



Review

Expedition into Taurine Biology: Structural Insights and Therapeutic Perspective of Taurine in Neurodegenerative Diseases

Mujtaba Aamir Bhat ^{1,†}, Khurshid Ahmad ^{2,†} , Mohd Sajjad Ahmad Khan ³,
Mudasir Ahmad Bhat ¹, Ahmad Almatroudi ⁴ , Safikur Rahman ^{5,*} and Arif Tasleem Jan ^{1,*}

¹ School of Biosciences and Biotechnology, Baba Ghulam Shah Badshah University, Rajouri 185234, India; mujtaba868@gmail.com (M.A.B.); bhatmudasirrashid@gmail.com (M.A.B.)

² Department of Medical Biotechnology, Yeungnam University, Gyeongsan 38541, Korea; ahmadkhursheed2008@gmail.com

³ Department of Basic Sciences, Imam Abdulrahman Bin Faisal University, Dammam 31451, Saudi Arabia; khanmsa@hotmail.com

⁴ Department of Medical Laboratories, College of Applied Medical Sciences, Qassim University, Qassim 51431, Saudi Arabia; aamtrody@qu.edu.sa

⁵ Munshi Singh College, BR Ambedkar Bihar University, Muzaffarpur, Bihar 845401, India

* Correspondence: shafique2@gmail.com (S.R.); atasleem@bgsbu.ac.in (A.T.J.)

† Authors contributed equally to this work.

Received: 29 February 2020; Accepted: 2 June 2020; Published: 5 June 2020



Abstract: Neurodegenerative diseases (NDs) are characterized by the accumulation of misfolded proteins. The hallmarks of protein aggregation in NDs proceed with impairment in the mitochondrial function, besides causing an enhancement in endoplasmic reticulum (ER) stress, neuroinflammation and synaptic loss. As accumulation of misfolded proteins hampers normal neuronal functions, it triggers ER stress, which leads to the activation of downstream effectors formulating events along the signaling cascade—referred to as unfolded protein response (UPRER)—thereby controlling cellular gene expression. The absence of disease-modifying therapeutic targets in different NDs, and the exponential increase in the number of cases, makes it critical to explore new approaches to treating these devastating diseases. In one such approach, osmolytes (low molecular weight substances), such as taurine have been found to promote protein folding under stress conditions, thereby averting aggregation of the misfolded proteins. Maintaining the structural integrity of the protein, taurine-mediated resumption of protein folding prompts a shift in folding homeostasis more towards functionality than towards aggregation and degradation. Together, taurine enacts protection in NDs by causing misfolded proteins to refold, so as to regain their stability and functionality. The present study provides recent and useful insights into understanding the progression of NDs, besides summarizing the genetics of NDs in correlation with mitochondrial dysfunction, ER stress, neuroinflammation and synaptic loss. It also highlights the structural and functional aspects of taurine in imparting protection against the aggregation/misfolding of proteins, thereby shifting the focus more towards the development of effective therapeutic modules that could avert the development of NDs.

Keywords: aggregation; neurodegenerative diseases; osmolytes; protein folding; therapeutics; unfolded protein response

1. Introduction

The human brain is a complex organ of the human body, consisting of different cells, such as neurons, oligodendrocytes, microglia, astrocytes, etc., that work in a coordinated manner and regulate spatiotemporally. The underlying homeostasis network that regulates the complex architectural of the brain, being robust at the beginning (young age), shows a gradual decline in terms of functioning with age, thereby resulting in cognitive decline and, as such, development of a variety of neurodegenerative diseases (NDs) [1]. The lack, on the therapeutic front, of treatments for slowing the rate of occurrence of NDs, these often become devastating, not only for the patients and their families (for care and dependency), but often also leaving a deep scar in terms of the mounting economic burden. With huge socioeconomic constraints, the etiology of NDs [Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS) and others] has become a burning issue that needs properly addressing, not only in terms of understanding the disease mechanism, but also in terms of the advancement of developing potential treatment regimes that can control the progression of the NDs [2–7].

In view of the hallmarks of NDs, taurine displays a series of beneficial effects that appear promising in combating the menace of NDs. Of these, taurine stabilizes membrane proteins (and as such maintains their structural integrity [8–10]), reduces apoptosis by modulating neuroinflammatory responses [11,12], exerts antioxidant effects by reducing ischemic and traumatic insults [13,14], exerts neuromodulatory effects by acting as an agonist of GABA and glycine receptors [15], and improves different correlates of memory [16,17], thereby augmenting learning and memory process [18–20]. The absence of disease-modifying therapeutic targets in different NDs, and the exponential increase in the number of cases, makes it critical to explore new approaches to treating these devastating NDs. The present article contains recent and useful information pertaining to the etiology of NDs and factors that contribute to the development of NDs (in particular mitochondrial dysfunction, endoplasmic reticulum stress, neuroinflammation and synaptic loss, which progress to neuronal death), together with the biology of taurine, a major cellular osmoprotectant that overcomes the toxicity that arises due to aggregation of misfolded proteins. Taurine thereby imparts protection against oxidative stress, via regulation of protein folding/unfolding.

2. Neurodegeneration

The pattern of vulnerability that turns resilient neurons into susceptible ones differs among NDs. AD is a progressive form of ND that shows either familial (FAD; early onset) or sporadic (SAD; showing late onset) origin [3]. FAD accounts for 5% of AD cases, and arises predominantly due to mutations in the amyloid precursor protein (APP) and Presenilin 1 and 2 (PS1 and PS2) [21–26]. Mutations lead to the formation and thus accumulation of neurofibrillary tangles (tau tangles; hyperphosphorylated tau protein) and plaques of amyloid- β ($A\beta$) in and around neurons, causing synaptic impairment and neuronal death, which ultimately leads to cognitive alteration and behavioral changes [2,3,7,27–33]. However, late onset of AD (LOAD), accounting for 90% of Alzheimer's cases, is believed to have many risk factors associated particularly with ageing, genetic polymorphism at different gene loci (such as R47H mutation in Trem2), and the presence of ApoE4 allele [34,35]. PD has well-established, environmentally acquired and genetic risk factors associated with it. PD shows an early onset that arises due to mutations in Parkin (PARK2)- and PTEN-induced putative kinase (PINK1), while late onset PD arises due to mutations in α -synuclein (SCNA), ubiquitin C-terminal hydrolase L1 and leucine rich repeat kinase 2 (LRRK2) genes, leading to the formation of Lewy bodies (LBs; accumulation of α -synuclein and parkin substrate) [36–40]. Prion disease is caused by the misfolding of the prion proteins. With major contributions from sporadic types, 5–15% of cases show a genetic predisposition, with mutations in the prion protein gene (PRNP) located on chromosome 20 in humans [40]. Prions, being infective entities, are capable of triggering the refolding, and thus aggregation, of native proteins to oligomers and fibrils [41]. Misfolding of Cu/Zn superoxide dismutase (Cu/Zn SOD) is a characteristic

feature of both familial and sporadic form of ALS [42–44]. A highly conserved nuclear protein TDP43 encoded by the TARDBP gene also contributes significantly to the occurrence of ALS [3,45].

As a major hallmark of NDs, protein aggregation, and their accumulation in different parts of the central nervous system (CNS), hinders not only the synaptic transmission process, but also impairs mitochondrial function, along with enhancing endoplasmic reticulum (ER) stress [46,47] (Figure 1). The information on NDs in association with mitochondrial dysfunction, ER stress, neuroinflammation and synaptic loss that ultimately lead to neuronal death, are discussed with respect to their involvement in AD.

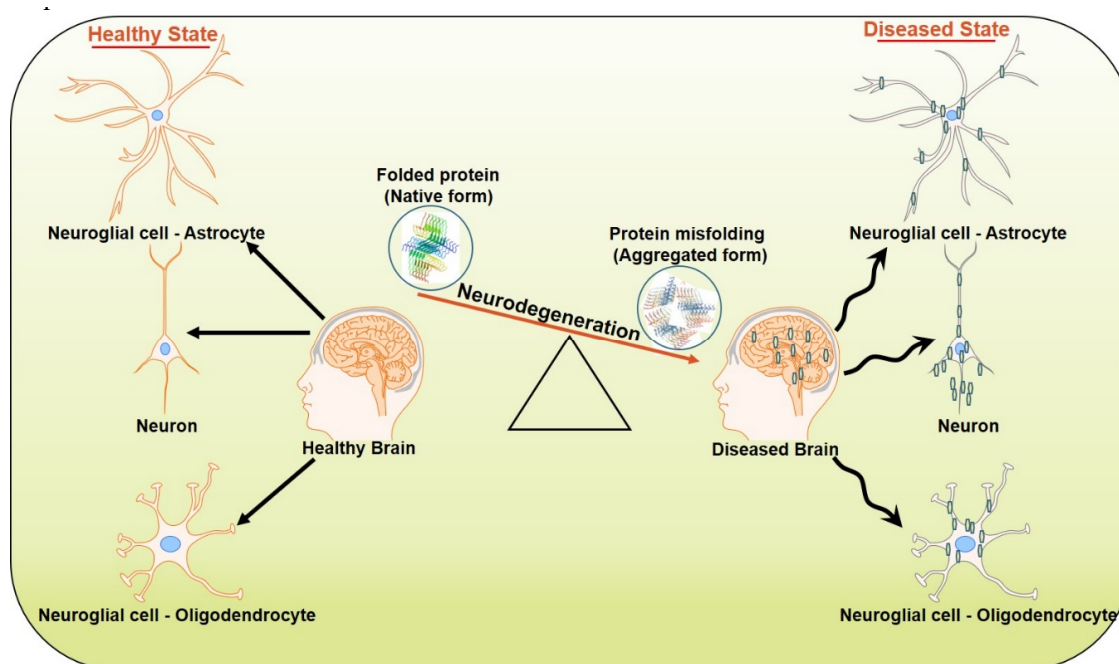


Figure 1. Progression of neurodegenerative diseases.

2.1. Mitochondrial Dysfunction

As a vital cellular organ, mitochondria are associated with the regulation of cellular metabolism. Performing vital functions, impairment of the enzymatic machinery, particularly of the tricarboxylic acid cycle, hampers the functions of the mitochondria processes and also affects the overall functionality of the cell. Acting as a source of energy, impairment of the mitochondrial enzymatic machinery has the consequences of reducing energy metabolism in the brain. Studies of mitochondrial functioning in the AD brain revealed a greater extent of impairment in the functioning of the pyruvate dehydrogenase and α -ketoglutarate dehydrogenase complexes, followed by isocitrate dehydrogenase [48,49]. Impairment in the mitochondrial enzymes, which leads to an imbalance in the energy status of brain, often has serious consequences for brain functioning (damage of neurons), and thereby for the development of neurodegeneration [50–52].

Increase in $A\beta$ aggregation and deposition leads to oxidative damage via the enhancement of the production of H_2O_2 [53]. $A\beta$ accumulation in the synaptic mitochondria leads to high levels of cyclophilin D [CypD; mitochondrial permeability transition pore (mPTP)], which causes significant changes in synaptic Ca^{2+} [54]. Translocation of CypD from the matrix to mPTP (CypD–mPTP) increases its interaction with adenine nucleotide translocase, resulting in the collapse of membrane potential via the opening of the pore, and thereby leads to the death of the neurons. Additionally, inhibition of the mitochondrial electron transport chain triggers the production of ROS (Reactive Oxygen Species), capable of damaging proteins, lipids and nucleic acids. Increased production of ROS acts as a trigger for autophagy, which subjects mitochondria to mitophagy [54,55] (Figure 2).

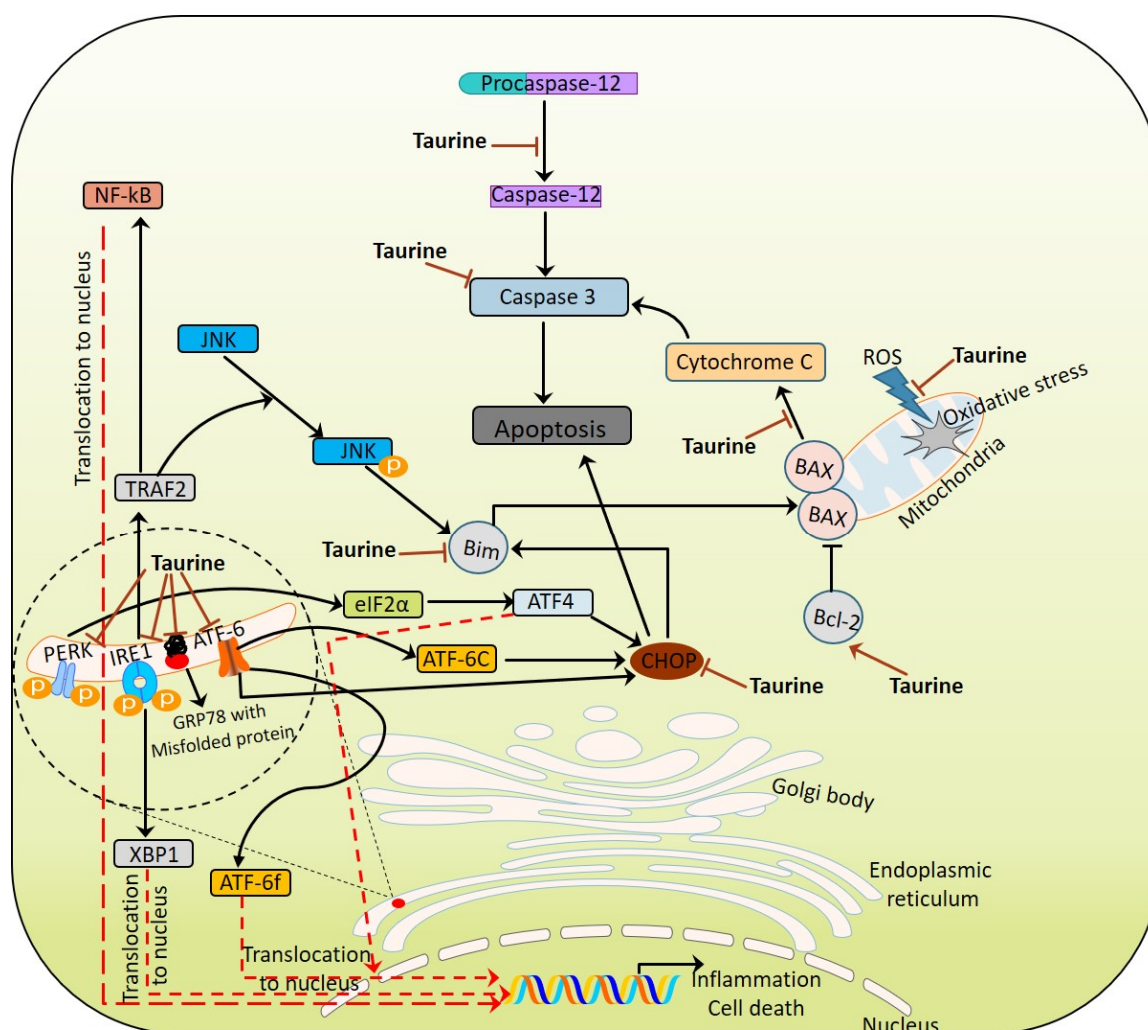


Figure 2. Taurine combatting Mitochondria—Endoplasmic Reticulum stress module.

