Taurine Metabolism in Humans


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Abstract

Taurine is a sulfur-containing compound that humans synthesize from the amino acid methionine. Taurine is present in dietary food and some artificial drinks, although body taurine content remains normal with minor taurine ingestion. Taurine is present in human skeletal muscle, heart, and liver, but distribution in other tissues is not well known. The human kidney modifies urinary taurine excretion depending on dietary taurine intake, so that urinary excretion is reduced when taurine availability is low while urinary excretion increases with abundant taurine consumption. Two human transporters are known to carry taurine across the plasma membrane, SLC6A6 (TaurT) and SLC36A1 (PAT1). No congenital deficiency of these transporters has been identified. The biological actions of taurine are not fully established. Taurine binds acyl groups, although little is known about the enzymes involved in the formation of acyl-taurine derivatives. Taurine is attached to the mitochondrial transfer RNA for leucine and lysine and this modification is required for normal protein translation in the mitochondrial network. Like glycine, taurine conjugates bile acids to facilitate their secretion into bile. In the intestinal lumen, conjugated bile acids improve fat absorption, including fat-soluble vitamins. Plasma level of acetyl-taurine increases after exercise, suggesting that taurine contributes to reduce excess intracellular acetyl-coA content, like L-carnitine. Taurine supplementation may have beneficial effects on exercise performance. A vascular effect of taurine improving arterial stiffness has been reported. Taurine administration may lower plasma triglyceride level in obese individuals. No major effect of taurine on glycemic control in patients with diabetes has been documented.

Keywords: Methionine; diabetes mellitus; obesity; triglycerides; N-acetyl-taurine; mitochondrial transfer RNA

Abbreviations

BAAT: Bile acid-coA:Amino acid N-acyltransferase; BMI: Body Mass Index; MAT: Methionine Adenosyltransferase; MELAS: Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes; MERRF: Myoclonus Epilepsy Associated with Ragged Red Fibers; tRNA: Transfer RNA

Introduction

Taurine is an abundant intracellular compound of human cells, particularly skeletal muscle and liver, but its biological function remains elusive. The present review summarizes information on taurine metabolism and its physiological effects in human beings, as species differences preclude translation of animal investigations to human pathophysiology. Taurine is 2-amino-ethane-sulfonic acid, a sulfur-containing zwitterionic compound. (Figure 1) Humans synthesize taurine from methionine and obtain it from dietary sources [1]. Taurine is predominantly intracellular and moves across the plasma membrane through two transporters, SLC6A6 (TaurT) and SLC36A1 (PAT1) [2,3]. The physiological role of taurine in humans is uncertain, but its ability to bind acyl groups (Figure 2) may contribute to explain some of its biological actions. Taurine attaches to mitochondrial transfer RNA (tRNA) for leucine and lysine and this modification is required for mitochondrial protein translation [4]. The mechanism that permits taurine passage through the mitochondrial membrane has not been elucidated. Like glycine, taurine conjugates bile acids, allowing their excretion into bile from the hepatocyte [5]. Like L-carnitine, taurine binds acetyl groups, forming acetyl-taurine. During physical activity, there is a marked elevation of plasma acetyl-taurine level, suggesting that this derivative is generated to buffer excess acetyl-coA in the skeletal muscle, similarly to acetyl-carnitine [6]. Taurine attaches other acyl groups to form N-acyl-taurine conjugates. In vitro studies suggest that N-arachidonoyl-taurine may restore gating of mutated potassium channels Iks that cause congenital long QT syndrome [7]. Taurine role in human metabolism is uncertain. A few investigations have shown that taurine supplementation increases nitrogen balance in athletes, lowers plasma triglyceride level in obese subjects, and increases fat oxidation during exercise [8].

Endogenous Synthesis of Taurine in Humans

Humans obtain taurine both via dietary consumption and endogenous synthesis, but plasma taurine concentration remains normal in healthy individuals despite limited oral intake, suggesting that endogenous synthesis is sufficient to maintain taurine content in healthy adult subjects [9,10].

Dietary Sources of Taurine

The range of daily taurine intake is very wide, from almost negligible amounts to more than 1 g. Among American subjects, the average daily intake of taurine has been estimated to be approximately 40–400 mg [1]. Taurine content in seafood is high while terrestrial fruits and vegetables generally contain a low amount [11]. Red algae contain relatively high amounts of taurine while the taurine content is low in brown and green algae from the Sea of Japan. Among taurine-rich red edible algae are mafunori, fukurofunori, kabanori, and ogonori [12]. Taurine is an ingredient in some so-called “energy drinks” such as Red Bull, Monster, and Rockstar, each serving (250 mL) containing approximately 1 g (8000 μmol) of this compound. In recent years, the intake of these drinks has become a considerable dietary source of taurine [13,14].

Endogenous Synthesis of Taurine in Humans

Plasma taurine levels are not significantly different among healthy adults consuming different amounts of taurine, suggesting that humans have a considerable capacity to synthesize this compound and preserve it [1]. Investigations using labeled oxygen confirm that humans synthesize taurine [9].
**Figure 1:** Chemical structure of Taurine.

