

**TAURINE, "A Key Amino Acid in the Drug Discovery" - A Review**

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ABSTRACT

Taurine is a unique amino acid in the animal kingdom. It is a sulphur containing amino acid found in brain tissue and in high concentrations in excitable tissue. It has been suggested that taurine may sub serve a neurotransmitter type function in central nervous system. Available evidence implies that taurine may serve a homeostatic function in excitable tissue such as nerve and muscle by stabilizing membrane in these tissues through the regulation of cell membrane permeability to ions. The calcium induced changes in membrane serves as signals for hormone and neurotransmitter release, for excitation-contraction responses and as signals for other processes. Taurine reduces the development of atherosclerosis. Experimental evidences suggest that taurine has anxiolytic like effects on anxiety animal models, and this effect may be mediated by the interaction of taurine with 5-HT and GABA system. This amino acid has a depressant effect in central nervous system, suppressing neuronal activity in spinal cord and brain.

1. INTRODUCTION

Taurine, or 2-aminoethanesulfonic acid, is an organic acid widely distributed in animal tissues. It is a major constituent of bile and can be found in the large intestine and accounts for approximately 0.1% of total human body weight. Taurine has many fundamental biological roles such as conjugation of bile acids, ant oxidation, osmoregulation, membrane stabilization and modulation of calcium signaling. It is essential for cardiovascular, function, and development and function of skeletal muscle, the retina and the central nervous system.^[1] Taurine is a derivative of cysteine, an amino acid which contains a sulfhydryl group. Prematurely born infants are believed to lack the enzymes needed to convert cystathionine to cysteine, and may, therefore, become deficient in taurine.^[2] Taurine is present in breast milk, and has been added to many infant formulas. It is released from retina when the retina is stimulated electrically or by light. Outer nuclear layer of retina contain the highest concentration of taurine.^[3] Taurine occurs naturally in food, especially in seafood and meat. in various study it is reported that the mean daily intake from diets was determined to be around 58mg,200mg,400mg.

2. BIOSYNTHESIS OF TAURINE:**2.1 In pancreas**

Mammalian taurine synthesis occurs in the pancreas via the cysteine sulfinic acid pathway. In this pathway, the sulfahydryl group of cysteine is first oxidized to cysteine sulfonic acid by the enzyme cysteine dioxygenase.^[4] Cysteine sulfonic acid, in turn, is decarboxylated by sulfonoalanine decarboxylase to form hypotaurine. It is unclear whether hypotaurine is then spontaneously or enzymatically oxidized to yield taurine

2.2 In CNS

Four routes are there in which taurine was biosynthesized.

2.2.1 CSA Decarboxylase route:

It is the generally accepted most relevant route in CNS. It involves the metabolic sequence of cysteine, CSA, hypotaurine and taurine.

2.2.2 Cystine dioxygenase route:

Cysteine on reaction with cysteine dioxygenase it converts to CSA.

In liver this is major route of catabolism of sulfur amino acid the bulk of CSA undergoing oxidation to inorganic sulfate via intermediate of β sulfinyl pyruvate.

2.2.3: The cystic acid decarboxylase route:

This enzyme activity is regulated by presence of light. Brain tissue has the ability to decarboxylate cystate.^[5] Cystate a labeled substrate which avoid the problem of being produced by paths other than direct decarboxylation.

2.2.4: Cystamine deoxygenase route:

Cystamine dioxygenase present in high amounts in mammalian kidney and lesser extent in heart. This route has no significance in CNS. Bulk of taurine is obtained by transport from the circulation a small amount is biosynthesized in neuron. Process of biosynthesis may be part of an antioxidant mechanism protecting neuronal membrane while part of biosynthesis may fulfill specific neuro-modulatory and membrane stabilizing functions.

3. TRANSPORT OF TAURINE

It is directly involved in an electrogenic sodium/taurine transport mechanism. Cellular transport of taurine is extremely efficient binding to transport site is sodium dependant.^[6] The ratio of natural molecules to taurine mole transported varies from 3:1 to 1:1 depending on tissue. In brain slices at least 3 Na⁺ molecules are needed for transport of taurine and at least and two for transport of hypotaurine. Transport of taurine occur in both glial and neurons. But glial cells have greater transport in neurons and astrocytes. Taurine deficiency leads to stimulation in the retinal transport of taurine. In mammalian retina taurine transport is concentrated in neuronal amoxine cell and photoreceptor and pigment epithelium. In baboons removal of pigment epithelium from the choroid leads to 72% fall in taurine transport. In man exogenous taurine transport across the pigment epithelia is need for maintenance of retinal electro physiology.

