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Physio-Pharmacological Potentials of Taurine: A Review in Animal and Human Studies

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ABSTRACT
Taurine, a sulfur-containing non-protein amino acid is one of the most prevalent amino acids in all mammalian plasma and tissues. The objective is to identify the therapeutic role of taurine in animal models and human systemic physiology. Various electronic databases, including author, year of publication, country, purpose, data collection, significant findings and research focus/domain were used in search of published material referencing assessment of the physio-pharmacological potentials of taurine. Taurine protects against a wide range of pathophysiological conditions, including neurological abnormalities, mitochondrial malfunction, metabolic disease, reproductive failure and poor fetal development. Taurine was also reviewed to possess antioxidant, reno-protective, hemo-protective, hepato-protective and anti-inflammatory potentials as well as cardio-protective and anti-aging effects. Taurine, found in excitable tissues, protects systemic physiology against maladaptive responses. Further research is needed to determine if taurine insufficiency can monitor maladaptive responses. Although, clinical trials are also needed to determine optimal therapeutic doses.

KEYWORDS
Taurine, health, systemic physiology, maladaptive responses, antioxidant, fetal development, repro-protective potential

INTRODUCTION

Taurine, a 2-aminomethane sulfonic acid, is mostly found in almost all cells, especially excitable ones[1]. Its cytoprotective activities have a substantial impact on the health and nutritional state of numerous species, regulating essential cellular events and balancing life and death[2]. Taurine's physiological functions have piqued the interest of researchers because of its cytoprotective properties[3-6].

Taurine has received interest in infant formula, dietary supplements and energy drinks due to its possible medicinal applications[7]. Clinical investigations demonstrate that taurine is a necessary ingredient in several species, such as cats and foxes[8]. Taurine is categorized as a conditionally necessary or useful nutrient in humans, with higher tissue retention than in cats or foxes[8]. Humans, unlike cats, do not show obvious indications of taurine insufficiency, albeit parenteral feeding has been linked to taurine deficiency[9]. Human studies have demonstrated taurine's nutritional significance, with increased dietary consumption lowering the incidence of hypertension and hypercholesterolemia[10]. In obese women, taurine supplementation decreases body mass index and inflammatory markers[11-13]. Taurine's cytoprotective

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actions contribute to better clinical and nutritional health. The current study examines the physio-pharmacological pathway behind taurine's cytoprotective effect, the impact of taurine on a variety of disorders and the nutritional value of taurine supplementation.

COMMON AND SCIENTIFIC NAMES

Taurine, commonly known as 2-aminoethanesulfonic acid, has a molecular formula of H2NCH2CH2SO3H (Formula: C2H7NO3S) (Fig. 1) and a recognized abbreviation of Tau[14-16].

Biochemistry and functions: Taurine is a crystalline substance that is tasteless, colorless and has a pH of 1.73417. It has a melting point between 325 and 328°C. Its zwitter ionic nature necessitates active transport in order to maintain high-concentration gradients in tissues like the retina and neurons. Neither inorganic sulfate nor organic sulfur can be found in taurine. Significant additional roles for taurine have been demonstrated in lipid metabolism, calcium homeostasis, heart failure, prevention of ischemic cardiac damage, cardiomyopathy, reduction of hypertension, osmoregulation, glucose metabolism regulation, immunity and inflammation regulation, antioxidant/free radical scavenger and membrane stabilization[2,17-19]. The metabolic actions of taurine and its possible medical benefits are further examined.

Taurine homeostasis in the body: Absorption, distribution, excretion and synthesis of taurine are all part of an organism's homeostasis process, with intestinal uptake and liver production providing for dietary requirements[20-22].

Taurine absorption: TauT and PAT1 transporters control how much taurine is transported in the small intestine. Type 2 diabetes and inflammation may both increase transport while decreasing absorption[20].

Taurine distribution: Taurine is absorbed in the gut and then released non-saturable into the bloodstream, where it reaches a plasma concentration of 10-100 μM[23]. TauT or PAT1 transporters then absorb taurine, with TauT serving as the primary absorption mechanism. The range of tissue taurine concentrations is 5-50 mM, with metabolically active tissues containing the highest levels[24]. The biggest source of taurine is found in skeletal muscle, which makes up more than 70% of the body's total taurine content.

Taurine excretion: Due to a lack of enzymes, mammals cannot digest taurine. It eventually ends up in feces after being expelled by the kidney or converted to bile acids. The amount of taurine in the body is controlled and cats given high doses of taurine have increased urine excretion[25]. Increased faecal bile acid excretion and urinary taurine levels may be indicators of dietary seafood consumption.

