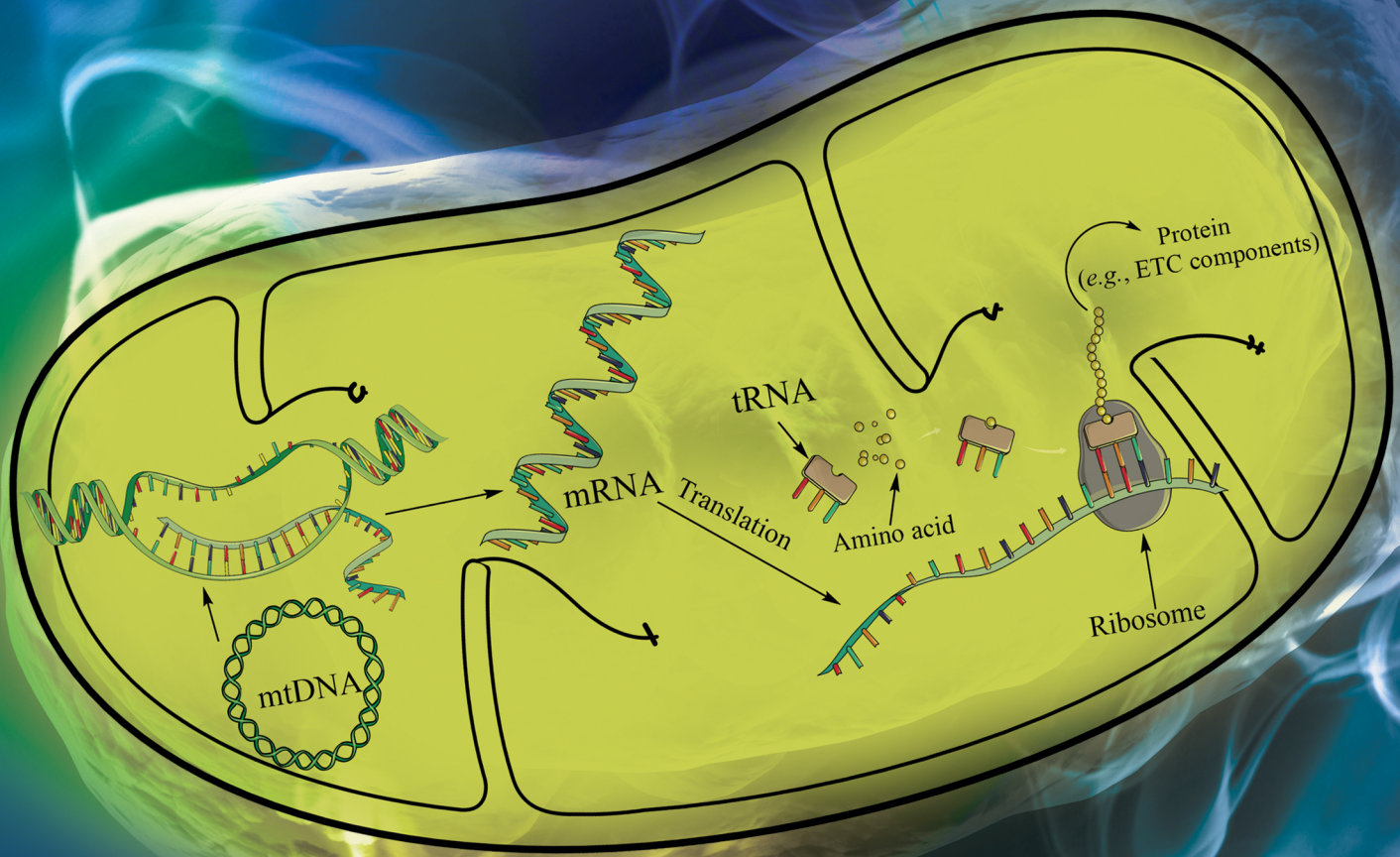
TAURINE AND THE MITOCHONDRION: APPLICATIONS IN THE PHARMACOTHERAPY OF HUMAN DISEASES



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Taurine and the Mitochondrion: Applications in the Pharmacotherapy of Human Diseases

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ISBN (Online): 978-981-5124-48-4

ISBN (Print): 978-981-5124-49-1

ISBN (Paperback): 978-981-5124-50-7

First published in 2023.

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PREFACE

The use of safe molecules for treating diseases has always been of special interest in medical sciences. During research on the application of potential drug candidates for the treatment and prevention of human disease, the application of the amino acid taurine received attention from the authors. The use of the amino acid taurine in the treatment of human diseases has also attracted the attention of many researchers in various fields of biomedical sciences. Numerous studies revealed that taurine could treat and prevent a wide range of diseases by affecting the fundamental signaling pathways and cellular function. The effect of taurine on mitochondria is one of this substance's key mechanisms in preventing cell damage. In the present book, the effects of taurine on mitochondria and its relationship with the treatment of various human diseases have been given special attention and widely discussed. Researchers in biomedical sciences could widely use the data provided in this book. We hope that attention to compounds such as the amino acid taurine, a safe molecule that causes no significant side effects even at very high doses, can lead to the development of new and effective strategies in the pharmacotherapy of various human diseases.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENT

The current study was financially supported by the Vice-Chancellor of Research Affairs, Shiraz University of Medical Sciences, Shiraz, Iran (Grants: 12203/12028/11738/ 12806/12243/23158/23024/16259/13555).

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DEDICATION

"Everything passes and vanishes; Everything leaves its trace; And often, you see in a footstep What you could not see in a face!" William Allingham

Dedicated to my beloved ones!

Reza Heidari

Mainly thanks to my wife (Samira Sabouri) and my lovely son (Adrian Ommati), who provide a calm and happy environment to create this work. I dedicate it to my parents (Mr. Hossein Ommati and Mrs. Akram Pirouzfar) for all the support and valuable things they have taught me and for their sincere love.

M. Mehdi Ommati

CHAPTER 1

Taurine: Synthesis, Dietary Sources, Homeostasis, and Cellular Compartmentalization

Abstract: Taurine (β-amino acid ethane sulfonic acid; TAU) is a sulfur-containing amino acid abundant in the human body. Although TAU does not corporate in the protein structure, many vital physiological properties have been attributed to this amino acid. TAU could be synthesized endogenously in hepatocytes or come from nutritional sources. It has been found that the source of body TAU varies significantly between different species. For instance, some species, such as foxes and felines, are entirely dependent on the nutritional sources of TAU. On the other hand, TAU is readily synthesized in the liver of animals such as rats and dogs. The TAU synthesis capability of the human liver is negligible, and we receive this amino acid from food sources. The distribution of TAU also greatly varies between various tissues. Skeletal muscle and the heart tissue contain a very high concentration of TAU. At subcellular levels, mitochondria are the primary targets for TAU compartmentalization. It has been found that TUA also entered the nucleus and endoplasmic reticulum. The current chapter discusses the synthetic process and dietary sources of TAU. Then, the transition of TAU to sub-cellular compartments will be addressed. Finally, the importance of TAU homeostasis in the pathogenesis of human disease is mentioned.

Keywords: Amino acid, Food sources, Human disease, Mitochondrion, Mitochondrial cytopathies, Nutraceuticals, Nutrition.

INTRODUCTION

Using endogenous compounds with minimum adverse effects has always been a plausible approach to managing human diseases. In this context, since its discovery in the OX bile in 1827, taurine (TAU) has become the subject of a plethora of investigations in biomedical sciences [1]. Many physiological roles have been detected for TAU. Nowadays, it is well-known that TAU acts as an osmolyte in many biological systems, contributes to many metabolic processes such as bile acids conjugation, and even could be applied as a biomarker on some occasions [2 - 6].

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Although TAU is readily synthesized in the liver of many species (*e.g.*, Dogs), some other species, including humans, depend on the dietary sources of this compound [7]. It has been found that some tissues such as the skeletal muscle, heart, brain, and reproductive organs contain a huge amount of TAU in humans. Hence, this amino acid could play a pivotal role in the function of these organs.

Several pharmacological roles have also been identified for TAU, and these effects are growing every year. It has been found that TAU could protect different organs against xenobiotics, provide neuroprotective properties, mitigate skeletal muscle damage and enhance its functionality, improve human reproductive indices, prevent and/or cure cardiovascular disease, provide protection against liver diseases and many other pharmacological properties [8 - 26].