2.2. ER Stress

As a vital cellular organ, ER is involved in the synthesis of proteins. Any disruption in the ER synthetic machinery causes unfolded or misfolded proteins to accumulate in the lumen of the ER [56,57]. The cell has a unique way of trafficking unfolded or misfolded proteins to the cytoplasm for degradation, in a process referred to as ER-associated protein degradation (ERAD) [58,59]. Saturation in the unfolded or misfolded protein trafficking machinery leads to ER stress, which elicits a dynamic signaling cascade referred to as unfolded protein response (UPR^{ER}) [4,5,60–63]. UPR^{ER} is mediated by three transmembrane proteins, inositol requiring enzymes-1 (IRE-1), PKR like ER kinase (PERK) and activating transcription factor-6 (ATF6), which act as stress sensors (triggers signaling downstream via transcription factors) in the ER [56,63,64]. In the normal state, the luminal domains of stress sensors remain bound with a chaperone, BiP (Binding immunoglobulin protein), thereby inhibiting activity at the surface of the cytosolic domain. During stress, BiP release brings about dimerization of IRE-1 and PERK, that together initiates signaling across the UPR signaling cascade [4,5,61,62]. In the UPR signaling cascade, PERK exerts an inhibitory effect on the eukaryotic translational initiation factor 2α (eIF2 α), causing rapid attenuation of the translational event [65]. At the same time, it favors the translation of ATF4 (Activating Transcription Factor-4), capable of controlling the expression of genes related to amino acid metabolism, autophagy and apoptosis [64,66–68]. Activation of IRE-1 halts the expression of genes associated with ER protein translocation, lipid synthesis and the folding of proteins, via the splicing of X-box binding protein-1 (XBP-1) [69]. The third transducer of UPR^{ER} , ATF6, upon

activation is translocated into the Golgi complex, and cleaved by site 1 protease and site 2 protease to release the active N terminus part, which is in turn involved in the upregulation of genes associated with normal ER functioning, such as XBP1, CHOP, etc. [64,66]. In the *Drosophila melanogaster*, AD model, the reduction of Ca^{2+} release from ER stores via *Xbp-1* over-expression imparts protection against $\text{A}\beta$ toxicity [70,71]. Together, initial UPR seems protective as it favors the expression of chaperons promoting refolding (degradation in the event of failing to bring about refolding), while prolonged stress conditions trigger additional pathways that in turn lead to cellular apoptosis [72].

2.3. Neuroinflammation.

Being multifaceted processes, NDs involve different cell types in the brain. Of them, microglia—implicated in the innate immunity of the brain—plays an important role in the progression of NDs, in particular AD [73,74]. Exhibiting a high expression of AD risk factor genes, microglia-mediated increases in proinflammatory cytokines have been reported both from patients with AD and from disease models of the disease, and has been found to contribute to neuronal cell death [75,76]. Activating NLRP3 inflammasome, the aggregation of $\text{A}\beta$ and α -syn (α -Synuclein) led to enhanced production of proinflammatory cytokines interleukin (IL)-1 β and IL-18 [77,78], the binding to neuronal receptors of which initiates a series of cytotoxic events, i.e., the aberrant influx of calcium and the activation of the JNK (c-Jun N-terminal kinase) signaling pathway [79,80]. Simultaneously, activation of the microglial NLRP3 inflammasome enhances $\text{A}\beta$ aggregation and its spread, thereby creating a feedback loop that exacerbates neuronal cell death [81]. Additionally, $\text{TNF}\alpha$ production by microglia potentiates neuronal excitotoxicity, which progresses to neuronal cell death via signaling through the death receptors expressed on neurons [82,83].

2.4. Synaptic Loss

Referring to the conjunction between the axon of one neuron and the dendritic spine of another neuron, synaptic plasticity (formation and elimination) in neuronal circuits maintains the structure-based long-term potentiation (LTP) essential in memory formation [84,85]. Of the different cell subsets, microglia (constituting 10–15% of brain cells) and astrocytes [major glial cells in the central nervous system (CNS)] provide trophic support to neurons, besides performing roles in the refinement and coordination (synaptogenesis; neurotransmitter release and synaptic transmission) of neural circuits [86–88]. In NDs, an accumulation of toxic protein aggregates at synapses causes synaptic dysfunction that often increases the vulnerability of neurons to becoming primed for removal [89–91]. Contributing to neural network formation, for shaping brain connectivity, glial subset cell populations (astrocytes and microglia) perform the pruning of weaker synapses in early development ([92–95] and references therein). Though several pathways—such as the fractalkine pathway, complement pathway, etc.—have been implicated in the synaptic elimination process [94,96,97], the pathological consequences of NDs are observed in response to internal glial defects (genetic mutations) or dysfunctional regulation in the execution of the pathways. It is now well established that astrocytes and microglia play important roles in refining synaptic connections (synaptic elimination) in the context of the development of different NDs. A major hypothetical mechanism involved is the activation of the complement system, preferably C3 and C1q, followed by their active deposition at synaptic terminals, thereby priming aberrant removal (synaptic elimination) [98–101]. In AD, the accumulation of $\text{A}\beta$ at synapses (excitatory) occurs even before its accumulation as plaques in the extracellular milieu, as reported in both mouse and human studies [102–104]. The accumulation of oligomeric $\text{A}\beta$ at synapses impairs LTP, which progresses with the weakening of the synapse and the induction of synaptotoxicity [105,106]. The effect of synaptic LTP impairment and synaptotoxicity were prevented on administration of C1q neutralizing antibodies, and even in the C1q knockout mouse model [100,107]. Additionally, microglia that lies close to $\text{A}\beta$ plaques, upregulating ApoE4 expression in the TREM2 dependent pathway, is found to be associated with enhancement of the synaptic loss [108,109]. Microglia-mediated release of C1q, together with proinflammatory cytokines ($\text{TNF}\alpha$ and IL-1 α), regulate astrocytic function [110].

Conversely, the astrocyte-mediated release of NF- κ B induces Wnt-dependent microglial proliferation; thereby regulating microglial phenotypes [111,112]. Acting together in the efficient remodeling of the synapse, microglia and astrocytes together coordinate in the ensuing efficient remodeling of the synapse.

3. Taurine—A Savior

Taurine (2-amino-ethanesulfonic acid) is among the most abundant amino acids in mammals [113–115]. The history of taurine dates back to 1827, with its isolation from the bile of *Bos Taurus* [116]. However, its origin seems more ancient in terms of phylogeny; it is present in higher amounts in algae, absent among viruses and bacteria (except *Bacillus subtilis*, where it serves as a source of carbon, nitrogen and sulfur), found in trace amounts among fungi and plants, and found at higher concentrations among animals [113,117]. Taurine is considered a conditionally essential nutrient for humans [118]. It is considered safe for humans as it does not exert any genotoxic, teratogenic or carcinogenic effect within the human body [13,119,120]. The European Food Safety Authority (EFSA) has set 1000 mg/kg/per day as the No Observed Adverse Effect Level (NOAEL) regarding the consumption of taurine as part of energy drinks [13].

Required in large amounts, its requirement among humans is fulfilled by endogenous synthesis, preferentially in the liver and kidneys, or through its procurement as part of the diet [121,122]. As endogenous taurine synthesis does not fulfill the physiological requirements of humans, they rely on dietary supplementation to fulfill their need for taurine. Though colostrum containing high levels of taurine fulfills initial taurine requirement among new-borns, this is followed by supplementation as an addition to infant formulas [121]. Adults fulfill their requirement for taurine via retention in greater amount across different tissues. Categorized as a non-essential amino acid (due to endogenous synthesis), its incorporation into proteins has not been reported. The popularity of taurine comes from its involvement in diverse physiological functions; as a neurotransmitter [123,124], as an osmolyte [125–127], as a trophic factor in CNS development [128] and as a neuroprotector in glutamate (Glu)-induced neurotoxicity [129,130], maintaining structural integrity of the membrane [8,9] and regulating calcium homeostasis [131,132]. Additionally, taurine has been found to be involved in modulating inflammation [133,134], and acting as an antioxidant in scavenging free radicals [135,136] and in reducing apoptosis [137,138].

4. Structure and Physicochemical Properties

Taurine ($\text{NH}_3^+ \text{--CH}_2 \text{--CH}_2 \text{--SO}_3^-$) is a sulfur β -amino acid that resembles, in its structure, an inhibitory neurotransmitter γ -aminobutyric acid (GABA) [122]. In its structure, the amino group (NH_3^+) located on the β -carbon and carboxylic (CO_3^-) group of amino acids is replaced by a sulfonic (SO_3^-) acid group. The presence of sulfonic (SO_3^-) acid group attributes taurine with unique physicochemical properties; a pKa value of ~ 2 (very low; more acidic than aspartate and GABA) for the sulfonic acid group, and a pKb value of 9 for the amine group, which results in the zwitterion state of the molecule at physiological pH [139]. Taurine concentration is higher in plasma (80 μM) and varies greatly among tissues [140]. It undergoes cyclization via the intramolecular hydrogen bond. The cyclic conformation of taurine hinders its transport by passive diffusion across the biological membrane. Transport of taurine across the intestinal surface occurs by either high-affinity Na^+/Cl^- taurine transporter, Tau-T encoded by *SLC6A6* gene, and/or proton (H^+)-coupled amino acid transporter (PAT1; low affinity but a major taurine transporter) [141,142]. Anderson et al. (2009) reported that PAT1 is a major transporter of taurine during meals, while its counterpart acts as a major transporter at low concentrations, i.e., in between meals [143].

5. Taurine Biosynthesis

The synthesis of taurine occurs from primary metabolites, methionine and cysteine, generated in different metabolic pathways. Synthesis begins with the conversion of methionine to cysteine via

S-adenosylmethionine, S-adenosylhomocysteine, homocysteine and cystathionine intermediates [144] (Figure 3).

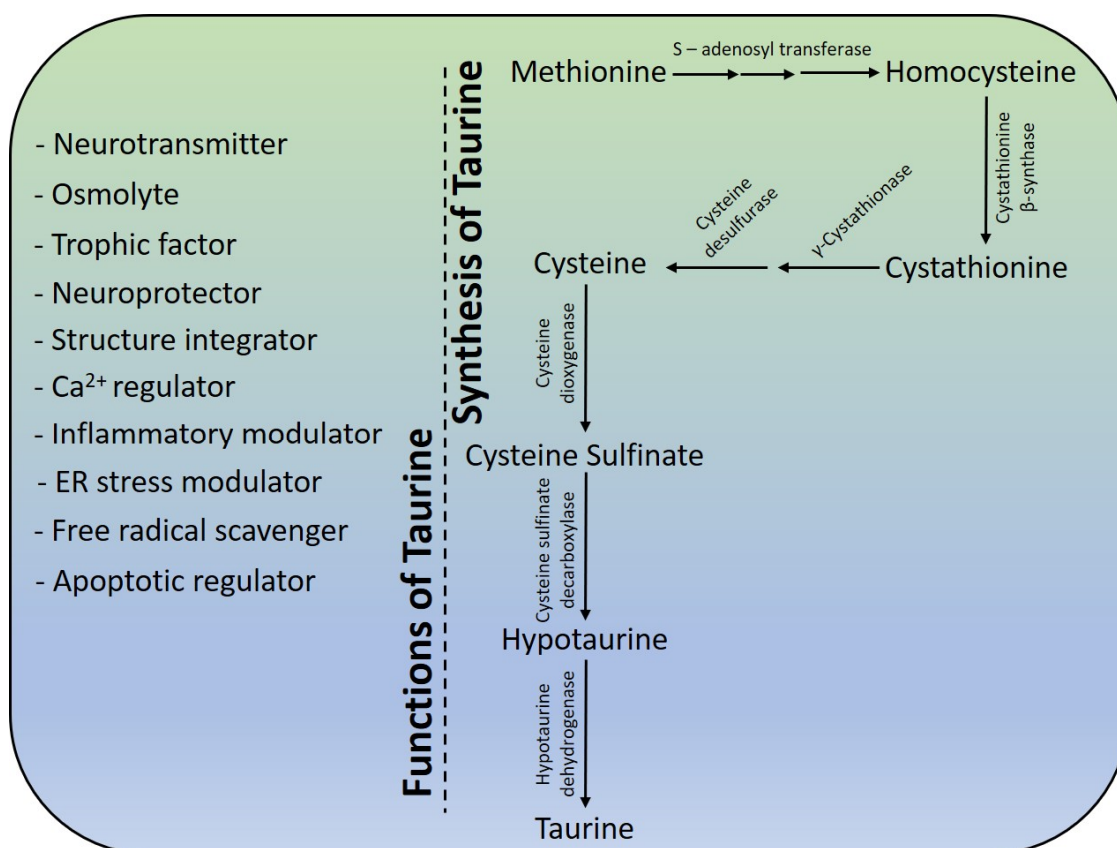


Figure 3. Structural and functional aspects of osmolyte taurine.

