Review

New solutions for old challenges in glaucoma treatment: is taurine an option to consider?

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Igor Iezhitsa[1, 2, *], Renu Agarwal[1]

Abstract

Glaucoma is a range of progressive optic neuropathies characterized by progressive retinal ganglion cell loss and visual field defects. It is recognized as a leading cause of irreversible blindness affecting more than 70 million people worldwide. Currently, reduction of intraocular pressure, a widely recognized risk factor for glaucoma development, is the only pharmacological strategy for slowing down retinal ganglion cell loss and disease progression. However, retinal ganglion cell death and visual field loss have been observed in normotensive glaucoma, suggesting that the disease process is partially independent of intraocular pressure. Taurine is one of the agents that have attracted attention of researchers recently. Taurine has been shown to be involved in multiple cellular functions, including a central role as a neurotransmitter, as a trophic factor in the central nervous system development, as an osmolyte, as a neuromodulator, and as a neuroprotectant. It also plays a role in the maintenance of the structural integrity of the membranes and in the regulation of calcium transport and homeostasis. Taurine is known to prevent N-methyl-D-aspartic acid-induced excitotoxic injury to retinal ganglion cells. A recently published study clearly demonstrated that taurine prevents retinal neuronal apoptosis both *in vivo* and *in vitro*. Protective effect of taurine may be attributed to direct inhibition of apoptosis, an activation of brain derived neurotrophic factor-related neuroprotective mechanisms and reduction of retinal oxidative and nitrosative stresses. Further studies are needed to fully explore the potential of taurine as a neuroprotective agent, so that it can be applied in clinical practice, particularly for the treatment of glaucoma. The objective of current review was to summarize recent evidence on neuroprotective properties of taurine in glaucoma.

Key Words: apoptosis; excitotoxicity; glaucoma; oxidative and nitrosative stresses; retinal neuroprotection; taurine

Introduction

Glaucoma, a group of progressive optic neuropathies, is characterized by progressive retinal ganglion cell (RGC) loss and visual field defects. It is recognized as the leading cause of irreversible blindness affecting more than 70 million people worldwide. According to one estimation, the number of patients with glaucoma will increase to 111.8 million by 2040, disproportionally affecting more people in developing countries (Tham et al., 2014). The pathogenesis of glaucoma remains debatable, however, it is proposed to involve excitototoxicity, endothelin receptor activation, mitochondrial dysfunction, endoplasmic reticulum stress, oxidative stress, axonal transport failure, neurotrophic factor deprivation and activation of intrinsic and extrinsic apoptotic cascades (Agarwal et al., 2009). Currently, reduction of intraocular pressure, a widely recognized risk factor for development of glaucoma, is the only pharmacological strategy for slowing down RGC loss and disease progression. However, RGC death and visual field loss have been observed in normotensive patients, suggesting that the disease process, at least partially, is independent of intraocular pressure. Therefore, an expectation that the RGC loss could be prevented secondary to intraocular pressure reduction across all groups of patients seems implausible. In fact, over the past decade, numerous strategies have been explored to prevent RGC death independent of intraocular pressure reduction. Among them, various neuroprotective strategies and their corresponding pharmacological agents have been tested in pre-clinical animal models with varying success.

Taurine (TAU) is one of the agents that has attracted the attention of researchers recently. TAU was first discovered in ox bile in 1827 and until 1975, it was not classified as an essential amino acid for human nutrition (L'Amoreaux, 2012). It is a non-protein amino acid abundantly distributed in the human body. It can be synthesized endogenously from methionine and cysteine in the presence of vitamin B6, but obtaining it from dietary sources or supplements is necessary to maintain optimum levels. It is important to note that vegetarian and vegan foods do not contain much TAU. As a result, it may be especially important for people who follow these diets to take supplements.

