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Taurine as a universal carrier of lipid soluble vitamins: a hypothesis

Review Article

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Summary. In the literature taurine is characterized as a non-specific growth or blood clotting factor, an antioxidant, a membrane protector, or a regulator of calcium ion homeostasis, just as vitamins A, D, E, F, and K are similarly characterized. On the basis of recent finding concerning the relationship between taurine and the aldehyde of vitamin A-retinal (Petrosian and Haroutounian, 1988, 1998; Petrosian et al., 1996), as well as on the basis of data from the literature, we now suggest a hypothesis that taurine promotes the bioavailability of the lipid soluble vitamins A, D, E, K, and F, probably by forming different types of water soluble, easily hydrolyzable complexes. It is quite possible that the ability of taurine to convert lipids and lipid soluble substances into a water soluble state is the key to understanding the unusually wide diversity of biological phenomena associated with taurine. This form of delivery may be an additional, secondary mechanism for the transport of lipid soluble vitamins, which was probably acquired early in evolution, and remains extremely important for mammals and humans directly after birth for a variety of physiological functions such as: vision in normal and in emergency situations, rapid blood clotting, sperm eruption, and situations requiring a prompt consumption of lipid soluble vitamins characteristic of excitable systems. Clearly, the role of taurine in the physiology of the water insoluble vitamins remains an enigma and is worthy of further investigations.

Keywords: Taurine – Vitamin A – Vitamin D – Vitamin E – Vitamin K – Linoleic acid

Introduction

Of the amino acids which are widespread in nature, taurine is the most heat stable among the most water soluble and after glycine is the most water

soluble among the most heat stable. Taurine is the dominant free amino acid in many species in the human is second highest in concentration after glutamic acid (see Sturman and Hays, 1980). Taurine is completely lacking in many plants and is about 100–1,000 times lower in concentration in nuts than in animal tissues (Pasantes-Morales et al., 1989b). Historically, the first unique feature of taurine to be noticed was its ability to conjugate with bile acids (Tiedman and Gmelin, 1927; Demarcay, 1834; Jacobsen and Smith, 1968), and since the 1950s it has been demonstrated that taurine is the main organic osmolite in marine species (Awapara, 1962). Parallel with this progress, the action of taurine in many (almost all) unrelated biological processes was identified and strengthened the belief in the existence of one central or a limited number of basic mechanisms which may allow unification of the unusually diverse roles of taurine (see van Gelder, 1983; Huxtable and Sebring, 1986; Gurevich, 1986; Huxtable, 1990; Petrosian et al., 1996). Huxtable's "Trinitarian" hypothesis, based mainly on interaction between taurine, calcium ions and phospholipids is one attractive explanation (Huxtable, 1990). However, in this review we will focus our attention mainly on the water solubilizing capability of taurine.

The ability of taurine to convert lipids and lipid soluble substances into a water soluble state plays a key role that is not fully understood. Currently, it is well established that emulsification of lipids by taurocholic acid is one of the facilitating mechanisms in the transport of lipids in the liver- intestinal system (see Nakashima et al., 1996). On the basis of our recent finding concerning the relationship between taurine and the aldehyde of vitamin A-retinal (Petrosian and Haroutounian, 1988; Petrosian et al., 1996), as well as on the basis of data from the literature, we now suggest a hypothesis that taurine promotes the bioavailability of the lipid soluble vitamins A, D, E, K, and F, probably by forming different types of water soluble, easily hydroxyable complexes. The unusual diversity of the action of taurine may be due to its ability to facilitate the transport of water insoluble vitamins A, D, E, K, and F. This may be the reason that taurine is sometimes considered a subvitamin. With respect to the lipid soluble vitamins, especially vitamin A, there are very convincing indications in favor of the proposed hypothesis. On the contrary, in other cases there are only slight hints, or even severe contradictions. For greater clarity, we will consider separately the relationship between taurine and each lipid soluble vitamin.

Vitamin A and taurine

It is widely known that vitamin A and related retinoids play a central role in many essential biological processes including: vision, which is exclusively based on 11-cis retinal in all known animal species (Wald, 1968); fetal development and regulation of proliferation and differentiation of many types of cells throughout life (see Blomhoff, 1994); proper functioning of both male and female reproductive organs (see Eskild and Hanso, 1994); and control of gene expression via multiple nuclear receptors for all-trans retinoic acid,

providing a direct link between biological effects and retinoids (see Kastner et al., 1994).