As mentioned, we receive our body TAU from dietary sources. Several TAU-rich foodstuffs have been identified. Seafood is rich in TAU. Hence, in countries that consume the types of foods (*e.g.*, Japan), people benefit from the positive effects of TAU. On the other hand, there is no TAU in herbal products, and herbivores could develop signs of TAU deficiency.

In the current chapter, the dietary sources of TAU are introduced, its absorption from the gastrointestinal tract is discussed, a brief overview of the synthesis of this amino acid in the liver is highlighted, its distribution in different organs is mentioned, and finally, its cellular compartmentalization is described.

TAURINE SYNTHESIS, DIETARY SOURCES, AND CELLULAR COMPARTMENTALIZATION

Taurine (β-amino acid ethane sulfonic acid; TAU) is endogenously synthesized in the liver hepatocytes from the amino acid cysteine and methionine [6, 27, 28] (Fig. **1**). Hence, the liver is the main organ responsible for TAU synthesis. The endogenous synthesis of TAU occurs *via* the cysteine sulfinic acid pathway (Fig. **1**). The enzyme responsible for TAU synthesis is dependent on cysteine bioavailability [28, 29]. Thus, TAU synthesis is dependent on the amount of protein intake and the availability of the precursor amino acids (methionine and cysteine) [6]. On the other hand, the ability of hepatocytes to synthesize TAU is widely variant between different species [30, 31]. Some species, such as foxes and felines, are entirely dependent on the dietary sources of TAU [30, 31]. TAU deficiency in these species could lead to severe anomalies, including retinal degeneration, cardiovascular disturbances, reproduction defects, and even animal death [30 - 34]. This evidence mentions the key physiological roles of TAU in some mammalians. Cysteine sulfonate decarboxylase (CSD) activity as a rate-limiting enzyme involved in TAU synthesis has been measured in the liver of various species (Table **1**). The activity of this enzyme in humans, as well as cats,

is negligible (Table **1**). On the other hand, animals such as dogs and rats have a considerable CSD activity in their liver (Table **1**) [1]. Hence, they could readily synthesize TAU from methionine and cysteine (Fig. **1**) and do not need to intake TAU from dietary sources [35].

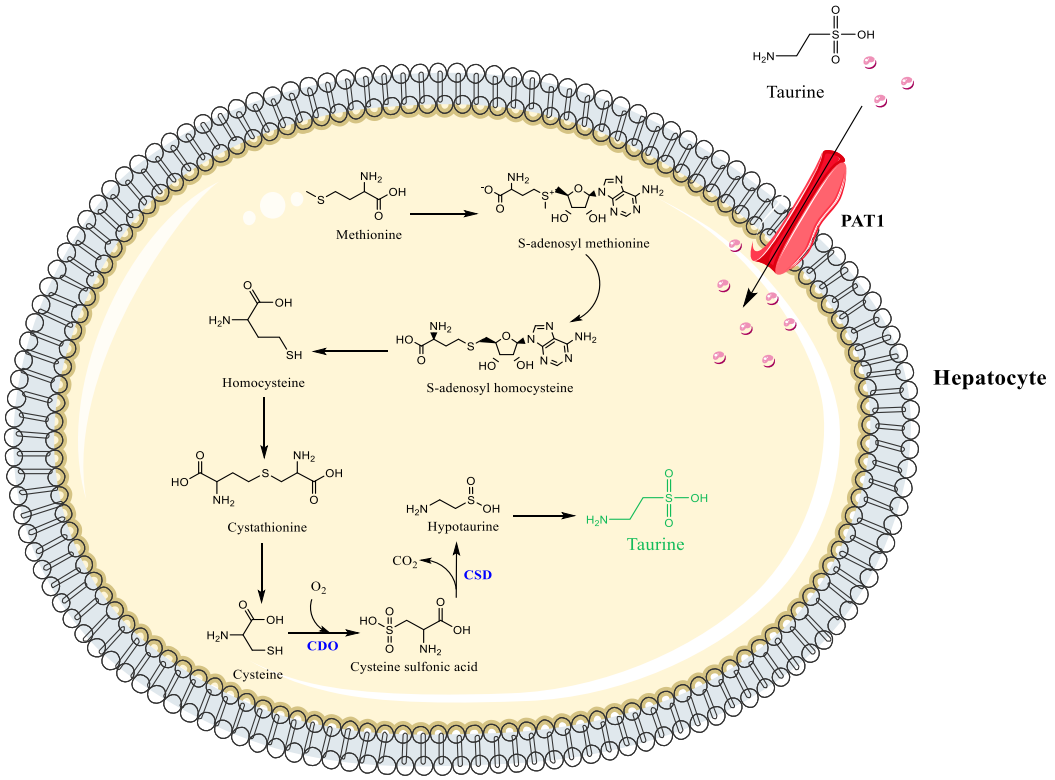

Fig. (1). Specific transporters uptake TAU from the bloodstream to various organs. The TAU uptake capability of different organs is widely varied. Taurine (TAU) is also endogenously synthesized in hepatocytes. TAU synthesis capability of some species such as fox and felines is very low, and these species are entirely dependent on the dietary sources of TAU. TAU could be readily uptaken by cells through transporters (*e.g.*, PAT1). The capacity of our hepatocytes is negligible for TAU synthesis. Thus, humans also greatly rely on the nutritional origins of TAU. CDO: Cysteine deoxygenase; CSD: Cysteinesulfinate decarboxylase; PAT1: Polyamine transporter 1.

It has been found that CSD activity is exceptionally high in oysters (*e.g.*, *Crassostrea gigas*). Therefore, oysters are an excellent food source of TAU in some regions [36] (Fig. **2**). Interestingly, approximately 80% of the total amino-acid content of oysters is TAU [36]. Oysters are widely used in England, Japan, Italy, and Spain [36].

CHAPTER 2

Taurine and the Mitochondrion

Abstract: Several studies have evaluated the subcellular compartmentalization of taurine (TAU) and its cellular and molecular mechanisms of action. Meanwhile, it has been found that TAU is largely uptaken by mitochondria. TAU could improve mitochondrial function by incorporating it into the basic mitochondrial structures and protein synthesis (*e.g.*, mainly mitochondrial electron transport chain components). Several other mechanisms, including the enhancement of mitochondrial calcium sequestration, regulation of mitochondria-mediated reactive oxygen species (ROS) formation, prevention of mitochondria-mediated cell death, and mitochondrial pH buffering, are also involved in the mitochondrial function regulatory properties of TAU. Therefore, TAU has been used against a wide range of pathologies, including mitochondrial injury. In the current chapter, a review of the approved molecular mechanism for the effects of TAU on mitochondria is provided. Then, the applications of TAU on a wide range of complications linked with mitochondrial impairment are discussed. The data collected here could give a better insight into the application of TAU as a therapeutic agent against a wide range of human diseases.

Keywords: Amino acid, Bioenergetics, Energy metabolism, Mitochondrial cytopathies, Mitochondrial disease, Mitochondrial impairment.

INTRODUCTION

The mechanisms of cytoprotection provided by taurine (TAU) have been widely investigated. Earlier, it was proposed that TAU could act as a direct radical scavenger [1 - 4]. However, later it became clear that TAU is a weak scavenger of reactive species [1 - 4]. Further studies revealed that mitochondria are the major place where TAU provides its cytoprotective properties by regulating this organelle [3, 5 - 11]. Nowadays, it is clear that TAU accumulates in mitochondria in high quantities [7, 12 - 14].

Several essential roles have been attributed to TAU in cellular mitochondria [7, 12, 13]. First, it is well-known that TAU contributes to basic mitochondrial structures such as tRNA [4, 13]. It has been found that mitochondria lacking TAU-modified tRNA couldn't synthesize their proteins (*e.g.*, mitochondrial respiratory chain complexes), and their function is impaired [13, 15]. On the other hand, it has been found that TAU regulates mitochondrial calcium homeostasis,

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prevents the release of cell death mediators from forming this organelle, and finally boosts energy (ATP metabolism) [10, 13, 16 - 22].

Many examples of human diseases are connected to mitochondrial impairment and disturbed energy metabolism. Skeletal muscle disease, neurodegenerative disorders, cardiovascular complications, liver disease, and reproductive anomalies have been identified with mitochondrial disturbances [23 - 37]. Therefore, it seems that targeting mitochondria in these complications could serve as a viable therapeutic option.