4. RELEASE OF TAURINE:

Three kinds of cellular release are there for taurine. First is the basal release i.e leaking of taurine through membrane.^[7] Second kind of release which is occasionally conflated with first is release via reversal of active transport system i.e; release with Na⁺ via β amino acid and carrier^[8], and stimulated efflux is of third kind. A sudden and large in efflux rate occur when cells is depolarized. There are convincing evidences that endogenous taurine is released with sufficient speed or in sufficient quantity from nerve terminals to initiate rapid changes in ion permeability and potential

5. BINDING OF TAURINE:

Binding of amino acid can occur to transport site, receptor site or non functional sites. Binding to transport site is Na⁺ dependant while receptor binding is Na⁺ independent.

6. TAURINE INTERACTION WITH NEUROTRANSMITTER^[9]

6.1 Dopamergic interactions:

Taurine increases the release of dopamine. The uptake of dopamine into the synaptic vesicles has shown to be chlorine dependent. As taurine increases the chlorine conduction its effect on dopamine release may be secondary to effect on chlorine. Taurine also increases synthesis of dopamine.

6.2 Serotonergic interactions:

It decreases the serotonin turnover in hypothalamus. Taurine induced hypothermia is reduced if brain serotonin content is lowered by p-chlorophenylamine treatment. Stimulatory effect of taurine on prolactin secretion is mediated serotonergically.

6.3 Cholinergic interactions:

Taurine decreases the release of acetylcholine from the abdominal ganglion of cockroach. The coexistence of decarboxylase and acetyl transferase in motor neuron indicates a possible physiological presynaptic action of taurine. Taurine has post synaptic action inhibiting non competitively carbamylcholine induced contraction of frog gastro muscle.

6.4 Interactions with glutamate:

Influence of taurine on the glutamate is indicated by finding that taurine stimulate glutamic acid decarboxylase in the brain of genetically epileptic rat^[10]. In rat cerebellar granular cells taurine had little effect on the evoked release of glutamate .It inhibit glutamate induced depolarization in number of system

6.5 Interactions with GABA:

Like GABA taurine hyperpolarizes excitable membrane by increase Cl⁻ conductance. As a result taurine and GABA exhibit Synergic effect on neuronal ending, both antagonize the analgesic effect on morphine. Electrophysiological actions of taurine &GABA are differentiated on frog retinal ganglion cells. Both agents depolarize dorsal root of frog spinal cord. GABA increases the amplitude of cortical evoked potential within 30sec of application while response to taurine takes about 3min to develop.

6.6 Interactions with hormones:

By central administration of taurine circulating prolactin levels increases. Neither neigher taurine nor TAG affects the pituitary secretion of luteinizing hormone. Taurine can increase the release of somatostatin (detected immunologically) from cultured rat cerebral cortex cells. Release of growth hormone is also stimulated by taurine^[11]

7. TAURINE IN EPILEPSY

Clonic-tonic seizures originating in the brain stem and cerebellum are nearly abolished with taurine and GABA, but increased by L-cysteine and L-arginine. Isothionic acid a metabolite of taurine increases the occurrence of these seizures^[12]. Taurine plays a modulating role as a membrane stabilizer and that its absence or lowered concentration is responsible for hyper reactivity of cells in epilepsy. Taurine works as an inhibitory transmitter in cerebellum. Taurine solutions are administered intravenously because of its ability to cross the blood brain barrier in normal mice. It has an ability to depress seizure activity. It also has a role as an inhibitory neurotransmitter^[13]. It is possible that defects in the CNS metabolism of taurine could be one of the causes of increased seizure susceptibility.^[14] Taurine administration produced the recovery of taurine brain deficit and decreased epilepsy. The epileptic activity reappeared and showed a slow increase, reaching maximum steady values in about 2 days^[15]. Further taurine administration produced more pronounced anti epileptic effects.