The significance of taurine in vision was first discovered in cats after utilizing taurine-free diets (Hays et al., 1975; Schmidt et al., 1977). A decrease of ~50% in the levels of taurine in the retina, caused either by a taurine deficient diet in animals (cat, monkey) with low liver capacity for taurine synthesis (Hays et al., 1975; Schmidt et al., 1977; Sturman, 1990; Imaki et al., 1993) or by treatment with the taurine transport antagonist guanidinoethane sulfonate (GES) in rats which have some limit for taurine synthesis in their retina (Pasantes-Morales et al., 1983; Lake, 1989), causes serious alterations in the retinal structure. Interestingly, the most severe retinal damage appears in the regions of highest rhodopsin content (Hayes et al., 1975; Schmidt et al., 1977; Pasantes-Morales et al., 1983; Sturman et al., 1984; Lake, 1989; Imaki et al., 1993). Taurine deficiency produces a noticeable reduction of rhodopsin levels in rat photoreceptors (Lake, 1989) and causes a drop of amplitude of the a and b-waves of the electroretinogram (ERG) (Schmidt et al., 1977; Lake, 1989).

Now we will pose a question – why does taurine deficiency cause severe damage of the retinal rod outer segment (ROS) structure? One possible answer may be realized in the studies of Pasantes-Morales and colleagues (Pasantes-Morales and Cruz, 1985; Pasantes-Morales et al., 1989a) that taurine and its naturally occurring analogue, homotaurine, exert a powerful protective action against light-induced damage of isolated frog ROSs. Alternatively, it was demonstrated that on a taurine-free diet ROSs are more easily destroyed. A reason for this observed action of taurine may be that taurine is one of the main osmolites within the retina and its deficiency causes retinal degradation (Pasantes-Morales et al., 1990, 1998).

Another explaination as to why a taurine-free diet causes severe retinal damage is related to the finding that taurine is involved in transportation of retinoids between the photoreceptors and the pigment epithelium, by forming a water soluble and easily hydrolyzable complex between taurine and retinal – retinylidene taurine (also called tauret) (Fig. 1). (Petrosian and Haroutounian, 1988, 1990, 1998; Petrosian et al., 1996, 2000a,b). It is necessary to note that tauret has been shown to be an endogenous substance in various eye structures, and that the capacity of these eye structures to synthesize tauret has been confirmed (Petrosian et al., 1996, 2000a). Another strong argument in favor of this last explanation are data demonstrating the capability of 11-*cis* tauret to regenerate rhodopsin in the ROSs (Petrosian et al.,

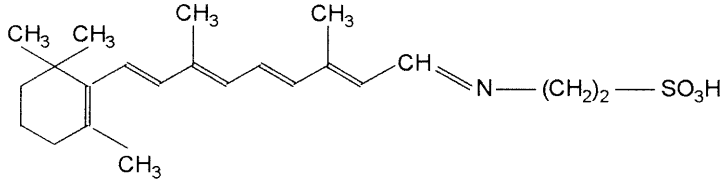

Fig. 1. All-trans retinylidene taurine – tauret

1996). Also all-*trans* retinal – a highly toxic substance that appears in a free form after illumination – can be removed quickly by conjugation with taurine to prevent damage to the ROS. Hence, taurine deficiency initiates the deterioration of rhodopsin regeneration and the lack of the all-*trans* retinal removal process in the ROSs. Consequently, taurine deficiency causes retinal damage leading to blindness. The possibility of the existence of highly specialized molecular channels for tauret in the ROSs (Petrosian and Haroutounian, 1988, 1990, 1998; Petrosian et al., 1996) indicates a unique relationship between taurine and retinoids.