Biosynthesis of taurine: Cysteine dioxygenase (CDO) and cysteine-sulfinate decarboxylase (CSAD) convert cysteine to taurine, generating cysteine-sulfinate and hypotaurine[26]. It undergoes an ambiguous oxidation process to get taurine. Coenzyme A breakdown is a minor synthesis route that results in cysteamine, which can then be oxidized to hypotaurine. Although, other tissues, such as the brain, lungs, skeletal muscle, adipose tissue and mammary glands, also produce taurine, the liver is in charge of maintaining taurine levels[26].

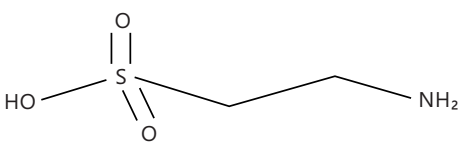

Fig.1: Showing molecular structure of taurine

Taurine concentrations in food can range from 1 mmol per 100 g of wet weight to 20 mmol per 100 mL[27]. The average daily consumption in omnivores is 1000-1500 mmol (125-188 mg)[28]. However, it is challenging to determine the general population's intake of taurine due to the absence of updated food tables. There has been a surge in energy drinks with a high taurine concentration and compared to omnivores, vegans may have significantly lower plasma taurine levels and urinary excretion. Unknown is the magnitude of this drop in tissue taurine content and plasma taurine.

Transporters of taurine: The high-affinity, low-capacity, Na^+-dependent TauT transporter and the high-capacity, proton-coupled, but Na^+-independent b-amino acid transporter PAT1 allow TauT/PAT1 cells to accumulate taurine[29]. With binding taking place in the first N-terminal extracellular loop and gating and ionic binding to TauT, taurine transport is Na^+ and Cl^- dependent. Taurine binding and the start of the transport cycle both require Na^+ ions. Because Na^+ is recycled to the extracellular compartment by the Na^+/K^+-ATPase, TauT-mediated taurine absorption in EATC is electro-neutral. The second Na^+ is more easily bound to TauT with the help of Cl^- ions[29].

Due to acidification, osmotic swelling, exposure to reactive oxygen species and activation of serine/threonine kinase protein kinase C (PKC)[29], tauT activity is downregulated in a variety of cell types. TauT's structural changes brought on by PKC-mediated phosphorylation prohibit taurine from binding to Arg-324. Taurine uptake that is Na^+-dependent is stimulated by PKA, but this effect is eliminated by PKC activation. Through Thr-28 phosphorylation, casein kinase 2 inhibits TauT activity by raising TauT0's affinity for Na^+ and decreasing the Na^+/taurine stoichiometry for taurine transport. Gene transcription has a role in the long-term control of TauT function, with downregulation occurring after p53 activation, exposure to high extracellular taurine levels and hypotonicity[29]. After being exposed to a hypertonic solution, the tonicity-responsive enhancer binding protein (TonEBP/NFAT5) is upregulated. TauT mRNA abundance, translation and activity are decreased in primary human trophoblasts, NIH3T3 and ELA murine fibroblasts when rapamycin mTOR is inhibited. Following hypertonic exposure, enhanced TauT activity may be due to increased mTOR-dependent TonEBP activity[29]. Through the activation of mTOR, the low-affinity, high-capacity transporter PAT1 is linked to cellular amino acid sensing and cell proliferation[29].

PHYSIO-PHARMACOLOGICAL POTENTIALS OF TAURINE

Membrane stabilizer: Taurine causes a variety of membrane-related activities in tissues[29]. It was first proposed as a membrane stabilizer in 1973. Its functions are explained by protein phosphorylation, taurine-phospholipid binding, antioxidant hypothesis and phospholipid N-methylation hypothesis. According to the protein phosphorylation hypothesis, taurine modulates calcium binding and transport, while the antioxidant hypothesis contends that taurine lessens the inflammatory response caused by cytotoxic oxidants. According to the phospholipid N-methylation theory, taurine's actions result from inhibition, which changes the structure and content of membranes.

Taurine and cell volume regulation: In order to control intracellular osmolality, morphology and processes including cell migration, metabolism and death, it is essential to control cell volume. Water-permeable mammals have systems for volume restoration in response to osmotic disturbance. The renal medulla, gut and airways are exposed to an isotonic extracellular medium while the kidneys control osmolality. In the EATC, the taurine release is responsible for 30% of the osmolyte loss and loading cells with radioactively labelled taurine can cause taurine tracers to be depleted[29-30].