**Figure 2:** Chemical structure of Acyl group.

**Figure 3:** Algorithm of Taurine synthesis pathway.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Reaction</th>
<th>Clinical Phenotype of Congenital Deficiency</th>
<th>Biochemical Phenotype of Congenital Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-methionine S-adenosyltransferase</td>
<td>Synthesis of S-adenosyl methionine from methionine + ATP</td>
<td>The clinical phenotype of MAT1A deficiency is variable. Some patients have brain demyelination or a peculiar breath odor.</td>
<td>Elevated plasma level of methionine. Reduced activity of MAT1A in the liver.</td>
</tr>
<tr>
<td>S-adenosyl homocysteine hydrolase</td>
<td>Cleavage of S-adenosyl homocysteine to adenosine + L-homocysteine</td>
<td>Developmental delay, hypotonia, muscle weakness, absent tendon reflexes, and hepatopathy</td>
<td>Elevated plasma level of S-adenosyl homocysteine, S-adenosyl methionine, and methionine</td>
</tr>
<tr>
<td>Cystathionine β-synthase</td>
<td>Condensation of homocysteine + serine to cystathionine</td>
<td>Dislocation of the lens, “marfanoid” habitus, central nervous system dysfunction, osteoporosis, bone deformities, venous and arterial thrombosis,</td>
<td>Elevated plasma concentration of total homocysteine</td>
</tr>
<tr>
<td>Cystathionine γ-lyase</td>
<td>Cleavage of cystathionine to α-ketobutyrate + cysteine + NH₄⁺</td>
<td>Patients with cystathioninuria are usually asymptomatic.</td>
<td>Elevated plasma and urine concentration of cystathionine</td>
</tr>
<tr>
<td>Cysteine dioxygenase</td>
<td>Oxidation of L-cysteine to cysteinesulfinate</td>
<td>No congenital deficiency has been documented</td>
<td></td>
</tr>
<tr>
<td>Cysteinesulfinate decarboxylase</td>
<td>Decarboxylation of cysteinesulfinate to hypotaurine</td>
<td>No congenital deficiency has been documented</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1:** Congenital deficiency of the enzymes involved in taurine synthesis.
The synthesis of taurine requires ATP, methionine, serine, and oxygen. The enzyme involved in this last reaction is unknown. The formation of homocysteine + serine generates cystathionine. Second, the incorporation of molecular oxygen to cystathionine β-synthase is a homotetramer that catalyzes the reversible conversion of S-adenosylhomocysteine to adenosine + L-homocysteine. S-adenosylhomocysteine hydrolyase has been purified from human placenta, revealing a tetrameric structure. The lysine 426 residue is essential to stabilize the quaternary structure of the protein [18].

S-adenosylhomocysteine hydrolase

S-adenosylmethionine serves as a methyl donor for a number of methylation reactions catalyzed by several methyltransferases. The removal of the methyl group converts S-adenosylmethionine into S-adenosylhomocysteine. Then, S-adenosylhomocysteine hydrolyase catalyzes the reversible conversion of S-adenosylhomocysteine to adenosine + L-homocysteine. S-adenosylhomocysteine hydrolyase has been purified from human placenta, revealing a tetrameric structure. The lysine 426 residue is essential to stabilize the quaternary structure of the protein [18].

**Main Characteristics of Taurine**

- It contains sulfur
- It is a zwitterion (bipolar ion)
- It requires transporters to cross human cell membranes
- It is predominantly intracellular
- Human muscle contains elevated amounts of taurine
- It binds some acyl groups

**Main actions of taurine in humans**

- Post-translational modification of transfer-RNA for leucine and lysine
- Conjugation to bile acids in the hepatocyte
- Formation of acetyl-taurine in skeletal muscle
- Taurine may enhance skeletal muscle fatty acid oxidation during exercise
- Taurine may decrease plasma triglyceride level
- Taurine has a vasodilator effect on human arteries and reduces arterial stiffness
- No conclusive effect on glycemic control or weight loss has been observed

**Table 2: Main characteristics and actions of taurine in the human body.**

Taurine is derived from the amino acid methionine, which is converted into S-adenosylmethionine. S-adenosylmethionine is a methyl donor for several methylation reactions, including the synthesis of sarcosine, creatine, and phosphatidylcholine. The release of the methyl group converts S-adenosylmethionine into S-adenosylhomocysteine, which is hydrolyzed into homocysteine + adenosine. Homocysteine can either be re-methylated to methionine or enter the so-called trans-sulfuration pathway to form cysteine and then taurine in several enzymatic steps. First, the condensation of homocysteine + serine generates cystathionine. Second, the cleavage of cystathionine produces cysteine + α-ketobutyrate + NH4+. Third, the incorporation of molecular oxygen to cysteine forms cysteine sulfinic acid. Fourth, the decarboxylation of cysteine sulfinic acid yields hypotaurine with the release of carbon dioxide (Table 1). Finally, the oxidation of hypotaurine renders taurine. The enzyme involved in this last reaction is unknown. The synthesis of taurine requires ATP, methionine, serine, and oxygen and produces adenosine, α-ketobutyrate, ammonium, and carbon dioxide, besides taurine (Figure 3) [9].

