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REVIEW ARTICLE

Role of taurine in the pathologies of MELAS and MERRF

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Abstract Taurine is an abundant β-amino acid that concentrates in the mitochondria, where it participates in the conjugation of tRNAs for leucine, lysine, glutamate and glutamine. The formation of 5-taurinomethyluridine-tRNA strengthens the interaction of the anticodon with the codon, thereby promoting the decoding of several codons, including those for AAG, UUG, CAG and GAG. By preventing these series of events, taurine deficiency appears to diminish the formation of 5-taurinomethyluridine and causes inefficient decoding for the mitochondrial codons of leucine, lysine, glutamate and glutamine. The resulting reduction in the biosynthesis of mitochondria-encoded proteins deprives the respiratory chain of subunits required for the assembly of respiratory chain complexes. Hence, taurine deficiency is associated with a reduction in oxygen consumption, an elevation in glycolysis and lactate production and a decline in ATP production. A similar sequence of events takes place in mitochondrial diseases MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) and MERRF (myoclonic epilepsy and ragged-red fiber syndrome). In both diseases, mutations in their respective tRNAs interfere with the formation of 5-taurinomethyluridine in the wobble position. Hence, the taurine-deficient phenotype resembles the phenotypes of MELAS and MERRF.

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Introduction

The mitochondrial diseases, which are a heterogenous group of disorders characterized by diminished respiratory chain activity, arise from mutations in either the mitochondrial or nuclear genome (Chinnery and Turnbull 2001). Mutations in the mitochondrial genome impact the synthesis of mitochondria-encoded proteins, which contribute to the assembly and makeup of respiratory chain complexes. Specific nuclear genes also affect respiratory chain function by altering the synthesis of mitochondria-encoded proteins, ensuring the assembly and integrity of respiratory chain complexes, modulating energy metabolism or delivering reducing equivalents to the respiratory chain.

Clinical and pathophysiological properties of MELAS

One of the most widely studied mitochondrial diseases is MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), which presents as a cluster of clinical symptoms, which commonly include several of the following: neurological deterioration, cardiomyopathy, diabetes, proteinuria, muscle weakness, retinopathy, severe disability and premature death (Table 1). Although at least 29 specific point mutations have been linked to MELAS, 80 % of the cases carry an adenine-to-guanine transition mutation (A3243G) located in position 3243 of mitochondrial DNA (Chomyn et al. 2000; Park

et al. 2003). Position 3243 is situated in a region of the DNA that codes for $tRNA^{Leu(UUR)}$.

The A3243G mutation mediates a decrease in respiratory chain flux by reducing respiratory chain complex activity and oxygen consumption (Bentlage and Attardi 1996; James et al. 1996; Pang et al. 2001; von Kleist-Retzow et al. 2007). Although MELAS is generally associated with a decrease in the activity of respiratory chain complexes I and IV (Finsterer 2007; James et al. 1996; Moraes et al. 1992; Obermaier-Kusser et al. 1991), a reduction in complex III activity has also been observed (Bentlage et al. 1995; Srivastava et al. 2009). This variability in respiratory chain activity is attributable to several complications unique to MELAS, including the involvement of multiple mutations in MELAS, the relationship between various mutation-linked $tRNA^{Leu(UUR)}$ defects and the influence of extraneous, mutation-independent factors on respiratory chain activity. Also complicating the relationship between genotype and phenotype is a feature shared by all mitochondrial diseases, the involvement of both nuclear and mitochondrial genes in respiratory function. Despite these complexities, it is widely accepted that inhibition of respiratory chain flux leads to diminished rates of ATP synthesis and an elevation in the production of lactate (James et al. 1999; Pallotti et al. 2004; Pang et al. 2001; von Kleist-Retzow et al. 2007). Sluggish rates of respiratory chain flux also increase the rate of mitochondrial superoxide production, a source of mitochondrial protein, lipid and DNA damage (Pang et al. 2001; von Kleist-Retzow et al. 2007).

