Ann. Rev. Nutr. 1981. 1:401–25

TAURINE IN METABOLISM

K. C. Hayes

Department of Nutrition, Harvard School of Public Health and the Nutrition Division, New England Regional Primate Research Center, Harvard Medical School, Boston, Massachusetts 02115

J. A. Sturman

Developmental Neurochemistry Laboratory, Department of Pathological Neurobiology, Institute for Basic Research in Mental Retardation, Staten Island, New York 10314

CONTENTS

0199-9885/81/0715-0401$01.00

INTRODUCTION

Taurine is rapidly emerging as one of the more interesting and ubiquitous of the amino acids. Long referred to as an end product of sulfur amino acid metabolism, it has become increasingly acknowledged as a factor involved in the functional regulation of many mammalian organ systems, with appreciable evidence accruing concerning its function in excitatory processes in the central nervous system (CNS) and muscle. Furthermore, from the nutritional point of view, an important role for taurine in biological systems is emphasized by the fact that it has been identified as a nutrient essential for at least one species, the cat, and apparently can be a limiting factor during growth of nonhuman primates as well.

The purpose of this review is to orient the reader concerning the known aspects of taurine in metabolism, with particular emphasis on the nutritional aspects and implications for taurine depletion and deficiency. It also underscores those aspects of metabolism where taurine has made promising impact for future investigation. Several reviews are available that deal with various aspects of taurine biochemistry and physiology (55, 124), as well as specific areas of taurine involvement in development (127), the central nervous system (9, 13, 37, 75), the eye (19, 86), and the heart (7, 11, 34, 53, 54).

TAURINE CHEMISTRY

Taurine (2-aminoethanesulfonic acid) has the amino group on the beta-carbon, not the alpha-carbon typical of most other amino acids, and has a sulfonic acid group in place of the more usual carboxylic acid group. It is a colorless, relatively tasteless compound with a molecular weight of 125 and is water soluble, but almost insoluble in ethanol or ether (55). Taurine derives its name from the fact that it was first isolated from ox bile (132), where it is conjugated with bile acids (42).

It is distributed throughout the animal kingdom where it is ordinarily encountered as a free amino acid. It is essentially absent in plants, with small amounts found in lower plant forms. The concentration of taurine in specific tissue and fluids varies widely; but at times, depending on the tissue and stage of development, it can be in greater concentration than other amino acids.

TAURINE BIOSYNTHESIS

The biosynthesis of taurine theoretically can proceed via several enzymatic processes linked to the metabolism of sulfur amino acids, involving the enzymatic oxidation and conversion of dietary cysteine derived either directly or via conversion from methionine (5, 55). Although several possible variations exist, extensive investigation has led to general acceptance that the major pathway for taurine biosynthesis in mammalian tissues follows that originating with methionine → cysteine → cysteinesulfinic acid → hypotaurine → taurine (11, 124; see also Figure 1). Evidence has also been provided for the possible formation of taurine via the fixation of sulfate with serine by 3'-phosphoadenosine-5'-phosphosulfate (PAPS)-sulfotransferase following activation of the sulfate to PAPS (11, 33), but this is not considered to be a significant pathway in most mammals. Sulfate conversion to taurine could not be detected in taurine-supplemented or taurine-depleted kittens (60).

Organs vary in their ability to synthesize taurine, as a function of both species and age. For example, the liver from the adult dog and rat have a high concentration of all enzymes required for taurine biosynthesis, whereas the brain contains adequate cysteinesulfinic acid decarboxylase (CSAD) activity, but tends to have limited activity of methionine adenosyltransferase and cystathionase. Liver from man, monkeys, and cats of all ages exhibits extremely low activity of CSAD, thus limiting taurine biosynthesis. Liver and brain from young animals demonstrate a lower synthetic capacity as compared to these tissues in the adult (69, 124). Thus, younger animals may depend more on dietary taurine and older animals may depend on dietary cystine and methionine for adequate supply of taurine. This point is reflected by differences in the degree of depletion of plasma and bile taurine pools in kittens or adult cats fed different levels of sulfur amino acids (83, 92).

Pyridoxal 5'-phosphate is required as coenzyme for cystathionine synthase, cystathionase, and CSAD (see 118, 121); a dietary deficiency of vitamin B_6 has a depressing effect on taurine biosynthesis (29, 123, 141). Such observations suggest that the fetus and newborn are dependent upon the dam to a great extent for their supply of taurine. Recent experiments have shown that 60% of the total taurine in rat pups at birth originated from the mother, and that by weaning, this had decreased to 13%, including 7% derived from the milk (J. A. Sturman, unpublished observation). The capacity for synthesis in liver tends to vary to a greater extent among species than does the capacity for the synthesis by the brain. Within the nervous system, taurine synthesis is restricted to the cell body and nerve terminals, since no CSAD activity is present in axons (121). Some CSAD activity has

been localized within the synaptomes prepared from brain homogenates (95).

There is little correlation between CSAD activity, taurine concentration, and taurine turnover in tissues of rats, rabbits, and guinea pigs. On the other hand, hepatic CSAD activity and the proportion of bile acids conjugated with taurine are highly correlated in those rodents (115). Such a correlation does not pertain to cats and New World primates, which conjugate bile acids almost totally with taurine (46, 92, 116), but with minimal CSAD activity in liver (46, 60).

Hormonal influences on CSAD have been described. Males demonstrate greater liver CSAD activity than do females, and estradiol injections decrease this activity (55). The implications of this sex difference have not been resolved, but it is noteworthy that dietary taurine depletion had a more pronounced detrimental effect on growth of female than of male monkeys (46). In addition, women are more prone to gallstone formation than are men, which may have implications concerning sex differences in taurine requirements for bile acid metabolism (see below).

Thyroxine decreases CSAD activity, possibly by depressing CSAD synthesis (55); and experimentally induced hypothyroidism results in increased concentrations of taurine in brain, which are corrected by thyroxine (47). In contrast, hydrocortisone increases CSAD activity (55), although the same hormone decreases taurine conjugation of bile acids by human fetal liver in vitro (38). From the opposite perspective, large oral doses of taurine (375–8000 mg/day) result in a substantial elevation of growth hormone in plasma of rats (76).

TAURINE METABOLISM

General Considerations

The only adequately documented metabolic reaction in which taurine participates is conjugation with bile acids in the liver (42, 50). Earlier literature refers frequently to isethionic acid and inorganic sulfate as mammalian catabolic products of taurine, but more recent work has minimized the importance of these reactions (26, 100, 105). The small amounts of these compounds derived from taurine in the intact animal are the result of bacterial metabolism. Thus, the functional role of taurine, including its well-defined role in conjugating bile acids, is attributable to the molecule itself and not to products of its metabolism.

From experiments in man (39) it does not appear that taurine synthesized by liver, and perhaps other organs, is released into the plasma for transport to other tissues. Presumably plasma taurine derived from the diet circulates in modest amounts by comparison to most plasma amino acids (5–20

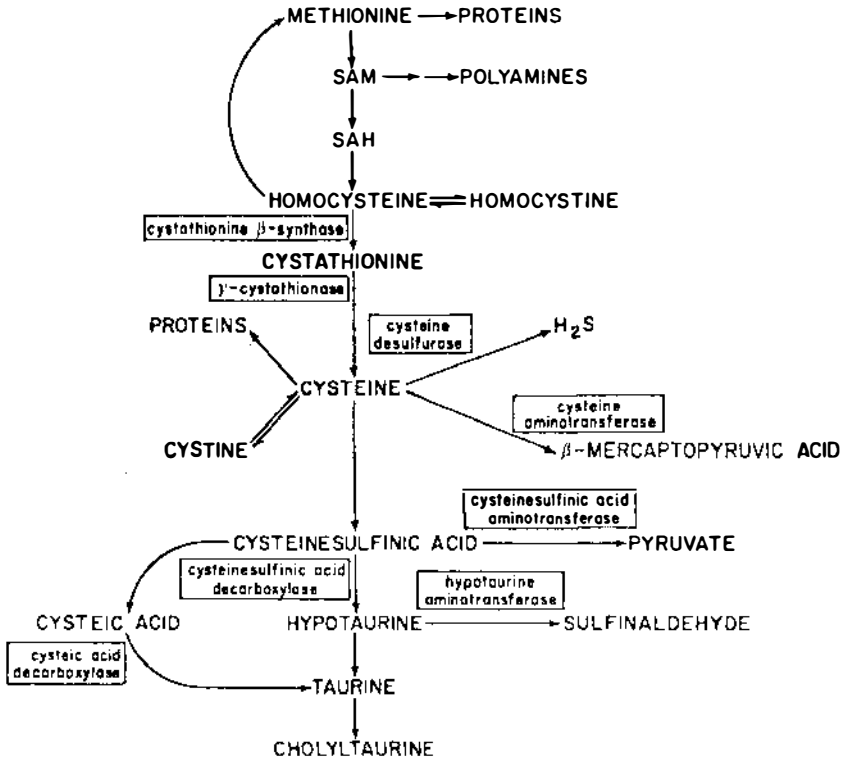

Figure 1 The metabolic pathway for sulfur amino acids indicates the route of taurine synthesis from methionine. The scheme includes vitamin B_6-dependent enzymes required by the pathway.