Body organs development: Insufficient synthesis of taurine in the human fetus results in problems with birth weight since taurine is an important amino acid throughout development. Mice that lack TauT are often smaller and have abnormalities in the growth of the heart and skeletal muscles[29-31].

Taurine supplementation has an impact on learning ability and low plasma taurine content can harm mental development[32]. These problems may be better studied using different animal models, such as CDO (cysteine dioxygenase) or CSAD (cysteine sulphinic acid dioxygenase).

Lung function improvement: Taurine affects mucus production and lung relaxation by acting as a weak agonist for GABAAR and GlyR receptors. In pathological conditions like asthma where immune cells secrete CysLTs, boosting mucus output and reversing taurine's relaxing actions on smooth muscle cells, it may have a role in lung regulation[29]. By decreasing inflammation and oxidative stress, taurine shields cells against lung damage[33].

Modulation of mitochondrial function: Protein translation and the production of ATP synthase depend on taurine for proper mitochondrial function. Reduced respiration in the liver mitochondria is a result of depletion, which might alter mitochondrial function. TauT knockout mice may be exercise-intolerant[29-30] and taurine supplementation may enhance mitochondrial function. Taurine might have a direct impact on the control of mitochondrial metabolism, possibly blocking PDH and possibly influencing sulfur and carbohydrate metabolism[34].

Antioxidative defence: Reactive oxygen species (ROS) are the main culprits in endogenous oxidant-induced cell damage and antioxidants like taurine can reduce ROS production, scavenge ROS, or block their actions[35]. Taurine guards against calcium excess scavenges hypochlorous acid and guards against mitochondrial damage[36]. In addition, it has cytoprotective effects on rat liver, decreasing lung tissue oxidative damage and lipid peroxidation[37]. By modulating Ca^{2+} homeostasis and boosting cardiac and skeletal muscle contraction under exhausting conditions, taurine supplementation may enhance exercise performance[38].

Modulation of muscle contraction: Guanidine-ethane-sulfonate reduces the taurine content of the extensor digitorum longus by 60%, which has an effect on the contractile performance of cardiac and skeletal muscle in taurine shortage. The effects of administration on exercise performance, rodent contractile function, exhaustion time, weariness and muscle protection are all improved[39]. Taurine reduces inflammation and oxidative stress, which reduces vascular stiffness[40].

Implicated in counteracting sarcopenia: Aging is the root cause of sarcopenia, a major health concern that affects the aged and is brought on by abnormalities in protein biosynthesis and breakdown. Taurine insufficiency may enhance taurine's potential in other applications by reducing the consequences of sarcopenia[41].

Treatment of duchenne muscular dystrophy: Duchenne muscular dystrophy, a deadly illness characterized by muscle loss and inflammation, is successfully treated in mice by taurine therapy[42]. The severity of the illness may be lessened with leupeptin and nNOS. When taurine levels are restored, inflammation is reduced and forelimb strength is improved[42]. Enhancing muscle strength with creatine is almost as effective.

Attenuating myotonic dystrophy: A condition known as myotonia results in delayed muscle relaxation after contraction. Treatment with taurine lessens the intensity of discharges and may be useful in treating congenital paramyotonia and sodium channel myotonia[2,29].

Prevention of cardiovascular disease: Further Randomized Controlled Trials (RCTs) are required before taurine is included in micronutrient supplements[43]. Taurine may help prevent and treat heart failure, hypertension, ischemic heart disease, atherosclerosis and diabetic cardiomyopathy.

Hypercholesterolemia: By enhancing cholesterol catabolism and bile acid excretion, taurine reduces hypercholesterolemia in animal models[44]. In people who are overweight or obese, it enhances lipid metabolism and may avoid cardiovascular disease. According to a study, pretreatment with 1.5 g day^{-1} of taurines restored any vasoconstriction that was already present[45]. Its effects on hyperlipidemia and the prevention of cardiovascular disease (CVD) require further study.

Hypertension: By lowering blood pressure through decreased Ca^{2+}, oxidative stress, sympathetic activity, inflammatory activity and renal function, taurine supplementation has been demonstrated to prevent the development of hypertension in animal models[44,45]. Recent clinical investigations have demonstrated an improvement in blood pressure and a 1.5-fold rise in plasma taurine concentration[45].