**L-methionine S-adenosyltransferase**

Methionine adenosyltransferase (MAT) catalyzes the synthesis of S-adenosylmethionine from methionine and ATP by transferring the adenosyl group of ATP to the sulfur atom of L-methionine. Three isoenzymes of human methionine adenosyltransferase have been identified. MATII (MAT2) is composed of catalytic (α2) and regulatory (β) subunits. Two separate genes encode the isoforms of MAT2. The gene MAT2A, located to 2p11.2, encodes the catalytic component (α2 subunit) while the gene MAT2B, located to 5q34, encodes the regulatory component (β subunit). MATI is a homotetramer of α1 subunits. MATI is a homodimer of α1 subunits. MATI and MATIII have been collectively named MATIA, as they contain only α1 subunits. The gene MAT1A, located to 10q22.3, encodes the α1 subunit and therefore the isoforms MATI and MATII (MAT1A). Mutations in the MATIA gene have been rarely documented since 1974. The clinical phenotype of MATIA deficiency is variable. Most individuals harboring mutations in the MATIA gene are asymptomatic, but they may show brain demyelination and an unusual breath odor. Plasma concentration of methionine is elevated. The activity of the isoenzyme of methionine adenosyltransferase MATIA is reduced in the liver of affected patients [15–17].

**S-adenosylhomocysteine hydrolase**

S-adenosylmethionine serves as a methyl donor for a number of methylation reactions catalyzed by several methyltransferases. The removal of the methyl group converts S-adenosylmethionine into S-adenosylhomocysteine. Then, S-adenosylhomocysteine hydrolyase catalyzes the reversible conversion of S-adenosylhomocysteine to adenosine + L-homocysteine. S-adenosylhomocysteine hydrolyase has been purified from human placenta, revealing a tetrameric structure. The lysine 426 residue is essential to stabilize the quaternary structure of the protein [18].

The AHCY gene encodes S-adenosylhomocysteine hydrolase, being located on 20q11.22. Two common alleles have been found in German and Japanese populations. In vitro studies suggest that the AHCY gene contributes to regulate cell proliferation, as down-regulation of this gene suppresses cell proliferation. S-adenosylhomocysteine hydrolyase mRNA and protein are highly expressed in most breast cancer cells compared with human breast MCF10A cells [19]. Congenital deficiency of S-adenosylhomocysteine hydrolyase is an autosomal recessive disorder identified in a few patients. Clinical onset usually occurs during infancy or childhood, but adult presentation has been reported. Clinical phenotype includesdevelopmental delay, hypotonia, muscle weakness, absent tendon reflexes, and hepatopathy. Hepatocellular carcinoma has been documented. Myelination is impaired in the nervous system and brain MRI reveals white matter atrophy. Biochemical phenotype is characterized by markedly elevated plasma concentration of S-adenosylhomocysteine and S-adenosylmethionine. Plasma level of methionine is also increased. Total homocysteine level is slightly above normal. Dietary methionine restriction can lower circulating levels of methionine in patients with S-adenosylhomocysteine hydrolyase deficiency, but normalization of serum methionine levels does not improve the clinical course of the disease in some patients. Therefore, the beneficial role of dietary methionine restriction in patients with S-adenosylhomocysteine hydrolyase deficiency remains unclear. Liver transplantation has been rarely performed and might be another treatment option for patients with this disease, although the long-term outcome is unknown [20–21].

It has been suggested that S-adenosylhomocysteine hydrolyase deficiency might lead to increased genome wide DNA methylation. However, in blood samples from patients with this disorder, DNA methylation is not a constant feature and seems to affect different genomic regions to different degrees [22].

**Cystathionine β-synthase**

Homocysteine may be either re-methylated to form methionine or enter the trans-sulfuration pathway to form cysteine. The enzyme cystathionine β-synthase is a homotetramer that catalyzes the first reaction of the trans-sulfuration pathway, the condensation of homocysteine + serine to generate cystathionine. The gene CBS, located to 21q22.3, encodes cystathionine β-synthase. Molecular defects in this gene cause cystathionine β-synthase deficiency (classical homocystinuria). Patients with this disorder show broad phenotypic variability. Clinical onset may occur during childhood, but some patients remain asymptomatic into adulthood. Clinical phenotype includes dislocation of the lens, severe myopia, excessive height and length of the limbs (“marfanoid” habitus), osteoporosis, bone deformities (pectus excavatum, pectus carinatum, genu valgus and scoliosis), venous thrombosis and arterial thromboembolism,
and central nervous system dysfunction including seizures, extrapyramidal deficit, developmental delay, intellectual disability, learning difficulties, psychiatric and behavioral problems. Cystathionine β-synthase deficiency is characterized by accumulation of homocysteine and depletion of cystathionine and cysteine. Elevation of plasma total homocysteine level is the biochemical hallmark of the disease. As pyridoxine administration may reduce the plasma level of total homocysteine, the intake of any pyridoxine supplement (including fortified foods and drinks) should be avoided for at least 2 weeks before sampling plasma for total homocysteine measurement. Therapy options include low-methionine diet, and administration of betaine and pyridoxine [23].

