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Review

Taurine is a future biomolecule for potential health benefits: A review

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Taurine is a sulfur-containing amino acid that is converted to a neutral beta-amino acid, chemically known as (2-Amino-ethane sulfonic acid) having chemical formula $C_2H_7NO_3S$. It was first isolated from Ox bile, and thus derives its name from the Latin word "Taurus", meaning 'ox' or 'bull'. This is the only amino acid that is extensively found in animal tissue. The richest source of taurine is meat whereas fish, human tissue, large intestine, and human breast milk are also good/prime sources. It is present in high concentrations in animal tissues, especially the heart, brain, retina, skeletal muscles, large intestines, plasma, blood cells, and leucocytes. Plant protein is devoid of taurine. It involves many functions from prevention to protection, osmoregulation, conjugation of bile, anti-oxidation, membrane stabilization, and modulation of calcium signaling. Hence it is also known as a poly-functional or wonderful molecule. Taurine is significantly involved in functions of the cardiovascular, skeletal muscle, retina, and the central nervous system. It differs from other neuroprotective amino acids due to the presence of sulfonic acid instead of carboxylic acid, and the presence of sulphonate makes it a strong acid. Dietary taurine is beneficial in treating bone-related disorders, neurodegenerative diseases, obesity, and immunological defense against microbes, through enhancing the metabolism/functions of monocytes, macrophages, and other cells of the immune system. The human body contains about 1% body weight as taurine. In this review, we have made attempts to provide synthesis, chemical, biological function of taurine, which may guide and facilitate further research in this area.

Key words: Taurine, spinal cord injury (SCI), taurus, intrauterine growth restriction (IUGR), diabetic peripheral neuropathy (DPN), osmolytes.

INTRODUCTION

Taurine is the unique non-essential amino acid that has betrayed much attention (Bkaily et al., 2020). It is the first amino acid discovered in 1827 by the German Scientists Tiedemann and Gmelin and were the first to extract taurine from the bile of ox (Bas Taurus); from that it derives its name, hence it is accepted as a part of our

planet formation. Biologically, it was created some 40 years ago when a good review was published (Jacobsen et al., 1968), which created the curiosity to dig deeper into this wonderful old molecule. It is true to say that taurine is a polyfunctional molecule because it is the only biomolecule involved in so many functions, ranging from defense to prevention (Gupta et al., 2003). Elevation in the level of taurine does not have any side effects, due to the saturable effect of the taurine transporter and the fact that it is usually removed through urine (Syed et al., 2007).

Taurine is released by the cell when there are some changes in inorganic osmolyte concentrations to make up for any loss of extracellular osmolarity (Pasantes-Morales, 2017). According to Pasantes-Morales (2017), and Schaffer and Kim (2018), it is a neutral zwitter ion. As taurine is a zwitterion, it does not contribute to membrane surface charge. The heart and brain are the only two organs that generate their taurine in a very limited quantity (Schaffer and Kim, 2018). It is found in abundant concentrations in human plasma (near 50-150 mol/L) (Bkaily et al., 2020), as well as in bile, saliva, and heart tissue (6 mol/L). During aging, taurine concentration decrease in the plasma. However, meat, milk, and fish oil are the source of taurine, but the richest source is meat. Daily consumption of meat in human beings provides 400 mg/day of taurine. The daily requirement of taurine in the human body is 3000 mg (Shao and Hathcock, 2008) whereas in published human trials, taurine dosages have ranged from 500 mg to 10 g per day (Shao and Hathcock et al., 2008). In American subjects', daily intake of taurine has been estimated to be 40-400 mg. Red algae have the highest taurine content whereas green and brown algae have lower taurine content from the Sea of Japan (Adeva-Andany et al., 2018). The human colostrums contain a high concentration of taurine, which is very essential for the development of the retina and brain. Taurine is mostly added in infant formula and parenteral solutions (Park et al., 2014). Taurine concentration in the body varies according to the weight of the subject, hence 70 g taurine is found in a person weighing 70 kg (Huxtable, 1992). Depending on species and cell type, its concentration varies in cells of mammalian and avian ranges from 5 to 60 mM (Wright et al., 1986). Taurine displays minimal complexities as it is a naturally occurring amino acid in the body. Studies based on toxicity did not produce genotoxic, carcinogenic, or teratogenic effects (Menzie et al., 2013) whereas in human beings it is sorted as an essential or functional nutrient (Gaull, 1986, 1989; Bouckenooghe et al., 2006). Taurine is synthesized by a human from methionine and obtained from dietary sources too (Adeva-Andany et al., 2018). It is also obtained from various types of food, but available in low amounts in milk derived products, such as cow's milk and ice cream, and it is available in high quantity in seafood such as shellfish, particularly mussels, scallops, clams, and in dark meat of chickens and turkeys (Table 1). Interestingly, level of taurine is not affected by cooking (Wojcik et al., 2010).

The European Food Safety Authority (EFSA) recommends that the *no observed adverse effect level* (NOAEL) of consuming energy drinks is 1000 mg/kg per day (Menzie et al., 2013). Taurine concentration is roughly four times higher in type I fibres than type II fibres in human skeletal muscles (Page et al., 2019). Taurine is a wonderful molecule as it maintains whole-body homeostasis (Ito et al., 2015). Some published studies on mouse models have shown effects on skeletal muscles due to disorders of lipid metabolism and glucose dysfunction (Ito et al., 2014), heart (Ito et al., 2008), liver (Warskulat et al., 2006), CNS (Sergeeva et al., 2007), and has been seen in them when a taurine deficiency has been induced in mice by knockout of taurine transporter.

