

Taurine, A Wonderful Molecule: A Review Article

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Abstract

Taurine chemically known as 2 aminoethanesulfonic acid; $\text{NH}_2\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ it's a non essential amino acid, due to absence of carboxyl group it does not participate in protein synthesis, it does not metabolized and thus not involved in gluconeogenesis, thereby not constituting a direct energy source, This wonderful molecule was discover in 1827 by two German scientist Tiedemann and Gmelin from bile of ox (*Bos taurus*), Ten years later, this amino acid got its name as Taurine by Demarcay, and 20 years later Jacobsen and Smith discovered that its structure contains sulfur. In a wide variety of invertebrate and vertebrate tissues the natural occurrence of taurine has been recognized, It is also present in plants algae and fungi. In this review we try to cover all possible beneficial role of taurine.

Keywords: Taurine, 2 aminoethanesulfonic acid; DED, Sulfur, gluconeogenesis, carboxyl group, hypotaurine.

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INTRODUCTION

Taurine, chemically known as 2-aminoethanesulfonic acid; $\text{NH}_2\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$ is a nonessential amino acid that does not participate in protein synthesis due to the absence of a carboxyl group, is not metabolized, and thus is not involved in gluconeogenesis and thus is not a direct source of energy. It is present in abundance in many mammalian tissues such as retina, skeletal muscle, liver, platelets, and leukocytes and exerts many physiological activities, especially in electrically excitable tissues such as heart and brain. The presence of sulfonic acid instead of carboxylic acid makes it highly acidic and it is a zwitterionic amino acid ($\text{pK}_1=1.5$, $\text{pK}_2=8.8$). Due to its zwitterionic nature, it is very water soluble and lipophilic, so the diffusion of taurine across the lipophilic membrane is sluggish because of this property. Because of the zwitterionic property, it has a very strong dipole. Its isoelectric points are between carboxylic amino acids such as GABA, b-alanine and glycine and acidic amino acids such as aspartate and glutamate. Due to the particular ionic character of taurine, the membrane modulates its action as well as its interaction with Ca^{2+} and other cations. Taurine is

more acidic than aspartic acid, glycine, β -alanine, and γ -aminobutyric acid (GABA) because its pK_a is 1.5. Compared to GABA, glycine, and β -alanine, taurine is less basic than these amino acids, as the pK_b value of taurine is 8.82. Due to its cyclic confirmation with an intramolecular hydrogen bond, taurine exhibits low passive diffusion. Its biosynthesis occurs in the liver, kidney, and to a lesser extent in the brain, where taurine is obtained by the enzymatic reaction of hypotaurine. The endogenous synthesis of taurine depends on nutritional status, protein intake, and the amount of available cysteine in the body, so that its synthesis varies greatly from individual to individual (Luca *et al.*, 2015). Overall, it can be said that its content depends on cysteine/methionine metabolism and that two different pathways are involved in the biosynthesis of taurine.

Biosynthesis of Taurine

First, the oxidation of cysteine to cysteine sulfinic acid occurs with the participation of the enzyme cysteine dioxygenase (CDO), then the enzyme cysteine sulfinic acid decarboxylase (CSAD) converts cysteine sulfinic acid to hypotaurine, and finally hypotaurine is converted to taurine by oxidation. The importance of the enzyme cysteinesulfinic acid

decarboxylase (CSAD) is evidenced by a study that found that death of third generation (G3) mouse models CSAD KO (knock out) occurs within 24 hours of birth.

The second biosynthetic pathway of taurine synthesis involves cysteine, which can be conjugated with coenzyme A (CoA) to release cysteamine upon CoA turnover. Throughout this process, the enzyme 2-aminoethanethiol dioxygenase (ADO) is actively involved in the conversion of cysteamine to hypotaurine. However, during prenatal life, the biosynthetic capacity is very high and begins to decrease with the onset of adulthood. Taurine concentration is very low in old age and in certain pathological conditions such as trauma or sepsis. This miraculous molecule was discovered in 1827 by two German scientists, Tiedemann and Gmelin, from the bile of cattle (*Bos taurus*). Ten years later this amino acid was named taurine by Demarcay, and 20 years later Jacobsen and Smith discovered that its structure contains sulfur. The natural occurrence of taurine has been demonstrated in a variety of vertebrate and vertebrate tissues. It is also found in plants, algae and fungi, while it is commercially synthesized from ethylene oxide or monoethanolamine.