The formation of cystathionine from homocysteine occurs through a condensation reaction, catalyzed by cystathionine β -synthase in the presence of the serine molecule. The proceeding reactions from cystathionine to cysteine (generated in the pathway or obtained through the diet), and finally to taurine, occurs via cysteine sulfinic acid and hypotaurine. Low concentrations of enzymes, cysteine dioxygenase (CDO) and cysteine sulfinic acid decarboxylase (CSAD), catalyzing the conversion of cysteine to hypotaurine via cysteine sulfinic acid, being rate-limiting, contribute low levels of taurine produced by the endogenous pathway. In the taurine synthesis pathway, vitamin B6 (pyridoxal phosphate) acts as co-factor for three enzymes: cystathionine β -synthase, γ -cystathionase and CSAD [145]. The addition of two minor modifications in the major taurine biosynthesis pathway have also been reported: (1) One that operates in the brain and liver with the diversion of cysteine sulfinic acid to cysteic acid (catalyzed by cysteine sulfonic acid dehydrogenase), and finally to taurine by CSAD; (2) A second that operates in the kidney with the diversion of cysteine to cysteamine via the pantothionate pathway, and finally to hypotaurine by cysteamine dioxygenase [146,147].

6. Neuroprotective Effects of Taurine

A detailed description of the neuro-developmental effects of taurine are discussed under the following sub-headings and Table 1:

Table 1. Role of Taurine in Neurodegeneration.

Disease	Hallmark of Disease	Taurine Effect	Reference
Alzheimer's disease	Cerebral plaques consisting of β -amyloid peptides ($A\beta$ s) and intracellular neurofibrillary tangles (NFTs), mainly composed of hyperphosphorylated tau	Induces the synaptic potentiation, antioxidant property, inhibits neuronal death by increasing inhibitory neuro transmission via $GABA_A$ and glycine receptor stimulation, suppresses mPTP opening and reverse mitochondrial function, attenuates $A\beta$ -induced Ca^{2+} and ROS generation, pores open, reduces the mitochondrial membrane potential and increases ATP production, prevents mitochondrial dysfunction, shifts the ratio of Bcl-2:Bax in favor of cell survival, inhibits the formation of the Apaf-1/caspase-9 complex (apoptosome), suppresses upregulation of Caspase-12 and CHOP, suppresses ATF6 and IRE1 pathway, acts as GABA and the $GABA_A$ receptor agonists, inhibits the Na^+/Ca^{2+} exchanger reverse mode, inhibits L-, P/Q-, N-type voltage-gated calcium channels, prevents Ca^{2+} influx through NMDA receptor calcium channels, inhibits calcium release	[148–152]
Parkinson's disease	Loss of dopaminergic nigrostriatal neurons, intra-cytoplasmic Lewy bodies (LBs), intra-axonal Lewy neurites (LNs)	Scavenges ROS by inducing the activity of endogenous anti-oxidants, catalases and glutathione peroxidase (GSHPx), reduces mitochondrial ROS to promote normal functioning by increase in anti-oxidant protection, suppresses upregulation of Caspase-12 and CHOP, suppresses ATF6 and IRE1 pathway, suppresses microglial M1 polarization via NOX2-NF- κ B pathway	[150,153,154]
Amyotrophic lateral sclerosis	Neuronal death (motor) in the nervous system, mutations in the protein SOD1	Neuroprotective effects, against excitotoxicity induced by glutamate in motor neuronal cell lines, protects motor neuron from oxidative stress	[155,156]

6.1. As Antioxidant Molecule

Oxidative stress, which arises from the over-production of ROS, such as hydrogen peroxide (H_2O_2), hydroxyl radical ($\cdot OH$), superoxide ion ($O_2^{\cdot -}$), etc., is known to play an important role in the development of NDs [157,158]. Despite the fact that the cellular protection mechanism offered by taurine is elusive, it is considered as a cellular antioxidant. Its antioxidant property in neutralizing ROS is believed to be attributed to its sulfonic group, as revealed in an in vitro study where it was found to be neutralizing the effect of H_2O_2 [159]. It was also found to be attributing protective effect against hypochlorous acid and nitric oxide [136,160,161]. Its indirect protection mechanisms include counter-protection, in reducing the deleterious effect of ROS via alteration of membrane lipid content, which reduces the fluidity of the membrane and as such the efflux of water and ions from the cell [160,162,163]. Additionally, taurine offers protection to cells on exposure to toxins via maintenance of the levels of antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase and thioredoxin reductase [164–167].

6.2. As Stabilizer in Regulating Protein Folding/Unfolding

The folding of proteins is essential for ensuring the functional state of a protein. Having less influence on the sequence of amino acids, the folding of a polypeptide chain is largely determined by the solvent that possesses a heterogeneous composition of ions, chaperones, salts and low molecular weight compounds [168]. As the solvent environment determines the folding state of a protein, studies have revealed its manipulation as a strategy for avoiding diseases that result from defects in

protein folding [169–171]. Cells often face environmental insults that are both extrinsic (pH, high salts, extremes of temperature, etc.) and intrinsic (high concentration of denaturants such as urea), which emerge as challenges to folding proteins into functionally active conformational states [168,172,173]. Failure to cope with cellular challenges and hostile environments often leads to proteopathies (protein destabilization followed by aggregate or amyloid formation) [174,175]. Taking AD and PD into consideration, protein intermediates that arise due to mutations are kinetically unstable, and often lead to aggregate or amyloid formation (a state that can never be reversed to native conformation) [171,176].

As a quality control system, cells or organisms overcome such hostile environments by enhancing the accumulation of small organic (amino acids and their derivatives, methylamines, etc.) entities, referred to as osmolytes. Increasing the values of the T_m (melting temperature) and C_m (melting concentration) of proteins, the correction of folding defects via reduction in the aggregation of proteins is the major attribute of osmolytes [177–186]. The osmoregulatory property of taurine corresponds to its presence at higher concentrations in cells exposed to higher levels of oxidants [187–189]. The anomalous behavior of taurine (increasing under oxidative stress and decreasing under hypo-osmotic conditions) forms part of the mechanism by which it imparts protection to cells from extra-stretching under an osmotic imbalance condition [190]. Capable of establishing water-mediated interactions, taurine gives stability to proteins against stress conditions capable of causing protein denaturation [191–195]. NMR (Nuclear magnetic resonance spectroscopy) studies revealed the involvement of taurine in the refolding of denatured proteins [196], while spectroscopic and calorimetric studies revealed its role in increasing the thermal stability of lysozyme [197,198]. Khan et al. revealed the role of taurine in counteracting the denaturing of proteins by urea, via increasing the stability of the protein for the maintenance of its function [199]. In their studies of measuring the enzymatic activity and thermal stability of proteins, they found the effect of taurine to be protein-specific. In addition to the protein stabilizing effect, taurine, at millimolar concentrations, is reported to play a role in preventing aggregation of the proteins [7,200,201].

Progression of proteins from the monomeric to fibrillar stage accompanies their aggregation. Representing a significant hallmark of NDs, this serves dual purpose, in the early-stage diagnosis of disease as well as in developing therapeutics for them. In the case of AD, taurine supplementation exerts its therapeutic effect by reducing $A\beta$ aggregation [202]. Kim et al. demonstrated that oral administration of taurine to a APP/PS1 transgenic mouse model relieves its cognitive defects via decreasing the $A\beta$ levels [203]. A similar effect of relieving cognitive effects was observed in the studies on the AD mouse model [202]. Attenuation in the aggregation of α -synuclein was observed in the PD mouse model developed by intoxication of paraquat and maneb [154]. Thioflavin T (ThT) emission monitoring of glucagon fibrillation via enhancement in osmolytes revealed taurine-mediated protection, observed as extension in the lag phase [204].

6.3. As Inhibitory Neuromodulator

The release of taurine as part of neurotransmission seems independent of the Ca^{2+} influx, as no vesicular transporter has been reported for taurine [205]. Considering the importance of taurine in the CNS, its release occurs via volume-sensitive organic anion channels, or through a mechanism that involves reversal of Tau-T functioning [206]. Taurine-mediated modulation of voltage gated Ca^{2+} channel functioning involves the binding of taurine to GABA/glycinergic receptors, which results in neuronal hyperpolarization. As basal unstimulated taurine release is low in the neonatal stage, various stimuli (such as hypoosmotic stimulation, volume change, glutamate, adenosine, etc.) trigger its release from the immature neural cortex [207–209]. As a potent neuroprotectant, taurine buffers the toxic effect in the CNS that arises as a result of an imbalance between inhibitory (e.g., GABA) and excitatory (e.g., glutamate) neurotransmitters [210]. On the one hand, while it protects the CNS from excitotoxicity by glutamate, it on the other hand prevents neuronal hypertoxicity by reducing GABA levels or the activity of the GABA receptors. Taurine acts as a weak agonist of GABA ($GABA_A$, ionotropic $GABA_B$ and metabotropic $GABA_C$) receptors; it can therefore replace GABA for binding to the receptor and

inhibiting neuronal excitability [15,210,211]. Regulation of the GABA_A receptor is complex. Acute taurine administration has an activator effect on the GABA_A receptor and the chronic taurine level that leads to downregulation of the GABA_A receptor, causing upregulation of the glutamate decarboxylase that catalyzes the rate limiting step reaction in GABA biosynthesis. Additionally, taurine acts as a partial agonist of glycine and NMDA (ionotropic glutamate receptor subtype) receptors [211,212]. Together, the operation of the complex interactive network, between taurine and the GABAergic and Glycine and/or NMDA receptors, largely defines its functionality in the CNS.

6.4. Energy Metabolism Modulator

Taurine plays a vital role in energy metabolism; it acts as a key regulator, to maintain the production level of superoxides and oxidative phosphorylation. The ratio of NADH/NAD⁺ is raised by its deficiency, which effects the activity of complex I, resulting in a disturbance of the energy metabolism and oxidative stress via respiratory chain impairment, and also leads to the inactivation of 3-NADH-sensitive enzymes (α -ketoglutarate dehydrogenase, isocitrate dehydrogenase and citrate synthase) [213]. The pyruvate oxidation decreases due to taurine deficiency, and the activity of pyruvate dehydrogenase is stopped due to the elevating ratio of NADH/NAD⁺, which results in pyruvate deficiency due to the substantial conversion of pyruvate to lactate. In taurine-deficient hearts, the oxidation of glucose is declined, which in turn affects the biosynthesis of ATP. In the human liver, taurine biosynthesis is very low, and the diet is its main source. As per the study of Jeejeebhoy et al. (2002), patients with heart failure have been found taurine-deficient, and so for cardiovascular diseases it is considered as a therapeutic agent by providing its supplements to patients for the restoration of taurine levels, which results in proper contractile functions [214].

6.5. As ER Stress Modulator

ER stress, having its background in the misfolding of proteins, oxidative stress and the enhancement of intracellular Ca²⁺, interferes with signaling across neurons, which ultimately progresses to neuronal cell death. Stress-mediated activation of unfolded protein response (UPR^{ER}) relieves cells of the stress condition through the activation of downstream signaling across three cascades—PERK, IRE1 and ATF6—towards restoration of the balance between synthesis/folding and the degradation of proteins. The activation of signaling cascades is mediated by dissociation of glucose regulated protein-78 (GRP-78) from PERK, IRE1 and ATF6, which initiates downward signaling in order to overcome ER stress. Under prolonged stress conditions, UPR fails in restoring the correct folding of proteins, and as such directs cells to apoptosis via the activation of pro-death components, such as the C/EBP homologous protein (CHOP), Caspase 12 and JNK [215–217]. Taurine is believed to be involved in restoring current folding of proteins, either through reduction in oxidative stress or through providing suitable osmotic conditions for proteins to fold [218]. As a neuro-protectant, taurine restores the structural integrity and functionality of ER through the reduction of intracellular Ca²⁺ levels and Ca²⁺-mediated oxidative stress, as well as the Bax/Bcl-2 ratio [150,219].

6.6. As Neuroinflammatory and Synaptic Loss Modulator

Taurine supplementation has been found to reduce the secretion of TNF α , IL-1 α , IL-1 β , IL-6, etc. [220]. The effect was observed as a decrease in the expression of inflammatory stress markers. As neuroinflammation and synaptic loss pertains to activation of glial cells and the release of proinflammatory cytokines, inactivation of the microglia-mediated inflammation and activation of the NOX2-NF- κ B pathway count as taurine-mediated neuroprotection effects [154]. For initiation of the neuroinflammatory cascade, intracerebral hemorrhage (ICH) plays a significant role, however, administration of a high dose of taurine in ICH model rat ameliorates white matter injury and neuronal damage. The effect was associated with the reduction of inflammatory mediators expression, glial activation, neutrophil infiltration and enhanced expression of CBS (cystathionine- β -synthase), etc. [12]. In the maneb- and paraquat-induced mice model of PD, taurine inactivated microglia-mediated

neuroinflammation, marked by downregulation of proinflammatory cytokines such as $\text{TNF}\alpha$, $\text{IL1}\beta$, etc. [154]. In AD, $\text{A}\beta$ -induced inflammation is limited by reactive astrocytes. In the wild type and transgenic mice models of AD, oral administration of taurine induced increases in a number of reactive astrocytes [203]. The mtSOD1(G93A) transgenic cell line model of ALS also responds to taurine, with regards to neurotoxic injury [155].

6.7. As Ca^{2+} Homeostasis and Apoptotic Modulator

Glutamate, an excitatory neurotransmitter in the CNS, plays an important role in the survival and differentiation of neurons, besides maintaining neuronal plasticity for smooth synaptic transmission [221–223]. It was found that excessive amounts of extracellular glutamate induce cellular damage, which progresses to cell death via increases in the amount of intracellular free Ca^{2+} [224]. Taurine exerts its neuroprotective effect through maintenance of the structural integrity of the membrane that leads to decreases in the intracellular Ca^{2+} levels [225]. It prevents entry of Ca^{2+} into neurons via interference with the L, N and P/Q type of Ca^{2+} channels [226], besides formulating the operation of a reverse module $\text{Na}^+/\text{Ca}^{2+}$ exchanger [224,225,227]. As its indirect mode of operation, taurine enhances the activity of sarcoplasmic Ca^{2+} -ATPase associated with the maintenance of cytosolic Ca^{2+} homeostasis, via uptake of cytosolic Ca^{2+} [228].

