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Review article

# Roles of taurine in cognitive function of physiology, pathologies and toxication

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ABSTRACT

Taurine is a key functional amino acid with many functions in the nervous system. The effects of taurine on cognitive function have aroused increasing attention. First, the fluctuations of taurine and its transporters are associated with cognitive impairments in physiology and pathology. This may help diagnose and treat cognitive impairment though mechanisms are not fully uncovered in existing studies. Then, taurine supplements in cognitive impairment of different physiologies, pathologies and toxicologies have been demonstrated to significantly improve and restore cognition in most cases. However, elevated taurine level in cerebrospinal fluid (CSF) by exogenous administration causes cognition retardations only in physiologically sensitive period between the perinatal to early postnatal period. In this review, taurine levels are summarized in different types of cognitive impairments. Subsequently, the effects of taurine supplements on cognitions in physiology, different pathologies and toxication of cognitive impairments (e.g. aging, Alzheimer' disease, streptozotocin (STZ)-induced brain damage, ischemia model, mental disorder, genetic diseases and cognitive injuries of pharmaceuticals and toxins) are analyzed. These data suggest that taurine can improve cognition function through multiple potential mechanisms (e.g. restoring functions of taurine transporters and γ-aminobutyric acid (GABA) A receptors subunit; mitigating neuroinflammation; up-regulating Nrf2 expression and antioxidant capacities; activating Akt/CREB/PGC1α pathway, and further enhancing mitochondria biogenesis, synaptic function and reducing oxidative stress; increasing neurogenesis and synaptic function by pERK; activating PKA pathway). However, more mechanisms still need explorations.

## 1. Introduction

### 1.1. Taurine physiology

#### 1.1.1. Molecular structure and metabolism of taurine

Taurine refers to a special amino acid containing sulfonate group and lacking carboxyl group (Fig. 1). It was first isolated from bull bile in 1827 by Friedrich Tiedemann and Leopold Gmelin [1]. Apart from dietary intake, endogenous taurine primarily originates from three synthetic pathways in body. The first one is the cysteine sulfinic acid pathway, which includes three sequential enzymatic reactions of cysteine: the cysteine dioxygenase (forming cysteine sulfinic acid), sulfinoalanine decarboxylase (forming hypotaurine) and hypotaurine dehydrogenase (forming taurine) [2]. The second one is the transsulfuration pathway, which converts homocysteine into cystathionine by cystathionine β-synthase; then cystathionine is converted to cysteine by cystathionine gamma-lyase, which enters the first synthesis pathway again [3]. The third source of taurine is coenzyme A degradating end product, which is cysteamine. It is oxidated to hypotaurine by 2-aminoethanethiol dioxygenase, and it also enters into the first synthesis pathway [4]. Taurine is not incorporated into protein and degraded in body. Taurine metabolites in body are generally conjugated derivatives with bile acid by its intermediate metabolite of *N*-acyltaurine in liver [5]. N-acyl-taurine is catalyzed into taurine conjugation of bile acid by bile acid-coenzyme A:amino acid N-acyltransferase. Furthermore, taurine also participates in metabolisms of exogenous substances by conjunction (e.g. two peroxisome proliferator-activated receptors agonists) [6]. In skeletal muscle, N-acyl-taurine is the only

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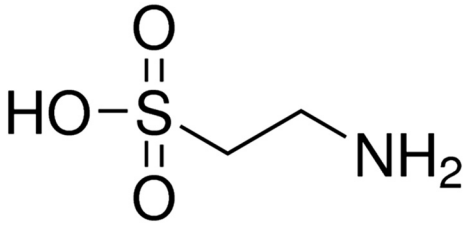

**Fig. 1.** Chemical structure of taurine.

metabolite of taurine by conjugating with acetate through an unknown enzyme catalytic process [7].

#### 1.1.2. Biological function of taurine

It has been proved that taurine is distributed almost in every tissue of animals and it exhibits many biological functions including bile salt conjugation, osmoregulation, membrane stabilization, calcium modulation, anti-oxidation and immunomodulation [8]. For some animals (e.g. felines and foxes) which are unable to synthesize taurine or other animals with more intrinsic depletion, taurine shortage can directly induce cardiomyopathy, retinal degeneration and reproduction defects [9,10]. A growing number of reports showed that taurine has different biological effects in different systems or organs (e.g. cardiovascular system [11], skeletal muscle [12], retina [13], liver [5], kidney [14], and the nervous system [15]). First, it is well known that taurine can conjugate with bile acids in liver, thus contributing to normal bile excretion [5]. Another study reported that taurine can conjugate tRNA of mitochondria, thus promoting protein translations in mitochondrial network without being incorporated into protein [16]. In skeletal muscle, taurine can promote calcium ion dependent excitation-contraction, regulate cellular volume, keep antioxidant defense to maintain normal skeletal muscle function [12] and improve skeletal muscle differentiation and growth [17]. In cardiovascular system, taurine can mitigate atherosclerosis and coronary heart diseases by reducing the apolipoprotein B100 level or improving the effectiveness of cardiac contractions [18]. Taurine can ameliorate congestive heart failure by increasing the force of cardiac muscle contraction [11]. Recently, a meta-analysis suggested that taurine has antihypertensive effects in human [19]. In addition, taurine keeps normal kidney function by regulating osmolyte, cell cycle and apoptosis [14]. Taurine is also known for its application in eye health-care. It is vital to maintain normal retinal development [20] and function that may be associated with regulating calcium ion balance and inhibiting protein phosphorylation signal [13]. Furthermore, taurine supplement can prevent against some common diseases (e.g. obesity [8], diabetes and metabolic syndrome [21]).