Compared to glutamate, alanine and glycine, taurine is one of the most abundant organic osmolytes (Bkaily et al., 2020). Recently, taurine was proved to be a potent negotiator in the treatment of myotonia, fatigue and alcoholism (Xu et al., 2008). Previously published studies reveal that a high concentration of taurine is found in the epidermis, especially in the epidermal granular layer (Lobo et al., 2001), and with advancing age, concentration of taurine declines as studies reveal that it plays an important role in protecting skin from harmful UV rays and in moisture retention by exerting osmoregulatory and anti-inflammatory effects (Janeke et al., 2003; Anderheggen et al., 2006; Rockel et al., 2007). It is an important component for maintaining normal skin function. A recent study published by Yoshimura et al. (2021) showed that skin samples of hairless mice and Sprague Dawley rats with advanced age content of taurine significantly declines in both the dermis and epidermis, whereas taurine content remains unchanged in the sole.

The immunohistochemical analysis also revealed that reduced taurine content of the skin in older animals were found to be more localised than younger animals, despite no significant variations in localisation between the two age groups. When taurine was added to the drinking water of elderly mice, with 3% (w/v) up to 4 weeks, inclination in taurine level was seen in the epidermis, but not the dermis. Taurine-rich oral ingestion, capsules, and beverages are mostly the common mode of taurine

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Table 1. Taurine contents in foods.

Food items	mg (mean)/100 g
Beef/raw	43
Pork raw	61
Chicken/raw dark meat	169
Turkey/raw dark meat	306
Turkey	932
Lamb/raw dark meat	47
Ham/baked	50
Tuna/canned	42
White fish/raw	151
Mussels/raw	655
Oysters/fresh	70
Cod/frozen	31
Clams/fresh	240
Clams/canned	152
Pasteurized milk	6
Cheddar cheese	Not detected
Yogurt/low fat plain	3.3
Ice cream/vanilla	1.9
Fruit, vegetables, seeds, nuts	Not detected
Grain, beans peanuts, cereals	Not detected
Cow's milk, homogenized	151 (Spitze et al., 2003)
Chicken leg	337 (Spitze et al., 2003)
Yeast	112 (Spitze et al., 2003)
Phaeophyta (*Laminaria japonica*)	16.6 (Spitze et al., 2003)
Rhodophyta (*Gelidium subcostatum*)	125 (Spitze et al., 2003)
Rhodophyta (*Grateloupia elliptica*)	24.8 (Spitze et al., 2003)
Cod	1080 (Spitze et al., 2003)
Whey	660 (Spitze et al., 2003)

Taurine content is expressed in mg (mean)/100 g wet weight.
Source: Stapleton et al. (1994), Rana and Sanders (1986), *Lourenco and Camilo (2002), and Spitze et al. (2003).

consumption/supplementation (Ghandforoush-Sattari et al., 2010). Mostly after ingestion, plasma concentration of taurine elevates ~ 10 min and generally peaks (0.03 to 0.06 mmoL) ~ 1 h following ingestion. Adding taurine in sperms preserved at room temperature helps in enhancing the antioxidant ability of sperm, maintains acrosome integrity rate as well as improves the quality of semen preserved at room temperature (Zhang et al., 2021).

As we know, seaweeds of Japan seacoast are rich in taurine especially red algae like mafunori (*Gloiopeltis tenax*)/fukurofunori (*Gloiopeltis furcata*), kabanori (*Gracilaria textorii*), and ogonori (*Gracilaria vermiculophylla*); hence, these algae may be used to create functional foods which are the richest source of naturally occurring taurine (Kawasaki et al, 2017). So due to their habit of eating seaweeds, shellfish, and fishes that are richest source of taurine, Japanese and South Koreans have much higher urinary taurine excretion, a marker of the dietary intake of taurine than the subjects of other countries, including Europe and North America as it is proved by world-wide epidemiological study (Kawasaki et al, 2017).

THE UNIQUE CHEMISTRY OF TAURINE

Taurine is highly acidic, that it almost makes it a zwitterionic. Because of its zwitterionic nature, it is highly water-soluble and lipophilic; hence, due to this character Taurine diffusion via the lipophilic membrane is sluggish. The biological membrane's impermeability to taurine possibly explains the extremely large concentration gradients maintained across the membrane. Due to the zwitterionic characteristic, it has a very strong dipole. Its iso-electric points fall between carboxylic amino acids

like; GABA, beta-alanine, and glycine and acidic amino acids like aspartate and glutamate. Because of taurine's particular ionic character, the membrane modulates its action as well as its interaction with Ca^{2+} and other cations. Taurine is mostly acidic than aspartic acid, glycine, β-alanine and γ-aminobutyric acid (GABA) as its pKa value is 1.5, whereas in comparison to GABA, glycine, and β-alanine, taurine is less basic than these amino acids as pKb value of taurine is 8.82. Due to its cyclic confirmation with an intramolecular hydrogen bond, taurine displays low passive diffusion (Gupta et al., 2005; Chung et al., 2012). Taurine is a monobasic acid shown by X-ray crystallography, and it always exists as a free amino acid as it does not take part in peptide formation. The sulphur in taurine is present in form of sulphonate and may further be oxidized to sulfate. The lowest and highest oxidation state of sulphur is -2 and +6 respectively. There are three conformational forms of taurine according to its conformational analysis in which most stable conformational form is cyclic state.