Glutamate-mediated accumulation of intracellular Ca^{2+} in mitochondria leads to increases in the production of ROS [229]. Together, ROS-mediated oxidative stress and enhanced Ca^{2+} triggers breach the mitochondrial membrane's permeability, there by leading to the release of pro-apoptotic factors that ultimately causes cell progression to apoptosis [230]. In this process, cell progression to the apoptotic process is regulated by the balance of bcl-2-like protein 4 (Bax) to B-cell lymphoma 2 (Bcl-2) proteins. An enhancement of the intracellular Ca^{2+} , mediated by glutamate, activates calpain (Ca^{2+} -dependent protease), which is capable of cleaving Bcl-2. Simultaneously, glutamate induces dimerization of Bax via conformational changes in the structure of Bax, which causes the release of cytochrome C from mitochondria. With non-functional Bcl-2 (inactivated by calpain cleavage), Cyt C-mediated activation of Apaf-1 causes downstream signaling along the caspase cascade, thereby promoting apoptosis [231]. Together, glutamate-mediated increases in Bax and Bcl-2 promote apoptosis, while a decline of Bax to Bcl-2 ratio mediated by taurine prevents the progression of cells to apoptosis [231,232].

7. Conclusions

The aggregation of misfolded proteins that leads to the generation of plaques, tangles, Lewy bodies, etc., and their deposition in different cell subsets of the brain and in the extracellular milieu, finally proceeds to the development of different NDs. Despite the fact that studies are performed on different fronts to understand disease occurrence, and as such disease progression that affects normal brain function, there still lies a void in understanding the contribution of risk factors, the genetic aspects of occurrence of the diseases, and the development of potent therapeutics that could combat these devastating brain diseases. Mitochondrial dysfunction, ER stress, neuroinflammation and synaptic loss with subsequent neuronal death are considered as the foremost causes in the development of NDs. In the search for effective therapeutic possibilities, taurine—an osmolyte with wide occurrence in humans—has proven its ability to promote protein folding under stress conditions. It effectively mitigates the severity of consequences that arise due to protein misfolding, and thereby keeps a check on the progression of brain diseases such as AD. The remarkable properties of taurine as an antioxidant molecule, as a stabilizer in regulating protein folding/unfolding, as a modulator of apoptosis and in Ca^{2+} homeostasis, helps in attenuating the symptomology of misfolded protein aggregation. As a neuroprotective molecule, its alleviation of protein aggregation leads to improvement in neuronal function, thereby averting the neuronal damage that reduces brain functioning in different NDs. Further studies are needed to gain a deeper insight into taurine functioning, and to investigate its mode of operating and mechanism of protection in combating the occurrence, and as such progression,

of different NDs. This would pave the way for researchers working in the field to developing potent therapeutics for employment in overcoming the plethora of different NDs.

Author Contributions: A.T.J. and S.R. conceived the idea. M.A.B. (Mujtaba Aamir Bhat), M.A.B. (Mudasir Ahmad Bhat), S.R. and A.T.J. contributed to the writing of the manuscript. M.A.B. (Mujtaba Aamir Bhat), K.A., M.S.A.K., M.A.B. (Mudasir Ahmad Bhat), A.A., S.R. and A.T.J. contributed to revision of the contents and in the designing of figures and tables. M.A.B. (Mujtaba Aamir Bhat), S.R. and A.T.J. edited the manuscript and contributed to the compilation of data for designing of figures. All authors have read and agreed to the published version of the manuscript.

Funding: The work was supported by Department of Science and Technology, India under Science and Engineering Research Board (DST-SERB) grant no. CRG/2019/004106.

Acknowledgments: The authors would like to thank their colleagues for help in improving the contents of the manuscript.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Johnson, I.P. Age-related neurodegenerative disease research needs aging models. *Front. Aging Neurosci.* **2015**, *7*, 168. [[CrossRef](#)]
2. Jan, A.T.; Azam, M.; Rahman, S.; Almigeiti, A.M.S.; Choi, D.H.; Lee, E.J.; Haq, Q.M.R.; Choi, I. Perspective Insights into Disease Progression, Diagnostics, and Therapeutic Approaches in Alzheimer's Disease: A Judicious Update. *Front. Aging Neurosci.* **2017**, *9*, 356. [[CrossRef](#)] [[PubMed](#)]
3. J Jan, A.T.; Malik, M.A.; Rahman, S.; Yeo, H.R.; Lee, E.J.; Abdullah, T.S.; Choi, I. Perspective Insights of Exosomes in Neurodegenerative Diseases: A Critical Appraisal. *Front. Aging Neurosci.* **2017**, *9*, 317. [[CrossRef](#)] [[PubMed](#)]
4. Rahman, S.; Jan, A.T.; Ayyagari, A.; Kim, J.; Kim, J.; Minakshi, R. Entanglement of UPRER in Aging Driven Neurodegenerative Diseases. *Front. Aging Neurosci.* **2017**, *9*, 341. [[CrossRef](#)] [[PubMed](#)]
5. Rahman, S.; Archana, A.; Jan, A.T.; Minakshi, R. Dissecting Endoplasmic Reticulum Unfolded Protein Response (UPR(ER)) in Managing Clandestine Modus Operandi of Alzheimer's Disease. *Front. Aging Neurosci.* **2018**, *10*, 30. [[CrossRef](#)]
6. Feigin, V.; Abajobir, A.A.; Abate, K.H.; Abd-Allah, F.; Abdulle, A.M.; Abera, S.F.; Abyu, G.Y. Global, regional, and national burden of neurological disorders during 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol.* **2017**, *16*, 877–897. [[CrossRef](#)]
7. Sami, N.; Rahman, S.; Kumar, V.; Zaidi, S.; Islam, A.; Ali, S.; Ahmad, F.; Hassan, M.I. Protein aggregation, misfolding and consequential human neurodegenerative diseases. *Int. J. Neurosci.* **2017**, *127*, 1047–1057. [[CrossRef](#)]
8. Moran, J.; Salazar, P.; Pasantés-Morales, H. Effect of tocopherol and taurine on membrane fluidity of retinal rod outer segments. *Exp. Eye Res.* **1987**, *45*, 769–776. [[CrossRef](#)]
9. You, J.S.; Chang, K.J. Effects of taurine supplementation on lipid peroxidation, blood glucose and blood lipid metabolism in streptozotocin-induced diabetic rats. *Adv. Exp. Med. Biol.* **1998**, *442*, 163–168. [[CrossRef](#)]
10. Roychoudhury, A.; Bieker, A.; Haussinger, D.; Oesterhelt, F. Membrane protein stability depends on the concentration of compatible solutes—a single molecule force spectroscopic study. *Biol. Chem.* **2013**, *394*, 1465–1474. [[CrossRef](#)]
11. Taranukhin, A.G.; Taranukhina, E.Y.; Saransaari, P.; Pelto-Huikko, M.; Podkletnova, I.M.; Oja, S.S. Taurine protects cerebellar neurons of the external granular layer against ethanol-induced apoptosis in 7-day-old mice. *Amino Acids* **2012**, *43*, 1705–1711. [[CrossRef](#)] [[PubMed](#)]
12. Zhao, H.; Qu, J.; Li, Q.; Cui, M.; Wang, J.; Zhang, K.; Liu, X.; Feng, H.; Chen, Y. Taurine supplementation reduces neuroinflammation and protects against white matter injury after intracerebral hemorrhage in rats. *Amino Acids* **2018**, *50*, 439–451. [[CrossRef](#)] [[PubMed](#)]
13. Menzie, J.; Prentice, H.; Wu, J.Y. Neuroprotective Mechanisms of Taurine against Ischemic Stroke. *Brain Sci.* **2013**, *3*, 877–907. [[CrossRef](#)] [[PubMed](#)]
14. Sun, M.; Zhao, Y.; Gu, Y.; Xu, C. Anti-inflammatory mechanism of taurine against ischemic stroke is related to down-regulation of PARP and NF-kappaB. *Amino Acids* **2012**, *42*, 1735–1747. [[CrossRef](#)] [[PubMed](#)]

15. Albrecht, J.; Schousboe, A. Taurine Interaction with Neurotransmitter Receptors in the CNS: An Update. *Neurochem. Res.* **2006**, *30*, 1615–1621. [[CrossRef](#)] [[PubMed](#)]
16. Chepkova, A.N.; Doreulee, N.; Yanovsky, Y.; Mukhopadhyay, D.; Haas, H.L.; Sergeeva, O.A. Long-lasting enhancement of corticostriatal neurotransmission by taurine. *Eur. J. Neurosci.* **2002**, *16*, 1523–1530. [[CrossRef](#)]
17. Sergeeva, O.A.; Chepkova, A.N.; Doreulee, N.; Eriksson, K.S.; Poelchen, W.; Monnighoff, I.; Heller-Stilb, B.; Warskulat, U.; Haussinger, D.; Haas, H.L. Taurine-induced long-lasting enhancement of synaptic transmission in mice: Role of transporters. *J. Physiol.* **2003**, *550*, 911–919. [[CrossRef](#)]
18. El Idrissi, A.; Shen, C.H.; L'Amoreaux, W.J. Neuroprotective role of taurine during aging. *Amino Acids* **2013**, *45*, 735–750. [[CrossRef](#)]
19. El Idrissi, A. Taurine improves learning and retention in aged mice. *Neurosci. Lett.* **2008**, *436*, 19–22. [[CrossRef](#)]
20. Neuwirth, L.S.; Volpe, N.P.; El Idrissi, A. Taurine effects on emotional learning and memory in aged mice: Neurochemical alterations and differentiation in auditory cued fear and context conditioning. *Adv. Exp. Med. Biol.* **2013**, *775*, 195–214. [[CrossRef](#)]
21. Selkoe, D.J. Alzheimer's disease results from the cerebral accumulation and cytotoxicity of amyloid beta-protein. *J. Alzheimer's Dis.* **2001**, *3*, 75–80. [[CrossRef](#)] [[PubMed](#)]
22. Selkoe, D.J. Alzheimer's disease: Genes, proteins, and therapy. *Physiol. Rev.* **2001**, *81*, 741–766. [[CrossRef](#)] [[PubMed](#)]
23. Scheltens, P.; Blennow, K.; Breteler, M.M.; de Strooper, B.; Frisoni, G.B.; Salloway, S.; Van der Flier, W.M. Alzheimer's disease. *Lancet* **2016**, *388*, 505–517. [[CrossRef](#)]
24. Sun, L.; Zhou, R.; Yang, G.; Shi, Y. Analysis of 138 pathogenic mutations in presenilin-1 on the in vitro production of Abeta42 and Abeta40 peptides by gamma-secretase. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E476–E485. [[CrossRef](#)]
25. Weggen, S.; Behr, D. Molecular consequences of amyloid precursor protein and presenilin mutations causing autosomal-dominant Alzheimer's disease. *Alzheimer's Res.* **2012**, *4*, 9. [[CrossRef](#)]
26. Bertram, L.; Tanzi, R.E. The genetic epidemiology of neurodegenerative disease. *J. Clin. Investig.* **2005**, *115*, 1449–1457. [[CrossRef](#)]
27. Haass, C.; Selkoe, D.J. Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimer's amyloid beta-peptide. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 101–112. [[CrossRef](#)]
28. Cleary, J.P.; Walsh, D.M.; Hofmeister, J.J.; Shankar, G.M.; Kuskowski, M.A.; Selkoe, D.J.; Ashe, K.H. Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. *Nat. Neurosci.* **2005**, *8*, 79–84. [[CrossRef](#)]
29. Selkoe, D.J. Alzheimer disease: Mechanistic understanding predicts novel therapies. *Ann. Intern. Med.* **2004**, *140*, 627–638. [[CrossRef](#)]
30. Selkoe, D.J. Cell biology of protein misfolding: The examples of Alzheimer's and Parkinson's diseases. *Nat. Cell Biol.* **2004**, *6*, 1054–1061. [[CrossRef](#)]
31. Citron, M. Alzheimer's disease: Treatments in discovery and development. *Nat. Neurosci.* **2002**, *5*, 1055–1057. [[CrossRef](#)] [[PubMed](#)]
32. Minter, M.R.; Taylor, J.M.; Crack, P.J. The contribution of neuroinflammation to amyloid toxicity in Alzheimer's disease. *J. Neurochem.* **2016**, *136*, 457–474. [[CrossRef](#)] [[PubMed](#)]
33. Atwood, C.S.; Bowen, R.L. A Unified Hypothesis of Early- and Late-Onset Alzheimer's Disease Pathogenesis. *J. Alzheimer's Dis.* **2015**, *47*, 33–47. [[CrossRef](#)] [[PubMed](#)]
34. Guerreiro, R.; Wojtas, A.; Bras, J.; Carrasquillo, M.; Rogaeva, E.; Majounie, E.; Cruchaga, C.; Sassi, C.; Kauwe, J.S.; Younkin, S.; et al. TREM2 variants in Alzheimer's disease. *N. Engl. J. Med.* **2013**, *368*, 117–127. [[CrossRef](#)] [[PubMed](#)]
35. Jonsson, T.; Stefansson, H.; Steinberg, S.; Jonsdottir, I.; Jonsson, P.V.; Snaedal, J.; Bjornsson, S.; Huttenlocher, J.; Levey, A.I.; Lah, J.J.; et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *N. Engl. J. Med.* **2013**, *368*, 107–116. [[CrossRef](#)]
36. Chesselet, M.F. In vivo alpha-synuclein overexpression in rodents: A useful model of Parkinson's disease? *Exp. Neurol.* **2008**, *209*, 22–27. [[CrossRef](#)]
37. Kalia, L.V. Biomarkers for cognitive dysfunction in Parkinson's disease. *Parkinsonism Relat. Disord.* **2018**, *46*, S19–S23. [[CrossRef](#)]
38. Kalia, L.V.; Lang, A.E. Parkinson's disease. *Lancet* **2015**, *386*, 896–912. [[CrossRef](#)]