Aminoacyl hypothesis of MELAS

Information gleaned on the pathophysiology of MELAS has largely relied on the use of cybrids, which are artificial cells prepared by transferring A3243G-containing mitochondrial DNA into human cell lines lacking mitochondrial DNA. Two theories on the pathophysiology of MELAS emerged from studies using A3243G-containing cybrids. One of the hypotheses, referred to in this review as the aminoacyl hypothesis, attributes the pathophysiology of MELAS to impaired $tRNA^{Leu(UUR)}$ stability, lower aminoacyl-$tRNA^{Leu(UUR)}$ content and diminished mitochondrial protein synthesis. Proponents of the aminoacyl hypothesis have provided convincing evidence that $tRNA^{Leu(UUR)}$ and leucyl-$tRNA^{Leu(UUR)}$ content are reduced in cybrids harboring the A3243G mutation (Chomyn et al. 2000; Li and Guan 2010; Park et al. 2003). Their studies have also shown that a reduction in leucyl-$tRNA^{Leu(UUR)}$ content diminishes the rate of transcription of mitochondria encoded proteins whose mRNAs contain multiple UUR (UUG and UUA) codons, where UUR represents the two leucine codons (UUA and UUG) that interact with the anticodon of $tRNA^{Leu(UUR)}$. Table 2 shows that the mitochondria-encoded proteins exhibiting

Table 1 Properties of MELAS, MERRF and taurine-deficient phenotypes

System	MELAS phenotype	MERRF phenotype	Taurine deficiency phenotype
Cardiovascular	Cardiomyopathy (3 %)	Cardiomyopathy (33 %)	Cardiomyopathy
	Cardiac conduction defects	Cardiac conduction defects (22 %)	Cardiac conduction defects
Muscle	Myopathy (53 %)	Myopathy	Myopathy
	Exercise intolerance	Exercise intolerance (80 %)	Exercise intolerance
		Ragged red fibers (92 %)	
CNS and peripheral nerves	Seizures (50 %)	Myoclonus epilepsy (100 %)	Seizures
	Stroke-like episodes (48 %)	Stroke-like episodes (mild)	
	Ataxia (24 %)	Cerebellar ataxia (100 %)	
	Polyneuropathy (5 %)	Neuropathy	Neuropathy
	Dementia (27 %)	Dementia (75 %)	
	Chronic external opthalmoplegia (28 %)	Opthalmoplegia (11 %)	
Endocrine	Short stature (15 %)	Short stature (57 %)	Short stature
	Lipomatosis (1 %)	Lipomatosis (3 %)	Lipid metabolic defects
	Lactic acidosis	Lactic acidosis (83 %)	Lactic acidosis
	Diabetes (15 %)		
Eye	Retinopathy (15 %)	Pigmentary retinopathy (15 %)	Retinopathy
	Optic atrophy (1 %)	Optic atrophy (39 %)	Optic atrophy
Ear	Deafness	Deafness (91 %)	Auditory defects

The percentage of 62 individuals with MERRF (Hirano and DiMauro 1996) or 45 individuals with MELAS (Sproule and Kaufmann 2008) that exhibit specific symptoms is shown

Table 2 Codon usage for 13 mitochondria-encoded proteins

Gene	No. of codons								
	Leucine			Lysine		Glutamine		Glutamic acid	
	CUN	UUA	UUG	AAA	AAG	CAA	CAG	GAA	GAG
ND1	57	5	1	6	1	6	0	8	3
ND2	55	8	1	10	2	8	2	5	1
ND3	18	10	1	3	0	3	0	3	2
ND4	87	8	1	10	1	9	1	9	0
ND4L	22	1	0	0	0	1	0	2	0
ND5	95	7	2	20	1	16	3	8	1
ND6	3	8	8	8	0	8	3	0	0
Cyt b	55	7	2	8	1	8	0	4	0
COX I	55	7	0	9	1	5	1	7	3
COX II	28	4	1	4	0	6	1	8	3
COX III	31	3	0	3	0	9	0	5	2
ATPase 6	39	4	1	5	1	7	0	3	0
ATPase 8	8	1	1	6	1	3	0	1	0