μmol/dliter). When measuring plasma taurine, one must be careful to remove platelets since they represent an extremely rich source of taurine and may serve to exaggerate plasma concentrations (13).

Taurine is readily excreted by the kidney and, like γ-amino butyric acid and β-alanine, is poorly reabsorbed by the proximal renal tubules of the rat, presumably by a common transport system (20). Consequently the urine usually contains a concentration of taurine equal to or greater than that of plasma. Furthermore, depression in the plasma level leads to low or absent urinary taurine (32, 60, 131), which can serve as a crude index of taurine status. Rats deficient in vitamin B_6 appear to increase their renal reabsorption of taurine as a conservation mechanism (123).

It is uncertain which factors control tissue concentrations of taurine. The liver has the most variable taurine content, presumably because it is the only organ in which taurine is metabolized and exported as a bile acid conjugate

to aid fat absorption in the small intestine. This process is accelerated during periods of food ingestion, reducing liver taurine content as it becomes conjugated with bile acids. Rat liver regenerating after partial hepatectomy has a low taurine concentration accompanied by an accumulation of hypotaurine (120). This compound, the immediate precursor of taurine, is rarely detected in mammalian tissue; neither the reason for its accumulation after partial hepatectomy nor the mechanism of its normal conversion to taurine have been adequately documented.

Although the concentration of taurine in tissues varies somewhat from species to species, certain tissues and fluids are noteworthy for their taurine content (Table 1). These include bile, in those species that conjugate bile acids with taurine, and retina, which maintains a considerably higher concentration than most tissues. Because of its total mass, muscle constitutes the largest reservoir of body taurine, representing more than 75% of the total body pool in rats. Cardiac muscle and brain have relatively high concentrations. These data are particularly intriguing since taurine is relatively inert and remains as the free amino acid in cells rather than being incorporated into peptides or larger proteins by the process of protein synthesis in contrast to most other amino acids.

Brain

In the CNS taurine is one of the major free amino acids, being highest in concentration in the developing brain (4–20 μmol/g) but second in concentration (1–9 μmol/g) to glutamic acid in the adult brain (128). The localization of taurine in the CNS of different species follows a relatively uniform regional pattern, with the possible exception of the olfactory bulb (128) and optic nerve (119, 139).

Taurine is readily accumulated in the brain of the rat fetus, and in the developing rat brain it has a slower rate of turnover (44-day half-life) than does taurine in the adult brain (22-day half life). The latter has the advantage of a matured enzymatic capacity for in situ biosynthesis and, thus, assured availability of its taurine requirement. The brain of the newborn rat contains 10% or more of the total body taurine pool, which falls by maturity to 5% due to growth and expansion of the body muscle mass (119). Certain of the dynamics of taurine uptake and metabolism by brain of various species undoubtedly depend upon the relative maturity of the brain. The immature brain from fetal and infant rhesus monkeys fails to accumulate an injected dose of S^{35}-taurine as rapidly as the fetal rat brain (129). Infant rat brains accumulate appreciable amounts of taurine (7% of the total taurine present at 5 days after birth) from the high concentration available in milk, especially at the beginning of lactation (126), indicating that colostrum contributes to tissue taurine pools in newborn mammals,

Table 1 Taurine concentrations in tissues of adult mammals[a]

Species	Plasma (μmol/dliter)	Tissue (μmol/g)			
		Liver	Heart	Brain	Muscle
Human	8	2	6	2	5
Monkey					
rhesus	10	3	11	2	4
cynomolgus (6 mo)	19	5	14	8	14
cebus (6 mo)	17	16	17	7	20
Cat	11	10	14	2	8
Rat	45	3	27	3	7
Dog	—	—	10	2	—
Rabbit	—	—	16	2	5
Mouse	—	—	43	9	—

[a]Adapted from several references (34, 61, 124, 126, 129).

even in those species known to have substantial synthetic capacity. Unpublished data (J. A. Sturman) indicate that of the total taurine content present in rat brain at weaning, 12% originated from the mother while in utero, 5% originated from the milk, and 83% was biosynthesized (not necessarily by the brain).

Pineal and Pituitary Glands

The pineal and pituitary glands maintain relatively high concentrations of taurine (9, 135). In the case of the pineal gland, taurine concentration has been related to light exposure and is thought to be related to circadian rhythms (35). Release of taurine from the pineal gland is stimulated by a β-adrenergic mechanism (140), reminiscent of the β-adrenergic influence on taurine in cardiac muscle (6). The pituitary provides a definite link between taurine and the neuroendocrine system. Increased hypothalmic levels of taurine are associated with hypophagia, decreased water intake, and hypothermia, whereas increased urinary taurine occurs during various forms of stress associated with the release of ACTH from the pituitary. These relationships between taurine and endocrine function await further investigation.

Retina

Taurine is the most abundant free amino acid in the retina (30–40 μmol/g), where it tends to be concentrated in the outer segments of rods and cones, the synaptic region of the inner plexiform layer, and the pigment epithelium (56, 57, 84, 142). Unlike the brain, the taurine concentration of the retina increases following birth, in conjunction with retinal development (124). Presumably, an appreciable amount of taurine is sequestered from the

plasma by the retinal pigment epithelium via active transport against a concentration gradient (24, 65) and is transferred to inner aspects of the retina (64, 84, 91) over a period of several days. Uptake of plasma taurine occurs even though a mechanism for synthesis is presumably present in the retina itself (70, 77). The retinal depletion of taurine, which occurs much more slowly than other tissues and fluids, except bile, in the cat deprived of dietary taurine (60), results in a dramatic retinopathy and blindness. This process has recently been shown to be accompanied by tapetal disruption and degeneration. Investigation of these degenerative processes has provided considerable insight into the possible function of taurine (see below).

Bile

Species vary in their conjugation of bile acids with taurine (42), the implications of which are interesting in terms of the biology and requirements of taurine in different species. Vessey (136) has reviewed the biochemical reasons for taurine or glycine conjugation of bile acids. The same enzyme appears responsible for conjugation with either amino acid (38, 136). This transfer enzyme seems to prefer taurine to glycine in most species, but in certain species such as the cat (40, 43, 92) conjugation with glycine does not occur, even when taurine is limiting. Thus, conjugation depends on two factors, the relative hepatic availability of either taurine or glycine and the enzymatic affinity for these two amino acids. A case in point is the depressed availability of taurine for bile acid conjugation brought about by vitamin B_6 deficiency (29).

Man normally conjugates 25% of his bile acids with taurine and increases this to more than 90% when fed supplemental taurine (31, 111, 125). Human fetuses and newborn infants conjugate bile acids exclusively with taurine and some time after birth convert primarily to glycine (16, 25, 38, 88, 138) when consumption of taurine declines. The conversion of glycine conjugation is hastened when infants are fed synthetic formulas that contain essentially no taurine compared to human milk, which has a considerable concentration of taurine (15) (see Table 2). Plasma and urinary taurine concentrations also decline in infants fed taurine-poor formulas (32, 101). Glycine feeding has no effect on the glycine/taurine (G/T) ratio present in bile acid conjugates (111). However, in the clinical circumstance of myxedema a markedly elevated G/T ratio exists that can be corrected by thyroxine (48). This seems incongruous with the thyroxine-induced depression of CSAD activity (55). Adrenalectomy depresses taurine conjugation of bile acids in the rat; activity can be restored by cortisone (49), presumably due to the previously mentioned cortisone-induced stimulation of CSAD activity.