In the early 1970s, TAU was reported to play an important role in maintaining normal vision as it was found in high

[1]School of Medicine, International Medical University, Kuala Lumpur, Malaysia; [2]Volgograd State Medical University, Research Centre for Innovative Medicines, Volgograd, Russian Federation

*__Correspondence to:__ Igor Iezhitsa, PhD, igoriezhitsa@imu.edu.my or iezhitsa@yandex.ru.

https://orcid.org/0000-0002-2852-8486 (Igor Iezhitsa)

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concentrations in the retina and lateral geniculate nuclei (Guidotti et al., 1972). TAU depletion was shown to induce photoreceptor degeneration, involving cone photoreceptors more than the rod photoreceptors (Militante and Lombardini, 2002) and recently it was found to trigger RGC loss (Gaucher et al., 2012). It has been observed that TAU can directly prevent RGC degeneration, occurring either in serum-deprived pure RGC cultures or in animal models presenting with the RGC loss (Froger et al., 2013). Furthermore, TAU supplementation was also shown to increase RGC densities in DBA/2J mice, in rats with retinal vein occlusion and in P23H rats as compared with the control group rats drinking TAU-free water (Froger et al., 2012). Behavioral studies using rhesus monkeys showed that TAU deficiency results in retinal degeneration and visual acuity loss (Neuringer and Sturman, 1987). Significant retinal neuronal loss was also observed in rats that had low retinal TAU content after exposure to high-intensity light (Rapp et al., 1988). Furthermore, TAU depletion caused specific changes in the activity of protein kinases in the retina, suggesting involvement of TAU in endogenous protein phosphorylation (Militante and Lombardini, 2002). The objective of current review was to summarize recent evidence on neuroprotective properties of TAU in glaucoma. An online search of PubMed was performed with the search terms taurine, neuroprotection, neurodegeneration, glaucoma, retina alone and in combinations. A total of 51 papers published between 1975 and 2020 were included in this review.

Taurine Prevents Excitotoxic and Ischemic Damages to Retinal Ganglion Cells

Some of the pharmacological properties of TAU seem to be extremely relevant to its potential use as a neuroprotective agent in glaucoma. In this regard, TAU is known to prevent N-methyl-D-aspartic acid (NMDA)-induced excitotoxic injury to RGCs (Froger et al., 2012; Jafri et al., 2019; Lambuk et al., 2019). In NMDA-exposed RGCs, treatment with TAU has been shown to increase the mitochondrial capacity to sequester calcium, thus reducing free intracellular calcium ions $[Ca^{2+}]_i$ (El Idrissi, 2008; Froger et al., 2012). TAU was also reported to modulate $[Ca^{2+}]_i$ through voltage-dependent Ca^{2+} and Na^+ channels (Militante and Lombardini, 1998) and this effect may contribute to its neuroprotective effects against glutamate-induced excitotoxicity (Vesce et al., 2004). In photoreceptors, TAU has been suggested to play the role of organic osmolyte and modulator of ion flux (Pasantes-Morales et al., 1984). In our recent studies (Jafri et al., 2018; Nor Arfuzir et al., 2018; Lambuk et al., 2019), neuroprotective effects of TAU were observed against NMDA- and endothelin (ET-1) induced retinal and optic nerve injury. Retinal morphology in the TAU pre-treated rats was found to be similar to the control retinas with higher number of intact nuclei in inner retinal layers compared to rats treated with NMDA or ET-1 alone. The retinal morphometry showed that in TAU treated rats, the ganglion cell layer was significantly thicker and the number of retinal cells in ganglion cell layer was significantly greater than those receiving NMDA or ET-1 alone. In the optic nerve, the axonal swelling was found to be less frequent and less marked in the TAU-treated group in comparison with NMDA or ET-1 treated groups. Additionally, no marked glial cell changes were observed in the TAU-treated group. Semi-quantitative assessment also showed a significantly decreased optic nerve damage in the TAU-treated group, with almost 50% reduction in the mean grading for severity of damage compared to NMDA and ET-1 groups (Jafri et al., 2018; Nor Arfuzir et al., 2018; Lambuk et al., 2019).