BIOSYNTHESIS OF TAURINE

Taurine is obtained by the enzymatic reaction of hypotaurine. Based on the nutritional state, protein uptake and amount of cysteine availability in an individual's body decides the endogeneous synthesis of taurine, thus its synthesis highly varies from individual to individual (Luca et al., 2015). The availability of cysteine, on the other hand, is determined by the metabolic balance between homocysteine and methionine, folic acid, vitamin B_{12}, and the efficiency of the enzyme methyl-hydro folate reductase.

Compared to rats, taurine synthesis in human through methionine and cysteine is exceedingly lower because of the lower concentration of cysteine sulfinate decarboxylase (a key enzyme in taurine synthesis) in young adult men relative to rats (about three orders of magnitude) (Sturman and Hayes, 1980; Wu, 2020). In comparison to avian and livestock (chickens and ducks, cattle, pigs, and sheep), humans have the lowest capacity to synthesize taurine at any stage of life. A healthy adult's daily taurine production ranges from 50 to 125 mg, depending on his protein intake, nutritional state, and hepatic enzyme activity (Jacobsen and Smith, 1968; Wu, 2020). Due to reduced availability of the amino acid precursors or the suboptimal function of the liver, taurine production in the body is impeded as a result of stress or pathological situations such as heat stress, infection, obesity, diabetes, and cancer. Despite the presence of the maximum amount of precursors of taurine synthesis in infants' and children's diets, they are unable to synthesize enough amount of taurine (Geggel et al., 1985; Wu, 2020). Individuals who only consume plant products are at high risk of taurine deficiency as methionine and cystine (the two precursors of taurine synthesis) are present at very low quantities in most plant-derived proteins (e.g., corn, potato, rice, wheat, and vegetables) (Hou et al., 2019; Wu, 2020).

Algorithm of taurine biosynthesis

Methionine

←↓L-methionineS -adenosyltransferase

S-adenosylmethionine

←↓

S-adenosylhomocysteine

Adenosine ←↓

Homocysteine **S-adenosylhomocysteine hydrolase**

Addition of serine↓Cystathionine beta-synthase

Cystathionine

alphaketobutyrate ←↓

Cysteine

Addition of O_2↓ Cysteine dioxygenase

Cysteine sulfinate

←↓cysteine sulfinate decarboxylase

Hypotaurine

Addition of oxygen↓

Taurine

Taurine distribution

In the human body, it is the most prevalent intracellular amino acid. It is not incorporated into proteins and most of it is free due to the absence of carboxyl group and hence not metabolized; besides, it does not participate in gluconeogenesis and therefore does not constitute a direct energy source, whereas in small amounts, it is present as a small peptide in the human brain (Stapleton et al., 1994; Baliou et al., 2021). Its biosynthetic capacity is high in prenatal life, and with aging, continuously starts declining till it reaches its lowest concentration in the elderly stage; further, its concentration also declines during pathological conditions like trauma or sepsis. Because of this reason, taurine biosynthesis does not produce enough amount of taurine required for homeostasis, hence an exogenous dietary supply of taurine becomes necessary (Redmond et al., 1998; Baliou et al., 2021). Taurine content in the body depends on dietary intake of animal/sea origin (Bella et al., 2000). In comparison to individuals on an omnivore diet, taurine content is almost half in vegans (Hansen et al., 2001). Based on taurine uptake, urinary fractional excretion of it ranges between 0.5 to 80.0% (Chesney et al., 1985, 2010; Baliou et al., 2021).

MOLECULAR BASIS OF TAURINE ACTION AGAINST NEUROLOGICAL DISORDERS

Modulation of neuroinflammation

Franscescon et al. (2020), in his study, have shown that taurine is a promising candidate for reducing schizophrenia-like symptoms as it is a neuropsychiatric disorder that affects around 1% of people.

