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TAURINE IN NUTRITION AND BRAIN DEVELOPMENT

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ABSTRACT

The past decade has seen a remarkable increase in interest among members of the nutrition community in the amino acid taurine. Evidence for depletion of taurine pools in infants on low-taurine artificial formula and reports of retinal abnormalities in cats on taurine-free diets have led to suggestions that taurine may be an essential nutrient for some species. Because of its postulated role(s) as an inhibitory neurotransmitter or neuromodulator, there has also been interest in taurine's effects on nervous tissue. Taurine is the only major amino acid to decrease in concentration during brain development. Thus, it has been hypothesized that taurine may have a specific role in brain ontogeny in addition to its role(s) in the mature brain. Recent demonstrations of abnormal brain development in taurine-deficient cats and monkeys lend credence to this hypothesis and a report of taurine stimulation of Na,K-ATPase in young but not mature hamster brain suggests a possible mechanism for this function.

Key Words: Taurine depletion; Taurine requirements; Brain development

Taurine was discovered over 150 years ago but is still poorly understood in terms of function and importance. Even its relatively simple two carbon structure, illustrated in Fig. 1, can be seen as contradictory. Taurine is technically an amino acid, but because the amino group is on the β-carbon and the acid group is sulfonic rather than carboxylic acid, it is not used as a structural unit in protein. Therefore, it is unlike other common amino acids whose primary roles involve protein synthesis.

Consideration of taurine's function is also intriguing because of its widespread distribution. It is the most common or next to most common amino acid in many mammalian free amino acid pools (1). However, it participates in few chemical reactions, and for decades its only known role was in bile acid conjugation. Because this accounts for approximately 1% of the body taurine pool, it is probably not taurine's only function (2).

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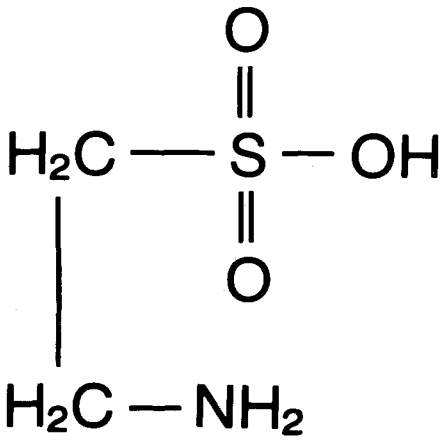

FIG. 1:
Structural formula of taurine.

In the past 15 to 20 years, numerous investigators have studied other possible roles for taurine. Following the publication of two seminal papers showing severe retinal degeneration in cats on taurine-free diets (3) and depletion of taurine pools in human infants on taurine-deficient formulas (4), much interest has focussed on its nutritional significance. More recent reports of abnormal brain development in taurine-deficient kittens (5) link taurine's importance as a nutrient with its roles in nervous tissue. However, many questions remain with regards to the general mechanism of taurine's function as well as the specific mechanism of its role in brain development.

This review article begins with a discussion of the nutritional importance of taurine. Recent theories regarding the biochemical actions of taurine are examined, followed by a discussion of its postulated effects in the brain and its importance in brain development. The article presents a possible link between taurine and Na,K-ATPase activity as a mechanism for taurine's role in brain development and discusses the relevant experimental data.

NUTRITIONAL SIGNIFICANCE OF TAURINE

Taurine Depletion

Changes in taurine levels are a function of the balance between the amount of taurine being added to the body pool (either from endogenous synthesis or exogenous sources) and the amount being removed (primarily via the urine). The ability of mammals to synthesize taurine varies with species and age. When exogenous sources of the amino acid are limited, some species compensate with increased renal retention. Other species appear unable to adapt in this way. Thus, taurine depletion is seen when mammals with limited synthetic capacity and/or limited renal adaptation are given low-taurine diets.

Biosynthesis of taurine has been demonstrated in various mammalian tissues (for review, see 6). Although several pathways exist, the preferred pathway is believed to involve oxidation of cysteine to 3-sulfinoalanine (cysteinesulfinic acid) with subsequent oxidation and decarboxylation to taurine, illustrated as in Fig. 2 (7-9). The rate limiting enzyme in the pathway is considered to be the vitamin B_6 dependent 3-sulfinoalanine decarboxylase (SAD), also known as cysteine sulfinic acid decarboxylase (EC 4.1.1.29) (10).