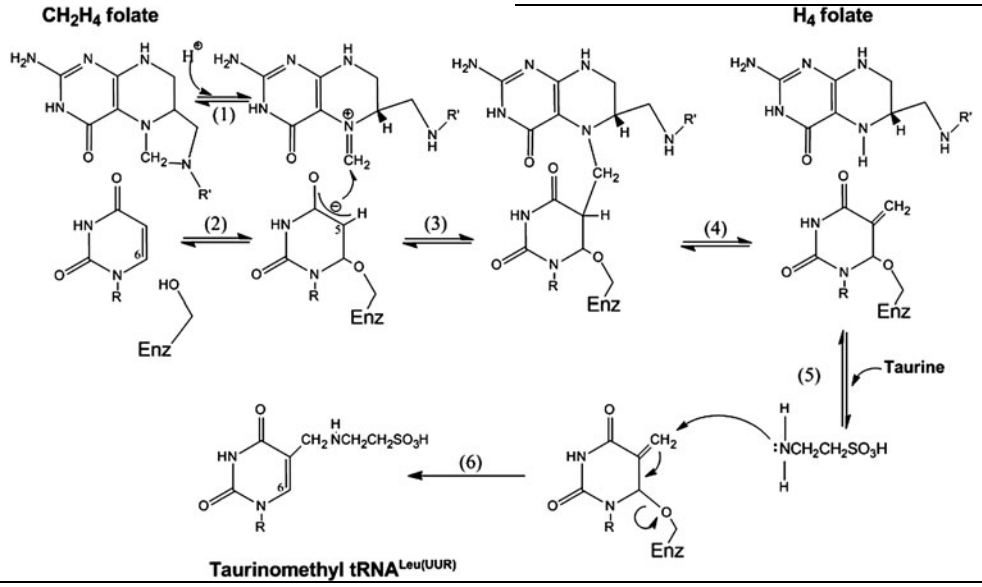
the greatest dependence on UUR codons are ND6, ND3 and A8. However, the dependence of each mitochondrial protein on mitochondrial-specific leucine codons (UUA, UUG and CUN) is distinct. Although leucine only makes up 11 % of the secondary structure of ND6, 84 % of the leucine residues of ND6 are derived from the UUR codons. On the other hand, while 38 % of the leucine residues of ND3 are dependent on UUR codons, over 25 % of the amino acid composition of ND3 are leucine residues. In this regard, it is relevant that both ND3 and ND6 serve as subunits of complex I, with ND6 assuming the added role of facilitating complex I assembly (Ugalde et al. 2003). In contrast to the stark UUR dependence of ND3 and ND6, UUR bases represent less than 10 % of all leucine codons in the mRNAs of ND4L and ND5. Thus, the aminoacyl hypothesis predicts that the MELAS mutation mediates a deficiency in ND3 and ND6 and a resulting reduction in complex I activity, a prediction borne out by clinical studies. The aminoacyl hypothesis also predicts that the activity of complex V is dependent upon UUR codons while complex IV is largely unaffected by the status of UUR decoding. Indeed, both COI and COIII, which are subunits of complex IV, contain few UUR codons.

To test the major premises of the aminoacyl hypothesis, Flierl et al. (1997) examined the rates of ^{3}H-leucine and ^{35}*S*-methionine incorporation into mitochondria-encoded proteins of a lymphoblastoid cell line harboring a mitochondrial DNA mixture consisting of 70 % A3243G mutation and 30 % wild-type, which together result in reduced cytochrome *c* oxidase activity but little change in complex I activity. Because ^{35}*S*-methionine incorporation is a measure of overall mitochondrial protein synthesis while ^{3}H-leucine incorporation takes into consideration the effect of the A3243G mutation-mediated protein synthetic defect, the data were expressed as the ^{3}H/^{35}S ratio for individual mitochondria-encoded proteins. The greatest mutation-mediated reduction in the ^{3}H/^{35}S ratio was found for ND3 and ND6, with the smallest reduction observed for ND4L. The large decreases in the ^{3}H/^{35}S ratios for ND3 and ND6 are consistent with the large number of UUR codons in the mRNA of the two proteins. Less clear is the basis underlying the relatively normal complex I activity despite impaired biosynthesis of ND3 and ND6. Moreover, the loss of complex IV activity in the lymphoblastoid cells harboring the A3243G mutation is disproportionate to the minor change in COI–COIII biosynthesis. In the case of complex IV, a poor correlation exists between the rate of COI–COIII biosynthesis and the UUR content of COI–COIII mRNA. Although a similar uncoupling of protein synthesis from codon number has been previously described (Chomyn et al. 2000), the mechanism underlying these unexpected findings is unknown but probably related to the complexities of the respiratory complexes. For example, it is recognized that the activity of complex IV depends upon the rate of mitochondria encoded protein COI–COIII biosynthesis and turnover, the biosynthesis and turnover rate of numerous nuclear-encoded proteins, the assembly of the complex IV subunits, the factors that stabilize complex IV structure and the factors that modulate enzyme activity. Clearly, further studies are warranted to clarify the regulation of these complex events in cells harboring the A3243G mutation. Also complicating the interpretation of the mechanistic data is the existence of