8. TAURINE IN CARDIOVASCULAR SYSTEM

Taurine reduces the development of atherosclerotic lesion through a mechanism involving its antioxidant activity. Taurine reduces the development of atherosclerosis, albeit without lowering serum cholesterol^[16]. It markedly reduces elevated blood pressure, attenuated renal dysfunction and reduction in serum nitrous oxide levels. Taurine can scavenge oxygen free radicals and can act as a membrane stabilizer that can maintain membrane organization against lipid peroxide attack, prevent water influx and avoid cell swelling

8.1 Taurine in ischemia-reperfusion of the heart

Taurine protects against Ca^{2+} paradox-induced cardiac injury by preventing Ca^{2+} overload in cardiomyocytes and cell death^[17]. Because the increase of intracellular Na^+ is a critical step in cardiac damage due to Ca^{2+} paradox or I-R, taurine supplementation may reduce the intracellular Na^+ concentration, and subsequently reduce Ca^{2+} overload by inhibition of the Na^+-Ca^{2+} exchanger. This effect offers another possible mechanism that explains how taurine protects the heart from I-R-induced damage. Furthermore, taurine may provide cardio protection under conditions of I-R, by virtue of its antioxidant properties, and may prevent oxidant-mediated damage of the cardiomyocytes membrane and subsequent intracellular Ca^{2+} overload^[18].

8.2 Taurine in cardiac heart failure

The majority of symptomatic patients with CHF is malnourished, and have a relative deficiency of taurine. Parenteral administration of taurine (200 mg/day for

seven days) has been reported to partially protect against myocardial cell necrosis induced by a toxic dose of isoprenaline in chick hearts reported that taurine can lower left ventricular end-diastolic pressure in patients with heart failure^[19]. In a clinical trial, the effect of oral administration of taurine (3 g/day) and coenzyme Q10 (30 mg/day) in 17 patients with CHF secondary to ischemic or idiopathic dilated cardiomyopathy was compared. In the taurine-treated group, unlike the coenzyme Q10-treated group, an improvement of the systolic left ventricular function was observed after six weeks^[20].

Positive inotropic effect of that could be due to its effect that Ca^{2+} is an important factor in mediating the effects of taurine in the heart.

8.3 Antiatherogenic potential of Taurine

Low-density lipoproteins (LDL) are known to contribute to the formation of plaque in the arterial wall, oxidized LDL can further^[21] exacerbate plaque formation. In hypercholesterolemia, dietary supplementation with taurine has been found to improve the serum lipid profile. High cholesterol-fed rats treated with taurine (15 g/kg/day) for five weeks showed a 37% reduction in plasma LDL, a 32% reduction in total cholesterol and a 43% reduction in triglyceride (TG) levels when compared with control rats fed the same diet without taurine. Platelets from humans with normal taurine status showed an increase in resistance to aggregation by 30% to 70% when supplemented with taurine at 400 mg/day or 1600 mg/day, respectively.

8.4 Interaction of taurine and angiotensin II

Angiotensin II is an important hormone that plays a key role in the maintenance of cardiovascular homeostasis. Experimental and clinical studies have shown that angiotensin-converting enzyme inhibitors prevent cardiac remodelling, improve heart function and reduce mortality^[22]. Taurine has also been found to partially block the effects of Ang II, implying that taurine may interfere with different actions of Ang II in cardiovascular cells.

8.5 Antihypertensive action of taurine

An injection of taurine in the anterior hypothalamus area has been reported to decrease BP; this taurine effect seems to be mediated by β -adrenoceptors. Thus, the antihypertensive effect of taurine may be partially attributed to its effect on the central nervous system^[23]. Taurine (1% to 2% w/v in drinking water) was found to prevent high-fructose diet-induced hypertension in rats. Taurine was also found to prevent an increase in platelet $[Ca^{2+}]_i$ in high-fructose diet-induced hypertensive rats. Although taurine deficiency in uni-nephrectomized rats

has been shown to accelerate the development of hypertension in response to high dietary NaCl

9. EFFECT OF TAURINE IN DIABETES

Safe and effective nutritional supplements that could be given along with the regular treatment of the patients that might reduce the need for insulin replacement therapy. Our hypothesis is that supplementation of Taurine in the diets of diabetic patients might reduce the dose or need for insulin replacement therapy and protect them against oxidative stress that is responsible for the complications of diabetes mellitus^[24].

The tissue levels of taurine are not changed in every organ system studied in these NIDDM rats. However, taurine also increases the excretion of cholesterol via conversion to bile acid and would be expected to improve insulin resistance. Another study reveals the fact that taurine is also helpful in preventing the transmission of diabetes from a pregnant woman to her baby. Hence, taurine is recommended in appropriate dosage to be administered to pregnant as well as lactating mothers.