Currently there are both direct and indirect evidence indicating a close relationship between taurine and vitamin A in the retina. It has been established *in vitro* that taurine specifically stimulates proliferation of human and rabbit retinal pigment epithelium (RPE) (Gabrielian et al., 1992). Taurine induces regeneration of goldfish retina in culture, which may be partially due to increasing calcium ion influx (Lima et al., 1993). It has also been reported that a taurine complex containing a heat stable component (<1 kDa) that was extracted from the retina, stimulates rod photoreceptor development in culture (Altshuler et al., 1993). So it appears quite possible, that a central physiological role is played by another tauretlike substance, namely a conjugate of taurine and retinol – a sulfoether compound (Fig. 2).

Taurine based vitamin A transport is a clue to understanding another biological phenomenon which was intensively investigated by John Sturman and colleagues concerning the increase of taurine content in the developing brain (see Sturman and Hayes, 1980). Taurine based vitamin A transport may also help explain the beneficial influence of taurine on preterm infants (Chesney et al., 1998) as well as the presence of taurine in human and mammalian milk. In the first days after lactation, taurine levels are particularly high (see Meister, 1965; Sturman and Hayes, 1980). In particular, taurine exceeds other amino acids in human milk by 4–200 times (Takanami and Miura, 1963; Sturman and Hayes, 1980). The need for high taurine levels in these cases may be due to the ability of taurine to facilitate vitamin A transport by forming a sulfoether of taurine with vitamin A, which may provide the infant with the necessary amount of available vitamin A during this intense phase of growth. Supporting such an assumption are data obtained during an evaluation of the influence of taurine deficiency in long-term total parenteral nutrition (TPN) on eye function (Vinton et al., 1990; see Chesney, 1998). These studies revealed both ERG abnormalities and a

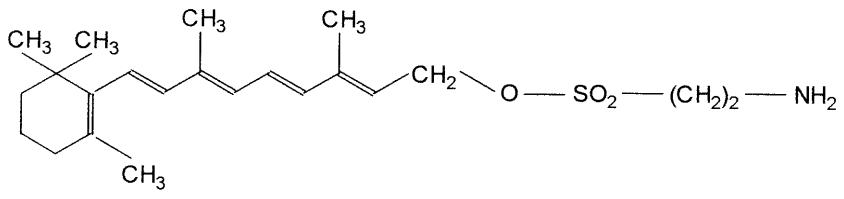

Fig. 2. All-trans retinolat taurine

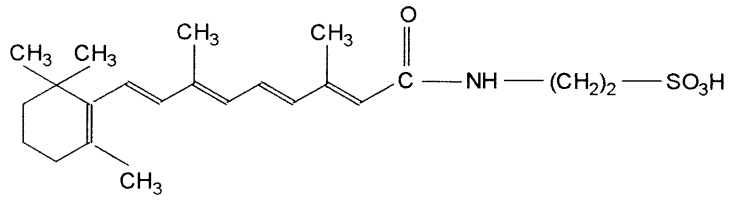

Fig. 3. All-trans N-retinoyl taurine

vitamin A increase in the plasma of children and one-third of the tested adults.

There are also other direct correlations between taurine and vitamin A in animal models. Elevation of the retinol level in the liver has been observed in taurine-deficient kittens (Lehmenn et al., 1990). In cats with hypertrophic cardiopathy, hyperthyroidism, or with uncertain diagnosed cardiovascular diseases, the level of taurine in the plasma is always noticeably decreased. In the case of dilated cardiopathy, taurine concentration in the plasma was the lowest, being only 38% of the normal value. In contrast to taurine levels in this cardiovascular disease, retinol levels in the plasma were from 15 to 40% higher than plasma retinol levels in healthy cats (Fox et al., 1993). Diet supplementation with 13-*cis* retinoic acid in methionine-supplemented rats caused marked elevation in taurine levels in the liver (Schalinske and Steele, 1991).

The existence of other tauret-like substances such as retinoyl taurine which is a conjugate – an amide of taurine with retinoic acid (Fig. 3) can also be predicted. In this case, instead a Shiff base, an aldimine – a peptide bond is expected; this substance will also be easily hydrolyzed. Such a molecule would readily promote delivery of retinoic acid between the water and lipid phases and so may facilitate delivery of retinoic acid to the cell, which would then be directly involved in the gene expression process (see Kastner et al., 1994). There are considerable data in favor of this assumption such as the following: 1) taurine-augmented proliferative responses of T cells from both young and old mice (Negoro and Hara, 1992); 2) incubation with 0.1 mM taurine significantly increases thymidine incorporation in chick cultured B cells and enhances their proliferation (Porter et al., 1993); and 3) taurine has a positive effect on the preimplantation development of mouse embryos *in vitro* (Dumoulin et al., 1992).