compensatory responses that elevate mitochondrial mass, thereby increasing the activity of all respiratory complexes within the cell (Sproule and Kaufmann 2008).

Wobble hypothesis of MELAS

The Wobble hypothesis of MELAS traces the respiratory defects to inefficient decoding of the UUG codon. According to the wobble hypothesis, the A3243G mutation interferes with the conjugation of taurine with a wobble position uridine of $tRNA^{Leu(UUR)}$, a reaction that stabilizes U-G pairing in the anticodon loop (Kirino et al. 2005; Kurata et al. 2008). Suzuki et al. (2002) identified the product of the conjugation reaction as 5-taurinomethyluridine-$tRNA^{Leu(UUR)}$, but no information has been provided on the enzyme catalyzing the reaction. However, recent work in our laboratory suggests that the conjugation enzyme (5-taurinomethyl-$tRNA^{Leu(UUR)}$ synthase) is folate-dependent and appears to catalyze the following reaction:



According to Watson–Creek pairing, the AAU anticodon of $tRNA^{Leu(UUR)}$ readily interacts with the codon UUA, but exhibits a weak interaction with the UUG codon. However, the binding between uridine and guanidine is strengthened when uridine is converted to 5-taurinomethyluridine. The facilitation of U–G pairing has no effect on AAU–UUA pairing but facilitates AAU–UUG pairing, thereby allowing the decoding of the UUG codon (Kirino et al. 2004; Kurata et al. 2008). The wobble hypothesis maintains that the underlying defect in MELAS is a mutation that causes a deficiency in 5-taurinomethyluridine-$tRNA^{Leu(UUR)}$ and a resulting impairment in UUG decoding. Consequently, the biosynthetic rate of UUG-dependent mitochondrial proteins declines. Table 2 shows that 42 % of leucine residues in ND6 are UUG dependent while only 10 % of those residues are UUG dependent in A8. Therefore, it is relevant that the biosynthesis of ND6 and A8 are severely impaired in human B-lymphoblastoid cells harboring the A3243G mutation (Flierl et al. 1997). Moreover, the biosynthesis of NDL4, a mitochondria-encoded protein whose mRNA lacks UUG codons, is unaffected by the A3243G mutation. These changes are consistent with the common MELAS phenotype, which contains reduced complex I activity. Yet, the observation that the biosynthesis of UUG-independent proteins, such as COI and COIII, is reduced in cells harboring the A3243G mutation is seemingly inconsistent with the wobble hypothesis (Flierl et al. 1997). Thus, the protein synthetic results provide support for the notion that modification of the wobble base regulates complex I activity, however, it provides no adequate explanation for the observed decrease in complex IV activity.

Much of the detailed mechanistic information on the wobble hypothesis has been gleaned from studies utilizing cybrids. However, the use of cybrids to obtain mechanistic information has been questioned, as the A3243G mutation produces different phenotypes in HeLa cell cybrids than in osteosarcoma or lung carcinoma cybrids (Jacobs and Holt 2000). This concern has led some investigators to utilize fibroblasts from MELAS patients as a cellular model of the MELAS syndrome. The possibility of preparing an animal model containing the A3243G mutation has also been considered although it is technically difficult. Clearly, the development of new models is warranted to minimize

confounding variables that interfere with the interpretation of biochemical data.

Clinical and pathophysiological properties of MERRF

Myoclonic epilepsy and ragged-red fiber syndrome (MERRF) is a maternally inherited mitochondrial disease in which more than 80 % of the cases are caused by a transition adenine-to-guanine mutation at position 8344 (A8344G) of human mitochondrial DNA (Du et al. 2009). This mutation, located in a region that codes for $tRNA^{Lys}$, has been primarily detected in skin fibroblasts, urinary epithelial cells, oral mucosa, hair follicles and muscle cells (Finsterer 2012).