### Cystathionine γ-lyase

Cystathionine γ-lyase (cystathionase) is a tetramer that catalyzes the cleavage of cystathionine to cysteine + α-ketobutyrate (2-ketobutyrate) + ammonium (NH4+), the second reaction in the trans-sulfuration pathway [24]. The gene CTH encodes cystathionine γ-lyase, being located to 1p31.1. Mutations in CTH gene lead to cystathioninuria, an autosomal recessive disorder characterized by elevated plasma and urine concentration of cystathionine with no major clinical repercussion [25,26].

Besides cysteine, cystathionine γ-lyase generates 2-ketobutyrate, which is thought to be the precursor of 2-hydroxybutyrate, although the enzyme that catalyzes the conversion of 2-ketobutyrate into 2-hydroxybutyrate in humans is unknown. Some investigations have found a positive association between plasma level of 2-hydroxybutyrate and insulin resistance. The RISC (Relationship of Insulin Sensitivity to Cardiovascular Risk) study includes a cohort of nondiabetic participants with a broad spectrum of insulin sensitivity and glucose tolerance. Plasma 2-hydroxybutyrate concentration is able to segregate insulin-resistant from insulin-sensitive subjects independently of body mass index (BMI) in this trial [27]. Among African American women, the plasma level of 2-hydroxybutyrate is higher in obese type 2 diabetic compared to obese non-diabetic subjects [28].

It has been proposed that the activity of the enzymes cystathionine β-synthase and cystathionine γ-lyase might produce hydrogen sulfide (H2S). However, production of hydrogen sulfide in humans and the potential clinical relevance of this compound have not been demonstrated [29].

### Cysteine dioxygenase

Human cysteine dioxygenase is an iron-containing enzyme that catalyzes the irreversible oxidation of L-cysteine to cysteinesulfinate (3-sulfinoalanine) with addition of molecular oxygen to the sulfur atom of cysteine (L-cysteine + O2 → cysteinesulfinate). The crystal structure of human cysteine dioxygenase in complex with its substrate, L-cysteine, has been reported [30,31]. Northern blot analyses of human tissues reveal that cysteine dioxygenase mRNA is strongly expressed in the liver and weakly expressed in the heart, brain and pancreas. No cysteine dioxygenase message is detected in skeletal muscle, kidney and lung [32]. Human cysteine dioxygenase-1 (CDO1) gene has been mapped to 5p22.3 and encodes a single mRNA species [33]. No molecular defects leading to congenital deficiency of cysteine dioxygenase have been reported in this gene and therefore its role in human pathophysiology is unclear. Promoter methylation regulates the expression of the human cysteine dioxygenase-1 gene, so that hypermethylation silences the gene. The frequency of promoter methylation in this gene is higher in a variety of human tumours including colorectal cancer, breast, lung, bladder, stomach and esophagus, compared to normal tissues. The cysteine dioxygenase-1 gene is inactivated in cancer cell lines and its expression is re-activated by pharmacological dimethylation with 5-aza-2’-deoxycytidine therapy [34].

### Cysteinesulfinate decarboxylase

Little is known about human cysteinesulfinate decarboxylase. Similarly to histidine decarboxylase and glutamate decarboxylase, cysteinesulfinate decarboxylase belongs to group II of pyridoxal 5’-phosphate-dependent enzymes. It catalyzes the decarboxylation of cysteinesulfinate to generate hypotaurine and has been detected at human neuromuscular junctions. The gene CSAD encodes cysteinesulfinate decarboxylase, being located on 12q13.13. Mutations in this gene resulting in congenital deficiency of cysteinesulfinate decarboxylase have not been identified [35,36].

### Taurine Content in Adult Human Tissues, Plasma, and Urine

In the human body, taurine is predominantly intracellular; its plasma concentration being comparatively minute. Plasma taurine level is approximately 0.07 mM (in the range of 0.025 to 0.150 mM) whereas taurine concentration in skeletal muscle is 15.4 mM [37]. No differences exist between taurine level in arterial, portal venous, hepatic venous and renal venous plasma [38].

Acute taurine supplementation produces a marked increase in plasma taurine concentration that returns to baseline levels in approximately 8 hours. Oral administration of 4 g taurine to healthy volunteers increases plasma taurine concentration from 40 μM to 690 μM at 1.5 hours after administration [39]. Oral taurine administration at 6.0 g/day (2 g three times a day) for two weeks also increases plasma taurine concentration [40,41]. In patients with kidney failure, taurine supplementation may lead to accumulation of this compound [42]. In healthy subjects, a seven-day period of starvation induces a slight decrease in plasma taurine level, compared to baseline [43].