In contrast to the mentioned effects, the role of taurine in brain (especial cognitive function) arouses more attention. Earlier, taurine was found to be abundant in all brain regions, especially in the developmental stage [22]. In adults, only the olfactory bulb has high levels, which is also the place preserving neurogenesis [23]. Thus, taurine is often considered as a trophic factor for brain development, promoting proliferation of brain cells and protecting damages induced by toxic agents [24]. Its administration can also attenuate various nervous system disorders [15], including Alzheimer's disease (AD), Parkinson's (PD), Huntington's diseases, etc. In nervous system, due to the lack of certain receptors, taurine often plays physiological roles through three target receptors: GABA receptors, glycine receptors and *N*-methyl-D-aspartate (NMDA) receptors [25]. On cell level, taurine primarily regulates cell volume as an osmoregulatory factor, attenuates electrical signals and hyperpolarizes neurons by increasing influx of chloride ions [26] and preventing mitochondria dysfunction [27]. Further researches indicated that taurine or its analogues could induce the long-term potential in hippopotamus cells. Del Olmo N et al. first found that taurine administration induced long lasting potentiation in hippopotamus synapsis through its uptakes by uncertain taurine transporters [28]. Besides, it was proved that the taurine transporter substrate guanidinoethyl sulfonate induces mimic taurine action with the conversion of a decremental long-term synaptic potentiation (LTP) into a perdurable late-LTP [29]. The latter two effects provided evidences for the effect of taurine promoting cognitive function. Thus, cognitive effects have become a hot topic in the study of applications of taurine in nervous system. Thus far, taurine has been commonly used as a marker to reflect various cognitive impairments in the published data (Table 1), of which only a part underwent in-depth studies and mechanism discussions.

### 1.2. Taurine transporters

#### 1.2.1. Distribution of taurine transporters

To play physiological roles, taurine should be carried across the plasma membrane by taurine transporters. Two typical taurine transporters (TauT) have been verified. Solute carrier family 6 membrane 6 (SLC6A6, also named as TauT) is the most investigated taurine transporter, requiring a special ratio of sodium ion/chloride ion/taurine (2:1:1) [30]. This transporter is widely distributed in numerous organs (e.g. placenta and skeletal muscle [31], thyroid, heart, lung, brain, liver, kidney, gut, osteoblast) [32]. Another taurine transporter is proton-dependent carrier (PAT1), which is able to transporting other substrates (e.g. betaine, glycine, GABA, proline) [33]. PAT1 is

**Table 1**
Taurine changes in cognitive impairments.

| | Subjects of studies | Taurine changes | Mechanism |
|---|---|---|---|
| Human | Offspring of obese women | Possible taurine in fetus?↓ [62] | Taurine transporter activities↓ in placenta |
| | Preterm babies | Plasma taurine levels↓ [63] | Taurine shortage |
| | Children of obstructive sleep apnea | Urine taurine levels↓ [64] | Neurotoxicity and dysfunction |
| | Aged persons | Saliva taurine levels↓ [65] | Uncertainty |
| | AD patients | Taurine levels↓ in plasma [66], saliva [67], brain [68] and CSF [69] | Neurochemistrical pathology |
| | Succinic semialdehyde dehydrogenase deficiency | Taurine levels in CSF↑ [70] | Disruption of GABA homeostasis |
| Animal | Aging model | Brain taurine levels↑ [71] | Uncertainty |
| | AD model | Brain taurine levels↑ [72]; Brain taurine levels↓ [73,74] | Neurochemistrical pathology |
| | Diabetes model | Brain taurine levels [75–77]↑; Brain taurine levels [78]↓ | GABA A subunit and BDNF dysfunction ; inflammation |
| | Alcohol | Taurine levels in thalamus↓ [79] | Alcoholism |
| | Duchenne muscular dystrophy | Prefrontal taurine levels in↑ [80] | Lack of dystrophin |
| | Epileptogenesis model | Taurine levels in brain↓ [81] | Antiepileptogenic system↓ |
| | Iron deficiency | Taurine levels↑ [82] in perinatal period and↓ [83] in fetus and neonate | Underdeveloped hippopotamus |
| | Huntington's disease model | Taurine levels in striatum ↓ [84] | 128 CAG repeats |

AD: Alzheimer's disease; CSF: cerebrospinal fluid.

identified in different organs (e.g. gut, heart, skeletal muscle, liver, kidney, placenta, lung, brain, stomach, spleen and testis). Besides, other carriers may be involved in transporting taurine. It was found that GABA transporters in kidney can also accept taurine as the substance for transporting [34]. However, the process and mechanism remain unclear. Other potable transporters, including P-glycoprotein [35] and cytochrome P450 (CYP) 2D6 [36], which are associated with the elimination of brain taurine, also regulate taurine flowing into or out of brain. However, the mechanisms need further studies.

#### 1.2.2. Relationship between the taurine level and taurine transporters

Taurine balance in physiological state is affected by dietary intake, cellular synthesis and the regulation of taurine transporters. In body, the relationship between taurine levels determined by the former two factors and the status of taurine transporters (especially TauT) is more important for normal taurine functions. First, taurine transporters control relative balances of taurine contents in different body fluids. For instance, TauT controls the net flux of taurine from plasma into brain at blood brain barrier [37]. Therefore, it can maintain lower taurine concentration in brain (primarily inside brain cells [38]) than those in plasma [39]. Knockout of TauT causes decreased taurine levels and interrupted normal function in multiple organs due to impaired taurine transport and taurine depletion in a systemic summary [40]. Taurine depletion can also be induced by TauT inhibitor according to a recent report [41]. Thus, taurine supplement is needed to rectify abnormal physiological functions in these cases. For instance, taurine supplement to TauT knockout mice can correct striatal network activity which is associated with restored GABA effects [42].