A plethora of investigations revealed the positive effects of TAU supplementation on human diseases. Interestingly, TAU provides its protective properties mainly by affecting cellular power plants. In the current chapter, the basic concepts of the effects of TAU on mitochondrial function are highlighted. Then, the potential application of this amino acid for a wide range of human diseases focusing on the effects of TAU on mitochondria and its related complications are highlighted.

TAURINE IN THE BASIC MITOCHONDRIAL STRUCTURES

The positive effects of TAU on mitochondria have been repeatedly documented [5, 18, 38 - 40]. Many studies have also mentioned that TAU significantly suppresses mitochondria-mediated cell death [18, 41 - 43]. Several mechanisms have been noted regarding the effects of TAU on mitochondrial function and its association with cellular energy metabolism and cytoprotective mechanisms [17, 20]. Recently, an exciting finding revealed the incorporation of TAU in the synthesis and regulation of basic mitochondrial structures [15, 44, 45]. These results mention that TAU is not just a supplement agent but is essential for proper mitochondrial function. The pivotal role of TAU in mitochondrial function and structure is discussed herein.

Recent studies revealed that TAU incorporates the structure of transfer RNA (tRNA) in mitochondria [4, 13] (Fig. **1**). tRNA is a molecule that serves as a link between messenger RNA (mRNA) and protein synthesis. tRNA carries amino acids to ribosomes (Fig. **1**). Hence, tRNA is necessary for mRNA translation and protein synthesis [4, 13]. Mitochondrial DNA (mtDNA) encodes several proteins (*e.g.,* electron transport chain components) independently from the nuclear DNA. Hence, any defect in the mitochondrial tRNA structure could influence protein synthesis and, finally, mitochondrial function (Fig. **1**). Mechanistically, it has been found that TAU forms a conjugate with a uridine base in mitochondrial tRNA [13, 15]. This TAU conjugation leads to structural changes in mitochondrial tRNA, making it functional for amino acid transportation to ribosomes and, finally, appropriate mitochondrial protein synthesis [13, 15] (Fig. **1**). On the other hand, recent data revealed that defective mitochondrial tRNA

TAU modification activates several protease enzymes, leading to cell death [45]. Therefore, it is crucial to manage tRNA taurine deficiency in patients.

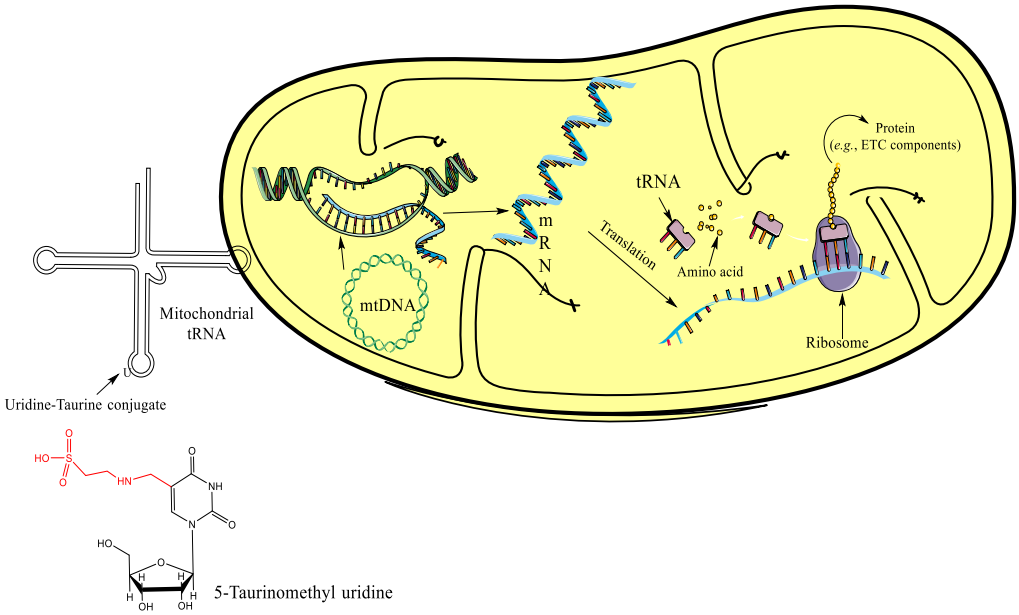

Fig. (1). Functional mitochondrial transfer RNA (tRNA) forms a conjugate with taurine. Mitochondrial tRNA lacking taurine modification cannot efficiently transport amino acids to ribosomes. Consequently, the synthesis of many proteins, including the mitochondrial respiratory chain components, could be disturbed. ETC: Electron transport chain. Taurine could find an application to alleviate mitochondrial tRNA defects in clinical settings.

Interestingly, it has been revealed that the formation of TAU-tRNA conjugate is hampered in several mitochondria-linked diseases [13, 46 - 48]. Mitochondrial tRNA lacking TAU modification is unstable and could not synthesize proteins correctly [65]. Consequently, the expression of several mitochondria-encoded proteins (*e.g.*, respiratory chain complexes) is suppressed [13, 46 - 48]. Excitingly, when mitochondrial oxidative phosphorylation is diminished (*e.g.*, lack of tRNA in TAU deficiency), an elevation in the glycolysis process and lactate production will occur, leading to metabolic acidosis. It has been found that TAU supplementation could significantly improve symptoms of patients with mitochondrial disorders related to impaired tRNA TAU modification [49, 50]. These findings provide clues for TAU application as a therapeutic option in clinical settings.

CHAPTER 3

Applications of Taurine in the Central Nervous System Disorders Linked with Mitochondrial Impairment

Abstract: Taurine (TAU) reaches a high concentration in the central nervous system (CNS). The physiological role of TAU in the CNS is the subject of many investigations. It has been suggested that this amino acid could act as a membrane stabilizer, a modulator of calcium signaling, a trophic factor for neuronal development, and even be proposed as a neurotransmitter in the CNS. Besides, several investigations revealed the neuroprotective properties of TAU in various experimental models. Multiple mechanisms, including the inhibition of the excitotoxic response, the blockade of cytoplasmic calcium overload, regulation of oxidative stress, and the positive effects of TAU on mitochondrial parameters, have been proposed for the neuroprotective properties of this amino acid. Today, it is well-known that mitochondrial function and energy metabolism play a pivotal role in the pathogenesis of various neurodegenerative disorders and xenobiotics-induced neurotoxicity. Hence, targeting mitochondria with safe and clinically applicable agents is a viable therapeutic option in various neurodegenerative disorders. In the current chapter, the effects of TAU on the CNS will be highlighted, focusing on the positive effects of this amino acid on mitochondrial parameters. The data could help the development of safe therapeutic agents against CNS complications.

Keywords: Brain injury, Energy crisis, Mitochondrial dysfunction, Neurodegenerative disease, Neurotoxicity, Oxidative stress.

INTRODUCTION

Neurological complications debilitate a large population worldwide annually. Stroke and brain ischemia, various types of head trauma, seizures, and hepatic encephalopathy are among the neurological complications that need urgent medical interventions [1 - 5]. On the other hand, neurodegenerative diseases refer to a wide range of complications that have become a crucial issue in the recent century [6, 7]. Neurodegenerative diseases are among the leading cause of disability worldwide [6, 7]. Alzheimer's disease, Parkinsonism, and Huntington's disease are debilitating neurodegenerative complications. Based on these data, it

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is crucial to identify the mechanism of brain injury in these complications and find safe and clinically applicable options against these disorders.

Although the mechanisms involved in CNS complications and neurodegenerative disease could be pleiotropic and multifactorial. Several interconnected mechanisms have been identified in these complications [8 - 18]. These mechanisms could serve as a therapeutic point of intervention to manage serious neurological complications as well as neurodegenerative diseases.

Based on a plethora of investigations over activation of n-methyl-D-aspartate (NMDA) receptors, named excitotoxicity, cytoplasmic calcium overload, oxidative stress, and mitochondrial impairment are the point of convergence for the mechanism of neuronal injury in central nervous system disorders [8 - 18]. All these events finally influence mitochondrial function and mitochondria-mediated cell death. On the other hand, brain tissue is a high energy (ATP) consuming organ [17, 18]. Therefore, it seems reasonable that targeting mitochondria could be a viable therapeutic approach against a wide range of neurological disorders. In this regard, several antioxidants and mitochondria-targeted compounds have been tested, and had more and less therapeutic properties against these complications.

