



# Taurine: an essential amino sulfonic acid for retinal health

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Taurine (2-amino-ethanesulfonic acid) is a naturally occurring amino sulfonic acid derived from cysteine and methionine metabolism. Its common name derives from the ox, as it was first isolated from the bile of an ox (Froger et al., 2014). The molecular structure of taurine differs from that of amino acids by the presence of a sulfonic acid, instead of the more common carboxylic acid group in the structure of amino acids. Despite this, taurine is considered a non-essential amino acid because it can be synthesized endogenously in the liver of most mammals. However, the endogenous synthesis of taurine is insufficient to supply the needs and most of it is obtained through diet.

Taurine is extensively expressed in most tissues, especially in excitable tissues (Froger et al., 2014). Indeed, high concentrations of taurine can be found in the retina and, in particular, in photoreceptors, which are the cells richest in taurine content. However, the role of taurine in the retina is not yet entirely clear, although it is thought to be essential for the survival and development of retinal cells (Froger et al., 2014), to be involved in the regulation of retinal pigment epithelium phagocytosis and may have antioxidant, anti-apoptotic and immunomodulatory properties, among others.

## Role of taurine in retinal neuron survival:

The origin of the interest in the study of the relationship between taurine levels and retinal health dates to more than 4 decades ago when the degeneration of the retina, in particular of the photoreceptors, was described in cats fed a taurine-free diet. Subsequent studies confirmed by histological and functional analysis that the absence of taurine and cysteine in the cat's diet resulted in retinal degeneration, as cats are not able to synthesize taurine endogenously [reviewed in (Froger et al., 2014)]. The necessity of taurine for normal visual development was then confirmed in monkey infants fed a taurine-free human infant formula and in humans who received long-term parenteral nutrition without taurine. Taurine is one of the most abundant amino acids in mammalian breast milk and retinal taurine levels are higher in newborns than in adults (Froger et al., 2014). In fact, taurine is believed to influence the development of newborns and even determine health and disease during development and in adulthood.

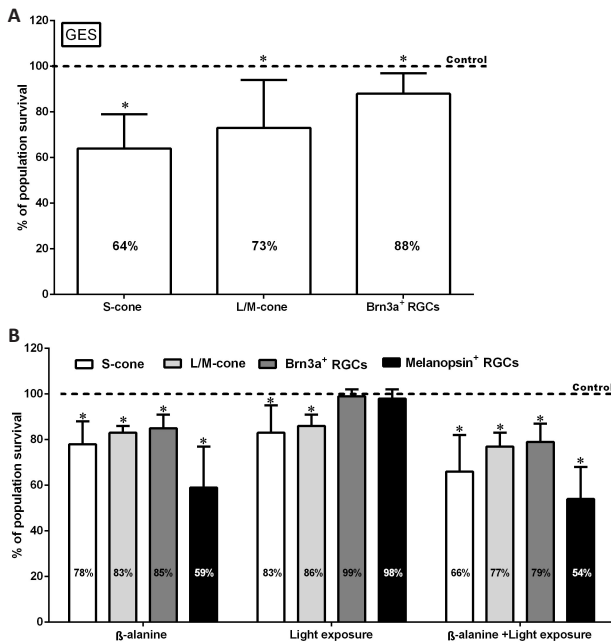
Currently, there are several methods to induce taurine depletion in animals. One of the most widely used are animal models of pharmacological taurine depletion using substances that block taurine transporter activity, as is the case of guanidoethane sulfonate (GES) and  $\beta$ -alanine. In 1983, it was proposed that pharmacological taurine depletion induced by both  $\beta$ -alanine and GES causes a similar pattern of retinal degeneration to that previously observed in cats (Pasantes-Morales et al., 1983). Both are structural analogs of taurine (Froger et al., 2014), and in the case of  $\beta$ -alanine, it is one of the most widely used dietary supplements for athletes today (Dolan et al., 2019). The structure of  $\beta$ -alanine is intermediate between alpha-amino acids and gamma-aminobutyric acid and although it is true that administered in small doses it may have positive effects, at doses from 3% in the drinking water it has deleterious effects (García-Ayuso et al., 2018b, 2019b; Dolan et al., 2019; Martínez-Vacas et al., 2021). To study the effects of permanent taurine depletion, a mutant knockout mouse model with a disrupted gene coding for the taurine transporter (*taut*<sup>-/-</sup> mice)