39. Olanow, C.W.; Tatton, W.G. Etiology and pathogenesis of Parkinson's disease. *Annu. Rev. Neurosci.* **1999**, *22*, 123–144. [[CrossRef](#)]
40. Sohrab, S.S.; Suhail, M.; Ali, A.; Kamal, M.A.; Husen, A.; Ahmad, F.; Azhar, E.I.; Greig, N.H. Role of viruses, prions and miRNA in neurodegenerative disorders and dementia. *Virusdisease* **2018**, *29*, 419–433. [[CrossRef](#)]
41. Scheckel, C.; Aguzzi, A. Prions, prionoids and protein misfolding disorders. *Nat. Rev. Genet.* **2018**, *19*, 405–418. [[CrossRef](#)] [[PubMed](#)]
42. Rakhit, R.; Chakrabartty, A. Structure, folding, and misfolding of Cu, Zn superoxide dismutase in amyotrophic lateral sclerosis. *Biochim. Biophys. Acta.* **2006**, *1762*, 1025–1037. [[CrossRef](#)] [[PubMed](#)]
43. Kumar, V.; Rahman, S.; Choudhry, H.; Zamzami, M.A.; Sarwar Jamal, M.; Islam, A.; Ahmad, F.; Hassan, M.I. Computing disease-linked SOD1 mutations: Deciphering protein stability and patient-phenotype relations. *Sci. Rep.* **2017**, *7*, 4678. [[CrossRef](#)] [[PubMed](#)]
44. Beckman, J.S.; Estevez, A.G.; Crow, J.P.; Barbeito, L. Superoxide dismutase and the death of motoneurons in ALS. *Trends Neurosci.* **2001**, *24*, S15–S20. [[CrossRef](#)]
45. Prasad, A.; Bharathi, V.; Sivalingam, V.; Girdhar, A.; Patel, B.K. Molecular Mechanisms of TDP-43 Misfolding and Pathology in Amyotrophic Lateral Sclerosis. *Front. Mol. Neurosci.* **2019**, *12*, 25. [[CrossRef](#)] [[PubMed](#)]
46. Cabral-Miranda, F.; Hetz, C. ER Stress and Neurodegenerative Disease: A Cause or Effect Relationship? *Curr. Top. Microbiol. Immunol.* **2018**, *414*, 131–157. [[CrossRef](#)]
47. Xiang, C.; Wang, Y.; Zhang, H.; Han, F. The role of endoplasmic reticulum stress in neurodegenerative disease. *Apoptosis* **2017**, *22*, 1–26. [[CrossRef](#)]
48. Swerdlow, R.H.; Burns, J.M.; Khan, S.M. The Alzheimer's disease mitochondrial cascade hypothesis: Progress and perspectives. *Biochim. Biophys. Acta* **2014**, *1842*, 1219–1231. [[CrossRef](#)]
49. Hoekstra, J.G.; Hipp, M.J.; Montine, T.J.; Kennedy, S.R. Mitochondrial DNA mutations increase in early stage Alzheimer disease and are inconsistent with oxidative damage. *Ann. Neurol.* **2016**, *80*, 301–306. [[CrossRef](#)]
50. Hirai, K.; Aliev, G.; Nunomura, A.; Fujioka, H.; Russell, R.L.; Atwood, C.S.; Johnson, A.B.; Kress, Y.; Vinters, H.V.; Tabaton, M.; et al. Mitochondrial abnormalities in Alzheimer's disease. *J. Neurosci.* **2001**, *21*, 3017–3023. [[CrossRef](#)] [[PubMed](#)]
51. Mosconi, L.; Brys, M.; Switalski, R.; Mistur, R.; Glodzik, L.; Pirraglia, E.; Tsui, W.; De Santi, S.; de Leon, M.J. Maternal family history of Alzheimer's disease predisposes to reduced brain glucose metabolism. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 19067–19072. [[CrossRef](#)] [[PubMed](#)]
52. Krishnan, K.J.; Ratnaik, T.E.; De Gruyter, H.L.; Jaros, E.; Turnbull, D.M. Mitochondrial DNA deletions cause the biochemical defect observed in Alzheimer's disease. *Neurobiol. Aging* **2012**, *33*, 2210–2214. [[CrossRef](#)] [[PubMed](#)]
53. Huang, X.; Atwood, C.S.; Hartshorn, M.A.; Multhaup, G.; Goldstein, L.E.; Scarpa, R.C.; Cuajungco, M.P.; Gray, D.N.; Lim, J.; Moir, R.D.; et al. The A β Peptide of Alzheimer's Disease Directly Produces Hydrogen Peroxide through Metal Ion Reduction. *Biochemistry* **1999**, *38*, 7609–7616. [[CrossRef](#)] [[PubMed](#)]
54. Perez, M.J.; Ponce, D.P.; Aranguiz, A.; Behrens, M.I.; Quintanilla, R.A. Mitochondrial permeability transition pore contributes to mitochondrial dysfunction in fibroblasts of patients with sporadic Alzheimer's disease. *Redox Biol.* **2018**, *19*, 290–300. [[CrossRef](#)] [[PubMed](#)]
55. Ramirez, A.T.; Liu, X. Dual Perturbation of Electron Transport Chain (ETC) Complex and ATP Synthase Triggers PINK1/Parkin-dependent Mitophagy. *FASEB J.* **2018**, *32*, 543–549. [[CrossRef](#)]
56. Schroder, M.; Kaufman, R.J. The mammalian unfolded protein response. *Annu Rev. Biochem.* **2005**, *74*, 739–789. [[CrossRef](#)]
57. Moneim, A.E. Oxidant/Antioxidant imbalance and the risk of Alzheimer's disease. *Curr. Alzheimer. Res.* **2015**, *12*, 335–349. [[CrossRef](#)]
58. Duennwald, M.L.; Lindquist, S. Impaired ERAD and ER stress are early and specific events in polyglutamine toxicity. *Genes. Dev.* **2008**, *22*, 3308–3319. [[CrossRef](#)]
59. Yoshida, H. ER stress and diseases. *FEBS J.* **2007**, *274*, 630–658. [[CrossRef](#)]
60. Park, K.W.; Eun Kim, G.; Morales, R.; Moda, F.; Moreno-Gonzalez, I.; Concha-Marambio, L.; Lee, A.S.; Hetz, C.; Soto, C. The Endoplasmic Reticulum Chaperone GRP78/BiP Modulates Prion Propagation in vitro and in vivo. *Sci. Rep.* **2017**, *7*, 44723. [[CrossRef](#)]
61. Rahman, S.; Archana, A.; Jan, A.T.; Dutta, D.; Shankar, A.; Kim, J.; Minakshi, R. Molecular Insights Into the Relationship Between Autoimmune Thyroid Diseases and Breast Cancer: A Critical Perspective on Autoimmunity and ER Stress. *Front. Immunol.* **2019**, *10*, 344. [[CrossRef](#)] [[PubMed](#)]

62. Rahman, S.; Archana, A.; Dutta, D.; Kumar, V.; Kim, J.; Jan, A.T.; Minakshi, R. The onus of cannabinoids in interrupting the molecular odyssey of breast cancer: A critical perspective on UPR(ER) and beyond. *Saudi Pharm. J.* **2019**, *27*, 437–445. [[CrossRef](#)] [[PubMed](#)]
63. Minakshi, R.; Rahman, S.; Jan, A.T.; Archana, A.; Kim, J. Implications of aging and the endoplasmic reticulum unfolded protein response on the molecular modality of breast cancer. *Exp. Mol. Med.* **2017**, *49*, e389. [[CrossRef](#)] [[PubMed](#)]
64. Walter, P.; Ron, D. The unfolded protein response: From stress pathway to homeostatic regulation. *Science* **2011**, *334*, 1081–1086. [[CrossRef](#)]
65. Harding, H.P.; Zhang, Y.; Ron, D. Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. *Nature* **1999**, *397*, 271–274. [[CrossRef](#)]
66. Haze, K.; Yoshida, H.; Yanagi, H.; Yura, T.; Mori, K. Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. *Mol. Biol. Cell* **1999**, *10*, 3787–3799. [[CrossRef](#)]
67. Okada, T.; Yoshida, H.; Akazawa, R.; Negishi, M.; Mori, K. Distinct roles of activating transcription factor 6 (ATF6) and double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase (PERK) in transcription during the mammalian unfolded protein response. *Biochem. J.* **2002**, *366*, 585–594. [[CrossRef](#)]
68. Lee, A.H.; Iwakoshi, N.N.; Glimcher, L.H. XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. *Mol. Cell Biol.* **2003**, *23*, 7448–7459. [[CrossRef](#)]
69. Shaffer, A.L.; Shapiro-Shelef, M.; Iwakoshi, N.N.; Lee, A.H.; Qian, S.B.; Zhao, H.; Yu, X.; Yang, L.; Tan, B.K.; Rosenwald, A.; et al. XBP1, downstream of Blimp-1, expands the secretory apparatus and other organelles, and increases protein synthesis in plasma cell differentiation. *Immunity* **2004**, *21*, 81–93. [[CrossRef](#)]
70. Loewen, C.A.; Feany, M.B. The Unfolded Protein Response Protects from Tau Neurotoxicity In Vivo. *PLoS ONE* **2010**, *5*, e13084. [[CrossRef](#)]
71. Prussing, K.; Voigt, A.; Schulz, J.B. Drosophila melanogaster as a model organism for Alzheimer’s disease. *Mol. Neurodegener.* **2013**, *8*, 35. [[CrossRef](#)] [[PubMed](#)]
72. Ikeyama, S.; Wang, X.T.; Li, J.; Podlutzky, A.; Martindale, J.L.; Kokkonen, G.; van Huizen, R.; Gorospe, M.; Holbrook, N.J. Expression of the pro-apoptotic gene gadd153/chop is elevated in liver with aging and sensitizes cells to oxidant injury. *J. Biol. Chem.* **2003**, *278*, 16726–16731. [[CrossRef](#)] [[PubMed](#)]
73. Heneka, M.T.; Golenbock, D.T.; Latz, E. Innate immunity in Alzheimer’s disease. *Nat. Immunol.* **2015**, *16*, 229–236. [[CrossRef](#)] [[PubMed](#)]
74. Hansen, D.V.; Hanson, J.E.; Sheng, M. Microglia in Alzheimer’s disease. *J. Cell Biol.* **2018**, *217*, 459–472. [[CrossRef](#)]
75. Zhang, Y.; Sloan, S.A.; Clarke, L.E.; Caneda, C.; Plaza, C.A.; Blumenthal, P.D.; Vogel, H.; Steinberg, G.K.; Edwards, M.S.; Li, G.; et al. Purification and Characterization of Progenitor and Mature Human Astrocytes Reveals Transcriptional and Functional Differences with Mouse. *Neuron* **2016**, *89*, 37–53. [[CrossRef](#)] [[PubMed](#)]
76. Srinivasan, K.; Friedman, B.A.; Larson, J.L.; Lauffer, B.E.; Goldstein, L.D.; Appling, L.L.; Borneo, J.; Poon, C.; Ho, T.; Cai, F.; et al. Untangling the brain’s neuroinflammatory and neurodegenerative transcriptional responses. *Nat. Commun.* **2016**, *7*, 11295. [[CrossRef](#)]
77. Codolo, G.; Plotegher, N.; Pozzobon, T.; Brucale, M.; Tessari, I.; Bubacco, L.; de Bernard, M. Triggering of inflammasome by aggregated alpha-synuclein, an inflammatory response in synucleinopathies. *PLoS ONE* **2013**, *8*, e55375. [[CrossRef](#)]
78. Voet, S.; Srinivasan, S.; Lamkanfi, M.; van Loo, G. Inflammasomes in neuroinflammatory and neurodegenerative diseases. *Embo. Mol. Med.* **2019**, *11*. [[CrossRef](#)]
79. Curran, B.P.; Murray, H.J.; O’Connor, J.J. A role for c-Jun N-terminal kinase in the inhibition of long-term potentiation by interleukin-1beta and long-term depression in the rat dentate gyrus in vitro. *Neuroscience* **2003**, *118*, 347–357. [[CrossRef](#)]
80. Allan, S.M.; Tyrrell, P.J.; Rothwell, N.J. Interleukin-1 and neuronal injury. *Nat. Rev. Immunol.* **2005**, *5*, 629–640. [[CrossRef](#)]
81. Venegas, C.; Kumar, S.; Franklin, B.S.; Dierkes, T.; Brinkschulte, R.; Tejera, D.; Vieira-Saecker, A.; Schwartz, S.; Santarelli, F.; Kummer, M.P.; et al. Microglia-derived ASC specks cross-seed amyloid-beta in Alzheimer’s disease. *Nature* **2017**, *552*, 355–361. [[CrossRef](#)] [[PubMed](#)]