Taurine (TAU) is abundantly found in the brain tissue [19 - 22]. On the other hand, it has been found that this amino acid and its derivatives could significantly alleviated neurological disorders associated with mitochondrial complications [17, 23 - 28]. More interestingly, TAU revealed tremendous protective effects against neurodegenerative disorders in clinical trials [18, 29 - 32]. All these data make TAU an excellent candidate for the management of neurological disorders in humans.

The neuroprotective properties of TAU seem to be mediated through the positive effects of this amino acid on mitochondrial function [17, 23 - 27]. It has been found that TAU prevents mitochondria-mediated cell death, suppresses excitotoxicity-mediated neuronal damage, decreases oxidative stress in CNS, and enhances ATP metabolism [17, 23 - 27].

In the current chapter, the effects of TAU on a wide range of human neurological disorders is discussed focusing on the positive effects of this amino acid on mitochondrial indices. These data could provide clues for future drug development against many neurological disorders.

THE PLEIOTROPIC ROLES OF TAURINE IN THE CENTRAL NERVOUS SYSTEM (CNS)

Brain tissue contains a high concentration of taurine (TAU) [33]. The transfer of

TAU to the CNS and neural cells is a transporter-mediated process [34, 35]. Some physiological roles, including the osmoregulatory properties, have been attributed to TAU in the CNS [36]. However, it has been repeatedly mentioned that several neurological disorders benefit from exogenous TAU supplementation [32, 37 - 39]. The effects of TAU on seizure and epilepsy, Alzheimer's disease (AD), brain trauma, Huntington's disease (HD), stroke, and Parkinson's disease (PD) have experimentally or clinically been investigated [32, 38, 39]. Some investigations even mentioned that TAU plays a role in neuromodulation and neurotransmission [40 - 42]. Nevertheless, the mechanism of action of this amino acid in the CNS is not fully cleared so far.

Some investigations mentioned that TAU could act as an osmolyte to regulate cell volume in astrocytes and neurons during stressful conditions [43, 44]. Although many studies have approved the osmoregulatory properties of TAU, today, we know that other and more important mechanisms could also be involved in the positive effects of TAU in the CNS. The positive impact of TAU on mitochondrial function and energy metabolism in the brain is one of the most elusive mechanisms of action of this amino acid in the CNS. The current chapter will discuss the effects of TAU on stroke and stroke-like episodes, AD, HD, hepatic encephalopathy, PD, trauma, and seizure, which are connected to mitochondrial impairment and energy crisis.

Before discussing the role of mitochondrial impairment in CNS disorders, we should explain a term named "excitotoxicity", which is believed to be involved in the pathogenesis of numerous CNS disorders. Excitotoxicity is also directly connected to mitochondrial impairment and oxidative stress. Glutamate (Glu) is the primary excitatory neurotransmitter in the CNS. It has been found that Glu levels are increased in several neurodegenerative diseases such as HD, AD, stroke, seizure, and brain trauma [8 - 16]. Increased Glu activates the N-Methyl-D-aspartate (NMDA) receptors. The hyper-activation of NMDA receptors is known as the excitotoxic response [45 - 47] (Fig. **1**). Excitotoxicity has several consequences in the CNS [45 - 47]. Detrimental events such as dramatically increased ROS levels, high nitric oxide (NO) levels, and peroxynitrite ($NOO^{\bullet}$) formation could occur upon excitotoxicity [10, 48]. Hence, the excitotoxic response is connected to oxidative/nitrosative stress. The disturbances in cellular Ca^{2+} homeostasis are another deleterious event that ensues NMDA receptors' hyper-activation and excitotoxicity [10, 48] (Fig. **1**). There are several clues that neural mitochondria are also severely damaged during excitotoxicity. It has long been known that oxidative/nitrosative stress is firmly linked to mitochondrial impairment [49]. On the other hand, high cytoplasmic Ca^{2+} levels disturbed mitochondrial function and dissipated mitochondrial membrane potential ($\Delta\Psi_m$). Hence, Ca^{2+} overload and excitotoxicity could impair mitochondrial function in

CHAPTER 4

Taurine and the Cardiovascular System: Focus on Mitochondrial-related Pathologies

Abstract: It is well-known that taurine (TAU) concentration in the excitable tissues, such as the myocardium is exceptionally high (up to 30 mM). TAU accumulation in the cardiomyocytes is a transporter-mediated process. Therefore, this amino acid should play a critical role in cardiac tissue. Several studies revealed that a decrease in cardiac TAU could lead to atrophic cardiomyopathy and impaired cardiac function. At subcellular levels, the effects of TAU on mitochondria and energy metabolism are an essential part of its function in the heart. Besides, it has been found that exogenous TAU supplementation significantly enhanced cardiac mitochondrial function and ATP levels. In the current chapter, the effects of TAU on cardiovascular diseases linked with mitochondrial impairment are highlighted, and the role of TAU as a cardioprotective agent is discussed. The data collected here could provide clues in managing a wide range of cardiovascular complications connected with the energy crisis and mitochondrial dysfunction.

Keywords: Arrhythmia, Cardiovascular diseases, Cardiomyopathy, Energy Crisis, Heart disease, Mitochondrial impairment.

INTRODUCTION

Cardiovascular diseases (CVDs) refer to a wide range of complications that could severely affect patients' quality of life [1, 2]. More importantly, CVDs are among the leading cause of mortality worldwide [3]. Several pathological conditions, including disturbed plasma lipids, formation of atherosclerotic plaques, hypertension, and congenital heart tissue defects, could contribute to CVDs [4, 5]. On the other hand, heart tissue demands an immense energy value daily to properly pump enough blood through the body [6 - 8]. Actually, heart tissue contains numerous mitochondria that make this process possible [6 - 8].

It is well-established that cardiac tissue has a very high level of taurine (TAU) [9 - 12]. It seems that TAU plays a pivotal role in regulating cardiac tissues mitochondrial function and energy metabolism since TAU depleted models revealed deleterious cardiac defects, which finally lead to animals' death [13 - 15]. TAU depletion could also cause various disorders in other organs [16]. Most

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of the cardiac TAU content is localized in the cellular mitochondria. It is well-known that TAU regulates mitochondrial respiratory chain activity, decreases mitochondria-mediated reactive oxygen species formation, blunts mitochondria-mediated cell death, and enhances mitochondrial energy metabolism in the heart [17 - 23]. These features make TAU an ideal cardioprotective for a wide range of CVDs.

Interestingly, many clinical studies revealed the positive effects of TAU in CVDs. It seems that cardiomyocytes' mitochondria are the primary place for the cardioprotective mechanisms of action of TAU. The current chapter describes the effects of TAU on mitochondrial function as a plausible mechanism of its action. Then, the application of this amino acid in a variety of CVDs is highlighted. The data collected in this chapter could develop safe and clinically applicable therapeutic options in CVDs.

TAURINE AND THE CARDIOVASCULAR SYSTEM

The effects of TAU on the cardiovascular system are one of the most investigated biological properties of this amino acid [9, 11, 24 - 28]. Several studies mentioned the positive effects of TAU in the cardiovascular system [9]. Antihypertensive, anti-atherosclerotic plaque formation and anti-hyperlipidemia properties of TAU are repeatedly reported in experimental models and clinical trials [9, 29 - 33]. The effects of TAU on cardiac complications such as arrhythmia, myocardial infarction, and heart failure have also been widely investigated [34 - 37].

A high level of taurine (TAU) is found in cardiomyocytes (up to 30 mM). TAU uptake by cardiomyocytes is a transporter-mediated process [38, 39]. Several physiological roles have been proposed for TAU in the heart tissue [9, 27, 32, 40 - 43]. It has been mentioned that TAU could act as a vital osmoregulator in the heart [9, 27, 32, 40 - 43]. Moreover, TAU regulates the proteins phosphorylation process and cytoplasmic calcium (Ca^{2+}) levels in cardiomyocytes [44]. The increase in Ca^{2+}-ATPase activity plays a pivotal role in the effects of TAU on cardiomyocytes' Ca^{2+} levels [21, 45] (Fig. **1**). It is well-known that Ca^{2+} signaling plays a fundamental action in the excitation-contraction coupling of the cardiac muscle. Therefore, enough TAU concentration guarantees proper cardiac contraction and preserves cardiac output. Based on these data, TAU could regulate various basic parameters in the cardiovascular system (Fig. **1**). Therefore, it is important to investigate the molecular mechanisms of TAU action in cardiovascular diseases.