Table 2 Taurine concentration in milk of various species[a]

Species	Concentration (μmol/dliter)
Taurine as the most concentrated amino acid	
gerbil	595
cat	287
dog	264–191[b]
monkey (rhesus)	61–56[b]
mouse	75
Taurine as the second most concentrated amino acid	
human	41–34[b]
chimpanzee	71–26[b]
baboon	38
rat	63–15[b]
sheep	68–14[b]
Taurine not among the top four amino acids	
rabbit	14
cow	31–1[b]
horse	3
guinea pig	56

[a] Adapted from Rassin et al (96).
[b] Difference between early and late lactation

Heart and Skeletal Muscle

Although skeletal muscle contains the largest mass of body taurine, experiments related to the metabolism and effect of taurine on muscle have focused primarily on rodent cardiac muscle, where it is highly concentrated (61). Despite long recognition and extensive investigations, definitive conclusion as to its mechanism of action has not been reached. Since the finer points of taurine involvement in the heart are the subject of other reviews (11, 34, 53, 54), only an overview of its cardiac involvement is provided.

The cardiac focus on taurine was sharpened by the observation that it accumulates in heart muscle under conditions of stress (54). Thus, stress encountered clinically in congestive heart failure (54), chronically induced by exercise as in swimming (72), or experimentally induced by injection of the ionotropic drug, isoproterenol, which stimulates calcium flux (18), all increase the taurine content of cardiac muscle. This increase in taurine is thought to result from adrenergic stimulation of cyclic AMP-dependent processes (73), resulting in a positive ionotropic effect and thereby enhancing intracellular calcium concentration or availability (17, 21, 23). These changes also prevent premature ventricular contractions induced by digoxin or epinephrine (30, 98). Curiously, in preliminary studies with

taurine-depleted kittens, a five- to ten-fold reduction in cardiac taurine concentration did not appear to render the heart more susceptible to electrically induced preventricular fibrillation (K. C. Hayes, unpublished data). This is in keeping with the observation that estimates of taurine in cardiac muscle from several species cover a wide range of concentrations (Table 1), leading to the conclusion that the normally encountered concentration in muscle does not reflect the requirement for minimal function, i.e. muscle must contain excess taurine.

The accumulation of taurine in heart muscle is thought to reflect the net uptake from plasma and not result from in situ biosynthesis. In fact, the heart is peculiar in that the synthetic pathway for taurine seems to be limited by the absence of a major synthesizing enzyme, CSAD, even though tracer doses of S^{35}-cystine injected into the heart are converted to taurine. Furthermore, the uptake of taurine by cardiac muscle occurs via a transport mechanism specific to β-amino acids (54) and generally proceeds against a concentration gradient that may be as high as 400 to 1. Uptake appears saturable at approximately 200μM (54).

Other Tissues

Like the endocrine glands in the brain, the adrenal gland has a high concentration of taurine, which would suggest that taurine may play an important functional role in this organ (79).

The liver ordinarily maintains a generous concentration of taurine in most species that conjugate bile acids with taurine. This is generally associated with high CSAD activity, indicating that synthesis is accommodating that conjugating function. On the other hand, liver depletion resulting from taurine-free diets tends to be rapid and almost total in species such as the cat and nonhuman primate (46, 60) in which hepatic synthesis is relatively poor. However, hepatic depletion of taurine appears to be without appreciable deleterious effect on that organ or on bile acid metabolism per se in those species so far examined.

TAURINE TURNOVER

An injected dose of radioactive taurine exchanges with unlabeled taurine in all tissues of every mammal examined to date (mice, rats, cats, primates). The exchange process and subsequent elimination of the radioactive taurine vary greatly from organ to organ. For example, parenchymal organs such as liver, kidney, and pancreas exchange rapidly with injected radioactive taurine; and the half-life of the taurine pool in these tissues is rapid ($<$1 day), whereas taurine in tissues such as heart, skeletal muscle, and brain exchanges slowly with a slower half-life ($<$3 days) (114). In the rat the

exchange of injected radioactive taurine with endogenous taurine of the brain occurs rapidly in utero, suggesting that this ability for rapid taurine uptake may be related to brain development (127).

Two separate taurine pools, with a slow and fast turnover, have been identified in the rat and in man (117, 125). In both species, the major route of elimination is the urine, in which approximately 25% of the radioactivity is present as inorganic sulfate, formed by the gut flora. Supplemental dietary taurine is rapidly excreted in the urine. The only discernible metabolic effect of excess dietary taurine is an increased rate of turnover of tissue taurine, and an increased proportion of bile acids conjugated with taurine compared to glycine. The slow turnover of the bulk of the taurine in mammals is a property unique to taurine among the free amino acids.

TAURINE DEPLETION

Most mammals derive at least some taurine from their diet and the rest from biosynthesis in vivo. The proportion derived from each source varies greatly from species to species; and in some cases, taurine derived from biosynthesis is limited by low activities of biosynthetic enzymes. Thus, rats maintained on a taurine-free diet suffer no ill effects since they normally biosynthesize the bulk of their body taurine. Other species, however, do not have such a great biosynthetic capability and, when deprived of dietary taurine, respond by decreasing the body taurine content.

Taurine Deficiency in Cats

The cat suffers a ten-fold reduction of taurine concentration in most tissues within a few months of dietary deprivation (130). This species synthesizes a limited amount of taurine from methionine or cystine (although not from inorganic sulfate), but not enough to maintain tissue taurine pools (14, 60). Some fluids and tissues resist depletion, noteably bile, retina and olfactory bulb, suggesting that taurine may be more important for the functions of these systems than it is for others (2, 60, 130). Eventually the retinal and tapetum lucidum taurine concentrations decrease, resulting in the degenerations described in more detail below.

The cat cannot respond to decreased taurine availability by conjugating more bile acids with glycine, but it secretes an increased amount of unconjugated bile acids instead (92). This phenomenon was also observed during infusion of sodium cholate into isolated, perfused livers. The liver of the rat synthesizes sufficient taurine to conjugate the cholate and does not alter its G/T ratio to accomplish this, whereas the liver of the cat is unable to meet the increased demand for taurine (41). No adverse consequences of taurine depletion in the olfactory bulb have yet been noted, although taurine admin-

istered to the olfactory bulb is known to affect aggressive behavior in rats (74). The role of taurine in olfaction may have far-reaching implications in terms of taste and smell perception, as well as behavior.

Taurine-depleted cats manifest no overt neurological symptoms, and the taurine remaining in brain distributes normally among the subcellular components (97). One might expect selective conservation of taurine by the synaptosomes if taurine plays an important role in excitatory function. Furthermore, capacity of the brain to biosynthesize taurine, as measured by activity of CSAD, is not altered by taurine depletion.

Retinal and Tapetal Degeneration

The consequences of taurine depletion in the cat retina have been carefully documented. Cats, whether kittens or adults, fed a taurine-free casein diet for periods ranging from 6 months to 2 years develop a granular, hyperreflective white zone in the area centralis of the normally yellow-green tapetum lucidum. This lesion is associated with depressed or absent electroretinograms (ERG) (14, 44, 107, 108), structural disintegration of the photoreceptor cell outer segments (45), and depletion of retinal taurine. These morphological changes are generally observed when the taurine concentration in retina has been decreased by a factor of 2 or more. Earliest changes are detected in the cone ERG implicit time and in rod and cone ERG amplitudes, which correlate with a depressed retinal taurine concentration (14, 107, 108). The functional impairment of the visual system caused by taurine depletion occurs before any structural alterations have taken place.

Ultrastructural study of the tapetum lucidum has revealed disorganization of the lattice arrangement of the tapetal rods in these same taurine-depleted cats (139). Fragmentation of the membranes surrounding the rods leads to their disruption associated with dissolution and loss of tapetal cells as degeneration progresses. Compression and thinning of the tapetum occurs in areas underlying the zone of photoreceptor cell degeneration and loss. This recent observation is of special interest for two reasons. First, it is the second example of the structural involvement of taurine with a biological cell (the first being the photoreceptor cells in the retina). Second, the decreased taurine content of cat tapetum during dietary taurine restriction is accompanied by a loss in tapetal zinc. Both taurine and zinc are located in the membrane surrounding the tapetal rods (J. A. Sturman, unpublished data). This association between zinc and taurine has been observed previously in the synapses of the mossy fiber system in the hippocampus (78) and has been discussed in relation to epilepsy (8).

Taurine Deficiency in Primates

Since the observation that deprivation of dietary taurine results in taurine deficiency and retinal degeneration in the cat, the potential role of taurine in nutrition of other species, especially in man, has received considerable attention. Human infants, both pre-term and full-term, fed synthetic, taurine-free formulae derived from partially purified cow's milk proteins, have progressively decreasing plasma taurine concentrations and excrete less taurine in the urine than infants fed human milk (32), primarily because man has a poor ability to biosynthesize taurine (55).