82. Guadagno, J.; Xu, X.; Karajgikar, M.; Brown, A.; Cregan, S.P. Microglia-derived TNF α induces apoptosis in neural precursor cells via transcriptional activation of the Bcl-2 family member Puma. *Cell Death Dis.* **2013**, *4*, e538. [[CrossRef](#)] [[PubMed](#)]
83. Neniskyte, U.; Vilalta, A.; Brown, G.C. Tumour necrosis factor α -induced neuronal loss is mediated by microglial phagocytosis. *FEBS Lett.* **2014**, *588*, 2952–2956. [[CrossRef](#)] [[PubMed](#)]
84. Matsuzaki, M.; Honkura, N.; Ellis-Davies, G.C.; Kasai, H. Structural basis of long-term potentiation in single dendritic spines. *Nature* **2004**, *429*, 761–766. [[CrossRef](#)] [[PubMed](#)]
85. Harris, K.M.; Weinberg, R.J. Ultrastructure of synapses in the mammalian brain. *Cold Spring Harb. Perspect. Biol.* **2012**, *4*, a005587. [[CrossRef](#)]
86. Chever, O.; Dossi, E.; Pannasch, U.; Derangeon, M.; Rouach, N. Astroglial networks promote neuronal coordination. *Sci. Signal.* **2016**, *9*, ra6. [[CrossRef](#)]
87. Reemst, K.; Noctor, S.C.; Lucassen, P.J.; Hol, E.M. The Indispensable Roles of Microglia and Astrocytes during Brain Development. *Front. Hum. Neurosci.* **2016**, *10*, 566. [[CrossRef](#)]
88. Allen, N.J.; Lyons, D.A. Glia as architects of central nervous system formation and function. *Science* **2018**, *362*, 181–185. [[CrossRef](#)]
89. Henstridge, C.M.; Sideris, D.I.; Carroll, E.; Rotariu, S.; Salomonsson, S.; Tzioras, M.; McKenzie, C.A.; Smith, C.; von Arnim, C.A.F.; Ludolph, A.C.; et al. Synapse loss in the prefrontal cortex is associated with cognitive decline in amyotrophic lateral sclerosis. *Acta Neuropathol.* **2018**, *135*, 213–226. [[CrossRef](#)]
90. Crimins, J.L.; Rocher, A.B.; Luebke, J.I. Electrophysiological changes precede morphological changes to frontal cortical pyramidal neurons in the rTg4510 mouse model of progressive tauopathy. *Acta Neuropathol.* **2012**, *124*, 777–795. [[CrossRef](#)]
91. Soto, C.; Pritzkow, S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. *Nat. Neurosci.* **2018**, *21*, 1332–1340. [[CrossRef](#)] [[PubMed](#)]
92. Sipe, G.O.; Lowery, R.L.; Tremblay, M.E.; Kelly, E.A.; Lamantia, C.E.; Majewska, A.K. Microglial P2Y₁₂ is necessary for synaptic plasticity in mouse visual cortex. *Nat. Commun.* **2016**, *7*, 10905. [[CrossRef](#)] [[PubMed](#)]
93. Yang, J.; Yang, H.; Liu, Y.; Li, X.; Qin, L.; Lou, H.; Duan, S.; Wang, H. Astrocytes contribute to synapse elimination via type 2 inositol 1,4,5-trisphosphate receptor-dependent release of ATP. *eLife* **2016**, *5*, e15043. [[CrossRef](#)] [[PubMed](#)]
94. Filipello, F.; Morini, R.; Corradini, I.; Zerbi, V.; Canzi, A.; Michalski, B.; Erreni, M.; Markicevic, M.; Starvaggi-Cucuzza, C.; Otero, K.; et al. The Microglial Innate Immune Receptor TREM2 Is Required for Synapse Elimination and Normal Brain Connectivity. *Immunity* **2018**, *48*, 979–991. [[CrossRef](#)]
95. Henstridge, C.M.; Tzioras, M.; Paolicelli, R.C. Glial Contribution to Excitatory and Inhibitory Synapse Loss in Neurodegeneration. *Front. Cell Neurosci.* **2019**, *13*, 63. [[CrossRef](#)]
96. Schafer, D.P.; Lehrman, E.K.; Kautzman, A.G.; Koyama, R.; Mardinly, A.R.; Yamasaki, R.; Ransohoff, R.M.; Greenberg, M.E.; Barres, B.A.; Stevens, B. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* **2012**, *74*, 691–705. [[CrossRef](#)]
97. Chung, W.S.; Clarke, L.E.; Wang, G.X.; Stafford, B.K.; Sher, A.; Chakraborty, C.; Joung, J.; Foo, L.C.; Thompson, A.; Chen, C.; et al. Astrocytes mediate synapse elimination through MEGF10 and MERTK pathways. *Nature* **2013**, *504*, 394–400. [[CrossRef](#)]
98. Shi, Q.; Colodner, K.J.; Matousek, S.B.; Merry, K.; Hong, S.; Kenison, J.E.; Frost, J.L.; Le, K.X.; Li, S.; Dodart, J.C.; et al. Complement C3-Deficient Mice Fail to Display Age-Related Hippocampal Decline. *J. Neurosci.* **2015**, *35*, 13029–13042. [[CrossRef](#)]
99. Lui, H.; Zhang, J.; Makinson, S.R.; Cahill, M.K.; Kelley, K.W.; Huang, H.Y.; Shang, Y.; Oldham, M.C.; Martens, L.H.; Gao, F.; et al. Progranulin Deficiency Promotes Circuit-Specific Synaptic Pruning by Microglia via Complement Activation. *Cell* **2016**, *165*, 921–935. [[CrossRef](#)]
100. Hong, S.; Beja-Glasser, V.F.; Nfonoyim, B.M.; Frouin, A.; Li, S.; Ramakrishnan, S.; Merry, K.M.; Shi, Q.; Rosenthal, A.; Barres, B.A.; et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* **2016**, *352*, 712–716. [[CrossRef](#)]
101. Michailidou, I.; Naessens, D.M.; Hametner, S.; Guldenaar, W.; Kooi, E.J.; Geurts, J.J.; Baas, F.; Lassmann, H.; Ramaglia, V. Complement C3 on microglial clusters in multiple sclerosis occur in chronic but not acute disease: Implication for disease pathogenesis. *Glia* **2017**, *65*, 264–277. [[CrossRef](#)] [[PubMed](#)]

102. Almeida, C.G.; Tampellini, D.; Takahashi, R.H.; Greengard, P.; Lin, M.T.; Snyder, E.M.; Gouras, G.K. Beta-amyloid accumulation in APP mutant neurons reduces PSD-95 and GluR1 in synapses. *Neurobiol. Dis.* **2005**, *20*, 187–198. [[CrossRef](#)] [[PubMed](#)]
103. Sokolow, S.; Henkins, K.M.; Bilousova, T.; Miller, C.A.; Vinters, H.V.; Poon, W.; Cole, G.M.; Gyls, K.H. AD synapses contain abundant Abeta monomer and multiple soluble oligomers, including a 56-kDa assembly. *Neurobiol. Aging* **2012**, *33*, 1545–1555. [[CrossRef](#)] [[PubMed](#)]
104. Takahashi, R.H.; Capetillo-Zarate, E.; Lin, M.T.; Milner, T.A.; Gouras, G.K. Accumulation of intraneuronal beta-amyloid 42 peptides is associated with early changes in microtubule-associated protein 2 in neurites and synapses. *PLoS ONE* **2013**, *8*, e51965. [[CrossRef](#)]
105. Shankar, G.M.; Li, S.; Mehta, T.H.; Garcia-Munoz, A.; Shepardson, N.E.; Smith, I.; Brett, F.M.; Farrell, M.A.; Rowan, M.J.; Lemere, C.A.; et al. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat. Med.* **2008**, *14*, 837–842. [[CrossRef](#)]
106. Wu, H.Y.; Hudry, E.; Hashimoto, T.; Kuchibhotla, K.; Rozkalne, A.; Fan, Z.; Spires-Jones, T.; Xie, H.; Arbel-Ornath, M.; Grosskreutz, C.L.; et al. Amyloid beta induces the morphological neurodegenerative triad of spine loss, dendritic simplification, and neuritic dystrophies through calcineurin activation. *J. Neurosci.* **2010**, *30*, 2636–2649. [[CrossRef](#)]
107. Bie, B.; Wu, J.; Foss, J.F.; Naguib, M. Activation of mGluR1 Mediates C1q-Dependent Microglial Phagocytosis of Glutamatergic Synapses in Alzheimer's Rodent Models. *Mol. Neurobiol.* **2019**, *56*, 5568–5585. [[CrossRef](#)]
108. Krasemann, S.; Madore, C.; Cialic, R.; Baufeld, C.; Calcagno, N.; El Fatimy, R.; Beckers, L.; O'Loughlin, E.; Xu, Y.; Fanek, Z.; et al. The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in Neurodegenerative Diseases. *Immunity* **2017**, *47*, 566–581. [[CrossRef](#)]
109. Tzioras, M.; Davies, C.; Newman, A.; Jackson, R.; Spires-Jones, T. Invited Review: APOE at the interface of inflammation, neurodegeneration and pathological protein spread in Alzheimer's disease. *Neuropathol. Appl. Neurobiol.* **2019**, *45*, 327–346. [[CrossRef](#)]
110. Liddelow, S.A.; Guttenplan, K.A.; Clarke, L.E.; Bennett, F.C.; Bohlen, C.J.; Schirmer, L.; Bennett, M.L.; Munch, A.E.; Chung, W.S.; Peterson, T.C.; et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* **2017**, *541*, 481–487. [[CrossRef](#)]
111. Ouali Alami, N.; Schurr, C.; Olde Heuvel, F.; Tang, L.; Li, Q.; Tasdogan, A.; Kimbara, A.; Nettekoven, M.; Ottaviani, G.; Raposo, C.; et al. NF-kappaB activation in astrocytes drives a stage-specific beneficial neuroimmunological response in ALS. *EMBO J.* **2018**, *37*, e98697. [[CrossRef](#)]
112. Jha, M.K.; Jo, M.; Kim, J.H.; Suk, K. Microglia-Astrocyte Crosstalk: An Intimate Molecular Conversation. *Neuroscientist* **2019**, *25*, 227–240. [[CrossRef](#)]
113. Huxtable, R.J. Physiological actions of taurine. *Physiol. Rev.* **1992**, *72*, 101–163. [[CrossRef](#)]
114. Oja, S.S.; Saransaari, P. Properties of Taurine Release in Glucose-Free Media in Hippocampal Slices from Developing and Adult Mice. *J. Amino Acids* **2015**, *2015*, 254583. [[CrossRef](#)]
115. Lambert, I.H.; Kristensen, D.M.; Holm, J.B.; Mortensen, O.H. Physiological role of taurine—from organism to organelle. *Acta Physiol. (Oxf)* **2015**, *213*, 191–212. [[CrossRef](#)]
116. Demarcay, H. Ueber die natur der Galle. *J. Für Prakt. Chem.* **1838**, *15*, 193–212. [[CrossRef](#)]
117. Nakashio, S.; Nakanishi, T.; Koshikawa, T.; Nishihara, T.; Ichikawa, T.; Kondo, M. Identification of taurine occurring sporulating cells of *Bacillus subtilis*. *Microbios* **1982**, *33*, 73–80.
118. Bouckenooghe, T.; Remacle, C.; Reusens, B. Is taurine a functional nutrient? *Curr. Opin. Clin. Nutr. Metab. Care* **2006**, *9*, 728–733. [[CrossRef](#)]
119. Murakami, Y.; Tsuyama, M.; Kobayashi, Y.; Kodama, H.; Iba, K. Trienoic fatty acids and plant tolerance of high temperature. *Science* **2000**, *287*, 476–479. [[CrossRef](#)]
120. Zhang, M.; Izumi, I.; Kagamimori, S.; Sokejima, S.; Yamagami, T.; Liu, Z.; Qi, B. Role of taurine supplementation to prevent exercise-induced oxidative stress in healthy young men. *Amino Acids* **2004**, *26*, 203–207. [[CrossRef](#)]
121. Park, E.; Park, S.Y.; Dobkin, C.; Schuller-Levis, G. Development of a novel cysteine sulfinic Acid decarboxylase knockout mouse: Dietary taurine reduces neonatal mortality. *J. Amino Acids* **2014**, *2014*, 346809. [[CrossRef](#)] [[PubMed](#)]
122. Froger, N.; Moutsimilli, L.; Cadetti, L.; Jammoul, F.; Wang, Q.P.; Fan, Y.; Gaucher, D.; Rosolen, S.G.; Neveux, N.; Cynober, L.; et al. Taurine: The comeback of a nutraceutical in the prevention of retinal degenerations. *Prog. Retin. Eye Res.* **2014**, *41*, 44–63. [[CrossRef](#)] [[PubMed](#)]

