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Abdeslem El Idrissi
William J. L'Amoreaux *Editors*

Taurine 8

Volume 2: Nutrition and Metabolism, Protective Role, and Role in Reproduction, Development, and Differentiation

Advances in Experimental Medicine and Biology

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Editors

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Volume 2: Nutrition and Metabolism, Protective Role, and Role in Reproduction, Development, and Differentiation

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Preface

The organizing committee wishes to thank all attendees of the 18th International Taurine Meeting that took place in Marrakesh, Morocco, from April 7th to 13th. This year, the conference highlighted the "*Mystique of Taurine*." Taurine investigators have had the privilege of attending these scientific meetings on three continents: Asia, Europe, and North America. This marked the first time that our conference was held in Africa. As a result, we present here the data from investigators from five of the six continents (sadly taurine research has yet to hit Antarctica). With this geographical expansion, the interest in taurine research has exponentially grown. This international meeting was attended by approximately 120 scientists. We present here information on the roles of taurine in a variety of organ systems, from the brain to the reproductive system and every system in between. As you are keenly aware, there is certainly a mystique to taurine. Is it beneficial or harmful? Does it protect cells or induce cell death? Can it be used in conjunction with another molecule to benefit health or cause death? The answer (or at least a hint to the answer) to these and other questions lies within this body of works. Of course, not all questions were answered but there were many discussions that generated numerous new ideas that will be taken home and tested in the laboratory.

This meeting was also unique in that many undergraduate and graduate students from the College of Staten Island/CUNY attended and presented their research as part of a study abroad program. This opportunity represented the first time that most of these students attended an international conference. More importantly, it served to stimulate interest in taurine research and recruit future taurine researchers. We are greatly appreciative for the overwhelming support of the College of Staten Island's administration, particularly Dr. Deborah Vess, Associate Provost for Undergraduate Studies and Academic Programs; Dr. William Fritz, the provost; Renee Cassidy, study abroad advisory from The Center for International Service;

Debra Evans-Greene, Director of the Office of Access and Success Programs; and Dr. Claude Braithwaite of the City College of New York and the Louis Stokes Alliance for Minority Participation.

The abstracts of the conference were published in the journal “Amino Acids” (Vol. 42, Issue 4). We thank Drs. Lubec and Panuschka for making this possible.

Because of the success of this meeting, the organizing committee wishes to gratefully acknowledge the following:

- Taisho Pharmaceutical Co., Ltd., Tokyo Japan for their generous financial support.
- Professor Dr. Gert Lubec, FRSC (UK), Medical University of Vienna and Editor in Chief of AMINO ACIDS.
- Dr. Claudia Panuschka, Springer Wien, New York, Senior Editor Biomedicine/ Life Sciences.
- Dr. Portia E. Formento, Editor, Biomedicine, Springer US.
- Dr. Melanie Tucker (Wilichinsky) Editor, Genetics and Systems Biology, Springer US.

On behalf of the organizing committee, I thank all the attendees of the 18th international Taurine Meeting and the sponsors that made this meeting possible.

Staten Island, NY, USA Abdeslem El Idrissi

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Part I
Taurine in Nutrition and Metabolism

Chapter 1
Taurine, Glutathione and Bioenergetics

Svend Høime Hansen and Niels Grunnet

Abstract Biochemistry textbook presentations of bioenergetics and mitochondrial function normally focus on the chemiosmotic theory with introduction of the tricarboxylic acid cycle and the electron transport chain, the proton and electrical gradients and subsequent oxidative phosphorylation and ATP-production by ATP synthase. The compound glutathione (GSH) is often mentioned in relation to mitochondrial function, primarily for a role as redox scavenger. Here we argue that its role as redox pair with oxidised glutathione (GSSG) is pivotal with regard to controlling the electrical or redox gradient across the mitochondrial inner-membrane. The very high concentration of taurine in oxidative tissue has recently led to discussions on the role of taurine in the mitochondria, e.g. with taurine acting as a pH buffer in the mitochondrial matrix. A very important consequence of the slightly alkaline pH is the fact that the NADH/NAD^+ redox pair can be brought in redox equilibrium with the GSH redox pair GSH/GSSG.

An additional consequence of having GSH as redox buffer is the fact that from the pH dependence of its redox potential, it becomes possible to explain that the mitochondrial membrane potential has been observed to be independent of the matrix pH. Finally a simplified model for mitochondrial oxidation is presented with introduction of GSH as redox buffer to stabilise the electrical gradient, and taurine as pH buffer stabilising the pH gradient, but simultaneously establishing the equilibrium between the NADH/NAD^+ redox pair and the redox buffer pair GSH/GSSG.

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Abbreviations

GSH	Glutathione
GSSG	Oxidised glutathione
ROS	Reactive oxygen species

1.1 Introduction

The chemiosmotic theory proposed by Peter Mitchell in the 1960s is today accepted as the basis for the understanding of the oxidative phosphorylation and subsequent ATP production in the bioenergetic processes in the mitochondria (Mitchell 1966, 1968; Nicholls and Ferguson 2002). The presentation in most biochemical textbooks focuses on the pH and the electrical gradients across the mitochondrial membranes. The gradients combine to form an electrical potential ΔE_{Total} for moving protons across the inner-membrane:

$$\Delta E_{\text{Total}} = \Delta\Psi - \log(10)\frac{\text{RT}}{\text{F}}\Delta\text{pH}. \tag{1.1}$$

This potential, often referred to as the proton-motive force, drives by use of proton movement the ATP production through the ATP synthase protein complex localised in the mitochondrial inner-membrane.