The consequences of potentially depressed taurine concentrations in tissues from human infants is unknown, but the possible implications of a dietary taurine requirement for human infants have prompted studies of depletion in developing primates. Two species were examined: cebus monkeys, which ordinarily conjugate bile acids only with taurine (and therefore might be expected to respond in a similar fashion to the cat), and cynomolgus monkeys, which conjugate bile acids with glycine and taurine (and therefore might be expected to respond in a fashion similar to man). Infants of both species have extremely limited capacity to synthesize taurine and suffered a decrease in taurine concentration in most tissues when fed a taurine-free, soy protein infant formula; the retina revealed the smallest decrease (46). As might be predicted, cebus monkeys continued to conjugate bile acids exclusively with taurine, even though the concentration of taurine in liver was reduced dramatically to meet this demand. Cynomolgus monkeys responded by increasing the proportion of bile acids conjugated with glycine and experienced no change in their low concentration of hepatic taurine. The most notable results of this study were a significant growth depression (16%) in all monkeys fed the taurine-free diet (46) and stability of the taurochenodeoxycholic acid pool (116). These results require confirmation and longer term investigations are necessary before a meaningful interpretation can be drawn.

Growth Rate Factor

In those species, including man, that possibly require dietary taurine, a primary factor for determining that requirement may be body growth rate and the demand imposed by an expanding muscle mass. Whereas cats (60), humans (55), and nonhuman primates (46) are all limited in their ability to synthesize taurine based on CSAD activity (Table 3), only cats have developed the degenerative retinopathy. Although nonhuman primates substantially depress their plasma and tissue taurine concentrations when fed a taurine-free diet, their rate of growth is less than that of kittens and the associated decrease in whole body taurine is less severe. As a consequence,

Table 3 CSAD activity in brain and liver of adult mammals[a]

Species	Brain[b]	Liver[b]
Human	7	<1
Monkey		
rhesus	5	5
cynomolgus	1	0
cebus	2	2
Cat	59	4
Rat	63	468
Dog	54	412
Rabbit	25	14
Guinea pig	6	3

[a] Adapted from several references (46, 55, 124).

[b] In μmol of CO_2/mg of protein/h.

the decline in retinal taurine was less than 15% (46). In human infants fed taurine-free milk formulas, taurine depletion of plasma and urine was even less remarkable than that in nonhuman primates (32), suggesting that their taurine pools, including retina, would be less stressed by the lack of dietary taurine. Furthermore, an accelerated growth rate probably contributes to risk only if the bile acids in a species are conjugated exclusively with taurine that must be obtained from the diet.

Dietary Taurine Requirement

These diet manipulations indicate that the requirement for dietary taurine is subject to qualifications of age and species. Taurine supply seems most critical during development of the CNS and muscle, in which the largest pools exist and presumably function. This point is emphasized by the high concentration of taurine in the milk of early lactation (96). The dietary requirement for mature mammals is different. The adult rat apparently needs no dietary taurine, although it does normally receive taurine in its diet. Similarly, adult human vegetarians have not been reported to suffer from taurine depletion, but more extensive examination and documentation of their taurine status is desirable. In its normal ecological niche a carnivore, such as the cat, would not be compromised, since meat and fish are rich sources of taurine. However, when fed a diet arbitrarily restricted by the designs of man, including processed dog foods (1), this ecological niche can be jeopardized and blindness can result. It is ironic that the most severe retinal degeneration observed clinically in cats by one of us resulted from a vegetarian owner making her cats consume a vegetarian diet (K. C. Hayes, unpublished data).

The amount of dietary taurine required to prevent retinal degeneration in cats has not been established, but an accurate estimate of the requirement should ultimately distinguish between a level that maintains a normal ERG and one that simply prevents ophthalmascopically detectable degeneration of the retina and tapetum. The latter roughly parallels the plasma taurine profile. Dietary levels of methionine, cystine, and sulfate probably contribute to the dietary taurine requirement. Adult cats fed a diet with normal amounts of sulfur amino acids (SAA = 1.55%) maintain greater plasma taurine levels than cats fed a low level of SAA (0.78%) (83), and dietary sulfate has a sparing effect on SAA oxidation and taurine excretion (67). From the data currently available, the intake required to maintain a normal plasma taurine level in kittens and cats probably lies between 500–1000 ppm in the diet.

TAURINE AND BILIARY PHYSIOLOGY

The comparative relationship of taurine to bile acid and lipid metabolism is of consequence to man since metabolism of cholesterol appears to be associated with the G/T ratio in bile. Thus, herbivores, such as the rabbit and guinea pig, which normally do not consume cholesterol, have a high G/T ratio and a low level of hepatic taurine synthesis (115), whereas omnivores, such as the rat, man, and monkey, which consume considerable amounts of cholesterol, have appreciable pools of taurochenodeoxycholic acid (taurochenic acid) and lower G/T ratios than herbivores. A large taurochenic acid pool would appear to be an advantage for alleviating lithogenic bile, since dietary chenic acid supplements prevent and dissolve gallstones (51). Chenic acid also exerts a feedback inhibition on cholesteryl ester formation (81), enhances biliary cholesterol secretion (90), and is associated with less cholesterol absorption than cholic acid (93, 112). Finally, cholestyramine, an effective resin utilized for lowering serum cholesterol, does so while preferentially removing taurochenic acid (3, 58), but regularly induces gallstone formation in the process (3).

Interestingly, in cynomolgus monkeys undergoing depletion of their tissue taurine pools during dietary deprivation of taurine, the chenic acid pool maintains its taurine concentration even as the cholic acid pool shifts to conjugation with glycine (116). The converse occurs in guinea pigs fed a taurine supplement, i.e. they dramatically increase their bile acid synthesis, decrease their G/T ratio, and increase taurochenic acid turnover (59). In obligate taurine-conjugating rats and cebus monkeys fed diets containing cholesterol and a low level of sulfur amino acids, an elevation in serum cholesterol occurs that can be normalized by dietary supplementation of cystine (89) or taurine (109). These observations suggest a prominent role

of the taurochenic acid pool in regulating cholesterol metabolism and lithogenicity of bile, an implication that warrants further scrutiny since the G/T ratio can be manipulated by dietary taurine in omnivores, such as man.

TAURINE FUNCTION

Clues concerning the function of taurine come from many quarters, but most are consistent with the hypothesis that it acts as an inhibitory neuromodulator, or neurotransmitter, of excitatory processes in the nervous system and muscle. Of interest in general metabolism are reports that taurine also has what may be considered an indirect, perhaps pharmacologic, influence on hormonally controlled aspects of metabolism.

CNS Function

The relationship between taurine and brain function has been appreciated for many years. Numerous studies indicate that taurine has a general depressant effect on the CNS (7, 9, 13, 63, 75) and may even have adverse effects on inhibitory or short-term, labile memory functions, but not on established response patterns (87). In this capacity taurine exerts a generalized depressant activity on neural excitation. This effect has been utilized in treatment of certain familial cases of human (9) and feline (134) epilepsy or to demonstrate anticonvulsant activity in experimentally induced strychnine and cobalt seizures in animals (9).

Consideration of the taurine-CNS relationship has focused on whether its depressant action is that of an inhibitory neurotransmitter or neuromodulator (9, 63). The high affinity uptake of taurine by synaptosomal preparations, its release from CNS preparations via electrical stimulation, as well as its potassium-induced depressant activity on various CNS neurons all suggest a neurotransmitter function. However, whereas neurotransmitters tend to be localized in the spinal cord or thalamic synapses, taurine appears to be evenly distributed in these neural tissues. Thus, when viewed in terms of its distribution, enhanced release by the nerve impulse, modulation of the release of other neurotransmitters, and influence on calcium transport in excitable tissues, taurine appears to modulate membrane excitability by decreasing the intracellular calcium concentration (52) and inhibiting the release of other neurotransmitting agents. Its influence on movement of calcium ions helps to explain its anticonvulsant role. The possibility exists, of course, that taurine functions as a neuromodulator in one set of circumstances and as a neurotransmitter in another, such as in the retina (7).