9.1 Taurine and diabetic cardiomyopathy

Cardiovascular disease is responsible for 80% of deaths among diabetic patients. In chronic diabetes^[25], intracellular accumulation of sorbitol, resulting from high extracellular levels of glucose, leads to the depletion of intracellular taurine levels, and is associated with the development of diabetic cardiomyopathy. In type 1 diabetes, platelet aggregation may cause an increased risk of cardiovascular events; it has been demonstrated that platelet taurine levels are lower in diabetic patients. When supplemented with taurine (1.5 g/day for 90 days), both plasma and platelet taurine levels were increased in diabetic patients. These were associated with a decrease in platelet aggregation induced by arachidonic acid. That taurine decrease the TG and LDL levels in streptozotocin (STZ)-induced diabetic rats; however, the duration and dose of taurine treatment was an important determinant of the beneficial actions of taurine.

10. TAURINE IN RETINA

The retina contains an extremely high amount of taurine; two notable exceptions of tissues with higher taurine levels are the neurohypophysis and pienal gland of rat^[26]. Taurine is an essential component of diet, and that its absence leads to severe retinal damage involving the outer segment of photoreceptor and the tapetum. Other than taurine glycine and GABA has a similar protective effect but since they are not present in high concentrations in the ROSs. Addition of taurine prevents the destruction of rod outer segment (ROSs) in calcium-free medium and modifies Ca²⁺ fluxes within these

structures^[27]. Both Ca²⁺ and taurine are intimately involved in mechanism to maintain and stabilize the structural and functional integrity of photoreceptor membrane^[28]. A second possible function for taurine in retina is that it regulates Ca²⁺ transport. Taurine has a biphasic effect on Ca²⁺ accumulation depending upon the concentration of Ca²⁺, at high Ca²⁺ concentrations taurine is inhibitory in the chick, frog and rat. While at low concentrations and in the presence of ATP taurine is stimulatory. A third possible function for taurine in retina is as a regulator of signal transduction due to its effect on protein phosphorylation. Taurine has inhibitory effect on protein phosphorylation possible functions of taurine in retina include (1) protection of photoreceptor- based on shielding effect of taurine on rod (ros) outer segment exposed to light and chemicals (2) regulation of Ca²⁺ transport based on modulatory effect of taurine on Ca²⁺ fluxes in the presence and absence of ATP. (3) Regulation of signal transduction- based on inhibitory effect of taurine on phosphorylation.

The many possible functions of taurine include^[29]:

- a) Neurotransmitter (or neuromodulator) in CNS
- b) Stabilizer of biological membrane in many tissues which affects cardiovascular functions
- c) Protector of rod outer segments (ROSs) from exposure to toxic levels of light and chemicals.
- d) modulator of calcium binding and fluxes

11. ROLE OF TAURINE IN HAIR TREATMENT

L-taurine is an amino acid that when used orally at doses greater than 500 mg. Acts as anti-fibrotic agent (inhibits the inflammation mediated hardening of the hair follicle matrix), thus addressing the primary mechanism of the gradual follicle miniaturization seen in MPB, oral supplementation with daily Taurine 150 mg + Catechin 75 mg + Zinc 15 mg (Inneov Trico masse) in the treatment of women with fine hair, hair fragility and decreased hair thickness.

12. TAURINE IN ENERGY DRINKS

Most of the energy drinks contains taurine, an amino acid. Companies that market energy drinks claim taurine can improves mental performance and gives you energy. However, medical research doesn't support these claims. On serving of energy drink contain 100 calories, 27g of sugar, 1.7 mg of vitamin B2, 20mg of vitamin B3, 2mg of vitamin B6, 6mcg of vitamin B12, 180mg of sodium, 1000mg of taurine and 200mg of *Panax ginseng*. Energy drinks, include monster energy drink, market taurine as a substance that enhances the entry of glucose in to muscles- which improves endurance because the body uses the glucose in times of stress. Taurine along with

caffeine may actually cause a “crash” effect after consumption. The European food safety authority (EFSA) concluded in 2009 that exposure to taurine at the levels found in energy drinks, including monster energy appears to be safe.