MERRF is characterized by a preferential reduction in complexes I and IV (Chomyn 1998; Sarnat and Marin-Garcia 2005), although the A8344G mutation has also been associated with reduced complex III activity (Bindoff et al. 1991). Fibroblasts obtained from MERRF patients exhibit severe reductions in glutamate/malate-dependent respiration, but minimal changes in succinate-dependent respiration, a finding ruling out a defect in complex II (James et al. 1996). MERRF fibroblasts are also characterized by a decrease in ATP biosynthesis, although an overt decrease in cellular ATP levels only develops upon stimulation in ATP demand (Antonicka et al. 1999; James et al. 1999). Cells harboring 100 % of the A8344G mutation exhibit very severe reductions in cytochrome *c* oxidase activity and oxygen consumption (Masucci et al. 1997). Yet cybrids containing mitochondrial DNA from MERRF patients exhibit hyperoplasmy, a term referring to the coexistence of mutant and wild-type mitochondrial DNA within the same cell. Although hyperoplasmy is associated with cellular-dependent effects, the clinical symptoms and biochemical features of MERRF are generally detected only at a relatively high threshold of the mitochondrial DNA A8344G mutant (Antonicka et al. 1999; Larsson et al. 1992; Yoneda et al. 1994). Thus, hyperoplasmy is a common cause of variability among patients harboring the A8344G mutation.

The aminoacyl hypothesis has also been implicated in the pathophysiology of MERRF. The adenine-to-guanine point mutation (A8344G) mutation, which is located in a region of mitochondrial DNA that codes for the T-loop of $tRNA^{Lys}$, is responsible for most cases of MERRF. Because the T-loop helps stabilize $tRNA^{Lys}$ structure through its interaction with the D-loop, it has been proposed that the A8344G mutation destabilizes $tRNA^{Lys}$ and enhances its enzymatic degradation (Enriquez et al. 1995). Although Enriquez et al. (1995) also found a reduction in lysyl-$tRNA^{Lys}$ content in A8344G containing cybrids, no A8344G-mediated alteration in aminoacylation has been consistently documented (Borner et al. 2000; Sissler et al. 2004; Yasukawa et al. 2001). Therefore, the evidence supporting a role for impaired aminoacylation in MERRF is not very convincing, particularly in light of evidence that impaired respiration has been observed despite normal levels of aminoacylation (Yasukawa et al. 2001).

In contrast to aminoacylation, the wobble modification defect appears to play an important role in the development of MERRF. Two reactions, thiolation and taurine conjugation, are involved in the posttranslational formation of 5-taurinomethyl-2-thiouridine-$tRNA^{Lys}$ (Umeda et al. 2005). In yeast, at least three enzymes (MTU1, MTO1 or MSS1 and a taurine transferase) are putatively involved in the formation of 5-taurinomethyl-2-thiouridine-$tRNA^{Lys}$. According to Murphy et al. (2004), both 2-thiolation and 5-taurinomethylation of the wobble uridine base enhance the interaction of the anticodon of $tRNA^{Lys(UUU)}$ with its codon pairs. While thiolation of the wobble uridine base plays a critical role in ensuring forceful interactions between the two lysine codons (AAA and AAG) and the UUU anticodon of $tRNA^{Lys}$ (Ashraf et al. 1999; Yasukawa et al. 2002), taurinomethylation of the wobble uridine strengthens U–G pairing through enhanced base stacking and hydrogen bonding (Cochella and Green 2004; Weixlbaumer et al. 2007). However, 5-taurinomethylation has no effect on the standard Watson–Creek base pairing between the wobble base uridine and the codon base adenine. Therefore, the thiolation of uridine facilitates the decoding of both AAA and AAG codons while taurine conjugation only facilitates the decoding of the AAG codon. In the case of MERRF, the thiolation and taurine conjugation reactions are both prevented, causing inefficient decoding of both AAA and AAG (Helm et al. 1999; Yasukawa et al. 2005).

