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# The Effects of Taurine on Central Nervous System

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**Abstract:** Taurine is a neuroprotective amino acid which regulates gene expression of neural stem and precursor cells, modulating inflammatory pathways in the central nervous system, suppressing apoptosis, antioxidant effect and controlling cell volume and water content of neurons. Taurine suppresses endoplasmic stress-mediated apoptosis through the ionotropic taurine receptor and the metabotropic taurine receptor. Due to its neuroprotective effect, taurine is successfully used in the prophylaxis and treatment of neurodegenerative disorders. This review aims to present current scientific information of the effects of taurine on the central nervous system and its use in alleviating central nervous system disorders.
**Keywords:** Central nervous system, Neuroprotective, Taurine.

## Taurinin Merkezi Sinir Sistemi Üzerindeki Etkileri

**Özet:** Taurin, nöral kök ve prekürsör hücrelerin gen ekspresyonunu düzenleyen, merkezi sinir sistemindeki enflamatuar yolları modüle eden, apoptozu baskılayan, antioksidan etkili ve nöronların hacmini ve su içeriğini kontrol eden nöroprotektif bir amino asittir. Taurin, iyonotropik taurin reseptörü ve metabotropik taurin reseptörü aracılığıyla endoplazmik stres aracılı apoptozu baskılamaktadır. Nöroprotektif etkisi nedeniyle taurin nörodejeneratif bozuklukların profilaksisinde ve tedavisinde başarıyla kullanılmaktadır. Bu derlemenin amacı, taurinin merkezi sinir sistemi üzerindeki etkilerini ve taurinin merkezi sinir sistemi hasarlarını hafifletmede kullanımını konusunda güncel bilimsel bilgiyi sunmaktır.
***Anahtar Kelimeler:*** *Merkezi sinir sistemi, Nöroprotektif, Taurin.*

## Introduction

Taurine is synthesized from the cysteine in the organism with molecular formula $C_2H_7N0_3S$ and molecular weight 125.15 g $mol^{-1}$ (Ripps and Shen, 2012). Taurine was first isolated from ox bile in 1827 by German scientists Friedrich Tiedemann and Leopold Gmelin (Tiedemann and Gmelin, 1827). The first step in the synthesis of taurine is the conversion of methionine to cysteine through transsulfuration. Cysteine is oxidized to cysteine sulfinic acid, and also converted to cysteamine, and cysteamine is oxidized to hypotaurine. Taurine is synthesized as a final product by the oxidation of hypotaurine (Menzie et al., 2013; Ripps and Shen, 2012). The major steps of taurine biosynthesis were presented in Figure 1.