13. SEPARATION TECHNIQUES

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Taurine is estimated by RP-HPLC either in isocratic or gradient modes. It is preferred due its sensitivity and flexibility^{[30][32]}. The HPLC methods include pre column and post column derivatization followed by ultraviolet, fluorescence or electrochemical detection. Since derivatization technique plays a key role in getting higher sensitivity, shorter analysis time and better resolution of complex biological samples, some derivatization reagents with sensitivity, stability, rapidity and simplicity are investigated for analysis of taurine. Typical reagents include o-Phthalaldehyde, 4-dinirofluorobenzene, fluorescamine, thiamine etc

O-Phthalaldehyde derivatization: OPA commonly used in RP-HPLC for determination of free aminoacids include taurine in complex biological samples, serum and urine. OPA reacts with taurine in the presence of a reducing agent such as 2-mercaptoethanol, urea or sodium sulfite to form a substituted iso-indole ring. This derivative has strong absorbance at 260 and 340 nm but also a strong fluorescence at 475nm.

2,4-Dinirofluorobenzene: Taurine react with DNFB to form DNP derivative with UV absorbance at 254 and 360nm. However the derivatization reaction usually takes more than 1hr at 40°C and thus it is not suitable for rapid assay of large number of samples.

1-Dimethylaminophthalene-5-sulphonyl chloride derivatization: It is for the determination of primary and secondary amines. Plasma or whole blood sample was diluted with a mixture of acetonitrile-methanol-triethylamine-water. Taurine was separated from other compounds on C₁₈ with a methanol-acetic acid-triethylamine aqueous mobile phase. The effluent was monitored fluorimetrically an excitation wavelength of 329nm and an emission wave length of 530nm^[30].

Ion chromatography: IC was a powerful technique for analyzing of inorganic cations and anions in aqueous system^[31]. Advantage of IC method over HPLC is pre or post column derivatization steps. Weakly ionized short chain organic acids are separated by ion exclusion chromatography with suppressed conductivity detection. Since the dissociation constant of taurine is too large. Taurine cannot be detected by UV due to the lack of ultraviolet chromophore.

Thin layer chromatography: It is really applied to analyze taurine in biological samples due to its low sensitivity and reproducibility. The formation of a volatile derivative of sulphonic function of taurine by GC is difficult.

Hyphenation procedures : Taurine is also analyzed by HPLC with inductively coupled plasma atomic emission spectrophotometry (ICP-AES) samples were separated on a cap cell pak amine column at 40°C with 2M ammonium phosphoric acid ammonia buffer (pH8)-methanol (4:1) as a mobile phase and phosphenebulization. ICP-AES detection at 180.73nm at emission line^[32]. The detection limit was 43mg and the RSD less than or equal to 2.2%. Biological samples are deprotonized immediately after collection and it is stored at -80°C. Taurine is analyzed by HPLC due to its high sensitivity, reliability and relatively short time. HPLC-ICP-AES proved to be effective for the analysis of taurine in biological samples. However they are not used widely due to its complex apparatus.

Electro- migration methods:

Capillary electrophoresis (CE) is mainly used electro-migration method for taurine analysis. It is an analytical counterpart to HPLC and offers a number of advantages over HPLC. Very little organic solvent in running buffer, short run time for separation, high separation efficiencies. Only fluorescamine is a suitable reagent for CE analysis. Kelly et al developed a rapid and highly selective capillary zone electrophoresis (CEZ) method for the determination of taurine in plasma^[33]. The separation is based on the difference in ionization of taurine from that of other amino acids due to the fact that taurine is a sulphur rather than a carboxylic amino acid. Addition of homotaurine plasma protein was precipitated with acetonitrile and supernatant was derivative with fluorescamine in the presence of borate buffer. Separation was carried out in the reverse polarity mode at 27.5KV with a diode array detector set at 266nm. A capillary conditioning solution was applied daily in order to suppress the residual electro-osmotic flow. The samples were homogenized in phosphate buffer of PH 7.5 and then deproteinized by perchloric acid. The supernatant was neutralized with trisodium phosphate sodium solution and then derivatized with trisodium phosphate solution and then derivatized with 9-fluorenylmethyl chloroformate (Fmoc) for 20min at room temperature. The derivatized taurine was well separated from 3-amino-1-propanesulphonic acid (internal standard) and glutathione by using 0.05 mol/l sodium phosphate (pH 2.5) as running buffer and then sensitively detected by fluorescence spectroscopy.

CONCLUSION

Taurine is present in high concentrations in all animal tissues but it is low in mammalian systems, due to its wide spectrum of biological activities in various tissues the study of taurine generates perhaps its greatest interest. In this review recent advances in taurine research have been critically examined. As taurine is a "conditionally essential" amino acid in the human we need a further investigation in clinical trials. Hence we conclude that taurine is a key

amino acid in the drug discovery process for the future therapeutic advancement in the treatment of various diseases.

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