In the meantime, mRNA levels, protein expressions and activities of TauT are also regulated by taurine levels. Several researches revealed that increased taurine levels down-regulate mRNA levels of TauT in astrocytes [43], activities of TauT in 3T3-L1 adipocytes [44] and both of them in hepatoblastoma HepG2 cells [45] in vivo. Besides, the activity, protein expression and nuclear localization of TauT were found to be down-regulated in mouse NIH3T3 fibroblasts following 24 h exposure to high extracellular taurine concentrations [46]. However, more comprehensive studies showed that taurine has bidirectional effects on mRNA levels, protein expressions or activities of TauT which are up-regulated by lower taurine levels and down-regulated by higher taurine levels. These effects have been observed in intestinal epithelial Caco-2 cells [47], corneal epithelial cells [48], renal LLC-PK1 cells [49] in vitro and the renal cortex in *Xenopus laevis* oocytes [50] in vivo. Another research [51] reported a shift of taurine transporting from release (synthesis in cell) to uptake in P2-fraction cells of rat brain with extracellular taurine concentrations varying from zero to 370 μmol/L. This suggested that intracellular taurine contents also affect transportation behaviors of taurine transporters. Under variations in physiological states (e.g. hypertonic condition in primary astrocytes [43] and in embryonic fibroblast cells [52]), increased taurine levels restored the elevated mRNA levels of TauT by hypertonicity treatment. However, the mechanism has been rarely revealed. In pathologies, taurine supplements up-regulate the decreased activities and protein expressions of TauT in the isoproterenol-induced myocardial injury model [53] and down-regulate increased protein expressions of taurine by inflammatory factor (tumor necrosis factor, TNF) [54]. The former process is related to the decreased ubiquitin-dependent proteasomal degradation of the tonicity-responsive element (TonE)/TonE-binding protein. Accordingly, taurine levels may play an important role in the balance of taurine transporters.

### 1.3. Cognitive function and cognitive impairment

Cognition is normal mental actions or processes for knowledge acquiring, understanding and thinking for acclimation. Degradation of cognitive function disturbs normal life, and it may even develop into dementia after a period of minimal symptoms. It was reported that the radio of cognitive impairment diagnosed aged over 65 years old is 14.9% [55]. The high prevalence may impose heavily social and family burdens and push the investigations of its pathological mechanisms and therapy methods. Thus far, the reason of cognitive impairment has still been unknown though its occurrence was usually attributed to several factors, including aging [56], diabetes [57], earlier AD, genetic diseases (e.g. Huntington's disease with CAG base repeats [58]) and other pathologies. Pharmaceutical treatment options [59] for dementia mostly focus on neurotransmitters including cholinesterase (AchE) inhibitors, NMDA receptor antagonists, serotonergic agents, dopamine blocking agents, and benzodiazepines. Recent studies indicated that taurine is able to ameliorate cognitive impairment. Beyond a neurotransmitter, taurine is a nutritional component (RedBull® beverage) in foodstuff which has been proved with a very safe levels of supplemental intake in normal healthy adults at 3 g per day [60]. Even, as the European Food Safety Authority acclaimed, no adverse effects [61] for up to 1 g per kg BW per day are ensured as a potential option for prevention and therapy of cognitive impairment. This review focuses on the role of taurine on cognitions in physiology, different pathologies of cognitive impairments and its anti-toxic experiments, as well as potential mechanisms.

## 2. Physiological role of taurine in cognitive function

### 2.1. The role of taurine in cognitive development before adulthood

It is well known that neural development is a critical base for individual cognitive ability. A noteworthy epidemiologic study [62] to determine the necessary of dietary taurine showed that lower plasma taurine levels are correlated with lower scores of Bayley mental development index (eighteen-month old) and Wechsler Intelligence Scale for children-revised arithmetic test (seven-year old) in preterm babies, reflecting cognitive abilities. Afterwards, Ditchfield AM found that obese women had lower activities of taurine transporters in placenta than those of controls [63]. In the meanwhile, maternal obesity under elevated levels of nutrients (fatty acids, glucose), hormones (leptin, insulin), and inflammatory factors was proved to increase the offspring's cognitive impairment [85]. Thus, taurine might be critical for cognitive developments in fetuses or babies. However, urinary taurine levels of 29 mentally retarded children were significantly higher than those of normal health children [86]. As the cognitive function was not assessed in the study, the relationship between taurine level and cognitive function is difficult to be built up because some mild mental retarded children can also learn reading to approximately the level of a normal child of nine to twelve [87]. In pediatric obstructive sleep apnea affecting cognitive developments [64], children accessed with cognitive impairment also showed lower taurine levels in urine.

In animal tests, the effects of taurine on the whole development of cognitive function exhibited time dependence. Arnold KE et al. found that higher taurine concentrations in milks of avian parents, after being supplied with high-taurine spiders, can induce much better cognitive functions in younger ages of their offspring compared with those of the control [88]. A contemporaneous animal experiment about the taurine treatments (0.4 g per kg BW per day) in four stage of pre-adult (lifelong, pre-weaning, post-weaning and control) [89] showed that mice only in the post-weaning group can learn the task much faster than controls. A noteworthy result in lifelong group was that there was a sensitive period between the perinatal to early postnatal period when taurine supplementation can retard learning in later life. However, no in-depth studies of the sensitive period have been conducted. Thus far, only Yoshida et al. [90], based on variations of the intracellular chloride ion concentrations in vitro, found the physiological effects of taurine with a transformation from excitatory to inhibitory. It was attributed to the target transformation of taurine action from glycine receptors to GABA A receptors throughout the postnatal stages. How taurine in holistic level affects cognitive development in perinatal stage should be

experimentally and clinically studied.

### 2.2. The effect of taurine on cognitive function of adult individuals

Though there were many reports about the protective role of taurine in cognitive functions of adults, limited epidemiological investigations have been published, most of which focused on the effects of taurine on aged persons and it will be discussed in the later part. This section focused on taurine effects in normal adult individuals. Thus far, there was only one acute study [91] which selected 48 habitual caffeine consumers (18 males, 30 females) but undergoing 24 h caffeine depriving and then receiving 2 g taurine per four separate days. After 60 min treatment, taurine administration can prolong choice reaction time but shorten the reaction time in the memory tasks. The result of better cognitive performances may be affected by habitual caffeine consuming. Therefore, diet complexity may affect the role of taurine in cognitive function, suggesting there is a certain degree of difficulty to clarify these processes and mechanism.

