Role of taurine in organs’ dysfunction and in their alleviation

Ramesh C. Gupta, Sung-Jin Kim

Abstract

Taurine, a sulphur amino acid found endogenously in human and in several others. It is significantly in higher concentration in mammals and has a number of physiological and pharmacological actions and also used in the therapy of important organ dysfunctions. It is essential for cat and conditional for humans. A patient on parenteral nutrition (PN) may develop taurine deficiency which may hamper proper growth and development. Taurine biosynthesis is limited to early stages and with advancing of age, synthetic capability further reduced to negligible, providing diet as only alternative source. Most of the marine and meat products generally contains considerable high amount of taurine but it is almost absent in plants, thus vegetarian may constitute a risk group. Its beneficial effects range from cardiotonic to anti-convulsant and protection of retina to liver from diseases. Being a constituent of bile salt, taurine also helps in reducing cholesterol content. It helps in alleviating hypertension, too. Taurine has been found to be effective in metabolic diseases like diabetes and metabolic bone diseases. Taurine has special role in preterm neonate care, and so also linked to disease of fetus origin. Apart from its special role in neonates and PN, taurine is a part of combination therapy as a nutritional supplement, in varieties of diseases. As everyone hate to like aging, the happiest addition is that taurine has a role in alleviating aging symptoms. Taurine along with its analogues may provide a hope to cope with this situation. Hence, taurine having this much beneficial action deserves to be compiled and reviewed, yet requires regular update.

Introduction

Taurine (2-amino ethane sulphonic acid), a sulphur containing amino acid was first isolated from ox bile in 1827. It is present in most of the mammals with variation in concentration from micro to milli molar. It is derived from methionine and cystein catabolism. The mammalian cell metabolism does not use taurine neither as source of energy nor as source of inorganic sulphate or organic sulphur and this amino acid is not also a part of any protein but remains free in intercellular water. The most ancient use of taurine in liver was amidation of different bile acids; however, the total consumption of taurine for this purpose is even less than 1% of its total body pool. A normal human of about 70 kg contains 1% of its total weight, as taurine e.g. 70 gm. Its concentration in the brain is only exceeded by glutamic acid. Such a high concentration generated number of questions, and taurine traveled a long journey to provide the answers [1,2]. Now, we know taurine is essential for cats, and conditionally essential for humans. It is regarded as preventive medicine and also behaves as a vitamin-like molecule. The involvement of taurine to cell welfare started even in the embryonic developmental stage where taurine deficiencies have been linked to various lessons, e.g. cardiomyopathy, retinal degeneration, growth retardation, disease of fetus origin like diabetes, making taurine as an essential amino acid for neonates. Taurine supplementation seems to be working well for neonates on PN [3,4]. However, significance of it is not confined to neonates only, it is further extended to children, adults, and elderly, due to its greater involvement in bile salt formation for reducing some symptoms associated with aging. On the clinical front, taurine utility has been patented for many; to name a few, epilepsy, congestive heart failure, hypertension, anti-alcoholic and antismoking; currently it is a part eye/ear drops, health drinks, antiaging and anti-diabetic supplements.

Perhaps taurine is the only endogenous biomolecule involved in so many actions to prevent and protect variety of organs, such as brain, eye, heart, and liver. In this mini review, we have tried to see every aspect where taurine has a role.
Taurine's unique physiochemical nature, a logic behind distinct behaviour

Taurine has unique physical constants in comparison to other neuroactive amino acids. A solubility of 10.48 gm/100 ml of water at 25°C, and pk_1 value of 1.5 makes it more acidic than glycine and aspartic acid, while pk_2 value of 8.82 gives it less basic character than glycine, GABA and β alanine. This distinct nature is primarily because of the presence of sulphonic group in place of carboxylic in other neuro active amino acids. Due to sulphonic group, taurine is not a part of major biopeptides and mostly occurs in free state and also does not take part in protein synthesis, Kreb’s cycle. Taurine is believed to have three different conformational stages of which cyclic is most stable. In taurine, sulphur is in the form of sulphonate which may oxidize to sulphate, thus sulphur; oxidation number in taurine is +4 and has a free energy of 260 kg/mole relative to sulphate. Animals usually utilize this energy of oxidation.