Congestive heart failure: Myocyte calcium overload increased oxidative stress and decreased myocardial energy generation is common in heart failure patients. Norepinephrine and angiotensin II activities are decreased by taurine, a Japanese-approved treatment[2]. Although, it increases exercise capacity, there is untapped potential for it to lessen mortality rates and the risk of overt heart failure. In Korean women with significant cardiovascular risk factors, taurine supplementation decreased plasma taurine levels, which may have beneficial effects on calcium homeostasis, atherosclerosis and coronary heart disease risk[46].

Diminishes atherosclerosis: The intricate process of atherosclerosis includes the intake of cholesterol-enriched lipoproteins, the recruitment of monocytes, the adherence of endothelial cells, the development of macrophages and the production of foam cells. By accelerating cholesterol regression, lowering cholesterol biosynthesis and safeguarding endothelial cells, taurine therapy lowers atherogenesis[2,47]. Additionally, it inhibits the proliferation of vascular smooth muscle cells and the reduction of oxidative stress[2,47].

Alteration of ischemia-reperfusion injury: Taurine is crucial in ischemia-reperfusion insults, which alter the course of damage treatment and injury outcomes[48]. It can be used in heart transplantation and bypass surgery to reduce oxidative stress and cellular necrosis, but it is not appropriate for acute cardioprotective agents such myocardial infarctions[20].

Reduction of myocardial arrhythmias: Digoxin and adrenaline are two examples of pro-arrhythmic substances that taurine inhibits[2]. Under the right circumstances, taurine plus L-arginine treatment effectively decreased cardiac arrhythmias in three patients, making it a potent antiarrhythmic agent[49].

Treatment of metabolic diseases:

- **Mitochondrial disease, MELAS:** Myopathy, encephalopathy, lactic acidosis and stroke-like events are some of the signs of taurine deficiency[50]. Mutations in tRNALeu that influence the amount of mitochondrial taurine and UUG-dependent proteins are the cause of MELAS (Fig. 2). The MELAS patients may benefit from taurine therapy[50]
- **Diabetes mellitus:** An autoimmune condition called diabetes mellitus causes high blood sugar and insulin resistance. The T-cell death causes type 1 diabetes, but type 2 diabetes is progressive and inhibits insulin activity. In mice, taurine therapy decreases the pathophysiology associated with diabetes, obesity and metabolic syndrome[51]. It lessens type II diabetic consequences by enhancing respiratory function, boosting ATP synthesis and reducing mitochondrial ROS generation. To ascertain if there is impaired renal re-absorption or decreased intestinal absorption, more research is required
- **Modulation of inflammatory diseases:** Joint stiffness, discomfort, inflammation and tissue destruction are all symptoms of arthritis, especially rheumatoid and osteoarthritis. Inflammation of the synovium, bone erosion and cartilage thinning are all symptoms of rheumatoid arthritis. Leukocyte recruitment occurs during the acute inflammatory phase, resulting in tissue damage. Taurine, which has a high neutrophil concentration, inhibits TNF- and protects against spinal cord injury[52] while, also acting as an anti-inflammatory and antioxidant

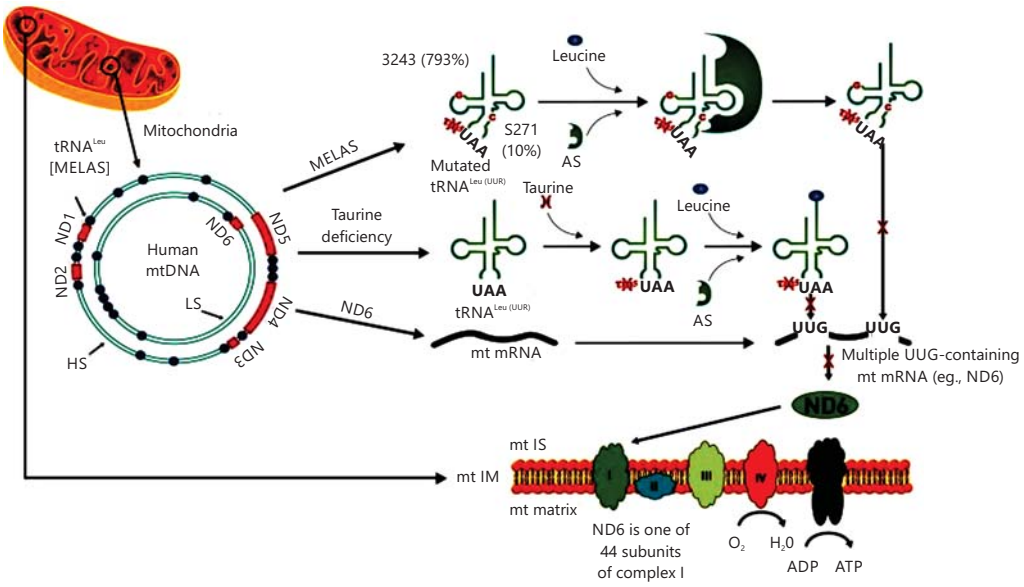

Fig. 2: Comparison of MELAS and taurine deficiency in mitochondria[50]