Retinal Function

Retinal taurine is concentrated in the photoreceptors where the process of illumination causes its release. Its sulfonic acid moeity may function as a

chelating agent to evoke changes in membrane permeability to certain ions, specifically increasing calcium concentration in the photoreceptors preceding their re-polarization. Calcium ion movement enhances taurine release, and most neurotransmitters seem to be released by a calcium-dependent process. Since calcium fluxes seem to increase excitability, concomitant release of taurine may serve to dampen or balance the excitatory process (102). *In vitro* experiments further suggest that retinal taurine specifically regulates calcium fluxes in a dose-dependent manner related to osmotically sensitive particles (85). In this sense, taurine qualifies as a neurotransmitter for some investigators, whereas others consider it an inhibitory neuromodulator of nervous excitability. The extremely large concentration present in photoreceptors (of the order of 100 mM) suggests the possibility of a structural function directly involving the photoreceptor membrane.

Heart Function

It has been suggested that taurine functions in cardiac muscle by interacting directly with the membrane via a low-affinity sarcolemmal-binding protein, which in turn secures the binding of calcium to the membrane. This calcium-binding process then mediates the action of taurine by an unknown mechanism (53, 104).

HORMONAL INTERACTIONS

Glucose and Insulin

Taurine has been associated with the function of several hormones, even though the specific relationship with each has not been established. For example, the ability of taurine to alter glucose utilization was noted many years ago (71), and at relatively high (200 mg/kg) intravenous or intraperitoneal doses taurine increases the insulin-like activity of plasma while decreasing blood glucose and increasing hepatic glycogen stores. This occurs in association with enhanced adenylate cyclase activity, suggesting that the taurine influence on the insulin system may be mediated by cyclic AMP (22). There is direct evidence that taurine exerts an action via cyclic AMP in the slime mold, *Dictyostelium discoideum* (J. M. Ashworth, unpublished data); and in *Harmannella culbertsoni* taurine stimulates the synthesis of cyclic AMP (94). In addition, similar i.v. or i.p. doses of taurine or a larger oral dose (300 mg/kg) administered to insulin-deficient alloxan diabetic rats and rabbits restored liver glycogen and reduced blood and urine glucose levels. These results suggest that taurine functions independently of insulin, although it was found to possess an insulinogenic action on fragments of isolated perfused pancreas (110). In other studies, taurine has protected against streptozoticin-induced hyperglycemia (133), whereas

the diabetic rat has developed elevated concentrations of taurine in cardiac and skeletal muscles (99). The latter presumably represented an increased taurine uptake, since synthesis and degradation in muscle is limited.

Epinephrine

Massive oral doses of taurine (4–7 g/kg/day) have affected the stress response of rats exposed to cold by preventing the decline of epinephrine in the adrenal gland. Both in vivo and in vitro taurine inhibited the release of epinephrine from adrenal medullary granules, whereas the stress-induced rise of plasma corticosterone was not affected by taurine. These observations suggest that taurine pharmacologically blocks the stress-induced rise in blood glucose by inhibiting epinephrine release, presumably by stabilizing the medullary granule membrane (79).

Thyroid Hormone

With the observation that the brain taurine concentration was increased in animals with hypothyroidism (47), it was proposed that the depressed metabolism associated with this condition might be due to an exaggerated inhibitory action of taurine on the CNS. An attempt was made to explore this hypothesis indirectly in hypothyroid, euthyroid, or hyperthyroid humans using the taurine concentration of blood platelets as a possible indirect measure of the corresponding brain synaptosomal taurine concentration. Surprisingly, in antithesis to the hypothesis, platelet taurine levels directly reflected the thyroid status rather than being inversely correlated (12).

Renin-Active Hormone

A relatively recent observation that requires further substantiation is the report that glutaurine (γ-L-glutamyl-taurine) has been isolated from the bovine parathyroid gland. It has been suggested as a putative hormone that increases plasma renin concentration and renin activity in rats and dogs. It has been hypothesized that this taurine-containing peptide elicits an increased membrane lability of juxtaglomerular cell granules in the kidney (27). This observation is of interest in light of the fact that dietary taurine has been shown to lower the elevated blood pressure of certain spontaneously hypertensive rats (80). Whether these two disparate observations are related remains to be determined.

Dietary Factors Influencing Taurine Metabolism

The relationship of zinc to the taurine modulation of epileptic seizures has been mentioned (8, 9). Zinc is incorporated in the enzyme glutamate dehydrogenase, which is involved in the synthesis of glutamic acid and is the probable neurotransmitter mediating hippocampal control of epileptic foci.

Not to be overlooked is the fact that oxidation and mobilization of taurine from tissues as well as urinary excretion of taurine are increased during zinc deficiency (4). It appears likely that the structural integrity of the zinc-rich membrane surrounding the tapetal rods in the feline tapetum lucidum is stabilized by a zinc-taurine interaction (J. A. Sturman, unpublished data). This association between zinc and taurine, functioning again at the membrane stabilization level, is a promising avenue for further investigation of the role of taurine in membranes. In this context it is of note that taurine has been reported to bind to calf brain synaptic membranes (62) and to membranes of the amoebae *Harmanella culbertsoni* (94).

Cognizant of the link between the metabolism of vitamin A and zinc (113), it is of special interest that vitamin A deficiency has been associated with excessive urinary excretion of taurine (66). The mechanism has not been revealed, but vitamin A deficiency in chicks increases oxidation and excretion of sulfur amino acids (103). Accelerated oxidation of sulfur compounds also occurs following whole-body irradiation where the urinary excretion of taurine is elevated (55).

Furthermore, vitamin E protects against radiation damage, while vitamin E deficiency in chicks produces so-called nutritional muscular dystrophy and is associated with increased taurine excretion. The association is noteworthy because it has been hypothesized that taurine is involved in the pathogenesis of hereditary muscular dystrophy in man and animals (10, 36). Whether or not these relationships are real and causal or simply represent secondary associations awaits further investigation.

Already discussed are the importance of vitamin B_6, folic acid, and adequate dietary SAA in the synthesis of taurine. In a similar vein, disruption of the SAA metabolic pathway due to inborn errors of metabolism (28) can depress synthesis of taurine. Fortunately for tissue function, restricted availability of taurine by whatever means leads to extraordinary conservation of the available taurine pool, particularly by those tissues that appear to have the greatest requirement (130).

CONCLUSION

It is apparent from the foregoing discussion that taurine is involved in a wide range of metabolic responses. These include its ascribed functional role in membranes, calcium flux, and possibly even cAMP activity. Thus, elucidation of the degree of dependency upon dietary supply assumes substantial importance, especially in view of its demonstrated role in certain organs, species, and ages. The potential metabolic ramifications involve structural changes in some species of such magnitude that blindness may result. Its involvement in other sensory faculties is only now being explored. Careful

dissection of the complicated metabolic interrelationships in which this sulfonic amino acid is involved will ultimately determine its place among dietary essentials for mammals, including man.

ACKNOWLEDGMENTS

Research in K. C. Hayes' laboratory was supported by the Department of Nutrition Fund for Research and Teaching and an N.I.H. Public Health Service Grant EY-00631. J. A. Sturman is supported by the Office of Mental Retardation and Developmental Disabilities of the State of New York, and by N.I.H. Public Health Service Grant HD-11129.