A series of arguments based on experimental observation can be given that the pH in the cytosol is about 7.0–7.4, and in the mitochondrial matrix pH is most likely in the range 7.8–8.5. In order to stabilise the ATP production, it seems evident that localisation of a pH buffer in the mitochondrial matrix is necessary (Hansen et al. 2010).

Furthermore, it is generally accepted that the proton-motive force can be considered as constant about 200 mV. It is generally accepted that no appreciable dependence on the matrix pH is observed [e.g. Fig. 4.5 in Bioenergetics 3 (Nicholls and Ferguson 2002)]. However, such constancy of two apparently independent contributions needs explanation from a theoretical argument (see later in Sect. 1.2.6 and Fig. 1.1).

1.2 Mitochondria: pH and Redox Buffering

1.2.1 Taurine: pH Buffer

Taurine has previously (Hansen et al. 2006, 2010) been presented as a compound that possesses the optimal characteristics to be a pH buffer in the mitochondrial matrix. Taurine is found ubiquitously in animal tissue with concentrations in the millimolar range. Notably high concentrations of taurine in oxidative tissue lead to

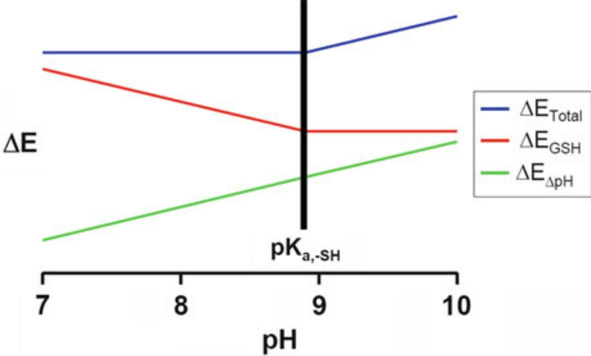

Fig. 1.1 Expected pH dependence of the total mitochondrial membrane potential ΔE_{Total} based on the assumption that glutathione controls the contribution from the electrical (or redox) gradient as the term ΔE_{GSH}. The ionisation constant for the thiol group in glutathione (see Table 1.3) is indicated with the vertical bar. Notice that the pH dependence of the GSH redox potential balances the potential contribution $\Delta E_{\Delta pH}$ from the pH difference, when pH is below the glutathione thiol ionisation constant $pK_{a,-SH}$

a compartmental argument on mitochondrial localisation (Hansen et al. 2006), which has later been confirmed by analytical determinations of taurine in isolated mitochondria (Jong et al. 2010). Ideally, the taurine concentration should be determined inside the mitochondrial matrix, but such analytical methods are currently not available.

Slightly alkaline pH is an ideal environment for beta-oxidation of fatty acids, and as the oxidation is very pH dependent, the existence of a pH buffer seems necessary to stabilise the oxidation (Hansen et al. 2010).

Furthermore, the original presentations of the chemiosmotic theory by Mitchell clearly emphasise the importance of the mitochondrial buffering capacities. The presence of a low-molecular-mass pH buffer in the matrix will thus increase the energy storage capacity (Mitchell 1966, 1968; Mitchell and Moyle 1967). The mitochondrial matrix-buffering should be remembered when evaluating mitochondrial function and dysfunction.

1.2.2 Redox Pairs NADH/NAD$^+$, NADPH/NADP$^+$, GSH/GSSG

Traditionally, when presenting the mitochondrial redox systems the major focus is given to the redox pair NADH/NAD $^+$, probably as a consequence of the fact that NADH is the product of the tricarboxylic acid cycle and subsequent substrate of the electron transport chain complexes. In addition, the NADPH/NADP$^+$ is traditionally presented, as NADPH is a product of matrix-localised oxidation.

Although NADH/NAD$^+$ and NADPH/NADP$^+$ without any doubt are directly involved in matrix-localised oxidation, the concentration of these compounds is not

sufficient to control the redox potential of the redox environment in the mitochondrial matrix. A detailed discussion on the redox environment of the cell has been reviewed (Schafer and Buettner 2001) with focus on the glutathione (GSH) and thioredoxin systems. In order to control the redox potential, it is concluded that in the mitochondrial matrix the only redox couple of compounds found in sufficient amount is the GSH/oxidised glutathione (GSSG) couple. Besides, when discussing oxidative stress and redox state the GSH system is accepted as the most important system (Jones 2006, Jones and Go 2010).

However, these three sets of redox pairs are interconnected through two simple enzyme pathways as follows:

(a) Transhydrogenase can interconvert the two sets of nicotinamide nucleotides:

$$\mathrm{NADP^+ + NADH \rightleftharpoons NADPH + NAD^+}.$$

(b) GSH reductase can subsequently convert NADPH to GSH:

$$\mathrm{NADPH + H^+ + GSSG \rightleftharpoons NADP^+ + 2GSH}.$$

1.2.3 pH Dependence of Redox Potentials

The redox potentials for the redox pairs can now be compared in order to evaluate the related equilibria for the redox pairs.