Source, availability and regulation of taurine

In human, diet is the main source of taurine, however endogenous taurine synthesis does occur but mostly at developmental stages and to lesser extend later also mainly in liver and brain. There are several synthetic pathways of taurine biosynthesis starting from methionine to cysteine and finally to taurine, involving a set of enzyme and vitamin B6 [5-6]. Taurine concentration is usually very high in marine orthopods, insect, fishes and birds. In mammals, taurine distributes ubiquitously, with high concentration generally found in platelets and electrically excitable tissue [7]. Taurine obtained from dietary source or synthesized endogenously is further regulated through a set of processes and active transport system. As practically endogenous synthesis is insufficient and insignificant, thus regulation has to provide an equilibrium between intake and excretion, through a process of accumulation, release, uptake, transport and metabolism. The accumulation of taurine is generally from dietary source. The release of taurine depends on cations but its uptake depends on sodium and temperature. Taurine transporters play a vital role and a number of taurine transporters have been recently identified [8]. Taurine metabolism is relatively slow but it further decreases with low supply. However, with enhanced dietary taurine supply, excess of taurine simply excreted through urine. To maintain adequate and regular supply of taurine, an effective transport and effective renal reabsorption system is necessary [9].

Physiological Actions of Taurine

The high concentration of taurine in almost all important tissues, have broadened its role from maintaining normality to participation in cell functions.

Bile salt formation

In general, taurine accelerates smooth flow of bile, helps in bile acid production and prevents bile mal functions and related diseases like cholestasis. All these actions reduce cholesterol level, in fact bile acid acts as a detergent to solubilize or emulsify the fats and to facilitate digestion. But emulsification of long chain triglycerides are done through bile salts which are better detergents than bile acids due to the presence of hydrophilic/lipophilic centers. These centers usually contain sulphonate/carboxylate containing derivatives of cholesterol ring. In human both carboxylate and sulphonate are present, sulphonate is in form of taurine and carboxylate is in form of glycine in a ratio of 3:1, but extraction of cholesterol from body is more from sulphonate conjugate; tauroconjugate (a taurine conjugate) rather than glucolate conjugate (a glycine conjugate). Thus by removing cholesterol taurine helps in preventing atherosclerosis [10].

Cardiovascular actions

More than 50% of the total free amino acid content of heart is taurine. Taurine has been found to exhibit a wide spectrum of action on cardiovascular system e.g. cardio-tonic, antiarrythmic, and chronotropic [11-12]. It also reduces blood pressure [13]. It is believed that taurine modulates calcium ions. Taurine supplementation with traditional chinese medicine has an edge over western combined therapy in acute viral myocarditis [14].

CNS actions

Taurine participates in a good number of actions in brain, e.g. anticonvulsant, modulation of neuronal excitability, learning and memory processes, anti-aggressive, anti-alcohol and many others [15]. Taurine also helps in speeding up the brain development. Though it is believed that taurine acts as neurotransmitter or modulator, its derivative glutaurine, a peptide, seems to acts as neurotransmitter. Taurine also takes part in regulation of calcium movement during depolarization and takes effective part in membrane stabilization. Taurine deficiency has been linked to
development of epilepsy and taurine supplementation has effective inhibitory effect [16], but because of poor liposolubility a large quantity for much longer duration is required. Taurine also plays a modulatory role in central respiratory control in acute hypoxia. Taurine and its derivative like calcium homo taurate are use as anti-alcoholic [17].

**Retinal activities**

Taurine pool is the highest among all amino acids in retina, and involved in protection of retina structure and functions. Taurine seems to be must for normal vision and its deficiency is marked by rational degeneration leading to blindness though such phenomenon has been observed in cats only where taurine supplementation has a corrective role [18], however this has yet to be established in humans. Abnormal electroretinogram associated with low plasma taurine have been detected which tends to normalize with taurine supplementation [19]. All these beneficial actions are believed to be through modulation of calcium fluxes and inhibition of protein phosphorylation, which involves antioxidation or osmoregulatory action of taurine [20].

**Renal actions**

Renal dysfunctions is primarily due to osmotic stress. It is believed that taurine along with other osmolytes has shielding effects on osmotic stress, thus helping in normalizing the renal function under osmotic stress. Taurine has been observed to spread in larger area like almost all medullar area, rather than limiting to glomeruli region, thus participating in a greater way to normalize the stress effect. It has been also reported that taurine depletion may be responsible for muscle fatigue prevalent in uremia and taurine supplementation has beneficial effects in chronic renal failure [21].

**Neonatal development**

Even in the embryonic stages taurine deficiency has been linked to several lesions, such as cardiomyopathy, retinal degeneration and growth retardation. Thus, it seems that taurine is essential for neonates, basically because of yet not fully developed synthetic capability as well as taurine renal re-absorption mechanism. If at this stage corrective measurement were not taken, then taurine deficiency might have deleterious effect on proper development of vital organs like brain, retina and many other important organs might not function well. This further necessitates taurine supplementation for neonates on parenteral nutrition [22].