In his study, he demonstrated the neuroprotective effects of taurine against the memory deficiency caused by MK-801 and hyperlocomotion, and underscores the increasing use of zebrafish models in studying the beneficial effects of various compounds against glutamate excitotoxicity. Taurine acts in neural stem /progenitor cell proliferation of developing brain (Shivaraj et al., 2012; Hernández-Benítez et al., 2012) where extracellular signal regulated kinase (ERK) 1/2-way may be associated with the development of synapses. Synapsin 1 and postsynaptic density protein which is involved in the development of synapses (Shivaraj et al., 2012) taurine influences the level of these proteins. In cats having deficiency of taurine, kittens have less brain weight and abnormal morphology of cerebellum and visual cortex with delayed migration of neuroblast and glioblast is also observed in the visual cortex. In taurine, deficient kitten pyramidal cell number is decreased and fine branching at the end of neurons (arborization) shows poor development. Taurine promotes cell proliferation of human fetal neurons and also involves influencing neurotransmission (Shivaraj et al., 2012). In a recent study, the antidepressant activity of taurine is demonstrated which may be connected to regulating the hypothalamic-pituitary-adrenal axis and promoting the genesis, survival, and increase of neurons inside the hippocampus (Wu et al., 2017; Liu et al., 2011) states that antenatal taurine supplementation can significantly improve the intrauterine growth restriction (IUGR) fetal brain development in the rat model. Antenatal taurine supplementation reduces apoptosis in cerebral cells of fetal rats, promotes cerebral cell regeneration and value-added differentiation, increases cerebral weight and might decrease cerebral injury caused by IUGR. Several studies have described the role of taurine in anti-neuro-inflammatory responses. After induced traumatic brain injury, it has been shown that taurine significantly increases effective recovery as well as reduces glial fibril acidic protein accumulation and water content in the penumbral region. Taurine can protect our brain from traumatic injury which is proved by various studies (Wang et al., 2016), however only very few have suggested that taurine can protect from axonal regeneration after injury. In his study, Niu et al. (2018) showed that in case of traumatic brain injury, taurine exerts protective effect against inflammation, apoptosis, and oxidative stress. He combined astrocytes with neuron cells and treated them with different concentrations of taurine (100, 200, and 300 mg/l) for 72 h, as well as levels of active oxygen, malondialdehyde, reduced glutathione, glutathione peroxidase, superoxide dismutase, catalase, acetylcholinesterase, tumor necrosis factor-α, interleukin-6, caspase-3, p53, B-cell lymphoma 2 and Bcl-2-associated X isolated proteins. These inflammatory, apoptotic, and oxidative markers increase significantly in damaged cells and return to normal levels following the addition of taurine. In his study, Lotocki et al. (2009) showed that in TBI, inflammation is a well-known critical event that occurs due to secretion of cytokines and activation of glial cells. When supplemented through taurine, it exerts its protective and oxidant effect by suppressing inflammatory cytokines such as TNF-α, IL-6, IL-1α, and IL-1β in spinal cord injury and TBI (Sun et al., 2014). In his study, Zhao et al. (2018) states that a high dose of taurine (50 mg/kg) supplementation significantly reduces pathological inflammation and white matter injury following intracerebral hemorrhage, and the mechanism may be related to upregulation of H_2S levels and reduced P2X7R expression. In his study, Su et al. (2014) showed the effects of taurine on traumatic brain injury in 72 rats on the functional outcomes of inflammatory cytokines, astrocyte activity, and cerebral edema. Taurine (200 mg/kg) was injected intravenously after injury or daily for 7 days. Taurine improves functional recovery except 1 day and reduced accumulation of glial fibrillary acidic protein and water content in the penumbral region at 7

days after TBI. Taurine lowers growth-related oncogen (GRO/KC) and interleukin (IL) -1b levels while elevating performance control levels, normal T cells expressed and secreted (RANTES) by 1 day and significantly suppresses 17 cytokines levels: eotaxin, Granulo-cyte colony-stimulating factor (G-CSF), Granulocyte-macrophage colony-stimulating factor (GMCSF), interferon-gamma (IFN-c), IL-1a, IL -1b, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-13, IL-17, leptin, monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-a), vascular endothelial growth factor (VEGF), and only increases MIP-1a levels per week. Heidar et al. (2017) states that during hepatic encephalopathy, brain injury caused by ammonia has been linked to oxidative stress, movement disorders, and cognitive deficits that, if improperly treated, permanent brain injury, coma, and death are all possible outcomes. Taurine supplementation (50, 100, and 200 mg/kg, gavage), reduces oxidative stress biomarkers of brain tissue in cirrhotic animals, and also suppress level of reactive oxygen species, lipid peroxidation, in addition to maintaining the antioxidant capacity of tissues and preventing the depletion of brain glutathione. Animals who were on oral taurine supplementation (200 mg/kg/day) have reported reduced level of ammonia in their plasma and brain. Zhang et al. (2021) in one of his study showed the beneficial effect of taurine against diabetic peripheral neuropathy (DPN). They demonstrated that taurine vitally reduced blood glucose level and extenuate resistant to insulin as well as dysfunction caused by nerve conduction in diabetic rats were also improved by taurine. Axonal morphology of damaged neurons of the sciatic nerve in diabetic rats is corrected by taurine; also, axonal outgrowth in dorsal root ganglion has been induced by taurine when it is exposed to high glucose. The sciatic nerve of diabetic rats and DRG neurons showed increased phosphorylation levels of PI3K, Akt, and mTOR when exposed to high glucose. As a result of their findings, taurine appears to be a latent candidate for axonopathy and could be a future therapy for DPN protection.

According to the latest investigation by Chupel et al. (2021), it was demonstrated that for neurodegeneration and cognitive impairments, there is major contribution of immunosenescence; however, these strategies can be attenuated by nonpharmacological strategies, exercises and through amino acid supplementation like taurine. As proven by their study and as we know with aging that taurine content decrease in the body, 48 women were enrolled in the study in 4 categories, that is, exercise training, taurine supplementation, exercise training plus taurine supplementation and control group. After 14 weeks of exercise twice a week and 1.5 g of taurine supplementation, they concluded that exercise combined with taurine supplementation appeared to be a good therapy for improving health-related outcomes in older people. A published study by Jangra et al. (2020) results showed that taurine inhibits RS-induced oxidative stress, neuroinflammation and apoptosis in restraint stress (RS) in rat model. Studies showed the beneficial role of taurine in the case of non-alcoholic fatty liver disease using female *Fxr*-null mice because their livers exhibit hepatic steatosis and inflammation, a significant decrease in the liver triglycerides, non-esterified fatty acids, and total bile acids were discovered to have high levels of hepatic damage-associated diagnostic indicators, when up to 4 weeks taurine (0.5%) mixed in drinking were given to them. These mice had significantly lower levels of genes related to oxidative stress (Hmox1 and Gsta1), as well as fatty acid synthesis genes (Acc1 and Scd1). The findings imply that consuming taurine reduces hepatic steatosis and dysfunction induced by a deficiency in FXR (Miyata et al., 2020).

