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Taurine: The comeback of a neutraceutical in the prevention of retinal degenerations

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ABSTRACT

Taurine is the most abundant amino acid in the retina. In the 1970s, it was thought to be involved in retinal diseases with photoreceptor degeneration, because cats on a taurine-free diet presented photoreceptor loss. However, with the exception of its introduction into baby milk and parenteral nutrition, taurine has not yet been incorporated into any commercial treatment with the aim of slowing photoreceptor degeneration. Our recent discovery that taurine depletion is involved in the retinal toxicity of the antiepileptic drug vigabatrin has returned taurine to the limelight in the field of neuroprotection. However, although the retinal toxicity of vigabatrin principally involves a deleterious effect on photoreceptors, retinal ganglion cells (RGCs) are also affected. These findings led us to investigate the possible role of taurine depletion in retinal diseases with RGC degeneration, such as glaucoma and diabetic retinopathy. The major antioxidant properties of taurine may influence disease processes. In addition, the efficacy of taurine is dependent on its uptake into retinal cells, microvascular endothelial cells and the retinal pigment epithelium. Disturbances of retinal vascular perfusion in these retinal diseases may therefore affect the retinal uptake of taurine, resulting in local depletion. The low plasma taurine concentrations observed in diabetic patients may further enhance such local decreases in taurine concentration. We here review the evidence for a role of taurine in retinal ganglion cell survival and studies suggesting that this compound may be involved in the pathophysiology of glaucoma or diabetic retinopathy. Along with other antioxidant molecules, taurine should therefore be seriously reconsidered as a potential treatment for such retinal diseases.

Abbreviations: CDO, cysteine dioxygenase; CNS, central nervous system; CSAD, cysteine sulfonic decarboxylase; DAPI, 4′,6-diamidino-2-phenylindole; DIV, days *in vitro*; DM, diabetes mellitus; DR, diabetic retinopathy; ERG, electroretinogram; GABA, γ-amino butyric acid; GFAP, glial fibrillary acidic protein; GCL, ganglion cell layer; INL, inner nuclear layer; NMDA, N-methyl D-aspartate; ONL, outer nuclear layer; OPL, outer plexiform layer; PAT1, proton-coupled amino acid transporter; RGC(s), retinal ganglion cell(s); ROS, reactive oxygen species; SAH, S-adenosylhomocysteine; SAM, S-adenosyl methionine; Tau-T, taurine transporter; VGB, vigabatrin; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; Tau-T KO, taurine-transporter knockout.

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Contents

1. Taurine: a “semi-essential” sulfur amino acid in the animal kingdom

1.1. Origin of taurine

2-Amino-ethanesulfonic acid, commonly known as taurine, was first isolated in 1827 from the bile of an ox, *Bos taurus*, accounting for its common name (Demarcay, 1838). In phylogenetic terms, taurine is an ancient molecule, because it is found at high concentrations in algae, but absent from most bacteria and viruses, although it has been described as a source of carbon, nitrogen and sulfur in *Bacillus subtilis* (Nakashio et al., 1982). Taurine is found in trace amounts in plants and fungi (Huxtable, 1992). By contrast, it is present at high concentrations in many animals, from insects to mammals, in which it is the most abundant amino acid-related molecule (Huxtable, 1992). Despite being an ancient amino acid, taurine is not incorporated into protein sequences. Moreover, although most taurine is obtained from the diet, this amino acid is considered to be non-essential because it can be synthesized endogenously in the liver of mammals, although this synthesis can be insufficient as in cats (see 1.3.).

1.2. Physicochemical properties

Taurine does not have the classical structure of an amino acid, with an amino moiety in the alpha position of the carboxyl group, but it is nevertheless considered to be an amino acid. Taurine is a free sulfur β-amino acid, in which the amino group is located on the beta-carbon. The molecular structure of taurine ($NH_3^+-CH_2-CH_2-SO_3^-$) is very similar to that of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system, in both the brain and the retina (Fig. 1). Taurine is analogous to β-alanine, a constituent of vitamin B_5, and to a synthetic compound called guanidoethane sulfonate (GES) (Fig. 1). Both these molecules are competitive inhibitors of taurine to the taurine transporter (Tau-T) activity (see 2.1.2.). Due to the presence of a sulfonic acid, rather than the carboxylic acid group more commonly found in amino acids (Fig. 1), taurine displays specific physicochemical properties, with a very low pKa value of ~2 for its acid group, whereas the pKa for the amine group is 9, resulting in a zwitterion state at physiological pH (Jacobsen and Smith, 1968; Okaya, 1966). Being taurine highly water soluble, it cannot diffuse across lipophilic membranes. This lack of ability to cross membranes results in steep concentration gradients between intracellular and extracellular compartments (Heinz and Walsh, 1958; Huxtable, 1992; Jacobsen and Smith, 1968), with intracellular concentrations up to 7000 time higher than extracellular concentrations (Piez and Eagle, 1958). Such concentration gradients are generated by an active Na^+-dependent selective taurine transporter (Tau-T), which takes taurine up into the intracellular compartment. Such uptake processes were initially suspected on the basis of pharmacological studies showing [^{3}H]taurine incorporation into cells (Kishi et al., 1988), and were subsequently definitively demonstrated by the molecular cloning of Tau-T (Liu et al., 1992; Uchida et al., 1993).

1.3. Taurine metabolism

The endogenous synthesis of taurine in various tissues, but mostly the liver and brain (Hayes and Sturman, 1981b; Huxtable, 1989) is one of the sources of this molecule in mammals. The principal metabolic pathway for the synthesis of taurine begins with L-methionine and/or L-cysteine metabolites (Fig. 2). In addition to this principal synthetic pathway, other theoretical biosynthesis routes are possible, making use of enzymatic pathways