The protective effects of TAU may be attributed to the inhibition of apoptosis signaling cascade by inhibiting the NMDA-induced increase of Ca^{2+} influx in retinal neurons and maintenance of retinal TAU level, which is critically important for endogenous retinal neuroprotection (Imaki et al., 1987; Schaffer et al., 2003; Schaffer and Kim, 2018). It has also been hypothesized that TAU could prevent the glutamate induced Ca^{2+} influx via voltage-dependent Ca^{2+} channels and ionotropic glutamate receptors in the retinal neurons by increasing the expression of glutamate transporters in glial cells, reducing the synaptic glutamate levels, and thus preventing excitotoxic damage to the retinal neurons (El Idrissi and Trenkner, 2004; El Idrissi, 2008; Wu et al., 2009; Zeng et al., 2010; Davinelli et al., 2017). Additionally, TAU was also shown to counteract glutamate-mediated excitotoxicity by opening Cl^- channels, enhancing GABA transmission or reducing NMDA-mediated transmission by acting at its GluN1/GluN2B receptor sub-type (Chan et al. 2013, 2015).

TAU Prevents Retinal Cell Apoptosis

TAU has also been shown to protect against mitochondria-initiated neuronal apoptosis (Kumari et al., 2013). TAU prevents ischemic neuronal death by acting as an antioxidant, downregulating a range of pro-apoptotic proteins while upregulating anti-apoptotic proteins. In ischemic stroke, TAU is released in the extracellular space resulting in a decrease in the concentration of intracellular TAU. The decrease in intracellular/extracellular TAU ratio attenuates the protective actions of TAU and potentiates neuronal damage during ischemia. The administration of exogenous TAU protects the ischemic neuronal death, an observation found to be evident in numerous experimental reports (Wu et al., 2009). These observations favorably correlate with our earlier findings showing the reduction of TUNEL-positive and caspase-3-positive cells in inner retina of TAU-pretreated groups compared to NMDA/ET-1-treated groups (Jafri et al., 2018; Nor Arfuzir et al., 2018; Lambuk et al., 2019). TAU pretreatment was also shown to decrease Bax/Bcl-2 activity compared to the NMDA group (Lambuk et al., 2019). These results are in line with the study of Wu et al. (2009) who demonstrated that TAU exerts neuroprotective effects through restoration of the Bax/Bcl-2 ratio by abolishing NMDA-induced calpain activation. In this study, TAU inhibited the glutamate-induced activation of calpain (a Ca^{2+}-dependent enzyme) that leads to a decreased heterodimerization of Bcl-2 and Bax, subsequent release of cytochrome C and activation of caspase-3 leading to apoptosis (Leon, 2008). Furthermore, in one of the studies, the antiapoptotic effect of TAU was shown to be attributed to inhibition of activator protein-1 (c-fos/c-Jun subunits) expression and decreased caspase-1 expression (Yu et al., 2007). Similarly, in our study (Lambuk et al., 2019), pretreatment with TAU was found to significantly reduce the NMDA-induced apoptotic death of retinal neurons by downregulating caspase-3 activity. El-Gohari (2016) and Taranukhin (2010) have also reported similar observations. Therefore, it can be proposed that TAU is a potent inhibitor of neuronal apoptosis and this effect of TAU involves suppression of caspases activities, calpains and proapoptotic proteins (Taranukhin et al., 2010; El-Gohari et al., 2016).