MERRF mutation is associated with impaired protein synthesis

Enriquez et al. (1995) found that cybrids harboring the A8344G mutation exhibit an exponential reduction in mitochondrial protein synthesis relative to the lysine content of the mitochondria-encoded proteins. This effect has been largely attributed to wobble modification deficiency and the resulting weakening of the U–G interaction, although the mutation is also associated with premature termination of translation (Yasukawa et al. 2002). As seen in Table 2, ND5 contains the largest number of lysine residues while ND2 is most dependent on AAG decoding. Therefore, in cybrids harboring the A8433G mutation, the biosynthesis of the two complex I subunits (ND2 and ND5) is severely depressed. On the other hand, mitochondria-encoded proteins (ND6, ND3, COXII and COXIII) whose mRNA contain less than 10 AAA codons and 0 AAG

codons retain the highest rates of protein biosynthesis in A8433G-containing cybrids. In MERRF, both AAG and AAA decoding are impaired, as both 5-taurinomethylation, which specifically improves AAG decoding, and 2-thiolation, which improves both AAA and AAG decoding, are reduced (Yasukawa et al. 2001). Based on the link between AAG decoding efficiency and the rate of protein synthesis in cybrids harboring the A8344G mutation, it is logical to assume that an exponential relationship exists between the number of AAG codons in specific mitochondria-encoded proteins and their rate of protein biosynthesis.

Symptoms and pathophysiology of taurine deficiency

The β-amino acid taurine (2-aminoethanesulfonate) is found in very high concentration in excitable tissues (Huxtable 1992). The two major sources of taurine in mammalian cells are diet and hepatic biosynthesis, with uptake via a taurine transporter responsible for the actual transfer of taurine from the blood to specific cells. Certain species, such as cats, have decreased capacity to synthesize taurine in the liver and rely on a dietary source to maintain normal taurine levels (Bagley and Stipanuk 1995). On the other hand, rodents, which are endowed with high levels of the rate-limiting enzyme of taurine biosynthesis, cysteine sulfinate decarboxylase, are resistant to dietary taurine

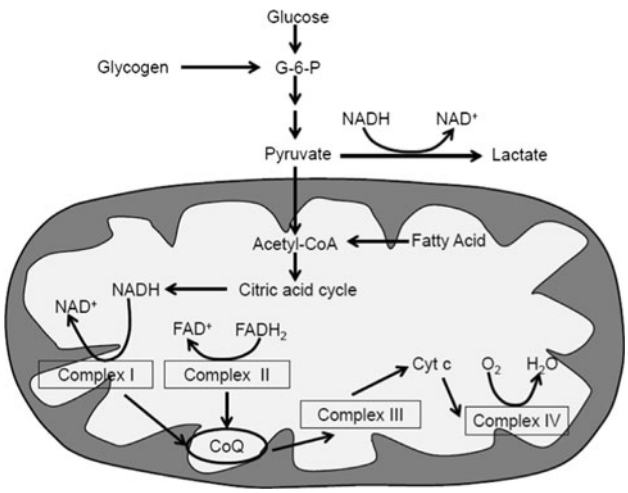


Fig. 1 Effect of taurine deficiency on energy metabolism. The initial insult to energy metabolism in taurine deficiency is reduced respiratory chain flux. Consequently, respiration declines, which prevents the entry of NADH into the respiratory chain. The elevation in the NADH/NAD^+ ratio feedback inhibits the citric acid cycle, slowing flux and preventing the entry of pyruvate. The decrease in ATP production initially stimulates glycolysis. However, the block in pyruvate entry and the elevation in the NADH/NAD^+ ratio lead to enhanced lactate production and a rise in the lactate/pyruvate ratio. Overall, these sequence of events result in enhanced anaerobic metabolism and diminished aerobic metabolism. *G-6-P* glucose-6-phosphate, *CoQ* coenzyme Q, *cyt c* cytochrome *c*

deficiency. In rodents, taurine deficiency is achieved by either inhibition or genetic elimination of the taurine transporter. Irrespective of the mechanism used to achieve taurine deficiency, most symptoms of the taurine-deficient phenotype are linked to mitochondrial dysfunction and are therefore resemble those of MELAS and MERRF (Table 1).