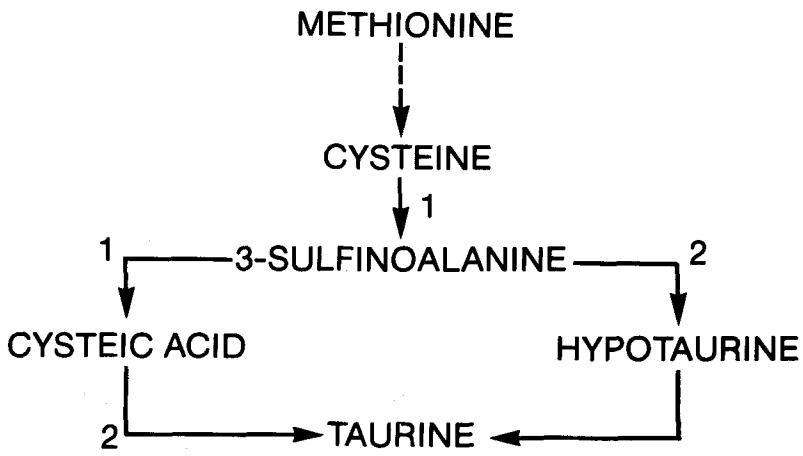

FIG. 2:
The 3-sulfinoalanine pathway of taurine biosynthesis. The enzymes involved are (1) cysteine dioxygenase (E.C.1.13.11.20) and (2) 3-sulfinoalanine decarboxylase (SAD) (E.C.4.1.1.29). The enzyme oxidizing hypotaurine to taurine is not yet clearly defined (adapted from 6).

The efficiency of the pathway varies from species to species and can be related to the variations in SAD activity presented in Table 1 (7). Because SAD activity in the rat is relatively high, rats can be maintained on taurine-free diets for long periods of time without showing depleted taurine pools. Huxtable and Lippincott (11) demonstrated that, over an 87 day period, adult rats on a taurine-free diet biosynthesized 54% of their body taurine. Rats receiving dietary taurine biosynthesized only 29%. These changes appeared to result from altered renal retention rather than altered synthetic rates. In another study, Chesney et al. (12) found that renal adaptation allowed maintenance of normal brain taurine levels in nursing and adult rats on low-taurine diets. Similarly, Sturman et al. (13) found that urinary excretion of taurine was almost non-existent in pyridoxine-deficient rats, allowing maintenance of normal plasma and tissue levels in the face of impaired biosynthesis.

Unlike rats, cats have low SAD activity and limited renal adaptation, and therefore, will develop taurine depletion when given taurine-free diets. Degree of depletion varies among body tissues and fluids, but liver and plasma generally show the most severe depletion (1%-5% of normal). Bile, olfactory bulb, and retina are more able to retain taurine (14-18). Neither SAD activity nor conversion of {^{35}S} cysteine to {^{35}S} taurine increase with taurine depletion (15). It seems then, that the cat's capacity to synthesize taurine cannot match its obligatory taurine losses, making it dependent on exogenous taurine.

Although SAD activity in the cat is low, the enzyme activity in humans is even lower. It is not surprizing then, that humans on taurine-free parenteral nutrition show depletion of plasma taurine (19-21), as well as intracellular taurine pools (22). However, the degree of depletion in humans (approximately 50%) is not as severe as that in cats (greater than 95%), probably because of a greater ability to conserve taurine at the kidney.

TABLE 1
Activity of 3-Sulfinoalanine Decarboxylase in Adult and Fetal Liver[a]

Species	Adult[b]	Fetal[b]
Man	0.3[c]	0.3[c]
Rhesus Monkey	5.0	3.5
Rat	468.0	8.8
Cat	4.5	7.1
Guinea Pig	3.0	1.7

[a] adapted from (8)
[b] nmol CO_2 produced /mg protein/hr
[c] tissue obtained at autopsy

In addition to the interspecies variations, taurine biosynthesis varies with age. As shown in Table 1, SAD activity is generally lower in fetal and neonatal animals than in adults, translating into an increased dependence on exogenous taurine in young mammals. Both Sturman (23) and Huxtable (24) studied the transfer of labelled taurine from rat dams to their pups in utero and during lactation, and found the mother to be a significant source of taurine for the pup. These results are supported by the finding of decreased retinal taurine levels in rat pups nursed by dams treated with the taurine analog guanidinoethyl sulfonate (GES), which results in the production of taurine depleted milk (25). Transfer of labelled taurine from mother to offspring has also been shown with the rhesus monkey (26).