The human kidney adjusts urinary taurine excretion according to taurine availability, so that taurine excretion falls when dietary taurine is scarce and increases when dietary intake is abundant [1]. The normal range of daily urinary taurine excretion is very wide, from 1400 to 2,650 μmol/day. In a multicenter study with the participation from 16 countries, Japanese population show the highest urinary taurine excretion values while Canadian and Russian individuals show the lowest urinary excretion, likely reflecting higher dietary taurine intake in Japan compared to other populations, particularly Canada and Russia [44]. Taurine administration to healthy subjects causes a large increase in the rate of urinary excretion. After administration of labeled taurine to healthy subjects, radioactivity in urine is retrieved predominantly as taurine, most of the remainder being present as sulfate, with less than 5% being present as isethionate, the deamination product of taurine. The fraction excreted as sulfate does not differ from that excreted during the normal taurine diet, suggesting that taurine conversion to sulfate does not augment with taurine supplementation [45]. The urinary taurine excretion decreases following starvation in healthy subjects, compared to baseline levels [46].

Taurine has been detected in several human tissues, including skeletal muscle, heart, liver, blood cells, and intestine. In healthy subjects, taurine is abundant in skeletal muscle. The taurine content is 15.4 mM while glutamine concentration, the most abundant amino acid in skeletal muscle, is 19.45 mM. Taurine content in skeletal muscle has been found more abundant in the slow, oxidative type 1 fibers than in the type 2 fibers [37]. Taurine supplementation to healthy volunteers for seven days increases plasma taurine concentration and increases threonine and glycine content in skeletal muscle, although the physiological relevance of this finding is uncertain [47]. In a small study, trained men have
greater taurine content in skeletal muscle than untrained men [48]. Administration of 6 g of taurine per day for 8 weeks to male athletes decreases 24-hour urinary nitrogen excretion by 33% and promotes positive nitrogen balance compared to placebo [49]. Taurine is abundant in biopsy specimens from the left ventricle of patients undergoing cardiac surgery [50]. Taurine concentration in whole blood is higher than taurine level in plasma, indicating that taurine is present in blood cells. Taurine content in granulocytes is greater than that of lymphocytes. The role of taurine in blood cells has not been elucidated [38]. Taurine has been detected in the duodenal mucosa and the colon of healthy individuals [51].

**Taurine Transporters**

There are two known human transporters that carry taurine across the plasma membrane, SLC6A6 (TauT) and SLC36A1 (PAT1).

**Taurine transporter SLC6A6 (TauT)**

The transporter SLC6A6 (solute carrier family 6 member 6) transports taurine, hypotaurine, and β-alanine. The activity of SLC6A6 is dependent on the presence of sodium (Na+) and chloride (Cl-) ions. The sodium/chloride/taurine stoichiometry for SLC6A6 is 2:1:1 [2]. The taurine transporter SLC6A6 has been cloned from human placenta, [52] thyroid cells, [53] and intestinal epithelial cell line Caco-2 [54]. Northern-blot analyses reveal a wide distribution of TauT in human tissues. There is abundant expression of the transcript in skeletal muscle and placenta [52]. The mRNA is also detectable in human heart, brain, lung, kidney, liver, pancreas, duodenum, ileum and colon [53]. The transporter has been identified in human osteoblasts [55]. In colorectal cancer cells, the SLC6A6 transporter is highly expressed compared to normal colonocytes [56]. In vitro studies show that a taurine rich medium down-regulates TauT activity in human intestinal Caco-2 cells, reducing taurine uptake by these cells [54].

The SLC6A6 gene is located to 3p25.1 and encodes the SLC6A6 transporter [52]. In patients with 3p syndrome, deletion of 3p25-pter (that includes SLC6A6) causes growth failure, facial dysmorphism, retinal changes, and mental retardation. It is unknown whether deletion of SLC6A6 may contribute to some phenotypic features of this syndrome [57]. No specific mutations in the SLC6A6 gene have been reported.

**Taurine transporter SLC36A1 (PAT1)**

The transporter SLC36A1 (PAT1) is a proton (H+)-dependent carrier that transports a number of substrates including taurine, betaine, γ-amino-butyric acid (GABA), amino acids such as glycine, proline, and alanine, and some drugs such as vigabatrin [58]. Human PAT1 has been cloned from the human intestinal cell line Caco-2 [3]. Northern blot analysis shows that human PAT1 mRNA is expressed ubiquitously in human tissues, with maximal expression in the small intestine. Moderate expression is identified in the brain, colon, kidney, lung, placenta, and testis. Expression is detectable at very low levels in the stomach, spleen, skeletal muscle, and heart. The message for the two taurine transporters (SLC6A6 and SLC36A1) has been identified in human gastrointestinal tract, suggesting that taurine uptake across the human intestinal brush-border membrane may occur via both of them [3].