The taurine-deficient phenotype is characterized by a drop in both cellular and mitochondrial taurine content, with the mitochondria showing resistance to significant declines in taurine levels. Although the mechanism responsible for the retention of taurine by the mitochondria is presently unknown, it likely relates to the role of taurine in maintaining the health of the electron transport chain. According to Jong et al. (2012), taurine deficiency results in significant reductions in respiratory chain complex activity and is accompanied by a 30 % reduction in oxygen consumption. Moreover, the respiratory control ratio, which is a measure of ADP-mediated stimulation in respiration, is significantly reduced in mitochondria obtained from taurine-deficient livers (Warskulat et al. 2006). Furthermore, the liver and skeletal muscle of offspring born to rat dams fed a low protein diet exhibit defects in respiratory chain activity that are largely prevented by taurine supplementation (Mortensen et al. 2010).

Although the levels of 5-taurinomethyluridine-$tRNA^{Leu(UUR)}$ in the taurine-deficient cardiomyocyte was not measured by Jong et al. (2012), the levels of the most UUG-dependent mitochondria-encoded protein (ND6) was found to be reduced nearly 40 %. On the other hand, the UUG-independent mitochondria-encoded protein (COI) was unaffected by taurine deficiency. The authors concluded that taurine deficiency reduces the availability of taurine for 5-taurinomethyluridine-$tRNA^{Leu(UUR)}$ formation, thereby weakening U–G pairing, initiating inefficient UUG decoding and reducing the rate of ND6 biosynthesis. Because ND6 is both a subunit and a facilitator of complex I assembly, ND6 deficiency leads to a decline in complex I activity and a reduction in oxygen consumption.

A previous study by Mozaffari et al. (1986) provides further support for the wobble hypothesis (Fig. 1). Hearts from rats treated with taurine transport inhibitors, guanidinoethanesulfonate or β-alanine, lose approximately 50 % of their myocardial taurine content. These hearts exhibit a major shift in glucose metabolism in favor of anaerobic metabolism, resulting in a twofold elevation in lactate production and a dramatic increase in the lactate/pyruvate ratio of the perfusate. Because the lactate/pyruvate ratio is proportional to the NADH/NAD^+ ratio, the utilization of NADH by the mitochondria of the taurine-deficient heart declines, an effect also seen in MELAS and MERRF. The development of a bottleneck in the respiratory chain also results in impaired ATP generation. The taurine-deficient heart becomes more dependent on glycolysis and less dependent

on aerobic metabolism for energy generation. High energy phosphate (creatine phosphate) levels fall, but the decline is limited by feedback upregulation of glycolysis.

Mitochondrial defects unique to taurine deficiency

The posttranslational modification of the wobble uridine bases of both $tRNA^{Leu(UUR)}$ and $tRNA^{Lys}$ have been clearly documented, however, Kurata et al. (2003) have provided further evidence that the wobble uridines of $tRNA^{Glu}$ and $tRNA^{Gln}$ also undergo 5-taurinomethylation. Therefore, taurine deficiency could be associated with decreases in the expression of mitochondria-encoded proteins whose mRNAs contain GAG and CAG. The mitochondria-encoded proteins that are highly dependent on CAG are ND2, ND5 and ND6 while ND1, ND3 and COI–III are more GAG-dependent. Thus, taurine deficiency could theoretically lower protein levels of ND1-3, ND5 and ND6, contributing to the decline in complex I activity in the taurine-deficient cardiomyocyte. However, the measurement of protein levels of several ND proteins rule out that possibility. Moreover, taurine deficiency has no effect on cytochrome *c* oxidase activity despite the sensitivity of COI–COIII on GAG decoding. These findings suggest that 2-thiolation mitigates the inefficient AAG, GAG and CAG decoding caused by the deficiency of the 5-taurinomethylated group. Thus, the taurine-deficient phenotype appears to be largely dependent on impaired UUG decoding.