In animal experiments, different routes of administration produced complete opposite effects. Sajid I et al. found that taurine administration (0.1 g per kg BW) for one week by intraperitoneal injection can improve muscular strength and memory performance of rats in Morris water maze [92]. However, in another earlier research, [93] intracerebroventricular taurine treatment prolonged the time of escape latency, swim distance, and distance to zone compared with the saline-administered rats. It might be the result of higher taurine concentrations in the CSF by extraneous taurine treatments, which broke the balance of taurine concentrations between extracellular fluid and brain cells. The mechanism of the inhibited results has been unclear.

### 2.3. The role of taurine in cognitive function of aging

Cognitive impairment, an important index of aging, is often characterized by the disorder of neurotransmitter pathways (e.g. GABAergic [94] and NMDA [95]). Different neurotransmitters may reflect different phages of cognitive impairment. Data regarding the relationship between taurine and cognitive function in aged peoples were obtained through nutritional surveys and clinical studies. Taurine concentrations in human brains gradually decrease with age [96] and the variation exhibits sex differences. According to a recent study [97] of exploring cerebrospinal fluid metabolome by hydrophilic interaction liquid chromatography, elevated taurine levels in CSF of health elderly women were observed compared with no significant variations of taurine levels in health elderly men. Interesting, it had been reported that elderly women had a high onset risk of age-related cognitive decline and deterioration than those of elderly males [98]. Thus, the result showed that the taurine level in CSF might be a marker monitoring potable cognitive decline. Another research [65] showed that saliva of elderly adults with mild cognitive impairments contained lower taurine contents than those of health elderly adults, providing a convenient way to assure occurrence of cognitive impairment. Thus, it is very important to understand whether taurine supplement in diet could ameliorate cognitive impairment. An epidemiological investigation [99] according to dietary history showed that past taurine intakes in 40 elder persons were positively associated with some cognitive functions (e.g. abilities of judgement and abstract thinking). Latest clinical study [100] recruiting forty-eight elderly women showed that taurine supplementation (1.5 g) once a day for 14 weeks remarkably reduced inflammation (decreased ratio of the IL-1β/IL-1ra) and maintained better integrity of blood brain barrier except for cognitive improvement. However, exercise application can intensify the effect of taurine so as to ameliorate mental state. Small dose or short time in taurine supplement may be the potential reason of no effect. It is probably because inflammation (tumor necrosis factor alpha) might damage the efflux of taurine from brain at the blood-brain barrier by up-regulating taurine transporter expressions [101], a potential therapeutic target in inflammation. However, there were short of clinical studies about the accurate role of taurine transporters in aging-related cognitive dysfunction occurring and the mechanism.

Still, some studies based on aged animal models provided many evidences. Recently, Zhu M et al. found that the reduction of taurine levels with aging in mouse brains occurred after 27 months compared with decreased *N*-acetyl-aspartate levels after 18 months by an accurate method of $^{1}$H-MRS quantitation [71]. A noteworthy result in this study was that reduced taurine levels were well correlated with decreased hippocampal volumes, suggesting that reduced taurine levels in brains may be correlated with cognitive impairment though no human investigations have been published. Before that, aged animals supplied with taurine had exhibited cognitive improvements in some experiments. El Idrissi A et al. found that taurine supplement can block cognitive impairments of aged mice which may be associated with increased levels of the neurotransmitters GABA and glutamate as well as the up-regulation of GABA synthetase expression (glutamate decarboxylase, GAD) in brain [56]. Shen CH et al. also found that taurine helped down-regulate β 2/3 subunit expression in GABA A receptor and increased the number of somatostatin-positive neurons in hippocampus of the aged [102]. This suggests that inhibitory neurotransmitters (GABA and glutamate, which were assumed closely associated with cognition function [103]) are targets of taurine in improving cognitive functions of aged mice. Gebara E et al. found that taurine treatment can increase hippocampal neurogenesis of middle-aged mice by activating neural stem cells/intermediate neural progenitors, contributing to its effect of improving cognitive function [96]. However, the signal pathway was not illuminated. However, two other studies showed that taurine in rat hippocampal during aging is not the key factor because taurine contents in hippocampus were slightly decreased (no significance) in middle-aged rats [104] or stable in old rats [105] regardless of whether taurine was inadequate in the diet. However, a latest research [106], using D-galactose-induced cognitive impairment model of aged mice, indicated that taurine administration (0.1 g per kg BW per day) can prevent cognitive impairment, neuronal degenerating and nucleus shrinking in hippocampus dentate gyrus area. The key molecules reflecting neuronal degeneration (glial fibrillary acidic protein and the cluster of differentiation marker Cd11b) and oxidative damage (advanced glycation end-products) were down-regulated by taurine treatment, suggesting a potable mechanism of maintaining cognition in aging. This was because glial fibrillary acidic protein expression was also up-regulated in Braak stage of AD and can be as a follow-up marker in clinical cognitive impairment of AD [107], despite of its variations in aging dementia [108]. Nevertheless, it cannot be ruled out that too little taurine was not enough to maintain cognitive function in aged animal.

## 3. The roles of taurine in pathological cognitive impairments

### 3.1. Alzheimer's disease

#### 3.1.1. Variations of taurine levels in AD patients with cognitive

Alzheimer's disease refers to a chronic neurodegenerative disease accounting for 60–70% of cases of dementia [109]. It was demonstrated that taurine may be critical for diagnosis, prevention and therapy of AD. In the process of diagnosis, taurine levels in AD patients seemed to be of a lot differences according to published documents. It had been revealed that inconsistent results of taurine levels included several parts: plasma, brain regions and CSF in AD patients of different stages. In plasma, a previous study indicated lower plasma taurine levels compared with no variation of those in CSF occurring in AD patients [66]. The result was consistent with that of a study [67] which measured saliva metabolome and demonstrated decreased saliva taurine levels in dementia patients, providing a convenient way to screening early dementia evidences. However, latest research [110] verified that lower plasma taurine levels are closely associated with a greater risk of