Previous studies have repeatedly mentioned the effects of TAU deficiency on cardiac function [9, 35, 46, 47]. It is well-known that TAU deprivation severely impaired cardiac function in some species, such as foxes, cats, and dogs [14, 48,

49]. Cardiomyopathy is a common pathological change associated with TAU deficiency [50 - 53]. Investigations in different experimental models also revealed that the inhibition of TAU transport to cardiomyocytes significantly influenced myocardial energy metabolism and led to impaired cardiac function [53]. Therefore, the regulation of ATP metabolism is one of the basic functions of TAU in the cardiac tissue [22, 54] (Fig. **1**). All these data indicate an essential role for TAU in normal cardiac function and highlight the importance of this amino acid in mitochondrial function as a primary mechanism for its cardioprotective properties (Fig. **1**).

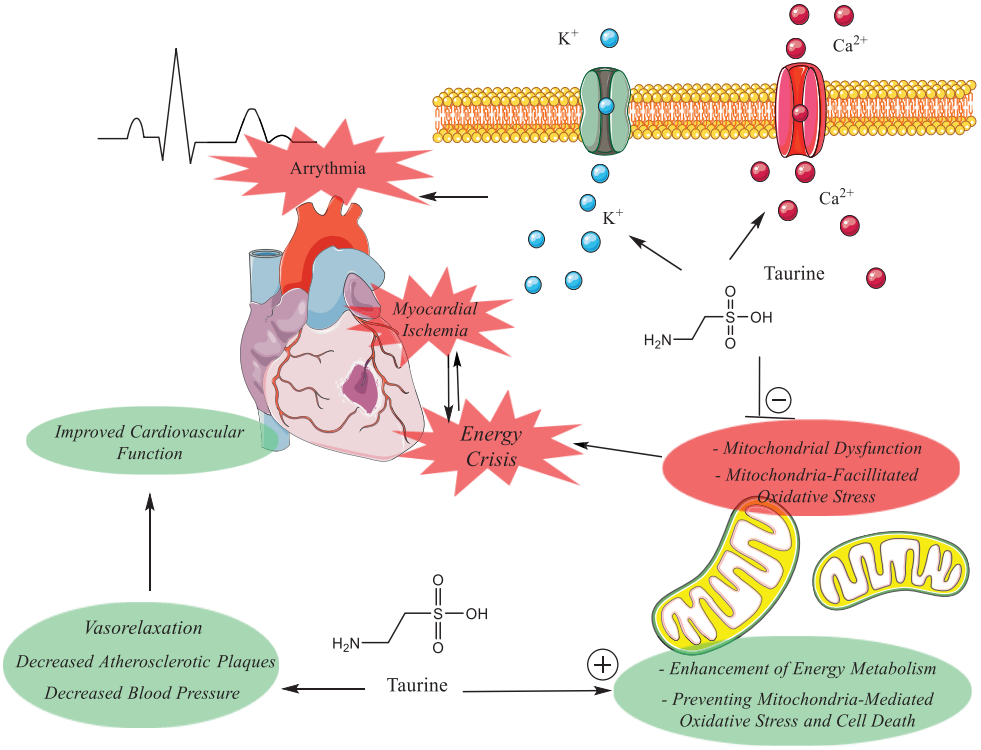

Fig. (1). Taurine regulates different parameters in the cardiovascular system. The effects of TAU on mitochondrial function and cardiomyocytes' energy status play a pivotal role in the effects of this amino acid in the cardiovascular system. TAU also regulates the level of crucial ions such as Ca^{2+} in cardiomyocytes. Ca^{2+} dyshomeostasis is associated with complications such as arrhythmia. The effects of TAU on parameters such as the formation of atherosclerotic plaques or decreasing blood pressure could also eventually decrease the risk of cardiovascular disease.

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide [55]. Arrhythmia, myocardial infarction, high blood pressure,

CHAPTER 5

Taurine and the Liver: A Focus on Mitochondria-related Liver Disease

Abstract: Although the liver is the leading site for taurine (TAU) synthesis, the level of this amino acid in hepatic tissue is relatively low. It is well-known that TAU is efficiently redistributed from hepatocytes to the circulation. However, the human body's capacity for TAU synthesis is negligible, and we receive a very high percentage of our body TAU from exogenous sources. Plasma TAU is taken up by several tissues, such as the skeletal muscle and the heart. The roles of TAU in liver function are the subject of many investigations. It has been found that TAU could have beneficial effects against xenobiotics-induced liver injury, alcoholism-associated hepatic damage, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), or even viral hepatitis infections. The inhibition of cytochrome P450, alleviation of oxidative stress, inhibition of inflammatory reactions, and the mitigation of tissue fibrosis are fundamental mechanisms proposed for the hepatoprotective properties of TAU. On the other hand, many studies indicate that hepatocytes' mitochondria are essential targets for the cytoprotective properties of TAU. The current chapter reviews the beneficial role of TAU on the most common liver disorders, focusing on the effects of this amino acid on mitochondrial function and energy metabolism.

Keywords: Hepatoprotection, Hepatotoxicity, Liver disease, Liver injury, Mitochondria, Oxidative stress.

INTRODUCTION

Although the liver is the main organ responsible for taurine (TAU) biosynthesis, the hepatic concentration of this amino acid is relatively low [1]. On the other hand, the TAU synthesis capacity of hepatic tissue is extremely variable between species [2, 3]. Some species such as foxes and felines are entirely dependent on the dietary sources of TAU [2, 3]. On the other hand, TAU is readily from the amino acids cysteine and methionine in the liver of dogs and rats [4 - 6]. The capability of a human liver for TAU synthesis is scarce and we receive almost all body TAU from dietary sources [7 - 10].

It has been found that TAU could play several pivotal roles in the liver. Many investigations revealed that TAU could effectively act as an antidote and protect

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the liver against xenobiotics such as drugs, alcohol, or a wide range of other toxicants [11 - 16]. Nowadays, it is well-known that TAU is a robust inhibitor of the enzyme CYP2E1 [11, 17 - 20]. CYP2E1 is an important liver enzyme responsible for the bioactivation of many hepatotoxicants such as ethanol, carbon tetrachloride, and thioacetamide [11, 17 - 20]. Therefore, the inhibitory effects of TAU on CYP2E1 play a fundamental role in its hepatoprotective properties. Moreover, it has been found that TAU activates basic metabolic pathways, for example, long-chain fatty acids metabolism, in the liver [21 - 23]. Hence, this amino acid could act as a good candidate for liver diseases such as fatty liver.

More interestingly, TAU revealed potent antifibrotic properties in the liver and many other organs [14, 24 - 35]. Several hepatic disorders have been identified which could entail liver fibrosis and organ failure [32, 33]. Actually, hepatic fibrosis is the leading cause of liver transplantation worldwide [36, 37]. Hence, finding chemicals that could blunt or even prevent this process has a huge clinical value. It has been found that TAU possesses antifibrotic properties by inhibiting stellate cell activation, decreasing the release of pro-inflammatory mediators, and blunting oxidative stress and its associated complications [14, 24 - 35].

The effect of TAU on hepatocytes mitochondria is one of the most interesting features of this amino acid. Several experimental models revealed that TAU could significantly enhance mitochondrial membrane potential ($\Delta\Psi_m$), decrease mitochondrial release of cell death mediators, blunt mitochondria-mediated ROS formation and oxidative stress, and finally enhance the ATP level [38 - 55].

In the current chapter, the effects of TAU on several fundamental mechanisms involved in the pathogenesis of hepatic disorders are discussed. In this context, the antifibrotic properties of TAU (*e.g.*, in diseases such as alcoholism) are widely described. Moreover, the therapeutic potential of TAU on other common liver disorders such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are discussed. Finally, the potential application of TAU against xenobiotics-induced liver injury is highlighted. In all these parts, the connection between the effects of TAU on mitochondrial indices and its relevance to these pathologies is considered.