Taurine supplementation role

Taurine improves immunocompetence, as well as protects visual function during diabetes (Xu et al., 2008). Taurine is used to inhibit induced cell remodelling by suppressing elevated levels of extracellular inorganic osmolyte as proved by many studies using different types of cell (Bkaily et al., 2020). Taurine acts as an effective osmoregulatory agent as proven by several studies in the literature (Pasantes-Morales, 2017; Schaffer and Kim, 2018). Some studies have shown that when there is an increase in volume, then it induces the release of intracellular taurine (Pasantes-Morales, 2017). Thus, hyposmolarity would induce the extracellular release of taurine, whereas hyperosmolarity would increase intracellular taurine. Ginguay et al. (2016) states that many clinical trials on taurine have promising results which encourage its therapy. Taurine's nutritional value has also been demonstrated in research (McCarty, 2017). Taurine is an essential nutrient in cats and foxes (Ripps and Shen, 2012). Taurine deficiency in these animals shortens their life spans and causes pathological changes (Ito et al., 2014a; Park et al., 2014). In human beings, overt symptoms of taurine deficiency do not easily develop, like in cats and foxes, although parenteral feeding is associated with taurine deficiency (Arrieta et al., 2014). In comparison to cats and fox, tissues of human beings have higher holding capacity of taurine although humans have no capacity to synthesize taurine in large amount. In a study conducted by the World Health Association involving 50 population groups in 25 different countries throughout the world, it was reported that increased consumption of taurine will protect from hypertension and hypercholesterolemia (Sagara et al., 2015). Body mass index is also reduced by taurine supplementation (Yamori et al., 2010); additionally, in case of obese women its supplementation also helps in reducing elevated levels of inflammation markers (Rosa

et al., 2014). Predominantly, it is intracellular and moves across the plasma membrane through SLC6A6 (Tau T) and SLC36A1 (PAT1) transporters (Maria et al., 2018). Bhat et al. (2020) states that taurine induces regulation of intrinsically disordered proteins (IDPs) or natively unfolded proteins. Waldron et al. (2018), in their meta-analysis, investigates the effect of oral administration of taurine on resting systolic and diastolic pressure in humans, and their finding reveals that blood pressure can be reduced to a clinically relevant magnitude and without any adverse effect by taurine ingestion at the stated doses and supplementation periods. Zeng et al. (2012) in one of his studies showed the beneficial effect of taurine supplementation on broiler lipid metabolism, they divided 241,1 day old Avian broilers were randomly separated into 5 groups each with three duplicates, for a period of 21-day. The groups were given basal diets containing 0% taurine (control group), 0.05, 0.10, 0.15 and 0.20% taurine, respectively. The results showed that 0.15% dietary taurine increased apparent metabolisable energy and crude fat digestibility (P=0.05), increased the activity of lipase in the pancreas and small intestine (P=0.05), and significantly decreased the content of serum total cholesterol (TC), triglycerides (TG), free fatty acids (FFA), glucose (GLU), and liver TG, FFA (P0.05) compared to the control group. Siefken et al, 2003 demonstrated that taurine transporter TAUT is present in human skin and that's the reason that epidermal keratinocytes is protected from dehydration because there is accumulation of taurine, In human epidermal region TAUT is expressed as a 69 kDa protein whereas it is absent in the dermis layer of skin. In epidermal itself highest concentration of TAUT is found in the outermost granular keratinocyte layer whereas in the stratum spinosum it is present in lower concentration. When Neonatal normal human epidermal keratinocytes cells were treated (NHEK) with taurine it was seen that it inhibit apoptosis induced either by osmotically or by UV rays. Taurine accumulation is also induced by environmental factors that also effects epidermal barrier function to water loss,taurineloss, taurine helps in preventing surfactant such as SDS induced dry and scaly skin by stimulating epidermal lipid synthesis & modulating the pro-inflammatory response (Waldmann-Laue et al, 2006).

In cardiac mitochondria high concentration of taurine is estimated approximately 70 nmoL/mg,taurine acts as mitochondrial buffer as it has been suggested that elevated level of taurine in heart muscles suppress mitochondrial apoptosis, oxidative and endoplasmic reticu-lum stress,Enzyme acyl-CoA dehydrogenases that controls β-oxidation of fatty acids are shown to have satisfactory activity with mitochondrial taurine serving as a mitochondrial buffering agent,as one of the study on rat model has shown that in taurine deficient heart the rate of β-oxidation of endogenous fatty acids was 31% lower in comparison to control heart (Kurtz et al, 2021). Taurine accumulation is also induced by environmental factors that also effects epidermal barrier function to water loss,taurine helps in preventing surfactant such as SDS induced dry and scaly skin by stimulating epidermal lipid synthesis (Waldmann-Laue et al, 2003).

Tumor necrosis factor-α (TNF-α), one of important proinflammatory cytokine,its production has been found to be downregulated by taurolidine, a derivative of taurine,In human periph-eral blood mononuclear cells from healthy donors which is stimulated by lipopolysaccharide (LPS) 1& INF-γ when treated with Taurolidine it mostly blocked the production of TNF-α by 50-90% (Wójcik et al, 2010).