123. Okamoto, K.; Kimura, H.; Sakai, Y. Antagonistic action of 6-aminomethyl-3-methyl-4H, 1,2,4-benzothiadiazine-1, 1-dioxide (TAG), and evidence for a transmitter role of taurine in stellate interneurons in the cerebellum. *Prog. Clin. Biol. Res.* **1983**, *125*, 151–160.
124. Lin, C.-T.; Song, G.-X.; Wu, J.-Y. Is taurine a neurotransmitter in rabbit retina? *Brain Res.* **1985**, *337*, 293–298. [[CrossRef](#)]
125. Wade, J.V.; Olson, J.P.; Samson, F.E.; Nelson, S.R.; Pazdernik, T.L. A possible role for taurine in osmoregulation within the brain. *J. Neurochem.* **1988**, *51*, 740–745. [[CrossRef](#)]
126. Schaffer, S.; Takahashi, K.; Azuma, J. Role of osmoregulation in the actions of taurine. *Amino Acids* **2000**, *19*, 527–546. [[CrossRef](#)]
127. Lambert, I.H. Modulation of volume-sensitive taurine release from NIH3T3 mouse fibroblasts by reactive oxygen species. In *Cell Volume and Signaling*; Springer: Berlin/Heidelberg, Germany, 2004; pp. 369–378.
128. Sturman, J.A. Taurine in development. *Physiol. Rev.* **1993**, *73*, 119–147. [[CrossRef](#)]
129. Tang, X.; Deupree, D.; Sun, Y.; Wu, J.-Y. Biphasic Effect of Taurine on Excitatory Amino Acid-Induced Neurotoxicity. In *Taurine 2*; Springer: Berlin/Heidelberg, Germany, 1996; pp. 499–505.
130. Ward, R.; Cirkovic-Velichovia, T.; Ledequue, F.; Tirizitis, G.; Dubars, G.; Datla, K.; Dexter, D.; Heushling, P.; Crichton, R. Neuroprotection by taurine and taurine analogues. *Adv. Exp. Med. Biol.* **2006**, *583*, 299–306. [[CrossRef](#)]
131. Schaffer, S.W.; Kramer, J.; Chovan, J.P. Regulation of calcium homeostasis in the heart by taurine. *Fed. Proc.* **1980**, *39*, 2691–2694.
132. El Idrissi, A. Taurine increases mitochondrial buffering of calcium: Role in neuroprotection. *Amino Acids* **2008**, *34*, 321–328. [[CrossRef](#)]
133. Marcinkiewicz, J.; Grabowska, A.; Chain, B.M. Modulation of antigen-specific T-cell activation in vitro by taurine chloramine. *Immunology* **1998**, *94*, 325–330. [[CrossRef](#)]
134. Marcinkiewicz, J.; Kontny, E. Taurine and inflammatory diseases. *Amino Acids* **2014**, *46*, 7–20. [[CrossRef](#)]
135. Ghosh, S.; Chowdhury, S.; Das, A.K.; Sil, P.C. Taurine ameliorates oxidative stress induced inflammation and ER stress mediated testicular damage in STZ-induced diabetic Wistar rats. *Food Chem. Toxicol.* **2019**, *124*, 64–80. [[CrossRef](#)]
136. Schaffer, S.W.; Azuma, J.; Mozaffari, M. Role of antioxidant activity of taurine in diabetes. *Can. J. Physiol. Pharm.* **2009**, *87*, 91–99. [[CrossRef](#)]
137. Li, J.; Zheng, L.; Wang, X.; Yao, K.; Shi, L.; Sun, X.; Yang, G.; Jiang, L.; Zhang, C.; Wang, Y.; et al. Taurine protects INS-1 cells from apoptosis induced by Di(2-ethylhexyl) phthalate via reducing oxidative stress and autophagy. *Toxicol. Mech. Methods* **2019**, *29*, 445–456. [[CrossRef](#)]
138. Li, K.; Inam, U.L.; Shi, X.; Zhang, M.; Wu, P.; Li, S.; Suleman, R.; Nisar, A.; Piao, F. Anti-apoptotic Effect of Taurine on Schwann Cells Exposed to High Glucose In Vitro. *Adv. Exp. Med. Biol.* **2019**, *1155*, 787–799. [[CrossRef](#)]
139. Jacobsen, J.G.; Smith, L.H. Biochemistry and physiology of taurine and taurine derivatives. *Physiol. Rev.* **1968**, *48*, 424–511. [[CrossRef](#)]
140. Sturman, J.A.; Hayes, K.C. The biology of taurine in nutrition and development. In *Advances in Nutritional Research*; Springer: Berlin/Heidelberg, Germany, 1980; pp. 231–299.
141. Munck, L.K.; Munck, B.G. Distinction between chloride-dependent transport systems for taurine and beta-alanine in rabbit ileum. *Am. J. Physiol.* **1992**, *262*, G609–G615. [[CrossRef](#)]
142. Thwaites, D.T.; Ford, D.; Glanville, M.; Simmons, N.L. H(+)/solute-induced intracellular acidification leads to selective activation of apical Na(+)/H(+) exchange in human intestinal epithelial cells. *J. Clin. Investig.* **1999**, *104*, 629–635. [[CrossRef](#)]
143. Anderson, C.M.; Howard, A.; Walters, J.R.; Ganapathy, V.; Thwaites, D.T. Taurine uptake across the human intestinal brush-border membrane is via two transporters: H⁺-coupled PAT1 (SLC36A1) and Na⁺- and Cl⁻-dependent TauT (SLC6A6). *J. Physiol.* **2009**, *587*, 731–744. [[CrossRef](#)]
144. Hayes, K.C.; Sturman, J.A. Taurine in metabolism. *Annu Rev. Nutr.* **1981**, *1*, 401–425. [[CrossRef](#)]
145. Yamaguchi, K.; Shigehisa, S.; Sakakibara, S.; Hosokawa, Y.; Ueda, I. Cysteine metabolism in vivo of vitamin B6-deficient rats. *Biochim. Biophys. Acta* **1975**, *381*, 1–8. [[CrossRef](#)]
146. Huxtable, R.J. Taurine in the central nervous system and the mammalian actions of taurine. *Prog. Neurobiol.* **1989**, *32*, 471–533. [[CrossRef](#)]

147. Dupre, S.; De Marco, C. Activity of some animal tissues on the oxidation of cysteamine to hypotaurine in the presence of sulphide. *Ital. J. Biochem.* **1964**, *13*, 386–390.
148. Wu, J.Y.; Prentice, H. Role of taurine in the central nervous system. *J. Biomed. Sci.* **2010**, *17* (Suppl. 1), S1. [[CrossRef](#)]
149. Sun, Q.; Hu, H.; Wang, W.; Jin, H.; Feng, G.; Jia, N. Taurine attenuates amyloid beta 1-42-induced mitochondrial dysfunction by activating of SIRT1 in SK-N-SH cells. *Biochem. Biophys. Res. Commun.* **2014**, *447*, 485–489. [[CrossRef](#)]
150. Pan, C.; Prentice, H.; Price, A.L.; Wu, J.Y. Beneficial effect of taurine on hypoxia- and glutamate-induced endoplasmic reticulum stress pathways in primary neuronal culture. *Amino Acids* **2012**, *43*, 845–855. [[CrossRef](#)]
151. Menzie, J.; Pan, C.; Prentice, H.; Wu, J.Y. Taurine and central nervous system disorders. *Amino Acids* **2014**, *46*, 31–46. [[CrossRef](#)]
152. Louzada, P.R.; Paula Lima, A.C.; Mendonca-Silva, D.L.; Noel, F.; De Mello, F.G.; Ferreira, S.T. Taurine prevents the neurotoxicity of beta-amyloid and glutamate receptor agonists: Activation of GABA receptors and possible implications for Alzheimer's disease and other neurological disorders. *FASEB J.* **2004**, *18*, 511–518. [[CrossRef](#)]
153. Alkholifi, F.K.; Albers, D.S. Attenuation of rotenone toxicity in SY5Y cells by taurine and N-acetyl cysteine alone or in combination. *Brain Res.* **2015**, *1622*, 409–413. [[CrossRef](#)]
154. Che, Y.; Hou, L.; Sun, F.; Zhang, C.; Liu, X.; Piao, F.; Zhang, D.; Li, H.; Wang, Q. Taurine protects dopaminergic neurons in a mouse Parkinson's disease model through inhibition of microglial M1 polarization. *Cell Death Dis.* **2018**, *9*, 435. [[CrossRef](#)] [[PubMed](#)]
155. Lee, N.Y.; Kang, Y.S. Taurine Protects Glutamate Neurotoxicity in Motor Neuron Cells. *Adv. Exp. Med. Biol.* **2017**, *975 Pt 2*, 887–895. [[CrossRef](#)]
156. Jung, M.K.; Kim, K.Y.; Lee, N.Y.; Kang, Y.S.; Hwang, Y.J.; Kim, Y.; Sung, J.J.; McKee, A.; Kowall, N.; Lee, J.; et al. Expression of taurine transporter (TauT) is modulated by heat shock factor 1 (HSF1) in motor neurons of ALS. *Mol. Neurobiol.* **2013**, *47*, 699–710. [[CrossRef](#)] [[PubMed](#)]
157. Yan, M.H.; Wang, X.; Zhu, X. Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease. *Free Radic. Biol. Med.* **2013**, *62*, 90–101. [[CrossRef](#)] [[PubMed](#)]
158. Copley, J.N.; Fiorello, M.L.; Bailey, D.M. 13 reasons why the brain is susceptible to oxidative stress. *Redox Biol.* **2018**, *15*, 490–503. [[CrossRef](#)]
159. Cozzi, R.; Ricordy, R.; Bartolini, F.; Ramadori, L.; Perticone, P.; De Salvia, R. Taurine and ellagic acid: Two differently-acting natural antioxidants. *Env. Mol. Mutagen.* **1995**, *26*, 248–254. [[CrossRef](#)]
160. Timbrell, J.A.; Seabra, V.; Waterfield, C.J. The in vivo and in vitro protective properties of taurine. *Gen. Pharmacol.* **1995**, *26*, 453–462. [[CrossRef](#)]
161. Redmond, H.P.; Wang, J.H.; Bouchier-Hayes, D. Taurine attenuates nitric oxide- and reactive oxygen intermediate-dependent hepatocyte injury. *Arch. Surg.* **1996**, *131*, 1280–1287. [[CrossRef](#)]
162. Wright, C.E.; Lin, T.T.; Lin, Y.Y.; Sturman, J.A.; Gaull, G.E. Taurine scavenges oxidized chlorine in biological systems. *Prog. Clin. Biol. Res.* **1985**, *179*, 137–147.
163. Hamaguchi, T.; Azuma, J.; Schaffer, S.W. Interaction of taurine with methionine: Inhibition of myocardial phospholipid methyltransferase. *J. Cardiovasc. Pharm.* **1991**, *18*, 224–230. [[CrossRef](#)]
164. Vohra, B.P.S.; Hui, X. Taurine Protects against Carbon Tetrachloride Toxicity in the Cultured Neurons and In Vivo. *Arch. Physiol. Biochem.* **2001**, *109*, 90–94. [[CrossRef](#)]
165. Flora, S.J.; Chouhan, S.; Kannan, G.M.; Mittal, M.; Swarnkar, H. Combined administration of taurine and monoisoamyl DMSA protects arsenic induced oxidative injury in rats. *Oxid. Med. Cell. Longev.* **2008**, *1*, 39–45. [[CrossRef](#)]
166. Yildirim, Z.; Kilic, N.; Ozer, C.; Babul, A.; Take, G.; Erdogan, D. Effects of taurine in cellular responses to oxidative stress in young and middle-aged rat liver. *Ann. N. Y. Acad. Sci.* **2007**, *1100*, 553–561. [[CrossRef](#)] [[PubMed](#)]
167. Nonaka, H.; Tsujino, T.; Watari, Y.; Emoto, N.; Yokoyama, M. Taurine prevents the decrease in expression and secretion of extracellular superoxide dismutase induced by homocysteine: Amelioration of homocysteine-induced endoplasmic reticulum stress by taurine. *Circulation* **2001**, *104*, 1165–1170. [[CrossRef](#)] [[PubMed](#)]

168. Yancey, P.H. Compatible and counteracting solutes: Protecting cells from the Dead Sea to the deep sea. *Sci. Prog.* **2004**, *87*, 1–24. [[CrossRef](#)] [[PubMed](#)]
169. Tanaka, M.; Machida, Y.; Nukina, N. A novel therapeutic strategy for polyglutamine diseases by stabilizing aggregation-prone proteins with small molecules. *J. Mol. Med.* **2005**, *83*, 343–352. [[CrossRef](#)] [[PubMed](#)]
170. Yang, D.S.; Yip, C.M.; Huang, T.H.; Chakrabarty, A.; Fraser, P.E. Manipulating the amyloid-beta aggregation pathway with chemical chaperones. *J. Biol. Chem.* **1999**, *274*, 32970–32974. [[CrossRef](#)]
171. Leandro, P.; Gomes, C.M. Protein misfolding in conformational disorders: Rescue of folding defects and chemical chaperoning. *Mini-Rev. Med. Chem.* **2008**, *8*, 901–911. [[CrossRef](#)]
172. Yancey, P.H. Proteins and counteracting osmolytes. *Biologist* **2003**, *50*, 126–131.
173. Yancey, P.H.; Clark, M.E.; Hand, S.C.; Bowlus, R.D.; Somero, G.N. Living with water stress: Evolution of osmolyte systems. *Science* **1982**, *217*, 1214–1222. [[CrossRef](#)]
174. Gregersen, N.; Bross, P.; Vang, S.; Christensen, J.H. Protein misfolding and human disease. *Annu Rev. Genom. Hum. Genet.* **2006**, *7*, 103–124. [[CrossRef](#)] [[PubMed](#)]
175. Chiti, F.; Dobson, C.M. Protein misfolding, functional amyloid, and human disease. *Annu Rev. Biochem.* **2006**, *75*, 333–366. [[CrossRef](#)] [[PubMed](#)]
176. Herczenik, E.; Gebbink, M.F. Molecular and cellular aspects of protein misfolding and disease. *FASEB J.* **2008**, *22*, 2115–2133. [[CrossRef](#)] [[PubMed](#)]
177. Singh, L.R.; Dar, T.A.; Rahman, S.; Jamal, S.; Ahmad, F. Glycine betaine may have opposite effects on protein stability at high and low pH values. *Biochim. Biophys. Acta* **2009**, *1794*, 929–935. [[CrossRef](#)]
178. Singh, L.R.; Poddar, N.K.; Dar, T.A.; Rahman, S.; Kumar, R.; Ahmad, F. Forty years of research on osmolyte-induced protein folding and stability. *J. Iran. Chem. Soc.* **2011**, *8*, 1–23. [[CrossRef](#)]
179. Rahman, S.; Rehman, M.T.; Singh, L.R.; Warepam, M.; Ahmad, F.; Dar, T.A. Salt potentiates methylamine counteraction system to offset the deleterious effects of urea on protein stability and function. *PLoS ONE* **2015**, *10*, e0119597. [[CrossRef](#)]
180. Rahman, S.; Warepam, M.; Singh, L.R.; Dar, T.A. A current perspective on the compensatory effects of urea and methylamine on protein stability and function. *Prog. Biophys. Mol. Biol.* **2015**, *119*, 129–136. [[CrossRef](#)]
181. Chowhan, R.K.; Ali, F.; Bhat, M.Y.; Rahman, S.; Singh, L.R.; Ahmad, F.; Dar, T.A. Alanine Counteracts the Destabilizing Effect that Urea has on RNase-A. *Protein Pept. Lett.* **2016**, *23*, 795–799. [[CrossRef](#)]
182. Rahman, S.; Ali, S.A.; Islam, A.; Hassan, M.I.; Ahmad, F. Testing the dependence of stabilizing effect of osmolytes on the fractional increase in the accessible surface area on thermal and chemical denaturations of proteins. *Arch. Biochem. Biophys.* **2016**, *591*, 7–17. [[CrossRef](#)]
183. Rahman, S.; Ali, S.A.; Islam, A.; Hassan, M.I.; Ahmad, F. Data on the role of accessible surface area on osmolytes-induced protein stabilization. *Data Brief.* **2017**, *10*, 47–56. [[CrossRef](#)]
184. Rahman, S.; Park, J.; Kim, J. Osmolytes Offset the Urea's Effect on Protein Structure and Function. In *Cellular Osmolytes: From Chaperoning Protein Folding to Clinical Perspectives*; Rajendrakumar, S., Laishram, D., Tanveer, A., Eds.; Springer: Singapore, 2017; pp. 77–96. [[CrossRef](#)]
185. Rahman, S.; Archana, A.; Azam, M.; Jan, A.T.; Dutta, D.; Minakshi, R. Role of Osmolytes and their Transporter Systems in Pathogen Survival and Pathogenicity. *Curr. Drug Metab.* **2018**, *19*, 992–1001. [[CrossRef](#)] [[PubMed](#)]
186. Rahman, S.; Islam, A.; Hassan, M.I.; Kim, J.; Ahmad, F. Unfoldness of the denatured state of proteins determines urea: Methylamine counteraction in terms of Gibbs free energy of stabilization. *Int. J. Biol. Macromol.* **2019**, *132*, 666–676. [[CrossRef](#)] [[PubMed](#)]
187. Green, T.R.; Fellman, J.H.; Eicher, A.L.; Pratt, K.L. Antioxidant role and subcellular location of hypotaurine and taurine in human neutrophils. *Biochim. Biophys. Acta* **1991**, *1073*, 91–97. [[CrossRef](#)]
188. Jeon, S.H.; Lee, M.Y.; Rahman, M.M.; Kim, S.J.; Kim, G.B.; Park, S.Y.; Hong, C.U.; Kim, S.Z.; Kim, J.S.; Kang, H.S. The antioxidant, taurine reduced lipopolysaccharide (LPS)-induced generation of ROS, and activation of MAPKs and Bax in cultured pneumocytes. *Pulm. Pharm. Ther.* **2009**, *22*, 562–566. [[CrossRef](#)] [[PubMed](#)]
189. Oliveira, M.W.; Minotto, J.B.; de Oliveira, M.R.; Zanotto-Filho, A.; Behr, G.A.; Rocha, R.F.; Moreira, J.C.; Klamt, F. Scavenging and antioxidant potential of physiological taurine concentrations against different reactive oxygen/nitrogen species. *Pharm. Rep.* **2010**, *62*, 185–193. [[CrossRef](#)]
190. Schaffer, S.; Kim, H.W. Effects and Mechanisms of Taurine as a Therapeutic Agent. *Biomol. Ther. (Seoul)* **2018**, *26*, 225–241. [[CrossRef](#)]