TAURINE AND THE LIVER

The liver is the main organ responsible for TAU synthesis [6, 20, 41, 56]. However, the liver capacity for TAU synthesis is considerably variable between species [2, 3]. TAU is readily synthesized from the amino acid cysteine in the liver of dogs, rats, and Guinea pigs [57, 58]. However, some species, such as foxes and felines, are entirely dependent on the dietary sources of TAU [2, 3, 59 -

61]. The TAU synthesizing capability of the human liver is also negligible, and we receive a high percentage of our body TAU from exogenous sources [7 - 10, 20, 62 - 65]. As mentioned in chapter 1, TAU is abundantly found in foods such as meat (*e.g.*, turkey meat) and seafood (*e.g.*, oyster and muscles) [7, 8, 10, 65].

Hepatocytes contain lower TAU concentrations in comparison with other tissues such as skeletal muscle, cardiomyocytes, and the brain [6, 20, 41, 56]. As mentioned, endogenous TAU synthesis of the human liver is low, and a considerable portion of body TAU is provided through dietary sources [6, 20, 41, 56]. However, a lower concentration of TAU in hepatocytes could also be connected to the transport systems responsible for distributing this compound from hepatocytes and its uptake from the bloodstream [6, 20, 41, 56]. It is well-known that TAU transporters (TauT) expression is highly variable between different tissues [4, 21, 66, 67]. When TAU reaches the bloodstream, its uptake by tissues with more TauT is fast and high. Skeletal muscles and cardiomyocytes express a very high level of TauT [21, 58, 67, 68]. Hepatocytes have a lower level of transporters for TAU uptake. Hence, the level of this amino acid could be lower due to this issue, especially in species dependent on its exogenous sources.

TAU plays several essential physiological roles in the liver [20, 69 - 72]. TAU could also play a role in detoxifying xenobiotics from the liver and protecting hepatic tissue against their harmful effects, such as oxidative stress [71]. Bile acid conjugation is one of the most established physiologic roles of TAU in the liver [20, 73]. TAU-conjugated bile acids are secreted to the intestine, where they could be excreted through the feces or degraded by gut bacteria. The osmoregulatory properties of TAU in hepatocytes, its role in regulating cytoplasmic Ca^{2+} homeostasis, and the effects of TAU on mitochondrial function and energy metabolism are also important roles attributed to this amino acid in hepatocytes [20, 69 - 72]. In the current chapter, the role of TAU in common liver disease, as well as xenobiotics-induced hepatotoxicity, is discussed, focusing on the effects of this amino acid on mitochondrial function and its linked events. The data collected here could help the development of therapeutic strategies against liver disease as one of the most common causes of morbidity and mortality worldwide.

TAURINE AND LIVER FIBROSIS

Tissue fibrosis is a complicated process that could occur in response to a wide range of stimuli [74]. Several liver diseases have been identified in this context, which could entail liver fibrosis, dysfunction, and finally, hepatic failure [75 - 79]. Alcoholism, infectious liver disease, metabolism disorders, and a wide range of xenobiotics could induce liver fibrosis [80, 81]. There is no pharmacological intervention for reversing the function of the fibrotic area in the liver to date.

CHAPTER 6

Taurine as an Anti-aging Compound: Focus on Mitochondria-related Mechanisms

Abstract: It has been well-established that mitochondria play a crucial role in aging. Thus, targeting mitochondria is a leading approach for anti-aging pharmacological interventions. On the other hand, the anti-aging effect of taurine (TAU) is an exciting feature of this amino acid. Effects of TAU on mitochondria-facilitated oxidative stress as well as mitochondria-mediated cell death, seem to play a pivotal role in its antiaging properties. The current chapter will discuss a good body of investigations that have converged at a consensus regarding mitochondria (dynamics and functionality) and oxidative stress as essential mechanisms involved in the aging process. In each part, the potential antiaging properties of TAU and its mechanisms of action are also highlighted. Finally, in the last section of this chapter, we described the possible role of recently-discovered signaling pathways (*i.e.*, aryl hydrocarbon receptors; AhR) on mitochondria and their relevance to senescence.

Keywords: Cell death, Endoplasmic reticulum stress, Oxidative stress, Reproduction, Senescence.

INTRODUCTION

There are many definitions of aging in various organs. As a general definition, aging could be interpreted as "a multifaceted event described by a typical time-dependent decline in physiological performances of creatures (human, animals, plants), interconnected with a rising risk of illness and death rate which eventually corresponded in the lifespan of organisms, and in which multi-factorial elements of genetic/hereditary and environmental components play a crucial moderating role in this phenomenon".

However, as mentioned, aging in various organs has a specific description. For instance, brain aging is described by several neurochemical alterations, comprising variations in the levels of structural proteins, neurotransmitters, and neuropeptides (*i.e.*, decrement in glutamate decarboxylase and somatostatinergic subpopulations of GABAergic neurons), as well as associated receptors (decrements in ionotropic GABA receptors). Changes in neurochemical parameters of the synaptic function associated with aging-related central

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function impairments (*i.e.*, memory and sensory performances and locomotion). Hence, Idrissi *et al.* have highlighted the crucial role of GABA inhibitory neurotransmission in the age-related decline in cognitive functions [1]. In the same vein, it has been shown that ionotropic GABA receptors, glutamate decarboxylase (GAD), and somatostatinergic subpopulations of GABAergic neurons considerably declined in the aged animal's brain. Several studies demonstrate that ionotropic GABA receptors, glutamate decarboxylase (GAD), and somatostatinergic subpopulations of GABAergic neurons are markedly decreased in experimental animal brains during aging. Hence, a decrement in cognition functionality in aging animals might be caused (at least in part) due to decreases in GABA inhibitory neurotransmission.

On the other hand, there are specific definitions for reproductive aging of both genders. A considerable reduction could occur in reproductive indices in a species- and sex-dependent manner. For instance, the reproductive functionality of females halts with the beginning of the menopause (menstrual cycle pauses in women reaching about 45 to 60 years old). In males, it is also defined as any decrement in androgen formation, sperm production, and sexual desire or function being the major phenotypes or reasons of aging that might be ascribed to impairments of male gonad. Hence, in men, this phenomenon initiates with a decline in male gonad activity and subsequently neuroendocrine alterations impacting on some indices of physiology and psychology, a natural manner well-known as andropause[1]. Hence, aging in the male reproduction system initiates with a combination of morphological and endocrinological alterations. However, reproductive aging happens gradually in men, and they also do not undergo a whole termination of reproductive ability. Hence, males could maintain their reproductive capacity through proper spermatogenesis and steroidogenesis until the approximate end of life [2 - 7].

Nevertheless, it has been well reported that the alterations in the reproductive capacity of aged men are individually erratic and depend on the daily life patterns and other xenobiotics, such as environmental elements [2, 6 - 8]. Meanwhile, it is getting progressively clear that one of the well-known indices for reproductive aging in men is the continuing decrement in biosynthesis and secretion of testosterone that initiates around 30- years old and gradually continues time-dependently [4, 5, 9 - 11]. Because of this alteration in steroidogenesis performance, hormone replacement therapy in aged men (testosterone therapy) and women (estrogen replacement therapy) is recommended. It has been a valuable target for in-depth studies in the last decades. Nevertheless, their risks and benefits remain enigmatic to this day. As mentioned, there are various definitions for aging in different endogenous systems. Approximately, all these investigations agreed on a general theory that aging occurs based on the two

crucial hypotheses. The first assumes that the lifespan is regulated by the expression of some specific genes *via* controlling of neuroendocrine system (hormone secretion) and consequent signaling routes. The second postulates a close relation between oxidative stress induction in various organs with enhancing age [12 - 15]. Meanwhile, these two routes are possibly more associated and will be discussed in detail in the following sections.