The gene SLC36A1 encodes SLC36A1 (PAT1), being located on 5q33.1 [58]. No mutations in this gene have been reported.

**Physiological Role of Taurine in Humans**

The biological roles of taurine in human physiology are not fully understood. Similarly to L-carnitine and glycine, taurine binds acyl groups generating acyl-taurine derivatives. In the hepatocyte, taurine is conjugated to bile acids prior to their excretion into bile. In skeletal muscle taurine is converted to acetyl-taurine when excessive acetyl-coA is generated. Little is known about the enzymes that catalyze the formation of acyl-taurines. Taurine is attached to the mitochondrial transfer RNA for leucine and lysine facilitating protein translation in the mitochondrial network. (Table 2) There is no conclusive evidence to suggest other clinically relevant biological actions of taurine in adults. A specific clinical syndrome secondary to taurine deficiency has not been defined. Congenital deficiency of the taurine transporters SLC6A6 (TauT) and SLC36A1 (PAT1) or the enzymes involved in taurine synthesis from cysteine (cysteine dioxygenase and cysteine sulfinate decarboxylase) has not been documented.

**Post-translational modification of mitochondrial tRNA for leucine and lysine**

In order to synthesize protein either in the cytosol or inside the mitochondrial network, each amino acid binds its paired transfer RNA forming an amino acyl-tRNA that directs the amino acid to its place in the polypeptide chain. In vitro studies show that taurine is incorporated to the human mitochondrial transfer RNA for leucine (tRNAleu) and lysine (tRNALys). The attachment of taurine to these tRNAs is required for protein translation in the mitochondrial network. Mitochondrial DNA mutations affecting the mitochondrial tRNA for leucine are responsible for a disorder named mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). In vitro studies reveal that normal taurine conjugation to tRNA is deficient in the mutant mitochondrial tRNA for leucine (tRNAleu) from patients with MELAS. As a result, the translation of components of the electron transport chain is compromised. Deficient taurine incorporation to the mutant tRNA has also been observed in another mitochondrial disorder, myoclonus epilepsy associated with ragged red fibers (MERRF) [4,59]. The enzyme that catalyzes taurine incorporation to mitochondrial tRNA in humans is unknown [60]. High-dose taurine supplementation (9-12 g per day) for 52 weeks to 10 patients with MELAS led to a reduction in the number of stroke-like episodes [61].

**Taurine conjugation to bile acids**

The excretion of bile acids from the hepatocyte into bile requires prior conjugation to taurine (or glycine). In the intestinal lumen, conjugated bile acids facilitate absorption of fat and fat-soluble vitamins A, D, E, and K. Cholic acid and chenodeoxycholic acids are primary C24 bile acids synthesized from cholesterol in hepatocytes. Before their excretion into bile, acyl-coA synthetases form the corresponding acyl-coA esters and the enzyme bile acid-coA:amino acid N-acyltransferase (BAAT) catalyzes the transfer of the acyl moiety to taurine or glycine, forming the respective taurine- or glycine- derivatives. BAAT has been purified from human liver and its cDNA has been isolated and characterized. This enzyme is a monomer that may utilize glycine and taurine as substrates. Tissue expression studies show strong expression of BAAT in the human liver [5].

The human gene BAAT located on 9q31.1 encodes this protein. Mutations in the BAAT gene leading to congenital deficiency of BAAT have been documented in a few patients [62]. In patients with BAAT deficiency, glycine or taurine conjugates of bile acids are absent in the bile, serum, and urine. In addition, the serum level of the unconjugated species is elevated due to the conjugation defect. Intestinal absorption of fat-soluble vitamins is deficient. Therapy with the conjugated bile acid glycocholic acid has been effective to ameliorate fat-soluble vitamin absorption in five patients with this disorder [63]. A method to improve the urinary profiling of inborn errors of bile acid synthesis has been developed [64].
Formation of N-arachidonoyl-taurine (C20:4 taurine) and N-oleoyl-taurine (C18:1 taurine)

Some patients with long QT syndrome harbor mutations in the Iks potassium channel that accelerate channel closing. In vitro studies suggest that N-arachidonoyl-taurine restores channel gating of different mutant channels. N-arachidonoyl-taurine might recover the dysfunction of mutated potassium channels that cause congenital long QT syndrome [7]. In vitro studies show that N-arachidonoyl-taurine (C20:4 taurine) and N-oleoyl-taurine (C18:1 taurine) inhibit cell proliferation in the human prostate adenocarcinoma cell line PC-3 [65].

Taurine and exercise

Human skeletal myocytes contain a high amount of intracellular taurine relative to plasma, suggesting that taurine may play a role in muscle function.