The ratio of the 3 compounds, retinal, retinol, and retinoic acid, to taurine in liver stellate cells, which represent 7% of the total cell number in the rat liver and about 9% in the human liver, is of significant interest since these liver cells have been identified as storage sites for vitamin A (Wake, 1994). It is especially of interest to clarify this relationship in different species – in relatively vitamin A-poor and in vitamin A-rich animals. In this respect, it would be most interesting to measure the levels of taurine, tauret, retinolat taurine, and N-retinoyl taurine in the vitamin A extra rich liver stellate cells of polar bears. Moreover, human sperm and seminal fluid have high taurine

(Holmes et al., 1992) and vitamin A concentrations, and in these cells and fluid one would also expect relatively high tauret, retinolat taurine, and N-retinoyl taurine levels.

The above-mentioned data support the concept that the 3 types of water-insoluble retinoids (vitamin A, retinal and retinoic acid), by conjugating with taurine to form tauretlike compounds (tauret, retinolat taurine and N-retinoyl taurine), may overcome the omnipresent problem of lipid compounds in aqueous solutions in tissues. The retinoid conjugates, now water soluble, can be hydrolyzed to the free retinoids after they reach their destination in the cells. This type of delivery system may be one of the additional secondary mechanisms in transport of retinoids, which as is well known is based on a class of retinoid binding proteins (see Sivaprasadarao and Findlay, 1994).

Vitamin D and taurine

The role of vitamin D in regulation of calcium and phosphate metabolism, especially in the bone and small intestine, is widely known. There is also growing evidence of the crucial role of taurine in the regulation of both calcium ions and phosphate (Schaffer et al., 1980; Pasantes-Morales et al., 1989a; see Huxtable, 1990; see Lombardini, 1991). It is important to note the well-established effects of taurine on calcium ion-dependent enzymes which could be relevant to many different essential biological processes (Lampson et al., 1983; Lombardini, 1985; Gurevitch, 1986).

The most direct evidence in favor of our assumption concerning the existence of a vitamin D-taurine conjugate (Fig. 4) is a taurine-free diet experiment performed by Zamboni and colleagues (Zamboni et al., 1993). To evaluate the influence of dietary taurine supplementation on vitamin D absorption, three groups of preterm infants were studied. The first group of preterm infants was fed a taurine-free formula, the second group was fed a taurine-supplemented formula (50 mg/100 g of powder), and the third group was fed human, not heat-treated milk. Plasma levels of taurine, total bile

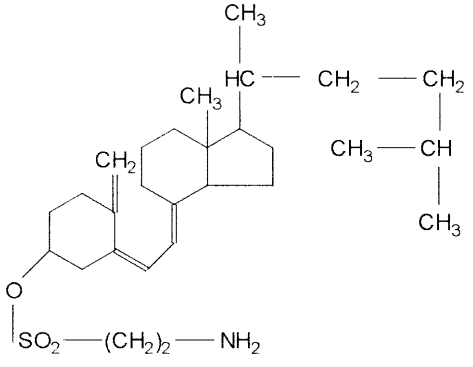

Fig. 4. Cholecalcipherolat taurine – conjugate taurine with vitamin D_3

acids, glyco-(GBA) and tauro-(TBA) conjugated bile acids, 25-hydroxy vitamin D_3 ($250HD_3$) and 1,25-dihydroxy vitamin D_3 ($1,250H2D_3$) were determined in all infants at birth in the blood of the umbilical cord and at one and three months of life. The preterm infants fed a taurine-free formula had lower plasma taurine levels than infants of the other groups at one and three months of life. In these infants, GBA predominated, with a G/T ratio of 1.1 and 1.4 at one and three months of life, respectively, whereas in all other infants TBA predominated with a G/T ratio always 1. Also, $250HD_3$ and $1.250H2D_3$ levels were significantly lower in preterm infants fed a taurine-free formula than in infants fed a taurine-enriched formula or human milk. Term infants fed a taurine-free formula did not show differences in the parameters studied in comparison to infants of the other groups. Low taurine dietary intake appears to compromise vitamin D absorption in preterm infants (Zamboni et al., 1993). Figure 4 shows a conjugate of taurine with vitamin D_3. It would be of interest to carry out investigations concerning other vitamins from group D.