Cells aging occurs with apparent symptoms. For instance, it has been shown that aged cells are often larger as compared with the fresh and young cells; it could be interpreted that aged cells have more waste materials as a result of progressive degeneration of various organelles (*e.g.*, formation of large-double membrane vacuoles containing damaged mitochondrial during autophagy process, called autophagosomes). Meanwhile, the nuclei of aged cells could be detected easily due to the high levels of heterochromatin, damaged DNA, and nuclear proteins. These alterations are not distinguishable in nuclear levels; because both proteins and lipids within the cytoplasm and cellular plasma membrane could be damaged, which could eventually lead to substantial alterations in membrane permeability and fluidity, subsequent molecular transport, and cellular signaling. Intracellular accumulation of these unwanted proteins and lipids in aged cells could increase the generation of reactive oxygen species (ROS) and consequently increase the risk of oxidative stress induction (as mentioned above; for details, see sections 2 to 4). Mitochondrial impairment is one of the hallmarks of aging. In this view, many in-depth investigations highlighted that the most noticeable feature in these aging cells and the aging process is recorded alterations in the structure and functionality of mitochondria (and their association with stem cell fate, innate immune system, inflammation, metabolic status, age-dependent pathology, and nuclear signaling) [2, 13, 16 - 22]. By aging the cells, mitochondria will also be senescent, which has characteristics such as structural damages (ranging from swelling and loss of cristae to the destruction of the matrix and membrane structure), which eventually lead to the generation of intracellular amorphous elements. These senescent mitochondria are generally known as giant mitochondria because they are larger than younger ones.

Meanwhile, it has been well reported that mitochondrial genome mutation and mitochondrial proteins alteration progressively increase in the aging process [23]. In the next section, we will discuss the relation between oxidative stress and aging-induced mitochondrial injury, as well as the ameliorative role of taurine (TAU) on these processes. For instance, it has been shown that because of the specific features of TAU (such as antioxidant properties), it has a crucial role on reproductive indices (as a testosterone stimulating factor, a sperm membrane stabilizer and motility factor, an anti-apoptotic and anti-autophagic agent) and anti-aging through mitochondrial-dependent and -independent signal pathways.

CHAPTER 7

Taurine and Skeletal Muscle Disorders: Highlighting the Mitochondria-dependent Mechanisms

Abstract: Skeletal muscle tissue contains a massive taurine (TAU) in millimolar concentrations. Several studies mentioned the importance of TAU in normal skeletal muscle function. It has been found that this amino acid plays a wide range of functions, ranging from osmoregulatory properties to the regulation of cytoplasmic Ca^{2+} homeostasis. Recent findings mentioned that TAU deficiency in the skeletal muscle leads to decreased exercise capacity, severe weakness, and muscle waste. On the other hand, it has been repeatedly shown that TAU supplementation could increase skeletal muscle performance in many disorders. These data mention the essential role of TAU in the skeletal muscle. Interestingly, it has been found that the effect of TAU on cellular mitochondria is an important feature of this amino acid in skeletal muscles. The current chapter highlights the physiological roles of TAU in muscle and its importance in the pathophysiology of skeletal muscle disorders. Then, the essential role of TAU in cellular mitochondria and its importance in muscle function is described. And the relevance of this amino acid in managing skeletal muscle pathologies is discussed.

Keywords: Amino acid, ATP, Bioenergetics, Cell death, Exercise, Muscle waste, Oxidative stress.

INTRODUCTION

Skeletal muscle is one of the most taurine (TAU)-containing tissues [1 - 3]. Physiologically, several functions, including the osmoregulatory properties, calcium (Ca^{2+}) ion regulation, and the phospholipids bio membranes, are attributed to TAU in the skeletal muscle [5 - 7]. Nowadays, it is well-known that TAU plays many other essential roles in the skeletal muscle. TAU plays a vital role in mitochondrial function and energy metabolism in skeletal muscles.

Many investigations revealed that TAU depletion had deleterious consequences on skeletal muscle function [4 - 6]. TAU depletion led to significant mitochondrial abnormalities (morphological and functional). Dissipation of the mitochondrial membrane potential ($\Delta\Psi_m$), mitochondrial permeabilization, enhan-

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ced mitochondria-mediated ROS formation, mitochondria-mediated cell death, and impaired energy metabolism are consequences of TAU depletion in the skeletal muscle [4 - 11]. It has also been found that skeletal muscle TAU depletion could enhance muscle senescence and atrophy [12]. These two later disorders could also be mitochondria-related mechanisms.

Another exciting feature of TAU is its use in energy drinks as well as by athletes to increase their stamina [13 - 15]. In this regard, it has been found that TAU could significantly enhance energy metabolism in the skeletal muscle. Moreover, TAU prevents muscle injury and efficiently enhances muscle recovery after heavy exercise [13 - 15].

Enhancement of protein catabolism, increased sarcoplasmic Ca^{2+}, oxidative stress, and inflammatory response are cellular processes that seem to be involved in the onset of muscle dysfunction [4, 16 - 18]. More importantly, there are robust clues about the significant role of mitochondrial function and cellular energy metabolism in skeletal muscle disorders with different etiologies [19 - 24]. Hence, it is essential to find pharmacological options against these disorders.

In the current chapter, a review of the physiological roles of TAU in skeletal muscle is provided. Then, the effects of this amino acid on mitochondrial function and its associated pathologies are highlighted. Finally, the application of TAU as a therapeutic agent against skeletal muscle disorders is discussed in detail. The data collected here might provide clues for developing effective therapeutic options against a wide range of skeletal muscle-related disorders or finding strategies to enhance human skeletal muscle strength for various purposes.

MECHANISMS OF TAURINE ACTION IN THE SKELETAL MUSCLE

Skeletal muscle is contained a considerable amount of TAU [1, 2, 25 - 27]. The TAU transporter TauT is highly expressed in the skeletal muscle and could primarily concentrate TAU in this tissue (>100 fold higher than plasma TAU concentration) [1, 2, 4, 25 - 27]. Due to the massive concentration of TAU in this tissue, this amino acid seems to play a crucial role in the skeletal muscle. The observation that skeletal muscle function is significantly impaired in experimental models of TAU deficiency highlights the vital role of this amino acid in muscle function [12, 28]. Significant muscle senescence and energy crisis occurred in TAU deficiency models [12]. Membrane stabilization and the action of TAU as an osmolyte are well-investigated physiological roles of this amino acid in the skeletal muscle [4]. Moreover, crucial functions such as regulating intracellular Ca^{2+} homeostasis are also attributed to TAU [26, 29 - 31]. Other actions of TAU in skeletal muscle include anti-inflammatory effects, antioxidant properties, and regulation of ion channels [4].

As mentioned, a good body of evidence indicates the crucial role of TAU in regulating mitochondrial function and enhancing organ performance in the skeletal muscle and many other organs [4, 32 - 41]. In this context, investigations of TAU deficient models revealed significant mitochondrial impairment, mitochondria-mediated cell death, and severe tissue atrophy in skeletal muscle [12, 28]. These studies revealed that TAU deficiency leads to the dissipation of mitochondrial membrane potential ($\Delta\Psi_m$), impaired mitochondrial respiratory chain complexes activity, decreased mitochondrial energy metabolism, increased mitochondrial permeabilization, and the release of cell death mediators from this organelle [12, 28]. On the other hand, several studies indicate the positive role of TAU supplementation in skeletal muscle mitochondrial indices in various experimental models [42 - 46]. The effects of TAU on many skeletal diseases also seem to be mediated through a mitochondria-dependent mechanism (Fig. **1**) [4, 16, 32].

TAURINE REGULATES ION CHANNELS IN THE SKELETAL MUSCLE

The regulation of skeletal muscle ion channels is a crucial mechanism for TAU in this tissue [4]. In this regard, the voltage-gated chloride channel, CLC-1, seems to be a significant target for TAU in skeletal muscles [4] (Fig. **2**). The Cl^- ion plays a key role in the sarcolemma's electrical stability and muscle relaxation [4]. Several genetic defects in CLC-1 have been identified. These mutations are directly related to myotonia-related muscle disorders [4]. Myotonia is a muscle disorder related to decreased Cl^- ion influx to the muscle fiber. This situation leads to delayed muscle relaxation, severe spasms, and muscle stiffness [4, 47 - 49]. Fortunately, a good body of evidence indicates the activation role of TAU on CLC-1 and myofibers Cl^- ion influx [4, 50 - 52] (Fig. **2**). Hence, TAU is able to decrease skeletal muscle excitability and spasms significantly. Interestingly, it has been found that long-term administration of TAU significantly diminished myotonic symptoms [4, 53 - 55]. Based on these data, the effects of TAU on CLC-1 and Cl^- ion current could have positive effects in muscular disorders such as myotonia. However, more clinical studies, especially with large sample sizes, are needed to confirm this effect of TAU and finally its application in clinical settings.