The ontogenetic importance of the transfer of taurine from the mother is implied by observations of increased hepatic taurine in rat dams prior to parturition, followed by rapid decreases in hepatic and plasma taurine during lactation (27,28). Comparison of human milk and plasma samples obtained at the same time show taurine concentration to be three to four times higher in the milk. This indicates active secretion of taurine into breast milk (29) and further emphasizes the importance of exogenous taurine to the neonate.

The human infant's dependence on exogenous taurine has been demonstrated in classic studies of both low birth weight and term infants (4,30-32). Infants fed casein-based formulas containing virtually no taurine had decreased plasma and urine taurine levels when compared to infants fed human milk. Because formulas based on bovine whey contain small amounts of taurine, infants on these formulas showed less severe depletion. Low taurine levels were also reported in infants given a combination of casein-based formula and supplementary parenteral nutrition (33). When the synthetic formulas were supplemented with taurine, plasma and urine taurine levels were similar to those of babies fed human milk. Low taurine levels were not associated with poorer growth rates (34) or with impaired bile acid kinetics (35).

Although the earlier discussion of taurine biosynthesis suggested that adult humans may also have limited taurine biosynthesis, taurine depletion is rare once weaning has occurred. Taurine is widely distributed in animal products with the highest values being reported for invertebrate sea foods (36,37). It has been suggested that people on vegan diets may be at risk for taurine depletion, (10). However, Rana et al. (38) found that subjects on vegan (taurine-free) diets did not have significantly lower levels of plasma taurine than omnivorous controls. All vegans had been on the diet for more than one year. Breast milk samples from

vegans had slightly lower levels of taurine than those obtained from women on omnivorous diets but the range of values in the two groups overlapped. These results as well as a recent report from Irving et al. (39) suggest that the ability of adult humans to synthesize taurine may be greater than previously believed. In the latter report, urine excretion of [^{18}O] taurine in subjects who had inhaled [$^{18}O_2$] for one hour was significantly higher than would be predicted from reported SAD activity levels. Further work is needed to clarify the biosynthetic capacity of adult humans.

In summary, then, mammals can either synthesize taurine or receive it exogenously from their diet or (in utero) from the mother. The sum of exogenous and endogenous taurine less metabolic losses gives the overall level of the body taurine pool. Because neonates and species such as humans and cats are limited in biosynthesis and/or renal adaptation, abnormal limitations in the exogenous taurine supply can lead to depletion in the body taurine pool. The question that remains, however, is whether a reduction in body taurine results in any functional problems. Evidence presented below suggests that it does.

Anatomical Consequences of Taurine Depletion

Cats. Because of the severity of taurine depletion in cats on taurine-free diets, most reports of functional deficits with taurine depletion involve this animal. Hayes et al. (3) observed that the retinal degeneration seen in cats on synthetic casein diets is prevented with the addition of taurine. Since the original report, the results have been confirmed by several investigators (14,40-42) and extended to show degeneration of the tapetum lucidum as well as the retina (18,43).

Recent investigations in Sturman's laboratory have examined the effect of taurine depletion on pregnancy in cats and development in the kittens. Queens maintained on taurine-free diets for six months or longer had increased incidence of abortions, resorptions, and stillbirths. Their milk was taurine-depleted, but otherwise normal in terms of protein and amino acid composition. The kittens that survived had depressed growth, and tissue taurine levels averaging 10% to 30% of controls. They also had abnormal hind limb development, peculiar gait, and thoracic kyphosis. Some of these symptoms suggest cerebellar dysfunction; subsequent examination of the cerebella from eight-week old taurine-deficient kittens did, in fact, show severe abnormalities. Many cells had not yet migrated from the external granule cell layer to the internal molecular layer, and some were still undergoing cell divisions which should have been completed by three weeks of age. Because of the strict timetable of cerebellar development, these delays must prevent the formation of many synaptic connections (16,44).