The redox equations for the redox pairs are as follows:

$$\mathrm{NAD^+ + H^+ + 2e^- \rightleftharpoons NADH}$$

$$\mathrm{NADP^+ + H^+ + 2e^- \rightleftharpoons NADPH}$$

$$\mathrm{GSSG + 2H^+ + 2e^- \rightleftharpoons 2\ GSH}.$$

As all three equations involve protons, the associated redox potentials become pH dependent according to the Nernst equations as follows:

$$E = E^0 - \frac{60\ \mathrm{mV}}{2} \log\left(\frac{[\mathrm{GSH}]^2}{[\mathrm{GSSG}]}\right) - 60\ \mathrm{mV}\cdot\mathrm{pH} \tag{1.2}$$

$$E = E^0 - \frac{60\ \mathrm{mV}}{2} \log\left(\frac{[\mathrm{NADH}]}{[\mathrm{NAD^+}]}\right) - \frac{60\ \mathrm{mV}}{2}\cdot\mathrm{pH} \tag{1.3}$$

$$E = E^0 - \frac{60\ \mathrm{mV}}{2} \log\left(\frac{[\mathrm{NADPH}]}{[\mathrm{NADP^+}]}\right) - \frac{60\ \mathrm{mV}}{2}\cdot\mathrm{pH}. \tag{1.4}$$

Table 1.1 Approximate midpoint redox potentials $E_{m,pH}$ (mV) at different pH values

Redox pair	pH = 7.0	pH = 7.5	pH = 8.0	pH = 8.5
$NADH/NAD^+$	−320	−335	−350	−365
$NADPH/NADP^+$	−320	−335	−350	−365
GSH/GSSG	−172	−202	−232	−262

Based directly on the values given in Table 3.2 in Bioenergetics 3 (Nicholls and Ferguson 2002). In their calculations the factor 2.303 RT/F from the Nernst equation was set to 60 mV (corresponding to $T = 302$ K or 29.2°C)

Please notice that in all the equations and calculations the factor log(10) RT/F from the Nernst equation has been set to 60 mV as in Bioenergetics 3 (Nicholls and Ferguson 2002). This approximation corresponds to a temperature of $T = 302$ K or 29.2°C.

The redox potentials for the redox pairs are pH dependent, but the Nernst equations show that $\Delta E/\text{pH} \approx -60$ mV/pH for GSH/GSSG, but $NADH/NAD^+$ and $NADPH/NADP^+$ has only a dependence of $\Delta E/\text{pH} \approx -30$ mV/pH.

The thiol group of GSH becomes deprotonated in alkaline pH above the pK_a for the thiol group, and thus leading to a simplified redox equilibrium

$$\text{GSSG} + 2e^- \rightleftharpoons 2\,\text{GS}^-$$

and an associated Nernst equation without any pH dependence as follows:

$$E = E^0 - \frac{60\text{ mV}}{2}\log\left(\frac{[\text{GS}^-]^2}{[\text{GSSG}]}\right). \tag{1.5}$$

The $pK_a = 9.0$ (25°C) for GSH can be found in Table 1.3, and a more detailed discussion can be found elsewhere, e.g. (Schafer and Buettner 2001). The pH dependence for the GSH redox potential is indicated as the ΔE_{GSH} curve in Fig. 1.1.

1.2.4 Redox Equilibrium $NADH/NAD^+$ and GSH/GSSG

From the Nernst equations above, the midpoint potentials can be calculated at relevant pH values in the range from 7.0 to 8.5 as presented in Table 1.1.

However, the midpoint potentials do not take into account the actual concentrations of the individual species. A better representation is obtained by the use of typical values for the redox pair concentrations and GSH pool concentration of 10 mM (Nicholls and Ferguson 2002; Wahllander et al. 1979). If these actual concentrations found in the mitochondrial matrix are inserted into Nernst's equation, the actual redox potentials as presented in Table 1.2 and Fig. 1.2 are obtained.

A surprising consequence when increasing the pH to slightly alkaline conditions at about pH 8.5 is now the result that the actual redox potentials for the $NADH/NAD^+$

Table 1.2 Approximate actual redox point potentials $E_{actual,pH}$ (mV) at different pH values

Redox pair	Typical ox/red ratio	pH = 7.0	pH = 7.5	pH = 8.0	pH = 8.5
$NADH/NAD^+$	10	−290	−305	−320	−335
$NADPH/NADP^+$	0.01	−380	−395	−410	−425
GSH/GSSG(when 10 mM)	0.01	−240	−270	−300	−330

Based directly on the values given in Table 3.2 in Bioenergetics 3 (Nicholls and Ferguson 2002). In their calculations the factor 2.303 RT/F from the Nernst equation was set to 60 mV (corresponding to T = 302 K or 29.2°C)