Taurine and central nervous system:

- **Stroke:** Glutamate toxicity, which overstimulates receptors and causes hyperexcitability and toxicity, is what causes stroke. In Fig. 3, taurine, a neuroprotective compound reduces Ca^{2+}, raises the Bcl-2/Bad ratio and inhibits ER stress to counteract glutamate damage[53]. It might lessen the severity of strokes, lessen ROS produced by NADPH oxidase and downregulate Nox2/Nox4[54]
- **Neurodegenerative diseases, such as Alzheimer's, Huntington's and Parkinson's disease:** Cell death, mitochondrial membrane collapse, calcium overload and increased ROS generation are all symptoms of neurodegenerative illnesses like stroke. Degenerative illnesses cause abnormalities in the respiratory chain; taurine therapy may lessen the severity of Parkinson's disease[55,56]
- **Fragile X Syndrome and Succinic Semialdehyde Dehydrogenase (SSADH) deficiency:** Fragile mice with the genetic ailment fragile X syndrome, which causes behavioral issues and intellectual deficits, have better memory retention. In SSADH-deficient individuals, taurine therapy has been demonstrated to enhance social behavior, coordination and activity[2]
- **Epilepsy:** Unbalances between excitatory and inhibitory neurotransmitters are the cause of seizures. Seizures brought on by stimulants are reduced by taurine[57]
- **Retinal degeneration:** The loss of photoreceptors and retinal degeneration are connected to taurine, a crucial vitamin for cats[58]. Taurine insufficiency has been linked to nuclear ganglion cell loss and degeneration, according to studies Gaucher *et al.*[59]. Vigabatrin, an anti-epileptic drug, can cause retinal degeneration[60]. In two individuals with succinic semialdehyde dehydrogenase insufficiency, taurine therapy partially mitigates the retinal damage brought on by vigabatrin treatment[2,61]

Repro-protective effects: Taurine promotes spermatogenesis, maturation and the activity of the testicular dehydrogenases (3-HSD, 17-HSD, G6PDH and LDH-X) and electrogenic pumps (Na^+/K^+, Ca^{2+}, Mg^{2+} and H^+-ATPase), as well as sexual ability in male animals[62-65]. It might lessen pathological harm to the male reproductive system, such as oxidative harm[35], reperfusion harm[66-68] and difficulties brought on by diabetes[69]. Through processes such as decreased oxidative stress, higher antioxidant capacity, inflammation, apoptosis and improved sperm mitochondrial energy metabolism, taurine also functions as a preventive agent against toxic damage from exogenous substances[35,70-72]. Taurine has also been linked to sperm preservation in hypothermia[62,64].