To separate postnatal from in utero effects, a group of normal queens was put on a taurine-free diet from one week prior to parturition until the completion of lactation. All pregnancies were completed normally. The kittens had normal birth weights but growth rates were decreased starting at three to five weeks of age. At eight weeks, the taurine-depleted kittens showed delayed migration of cells from the external granule cell layer. Both the growth depression and cerebellar abnormalities were prevented by supplementing kittens with taurine (45).

Abnormalities in development of the visual cortex in taurine-deficient kittens have also been reported (5). In the newborn kittens, neuroblasts had failed to migrate and differentiate normally. At the time of weaning (8 weeks), few pyramidal and nonpyramidal neurons were found; those that were seen were heavily spined with poor arborization. Protoplasmic astrocytes were, for the most part, undifferentiated. As with cerebellar development, the failure of normal migration and differentiation must result in permanent deficits in synaptic conections.

Primates. Although the most dramatic effects of taurine deficiency have been reported in the cat, similar results have been seen in monkeys. Both cebus and cynomolgus monkeys fed taurine-free formula from birth to 5 months of age had significantly decreased weight gain when compared to monkeys on a taurine supplemented diet. This was accompanied by plasma taurine levels 10% to 20% of normal and tissue taurine depletion of varying degrees (46).

Rhesus monkeys raised from birth on a taurine-deficient diet (Nutramigen) showed decreased cone electroretinogram (ERG) response at 10 months of age (47). No abnormalities were visible ophthalmoscopically at 18 and 26 months and ERGs were normal. However, ultrastructural examination of the retina at 26 months showed extensive disorientation, disintegration and vesiculation of the outer segment disc membrane in all cones. The authors suggested that, because the ERG was abnormal at 10 but not 26 months, ultrastructural damage may have been more severe at 10 months. Long term consequences could be severe if cortical connections were unable to develop properly in earlier development. Indeed, Sturman has recently reported changes in the development of the visual cortex in rhesus monkeys raised on taurine-free formula. At three months of age, the taurine-depleted monkeys had a thinner cortex but more clearly delineated cortical layers when compared to monkeys supplemented with taurine. The depleted monkeys also had reduced visual acuity (10).

Humans. Although infants given low taurine synthetic formula are known to be taurine depleted, no functional changes have been noted in this group. Presumably, these babies are put on solid (taurine containing) food before the taurine pool accumulated in utero is depleted below a critical level.

However, because the amino acid mixtures traditionally used in parenteral nutrition are taurine-free, there are now adults and children who have been without an exogenous supply of taurine for several years. As discussed earlier, this population does show depleted plasma and blood cell taurine levels. There are also reported cases of retinal dysfunction (19-21). In a group of 21 children on long term home parenteral nutrition and one child on enteral Vivonex (taurine free), plasma taurine concentrations were 47% of normal. Electroretinograms were recorded in eight children ($\geq$ 1 yr of age and on parenteral nutrition $\geq$ 6 months). All were abnormal. Four children also showed mild granularity of the retinal pigment epithelium. Four children were given taurine supplements for 12 weeks, after which plasma taurine levels and ERGs were normal.

The other taurine-depleted human population that has been reported is a group of patients with small intestinal bacterial overgrowth. Plasma taurine was decreased because of bacterial taurine catabolism, and abnormalities in cone function and pigment epithelium defects were found (48).

The problems seen in taurine depleted humans are not as severe as those seen in cats, just as the degree of depletion is not as severe in humans. However the types of abnormalities seen are similar. It is possible that if humans, particularly children, were deprived of taurine for longer periods of time, more severe abnormalities would be seen.

Is Taurine an "Essential" Nutrient?

While it is generally accepted that taurine is an essential nutrient for the cat (9,10) its essentiality for humans is controversial. Some nutritionists (29,49-51) have suggested that it may be a "conditionally essential nutrient"--i.e. a normally nonessential nutrient which, in some clinical circumstances, must be supplied exogenously because of inadeqauate endogenous synthesis (52). Rudman and Feller (51) list three criteria required to establish a deficiency state for a conditionally essential nutrient: subnormal plasma

levels of the nutrient in question; appearance of chemical, structural or functional abnormalities; and correction of the first two conditions by dietary supplementation of the nutrient. It must be noted that these criteria would also identify a conventional essential nutrient; conditional essentiality implies that the deficiency is seen only under abnormal clinical conditions.