191. Santoro, M.M.; Liu, Y.F.; Khan, S.M.A.; Hou, L.X.; Bolen, D.W. Increased Thermal-Stability of Proteins in the Presence of Naturally-Occurring Osmolytes. *Biochemistry* **1992**, *31*, 5278–5283. [[CrossRef](#)]
192. Taneja, S.; Ahmad, F. Increased thermal stability of proteins in the presence of amino acids. *Biochem. J.* **1994**, *303 Pt 1*, 147–153. [[CrossRef](#)]
193. Xie, G.F.; Timasheff, S.N. Temperature dependence of the preferential interactions of ribonuclease A in aqueous co-solvent systems: Thermodynamic analysis. *Protein Sci.* **1997**, *6*, 222–232. [[CrossRef](#)]
194. Xie, G.F.; Timasheff, S.N. Mechanism of the stabilization of ribonuclease A by sorbitol: Preferential hydration is greater for the denatured than for the native protein. *Protein Sci.* **1997**, *6*, 211–221. [[CrossRef](#)]
195. Anjum, F.; Rishi, V.; Ahmad, F. Compatibility of osmolytes with Gibbs energy of stabilization of proteins. *Biochim. Biophys. Acta* **2000**, *1476*, 75–84. [[CrossRef](#)]
196. Abe, Y.; Ohkuri, T.; Yoshitomi, S.; Murakami, S.; Ueda, T. Role of the osmolyte taurine on the folding of a model protein, hen egg white lysozyme, under a crowding condition. *Amino Acids* **2015**, *47*, 909–915. [[CrossRef](#)] [[PubMed](#)]
197. Arakawa, T.; Timasheff, S.N. The stabilization of proteins by osmolytes. *Biophys. J.* **1985**, *47*, 411–414. [[CrossRef](#)]
198. Bruździak, P.; Panuszko, A.; Kaczkowska, E.; Piotrowski, B.; Dagher, A.; Demkowicz, S.; Stangret, J. Taurine as a water structure breaker and protein stabilizer. *Amino Acids* **2018**, *50*, 125–140. [[CrossRef](#)]
199. Khan, S.; Bano, Z.; Singh, L.R.; Hassan, M.I.; Islam, A.; Ahmad, F. Testing the ability of non-methylamine osmolytes present in kidney cells to counteract the deleterious effects of urea on structure, stability and function of proteins. *PLoS ONE* **2013**, *8*, e72533. [[CrossRef](#)]
200. Santa-María, I.; Hernández, F.; Moreno, F.J.; Avila, J. Taurine, an inducer for tau polymerization and a weak inhibitor for amyloid- β -peptide aggregation. *Neurosci. Lett.* **2007**, *429*, 91–94. [[CrossRef](#)]
201. Chaturvedi, S.K.; Alam, P.; Khan, J.M.; Siddiqui, M.K.; Kalaiarasan, P.; Subbarao, N.; Ahmad, Z.; Khan, R.H. Biophysical insight into the anti-amyloidogenic behavior of taurine. *Int. J. Biol. Macromol.* **2015**, *80*, 375–384. [[CrossRef](#)]
202. Jang, H.; Lee, S.; Choi, S.L.; Kim, H.Y.; Baek, S.; Kim, Y. Taurine Directly Binds to Oligomeric Amyloid-beta and Recovers Cognitive Deficits in Alzheimer Model Mice. *Adv. Exp. Med. Biol.* **2017**, *975 Pt 1*, 233–241. [[CrossRef](#)]
203. Kim, H.Y.; Kim, H.V.; Yoon, J.H.; Kang, B.R.; Cho, S.M.; Lee, S.; Kim, J.Y.; Kim, J.W.; Cho, Y.; Woo, J.; et al. Taurine in drinking water recovers learning and memory in the adult APP/PS1 mouse model of Alzheimer's disease. *Sci. Rep.* **2014**, *4*, 7467. [[CrossRef](#)]
204. Macchi, F.; Eisenkolb, M.; Kiefer, H.; Otzen, D.E. The effect of osmolytes on protein fibrillation. *Int. J. Mol. Sci.* **2012**, *13*, 3801–3819. [[CrossRef](#)]
205. Kamisaki, Y.; Wada, K.; Nakamoto, K.; Itoh, T. Release of taurine and its effects on release of neurotransmitter amino acids in rat cerebral cortex. *Adv. Exp. Med. Biol.* **1996**, *403*, 445–454. [[CrossRef](#)] [[PubMed](#)]
206. Qiu, Z.; Dubin, A.E.; Mathur, J.; Tu, B.; Reddy, K.; Miraglia, L.J.; Reinhardt, J.; Orth, A.P.; Patapoutian, A. SWELL1, a plasma membrane protein, is an essential component of volume-regulated anion channel. *Cell* **2014**, *157*, 447–458. [[CrossRef](#)] [[PubMed](#)]
207. Saransaari, P.; Oja, S.S. Modulation of the ischemia-induced taurine release by adenosine receptors in the developing and adult mouse hippocampus. *Neuroscience* **2000**, *97*, 425–430. [[CrossRef](#)]
208. Saransaari, P.; Oja, S.S. Taurine and neural cell damage. *Amino Acids* **2000**, *19*, 509–526. [[CrossRef](#)] [[PubMed](#)]
209. Saransaari, P.; Oja, S.S. Characteristics of taurine release in slices from adult and developing mouse brain stem. *Amino Acids* **2006**, *31*, 35–43. [[CrossRef](#)]
210. El Idrissi, A.; L'Amoreaux, W.J. Selective resistance of taurine-fed mice to isoniazide-potentiated seizures: In vivo functional test for the activity of glutamic acid decarboxylase. *Neuroscience* **2008**, *156*, 693–699. [[CrossRef](#)]
211. Chan, C.Y.; Sun, H.S.; Shah, S.M.; Agovic, M.S.; Ho, I.; Friedman, E.; Banerjee, S.P. Direct interaction of taurine with the NMDA glutamate receptor subtype via multiple mechanisms. *Adv. Exp. Med. Biol.* **2013**, *775*, 45–52. [[CrossRef](#)]
212. Suarez, L.M.; Solis, J.M. Taurine potentiates presynaptic NMDA receptors in hippocampal Schaffer collateral axons. *Eur. J. Neurosci.* **2006**, *24*, 405–418. [[CrossRef](#)]
213. Schaffer, S.W.; Shimada-Takaura, K.; Jong, C.J.; Ito, T.; Takahashi, K. Impaired energy metabolism of the taurinedeficient heart. *Amino Acids* **2016**, *48*, 549–558. [[CrossRef](#)]

214. Jeejeebhoy, F.; Keith, M.; Freeman, M.; Barr, A.; McCall, M.; Kurian, R.; Mazer, D.; Errett, L. Nutritional supplementation with MyoVive repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction. *Am. Heart J.* **2002**, *143*, 1092–1100. [[CrossRef](#)] [[PubMed](#)]
215. Sokka, A.L.; Putkonen, N.; Mudo, G.; Pryazhnikov, E.; Reijonen, S.; Khiroug, L.; Belluardo, N.; Lindholm, D.; Korhonen, L. Endoplasmic reticulum stress inhibition protects against excitotoxic neuronal injury in the rat brain. *J. Neurosci.* **2007**, *27*, 901–908. [[CrossRef](#)] [[PubMed](#)]
216. Higo, T.; Hamada, K.; Hisatsune, C.; Nukina, N.; Hashikawa, T.; Hattori, M.; Nakamura, T.; Mikoshiba, K. Mechanism of ER stress-induced brain damage by IP (3) receptor. *Neuron* **2010**, *68*, 865–878. [[CrossRef](#)]
217. Anand, S.S.; Babu, P.P. Endoplasmic reticulum stress and neurodegeneration in experimental cerebral malaria. *Neurosignals* **2013**, *21*, 99–111. [[CrossRef](#)] [[PubMed](#)]
218. Ito, T.; Yoshikawa, N.; Inui, T.; Miyazaki, N.; Schaffer, S.W.; Azuma, J. Tissue depletion of taurine accelerates skeletal muscle senescence and leads to early death in mice. *PLoS ONE* **2014**, *9*, e107409. [[CrossRef](#)]
219. Pan, C.; Giraldo, G.S.; Prentice, H.; Wu, J.Y. Taurine protection of PC12 cells against endoplasmic reticulum stress induced by oxidative stress. *J. Biomed. Sci.* **2010**, *17*, S17. [[CrossRef](#)] [[PubMed](#)]
220. Niu, X.; Zheng, S.; Liu, H.; Li, S. Protective effects of taurine against inflammation, apoptosis, and oxidative stress in brain injury. *Mol. Med. Rep.* **2018**, *18*, 4516–4522. [[CrossRef](#)] [[PubMed](#)]
221. Behar, T.N.; Scott, C.A.; Greene, C.L.; Wen, X.; Smith, S.V.; Maric, D.; Liu, Q.Y.; Colton, C.A.; Barker, J.L. Glutamate acting at NMDA receptors stimulates embryonic cortical neuronal migration. *J. Neurosci.* **1999**, *19*, 4449–4461. [[CrossRef](#)]
222. Ikonomidou, C.; Bosch, F.; Miksa, M.; Bittigau, P.; Vockler, J.; Dikranian, K.; Tenkova, T.I.; Stefovskaja, V.; Turski, L.; Olney, J.W. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. *Science* **1999**, *283*, 70–74. [[CrossRef](#)]
223. Wu, G.; Meier, S.A.; Knabe, D.A. Dietary glutamine supplementation prevents jejunal atrophy in weaned pigs. *J. Nutr.* **1996**, *126*, 2578–2584. [[CrossRef](#)]
224. Chen, W.Q.; Jin, H.; Nguyen, M.; Carr, J.; Lee, Y.J.; Hsu, C.C.; Faiman, M.D.; Schloss, J.V.; Wu, J.Y. Role of taurine in regulation of intracellular calcium level and neuroprotective function in cultured neurons. *J. Neurosci. Res.* **2001**, *66*, 612–619. [[CrossRef](#)]
225. El Idrissi, A.; Trenkner, E. Growth factors and taurine protect against excitotoxicity by stabilizing calcium homeostasis and energy metabolism. *J. Neurosci.* **1999**, *19*, 9459–9468. [[CrossRef](#)] [[PubMed](#)]
226. Wu, H.; Jin, Y.; Wei, J.; Jin, H.; Sha, D.; Wu, J.Y. Mode of action of taurine as a neuroprotector. *Brain Res.* **2005**, *1038*, 123–131. [[CrossRef](#)] [[PubMed](#)]
227. Lazarewicz, J.W.; Noremborg, K.; Lehmann, A.; Hamberger, A. Effects of taurine on calcium binding and accumulation in rabbit hippocampal and cortical synaptosomes. *Neurochem. Int.* **1985**, *7*, 421–427. [[CrossRef](#)]
228. Ramila, K.C.; Jong, C.J.; Pastukh, V.; Ito, T.; Azuma, J.; Schaffer, S.W. Role of protein phosphorylation in excitation-contraction coupling in taurine deficient hearts. *Am. J. Physiol. Heart Circ. Physiol.* **2014**, *308*, H232–H239. [[CrossRef](#)] [[PubMed](#)]
229. Vesce, S.; Kirk, L.; Nicholls, D.G. Relationships between superoxide levels and delayed calcium deregulation in cultured cerebellar granule cells exposed continuously to glutamate. *J. Neurochem.* **2004**, *90*, 683–693. [[CrossRef](#)] [[PubMed](#)]
230. Prentice, H.; Modi, J.P.; Wu, J.Y. Mechanisms of neuronal protection against excitotoxicity, endoplasmic reticulum stress, and mitochondrial dysfunction in stroke and neurodegenerative diseases. *Oxid. Med. Cell Longev.* **2015**, *2015*, 964518. [[CrossRef](#)] [[PubMed](#)]
231. Leon, R.; Wu, H.; Jin, Y.; Wei, J.; Buddhala, C.; Prentice, H.; Wu, J.Y. Protective function of taurine in glutamate-induced apoptosis in cultured neurons. *J. Neurosci. Res.* **2009**, *87*, 1185–1194. [[CrossRef](#)]
232. Jeong, J.E.; Kim, T.Y.; Park, H.J.; Lee, K.H.; Lee, K.H.; Choi, E.J.; Kim, J.K.; Chung, H.L.; Seo, E.S.; Kim, W.T. Taurine exerts neuroprotective effects via anti-apoptosis in hypoxic-ischemic brain injury in neonatal rats. *Korean J. Pediatr.* **2009**, *52*, 1337–1347. [[CrossRef](#)]