Vitamin E and taurine

One of the main functions of compounds in the vitamin E group is to protect membrane lipids against oxygen damage. It is now well established that taurine also has such antioxidant properties in the retina (Pasantes-Morales and Cruz, 1985; Pasantes-Morales et al., 1989a) as well as in other tissues and organs. During the Taurine Symposium '97 in Tucson, Arizona a series of investigations on antioxidant actions of taurine were presented: Taurine protection of the liver against lipid peroxidation and membrane disintegration during rat hepatocarcinogenesis (You and Chang, 1998); Taurine inhibition of iron-stimulated catecholamine oxidation (Dawson et al., 1998); Uptake of taurine and taurine chloramine in murine macrophages and their distribution in mice with experimental inflammation (Kim et al., 1998); Taurine chloramine inhibits the production of superoxide anion, IL-6 and IL-8 in activated human polymorphonuclear leukocytes (Park et al., 1998); Myeloperoxidase (MPO) may mediate neutrophil adherence to the endothelium through upregulation of DL IB expression-an effect downregulated by taurine (Stapleton et al., 1998); No beneficial effects of taurine application on oxygen free radical production after hemorrhagic shock in rats (Niessen et al., 1998). There are numerous reports that taurine can immediately act as an antioxidant agent (see Dawson et al., 1998). On the other hand, it is not excluded that taurine may exert its antioxidative action by conjugation with different types of tocopherols, for example with α-tocopherol, or with similar compounds (Fig. 5) that exist endogenously. Thus taurine may potentially convert water insoluble E vitamins into water soluble forms. It is interesting to note that in certain cardiovascular diseases, there is a correlation between taurine and α-tocopherol levels, with taurine decreasing as much as 60% and α-tocopherol decreasing as much as 30% (Fox et al., 1993).

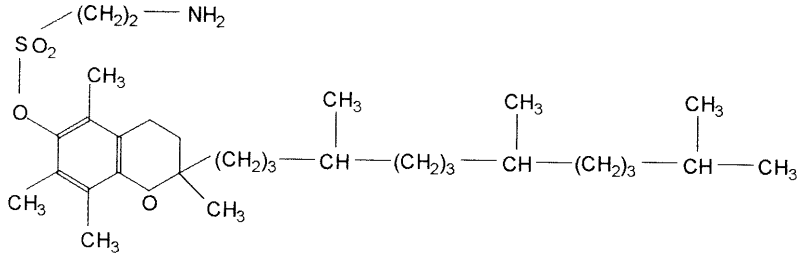

Fig. 5. 2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyl-tridecyl)-6-hydroxy chroman taurine ether or α-tocopherolat taurine – conjugate taurine with vitamin E – α-tocopherol

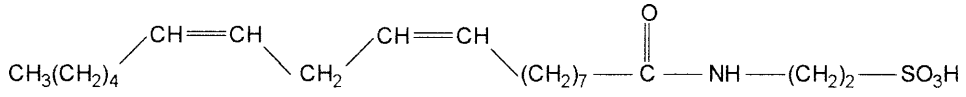

Fig. 6. Octadeca-9,12-dien-L-carboxyl taurine or linoloyl taurine – conjugate taurine with vitamin F – linoleic acid

Vitamin F and taurine

Because of the special relationship between membranes and lipids it is of interest to consider vitamin-like substances which were previously named vitamin F. Unsaturated fatty acids, linoleic and linolenic acids, can potentially conjugate with taurine (Fig. 6). It is quite possible that such complexes exist in nature. In this context, there is information that the levels of linoleic and linolenic acids decrease in patients on taurine-deficient diets during total parenteral nutrition (Vinton et al., 1990).