TAU Modulates Expression and Transport of Brain-Derived Neurotrophic Factor

The notion that TAU can prevent excitotoxic RGC loss is further supported by the observation that it also acts as a neuroprotective agent in a variety of conditions in which glutamate excitotoxicity is implicated (Louzada et al., 2004). Interestingly, TAU also possesses neurotransmitter properties as illustrated by its ability to elicit neuronal hyperpolarisation, by the presence of specific TAU synthesizing enzymes and receptors in the CNS, and by the presence of a taurine transporter system (Wu and Prentice, 2010). It is also important to note that increased intracellular Ca^{2+} resulting from excitotoxicity leads to neutrophin deprivation, hence

significantly reducing transport of neutrophins such as brain-derived neurotrophic factor (BDNF) to the RGCs (Quigley et al., 1995, 2000). BDNF is one of the neurotrophin factors known to be of vital importance in preserving neurons. Its enhanced expression is considered an indicator of greater neuronal survival in the CNS and retina (Hernández et al., 2008). In one of the studies, TAU pretreatment upregulated the expression of hippocampal BDNF in rats with mild-stress induced depression (Wu et al., 2017). Besides, treatment with TAU has been shown to increase BDNF expression after neurotoxic damage to the hippocampus (Zhang et al., 2017). Administration of TAU has also been shown to increase BDNF mRNA expression in the frontal cortex in rats after chronic alcohol withdrawal which was associated with decrease in the inhibitory function of gamma-aminobutyric acid (GABA) and increases in the excitatory function of glutamate (Hansen et al., 2017). It is noticeable that our earlier studies have also shown that pretreatment with TAU before exposure to NMDA upregulates the retinal expression of BDNF to the control level and this may underlie the anti-apoptotic effect of TAU (Lambuk et al., 2019).

TAU Suppresses Oxidative and Nitrosative Stress

The prospects of the benefits of TAU as a neuroprotective agent are also supported by other investigations showing that several mechanisms may, in fact, collectively contribute to its neuroprotective effects (**Figure 1**). For example, the study of Chen et al. (2009) demonstrated that TAU protects RGCs against hypoxic damage *in vivo* by preventing mitochondrial dysfunction. Similarly, TAU has been shown to improve the viability of glucose deprived cells by attenuating mitochondrial and endoplasmic reticulum stress in a dose-dependent manner (Yang et al., 2013). Another study using rat osteogenic sarcoma line, UMR-106, showed that TAU reduced H_2O_2-induced oxidative stress and apoptosis in a dose-dependent manner (Lou et al. 2018). Another study provided evidence that neuroprotection by TAU is associated with its antioxidant function (Jafri et al., 2018; Arfuzir et al., 2018). In our studies, the effect of TAU on oxidative stress was evaluated in NMDA and ET-1 exposed retina and it was observed that TAU increased the retinal reduced glutathione (GSH) level, which was in accordance with a previous study (Pushpakiran et al., 2004). The effect of TAU on GSH levels may be due to its ability to act as a pH-stabilizing buffer in mitochondria which helps to establish the equilibrium between the NADH/NAD(+) redox pair and the redox buffer pair of reduced/oxidized glutathione (GSH/GSSG) (Hansen and Grunnet, 2013). Studies done by Jafri et al. (2018) and Arfuzir et al. (2018) have also shown that superoxide dismutase (SOD) activity was upregulated in the retina after treatment with TAU. SOD plays an important role in scavenging free radicals and its improved activity after TAU treatment has been attributed to reduced ER stress (Nonaka et al., 2001). The activity of another antioxidant enzyme, catalase, was also found to be increased in our studies after TAU treatment (Jafri et al., 2018), which was in accordance with a previous study (Yu and Kim, 2009). In the same studies by Jafri et al. (2018) and Arfuzir et al. (2018), it was observed that the malondialdehyde contents