Pharmacokinetics of taurine

In humans, one-fourth of bile acids are conjugated with taurine before being absorbed, whereas by the action of tissue enzymes or by bacterial action, taurine is converted to isethionate which is further converted to CO_2, water, ammonia, or urea. On an empty stomach, bioavailability of taurine is improved; within 1-2.5 h there is a vast absorption of taurine in the gastrointestinal tract, whereas within 6-8 h after ingestion, taurine has been shown to return to baseline concentrations. The kidney regulates the concentration of taurine via urine excretion; which ranges from 65 to 250 mg daily (Ghandforoush-Sattari et al., 2010). Different muscle types having different concentrations of taurine 1-3 μmol/g taurine has been detected in glycolytic muscle fibres, whereas 15–20 μmol/g taurine has been found in oxidative muscle fibres(Hansen et al., 2010). For taurine import and export, different transporters and channels exist in muscle membrane (Hansen et al., 2010).

Taurine concentration gradually depleted in subjects with chronic kidney disease. Taking dietary L-glutamine supplementation helps in elevating the level of plasma taurine, in contrast to the absence of CKD. One of the previously published studies by Abbasian et al. (2021) showed in an animal model that in the case of CKD, depletion of taurine continuously occurs but it can be rectified by supplementation of L-glutamine.

Other beneficial role of taurine in various diseases

Taurine treatment has shown promising outcomes in the case of osteoarthritis (OA), a disease characterized by deformity in joints, pain stiffness, and swelling affecting a large population, as OA progressed. Collagen II, mRNA and protein levels fell, while ER stress markers (GRP78, GADD153, and Caspase-12) increased. As ER stress markers (GRP78, GADD153, and Caspase-12) increased, chondrocyte viability and Collagen II production were reduced, and apoptosis was promoted. However, in this

case, taurine treatment exhibited Anti OA effect by inhibiting these above phenomena. Neutralization of toxic aldehydes and detoxification of xenobiotics is another important function of taurine (Miyazaki et al., 2014). Osteoarthritis is one of the common diseases worldwide. Bian Y et al. (2018) proved in his study on animal model that after surgery, OA induced rat model became relieved from its symptoms after receiving taurine injection in a dose dependent manner. Histopathological analysis revealed that taurine helps in suppressing degeneration of cartilage, loss of matrix and expression of matrix metalloproteinase-3 (MMP-3) and CHOP. According to different studies performed by authors, peculiar features of stroke and neurodegenerative diseases, including Alzheimer's, Huntington's and Parkinson's diseases are ER stress, mitochondrial dysfunction, and oxidative stress (Prentice et al., 2015). In case of stroke due to release of the immense amount of neurotransmitter, glutamate which overstimulates postsynaptic neurons leading to a neuroexcitotoxic response, characterized by oxidative stress, calcium overload, ER stress, and in some cases cell death (Prentice et al., 2015).

Taurine treatment in the stroke model has been demonstrated to reduce glutamate-mediated toxicity by lowering oxidative stress and [Ca^{2+}] overload, as well as blocking two of the three UPR pathways, while taurine deficiency has been linked to ER stress (Schaffer et al., 2018). However, in chronic situation like Parkinson's, taurine levels decline (Engelborghs et al., 2004). Taurine is available to protect the CNS during the acute phase of the disease, but if BBB taurine transport fails and taurine cannot cross through the BBB itself, there is a lack of adequate concentration for neuroprotection, and the disease progresses to the chronic stage). In another investigation, taurine (200 mg/kg, i.p. for 7 days) was shown to protect against the increased formation of age-related lipid peroxidation products (Yildirim et al., 2011). By stimulating insulin receptors, taurine helps in enhancing insulin activity and thus played a major role in maintaining euglycemia. In the case of diabetes mellitus (Honsen et al., 2001; Maturo et al., 1988), lower concentration of plasma and platelets' taurine has been reported; thus, by taurine supplementation, platelets dysfunction and plasma concentration can be restored (Franconi et al., 1995; DeLuca et al., 2001). This is proved by one of the study on diabetic rat model where taurine supplementation improves glucose and fat metabolism as well as help in suppressing insulin resistance (Nakaya et al., 2000). In diabetic subjects, taurine deficiency can be observed by the lower rate of intestinal absorption of taurine and a higher renal excretion rate (Merheb et al., 2007). Decreased taurine concentration has been seen in the liver of diabetic animals (Nandhini et al., 2005). It is therefore confirmed that in diabetes development, taurine deficiency also plays a major role, and thus bioavailability of taurine is lower in diabetic subjects; this evidence can be confirmed by two published reports, one of which is Shi et al. (2003) that explains that in case of high glucose condition, activities of taurine transporters are inhibited, and the other by Hansen (2001) which showed that in response to the accumulation of intracellular sorbitol, depletion of intracellular taurine occurs.