Plasma taurine concentration increases after exercise

Plasma taurine concentration increases slightly following both short-term physical activity and endurance exercise, suggesting that skeletal muscle releases small quantities of taurine. In a subject exercising to 75% of his maximal oxygen consumption on a treadmill for 1.5 hours, plasma taurine level increased by 19% in comparison to the pre-exercise level [66]. Similarly, plasma taurine concentration increases slightly in healthy runners participating in the Rotterdam marathon and in the Tsukuba marathon after completing the event. Further, plasma taurine level increases in trained athletes after completion of a 100 km run in comparison to their respective pre-exercise level [6,67]. An increase in the extracellular level of taurine in skeletal muscle is observed in trained subjects performing a 7 hours bike race on high workload intensity [68].

Plasma acetyl-taurine concentration increases after exercise

During physical activity, skeletal muscle contraction generates acetyl-coA due to fatty acid oxidation (primarily during low-intensity exercise) and glucose oxidation (predominantly during high-intensity exercise). In order to avoid acetyl-coA accumulation within the mitochondria, intracellular compounds such as L-carnitine and taurine attach acetyl groups yielding acetyl-derivatives (acetyl-carnitine and acetyl-taurine). The enzyme that characterizes, but plasma N-acetyl-taurine increases markedly both after acute physical activity and after endurance exercise. In a subject running for an hour at 9 km/h, serum N-acetyl-taurine level increased immediately post-exercise from approximately 5 nM to 35 nM, returning to the baseline level approximately one hour post-exercise. In healthy runners participating in the Tsukuba marathon race, serum N-acetyl-taurine increases from 3.2 nM before the marathon to 18.8 nM immediately after the event, returning to the pre-exercise values after a day [6]. The increase in plasma acetyl-taurine post-exercise suggests that taurine is N-acetylated due to excessive formation of acetyl-coA in skeletal muscle during physical activity.

Effect of taurine supplementation on exercise performance

Some investigations find that taurine supplementation improves exercise performance in healthy subjects [69–71]. Seven-day taurine supplementation increases exercise time to exhaustion and maximal workload in healthy men [69]. Combined with amino acids, taurine administration (6.0 g/day for two weeks) attenuates delayed-onset muscle soreness [40]. However, other studies show no effect of taurine supplementation on exercise capacity [49,72–74]. A recent meta-analysis concludes that acute or chronic oral taurine supplementation in several doses may improve human endurance performance including time to exhaustion [75]. In patients with heart failure, taurine improves exercise capacity, enhancing exercise time and exercise distance [76]. In vitro studies using human cardiomyocytes harvested from patients undergoing cardiac surgery show that exposure to taurine does not alter the contraction behavior (isometric contractile force and duration of contraction) of the specimens compared with pre-exposure values [77]. In trained subjects, taurine ingestion increases fat oxidation during submaximal cycling exercise compared with placebo [72].

Role of taurine in obesity, glucose intolerance and diabetes mellitus

A number of studies have examined the role of taurine in obesity, glucose intolerance and diabetes and the effect of taurine supplementation on weight loss, insulin resistance, and glycemic control of diabetes. Plasma taurine level is not consistently altered in subjects with obesity or diabetes mellitus. Taurine supplementation has no clinically relevant beneficial effect on weight loss, insulin resistance or metabolic control of diabetes. Therefore, there is currently no evidence to suggest that dietary supplementation with taurine can be used to prevent the development of type 2 diabetes or treat the disease [78].

Plasma taurine concentration in obesity and diabetes

The CARDIAC (Cardiovascular Diseases and Alimentary Comparison) study is a multicenter cross-sectional survey designed to assess the effect of diet on cardiovascular risk. In this study, urinary taurine excretion is inversely related with BMI [79]. However, multiple linear regression analyses in a cross-sectional study that included participants with vascular disease and control individuals do not reveal the association of plasma taurine level with BMI. Adjusted means for taurine in normal weight, overweight, and obese individuals show nearly identical values in the three BMI groups [80]. In obese women recruited to participate in a 8-week body weight control program, body weight, body fat mass, and BMI decreased after the program, but there were no differences in serum taurine between the groups [81]. Plasma taurine concentration has been found slightly lower, [82,83] similar [84] and higher [10] in patients with diabetes mellitus compared to healthy individuals. Similarly, the urinary excretion of taurine has been found increased, [85] similar [86] and reduced [10] in patients with diabetes mellitus compared to healthy subjects.

Effect of taurine supplementation on weight loss, insulin resistance and glycemic control in patients with diabetes

Taurine supplementation to obese subjects provides no significant effect on weight loss. In a randomized double-blind clinical trial with overweight or obese non-diabetic participants, there is no effect of taurine supplementation (3 g/day for 7 weeks) on BMI, compared to placebo [8]. Similarly, in a randomized double-blind placebo-controlled study including obese women, there is no differential effect of taurine supplementation (3 g/day for 8 weeks) or placebo on weight loss. Both the placebo and taurine groups show slight reduction in weight (3%) with no differences between groups [87]. Likewise, randomized controlled trials find no beneficial effect of taurine supplementation on insulin resistance or metabolic control in patients with glucose intolerance or diabetes. In a randomized, double-blind, crossover study aimed to assess the...
effect of taurine supplementation on insulin action (determined by a euglycemic hyperinsulinemic clamp) in overweight first-degree relatives of patients with type 2 diabetes, there is no effect of taurine on insulin sensitivity [78]. In a randomized, double-blind, placebo-controlled trial, taurine supplementation (3000 mg/day) increases blood taurine level, but does not improve glycemic control or insulin levels in patients with type 2 diabetes compared to placebo [88]. Small studies show some favorable effect of taurine. In a small group of ten patients with type 1 diabetes, taurine supplementation (500 mg twice a day for 30 days) lowers the average insulin requirement, suggesting that taurine might improve insulin resistance [89]. In a small study with six overweight or obese men, oral taurine supplementation for 2 weeks ameliorates lipid-induced insulin resistance [90].