was generated (Heller-Stilb et al., 2002; Froger et al., 2014). These *taut*<sup>-/-</sup> mice suffer from plasma hypotaurinemia, and early-onset and progressive retinal degeneration (Heller-Stilb et al., 2002). Interestingly, in mice older than 3 months, when the outer nuclear layer was absent, the ganglion cell layer seems to have fewer cells than in naive animals (Heller-Stilb et al., 2002). This secondary loss of retinal ganglion cells is consistent with that reported in other animal models of inherited (García-Ayuso et al., 2018a, 2019a) or light-induced (García-Ayuso et al., 2018a, 2019a) retinal degeneration, confirming that retinal remodeling is a common phenomenon to all photoreceptor degenerations (García-Ayuso et al., 2018a, 2019a). Vigabatrin, an anti-epileptic drug, is an analog of gamma-aminobutyric acid with a similar chemical formula to taurine (Froger et al., 2014), and has also been related to taurine depletion (Jammoul et al., 2009). Visual field defects, electroretinographic alterations and decreased retinal nerve fiber layer thickness have been described in animal models and human patients treated with vigabatrin (Jammoul et al., 2009; Froger et al., 2014; Peng et al., 2017) and have been linked to taurine deficiency (Froger et al., 2014) and light sensitivity, probably secondary to taurine deficiency (García-Ayuso et al., 2018b). Finally, several studies have proposed that taurine treatment may prevent vigabatrin-induced retinal toxicity in rodents (Jammoul et al., 2009; Froger et al., 2014) and humans (Froger et al., 2014).

We have used rodent models with pharmacological taurine depletion by administration of GES or  $\beta$ -alanine to examine in detail the loss of retinal cells under taurine depletion and in combination with light exposure (Hadj-Said et al., 2016; García-Ayuso et al., 2018b, 2019b; Martínez-Vacas et al., 2021). An early work based on the model of pharmacological taurine depletion by administration of GES showed a parallel degeneration of photoreceptors, and in particular of cones, and retinal ganglion cells (Froger et al., 2014). We have used these models together with automatic quantification tools developed in our laboratory to analyze in detail the populations of retinal ganglion cells and S- and L/M-cones in rodents under taurine depletion (Hadj-Said et al., 2016; García-Ayuso et al., 2018b, 2019b). Thanks to our automatic quantification software, we have described that following 2 months of GES treatment there is a loss of 36% of the S-cone population (Figure 1A), 27% of the L/M-cone population (Figure 1A), and 12% of the retinal ganglion cell population (Figure 1A; Hadj-Said et al., 2016). Therefore, we established a gradient of cell degeneration due to taurine depletion in the mouse retina for the first time, showing that the most affected population was the S-cone population, followed by the L/M-cone population, and, lastly, the retinal ganglion cell population (Hadj-Said et al., 2016). Moreover, we described that the loss of both cone populations was higher in the dorsal retina, following a similar pattern to that observed in light-induced retinal degeneration (García-Ayuso et al., 2019a), which suggests a possible link between taurine depletion and a higher sensitivity to light damage. This fact was further supported by the greater affection of the S-cone population, which is the more sensitive cone population to light damage. Therefore, we concluded that taurine depletion might decrease the sensitivity threshold of retinal cells to light damage due to a lower level of antioxidant protection and increased photochemical stress. Regarding the retinal ganglion cell population, this population is not sensitive to light damage

(García-Ayuso et al., 2019a), but might be affected under taurine depletion due to oxidative stress (see below), which is a major contributor to retinal ganglion cell loss in several diseases.