Literature Cited

1. Aguirre, G. D. 1978. Retinal degeneration associated with the feeding of dog foods to cats. *J. Am. Vet. Med. Assoc.* 172:791–96
2. Anderson, P. A., Baker, D. H., Corbin, J. E., Helper, L. C. 1979. Biochemical lesions associated with taurine deficiency in the cat. *J. Anim. Sci.* 49:1227–34
3. Angelin, B., Einarsson, K., Leijd, B. 1979. Biliary lipid composition during treatment with different hypolipidemic drugs. *Eur. J. Clin. Invest.* 9:185–90
4. Anthony, W. L., Woosley, R. L., Hsu, J. M. 1971. Urinary excretion of radiosulfur following S^{35}-taurine injection in zinc deficient rats. *Proc. Soc. Exp. Biol. Med.* 138:989–92
5. Awapara, J. 1976. The metabolism of taurine in the animal. In *Taurine*, ed. R. Huxtable, A. Barbeau, pp. 1–19. New York: Raven
6. Azari, J., Huxtable, R. J. 1980. The mechanism of the adrenergic stimulation of taurine influx in the heart. *Eur. J. Pharmacol.* 61:217–23
7. Barbeau, A. 1975. The heart and taurine. *Can. J. Neurol. Sci.* 2:343–46
8. Barbeau, A., Donaldson, J. 1974. Zinc, taurine, and epilepsy. *Arch. Neurol.* 30:52–58
9. Barbeau, A., Inour, N., Tsukada, Y., Butterworth, R. F. 1975. The neuropharmacology of taurine. *Life Sci.* 17:669–77
10. Baskin, S. I., Dagirmanjian, R. 1973. Possible involvement of taurine in the genesis of muscular dystrophy. *Nature* 245:464–65
11. Baskin, S. I., Finney, C. M. 1979. Effects of taurine and taurine analogues on the cardiovascular system. *Sulfur Amino Acids* 2:1–18
12. Baskin, S. I., Klekotka, S. J., Kendrick, A. Z., Bartuska, D. G. 1979. Correlation of platelet taurine levels with thyroid function. *J. Endocrinol. Invest.* 2:245–49
13. Baskin, S. I., Leibman, A. J., Cohn, E. M. 1976. Possible functions of taurine in the central nervous system. *Adv. Biochem. Psychopharmacol.* 15:153–64
14. Berson, E. L., Hayes, K. C., Rabin, A. R., Schmidt, S. Y., Watson, G. 1976. Retinal degeneration in cats fed casein. II. Supplementation with methionine, cysteine, or taurine. *Invest. Ophthalmol.* 15:52–58
15. Brueton, M. J., Berger, H. M., Brown, G. A., Ablitt, L., Iyngkaran, N., Wharton, B. A. 1978. Duodenal bile acid conjugation patterns and dietary sulfur amino acids in the newborn. *Gut* 19:95–98
16. Callacombe, D. N., Edkins, S., Brown, G. A. 1975. Duodenal bile acids in infancy. *Arch. Dis. Chil.* 50:837–43
17. Chovan, J. P., Kulakowski, E. C., Benson, B. W., Schaffer, S. W. 1979. Taurine enhancement of calcium binding to rat heart sarcolemma. *Biochim. Biophys. Acta* 551:129–35
18. Chubb, J., Huxtable, R. 1978. Isoproterenol-stimulated taurine influx in the perfused rat heart. *Eur. J. Pharmacol.* 48:369–76
19. Cohen, A. I. 1978. Retinal organization and function: possible roles for taurine. In *Taurine and Neurological Disorders*, ed. A. Barbeau, R. J. Huxtable, pp. 249–64. New York: Raven
20. Dantzler, W. H., Silbernagl, S. 1976. Renal tubular reabsorption of taurine, gamma-aminobutyric acid (GABA) and beta-alanine studies by continuous microperfusion. *Pfluegers Arch.* 367: 123–28

21. Diacono, J., Dietrich, J. 1976. Effects of taurine on the transmembrane ionic currents of rat and guinea pig ventricular fibres. *Farmaco. Sci.* 31:277–83
22. Dokshina, G. A., Silaeva, T. Y., Yartsev, E. I. 1976. Some insulin-like effect of taurine. *Vopr. Med. Khim.* 22:503–7
23. Dolara, P., Agresti, A., Giotti, A., Sorace, E. 1976. The effect of taurine on calcium exchange of sarcoplasmic reticulum of guinea pig studied by means of dialysis kinetics. *Can. J. Physiol. Pharmacol.* 54:529–33
24. Edwards, R. B. 1977. Accumulation of taurine by cultured retinal pigment epithelium of the rat. *Invest. Ophthal. Visual Sci.* 16:201–8
25. Encrantz, J. C., Sjovall, J. 1959. On the bile acids in duodenal contents of infants and children. *Clin. Chim. Acta* 4:793–99
26. Fellman, J. H., Roth, E. S., Fujita, T. S. 1978. Taurine is not metabolized to isethionate in mammalian tissue. See Ref. 19, pp. 19–24
27. Feuer, L., Gaal, K. 1979. Effect of glutaurine on plasma renin activity in the rat and the dog. *Gen. Comp. Endocrinol.* 39:330–35
28. Finkelstein, J. D. 1974. Methionine metabolism in mammals: the biochemical basis for homocystinuria. *Metabolism* 23:387–98
29. Fujihira, E., Ohshima, T., Ushioda, I., Takahashi, N. 1974. Effect of biliary drainage on bile acid conjugation with taurine in vitamin B_6-deficient rats. *Chem. Pharm. Bull.* 22:1174–78
30. Fujimoto, S., Iwata, H., Yoneda, Y. 1976. Effect of taurine on responses to noradrenaline, acetylcholine and ouabain in isolated auricles from digitalized guinea pigs. *Jpn. J. Pharmacol.* 1: 105–10
31. Garbutt, J. T., Lack, L., Tyor, M. P. 1971. Physiological basis of alterations in the relative conjugation of bile acids with glycine and taurine. *Am. J. Clin. Nutr.* 24:218–28
32. Gaull, G. E., Rassin, D. K., Raiha, N. C. R., Heinonen, K. 1977. Milk protein quantity and quality in low-birthweight infants. III. Effects on sulfur amino acids in plasma and urine. *J. Pediatr.* 90:348–55
33. Gorby, W. G., Martin, W. G. 1975. The synthesis of taurine from sulfate. VIII. The effect of potassium. *Proc. Soc. Exp. Biol. Med.* 148:544–49
34. Grosso, D. S., Bressler, R. 1976. Taurine and cardiac physiology. *Biochem. Pharmacol.* 25:2227–32
35. Grosso, D. S., Bressler, R., Benson, B. 1978. Circadian rhythm and uptake of taurine by the rat pineal gland. *Life Sci.* 22:1789–98
36. Gruener, R., Markovitz, D., Huxtable, R., Bressler, R. 1975. Excitability modulation by taurine. Transmembrane measurements of neuromuscular transmission. *J. Neurol. Sci.* 24:351–60
37. Guidotti, A. 1978. Role of taurine in brain function. See Ref. 19, pp. 273–48
38. Haber, L. R., Vaupshas, V., Vitullo, B. B., Seemayer, T. A., De Belle, R. C. 1978. Bile acid conjugation in organ culture of human fetal liver. *Gastroenterology* 74:1214–23
39. Hardison, W. G. M. 1978. Hepatic taurine concentration and dietary taurine as regulators of bile acid conjugation with taurine. *Gastroenterology* 75: 71–75
40. Hardison, W. G., Proffitt, J. H. 1977. Influence of hepatic taurine concentration on bile acid conjugation with taurine. *Am. J. Physiol.* 232:E75–E79
41. Hardison, W. G., Wood, C. A., Proffitt, J. H. 1977. Quantification of taurine synthesis in the intact rat and cat liver. *Proc. Soc. Exp. Biol. Med.* 155:55–58
42. Haslewood, G. A. D. 1964. The biological significance of chemical differences in bile salts. *Biol. Rev.* 39:537–74
43. Hawkins, W. B., Hanson, P. C., Coon, R. W., Terry, R. 1949. Bile salt metabolism as influenced by pure amino acids and casein digests. *J. Exp. Med.* 90:461–73
44. Hayes, K. C., Carey, R. E., Schmidt, S. Y. 1975. Retinal degeneration associated with taurine deficiency in the cat. *Science* 188:949–51
45. Hayes, K. C., Rabin, A. R., Berson, E. L. 1975. An ultrastructural study of nutritionally induced and reversed retinal degeneration in cats. *Am. J. Pathol.* 78:505–24
46. Hayes, K. C., Stephan, Z. F., Sturman, J.A. 1980. Growth depression in taurine-depleted infant monkeys. *J. Nutr.* 110:119–25
47. Heinonen, K. 1975. Effects of hypothyroidism and thyroxine substitution on the metabolism of L-methionine, L-cystathionine and taurine in developing rat brain. *Acta Endocrinol.* 80:487–500
48. Hellström, K., Sjövall, J. 1961. Conjugation of bile acids in patients with hypothyroidism. *J. Atherosclerosis Res.* 1:205–10
49. Hellström, K., Strand, O. 1963. Effects of adrenalectomy and corticoid replacement on bile acid conjugation in bile