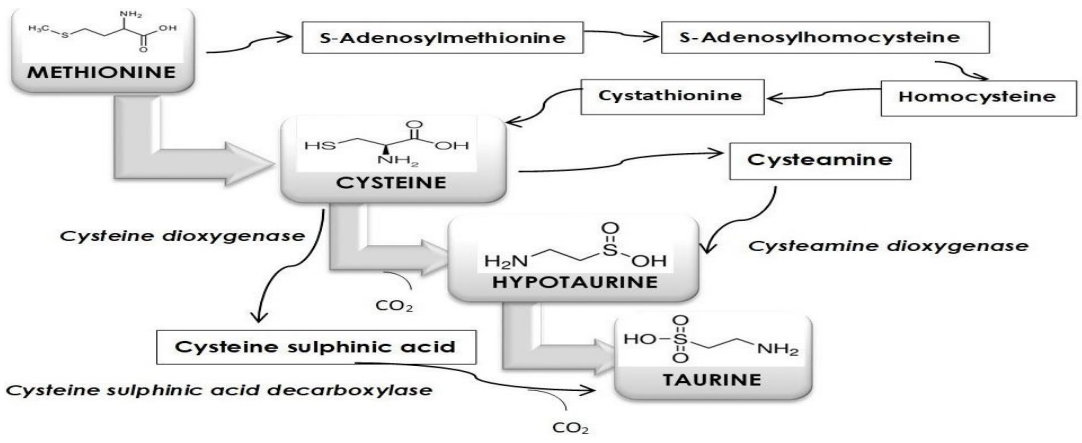


**Figure 1.** The major steps of taurine biosynthesis. ( Adapted from Menzie et al., 2013).

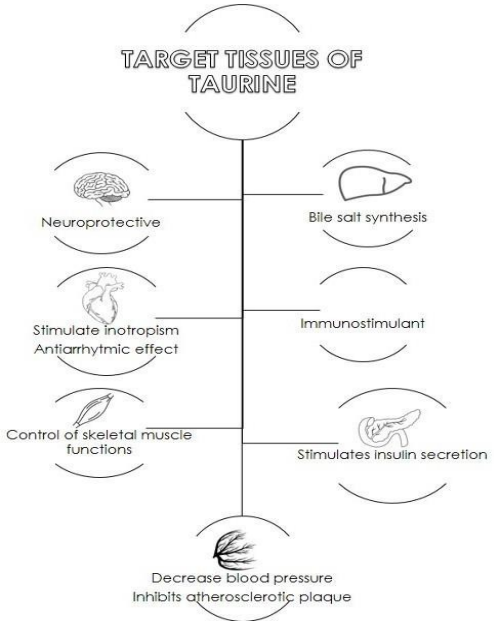


**Figure 2.** The effects of taurine in various tissues and organs (Adapted from De Luca et al., 2015)

**General effects of the taurine on organism:** Taurine controls the membrane excitability of the skeletal muscle and phenotypic properties (De Luca et al., 2015). Taurine has important effects such as neuromodulator, antioxidant, anti-inflammatory, antiarrhythmic, and anti-cholestatic (Chen et al., 2020; Jangra et al., 2020; Liu et al., 2017). Taurine is an effect on glycine receptors and reduces glycine affinity in postsynaptic neurons (Chan et al., 2013). Taurine inhibits hypothalamic leptin resistance (Camargo et al., 2015). Taurine stimulates
GABAA receptor-mediated action potentials in GABAergic neurons (Jia et al., 2008). The effects of taurine in various tissues and organs were presented in Figure 2.

**The effects of taurine on the central nervous system:** Taurine is found in the central nervous system and the neuroprotective effect of taurine has been reported by many studies (Ananchaipatana-Auitragoon et al., 2015; Foos and Wu, 2002; Reeta et al., 2017; Vitvitsky et al., 2011; Wang et al., 2007; Wu et al., 2005; Wu and Prentice, 2010; Zhang et al., 2017). Taurine shows these effects by promoting proliferation and survival of neural progenitor cells, acting as neuro-osmolyte, protecting against endoplasmic stress and neurotoxicity, and providing the cellular integrity of auditory neurons. (Hernández-Benítez et al., 2010; Pan et al., 2012; Rak et al., 2014; Hackett et al., 2016). A schematic view of the neuroprotective effect of taurine is presented in Figure 3.

**The effects of taurine on proliferation and survival of neural cells:** Taurine, which contributes to proliferation and survival of neural progenitor cells, is suggested to be a trophic factor for these cells. It has been reported

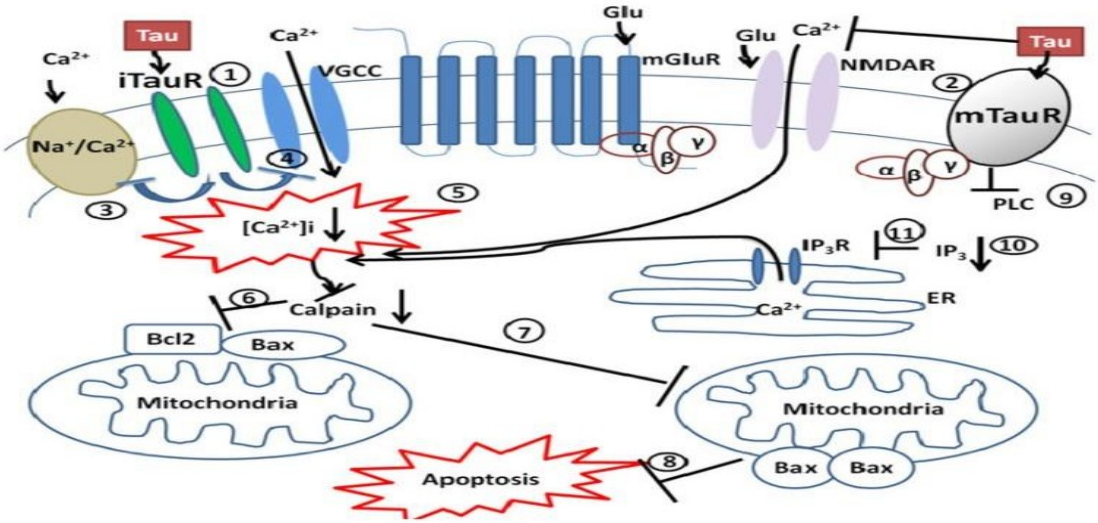


**Figure 3.** A schematic view of the neuroprotective effect of taurine via taurine receptors (1) Activated ionotropic taurine receptor (iTauR) and/or (2) metabotropic taurine receptor (mTauR) inhibits, sodium/calcium exchanger (3); (4) The inhibition of voltage-dependent calcium channels (VGCC) due to taurine-induced hyperpolarization causes intracellular calcium deprivation (5). Decreased intracellular calcium inhibits calpain and the calpain- induced breakdown of Bcl-2 and Bax is shaped (6). (7) Inhibition of the Bax homodimer leads to the inhibition of the mitochondrion-mediated death cascade (8). (9) Phospholipase C (PLC) is inhibited by the active mTauR (mTauR: bound to the inhibitor G protein) and results in reduced production of IP3 which attenuates calcium release from the endoplasmic reticulum (ER) (10) and causes ER stress and ER stress-mediated apoptosis (Menzie et al., 2013).