Properties of Taurine

Taurine is an antioxidant because it scavenges reactive oxygen species (ROS), thus reducing the formation of reactive oxygen species and suppressing the harmful effects of oxidative stress. The presence of taurine concentration determines its ability to scavenge free radicals. However, taurine is very effective against peroxy radicals (ROO⁻), superoxide anions (O₂⁻), nitric oxide (NO⁻) and peroxynitrite (ONOO⁻), but hydrogen peroxide is not scavenged by taurine. It exerts a protective effect on mitochondria, preventing the formation of ROS. When reacting with mitochondrial tRNAs and forming 5-taurinomethyluridine (tm5U) and 5-taurinomethyl-2-thiouridine, it contributes to the enhancement of the codon-anticodon interaction between the uridine-uridine-guanosine (UUG) codon and the adenosine-adenosine-uridine modified by taurine, optimize the translation of encoded proteins rich in UUG regions of subunits 5 (mt-ND5) and 6 (mt-ND6) of the respiratory chain complex I. The presence of taurine has been demonstrated in glia and synaptosomes, the synthesis of taurine is well documented in the brain, but its presence in the spinal cord is still unclear, but the presence of its precursor amino acid, cysteine, has been demonstrated in the cat spinal cord (Gaitode, 1970), while the presence of cysteine sulfinic acid has also been demonstrated in the mouse spinal cord (Baba *et al.*, 1980). Since we know that cysteine and methionine are precursors of taurine, it is reasonable to assume that the presence of these amino acids in the spinal cord contributes to taurine synthesis, but a detailed study is needed to prove this hypothesis. Although initial findings suggest a uniform distribution of taurine in the spinal cord (Yoneda *et al.*, 1978), the

enzyme cysteine sulfinic acid decarboxylase (CSD) is very active in the superficial part, the dorsal horn, suggesting an increased synthesis of taurine in the superficial region of the dorsal horn.

The study by Palkovits *et al.*, 1901, confirmed this observation with one of his findings of higher taurine content in the dorsal horn and lower in the ventral horn. The blood-brain barrier is responsible for the transport of taurine, including hypotaurine, β -alanine, and other β -amino acids, into the brain through a Na⁺ - and Cl⁻-dependent transport system with high affinity and low capacity, whereas the passive diffusion of taurine across the blood-brain barrier is negligible. The taurine transporter, known as the SLC6A6 transporter or Tau-T transporter, is mainly responsible for the uptake and efflux of taurine at both the luminal and albumin membranes. The GABA transporter SLC6A13, also known as GAT -2, is responsible for the transport of taurine across the membranes of the blood-brain barrier. Both of the above transporters, i.e., TauT and GAT -2, are also involved in the efficient transport of hypotaurine. A study in mice has shown that genetic deletion of the taurine transporter (TauT) suppresses taurine concentration in plasma and tissues, including the brain. In contrast, studies have demonstrated that taurine concentration increases in the brain of mice with a genetic deletion of GAT -2, suggesting that GAT -2 functions mainly as an efflux system for taurine from the brain into the blood. The taurine transporter Tau T is expressed mainly in astrocytes and to a very small extent in neurons, and expression of GAT -2 is restricted to leptomeninges and blood vessels. Volume-sensitive organic osmolyte anion channels, commonly referred to as volume-regulated anion channels (VRACs) and activated mainly during cell swelling, also play an important role in ubiquitous taurine transport. The taurine transporter Tau T is thought to be mainly responsible for taurine uptake in the brain parenchyma, whereas taurine release is mainly mediated by VRACs.

Schmid, R & Laehdesmaeki, P, *et al* 1975 reported in their studies on the uptake of taurine into synaptosomes and its release upon electrical stimulation as well as the binding of taurine to synaptosomal membranes. These observations from the aforementioned studies proved that taurine acts as a neurotransmitter in the central nervous system (CNS); in fact, taurine proved to be a modulator of inhibitory neurotransmission. The intracellular taurine concentration is estimated to be 400 times higher than the concentration in the extracellular space. When measured by microdialysis, extracellular taurine concentration in the brain is less than 10 μ mol/L and increases by at least an order of magnitude upon depolarization. After its release, taurine began to act on GABA and glycine receptors and is excreted by sodium-dependent transport, whereas taurine is not released exclusively at synapses but may be of glial

origin and mediate communication between astrocytes and neurons. Taurine is also abundant in semen, whose concentration (679 μM) is reported to be 10 times higher than in blood. This suggests the importance of taurine in the testes including germ cells (Holmes, R.P *et al* 1992).