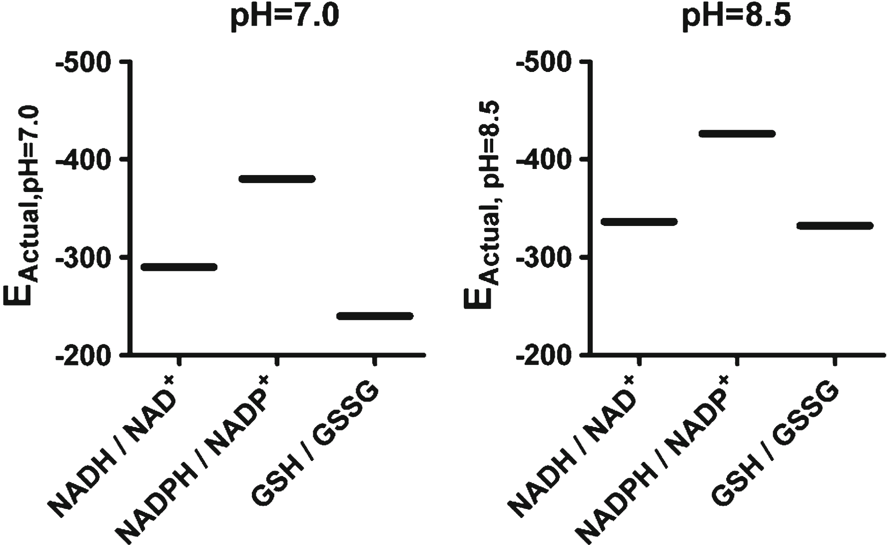

Fig. 1.2 Estimation of actual redox potentials $E_{actual,pH}$ (mV) for the redox pairs $NADH/NAD^+$, $NADPH/NADP^+$, and GSH/GSSG at pH = 7.0 and pH = 8.5, respectively. The concentrations of the compounds are based on the values given in Table 3.2 in Bioenergetics 3 (Nicholls and Ferguson 2002). At the slightly alkaline pH = 8.5, it is possible to obtain redox equilibrium between $NADH/NAD^+$ and GSH/GSSG

and the GSH/GSSG redox pairs become almost identical. That is in the pH range of 8.0–8.5, where taurine acts as a pH buffer, it is possible to obtain thermodynamic equilibrium between the $NADH/NAD^+$ and GSH/GSSG, whereas $NADPH/NADP^+$ acts as a sort of cofactor for the involved enzymes! Consequently, taurine can suddenly be given a very important supporting role to GSH in the mitochondrial matrix.

In a recent advanced theoretical and numerical calculation model for mitochondrial energetics only the $NADH/NAD^+$-redox couple was included (Wei et al. 2011), although the GSH/GSSG was included in a previous unifying hypothesis focusing on reactive oxygen species (ROS) and oxidative stress (Aon et al. 2010). Now, it seems that taurine also should be included in such calculation models due to its contribution to the mitochondrial pH buffering capacity.

Table 1.3 Chemical structures and ionisation constants for glutathione and taurine

Compound	Ionisation constants (25°C)
Glutathione (L-γ-glutamyl-L-cysteinylglycine)	$pK_a(-NH_3^+) \approx 9.2$ $pK_a(-SH) \approx 9.0$ The values depend on the protonation form of glutathione. (See Table 1.1 in (Rabenstein 1973) for further details)
Taurine (2-amino-ethane sulfonic acid)	$pK_a(-NH_3^+) = 9.0$ (Hansen et al. 2010)

1.2.5 Glutathione: Redox Buffer

Not only protons but also electrons need to be buffered during the metabolic processes in the mitochondria. The oxidative processes obviously involve electron transfers, requiring the redox buffers to provide the available electrons and thus ensure a stable redox environment. An excellent background presentation on the concept of cellular redox environments and redox buffer can be found elsewhere (Schafer and Buettner 2001).

In order to obtain redox buffering in a biochemical environment, thiol groups need to be involved through redox equilibria with disulphide formation. In general, available thiol groups for redox balanced are normally considered to be found in either thioredoxin proteins or in the tripeptide GSH (L-γ-glutamyl-L-cysteinylglycine), which is found in millimolar concentrations in the cytosol and mitochondria (Schafer and Buettner 2001; Wahllander et al. 1979). The thiol group in GSH accounts for the action as redox buffer of GSH. However, other proteins could be involved in the redox buffering, as a recent determination of exposed thiol groups in the mitochondrial matrix found an unexpected high concentration of free protein thiol groups (Requejo et al. 2010).

Focusing on the role of GSH as redox buffer (or actually any thiol group), it must be remembered that the redox potential of a thiol group is strongly pH dependent, as the thiol group has to be considered as a weak acid. However, GSH also contains an amino group (see Table 1.3). Actually, the ionisation constants, pK_a, for the amino and thiol groups in GSH have been reported to be similar, but slightly higher for the amino group as shown in Table 1.3 (Rabenstein 1973). Comparing with the ionisation constant of the amino group of taurine (Hansen et al. 2006, 2010), this value seems to be almost identical with the ionisation constant of the thiol group in GSH (see Table 1.3).

1.2.6 Controlling the Mitochondrial Inner-Membrane Potential

When accepting the hypothesis that GSH (or perhaps thiol groups in general) acts as redox buffer for the mitochondrial matrix it also means that the thiol/disulphide redox equilibrium is responsible for the electrical redox gradient across the mitochondrial inner-membrane corresponding to a potential difference ΔE_{GSH}. If it is also assumed that the redox potential in the cytosol can be considered as constant E_0, the electrical gradient contribution in equation (1.1) can be expressed as $\Delta\Psi = \Delta E_{GSH} + E_0$. When adding a potential contribution $\Delta E_{\Delta pH}$ from the pH difference, it means that the potential difference ΔE_{Total} (or proton-motive force) across the mitochondrial inner-membrane can be expressed as follows:

$$\Delta E_{Total} = \Delta E_{GSH} + \Delta E_{\Delta pH} + E_0. \qquad (1.6)$$

As shown in Fig. 1.1 this equation makes it possible to explain that the mitochondrial membrane potential has been reported to be independent on the matrix pH (see Fig. 4.5 in Bioenergetics 3, Nicholls and Ferguson 2002; Nicholls 1974). The higher concentration of taurine in mitochondria means that taurine acts as the primary pH buffer in the matrix, and the thiol group in GSH becomes protected from deprotonation and to focus on being a redox buffer in the oxidative matrix environment. With taurine as pH buffer, the matrix pH must be expected to be below the ionisation constant for the thiol group in GSH. Consequently, the mitochondrial membrane potential will be kept almost constant (see Fig. 1.1).