Taurine and plasma lipid concentration

Some trials find an association between taurine and plasma level of triglycerides. In healthy Japanese females, plasma triglyceride concentration is lower in the group with higher urinary taurine excretion compared to the group with lower taurine excretion [91]. In addition, taurine supplementation in overweight or obese college students (3 g/day for 7 weeks) decreases plasma triglyceride concentration compared to placebo [8].

Taurine and cardiovascular risk

In the multicenter cross-sectional CARDIAC trial, urinary taurine excretion is negatively associated with ischemic heart disease mortality rates [44]. This inverse association remains when Japanese data are excluded, suggesting that cardiovascular risk is lower in individuals with high urinary taurine excretion [79]. However, in a case-control study nested in the prospective New York University Women’s Health Study, there is no association between serum taurine levels and the risk of coronary heart disease [79,93]. However, in a case-control study nested in the prospective New York University Women’s Health Study, there is no association between serum taurine levels and the risk of coronary heart disease or stroke in the overall study population [92,93].

It has been hypothesized that taurine supplementation might enhance hydrogen sulfide (H2S) production and that this compound might exert some beneficial effect on human cardiovascular health. However, neither taurine-associated increased production of hydrogen sulfide nor the hypothetical beneficial role of this molecule has been clinically demonstrated [29].

Other effects of taurine in humans

In vitro studies show that taurine inhibits the contraction of isolated human radial artery induced by 5-hydroxytryptamine, calcium chloride, and potassium chloride. The mechanism underlying taurine-induced relaxation is uncertain, but large conductance calcium-activated potassium channels (BKCa) may be involved in the vasodilator effect of taurine [94]. Taurine supplementation (500 mg three times daily for 14 days) improved arterial stiffness in patients with type 1 diabetes enrolled in a double-blind cross-over study [95]. Similarly, taurine supplementation (2 g taurine 3 times per day for 14 days) attenuated the delayed increase in arterial stiffness after exercise in healthy men included in a double-blind randomized-controlled trial [41].

The taurine upregulated gene-1 (TUG1) encodes a long non-coding RNA. TUG1 levels are downregulated in human diabetic nephropathy. In addition, the expression of TUG1 is associated with various human tumors. Down-regulation of TUG1 inhibits proliferation and invasion in human glioblastoma U251 cell line [96].

Summary

Taurine is a sulfur-containing molecule that humans obtain from dietary sources and endogenous synthesis. Humans synthesize taurine from the amido acid methionine via homocysteine and the trans-sulfuration pathway. Plasma concentration of taurine decreases slightly following starvation, suggesting that endogenous synthesis and kidney preservation of taurine maintain body taurine content with very little dietary provision. Human tissue distribution of enzymes involved in taurine synthesis has been barely investigated and therefore tissues able to synthesize taurine in the human body are mostly unknown. Taurine is primarily an intracellular molecule, particularly abundant in skeletal muscle, heart, and liver, although the differential intracellular concentration of taurine in adult human tissues is not well known. As a zwitterion, the ability of taurine to cross freely human cell membranes is expected to be limited. Two transporters carry taurine across the plasma membrane, SLC6A6 (TAT2) and SLC36A1 (PAT1). These transporters are likely responsible for taurine absorption in the kidney tubule and the intestinal lumen. No mutations in the genes encoding these transporters have been documented. A number of biological actions have been proposed for taurine, but its physiological role remains elusive. No clinically relevant taurine-deficient state has been established in adult humans. Taurine binds the mitochondrial transfer RNA for leucine and lysine and this attachment is required for normal protein translation in the mitochondrial network. Like glycine, taurine conjugates bile acids to facilitate their secretion from the hepatocyte into bile. Since conjugated bile acids facilitate the intestinal absorption of fat and fat-soluble vitamins, taurine plays a role in this action. During physical exercise, an unknown enzyme synthesizes acetyl-taurine to release free co-A in skeletal muscle. Taurine supplementation may enhance exercise performance. Regarding glucose metabolism, plasma taurine level shows no consistent alteration in subjects with obesity or diabetes. In addition, taurine supplementation has no significant effect on weight loss or glycemic control in patients with diabetes. Taurine induces relaxation of human radial artery in vitro and improves arterial stiffness in vivo.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References


