergistic effects on lipid disturbance and oxidative stress. These effects were more pronounced than those of taurine or TPs alone.[129,130] Curcumin, obtained from turmeric extract, was shown to have significant anticarcinogenic and antioxidative effects in experimental studies. In diethyl nitrosamine-induced liver damage, a dietary combination of curcumin with taurine significantly reduced the extent of malignant changes, disrupted organelles, and caused mitochondria irregularities and infiltration of inflammatory cells. The combination resulted in normal plasma levels of IL-2 and IFN-γ.[131] The curcumin/taurine combination produce better results in cell-density than monotherapy in cultured human hepatoma cells.[132] BCAA supplementation increased taurine levels in the plasma of patients with liver cirrhosis by promoting CDO gene transcription,[39] and thus the combination of taurine with BCAA is a potential strategy for liver cirrhosis that requires further investigation.

7. Communication Between Organs

Metabolic alterations in a peripheral organ can affect the physiology of other peripheral tissues.[133,134] Organs communicate through hormonal signaling, feeding behavior, and control of energy homeostasis.[88] The skeletal muscle system and adipose tissue are recognized as endocrine organs. they secret myokines and adipokines, such as adiponectin and leptin, to target other metabolic organs (liver, skeletal muscle, and adipose tissue), thus modulating systemic energy homeostasis.[86,88,134,135] Mitochondria integrate multiple physiological signals and their abnormalities favor biological processes in other tissues. Taurine appears to have multiple effects, including in the skeletal muscle, heart, adipose tissue, and liver.

Chronic alcohol consumption contributes to an increase in ROS and the development of alcoholic liver disease[136] as well as triggers ERS in the adipose tissue and in liver.[137,138] Ethanol-induced ERS is related to decreased adiponectin expression in the adipose tissue and liver,[102] suggesting that adipose tissue is an important target for therapeutic interventions aimed to prevent ethanol-induced fatty liver.[29] Adipose tissue plays a vital role in regulating energy homeostasis in the skeletal and cardiac muscle and liver. This interorgan regulation is accomplished through the production of cytokines, such as adiponectin and leptin.[139] Adiponectin receptor 2 is mostly expressed in the liver, where it regulates lipid and glucose metabolism.[140] There is an association between adipose tissue and liver disease, and the development of therapeutic interventions targeting adipose tissue may be useful for ameliorating liver disease. Certain cytokines, such as IL-6 and TNF-α, are secreted in both the skeletal muscle and adipose tissue, performing a bioactive effect in energy metabolism.[88] Skeletal muscle, particularly type I fibers, have a potential therapeutic effect and inhibit the progression of obesity.[141] Adiponectin receptor 1 is predominantly expressed in the skeletal muscle.[142] HFD increased taurine levels and no difference was observed compared to the HF + taurine group, which is inconsistent with previous reports.[25] Adipose tissue participates directly in obesity-related cardiovascular diseases and coronary artery disease is associated with decreased serum adiponectin levels.[143] The liver plays an important role in regulating blood glucose levels through gluconeogenesis and glycogenolysis, with the latter serving as a main source of glucose in the serum during muscle contraction.

8. Conclusions

Taurine plays an important role in energy metabolism and exerts its effects either directly or indirectly by reversing histological abnormalities and improving metabolic activities. Under taurine deficiency, the skeletal muscle, heart muscle, liver, and adipose tissue show serious damage in physical function. Furthermore, combination with other bioactive drugs may have an additive effect, representing a new strategy for disease therapy. Under normal conditions, taurine supplementation strengthens energy metabolism. Furthermore, there is a relationship between these tissues in energy metabolism: if one tissue is damaged, other tissues may be affected through signaling molecules. Thus, the interaction of taurine and energy metabolism is multifaceted and involves multiple organs.

These findings are of great practical and scientific interest, and raise several important questions for further research: 1) The role of taurine in tissue communication in energy metabolism dysfunction has not been investigated. 2) The role of taurine in strengthening energy metabolism in various tissues remains unclear. 3) When TauT is knocked out, taurine levels are decreased in all tissues. It is essential to develop a method for knocking out TauT in single tissues to evaluate the role of taurine in energy metabolism. (4) Because modification τm^5U is lacking in mitochondrial tRNA from MELAS and MERRF, restoration of taurine modified uridine is a potential therapeutic strategy for treating mitochondrial encephalomyopathic disease, and the molecular pathogenesis of mitochondrial disease requires further analysis.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

adipose tissue, energy metabolism, liver, muscles, taurine

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