Vitamin K and taurine

Vitamin K, known as a blood clotting vitamin (see Dowd et al., 1995), serves as an essential cofactor for the carboxylase that activates the proteins of the blood clotting cascade. In prothrombin 10 molecules of glutamate, from residues 7 to 33, are carboxylated which after chelating calcium atoms can then be anchored to the anionic phosphate head groups of the phospholipid membrane surfaces of blood platelets and endothelial cells. As a result, in the blood plasma thrombin converts fibrinogen into insoluble protein fibrin, causing the blood to clott (see Dowd et al., 1995). It is noteworthy that since 1959 it has been known that there is an unusually high taurine concentration in blood platelets (Frendo et al., 1959). This initial report was confirmed by Ahtee and colleagues (Ahtee et al., 1974). Thus one can conclude that there is an as yet unknown role for taurine in the above described blood clotting sequence. Taking into account the close relationship between taurine and calcium ions, and between taurine and phospholipids, many possibilities can be suggested.

Another possible hypothesis for the role of taurine in the blood clotting mechanism may be based on the assumption that taurine is involved in the

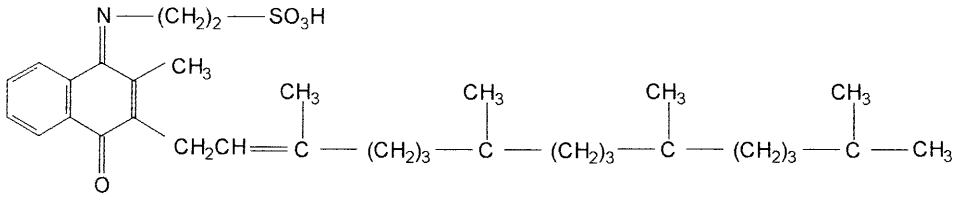

Fig. 7. 2-methyl-3-phityl-1,4-naphtochinolidine taurine – conjugate taurine with vitamin K_1

transport of vitamin K by forming a water soluble conjugate with vitamin K_1 (Fig. 7). It can also be proposed that there exist similar compounds with two taurine molecules or with vitamin K_2. On the contrary, taurine involvement in the blood clotting cascade probably is not merely reduced to the simple role of taurine being a water solubilizer of vitamin K. The ability of taurine to inhibit platelet aggregation induced by ADP or by other factors must also be considered (Gurevich, 1986; Hayes et al., 1989; Elizarova, 1996).

Conclusion

In the literature taurine is characterized as a non-specific growth or blood clotting factor, an antioxidant, a membrane protector, or a regulator of calcium ion homeostasis, just as vitamins A, D, E, F, and K are similarily characterized. Therefore, it appears likely that taurine and the water insoluble vitamins A, D, E, F, and K have a definite interrelationship since at first glance it is observed that both taurine and the water insoluble vitamins have almost the same spectrum of action. Indeed, based on an analysis of the literature, it is quite possible that the ability of taurine to convert lipids and lipid soluble substances into a water soluble state is the key to understanding the unusually wide diversity of biological phenomena associated with taurine. It is interesting to note that taurine is sometimes characterized as a metavitamin.

Owing to the amino and sulfonic reactive groups, taurine may form water soluble aldimines, ketamines and sulfoethers with all subtypes of vitamins A, D, E, F, and K. It is predicted that these tauret-like substances are easily hydrolyzable, which is probably the reason that they were ignored by most investigators until the present. In order to identify tauret (an endogenous conjugate of taurine and the aldehyde of vitamin A), special precautions have been taken during the preparation of the tissue samples to prevent its rapid hydrolysis (Petrosian et al., 1996, 2000a).

However attractive, it is still speculative to consider taurine as a subvitamin which promotes the water solubility of the water insoluble vitamins A, D, E, F, and K by forming different types of water soluble, easy hydrolyzable complexes. This form of delivery system may be an additional secondary mechanism for the transport of lipid soluble vitamins, which was probably acquired early in evolution, and remains extremely important for mammals and humans directly after birth for a variety of physiological functions such as: vision in normal and in emergency situations, rapid blood

clotting, sperm eruption, and situations requiring a prompt consumption of lipid soluble vitamins characteristic of excitable systems. Clearly, the role of taurne in the physiology of the water insoluble vitamins remains an enigma and is worthy of futher investigations.

Acknowledgements

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