$\beta$ -alanine deserves special mention because, as mentioned above, its deleterious effect has not always been clear (Dolan et al., 2019). However, it is now recognized that its administration in doses from 3% in the drinking water decreases taurine plasma levels and, as a result of this depletion, causes retinal degeneration (García-Ayuso et al., 2018b, 2019b; Martínez-Vacas et al., 2021). We have used  $\beta$ -alanine administration to quantitatively assess the retinal degeneration caused by taurine depletion in rats and we have shown that following 2 months of  $\beta$ -alanine (3%) treatment in the drinking water there is a loss of 22% of the S-cone population, 17% of the L/M-cone population (Figure 1B), 15% of the general population of retinal ganglion cells (immunodetected using Brn3a) and 41% of intrinsically photosensitive retinal ganglion cells (Figure 1B; García-Ayuso et al., 2018b). Therefore, we showed that intrinsically photosensitive retinal ganglion cells and S-cones are the most affected populations by  $\beta$ -alanine induced taurine depletion (García-Ayuso et al., 2018b), in accordance with our previous results using GES (Hadj-Said et al., 2016) and supporting the idea that taurine depletion decreases the threshold of retinal cells to light damage. To shed light on the possible link between taurine deficiency and increased sensitivity to light, we compared retinal degeneration in light-exposed animals between taurine depleted and non-taurine depleted animals, and we found that, when taurine-depleted animals were exposed to light, an additional 17% of S-cone (Figure 1B) and 9% of L/M-cone (Figure 1B) populations were lost compared to retinal degeneration caused by light exposure alone (García-Ayuso et al., 2018b). We then compared cell loss in taurine-depleted animals concerning whether they were exposed to light or not, and we found that light exposure increases the loss of S- and L/M-cone populations by 12% and 6%, respectively (Figure 1B; García-Ayuso et al., 2018b). However, we found no increased affection of either the general retinal ganglion cell population or the intrinsically photosensitive retinal ganglion cell population when animals were exposed to light, regardless of whether or not they were taurine depleted (García-Ayuso et al., 2018b). In a subsequent study, we analyzed the effect of taurine depletion in the retinal nerve fiber layer and axonal transport. In this study, we showed that taurine depletion caused a significant reduction of 8% in the thickness of the retinal nerve fiber layer which increased to 15% under light exposure (García-Ayuso et al., 2019b). Besides, we showed that in taurine-depleted animals there was a significantly higher loss of retinal ganglion cells traced with Fluorogold (21%) than immunodetected with Brn3a (16%), which is indicative of impaired retrograde axonal transport (García-Ayuso et al., 2018a, 2019a, b). One might think that a possible explanation for the impairment of the retrograde axonal transport is the compromised mitochondrial health under taurine depletion since retinal ganglion cell axons are richly provided with many mitochondria (Froger et al., 2014; García-Ayuso et al., 2019). In a more recent study using the same pharmacological model of taurine depletion, we have shown that taurine depletion caused: i) a significant shortening of photoreceptor outer segments, which was exacerbated under light exposure (Martínez-Vacas et al., 2021); ii) microglial cell activation and migration to the outer retinal layers (Martínez-Vacas et al., 2021); iii) oxidative stress in the inner and outer nuclear layers and the ganglion cell layer, specifically in retinal ganglion cells (Martínez-Vacas et al., 2021); iv) synaptic loss in the inner and outer plexiform layers that were exacerbated by light (Martínez-Vacas et al., 2021); and v) impairment of the phagocytic capacity of the retinal pigment epithelium (Martínez-Vacas et al., 2021). Interestingly, light exposure exacerbated oxidative stress in the outer retina but not in the ganglion cell layer, indicating that the oxidative



**Figure 1 | Percentage of retinal cell survival expressed as proportions to control.**

(A) Mean numbers of Brn3a<sup>+</sup> RGCs and S- and L/M-cones are shown as percentages of the values obtained in control retinas (horizontal interrupted line, 100%) in GES treated mice. (B) Mean numbers of Brn3a<sup>+</sup> RGCs, melanopsin<sup>+</sup> RGCs and S- and L/M-cones are shown as percentages of the values obtained in control retinas (horizontal interrupted line, 100%) in β-alanine treated, light exposed, and β-alanine treated and light exposed rats. Data were obtained from Hadj-Said et al. (2016), García-Ayuso et al. (2018, 2019) with permission. \*P < 0.05, vs. control eyes. GES: Guanidoethane sulfonate; RGCs: retinal ganglion cells.

stress observed in retinal ganglion cells was caused specifically by taurine depletion and that light did not affect this cell population (Martínez-Vacas et al., 2021), in agreement with our previous works (García-Ayuso et al., 2018b, 2019b).