that the increasing effect of taurine in neural precursor cells from the subventricular zone of the adult mouse brain (Hernandez et al., 2012) is 5 times greater than in embryonic cells (Hernández-Benítez et al., 2010). The researchers linked this finding to the fact that embryonic cells are growing in an environment rich in taurine. Taurine in developing brain tissue plays a role in neural stem/progenitor cell proliferation via ERK1/2 pathways and affects protein levels associated with

synapse development (Shivaraj et al., 2012). This study is stated to be the first evidence showing the effect of taurine on early postnatal neuronal development using a combination of *in vitro*, *ex-vivo,* and *in vivo* systems. Similarly, taurine has been reported to stimulate the proliferation and neurite outgrowth of neural stem cells, which was completely abolished by sonic hedgehog inhibitor cyclopamine, into spiral ganglia by activating the sonic hedgehog signaling pathway. It has been emphasized that and the important role of sonic hedgehog pathway underlying the protective effect of taurine on the auditory neural system (Huang et al., 2018).

**The effects of taurine as neuro-osmolyte:** Increased extracellular taurine levels during perfusions with Krebs-ringer bicarbonate in the rat dentate gyrus have been determined. This result indicates the possible involvement of taurine in osmoregulatory processes in the brain (Solís et al., 1988). Taurine functions as an osmolyte by controlling membrane content and water content of neurons during ion entry and exit by membrane depolarization of neuronal transmission in brain tissue (Olson and Martinho, 2006). Taurine, which is found intensely in the granular and molecular layers of the cerebellum, is defined as neuro-osmolyte (Hackett et al., 2016). During the local osmotic alteration, increased cellular hydration was accompanied by a marked increase in extracellular taurine levels in the rat brain has been demonstrated. The specificity, sensitivity, and reversibility of this increase in extracellular taurine strongly suggest a functional role in osmoregulation in the brain under normal as well as pathological conditions (Wade et al., 1988).

**The effect of taurine against endoplasmic stress:** Taurine has been reported to have a protective role against activation of endoplasmic stress pathways in rat primary cortical neuronal culture. It has been suggested that taurine exerts this effect by inhibiting the upregulation of caspase-12 and GADD153 / CHOP caused by hypoxia/reoxygenation (Pan et al., 2012). Taurine release in mouse hippocampal slices has been shown that regulated by ionotropic glutamate and the adenosine receptors and may counteract any excitotoxic effects of glutamate, particularly in the developing hippocampus (Oja and Saransaari, 2013). The levels of the endoplasmic reticulum stress protein markers GRP78, caspase-12, CHOP, and p-IRE-1 which has been markedly increased *in vitro* and *in vivo* model of rat focal middle cerebral artery occlusion significantly has been declined after taurine administration (Gharibani et al., 2013).

**The effects of taurine on cellular integrity of neurons:** Recently, taurine has been linked to neurite outgrowth, synaptogenesis, and synaptic transmission during the early stages of brain development in both vertebrate and invertebrate species (Mersman et al., 2020). Taurine protects the cellular integrity of auditory neurons and also promotes cellular survival (Rak et al., 2014). Hypoxic pulses given to the substantia nigra by the microdialysis probe have been shown to increase the extrasynaptic taurine level and decrease the taurine level as the osmolarity increases and it has been suggested that the non-synaptic taurine pool which is in substantia nigra plays a role in the defense of nigral cells in Parkinson's disease (Morales et al., 2007). Glial cells secrete taurine to prevent the harmful effects of extracellular hypotonicity on cell volume (Cardin et al., 2003; Deleuze et al., 2000).