**Interaction with ionic current and membrane stabilization**

A stable membrane is essential for cell to function and also to identify existence. Membrane is also a site for several electrophysiological changes. It is believed that taurine takes part in the stabilization of membrane by reducing excitability in nerve and muscle tissue, by participating in altering its conformation for permeability to ions and in inhibiting de-polarization. Taurine effects on membrane characteristics are linked to membrane ion interaction. To this, the involvement of calcium has been largely accepted, possibly through membrane phospholipids [23]. The involvement of other ions like K⁺, Mg²⁺, Zn²⁺, Cl⁻ are also recorded for various actions. Taurine has been regarded as a substitute of magnesium deficiency and taurine acts parallel to magnesium in reducing blood pressure and protecting arrythmia. A taurine derivative magnesium taurate is successful in alleviating diabetes [24].

**Endocrine and other metabolic actions**

In this category, taurine has a very active role in alleviating diabetes. Taurine and insulin both have mutual stimulating actions; in diabetes, low plasma and platelet content of taurine have been recorded that taurine supplementation has restorative effect. Taurine improves glucose and fat metabolism and reduces insulin resistance. Taurine also prevents diabetes associated micro angiopathy and attenuates hyperglycemia induced endothelial cell apoptosis. Such actions of taurine seem to be through its antioxidation action, scavenging of free radicals, and reactive oxygen species [25-26]. Apart from diabetes, taurine also has preventive role in osteoclast formation in metabolic bone diseases leading to bone loss. In osteoblast culture, taurine has stimulating action on bone cell formation [27, 45].

**Host defense action**

Taurine also takes part in host defense, generally through its antioxidation or osmo regulatory behavior. In general, antioxidant tries to hold free radicals as these radicals dam-
ages cellular components resulting in a diseased state. In diseased states, concentration of such antioxidants fell below the normal level, hence creates an adverse situation with further increase in free radicals. It is believed that taurine takes part in inhibition of such free radicals commonly known as reactive oxygen species (ROS), by acting as trap for such radicals and transform them to less toxic substances [28]. The other way by which taurine acts in host defense is through osmo-protection, where taurine modulates the entry of inorganic ions to cells and also helps in minimizing the effects of osmotic stress [29].

Radio protection

Taurine possess radio protective properties also. The exposure to irradiation, results extraction of large amount of taurine through urine. Intensive cytotoxic chemotherapy and/or radiation further leads to reduction in plasma taurine concentration; however, the clinical significance of taurine deficiency and radiation effect has yet to be fully established. Taurine supplementation improved the survival rates in mice after total body irradiation and also recovery from neutropenia [30].

Disease of fetus origin

Recent finding suggests taurine plays a vital role in fetus development. Such studies have greater significance when mother is suffering from metabolic disease like diabetes, with chances of transfer of such disease to offspring being high. In addition to this, a child raised on PN has been observed to have low birth weight. Low taurine level has been recorded in diabetic mother as well as in their offspring and subsequent generation such taurine deficiency may affect development of brain and insulin secretion [31]. However, high amount of taurine has been recorded in human breast milk to cow milk, mostly due to placental transport and an adequate supply of taurine during pregnancy and later in lactation may help in normal development of vital organs.

Taurine in patient care

The involvement of taurine in various physiological actions and beneficial effects of its supplementation has provided basis for its further utility in patient care. As taurine is nontoxic, endogenous substance and also a part of our diet. The importance of taurine further extends not only in therapy but also as a preventive medicine. There are convincing reports, that taurine deficiency has the potential to cause clinical consequences.

(a) Taurine deficiency, a possible like to patient risk

Taurine deficiency may occur due to inadequate synthetic ability or short supply from dietary sources. As synthetic capabilities tend to decline with ages, the only alternative is dietary supply. If dietary intake of taurine is severely restricted or absent for a prolonged period, in such situation depletion is likely to take place, and as a consequence of this, there are specific groups at risk for taurine depletion. The most effective risk groups are preterm neonates, patients on long term PN, and patients with hepatic, chronic renal failure, or diabetes [32].

(b) Taurine supplementation in patient health care management

Taurine is now more or less recognized as a conditional amino acid for human and its supplementation has beneficial effect on neonates to aged one.