incident dementia rather than AD. The insensitive variation of plasma taurine levels corresponding to AD suggested that the variation of plasma taurine levels did not accurately predict early AD occurrence. In brains of AD patients, significantly decreased taurine contents were firstly observed in special brain regions of postmortem studies: temporal cortex [68,111] compared with those of the control. Besides, in post-mortem brain samples of Down's syndrome with early genetic mental retardation similar to AD, taurine concentrations were not different from those of controls [112]. However, in AD patient biopsies of different phases, bidirectional variations of taurine levels were presented. First, Alom J et al. found that endogenous taurine contents in the CSF of AD patients were significantly reduced, suggesting a pathologic shift of balance occurring in neuronal environment. Csernansky JG et al. also found that taurine concentrations in CSF decreased in more advanced symptoms of AD [113]. However, another clinical investigation [114] launched in 14 patients with early stage probable AD and 17 age-matched controls showed that the ratio of plasma taurine and the product of the plasma levels of methionine and serine was significantly increased in early AD patients. However, plasma taurine levels were not significantly different from those of the health control, suggesting that early AD only exhibits imbalance in the metabolism of sulfur amino acid though the variation is not significant correlation with behavioral symptomatology. Even, taurine levels in CSF were correlated negatively with depression and behavioral disturbances in 202 patients of probable AD as a recent survey [69] described. These results showed that in early AD patients, higher taurine levels may play a protective role in nervous function, in which dementia subtype analysis was an important evidence. Thus, the variation of taurine levels in AD patients in nervous system may clinically predict different stages of pathology. In other words, the metabolic state of taurine in periphery or nervous system may be indexes (e.g. metabolic enzyme or its levels) reflecting cognitive function. In addition, taurine had been used for adjunctive therapy in AD patients in a recent clinical experiment [115], in which taurine administration (0.175 g, three times per day) could exert effective actions in reducing β-amyloid (Aβ) (1–42) content and improving cognitive function based on Borrelia Burgdorferi, which was almost of no effect alone. Thus, the clinical intervention of taurine may be a valuable option for AD prevention in future.

#### 3.1.2. AD animal model

Since AD is most primarily responsible for dementia events, many AD animal models were also used to explore how taurine affected AD development. First, the variation of taurine concentration in brain reflected potable pathological progress of AD. However, in different AD models, results about taurine concentrations were inconsistent. A previous research [72] showed that in different brain regions of an AD mouse model by the single-transgene of Aβ PPswe Tg2576, increased taurine concentrations in hippocampus and other three brain regions (rhinal cortex, midbrain, and cerebellum) were detected in six-month age compared with those of health mice. In contrast, other neurotransmitters decreased earlier including glutamate and *N*-acetyl aspartate (NAA) in one-month age and glutamate, NAA, myo-inositol, creatine, phosphocholine, GABA in three-month age. The result may suggest that taurine disorder was more possibly associated cognitive impairments of transgenic AD mice because the decline of cognitive function in this AD model occurred usually in six-month age, too [116]. However, animals of other AD models did not take on similar changes of taurine concentrations in brains. In a latest research [117], declined memory functions in $APP_{swe} \times PS1_{\Delta e9}$ transgenic AD mice were observed in 12 months of age. No significant variation of taurine contents in brain revealed that this AD model may not utterly duplicate what has just happened in AD patients. Moreover, aging also induced key effects on apparent characteristics in this AD model. Even, some reports showed decreased taurine concentrations in brains of AD animals. Salek RM et al. found that decreased taurine levels in cortex, frontal cortex, cerebellum, olfactory bulb, pons, midbrain and striatum of TgCRND8 transgenic mice in 2–3 months of age [73]. In a recent study, rats of AD model at eight weeks after being injected with Aβ 25–35 solution into bilateral hippocampus had impaired spatial learning and memory functions [74]. Taurine levels in hippopotamus were decreased together with Aβ formation and tau phosphorylation. The data suggested that taurine may be a selective marker in investigating AD pathology using various animal models and would possibly be helpful for accessing the accuracy of AD models.

Given the close association of taurine levels with AD pathology and cognition, exogenous administration of taurine will have direct effects on cognition. In APP/PS1 transgenic mouse model, cognitive impairments were rescued after six-week taurine treatment [118]. The amount of insoluble Aβ fraction was decreased as well. But the mechanism was not explored. Recently, two researches focused on Aβ polymerizing as one target of taurine acting. Jang H et al. found that taurine may intervene in the process of Aβ monomers aggregating into neurotoxic soluble oligomeric Aβ by binding oligomeric Aβ, which might explain why it ameliorated cognitive impairments in APP/PS1 transgenic AD mice [119]. However, taurine did not change the levels of Aβ plaques and oligomeric Aβ in the study, possibly just as an osmolyte interacting with Aβ. Alike, taurine-carbohydrate derivative was also designed to explore better the fibrillogenesis of Aβ in another study [120]. However, the mechanism of taurine improving cognitive function of AD animal should be more than its direct interaction with Aβ so that the signal pathway should be considered in the subsequent studies. From the functional perspective, activated protein kinase A (PKA) and phosphorylated cyclic Adenosine monophosphate response element-binding protein (pCREB) may be potential pathways for inducing synaptic potentiation and late phase LTP [28]. Furthermore, other mechanisms also need exploration to ascertain the way of taurine effecting AD cognition (e.g. tau protein abnormalities) [121].

### 3.2. STZ-induced cognitive impairment

There are two kinds of animal models of cognitive impairment by STZ administrations: intracerebroventricular pathway and periphery diabetes model. Javed H et al. used dementia model of Alzheimer's type induced by intracerebroventricular streptozotocin treatment to explore the effect of taurine in preventing cognitive impairment [122]. It was shown that the rats pre-treated with taurine (0.05 g per kg BW) for 15 days could bear streptozotocin challenge and fight deteriorations of cognitive functions and neurobehavioral activities. The up-regulated activities of antioxidant enzymes (glutathione peroxidase, glutathione reductase, glutathione-S-transferase, catalase, and superoxide dismutase) and improved acetylcholine levels by increased activities of AchE and decreased expressions of choline acetyltransferase in hippocampus played important roles in neuroprotections of taurine. A recent study [123] showed that taurine treatments (0.04 , 0.06 , 0.12 g per kg BW per day) following STZ administration remarkably ameliorate cognitive impairment by mitigating inflammation (e.g. decreased levels of TNF-α, IL-1β and reduced neuron apoptosis of brain) and down-regulating expression of rho kinase-II protein more than modulating oxidative stress.