1.3 Model for Mitochondrial Bioenergetics

A simplified model for mitochondrial bioenergetics can now be presented as in Fig. 1.3. The basic substrate acetyl-CoA is provided either from pyruvate oxidation by pyruvate dehydrogenase or from beta-oxidation of fatty acids. Subsequently, acetyl-CoA is oxidised to CO_2 with the reduction of NAD^+ to NADH by the tricarboxylic acid cycle. NADH is used by the electron transport chain to pump protons and thus creating a mitochondrial inner-membrane proton gradient. Besides the proton pumping, NADH is also used for setting up the GSH redox equilibrium. Several of the processes are stabilised through pH buffering by taurine.

1.4 Perspectives and Future Developments

The presented model for the mitochondrial function needs obviously to be extended with incorporation of the complexes from the electron transport chain, and with the formation of free radicals and ROS, which are well-known by-products from the electron transport chain. However, although such an extension of the model is in progress, it is by no means easily formulated. An initial observation to be included

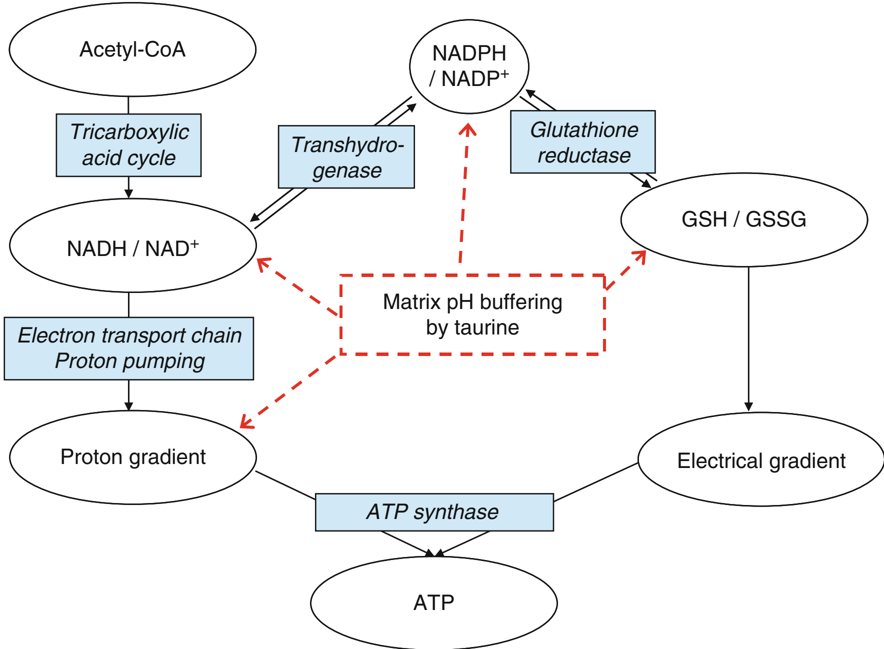

Fig. 1.3 Simplified model for mitochondrial function. The proton gradient is built up by the tricarboxylic acid cycle and subsequent electron transport chain. Simultaneously, the electrical gradient is established through a redox equilibrium between NADH/NAD$^+$ and the redox buffer GSH/GSSG. Several of these processes are stabilised by taurine as matrix pH buffer. The proton and electrical gradients drive together the ATP production by ATP synthase and associated proton movement

is the pH dependence of free radical and ROS formation (Selivanov et al. 2008). But also the roles of mitochondrial thiols in antioxidant scavenging and redox signalling have to be dealt with (Murphy 2012).

Further perspectives on mitochondrial function could be based on the increased reactivity of thiols and GSH with increasing pH. Consequently, the reported opening of mitochondrial ion channels or opening of the uncoupling proteins (UCP) due to GSH redox status or glutathionylation (Aon et al. 2007; Slodzinski et al. 2008; Mailloux et al. 2011) could be a direct response to increased pH in the matrix. That is the increased tendency to glutathionylation protects the matrix from excessive alkalinisation by opening the UCPs for incoming protons.

The consequence of taurine depletion on mitochondrial function has been discussed elsewhere (Hansen et al. 2010; Jong et al. 2012), as well as the results of GSH deficiency or depletion (Meister 1995; Aon et al. 2007). However, the elements in the presented model with focus on the interplay between taurine and GSH need to be included when analysing mitochondrial function and dysfunction, e.g. in diabetes (Hansen 2001; Hansen et al. 2010). Currently, the two compounds are hardly introduced in even advanced presentations or calculation models of mitochondrial function and bioenergetics.