**Conclusions and future directions:** In summary, our work confirmed that taurine depletion induced by both GES and β-alanine administration in the drinking water causes photoreceptor (Hadj-Said et al., 2016; García-Ayuso et al., 2018b; Martínez-Vacas et al., 2021) and retinal ganglion cell degeneration (Hadj-Said et al., 2016; García-Ayuso et al., 2019b; Martínez-Vacas et al., 2021), and also an impairment of the phagocytic capacity of the retinal pigment epithelium (Martínez-Vacas et al., 2021). Interestingly, retinal degeneration caused by taurine depletion slows down in the absence of light (Froger et al., 2014). So, it is tempting to speculate that taurine depletion and light act synergistically to induce photoreceptor degeneration (García-Ayuso et al., 2018b; Martínez-Vacas et al., 2021). Indeed, cones, and particularly S-cones, are the retinal neurons most sensitive to taurine depletion, which mainly affects their outer segments. The greater damage to the S-cones may be explained by their higher sensitivity to light, as this population is the most sensitive to blue light (short wavelength; the most phototoxic). It seems that the retinal ganglion cell population is affected independently of light exposure and may be more related to oxidative stress caused by taurine depletion (Martínez-Vacas et al., 2021), which also affects photoreceptors. Moreover, the observed retinal ganglion cell degeneration under taurine depletion is independent of photoreceptor loss, at least at the beginning, in contrast to what happens in inherited and acquired photoreceptor degenerations, in which, in the long term, a complete retinal remodeling eventually leads to secondary retinal ganglion cell degeneration (García-Ayuso et al., 2018a, 2019a). Nevertheless, this late retinal remodeling could also be observed after taurine depletion (Heller-Stilb et al., 2002), so we cannot rule out that, in the long term, there may also be a loss of retinal ganglion cells secondary to photoreceptor death due to taurine depletion. Finally, the observed relationship between taurine levels and retinal cell degeneration opens the way for the exploration of taurine as a possible therapeutic agent. Taurine is a

naturally occurring substance with few side effects, and when administered orally it is easily absorbed and crosses the blood-brain barrier. Thus, taurine dietary supplementation could be used as a therapeutic agent for retinal degenerations (Froger et al., 2014). Further studies are needed to clarify the role of taurine in the survival of retinal cells, as well as its possible use as a therapeutic agent in certain retinal diseases.

*This work was supported by Instituto de Salud Carlos III (ISCIII): P19/00203, co-funded by ERDF, "A way to make Europe" to MPVP and DGA, RD16/0008/0026 co-funded by ERDF, "A way to make Europe" to MPVP and RD21/0002/0014 financiado por la Unión Europea – NextGenerationEU; Fundación Robles Chillida to DGA; the RHU LIGHT4DEAF [ANR-15-RHU-0001] and IHU FORESIGHT [ANR-18-IAHU-0001] to SP.*

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Date of submission: February 17, 2022

Date of decision: April 13, 2022

Date of acceptance: July 5, 2022

Date of web publication: September 16, 2022

<https://doi.org/10.4103/1673-5374.353491>

How to cite this article: Di Pierdomenico J, Martínez-Vacas A, Picaud S, Villegas-Pérez MP,

García-Ayuso D (2023) Taurine: an essential amino sulfonic acid for retinal health. *Neural Regen Res* 18(4):807-808.

**Availability of data and materials:** All data generated or analyzed during this study are included in this published article and its supplementary information files.

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**Open peer reviewers:** Yong Liu, Army Medical University, China.

**Additional file:** Open peer review report 1.

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P-Reviewer: Liu Y; C-Editors: Zhao M, Liu WJ, Wang Lu; T-Editor: Jia Y