After injury, podocyte cells have the very least capacity to regenerate and proliferate as it is a terminally differentiated cell, and reduction in its number leads to diabetic neuropathy as well as precedes the development of renal dysfunction and albuminuria in diabetic patients and animal models of diabetes mellitus, taurine conjugated ursodeoxycholic acid hampers endoplasmic reticulum stress, and apoptosis that induced advanced glycation end products (AGEs) as it also eradicates the AGES induced expression of gluco**s**e-regulated protein 78. TUDCA action can be a new interventional treatment that may prove best in suppressing AGEs-induced apoptosis of mouse podocytes in diabetic nephropathy (Chen et al., 2008). Taurine helps in the prevention of mitochondrial dysfunction, as proved by Chen et al. (2008) using rat retinal ganglion cell line by exposing it to hypoxia for 24 h. Rikimaru et al. (2012) in their study used a culture system of the patient suffering from MELAS-derived pathogenic cells and observed that after treating it with a high concentration of taurine (40 mM for 4-day exposure) was unable to reverse the mitochondrial dysfunction. In their study, they showed that high taurine concentration in a dose-dependent manner (0, 20, and 60 mM) increases oxygen consumption rate, reduced oxidative stress, and increases mitochondrial potential. MELAS patients treated with taurine had a reduction in the spread of the ischemic infarct to other brain regions, according to their research. Taurine's protective actions were seen in these patients as an improvement in stroke-like episodes.

By consuming 30 g of beef, a 70 kg healthy male fulfills the daily need of taurine and carnosine (Wu, 2020). Nutritional supplementation of taurine has an immense role in elevating adiponectin levels as well as in decreasing inflammation markers (high-sensitivity C-reactive protein) and lipid peroxidation (TBARS) in obese women within 8 weeks of its supplementation (Rosa et al., 2014). Oral administration of 2 g taurine/day for 4 weeks resulted in clinically significant reductions in the frequency, duration, and intensity of muscle cramps in case of subjects with chronic liver diseases (Vidot et al., 2018), whereas long-term oral administration of taurine (9 or 12 g day^{-1}) for 52 weeks can reduce the genetic disorders caused by a point mutation in mitochondrial DNA as well as reduce the reappearance of stroke-like episodes in mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) (Ohsawa et al., 2019).

Taurine supplementation helps in suppressing

complication due to Hypoglycemic effect like diabetic complications such as diabetic nephropathy, retinopathy, and neuropathy (Imae et al, 2014),Taurine exerts protective effect on kidney by attenuating renal damage & suppressing the level of urea nitrogen (BUN) & creatinine in the blood (Imae et al, 2014).

Administration of taurine helps in the regression of atherogenesis through a different mechanism. Cholesterol level continuously declines due to the administration of taurine in atherogenic animals as demonstrated by many studies (Pettyet al., 1990; Murakami et al., 2010; Murakami et al., 1996). It was observed that in an animal on taurine treated diet, cholesterol level rapidly declines during the regression period of atherogenesis due to taurine's ability to increase the activity of the enzyme 7-hydroxylase, and to speed up the decomposition of cholesterol (CYP7A1) (Murakami et al., 2010; Murakami et al., 1996; Yokogoshi et al., 1999; Lam et al., 2006). By decreasing the activity of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase), taurine helps in inhibiting the hepatic biosynthesis of cholesterol esters and triglycerides (Bellentani et al., 1987).

Study by Miyata et al, 2021 demonstrated that in taurine-mediated cholesterol-lowering effect might bile acid/farnesoid X receptor (FXR) signaling is involved,their study showed that by reducing the ileal FXR signaling due to the alteration of ileal bile acid composition taurine partially plays role in cholesterol lowering.

Taurine can be an important preventive factor in case of coronary heart disease which can be emerge as an important molecule for public health. Analysis from the WHO Cardiovascular Diseases and Alimentary Comparison (Yamori Y et al 2010), a multi-center cross-sectional study,observed an inverse corelation between urinary excretion of taurine and Blood pressure (Wójcik et al, 2010).

Ommati et al. (2019) showed the potential effect of taurine on a mouse model of manganism against Mn neurotoxicity, when manganese-exposed mice were treated with different doses of taurine (50, 100, and 500 mg/kg, i.p) alleviated Mn-induced locomotor deficit. According to Yamori et al. (2009)**,** in a genetic rat model of stroke fed with a fish diet rich in taurine, 90% reduction in stroke incidence was observed. No association between serum taurine levels and stroke risk was observed in 14,274 women who were examined in a prospective-case study based on the New York University women's health study (Wu et al., 2016). Male infertility due to less sperm motility, depression, and cirrhosis may be prevented by taurine (Birdsall et al., 1998; Lourenço et al., 2002), and acute gastric ulcers as well as damaged colon cells are also healed by it (Wingenfeld et al., 2002; Son et al., 1996). Study by Chen et al, 2004 demonstrated in his study the hypocholesterolemic effect of taurine, they observed that formation of cholesterol gallstones increased by 71% to 100% due to taurine deficiency whereas there is 0% reduction by taurine supplementation, in addition taurine also helps in reduction of triglycerides (TG) so from their study it is concluded that taurine supplementation does not up-regulate LDL receptor protein level,and reduction in the cholesterol level in circulation is mainly due to its suppressive effect on TG secretion from the liver.