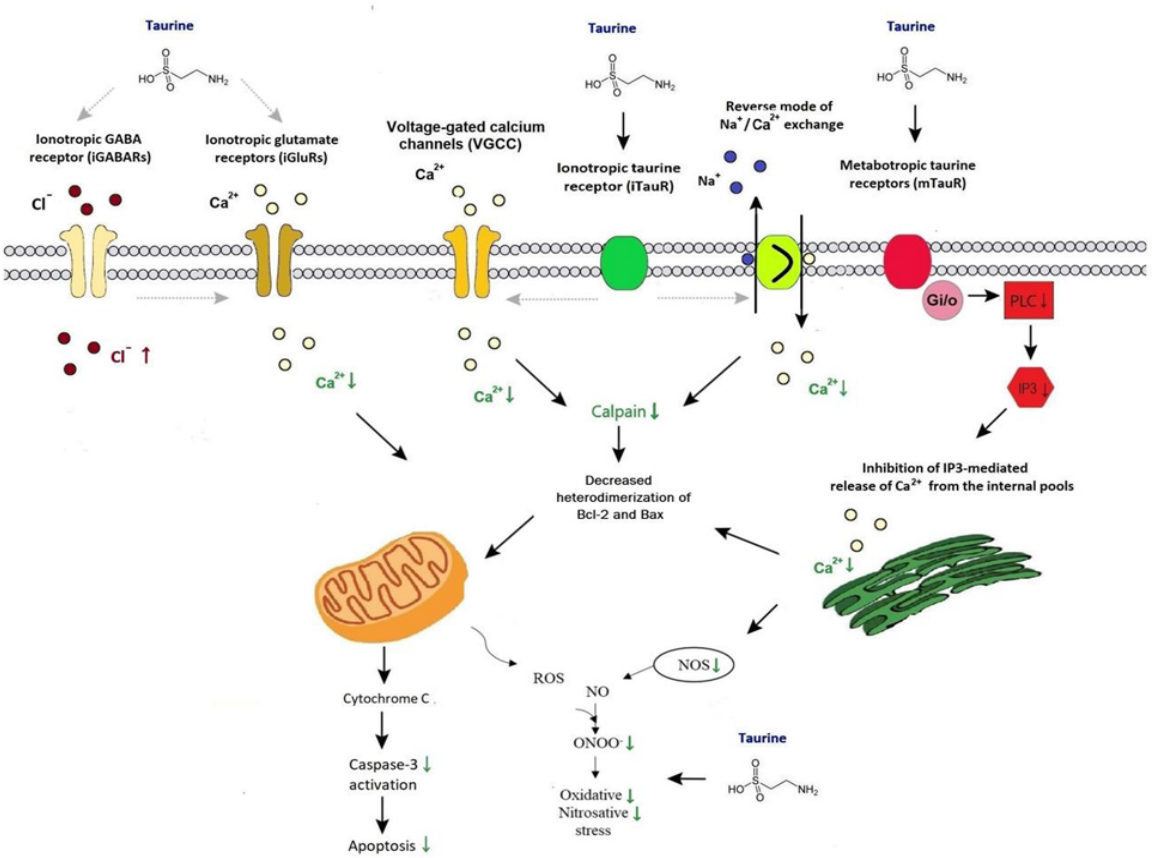

Figure 1 | **Taurine-mediated neuroprotection against glutamate-induced retinal cell death.**
Taurine activates both ionotropic taurine receptor (iTauR) and metabotropic taurine receptor (mTauR). Activated iTauR inhibits ability for the Na^+/Ca^{2+} exchanger to reverse and block voltage-gated calcium channels (VGCC). Both events lead to decrease in intracellular calcium concentration. Activation of mTauR by taurine inhibits phospholipase C (PLC) activity, resulting in reductions in inositol triphosphate (IP_3) formation and hence IP_3-mediated release of Ca^{2+} from the internal pools. As a result, taurine inhibits glutamate-induced activation of calpain (a Ca^{2+}-dependent enzyme), decreases heterodimerization of Bcl-2 and Bax, inhibits cytochrome C release, and prevents caspase-3 activation. Taurine also counteracts glutamate-mediated excitotoxicity by enhancing GABA transmission. Additionally, taurine exhibits a significant scavenging potential against peroxyl radicals, nitric oxide, and superoxide donors. Diagram was constructed based on concepts described by Wu and Prentice (2010), Oliveira et al. (2010) and Jakaria et al. (2019).

that indicate the extent of lipid peroxidation, in the retinas treated with TAU were significantly low compared to controls treated with NMDA/ET-1. This clearly shows the ability of TAU to efficiently scavenge reactive oxygen species and enhance antioxidant defenses. In a study done by Oliveira et al (2010), TAU exhibited a significant free radical scavenging potential against peroxyl radical, nitric oxide, and superoxide donors in a dose-dependent manner.