A study by Alahmar, A.T *et al* 2019 proved that abnormalities in sperm shape and motility are caused by oxidative stress and low expression of antioxidant enzymes such as superoxide dismutase (SOD) in the testis, one of the studies by Das, J.;*et al* 2009 in mice showed that oral administration of taurine exerted a protective effect against arsenic-induced oxidative stress in rats, suggesting that taurine administration plays an important role in testicular development, in another study by Tsounapi, P *et al.* 2012, the antioxidant property of taurine was demonstrated in streptozotocin-induced diabetic rats. Their study showed that administration of taurine in diabetic rats acted as an antioxidant in the seminiferous tubules, which harbor germ cells, and that proves that the intake of taurine through food improves the properties of sperm, their motility and number, which are closely related to male infertility. Due to taurine deficiency, dysregulation of intracellular calcium homeostasis may occur even though serum calcium levels are near normal or normal. Taurine deficiency results in dysregulation of intracellular calcium in osteoblast and osteoclast cells, leading to decreased bone growth and increased bone resorption, Studies have shown that high levels of taurine are found in bone as it promotes bone formation and suppresses bone resorption, as in osteoblasts, i.e. bone-forming cells, taurine transporters are present, which play a role in bone homeostasis (Ara Z *et al* 2022), the positive role of taurine in fetal development is explained by Sturman *et al.* When [35S]-labeled taurine is injected intraperitoneally into pregnant rats, it can be delivered to both the brain and liver of the fetus, suggesting that maternal taurine can be passed to the fetus via the placenta, Human placenta is a rich source of taurine because of its high taurine content. Through active transport, taurine is transported from the mother to the fetus via the placenta, as the concentration of taurine in fetal blood is higher compared to maternal blood.

Mottaghi S, *et al* 2022 in his recent randomized control trial on Subjects with Post Liver Transplantation Delirium in Abu-Ali Sina transplantation center in Shiraz, Iran from September 2020 to June 2021, demonstrated that when these subjects were administered 2g/d taurine from the first day post-LT till 30 days then they had reduced Delirium symptoms thus they concluded that taurine can prevent post-LT delirium, dramatically. In conclusion we can say that the newest insights regarding various biological roles of taurine its biosynthesis etc has been covered in this issue.

In another study by Li L *et al* 2022, the influence of taurine on the regulation of estrogen synthesis in the ovaries was demonstrated, In their study on an animal model, they observed that treatment with taurine increased the expression of miR-7a and Cyp19a1 in mouse ovaries and increased serum 17 β -estradiol (E2) concentration, while miR-7a 2 knockout mice have a reverse effect of taurine on E2 and taurine also downregulates the expression of Golgi apparatus protein 1 (Glg1), a downstream target gene of miR-7a2, a similar reverse phenomenon was observed in mice with Glg1 knockdown, in which the expression of Cyp19a1 and E2 synthesis were increased. Thus, the study concluded that taurine promotes E2 synthesis through activation of the p38/miR-7a/Glg1/Cyp19a1 pathway. The major reason behind its various roles could be its simple and specific structure that is very similar to the structures of other β -amino acids with amino and sulfo groups. More and more research is still going on taurine to prove its efficacy in every field.

According to Srivastava RN *et al.*, (2022) taurine concentration gradually decreases in individuals with chronic kidney disease, whereas plasma taurine concentration gradually increases in the absence of CKD when the individual is supplemented with L-glutamine, while one of the studies on animal model has shown that in CKD continuous taurine depletion can be compensated by supplementation with L-glutamine. Role of taurine in case of Spinal cord injury is still a hot topic of debate as more research need to be conducted on human as according to Ara Z, *et al* 2022 SCI is a life-threatening process and it greatly effects subjects' quality of life and families. According to Srivastava RN *et al* 2022, action of taurine in the case of spinal cord injury has been demonstrated since many years before as in case of SCI it acts as neurotransmitter, this interpretation also focuses the possible involvement of taurine in the anti-epileptic action on the spinal cord, in case of SCI high content of taurine is found in the neutrophils that migrate to the site of injury. One of the study on spinal cord compression model, it was shown that taurine treatment inhibit expression of the proinflammatory cytokine IL-6 and also decrease phosphorylation of STAT3 and expression of COX2. Study by Ruan Y, *et al* 2016 demonstrated that in diabetes, erectile dysfunction (ED) is more common when supplemented with taurine for 4 weeks, improvement in erectile function by potential antifibrotic activity was observed.