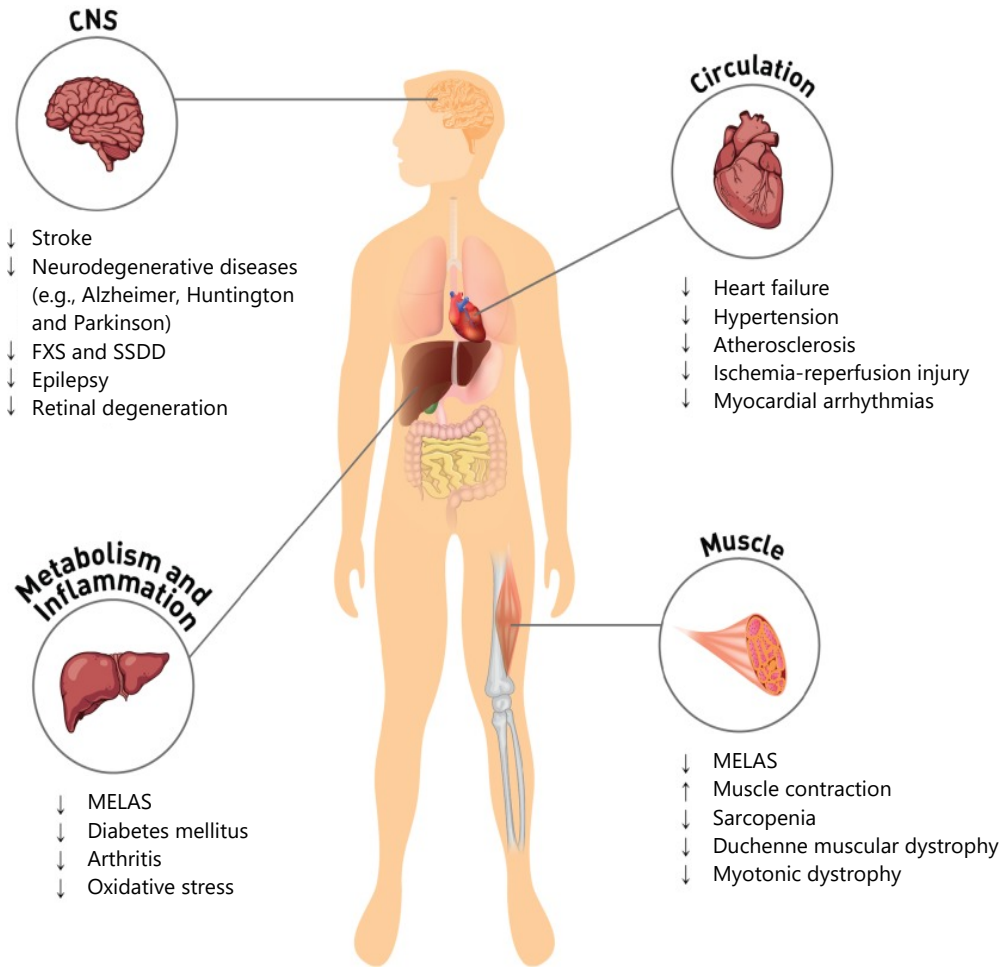

Fig. 3: Taurine-mediated protection against pathology and disease[53]

Hemato-protective effects: Taurine is required by blood cells, particularly neutrophils, lymphocytes and platelets[73]. Taurine is an essential component of energy drinks and healthy foods[74]. In fish, taurine suppresses hemolysis and perinatal taurine supplementation affects hematological parameters[75]. Taurine therapy inhibits hematotoxicity caused by marijuana bromate[76].

Retino-protective effects: Retinal cells are involved in the neurodegenerative process of OS, which calls for balanced redox signalling and antioxidant activity. Rodents have an abundance of taurine, an amino acid that may be used to cure and prevent retinopathies such as retinitis pigmentosa[41,61,77].

Anti-aging effects: A study shows that taurine supplementation may slow down the aging process, thus benefiting older individuals[8].

Reno-protective effects: Taurine is a known dietary supplement necessary for the prevention of kidney diseases such as acute kidney injury, glomerulonephritis, renal failure and diabetic nephropathy[78-80]. It controls the actions of renal cells, has anti-inflammatory and antioxidant characteristics and guards against hypertension and diabetic nephropathy. However, its therapeutic potential is constrained, necessitating more study.

Taurine is required for cellular homeostasis and other activities in organisms. Adverse reactions to regularly given drugs influence its potential application in human health protection. This article introduces taurine and discusses its pharmacological applications. However, more research on taurine's toxicity is

required before it can be made into a medicine. More study is needed to identify potential taurine signaling targets in diverse human disorders and to validate previous studies.

CONCLUSION

For therapeutic purposes, natural bioactive substances like taurine are being studied, enabling more complete and targeted clinical trials. Taurine is a substance that is found in excitable tissues and is crucial for protecting systemic physiology from adverse effects. It is necessary to conduct more studies to determine whether taurine deficiency may be utilized as a monitoring metric for maladaptive responses and whether taurine during and after treatment can inhibit or reverse maladaptive responses. Clinical studies are required to define the appropriate therapeutic dosages.

SIGNIFICANCE STATEMENT

Taurine has the ability to protect against a wide range of pathophysiological conditions, including neurological abnormalities, mitochondrial malfunction, metabolic disease, reproductive failure and poor fetal development. Despite different treatments, effective management continues to be a global concern. Taurine formation design could lead to prospective medications for health maintenance and the treatment of systemic illnesses. This review covers taurine's physio-pharmacological capabilities and underlying mechanisms, demonstrating its promise as a physiotherapeutic option.

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