Neonates

Premature neonates have greater requirement of taurine for their very fast growth rate, nervous and visual strengthening, but due to limited synthetic ability at this state and thus they need exogenously a lot. Such conditions with mature neonates have yet to be established. However, breast fed neonates generally do not show taurine deficiency. Formula fed neonates may get benefited from its supplementation also, and in most formula, taurine has been now added [33].

Other Than Neonates

Recent finding has advocated the beneficial effect of taurine supplementation to patients requiring long term PN and patients with hepatic problems, chronic renal failure, suffering from number of heart diseases. Now taurine is effective in diabetic control management. Patients on parenteral amino acid solutions are risk to taurine deficiency, as this solution does not contain taurine. In such patient’s low taurine contents in plasma, platelets and urine have been recorded [34, 35]. In addition, if taurine renal reabsorption is not efficient, this will lead further taurine
depletion from the body, creating a taurine deficient situation. This situation might affect the normal development of brain and retina. This will also affect bile acid conjugation, thereby increasing the risk of cholestasis [36], where taurine supplementation has beneficial effect. Taurine supplementation has positive effect on trauma. A 10 mg/kg taurine supplementation normalize taurine content in plasma and blood cell. Taurine also attenuate increase in pulmonary artery pressure and vascular resistance. A further linkage of taurine deficiency to pulmonary dysfunction in patient under PN has been suggested [37]. Patients with short bowel syndrome do not normally reabsorb bile salts (mostly taurine conjugate), such patients urgently require taurine supplementation and if such patients are on PN, in this situation taurine supplementation becomes absolutely necessary. A long term absence of adequate taurine in such patients increases risk for liver dysfunction. A below normal taurine level were also found in malnourished postoperative cancer patients and its supplementation has beneficial effect [38]. A 2 g daily taurine intake has been recommended for patients with congestive heart failure and a 3 g daily supplementation is effective for diabetic patients with other complicacy. Patients with liver damage or cirrhosis have found to be taurine deficient and taurine supplementation has restored the effect. Low plasma and muscle intracellular taurine concentration is associated in patients with chronic renal failure. A recent cross-over trial suggests nocturnal hemodialysis may increase taurine and improve uremia and taurine supplementation has provided beneficial effect [39].

**Beyond Taurine to Analogues**

Though taurine is clinically effective, it requires reasonably higher doses for longer duration; this is because of its slow permeability towards BBB, long half-life period and slow turnover rate. This necessitates to look into the structural modification of taurine to provide prodrugs. As taurine analogues are in use as anticonvulsant to anti-alcohol, anticancer, search for taurine analogues will be advantageous [43].

**Action Mechanism**

Designing mechanism is equivalent to reading mood, and predicting mood is always difficult task, but it becomes harder when the involvement is diverse in nature and this is true for taurine due to its vast involvement and unique physicochemical characteristic. It is believed that taurine actions are via osmoregulation, scavenging of ROS, modulation of ions, mostly calcium and interaction with membrane phospholipids. A number of mechanisms have been proposed in past suggesting taurine affects ion flux by acting directly with membrane. The structural resemblance of taurine to neutral phospholipids plays a major role in such mechanism [44]. Other hypothesis is based on calmodulin, where it is believed that taurine actions are mediated through inhibition of calmodulin [45].

**Conclusion**

This update provides a holistic view of the taurine’s presence actions and participation in correction of dysfunctions. Though much of its physiological actions have got strength from various studies of recent past, much more are still left, much more have to be obtained and proved. In one of such objectives, its concentration in various organs in diseased state has to be well recorded. In the absence of such data, it is difficult to understand how much amount of taurine is required to exert action. More
and more studies towards its depletion effect are valuable. Since diet is the major source, so its transport system and transporters must be well established, and the same as its renal re-absorption phenomenon. More interaction with ionic current other than calcium will be helpful in providing its modulatory role in ion flux. Since experimental findings are the backbone of clinical evaluation, the more experimental data are available the more scope for clinical success will be provided. More appropriately designed and well controlled clinical studies will further confirm its therapeutic roles and provide clue for many others. Taurine supplementation and PN studies should be studied in depth. Search for taurine analogues will be advantageous effort. This update in spite of its size, whatsoever information it may provide, will definitely be a form of energy to activate and stimulate further study in this small but a wonderful molecule and if this truly happens; taurine will emerge as a source and a remedy for 21st century diseases.

Acknowledgement

Dr. S. –J. Kim thanks KOSEF and KOFST for support through the 2000 Brain pool program. Dr. R. C. Gupta is thankful to KOSEF for a brain pool award and also to Nagaland University India for granting a leave of absence which enables him to undertake this work.

References