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Chapter 2
Molybdenum Cofactor Deficiency: Metabolic Link Between Taurine and S-Sulfocysteine

Abdel Ali Belaidi and Guenter Schwarz

Abstract Molybdenum cofactor deficiency (MoCD) is a rare inherited metabolic disorder characterized by severe and progressive neurologic damage mainly caused by the loss of sulfite oxidase activity. Elevated urinary levels of sulfite, thiosulfate, and S-sulfocysteine (SSC) are hallmarks in the diagnosis of both MoCD and sulfite oxidase deficiency. Sulfite is generated throughout the catabolism of sulfur-containing amino acids cysteine and methionine. Accumulated sulfite reacts with cystine, thus leading to the formation of SSC, a glutamate analogue, which is assumed to cause *N*-methyl-D-aspartate receptor-mediated neurodegeneration in MoCD patients. Recently, we described a fast and sensitive HPLC method for diagnostic and treatment monitoring of MoCD patients based on SSC quantification. In this study, we extend the HPLC method to the analysis of hypotaurine and taurine in urine samples and no interference with other compounds was found. Besides the known elevation of SSC and taurine, also hypotaurine shows strong accumulation in MoCD patients, for which the molecular basis is not understood. SSC, hypotaurine, and taurine urinary excretion values from control individuals as well as MoCD patients are reported and over 20-fold increase in taurine urinary excretion was determined for MoCD patients demonstrating a direct link between sulfite toxicity and taurine biosynthesis in MoCD.

Abbreviations

Moco	Molybdenum cofactor
MoCD	Molybdenum cofactor deficiency
SOD	Sulfite oxidase deficiency

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SSC S-sulfocysteine
HPLC High-performance liquid chromatography

2.1 Introduction

Molybdenum cofactor deficiency (MoCD) is a rare inherited metabolic disorder (Johnson et al. 1980; Johnson and Duran 2001) caused by defects in the biosynthesis of the molybdenum cofactor (Moco) leading to the simultaneous loss of activities of all molybdenum-dependent enzymes: sulfite oxidase, xanthine dehydrogenase, aldehyde oxidase, and the mitochondrial amidoxime-reducing component (Schwarz et al. 2009). Affected patients exhibit severe neurological abnormalities, such as microcephaly and seizures, and they usually die in early childhood (Johnson and Duran 2001). Sulfite oxidase deficiency (SOD) is less frequent but clinically indistinguishable from MoCD, which renders sulfite oxidase as the most important Moco enzyme in humans (Tan et al. 2005). Sulfite oxidase catalyzes the oxidation of sulfite, which is generated throughout the catabolism of sulfur-containing amino acids, to sulfate (Griffith 1987; Johnson and Duran 2001). Deficiencies of Moco and sulfite oxidase result in the accumulation of sulfite, a highly toxic molecule that breaks disulfide bridges in proteins and cystine, thereby affecting many protein and cellular functions (Zhang et al. 2004). Sulfite accumulation is accompanied by the formation of secondary metabolites such as thiosulfate and S-sulfocysteine (SSC) (Johnson and Duran 2001), which together with reduced homocysteine levels (Sass et al. 2004) are common biochemical indicators for MoCD and SOD.

Sulfite is generated throughout the catabolism of sulfur-containing amino acids in two steps. First, the cytosolic enzyme cysteine dioxygenase catalyzes the formation of cysteine sulfinic acid (CSA). Second, either CSA undergoes a transamination in mitochondria, which leads to the formation of sulfite, or it is decarboxylated in the cytosol leading to the formation of hypotaurine, which is further oxidized to taurine. In MoCD sulfite first accumulates in liver, where most of the catabolism of sulfur-containing amino acids takes place. Subsequently, accumulation of sulfite in plasma is detectable and finally sulfite crosses the blood–brain barrier triggering a devastating and progressive neuronal damage (Schwarz et al. 2009).

Using a knockout animal model for MoCD (Lee et al. 2002) a substitution therapy with cyclic pyranopterin monophosphate has been established (Schwarz et al. 2004) and recently a first successful treatment for an MoCD (type A) patient has been reported (Veldman et al. 2010). Before treatment was initiated, a manifested rapid increase of urinary sulfite, thiosulfate, and SSC values was recorded. However, within few days after treatment was initiated, a remarkable normalization of all MoCD biomarkers as well as a significant clinical improvement of the patient were observed. Recently, we reported the development of a new HPLC method for diagnosis and treatment monitoring of MoCD patients, which enables an accurate and sensitive measurement of urinary as well as serum SSC levels and is being currently used to diagnose the disease to monitor treated patients (Belaidi et al. 2011).

2.2 Methods

2.2.1 Creatinine Analysis

Creatinine determination was based on the Jaffe method and carried out as previously described (Belaidi et al. 2011). Briefly, 50 μl of diluted urine samples were mixed with 150 μl alkaline picrate solution (1.2% picric acid in 0.75 M sodium hydroxide) and the formation of an orange–red complex between creatinine and alkaline picrate was quantified by measuring the absorbance at 490 nm.

2.2.2 HPLC

HPLC analyses were carried out on an Agilent 1200 SL system (Agilent Technologies GmbH, Boeblingen, Germany). The chromatographic conditions were identical to the previously reported SSC quantification method (Belaidi et al. 2011). Automated pre-column derivatization with O-phthaldialdehyde (OPA) was used and the analyzed compounds were separated on a reversed-phase C18 column: XBridge (150 × 4.6 mm, 3.5 μm, Waters GmbH, Eschborn, Germany). For detection the UV absorbance at 338 nm was recorded and compound identification was achieved by comparing the retention time with that obtained for a standard. Peak area was used for calibration. SSC, hypotaurine, and taurine amounts were determined by standard addition and normalized to creatinine concentration.