fistula rats. *Acta Endocrinol.* 43:305–10
50. Hofmann, A. F. 1976. The enterohepatic circulation of bile acids in man. *Adv. Int. Med.* 21:501–34
51. Hofmann, A. F. 1977. Desaturation of bile and gallstone dissolution with chenodeoxycholic acid. *Am. J. Clin. Nutr.* 30:993–1000
52. Horrobin, D. F., Manku, M. S., Cunnane, S., Karmazyn, M., Morgan, R. O., Ally, A. I., Karmall, R. A. 1978. Regulation of cytoplasmic calcium: Interactions between prostaglandins, prostacyclin, thromboxane A2, zinc, copper and taurine. *Can. J. Neurol. Sci.* 5:93–96
53. Huxtable, R. J. 1978. Regulation of taurine in the heart. See Ref. 19, pp. 5–17
54. Huxtable, R. J., Chubb, J., Azari, J. 1980. Physiological and experimental regulation of taurine content in the heart. *Fed. Proc.* 39:2685–90
55. Jacobsen, J. G., Smith, L. H. 1968. Biochemistry and physiology of taurine and taurine derivatives. *Physiol. Revs.* 48:424–511
56. Keen, P., Yates, R. A. 1974. Distribution of amino acids in subdivided rat retinae. *Br. J. Pharmacol.* 52:118
57. Kennedy, A. J., Voaden, M. J. 1974. Free amino acids in the photoreceptor cells of the frog retina. *J. Neurochem.* 23:1093–95
58. Kenney, T. J., Garbutt, J. T. 1970. Effect of cholestyramine on bile acid metabolism in normal man. *Gastroenterology* 58:966–73
59. Kibe, A., Wake, C., Kuramoto, T., Hoshita, T. 1980. Effect of dietary taurine on bile acid metabolism in guinea pigs. *Lipids* 15:224–29
60. Knopf, K., Sturman, J. A., Armstrong, M., Hayes, K. C. 1978. Taurine: an essential nutrient for the cat. *J. Nutr.* 108:773–78
61. Kocsis, J. J., Kostos, V. J., Baskin, S. I. 1976. Taurine levels in the heart tissues of various species. See Ref. 5, pp. 145–53
62. Kumpulainen, E., Olkinuora, M., Lahdesmaki, P. 1979. Ability of calf brain synaptic membranes to bind [^{35}S]taurine to their Triton X-100 and chloroform extracts. *Neurosci. Lett.* 11: 215–18
63. Kuriyama, K. 1980. Taurine as a neuromodulator. *Fed. Proc.* 39:2680–84
64. Lake, N., Marshall, J., Voaden, M. J. 1977. The entry of taurine into the neural retina and pigment epithelium of the frog. *Brain Res.* 128:497–503
65. Lake, N., Marshall, J., Voaden, M. J. 1978. High affinity uptake sites for taurine in the retina. *Exp. Eye Res.* 27:713–18
66. Lamb, A. J., Naewbanij, J., Anzano, M. A. 1979. Altered taurine metabolism in vitamin A deficiency. *Fed. Proc.* 38:762 (Abstr.)
67. Lombardini, J. B., Medina, E. V. 1978. Effects of dietary inorganic sulfate, taurine and methionine on tissue levels of taurine in the growing rat. *J. Nutr.* 108:428–33
68. Lopez-Colome, A. M., Pasantes-Morales, H. 1980. Taurine interactions with chick retinal membranes. *J. Neurochem.* 34:1047–52
69. Loriette, C., Chatagner, F. 1978. Cysteine oxidase and cysteine sulfinic acid decarboxylase in developing rat liver. *Experientia* 34:981–82
70. Macaione, S., Tucci, G., De Luca, G., Di Girorgio, R. M. 1976. Subcellular distribution of taurine and cysteine sulphinate decarboxylase activity in ox retina. *J. Neurochem.* 27:1411–14
71. MaCallum, A. B., Divertz, C. 1942. The potentiation of insulin by sulfones. *Can. Chem. Process Ind.* 26:569–76
72. Mal'Chikova, L. S., Elizarova, E. P. 1978. Effect of swimming on the uptake and content of taurine in the rat heart. *Kardiologiia* 18:82–86
73. Mal'Chikova, L. S., Speranskaia, N. V., Elizarova, E. P. 1979. Effect of taurine on cyclic AMP and GMP levels in the hearts of rats exposed to stress. *Biull. Eksp. Biol. Med.* 87:134–37
74. Mandel, P., Mack, G., Kempf, E., Ebel, A., Simlet, S. 1978. Molecular aspects of a model of aggressive behavior: Neurotransmitter interactions. In *Interactions Between Putative Neurotransmitters in the Brain,* ed. J. F. Pujol, R. Samanin, pp. 285–303. New York: Raven
75. Mandel, P., Pasantes-Morales, H. 1978. Taurine in the nervous system. *Rev. Neurosci.* 3:157–93
76. Mantovani, J., Devivo, D. C. 1979. Effects of taurine on seizures and growth hormone release in epileptic patients. *Arch. Neurol.* 35:672–74
77. Mathur, R. L., Klethi, J., Ledig, M., Mandel, P. 1976. Cysteine sulfinate carboxylase in the visual pathway of adult chicken. *Life Sci.* 18:75–79
78. McLardy, T. 1962. Zinc enzymes and the hippocampal mossy fibre system. *Nature* 194:300–2
79. Nakagawa, K., Kuriyama, K. 1975. Effect of taurine on alteration in adrenal

functions induced by stress. *Jpn. J. Pharmacol.* 25:737–46
80. Nara, Y., Yamori, Y., Lovenberg, W. 1978. Effect of dietary taurine on blood pressure in spontaneously hypertensive rats. *Biochem. Pharmacol.* 27:2689–92
81. Neelon, V. J., Lack, L. 1977. The effect of bile salts on the formation and hydrolysis of cholesterol esters by rat liver enzymes. *Biochim. Biophys. Acta* 487:137–44
82. Newman, W. H., Frangakis, C. J., Grosso, D. S., Bressler, R. 1977. A relation between my ardial taurine content and pulmonary wedge pressure in dogs with heart failure. *Physiol. Chem. Phys.* 9:259–63
83. O'Donnell, J. A. III, Rogers, W. R., Morris, J. G. 1980. Effect of diet on plasma taurine in the cat. *J. Nutr.* 111: In press
84. Orr, H. T., Cohen, A. I., Lowry, O. H. 1976. The distribution of taurine in the vertebrate retina. *J. Neurochem.* 26: 609–11
85. Pasantes-Morales, H., Ademe, R. M. Lopez-Colome, A. M. 1979. Taurine effects on $^{45}Ca^{++}$ transport in retinal subcellular fractions. *Brain Res.* 172:131–38
86. Pasantes-Morales, H., Salceda, R., Lopez-Colome, A. M. 1978. Taurine in normal retina. See Ref. 19, pp. 265–79
87. Persinger, M. A., Valliant, P. M., Falto, H. 1976. Weak inhibitory behavioral effects of postnatal/preweaning taurine injections in rats. *Dev. Psychobiol.* 9:131–36
88. Poley, J. R., Dower, J. C., Owen, C. A., Stickler, G. B. 1964. Bile acids in infants and children. *J. Lab. Clin. Med.* 63:838–46
89. Portman, O. W., Mann, G. V. 1955. The disposition of taurine-S^{35} and taurocholate-S^{35} in the rat: dietary influences. *J. Biol. Chem.* 213:733–47
90. Poupon, R., Grosdemouge, M. L., Dumont, M., Erlinger, S. 1976. Influence of bile acids upon biliary cholesterol and phospholipid secretion in the dog. *Eur. J. Clin. Invest.* 6:279–84
91. Pourcho, R. G. 1977. Distribution of ^{35}S-taurine in mouse retina after intravitreal and intravascular injection. *Exp. Eye Res.* 25:119–27
92. Rabin, B., Nicolosi, R. J., Hayes, K. C. 1976. Dietary influence on bile acid conjugation in the cat. *J. Nutr.* 106: 1241–46
93. Raicht, R. F., Cohen, B. I., Mosbach, E. H. 1974. Effects of sodium taurochenodeoxycholate and sodium taurocholate on cholesterol absorption in the rat. *Gastroenterology* 67:1155–61
94. Raizada, M. K., Krishna Murti, C. R. 1973. Binding of taurine to *Hartmannella culbertsoni* membranes and the synthesis of cyclic AMP. *Curr. Sci.* 42:202–4
95. Rassin, D. K., Gaull, G.E. 1975. Subcellular distribution of enzyme of transmethylation and transsulphuration in rat brain. *J. Neurochem.* 24:969–78
96. Rassin, D. K., Sturman, J.A., Gaull, G. E. 1978. Taurine and other amino acids in milk of man and other mammals. *Early Hum. Dev.* 2:1–13
97. Rassin, D. K., Sturman, J. A., Hayes, K. C., Gaull, G. E. 1978. Taurine deficiency in the kitten: subcellular distribution of taurine and ^{35}S taurine in brain. *Neurochem. Res.* 3:401–10
98. Read, W. O., Weltz, J. D. 1963. Effect of taurine on epinephrine and digoxin-induced irregularities of the dog heart. *J. Pharmacol. Exp. Ther.* 139:283–89
99. Reibel, D. K., Shaffer, J. E., K sis, J. J., Neely, J. R. 1979. Changes in taurine content in heart and other organs of diabetic rats. *J. Mol. Cell Cardiol.* 11:827–30
100. Remtulla, M. A., Applegarth, D. A., Clark, D. G., Williams, I. H. 1977. Analysis of isethionic acid in mammalian tissues. *Life Sci.* 20:2029–36
101. Rigo, J., Senterre, J. 1977. Is taurine essential for the neonates. *Biol. Neonate* 32:73–76
102. Salceda, R., Pasantes-Morales, H. 1975. Calcium coupled release of ^{35}S taurine from retina. *Brain Res.* 96:206–11
103. Samonds, K. W., Kemmerer, A. R. 1969. Effect of vitamin A upon the fate of S^{35}-methionine in methionine deficient chickens. *Fed. Proc.* 28:489 (Abstr.)
104. Schaffer, S. W., Kramer, J., Chovan, J. P. 1980. Regulation of calcium homeostasis in the heart by taurine. *Fed. Proc.* 39:2691–94
105. Schaffer, S. W., Sevem, A., Chovan, J. 1978. New chromatographic procedure for measuring isethionic acid levels in tissue. See Ref. 19, pp. 25–28
106. Schmidt, S. Y. 1978. Taurine fluxes in isolated cat and rat retinas: Effects of illumination. *Exp. Eye Res.* 26:529–35
107. Schmidt, S. Y., Berson, E.L., Hayes, K. C. 1976. Retinal degeneration in cats fed casein. I. Taurine deficiency. *Invest. Ophthalmol.* 15:47–52
108. Schmidt, S. Y., Berson, E. L., Watson, G., Huang, C. 1977. Retinal degeneration in cats fed casein. III. Taurine defi-