Furthermore, TAU was shown to reduce retinal nitrosative stress after NMDA and ET-1 exposure. According to Jafri et al. (2018), retina pretreated with TAU showed a reduction in neuronal nitric oxide synthase expression after subsequent to NMDA exposure. This could be due to direct modulation of NMDA receptors by TAU (Chan et al., 2013, 2015). Besides, treatment by TAU, before NMDA and ET-1-induced retinal injury, was shown to restore endothelial nitric oxide synthase (eNOS) expression. The alteration in eNOS expression may be attributed to the improved endothelial function due to treatment with TAU. In the same studies, TAU was also shown to suppress the NMDA/ET-1-induced increase in inducible nitric oxide synthase (iNOS) expression, suggesting its antagonistic effect on NMDA and ET-1 receptors. TAU has also been shown to protect against iNOS-dependent DNA damage by suppressing the pro-inflammatory transcription factor nuclear factor Kappa B (Sugiura et al., 2013). Results from these studies showed that treatment with TAU effectively reduced retinal nitrosative stress after NMDA and ET-1 exposure. Therefore, neuroprotective effects of TAU may also be attributed to its ability to neutralize nitrogen free radicals and reduce nitrosative stress. Hence, it could be concluded that, TAU may not only inhibit RGC loss through its direct anti-apoptotic function, but also via its antioxidant properties by antagonizing the NMDA-induced excitotoxicity.

Our comparative study showed that pretreatment with TAU exerted a greater protective effect which was not as evident after co- or post-treatment. This could be due to the protective effect of TAU against the initial pathophysiological events by the subsequent NMDA administration. The less prominent protective effects of TAU after co- or post-treatment were perhaps due to its inability to interfere with the sequence of pathological events already set in by NMDA. It is also worth noting that the greater effectiveness of TAU pretreatment compared to co- or post-treatment as demonstrated by retinal and optic nerve morphology also appeared to correlate with greater expression of BDNF level. Hence, TAU seems to have a greater potential for application as pretreatment for prophylaxis rather than as co- and post-treatment. Furthermore, it is important to note that the effect of TAU in this study was observed after intravitreal administration, which may not be a feasible route of administration when therapeutic application in clinical setting is considered. Thus, further investigations to design its appropriate formulation are needed.

Conclusion

TAU has been shown to be involved in multiple cellular functions, including a central role as a neurotransmitter, as a trophic factor in CNS development, as an osmolyte, as a neuromodulator, and as a neuroprotectant. It also plays a role in the maintenance of the structural integrity of the membrane and in the regulation of calcium transport and homeostasis. A recently published study clearly demonstrated that TAU prevents the retinal neuronal apoptosis both *in vivo* and *in vitro*. Protective effect of TAU may be attributed to direct inhibition of apoptosis, an activation of BDNF-related neuroprotective mechanisms and reduction of retinal oxidative and nitrosative stress. Further studies are needed to fully explore the potential of TAU as a neuroprotective agent, so that it can be applied in clinical practice, particularly for the treatment of glaucoma. Many studies cited in this paper, administered TAU via intravitreal route, which may not be appropriate for long-term treatment in glaucoma patients. Hence, it is critically important to develop appropriate formulations for non-invasive administration of TAU for its future clinical application. Thus, further investigations on the development of its formulation are needed for its therapeutic application.

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