A study by Schaalán MF *et al* 2018 described the protective effect of taurine against azathioprine (AZA), an immunomodulatory and cytotoxic drug, due to its antioxidant and anti-inflammatory properties. In their study, they demonstrated that pre-treatment with TAU -Cl exerted a protective effect against AZA-induced atrophy of male reproductive testes. This finding opens a new phase of research in the use of TAU -Cl as a complementary approach to supportive

treatment of chemotherapy. According to Li JH *et al* 2006 taurine has been found in the testes of human being and has been identified as the major free amino acid of sperm cells and seminal fluid, Taurine transporters are located in the Leydig cells of the testes, which is the cellular source of testosterone in males, cremaster muscle, efferent ducts, and peritubular myoid cells surrounding seminiferous tubules (Aaronson DS, *et al* 2010), upon microbial and parasite infections huge amount of TauCl and taurine bromamine (TauBr) are produced by neutrophils and eosinophils, respectively, both the analogues of taurine has bactericidal, fungicidal and antiparasitic properties. To kill both gram positive bacteria such as Staphylococcus aureus and Staphylococcus epidermidis and gram negative bacteria such as Escherichia coli, Pseudomonas aeruginosa, and Proteus mirabilis, , physiologic concentrations of TauCl (12.5–50 μM) are high enough (Kim C *et al* 2014). One of the study by Eitzinger *et al.* 2012 had demonstrated that TauCl has enough potential to neutralize Shiga toxin of enterohemorrhagic E. coli by oxidizing the thiols and aromatic amino acids of the bacterial proteins. TauCl is effective against fungi and bacteria, killing fungal species such as Candida spp, Aspergillus spp, Fusarium moniliforme and Polytrichum commune, and also inactivating viruses, including human herpes simplex virus (HSV) types 1 and 2, adenovirus, human immunodeficiency virus (HIV)-1 and influenza virus. Taurine possesses antitumor properties, inhibits cancer cell proliferation and induces apoptosis in certain cancers by differentially regulating proapoptotic and antiapoptotic proteins (Ma N *et al* 2022). Microglial cells are readily stimulated by damage or immune stress, as we know, activated microglial cells begin to secrete inflammatory cytokines such as nitric oxide (NO), TNF- α , IL -1 β , and reactive oxygen species (ROS), and the synthesis and accumulation of these substances promote neuronal degeneration. A study of autistic brain cells of diseased children aged 6 to 16 years showed that in all three brain regions, viz. the hippocampus, cerebellum, and frontal cortex, showed a significant increase in ER (endoplasmic reticulum)

stress, which was due to the activation of ER stress signals, such as serine/threonine protein kinase/thoribonuclease IRE1, cyclic AMP -dependent transcription factor ATF-6- α (ATF6), and eukaryotic translation initiation factor-2- α kinase 3 (EIF2AK3, also known as RKR-like endoplasmic reticulum kinase (PERK)). Apoptosis also increased in all three brain regions due to increased activity of caspase 8 and PARP (poly (ADP -ribose) polymerase) degradation (Rubio-Casillas A *et al* 2022).

According to Shah Waliullah, *et al.* 2022 Osteosarcoma is most common primary malignancy of bone that represent 50-70% of skeletal tumour also known as osteogenic sarcoma it is highly destructive and second most common type of primary malignant tumour of bone after multiple myeloma. Some Previous studies have shown that long noncoding RNA taurine upregulated gene 1 (TUG1) expression get significantly higher in Osteosarcoma cells than that in adjacent normal bone tissues, thus in their studies they concluded that Upregulation of TUG1 was significantly correlated with the larger tumor size and advanced tumor-node-metastases stage of osteosarcoma patients (Wang Q *et al* 2018).

According to Shah Waliullah, *et al.* 2022, Liver, kidney, brain, retinas and placenta of mammals have high expression of taurine transporter, p53 and c-Jun regulates expression of TauT, as it is confirmed by various methodologies such as reporter gene assay, DNA binding, Western blot analysis, and immunohistochemistry. Expression of taurine transporter, TauT is upregulated by c-Jun whereas p53 downregulates its expression.