The other model of cognitive impairment by STZ is diabetes. It was verified that the process of diabetes development is often associated with cognitive impairments, and taurine seemed playing certain roles. Studies showed that taurine concentrations in special regions of brain (e.g. hippopotamus) were increased whether in type 2 diabetes db/db mice [75] or STZ-induced type 1 diabetic model [76] with cognitive decline. In low-capacity runner (LCR) rats and high-capacity runner (HCR) rats models derived from genetically heterogeneous stock rats after artificial selection according to low and high capacity in treadmill, increased taurine levels in LCR rats simulating aged diabetes or early AD were also observed in brain [77]. However, a previous experiment achieved an opposite result that hyperglycemia reduced brain taurine levels of STZ-induced young diabetic rats [78]. More researches and

further clinical investigations are required to uncover the pathological differences. In taurine interventions in cognitive dysfunction of diabetes, animal trials were under way. Greice Caletti et al. found that taurine treatment significantly improved short-term memories when they investigated the antidepressant effect of taurine in STZ-induced diabetes rats [124]. In this study, restored mRNA levels of α2 subunit in GABA A receptor and brain derived neurotrophic factor (BDNF) in hippocampi of diabetic rats following taurine intraperitoneal treatment (0.1 g/kg) for 30 days were considered as the potential targets of taurine. In another study, taurine intraperitoneal treatment (0.1 g per kg BW) for 30 days can attenuate cognitive impairments in STZ-induced diabetes rats. Better performance in behavioral and memory tasks may be due to reduced neuronal apoptosis and less loss of glial cells, compared to those in diabetes rats [125]. The possible mechanism was also related to restored redox balance and inflammatory balance, which may further result in cognitive dysfunction in hippocampus according to a latest research [126]. Anyhow, it was urgent to develop human epidemiological surveys and nutrition experiments of taurine in diabetes patients to improve cognitive function and life quality in future.

### 3.3. Ischemia model of cognitive impairment

In animal models of ischemia induced cognitive impairment, a carotid artery stenosis created by ligating the common carotid artery and then removing the operation was demonstrated to cause cognitive impairment [127]. The study showed remarkable lower cognitive scores of P300 latency and escape latency in the Morris water maze in rat model. Taurine treatment after stenosis removing can recover cognitive function, partly due to improved oxidative stress (malondialdehyde, superoxide dismutase and catalase) and inflammatory reaction (IL-1β and tumor necrosis factor). However, in the study, the taurine content in CFS was not measured and the mechanism of action was not explored. Besides, hypoxia was often the concomitant pathological event in the ischemia process, and it could aggravate neural damage and cognitive impairment. Malcangio M et al. found that survival time of mice after hypoxia was significantly prolonged by taurine treatment [128]. However, hypoxia was a complex pathological process with many mechanisms. Accordingly, how taurine affected cognitive function in hypoxia circumstance needs more studies.

### 3.4. Stress-induced cognitive decline

Different stresses in the course of life affect development and function of cognitive ability. It was proved that taurine treatment could ameliorate cognitive impairments in animal stress experiments. In gestation, taurine administration can significantly repair the cognitive impairments of juvenile rats after prenatal restraint stress [129]. In the stress, increased reactive oxygen species, up-regulated apoptosis and reductions of mitochondrial membrane potential, adenosine triphosphate and cytochrome *c* oxidase occurred in hippopotamus. Taurine administration restored these indexes through activating Akt/CREB/peroxisome proliferator-activated receptor-γ coactivator-1α (PGC1α). Activated PGC1α meant that mitochondria function and oxidative balance are well maintained. Recently, Sun Q et al. further confirmed that the protective effect of taurine against oxidative damage is attributed to up-regulated expressions of phosphorylated extracellular regulated protein kinases (ERK) and the nuclear translocation of nuclear factor (erythroid 2-derived)-like 2 (Nrf2) in corticosterone-induced stress model of oxidative damage in vitro [130]. In neonatal lactation period, taurine administration in vitro can increase electrophysiological input-output curves in hippocampal CA1 of adulthood after mild neonatal stressors treatment. So, it is necessary to supply taurine as early as possible to modify hippocampus function [131]. However, the effect of taurine on neonatal cognitive function has not been investigated. In late adolescent rats, taurine treatment (intraperitoneally 0.2 g and 0.5 g per kg BW per day) for 35 days can suppress cognitive impairment in chronic unpredictable mild stress-induced depression [132]. Enhanced hypothalamic-pituitary-adrenal axis was responsible for the effect. However, the epidemiological investigation and clinical experiment concerned as well as the mechanism that taurine affected cognitive function in stresses from gestation to adolescent were lack.

### 3.5. Mental disorder related cognitive impairment

Patients of mental disorders significant have many symptoms of distress or impairment of personal functioning. Cognitive impairment is a severe development result of mental disorder, further disturbing individual life and work. Taurine has been used to ameliorate cognitive disorder, in an attempt to prevent different mental disorders. In a randomized double-blind clinical study [133], patients with first-episode psychosis took taurine (4 g per day) for 12 weeks as an adjunctive therapy of antipsychotic medication. The symptoms of schizophrenia were significantly mitigated by taurine treatment, whereas composite cognitive scores were not increased. Even so, Omura Y et al. still assumed that optimal doses of taurine administration in onset of autism symptoms could significantly restore memory disturbances [134]. More clinical investigations are needed to explain the differences and detailed mechanisms for taurine applications.

