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 occurrence results 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 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 of 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 a biochemical 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 infants 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 well as the use of guanidinoethane sulfonate (GES) and β-alanine. In 1983, it was proposed that pharmacological taurine depletion induced by both β-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). Interestingly, in mice older than 3 months, when retinal taurine levels are low, the role of taurine in retinal health has not always been clear (Dolan et al., 2019). However, it is now recognized that its administration in doses from 3% in the rodent diet decreases taurine plasma levels and, as a result of this depletion, causes retinal degeneration (Garcia-Ayuso et al., 2018b, 2019b; Martinez-Vacas et al., 2021). We have used this model to quantitatively assess the retinal degeneration caused by taurine depletion in rats and we have shown that following 2 months of β-alanine (3%) treatment in GES-depleted animals, 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; Garcia-Ayuso et al., 2018b). Therefore, we showed that intrinsically photosensitive retinal ganglion cells and S-cones are the most affected populations by β-alanine induced taurine depletion (Garcia-Ayuso et al., 2018b), in accordance with our 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 increased sensitivity to light, we compared retinal degeneration in light-exposed animals between taurine depleted and non-taurine depleted animals, and we found that light-exposed 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 in the taurine naive alone (Garcia-Ayuso et al., 2018b). We then observed that retinal cell depletion was higher in taurine depleted than in taurine naive alone (Garcia-Ayuso et al., 2018b). In a subsequent study, we analyzed the effect of taurine depletion on 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 and 15% to 15% under light exposure (Garcia-Ayuso et al., 2019b). Besides, we showed that in taurine-depleted animals there was a significantly higher loss of retinal ganglion cells when animals were exposed to light, regardless of whether or not they were taurine depleted (Garcia-Ayuso et al., 2018b). 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 (Martinez-Vacas et al., 2021); ii) enhanced cell activation and migration to the outer retinal layers (Martinez-Vacas et al., 2021); iii) oxidative stress in the outer and inner segments of the ganglion cell layer specifically in retinal ganglion cells (Martinez-Vacas et al., 2021); iv) synaptic loss in the inner and outer plexiform layers that were exacerbated by light exposure; and v) impairment of the phagocytic capacity of the retinal pigment epithelium (Martinez-Vacas et al., 2021). Interestingly, light exposure exacerbated oxidative stress in the outer retina and the ganglion cell layer, indicating that the oxidative

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stress observed in retinal ganglion cells was caused specifically by taurine depletion and that light did not affect this cell population (Martinez-Vacas et al., 2021), in agreement with our previous works (Garcia-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; Garcia-Ayuso et al., 2018b; Martinez-Vacas et al., 2021) and retinal ganglion cell degeneration (Hadj-Said et al., 2016; Garcia-Ayuso et al., 2018b, Martinez-Vacas et al., 2021), and also an impairment of the phagocytic capacity of the retinal pigment epithelium (Martinez-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 (Garcia-Ayuso et al., 2018b; Martinez-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 (Martinez-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 (Garcia-Ayuso et al., 2018b, 2019a).

Nevertheless, this late retinal remodeling could also be observed after taurine depletion (Heller-Stibl 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 administrated orally it is easily absorbed and crosses the blood-brain barrier. Thus, taurine dietary supplementation could be used as a therapeutic approach 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.

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Figure 1 Percentage of retinal cell survival expressed as proportions to control.
(A) Mean numbers of Brn3a+ 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+ melanosin+ 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; Garcia-Ayuso et al., 2018b, 2019b with permission. *P < 0.05, vs. control eyes. GES: Guanidoethane sulfonate; RGCs: retinal ganglion cells.