2.3 Results

2.3.1 HPLC Determination of Hypotaurine and Taurine in Urine Samples

HPLC analysis of amino acids with OPA derivatization is one of the most sensitive methods for amino acid quantification with detection limits in the femtomole range. We previously developed a method for SSC determination in urine samples using pre-column derivatization with OPA, which resulted in fast and accurate measurement (Belaidi et al. 2011). In this study we extend the method to the measurement of hypotaurine and taurine in addition to SSC. Under the chromatographic conditions described above, separation was completed within 15 min using isocratic elution. Hypotaurine and taurine yielded sharp peaks eluting at 13.8 and 14.3 min, respectively, whereas SSC eluted at 8 min (Fig. 2.1a). Urine analysis in a sample derived from a healthy individual revealed the presence of very low amounts of SSC (4 mmol/mol creatinine), whereas hypotaurine and taurine levels were 25 and 30 mmol/mol creatinine, respectively (Fig. 2.1a). In contrast, analysis of a urine

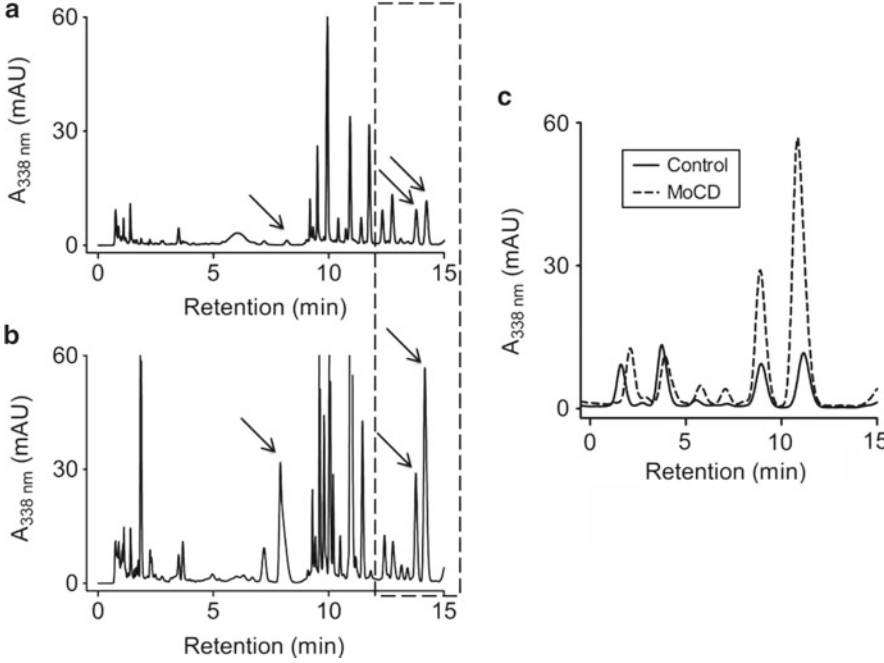

Fig. 2.1 HPLC analysis of hypotaurine, taurine, and SSC in a control individual (**a**) and an MoCD patient (**b**). An overlay of both chromatograms—control individual (*solid line*) and MoCD patient (*dashed line*)—highlighting hypotaurine and taurine peaks is shown in (**c**). SSC, hypotaurine, and taurine are highlighted in panels (**a**) and (**b**) by *arrows*

sample derived from an MoCD patient showed—in addition to an accumulated SSC peak—a clear accumulation of both hypotaurine and taurine (Fig. 2.1b). Comparison of the chromatograms derived from a healthy control sample (Fig. 2.1c, solid line) and an MoCD patient sample (Fig. 2.1c, dashed line) revealed a tenfold increase in the urinary excretion levels of hypotaurine and taurine in the MoCD patient (Fig. 2.1c).

2.3.2 Determination of Taurine Excretion Levels in Healthy and MoCD Patients

After confirming that hypotaurine and taurine excretion levels are up-regulated in an MoCD patient, the method was applied to the analysis of nine urine samples derived from MoCD patients as well as urine samples from control individuals. As expected, the SSC values were very low in control samples (1–9 mmol/mol creatinine), while hypotaurine and taurine levels ranged from 10 to 70 (median 21) and 30 to 100 (median 67) mmol/mol creatinine, respectively (Fig. 2.2a). In contrast, samples derived from MoCD patients showed, in addition to SSC accumulation