The classical function of the mitochondria is ATP generation and the regulation of energy metabolism. However, recent studies have focused on the role of mitochondria in apoptosis, cell signaling and ion transport. There is evidence that taurine influences all of these mitochondrial events. Palmi et al. (1999) initially introduced the concept that taurine might alter mitochondrial function by potentiating Ca^{2+} sequestration. In a follow-up study by the same group, taurine treatment was found to exert no direct effect on the mitochondrial permeability transition despite the dependence of the mitochondrial permeability transition on Ca^{2+} overload (Palmi et al. 2000). In apparent contrast to the study by Palmi et al. (2000), Chen et al. (2009) reported that taurine protects rat retinal ganglion cells against hypoxia-mediated activation of the mitochondrial permeability transition (Chen et al. 2009). In a related study, El Idrissi and Trenkner (1999) found that taurine treatment increases the mitochondrial electrochemical gradient of cerebellar granule cells while opposing the decline in the electrochemical gradient mediated by toxic levels of glutamate. Because taurine also diminishes glutamate-induced elevations in $[Ca^{2+}]_i$, it was concluded that taurine treatment attenuates glutamate-mediated toxicity by improving mitochondrial function and reducing glutamate-induced $[Ca^{2+}]_i$ rise (El Idrissi and Trenkner 2003). Mitochondrial calcium movement was also implicated in veratridine-mediated aspartate transport, an effect inhibited by taurine treatment and regulated by the respiratory chain (Molchanova et al. 2007). While excessive Ca^{2+} accumulation by the mitochondria plays a role in cell toxicity, mild Ca^{2+} entry into the mitochondria facilitates ATP production by activating several rate-limiting enzymes of energy metabolism. By modestly raising $[Ca^{2+}]_i$, taurine treatment would be expected to promote flux through the citric acid cycle and the delivery of reducing equivalents to the respiratory chain (Sang-Hoon et al. 2004).

Jong et al. (2012) have argued that maintenance of normal taurine homeostasis is essential for prevention of mitochondrial oxidative stress. This concept is supported by the work of Chang et al. (2004), who found that taurine treatment protects myocardial mitochondria against homocysteinemia-mediated reactive oxygen species (ROS) generation while enhancing mitochondrial Ca^{2+} uptake. Moreover, taurine treatment attenuates tamoxifen-mediated superoxide production by liver mitochondria (Parvez et al. 2008). Therefore, taurine regulates mitochondria through tRNA conjugation, as well as by modulating mitochondrial Ca^{2+} movement and ROS production.

Clinical significance of taurine deficiency-mediated mitochondrial dysfunction

Humans contain low levels of hepatic cysteine sulfinic acid decarboxylase, the rate-limiting enzyme of taurine biosynthesis. Therefore, the biosynthetic source of taurine in humans is limited. However, humans consume a diet rich in taurine. Moreover, the rate of taurine turnover is relatively low in humans. By comparison, species, such as cats, develop pathology in response to dietary taurine deficiency, an effect related to both poor rates of taurine biosynthesis and the loss of taurine from the body. Taurine loss is commonly associated with the daily elimination of taurine in the form of taurine-conjugated bile acids. Cats lose significant levels of taurine from the body via bile acid elimination, as taurine is the only conjugating agent of bile acids in cats. On the other hand, taurine loss in humans is muted because bile acid conjugation utilizes either taurine or glycine. Hence taurine is considered nutritionally essential for cats, nonessential for rodents and conditionally essential for humans (Gaull 1989).

Taurine-sensitive cells resist significant reductions in the taurine pool. Interestingly, the mitochondria are one of the organelles that exhibit an unusually high rate of taurine retention. Because platelets are rich in mitochondria, it is not surprising they contain significant levels of taurine.

Although there is evidence that platelet taurine may modulate platelet aggregation (Hayes et al. 1989), they also serve as a measure of whole body taurine content. Therefore, it is relevant that children undergoing total parenteral nutrition exhibit reduced platelet levels (Vinton et al. 1987). Nonetheless, there is no firm evidence that nutritional taurine depletion in humans has adverse physiological and clinical effects. One possible exception is tissue subjected to an ischemia–reperfusion insult, which triggers the release of large amounts of taurine. Because recovery of cellular function depends upon restoration of ATP levels, depletion of the mitochondrial taurine pool could have a devastating effect on the degree of ischemia–reperfusion injury. Taurine loss in the heart could be particularly detrimental because it likely increases the risk of developing heart failure, which is also a complication of MELAS and MERRF. Thus, the possibility that taurine therapy might reduce the risk of heart failure is worthy of consideration.

Conflict of interest The authors declare that there are no conflicts of interest.

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