### 3.6. Genetic diseases

Genetic diseases impairing cognitive function can be present with developmental progresses from moderate to severe intellectual disabilities. Genetic diseases inducing cognitive deficit contain kinds of diseases (e.g. AD [135], PD [136], Huntington's Disease [137], Down syndrome [138] and other diseases). Even in the same disease, different types of gene variations have been ascertained (AD [135] and PD [136]). The role of taurine in AD has been discussed above. This part mainly reviews the role of taurine in fragile x syndrome, succinic semialdehyde dehydrogenase deficiency and Angelman syndrome based on the present data. Bidirectional variations of taurine levels in different genetic diseases were observed in Table 1. A small amount of studies about taurine interventions were conducted. In animal model of FVB/NJ Fragile X knocking out, taurine treatment (intraperitoneally 0.05 g per liter) for over 4 weeks significantly restored the emotional learning and memory profiles to normal levels. The time of memory retention had been prolonged [139]. The effect of taurine was deemed to be related to increased activities of GABAergic neurons. However, another autosomal genetic disease, succinic semialdehyde dehydrogenase deficiency has symptoms of language deficit and intellectual disability, which is also related to disruption of GABA homeostasis. Cognitive impairment was not recovered by taurine administration [140] possibly because patients with elevated taurine levels of CSF in the disease [70] needed no more supplements. In addition, a rare neurodevelopmental disease, Angelman syndrome, can cause intellectual disabilities and absences of speech and ataxia. Taurine supplement can significantly improve learning skills in *Ube3a*$^{m-/p+}$ transgenetic mice [141]. Restored post-synaptic density-95 expressions and elevated pERK1/2-ERK1/2 ratios indicated that rectified synapsis function and activated cell proliferation signal accounted for the result. Therefore, in different genetic diseases, the inconsistent results and mechanisms still needed wide explorations in future.

## 4. Effects of taurine on cognitive impairments resulting from toxicities of pharmaceuticals and toxic substances

In the process of using clinical drugs, side effects often occurred. Some of them caused cognitive impairment, thereby affecting normal life of patients. Thus, it is significant to study how to avoid the potable cognitive dysfunction in therapy. Bhupinder P.S. Vohra had earlier found that taurine extracted from *Pegasus laternarius Cuvier* protected

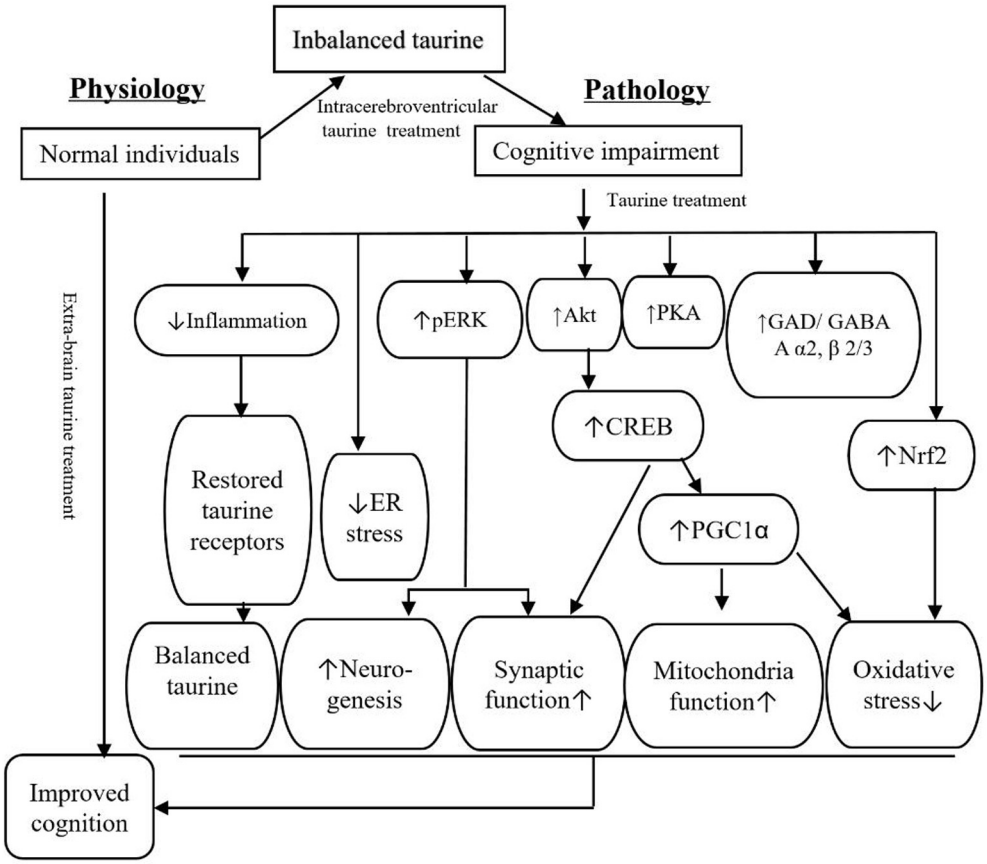


**Fig. 2.** Schematic mechanisms of taurine affecting cognition in physiologies and pathologies. Proposed mechanism includes anti-inflammation/balanced taurine, ameliorated ER stress and raises of pERK/PGC-1α/(neurogenesis and synaptic function), Akt/(synapsis mitochondria and anti-oxidation), Nrf2/anti-oxidation, PKA and GAD/GABA α2, β2/3 subunits. Akt: Protein kinase B; GABA: γ-aminobutyric acid; GAD: glutamate decarboxylase; ER: endoplasmic reticulum; pERK: phosphorylated extracellular regulated protein kinase; Nrf2: nuclear factor (erythroid 2-derived)-like 2; PGC-1α: PKA: protein kinase A; PGC-1α: peroxisome proliferator-activated receptor-γ coactivator-1α.

mice from memory impairments caused by four pharmaceuticals including alcohol, pentobarbital, cycloheximide, and sodium nitrite at three doses of 0.01 g, 0.02 g, 0.04 g per kg BW for either 10 days or 30 days [142]. In these pharmaceuticals, alcohol should be paid special attention because alcohol is also an important beverages component in everyday life. Decreased taurine concentrations in the thalamus were associated with cognitive impairments in ethanol fed mice according to an article [79]. A recent research [143] further showed that taurine supplementation to mothers consuming alcohol protected learning and memory impairments in offspring mice. However, if given after birth, the effects of taurine did not exist, hinting that the protecting role of taurine in neural development was timely. Likewise, isoflurane, a usual anesthetic, had a high toxic effect of cognitive deficits in the elderly. Zhang Y et al. found that if taurine administration before isoflurane exposure, the spatial memory impairment of experimental aged rats can be prevented. Endoplasmic reticulum (ER) stress and apoptosis which were the potential reason of cognitive deficits were also suppressed by taurine pretreatment [144].