ciency and ERG amplitudes. *Invest. Ophthal. Visual Sci.* 16:673–78
109. Seidel, J. C., Nath, N., Harper, A. E. 1960. Diet and cholesterolemia: V. Effects of sulfur-containing amino acids and protein *J. Lipid Res.* 1:474–81
110. Silaeva, T. Y., Dokshina, G. A., Yartsev, E. I., Iakovleva, V.V., Arkhangel'Skaia, T. E. 1976. The effect of taurine on the carbohydrate metabolism of diabetic animals. *Probl. Endokrinol.* 22: 99–103
111. Sjovall, J. 1959. Dietary glycine and taurine on bile acid conjugation in man. *Proc. Soc. Exp. Biol. Med.* 100:676–78
112. Smallwood, R. A., Hoffman, N. E. 1976. Bile acid structure and biliary secretion of cholesterol and phospholipid in the cat. *Gastroenterology* 71:1064–66
113. Solomons, N. W., Russell, R. M. 1980. The interaction of vitamin A and zinc: implications for human nutrition. *Am. J. Clin. Nutr.* 33:2031–40
114. Spaeth, D. G., Schneider, D. L. 1974. Turnover of taurine in rat tissues. *J. Nutr.* 104:179–86
115. Spaeth, D. G., Schneider, D. L., Sarett, H. P. 1974. Taurine synthesis, concentration, and bile salt conjugation in rat, guinea pig, and rabbit. *Proc. Soc. Exp. Biol. Med.* 147:855–58
116. Stephan, Z. F., Armstrong, M. J., Hayes, K. C. 1981. Bile lipid alterations in taurine-depleted monkeys. *Am. J. Clin. Nutr.* 34:204–10
117. Sturman, J. A. 1973. Taurine pool sizes in the rat: effects of vitamin B_6 deficiency and high-taurine diet. *J. Nutr.* 103:1566–80
118. Sturman, J.A. 1978. Vitamin B_6 and the metabolism of sulfur amino acids. In *Human vitamin B_6 requirements,* pp. 37–60. Washington DC: Natl. Acad. Sci.
119. Sturman, J. A. 1979. Taurine in the developing rabbit visual system: changes in concentration and axonal transport including a comparison with axonally transported proteins. *J. Neurobiol.* 10:221–37
120. Sturman, J. A. 1980. Formation and accumulation of hypotaurine in rat liver regenerating after partial hepatectomy. *Life Sci.* 26:267–72
121. Sturman, J. A. 1981. Cysteinesulfinic acid decarboxylase activity in the mammalian nervous system: Absence from axoms. *J. Neurochem.* 36:304–6
122. Sturman, J. A. 1981. Vitamin B_6 and sulfur amino acid metabolism. In *Vitamin B_6 Analytical Methodology and Criteria for Assessing Nutritional Status,* ed. R. D. Reynolds, J. E. Laklem. New York: Plenum In press
123. Sturman, J. A., Cohen, P. A., Gaull, G. E. 1969. Effects of vitamin B_6 deficiency on transsulfuration. *Biochem. Med.* 3:244–51
124. Sturman, J. A., Hayes, K. C. 1980. The biology of taurine in nutrition and development. *Adv. Nutr.* 4:231–99
125. Sturman, J. A., Hepner, G. W., Hofmann, A. F., Thomas, P. J. 1975. Metabolism of ^{35}S-taurine in man. *J. Nutr.* 105:1206–14
126. Sturman, J. A., Rassin, D. K., Gaull, G. E. 1977. Taurine in developing rat brain: transfer of ^{35}S-taurine to pups via the milk. *Pediatr. Res.* 11:28–33
127. Sturman, J. A., Rassin, D. K., Gaull, G. E. 1977. Taurine in development. *Life Sci.* 21:1–22
128. Sturman, J. A., Rassin, D. K., Gaull, G. E. 1978. Taurine in the development of the central nervous system. See Ref. 19, pp. 47–91
129. Sturman, J. A., Rassin, D. K., Gaull, G. E., Cote, L. J. 1980. Taurine in developing rhesus monkey brain. *J. Neurochem.* In press
130. Sturman, J.A., Rassin, D. K., Hayes, K. C., Gaull, G. E. 1978. Taurine deficiency in the kitten: exchange and turnover of ^{35}S taurine in brain, retina, and other tissues. *J. Nutr.* 108:1462–76
131. Thompson, D. E., Vivian, V. M. 1977. Dietary-induced variations in urinary taurine levels of college women. *J. Nutr.* 107:673–79
132. Tiedman, F., Gmelin, L. 1827. Einige nere Bestandtheile der Galle des Ochsen. *Ann. Physik. Chem.* 9:326–37
133. Tokunaga, H., Yoneda, Y., Kuriyama, K. 1979. Protective actions of taurine against streptozotocin-induced hyperglycemia. *Biochem. Pharmacol.* 28: 2807–11
134. Van Gelder, N. M., Koyama, I., Jasper, H. H. 1977. Taurine treatment of spontaneous chronic epilepsy in a cat. *Epilepsia* 18:45–54
135. Vellan, E. J., Gjessing, L. R., Stalberg, H. 1970. Free amino acids in the pineal glands of human brain. *J. Neurochem.* 17:699–701
136. Vessey, D. A. 1978. The biochemical basis for the conjugation of bile acids with either glycine or taurine. *Biochem. J.* 174:621–26
137. Voaden, M. J., Lake, N., Marshall, J., Morjaria, B. 1977. Studies on the distribution of taurine and other neuroactive

amino acids in the retina. *Exp. Eye Res.* 25:249–57
138. Watkins, J. B., Jarvenpaa, A. L., Raiha, N., Szczepanik Van-Leween, P., Klein, P. D., Rassin, D. K., Gaull, G. 1979. Regulation of bile acid pool size: Role of taurine conjugates. *Pediatr. Res.* 13:410 (Abstr.)
139. Wen, G. Y., Sturman, J. A., Wisniewski, H. M., Lidsky, A. A., Cornwell, A. C., Hayes, K. C. 1979. Tapetum disorganization in taurine-depleted cats. *Invest. Ophthalmol. Vis. Sci.* 18:1200–6
140. Wheler, G. H., Klein, D. C. 1980. Taurine release from the pineal gland is stimulated via a beta-adrenergic mechanism. *Brain Res.* 187:155–64
141. Yamaguchi, K., Shigehisa, S., Sakakibara, S., Hosokawa, Y., Ueda, I. 1975. Cysteine metabolism in vivo of Vitamin B_6-deficient rats. *Biochim. Biophys. Acta* 381:1–8
142. Yates, R. A., Keen, P. 1976. The distribution of free amino acids in subdivisions of rat and frog retinae obtained by a new technique. *Brain Res.* 107:117–26