CONCLUSION

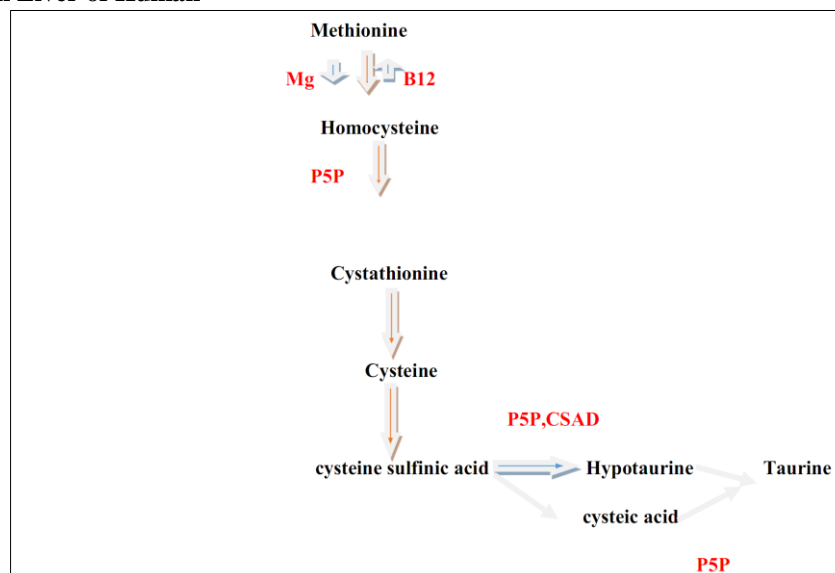
In conclusion, after reviewing different articles we find that taurine is a polyfunctional molecule. as it is involved in so many functions from protection to prevention.

Table 1: Taurine Concentration in Various Tissues

Tissue Type	Taurine Concentration	References
Human		
BRAIN	Developing: 4-20 $\mu\text{mol/g}$	Sturman JA, <i>et al</i> 1978
BRAIN	Adult: 1-9 $\mu\text{mol/g}$	Sturman JA, <i>et al</i> 1978
Heart	6 $\mu\text{mol/g}$; 15-25 $\mu\text{mol/g}$	Hayes KC, <i>et al</i> 1981, Sole MJ, <i>et al</i> 2000.
Liver	2 $\mu\text{mol/g}$	Hayes KC, <i>et al</i> 1981
Skeletal muscles	5 $\mu\text{mol/g}$	Hayes KC, <i>et al</i> 1981
Retina	30-40 $\mu\text{mol/g}$	Hayes KC, <i>et al</i> 1981
Plasma	50-80 $\mu\text{mol/g}$, 100 $\mu\text{mol/L}$	Hayes KC, <i>et al</i> 1981, Sole MJ, <i>et al</i> 2000. Hansen SH. <i>et al</i> 2001.
Leukocytes & platelets	13-17 $\mu\text{mol/L}$, 10-50 $\mu\text{mol/L}$	Hansen SH, <i>et al</i> 2001. Learn DB, <i>et al</i> 1990
RAT		
BRAIN	3 $\mu\text{mol/g}$, 5 $\mu\text{mol/g}$	Hayes KC, <i>et al</i> 1981. Spaeth DG, <i>et al</i> 1992.
Heart	20 ; 30 $\mu\text{mol/g}$	Huxtable RJ. <i>et al</i> 1992, Spaeth DG, <i>et al</i> 1974

Liver	3 $\mu\text{mol/g}$, 4 $\mu\text{mol/g}$	
Skeletal muscles	7 $\mu\text{mol/g}$, 16 $\mu\text{mol/g}$	
Retina	27; 50 $\mu\text{mol/g}$	
Plasma	360 $\mu\text{mol/L}$, 450 $\mu\text{mol/L}$	
Kidney	7 $\mu\text{mol/g}$, 9 $\mu\text{mol/g}$	

Taurine synthesis in Liver of Human



In human, Taurine is synthesized in the Liver with a magnesium-catalyzed methylation of methionine to form homocysteine, this process is reversed by the vitamin B12 and the folate dependent enzyme methionine synthetase, after that homocysteine donates its sulfur group to form cystathionine and under the influence of pyridoxal-5'phosphate (P5P) cystathionine is broken down to cysteine. Under the influence of enzyme cysteine deoxygenase, Cysteine is catalyzed and combines with dioxygen to become cysteine sulfinic acid, which is then decarboxylated by cysteine sulfinic acid decarboxylase (CSAD) and P5P to hypotaurine, after that Hypotaurine is oxidized to taurine by hypotaurine dehydrogenase. Whereas alternatively, taurine is formed following the oxidation of cysteine sulfinic acid to cysteic acid and the decarboxylation of cysteic acid by P5P (Huxtable RJ *et al* 2000).

By the above discussion it can be concluded that taurine is a polyfunctional molecule and taurine is an immunomodulator, most of the studies have been done on animal model and to validate its effect on human, more and more clinical trials need to be conducted.

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