Besides, taurine administration also ameliorated cognitive deficits caused by different environmental toxins. An inflame retardant of hexabromocyclododecanes can disrupt endocrine system and neural development, further undermining cognitive function. Taurine treatment, by up-regulating protein expressions of BDNF and nerve growth factor, significantly ameliorates cognitive deficits of developmental rats suffering from hexabromocyclododecanes [145]. This suggests the key role of taurine in neural development. Heavy mental pollution in environment also impaired neural cognition. In animal model of metallic poisoning, it is preliminarily revealed that taurine is vital to protect neural system and cognition function. For instance, taurine supplement by activating GABA A receptor and NMDA receptor can recover learning impairment in rats under lead exposures [146]. In the meantime, taurine treatment can also ameliorate impaired LTP and depotentiation (DP) in dentate gyrus of rat hippocampus [147], which accounts much for learning and memory. Moreover, taurine can ameliorate impaired spatial learning and memory ability of rats caused by manganese exposure [148]. Restored activities of AchE and choline acetyltransferase are critical for the effect. Up-regulated expression of taurine transporter in manganese exposure [149] suggests that nervous system may need more taurine to pass through blood brain barrier to maintain normal cognitive function.

## 5. Conclusion

Taurine is one of most abundant functional amino acids. Its physiological roles associated with cognitive impairment are being gradually unfolded due to abnormal fluctuations in plasma and brain of cognitive pathologies (Table 1). Clinical pathological studies suggested that increases of taurine levels might indicate onset phage of cognitive impairment [114] and decreases of its levels were negatively associated with occurrence of cognitive impairment [68,110,111], which helps diagnose and understand the optimal time for treatments. Imbalanced distribution of taurine in blood, CSF and brain cells may induce cognitive pathologies. Physiologically, taurine administration can boost cognitive development except for retarding effect in the sensitive period between the perinatal to early postnatal period [89]. The transformation of acting targets from excitatory glycine receptors to inhibitory GABA A receptors was proven as an alternative mechanism [90]. In adult rats, abnormal elevated levels in CSF by exogenous taurine administration induced cognitive impairment with an unclaimed mechanism [93]. Besides, expressions of taurine transporters regulated by some factors (e.g. inflammation) also remarkably affected taurine balance. For instance, the taurine transporter activating substance (guanidinoethyl sulfonate) could induce perdurable late-LTP in synaptic plasticity [29]. Pathologically, taurine supplement can mitigate cognitive impairments in pathologies and models: aging [102], AD model, STZ-induced diabetes [123–125] and brain damage [122,123],

ischemia model [127,128], stress model [129,132], mental disorder [133,134], genetic diseases [139,141] and cognitive injuries of pharmaceuticals and toxins [142–144,146–149]. The effects involved various mechanisms: restored expressions of taurine transporters by restoring GABA A receptors subunits following mitigating neuroinflammation [101]; up-regulated expression of taurine transporter for taurine efflux [149]; up-regulated Nrf2 expression and antioxidant capacities [130]; activated Akt/CREB/PGC1α enhancing mitochondria biogenesis, reducing oxidative stress and enhanced synaptic function by CREB [129]; increased neurogenesis and synaptic function by pERK [28] (Fig. 2). In addition, activated PKA [28], restored GABA synthesis [56] and receptors [102], and mitigated ER stress/apoptosis [144] were also important pathways for taurine to ameliorate cognitive impairment.

However, there were some potential interactions among these pathways and other potential pathways according to present studies. For example, taurine transporter knockout could induce sensitivities of extrasynaptic GABA A receptors [42] and the importance of this connection in cognition need to be assessed. Thus, more and more accurate mechanisms need to be further explored. Moreover, the effects of taurine on other pathologies of cognitive impairments (e.g. vascular cognitive impairment, the second most common type of dementia apart from AD [150] and some pathologies of cognitive impairment) (Table 1) have not been reported thus far. In particular, clinical trials are more important. Accordingly, there is a long way to go before ascertaining these pathological processes and more broad mechanisms.

## Abbreviations

| | |
|---|---|
| Aβ | β-amyloid |
| AchE | cholinesterase |
| AD | Alzheimer's disease |
| Akt | Protein kinase B |
| BDNF | brain derived neurotrophic factor |
| CSF | cerebrospinal fluid |
| CYP | cytochrome P450 |
| ER | endoplasmic reticulum |
| ERK | extracellular regulated protein kinase |
| GABA | γ-aminobutyric acid |
| GAD | glutamate decarboxylase |
| HCR | high-capacity runner |
| LCR | low-capacity runner |
| NAA | *N*-acetylaspartate |
| NMDA | *N*-methyl-D-aspartate |
| Nrf2 | nuclear factor (erythroid 2-derived)-like 2 |
| PAT1 | proton-dependent carrier |
| PD | Parkinson's |
| PGC-1α | peroxisome proliferator-activated receptor-γ coactivator-1α |
| PKA | protein kinase A |
| pCREB | phosphorylated cyclic adenosine monophosphate response element-binding protein |
| SLC6A6 | Solute carrier family 6 membrane 6 |
| STZ | streptozotocin |
| TauT | taurine transporter |
| TNF | tumor necrosis factor |
| TonE | tonicity-responsive element |

## Authors' contributions

Chaoran Chen and Shufang Xia contributed equally to this work. Zhenxing Xie designed the topic and others collected data of the latest.

## Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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