**Preventive effects of taurine against neurotoxicity:** Taurine has a neuroprotective effect against glutamate-induced neurotoxicity (Wu et al., 2005). Taurine inhibits not only the electrical activity of vasopressin neurons but also acts as an inhibitor of both central and peripheral vasopressin secretion during different physiological states (Engelmann et al., 2001). Taurine pretreatment has been shown a protective effect against unconjugated bilirubin-induced damage via reversal of the increased intracellular free calcium ion levels in primary neuronal cultures in a concentration-dependent manner (Zhang et al., 2010). The protective role of taurine treatment at 20 and 1 mM concentrations through activation of GABAA receptors in 1-methyl-4-phenylpyridinium ($MPP^+$) induced neurotoxicity rat model has been determined (O'Byrne and Tipton, 2000). Vohra et al. (2001) have reported that taurine protects neurons from the oxidative stress induced by carbon tetrachloride toxicity in a dose-dependent manner.

**The use of taurine in central nervous system disorders:** Increasing evidence has been indicated that the important roles of taurine administration in alleviating and treating central nervous system damage. Taurine has been reported to enhance the viability and proliferation of mouse cochlear neural stem cell cultures (Wang et al., 2015). Taurine reduces white matter damage and hippocampal neuronal death by suppressing calpain activation and protecting against gray and white matter damage in closed head-trauma rats (Gu et al., 2015). Taurine reinforcement in neural stem and precursor cells derived from mesencephalon of mouse embryos regulates cell proliferation and survival, gene expression of neural stem and precursor cells involved in adhesion and mitochondrial functions (Pasantes-Morales et al., 2015). It has been reported that taurine promote axonal regeneration in the spinal cord injury using

lampreys as an animal model (Sobrido-Cameán et al., 2020).

Taurine supplementation alleviates white matter damage by reducing brain edema, hemorrhagic lesion volume, and neuronal damage (Zhao et al., 2018; Seki et al. (2005) have suggested that taurine administration alleviates neuronal damage, inflammation, and white matter damage by upregulating the content of hydrogen sulfide in tissues around the hematoma and by suppressing P2X7R receptor expression. In this mentioned work, it has been determined that cerebrospinal fluid taurine concentration increased 1.8-fold in severe traumatic brain injury and declined to a control level of 67 hours after injury.

Taurine has been suggested to have an important potential in primary cortical neuron culture to reducing nickel-induced lactate dehydrogenase release, production of oxygen derivatives and mitochondrial superoxide levels, alleviation of superoxide dismutase and glutathione peroxidase activities reduction, and elimination of adverse effects of nickel in the nervous system (Xu et al., 2015). Astrocytes, which capable of producing taurine under proinflammatory signals, are responsible for changes in taurine levels after brain damage (Junyent et al., 2011). Taurine has been postulated that to reduce neurotoxicity and may be a promising target in the treatment of neurodegenerative diseases (Louzada et al., 2004; Paula-Lima et al., 2005). Cerebellum taurine content has been reported to decrease during the aging process in rats (Suárez et al., 2016). Taurine relieves streptozotocin-induced cognitive impairment via suppressing oxidative stress and inflammatory cytokines (Reeta et al., 2017). Caletti et al. (2018) set forth that long-term taurine treatment decreased oxidative stress, protects against DNA damage, and reduced inflammation in the diabetic rat brain.

Taurine has a potential neuroprotective effect via exhibiting antioxidative and mitochondria protective effects against manganese neurotoxicity (Ommati et al., 2019). In rats exposed to drinking water and sodium fluoride, taurine administration with oral gavage decreased the oxidative stress index in brain tissue, suppressed elevation in inflammatory biological markers, and reversed caspase-3 activity (Adedara et al., 2017). Taurine exhibit neuroprotective effects to dopaminergic neurons via inhibition of neuroinflammation which caused by microglia (Che et al., 2018). In a transgenic mouse model of Alzheimer's disease, administration of taurine via drinking water for 6 weeks has rescued cognitive deficits. Researchers have suggested that taurine can aid cognitive impairment and may inhibit Aβ-related damages (Kim et al., 2014). Taurine has neuroprotective effects against glutamatergic antagonist-induced memory deficit and hyperlocomotion in zebrafish (Franscescon et al., 2020).

## Conclusion

Both *in vivo* and *in vitro* researches have indicated that taurine has important effects on the central nervous system. Taurine has neurotrophic and neuroprotective effects by suppressing calpain activation through taurine receptors, coordinating gene expressions of neural stem and precursor cells, inhibiting sodium/calcium modifier, and endoplasmic reticulum stress-mediated apoptosis suppression. Taurine, which contributes to the proliferation and survival of neural progenitor cells, is a trophic factor for these cells. Taurine is involved in neural stem/progenitor cell proliferation in developing brain tissue and controls cell content and water content of neurons during ion entry and exit through membrane depolarization in neuronal transmissions. Taking into account the results of scientific studies based on the administration of taurine due to its neuroprotective effects, it is understood that taurine is an alternative option in the treatment of neurodegenerative diseases of both humans and animals

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