Gaull (50) suggests that Rudman and Feller's three conditions are met with the previously described parenterally nourished children (19,20). Under the conditions of administration of an abnormal diet (taurine-free) by an abnormal route (TPN), for a long period of time, endogenous taurine production is inadequate. Therefore, Gaull asserts that taurine should be considered as conditionally essential. Because the "condition" for this essentiality (i.e. the failure to supply exogenous taurine) is not an "abnormal clinical condition," Gaull's evidence for the fulfillment of Rudman and Feller's criteria can also be used to argue that taurine is a normally essential nutrient in children. More evidence regarding the consequences of taurine depletion in humans will be needed to settle the controversy. However, ethical considerations may preclude the completion of the necessary studies.

BIOCHEMICAL ACTIONS OF TAURINE

Although nutritionists have concentrated on the dietary significance of taurine, other scientists have focussed on its physiological roles. The best characterized of these is its conjugation of bile acids (53). There is also evidence for taurine's importance in cardiac action (54), reproduction (55), in the retina, and in the brain (6,56). In efforts to relate these varied functions, investigators have begun to define a central mechanism for taurine's action by examining its biochemical actions (9,50,57). They have proposed that the role of taurine is to protect cell membranes by removing toxic compounds and by counteracting ion and water leak at damaged membranes.

The most obvious example of detoxification by taurine is its conjugation of secondary bile acids. Lithocholic acid, a secondary bile acid produced by microbial degradation of chenodeoxycholic acid, induces cholestasis in a variety of experimental animals by affecting the structure and function of the bile canalicular membrane (58). Dorvil et al. (59) showed that pretreatment with taurine will prevent the cholestasis and morphological changes in guinea pigs injected with sulfolithocholate (S-LCA). Taurine conjugates of S-LCA are more soluble than glycine conjugates, and therefore more easily excreted in the urine. Other examples of taurine detoxification include its removal of retinol through the production of retinotaurine, its conjugation with exogenous organic toxins (60) and its attenuation of the toxic effects of endogenously produced hypochlorous acid (9).

The effects of taurine on cell growth and cell membranes have been demonstrated with cultured human lymphoblastoid cells. Although such cells can grow in a taurine-free medium, growth rates and viability are increased with the addition of taurine (61). Cell viability is decreased with exposure to retinol or retinoic acid. Any one of taurine, zinc, or α tocopherol will increase the number of viable cells. All three together give complete protection (62).

Reduced cell viability, correlating with increased malondialdehyde production, is seen with the addition of iron and ascorbate. While taurine prevents this reduction in cell viability, it does not prevent the lipid peroxidation. It has been suggested that taurine prevents cell death by preventing the Ca^{+2} influx that normally results from lipid peroxidation (60).

Although the theory that taurine acts as a membrane protector connects some of the diverse areas in which taurine is important, many questions remain. It appears that taurine's protective effects extend beyond the attenuation of toxic compounds, to a normalization of ion and water flux at damaged membranes. The mechanism for this is as yet unclear. As well, the relationship of these biochemical actions to the neurochemical effects of taurine as described below, remains to be clarified.

TAURINE IN THE BRAIN

Much of the interest in possible functions of taurine in the brain was sparked by the finding that taurine is one of the major free amino acids of mammalian central nervous tissue. It is the amino acid found in highest concentration in the immature brain, and in the mature brain, its concentration is exceeded only by glutamate (63). Distribution studies have shown that approximately 70% of the taurine is found in the soluble fraction (64). Taurine is enriched in the synaptosomal fraction where it is found in higher concentration than any other amino acid (56,65). Overall concentrations vary between species but are in the millimolar range.

Neurochemical Effects of Taurine

Although there has been long-standing controversy as to whether taurine functions as a neurotransmitter or as a neuromodulator, its effects on nervous tissue are well established. In general, it has an inhibitory action, inducing membrane hyperpolarization which results in decreased neuronal firing (6,66). Taurine also appears to decrease K^+ stimulated release of norepinephrine and acetylcholine and it potentiates stimulus evoked release of GABA (56). Again, taurine's effects are inhibitory--either decreasing release of an excitatory transmitter or increasing release of an inhibitory one.