Role in spinal injury

Almost 90% of all spinal trauma cases in developing countries do not receive any primary medical care or pre-hospital first aid while being transported to a large hospital (Srivastava et al. 2015). In case of the brain, the role of taurine is more or less developed but still, it is a topic of hot debate in case of spinal cord injury and controversies which is a healthy sign for future research. Since many years before a large number of studies demonstrated the action of taurine in the case of the spinal cord that it acts as a neurotransmitter, this interpretation also focuses its possible involvement in the anti-epileptic action on the spinal cord (Kurachi et al., 1985; Kudo et al., 1998). Chen et al., 2020 demonstrated the best therapeutic effect of taurine in combination with ascorbic acid as against SCI-induced rats, combined treatment of both drugs were given to them for 45 consecutive days; it was noticed that there is suppressed level of caspase-3, Bax, pro-NGF, and p53 mRNA expression by more than 30% compared to individual treatments, as well as altered antioxidant markers and induced lipid peroxidant to normal level in SCI-induced rats treated with taurine and ascorbic acid. However, studies are on-going to elucidate the possible role of taurine against SCI as taurine plays a potential role against brain and spinal cord damage caused by trauma. Taurine (2, 5, 15, and 50 mg/kg, IV for 7 days) protected the brain against closed head injury in rats by increasing neurological functioning and decreasing cerebral edoema and BBB permeability. In damaged tissues, taurine treatment boosted SOD activity and glutathione levels while decreasing malondialdehyde and lactic acid levels. Taurine treatment also inhibited cell death in the CA1 and CA3 subfields of the hippocampus (Sun et al., 2015; Dionyssiotis, 2012) where most of the spinal cord injury individuals are malnourished. Daniel et al. (2019) proposed that taurine is one of the most abundant free amino acids in the brain. Through his experiments, he proved that acute taurine treatment promotes axonal regeneration according to SCI in lampreys. This offers a new way to try to promote regeneration of axons after injury to the nervous system in mammalian models. It is still a topic of hot debate whether taurine acts as a neurotransmitter in the case of the spinal cord or not. In general, we can say that to become a neurotransmitter in the case of SCI, taurine should have to be present at the

axon or axon terminal. However, previously recorded data provides evidence of the taurine presence in axons of lamina 1 and 2 and also in the superficial dorsal horn (Lee et al., 1992). However, in the case of SCI as well as in TBI, elevated level of taurine has been seen to indicate its involvement in neuroprotection and regeneration following injury (Magnusson, 1994). Study by Nakajima et al. (2010) showed the beneficial role of taurine treatment at doses of (25, 80, 250, and 800 mg/kg, i.p.) in SCI rat model as changes in motor function disturbances and pathological abnormalities, as well as suppression in the level of IL-6 and myeloperoxidase in a dose-dependent manner, suppression in SCI mediated cyclooxygenase-2 and phosphorylated signal transducer, activation of transcription 3 expression, and reduction in neutrophil accumulation in the sub-arachnoid spaces.

Whereas studies by Chatterji (2017) and Singh et al (2018, 2020) on biofluids serum, urine, and CSF metabolites perturbation through NMR spectroscopy reveals that some metabolites have clear correlation with pattern of recovery in treated ASCI. Through their findings, we can say that may taurine as a metabolite can establish as a potential biomarker of neurological recovery in future.

In one of the recent studies by Vahdat et al. (2021) in the case of 32 TBI subjects who were randomized into two groups, the outcome of their study was that group that received 30 mg/kg/day of taurine, in addition to the Standard Enter a Meal for 14 days have a significant suppressed level of IL-6, one of the important inflammatory markers in TBI subjects as well as enhances the clinical outcome too, in comparison to control group.

CONCLUSION

In this review, we tried to focus on the taurine origin and its function in different parts of the body and how important this therapeutic molecule is, as it interacts with life processes and evidence for its ability to modify activities in major tissues. Involvement of taurine is due to its unique physiochemical character derived from alpha beta-amino sulphonic acid. In many animals especially in dogs and cats, it is so important that its deficiency causes abnormality. Taurine is considered a therapeutic agent due to exhibiting broad activities, especially for neurological disorders. According to the preceding explanation, its wide inhibitory and regulatory actions demonstrate its therapeutic potential in the treatment of CNS diseases, since from its discovery in 1827 a large number of functions of taurine have been elucidated in experiments focusing on skeletal muscle, cardiovascular system, reproductive and respiratory system. Through multiple processes, including anti-oxidation, energy production, neuromodulation, Ca^{2+} homeostasis, and osmoregulation, taurine's cytoprotective activity contributes to improvements in human clinical and nutritional health. Taurine plays a major role against anxiety, depression, neurodegenerative disease like stroke, epilepsy, trauma and chemical-mediated neuronal injuries as well as neurodevelopmental disorders, including Angelman syndrome and Fragile X syndrome. It is worth testing simple, water-soluble, and more lipophilic analogs as a pro-drug of taurine in spinal cord injury (SCI) as they have additional properties than taurine like N-chloro taurine (NCT), an analog of taurine which is more lipophilic than taurine and more effective in scavenging reactive oxygen species (Gupta et al., 2006). We are certain that, with further experimental and clinical trials, these analogues will form a new class of SCI treatments. A non-randomized controlled trial based on 107 patients with knee OA concluded that in patients with knee OA, vitamin D therapy has a minor but statistically significant therapeutic benefit (Sanghi et al., 2009, 2013), but now many studies are conducted to show taurine effect in case of OA as they get promising result on its supplementation. One of the recent study by Wang et al. (2018) on mouse model has shown that taurine treatment suppressed the OA symptoms and provides protective effect by suppressing MMP-3 and CHOP expression in mouse model, however more human trials on taurine supplementation are still needed in case of OA. One of the cross sectional study by Saraswati et al. (2019) on 56 OA subjects with grade II-IV were recruited in their study in which they demonstrated that taurine supplementation (59.77 mg per day), accelerates SOD dismutase activity. All these findings may open path for future research on taurine in various diseases.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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