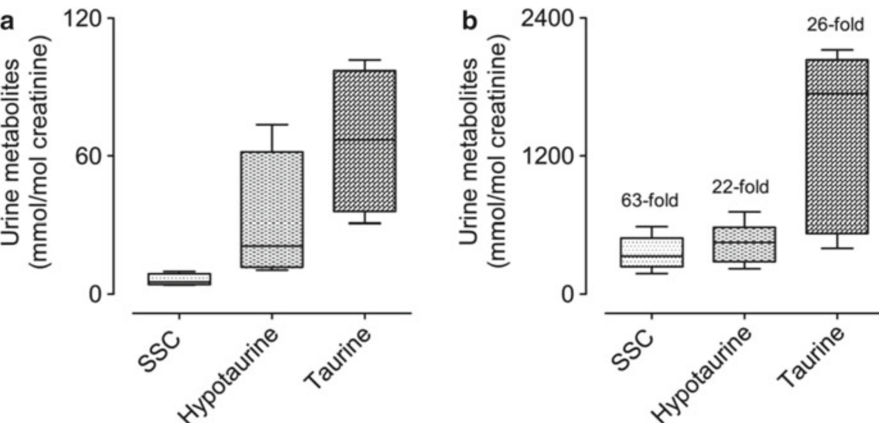

Fig. 2.2 Hypotaurine, taurine, and SSC urinary levels in control individuals and MoCD patients. Urine samples derived from control individuals and nine MoCD patients are shown in panel (**a**) and (**b**), respectively. In addition, numbers over the bars in panel (**b**) indicate the fold increase in the median value in MoCD patients for each metabolite. Metabolites in urine were normalized to creatinine concentration and horizontal bars show the median values

(180–600 mmol/mol creatinine, Fig. 2.2b), very high levels of both hypotaurine and taurine. The excretion levels of taurine were in the millimolar range and reached over 25-fold increase in the median value of healthy individuals, while a 21-fold increase in the median value of hypotaurine was found (Fig. 2.2b).

2.4 Discussion

MoCD is a rare metabolic disorder characterized by a severe and massive neurodegeneration leading to death in early childhood. SSC which is present at very low levels in healthy individuals (Johnson and Duran 2001; Belaidi et al. 2011) is one of the most elevated metabolites in MoCD patients and due to its structural similarity to glutamate, it is believed to act on NMDA receptors (Olney et al. 1975). In the past, many reports showed an important role of taurine in modulating glutamate and GABA signaling (El Idrissi and Trenkner 1999, 2004). Furthermore, taurine has been shown to prevent excitotoxicity through modulation of intracellular calcium homeostasis (El Idrissi and Trenkner 1999). Knowing the importance of calcium signaling in the glutamate-induced neurotoxicity and the fact that taurine and sulfite are both formed directly from CSA, we asked to which extent taurine is also affected in MoCD. We developed an HPLC method for the simultaneous detection of SSC, hypotaurine, and taurine in urine samples aiming to determine the excretion levels of those compounds in control and MoCD patients. Our results showed over 20-fold higher excretion values for hypotaurine and taurine in MoCD patients as compared

to control individuals. The fact that not only taurine but also hypotaurine, the direct precursor for taurine synthesis, are excreted in high levels in urine of MoCD patients provides evidence for an up-regulation of the entire taurine biosynthesis pathway from CSA via hypotaurine to taurine. Thus, an exclusive contribution of taurine transport is not the sole explanation. As a 64-fold increase in SSC levels was measured in MoCD patients, while only a 20-fold increase in both hypotaurine and taurine was found, we assume that sulfite-mediated SSC formation precedes the accumulation of taurine and hypotaurine, pointing to a more distal metabolic relationship. In summary, it remains unclear how sulfite and/or SSC contributes to this up-regulation. Due to the previously reported important role of taurine in preventing neurotoxicity (El Idrissi and Trenkner 1999), we speculate that taurine up-regulation may result from a compensatory effect to overcome the toxicity caused by SSC in the brain or a feedback inhibition of the sulfite branch in cysteine catabolism, thus leading to an increased taurine formation. Additional experiments are required to elucidate the effect of taurine, especially on the SSC-induced neurotoxicity.

2.5 Conclusion

Here we confirm the link between MoCD and taurine biosynthesis using a novel method for the simultaneous detection of SSC, taurine, and hypotaurine in healthy control individuals and MoCD patients. Interestingly, the analysis of urine samples derived from MoCD patients revealed over 20-fold increase in both hypotaurine and taurine levels as compared to control individuals, thus providing evidence for an up-regulation of the hypotaurine and taurine pathway and demonstrating a link between sulfite toxicity and taurine biosynthesis in MoCD patients. However, it remains unclear by which mechanisms taurine and hypotaurine are up-regulated in MoCD.

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Chapter 3
Taurine and Chinese Traditional Medicine Accelerate Alcohol Metabolism in Mice

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Abstract Excessive alcohol consumption is dangerous and causes serious damage to health. The main organ capable of alcohol oxidizing is liver which is also the main organ synthesizing taurine, a sulfur-containing β-amino acid, which is the major free intracellular amino acid presenting in many tissues of human and animals and exerting many physiologic and pharmacologic functions. To investigate the effect of taurine and Chinese traditional medicine on alcohol metabolism after acute alcoholic intake, male Kunming mice were administered with 60% alcohol (0.4 ml) intragastrically. Water, taurine, or taurine coadministration with Chinese traditional medicine was intragastrically administered to mice 30 min before or after alcohol intake. The disappearance of body-righting reflex was used to determine the intoxication of mice. Durations between alcohol intake and intoxication (tolerance time), intoxication and recovery (maintenance time) were recorded. The concentration of blood alcohol, levels of hepatic alcohol dehydrogenase (ADH), and acetaldehyde dehydrogenase (ALDH) were detected at 20, 50, 90, 120, and 150 min after alcohol intake. The results showed that taurine administered alone or together with Chinese traditional medicine could both significantly reduce the number of intoxicated mice, postpone the tolerance time, shorten the maintenance time, and could obvisouly decrease blood level of alcohol, increase hepatic levels of ADH and ALDH. The results indicated that taurine administered alone or

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