Taurine has some anticonvulsant properties, consistent with its inhibitory effects. In experimental animal models, concentration of taurine at the epileptogenic focus is low, giving a generalized increase in neuronal excitability and contributing to initiation of seizures. However, analyses of autopsy and biopsy samples from human epileptic brains have shown no consistent results with regard to taurine concentration. As well, attempts to use taurine in treatment of epilepsy have had both negative and positive results (6).

Taurine has been implicated in other central nervous processes such as thermoregulation, control of sleep, and regulation of drinking behavior (6,56).

Taurine in Brain Development

In addition to taurine's general roles as a neurotransmitter and/or neuromodulator, it has been hypothesized that taurine may have a specific role in brain development (67). This suggestion first came with the observation of unusually high taurine levels in the immature mammalian brain and a decrease in taurine concentration during development (68). Other functional amino acids such as glutamate, glutamine, GABA, aspartate, glycine, serine, and alanine increase during this time (69,70). Other studies show that a number of processes work together to ensure this high concentration. These include a) increased maternal taurine stores just prior to parturition (27), b) transfer of taurine from mother to offspring via milk (24) and c) net uptake of taurine by the immature brain (71). The recent reports of abnormal development in the cerebellum and visual cortex of taurine deficient cats and monkeys (5,10) provide experimental evidence for taurine's importance in brain ontogeny.

There is little discussion in the literature regarding possible mechanisms for this role. However, a report by Hastings et al. (72), suggests that taurine may stimulate Na,K-ATPase in the immature brain. These investigators observed a saturable dose-dependent stimulation of pubescent hamster brain Na,K-ATPase. Maximum stimulation occurred at approximately 125mM taurine concentration, with enzyme activity at 230% of control. The results were dependent on the age of the animal: when the experiment was repeated using mature hamsters, taurine did not significantly change enzyme activity.

The report is intriguing, especially when the actions of taurine and the effects of stimulation of Na,K-ATPase are compared. Decreased release of excitatory neurotransmitters such as acetylcholine is seen following both Na,K-ATPase stimulation (73) and taurine release (56). Also, taurine is thought to protect cells from the effects of ion-induced lipid peroxidation (9) similar to a proposed mechanism for catecholamine stimulation of Na,K-ATPase (74,75). Finally, taurine deficiency and Na,K-ATPase inhibition during brain development both result in decreased neuronal differentiation and arborization (5,76).

However, other investigators have failed to demonstrate taurine stimulation of Na,K-ATPase. Akera et al. (77) reported that taurine concentrations of up to 100mM had no effect on the activity of partially purified rat brain enzyme. Lombardini (78) found 20mM taurine to have no effect on rat retinal enzyme and Mrsny and Meizel (55) found taurine to inhibit hamster sperm Na,K-ATPase in a dose-dependent manner. Investigations in our laboratory have also failed to repeat the Hastings results (79). Nevertheless, it would be premature to discount the report of Hastings et al. entirely. The discrepancies between published reports of taurine's effect on Na,K-ATPase are similar to discrepancies already existing in the literature with regards to catecholamine modulation of Na,K-ATPase activity, despite more than 15 years of intensive research (for review see 95). It seems apparent that Na,K-ATPase activity is sensitive to factors which are not being controlled in some (or all) investigations. Clarification of these factors may help clarify the effect of both catecholamines and taurine on Na,K-ATPase activity.

Other investigators have suggested that taurine's actions in excitable tissues involve osmoregulation and interaction with membrane phospholipids (81), or inhibition of protein phosphorylation (78). However, these studies have not addressed the issue of why high levels of taurine appear to be necessary during periods of neuronal differentiation and development. Thus, the importance of these mechanisms in brain development remain to be investigated.

CONCLUSION

Although much has been learned about the roles and importance of taurine, there are still questions which must be addressed. It is apparent that taurine is an essential nutrient for the cat but its essentiality for humans is still debatable. There is also ample evidence of taurine's importance in the brain, especially in brain development. However the mechanism of this role remains to be elucidated.

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