TAU also regulates the activity of voltage-gated sodium channels (NaV1.4) in skeletal muscles [4] (Fig. **2**). It has been found that high concentrations of TAU (*e.g.*, 10 mM) can significantly reduce sodium (Na^+) current in the muscle fiber [4, 16, 56]. The role of TAU in blocking Na^+ channels could provide beneficial effects in muscular disorders such as myotonia, especially myotonic disorders associated with mutations in Na^+ channels (*e.g.*, paramyotonia congenita) [4].

CHAPTER 8

Taurine and the Renal System: Effects on Mitochondrial Function and Energy Metabolism

Abstract: Renal tissue is the main organ responsible for regulating the human taurine (TAU) pools. A large amount of intact (un-metabolized) TAU is excreted through the urine daily. On the other hand, it has been found that TAU plays a fundamental role in renal function. Several physiological roles, including regulating the blood flow, acting as an osmolyte, and controlling ions transport, are attributed to TAU in the kidneys. Besides, many investigations revealed that TAU could provide several pharmacological roles in renal disorders. It has been found that the antioxidant properties of TAU, its effects on processes such as the renin-angiotensin system, nitric oxide synthesis, and, most importantly, the regulation of mitochondrial function in the kidney could play a fundamental role in the pharmacological effects of this amino acid in the kidney. The current chapter provides a brief review of TAU's fundamental role in renal function. Then, the beneficial effects of TAU administration in renal disease are highlighted, focusing on the impact of this compound on mitochondria-related mechanisms. The data collected in this chapter might shed light on the potential clinical application of TAU as a safe drug candidate against a wide range of renal diseases.

Keywords: Chronic renal damage, Energy metabolism, Kidney disease, Renal injury.

INTRODUCTION

Taurine is mainly excreted in urine as an intact molecule [1, 2]. Actually, the kidney regulates the body's TAU pool. On the other hand, several vital processes are also regulated by TAU in the kidney [1, 3 - 7]. Some examples of TAU's action in the kidneys are regulating the blood flow, acting as an osmolyte, and controlling ions transport [1]. Kidneys profoundly regulate TAU homeostasis [1]. There are a plethora of investigations on the identification of transporters responsible for renal TAU excretion/reabsorption [1]. On the other hand, several physiological roles have been identified for TAU in the kidney [1, 4, 8 - 10]. The osmoregulatory properties of TAU are the best-known physiological role of this compound in the kidney [1].

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There are a plethora of investigations regarding the renoprotective properties of TAU [5, 11 - 15].

The antioxidant properties of TAU are another exciting feature of this amino acid in renal disease [11, 12, 14 - 18]. These studies noted robust effects of TAU in mitigating biomarkers of oxidative stress in the renal tissue [11 - 18].

The direct effect of TAU on reactive species is also an old concept believed to be responsible for the protective properties of this amino acid [19]. However, more studies revealed that TAU is a weak radical scavenger and practically reacts with no primary ROS forms [20].

An exciting and widely acceptable mechanism for the antioxidant properties of TAU in the kidney and many other organs is supposed to be mediated through the effects of this amino acid on mitochondrial function [21]. In this regard, a plethora of investigations mentioned that TAU supplementation improved mitochondrial indices of functionality and, more importantly, decreased mitochondria-facilitated ROS formation and oxidative stress. An essential part of the current chapter is devoted to the effects of TAU on renal mitochondria and its relevance to managing human renal disease.

THE CRITICAL ROLE OF CELLULAR MITOCHONDRIA AND ENERGY METABOLISM IN THE KIDNEY

Renal tissue consumes a tremendous amount of energy daily. Most of the ATP consumed by the kidney is used for the reabsorption of infiltrated chemicals through glomeruli [22]. Many chemicals, including glucose, amino acids, phosphine, vitamins, minerals, and several ions, are reabsorbed in an energy-dependent manner [23 - 26]. Renal tissue contains numerous mitochondria whose proper function guarantees appropriate ATP metabolism and renal function. Na^+/K^+ ATPase pump is an essential component of chemical reabsorption in the kidney [26, 27]. Actually, the Na^+/K^+ ATPase pump produces an electrochemical sodium gradient used for the reabsorption process of other chemicals in the kidney (Fig. **1**). As shown in Fig. (**1**), Na^+/K^+ ATPase pumps Na^+ out of the tubular cells and simultaneously imports K^+ ions into the cell. Both of these pumping gradients are against the concentration gradient of these ions and are energy (ATP) dependent processes (Fig. **1**). In renal cells, the Na^+ electrochemical gradient is used for reabsorption of many chemicals into the bloodstream (Fig. **1**).

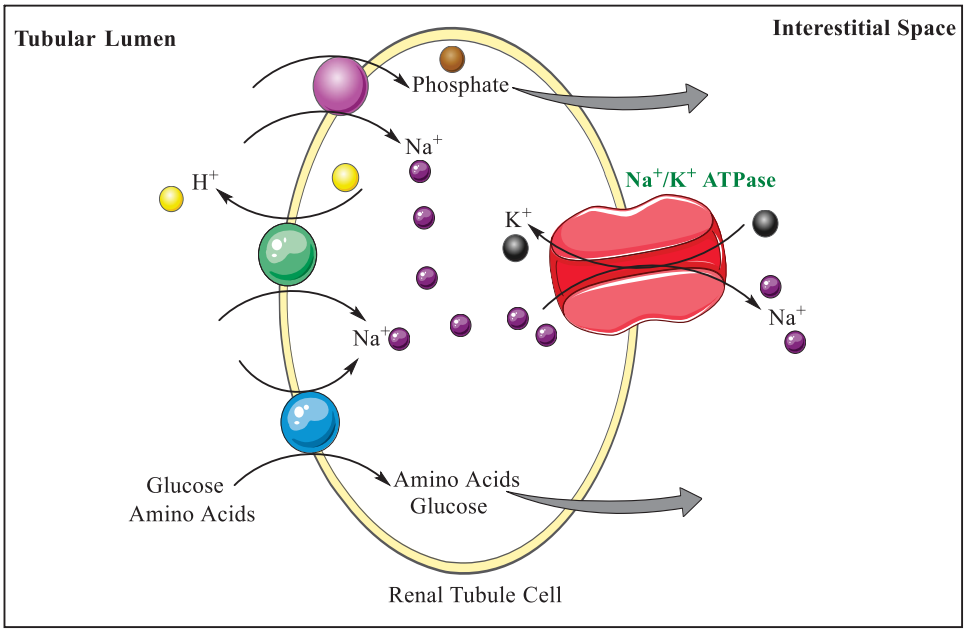

Fig. (1). Schematic representation of the pivotal role of enough ATP level and proper Na^+/K^+ ATPase pump for the reabsorption of chemicals from glomeruli. Any mitochondrial impairment and energy crisis could disrupt this process and lead to deleterious evenest such as essential molecules waste through urine and endangering organisms' life. Renal tissue contains numerous mitochondria that guarantee enough level of ATP required for these processes. Several diseases or xenobiotics could impair mitochondrial function and impair this restorative procedure.

As mentioned, ATP plays a critical role in renal function. In this regard, diseases or xenobiotics that could damage mitochondria could influence renal function and cause deleterious consequences such as body electrolyte disturbances [23, 28 - 33]. Therefore, targeting mitochondria could be a viable therapeutic intervention for many renal disorders.

Since its introduction as a safe and effective therapeutic agent, TAU has positively affected renal function. Most importantly, it has been found that TAU has tremendous effects on renal mitochondrial indices. Hence, this amino acid could be an excellent candidate for managing kidney diseases in clinical stages. In the forthcoming arts, the effects of TAU on renal disorders with a focus on the effects of this amino acid on mitochondrial function are provided.

CHAPTER 9

The Mechanism of Action of Taurine in the Digestive System

Abstract: Several transporters have been identified for taurine (TAU) absorption from the gastrointestinal (GI) tract. The Na^+/Cl^--dependent taurine transporter (TauT) and PAT1 (SLC36A1) are well-known TAU transporters in the GI. These transporters efficiently deliver TAU from GI to the bloodstream. On the other hand, no metabolic pathway has been identified for TAU in the human body. But, it has been found that GI-resident bacteria are able to metabolize TAU to sulfur-containing chemicals (*e.g.*, H_2S). Hence, GI is the primary place for TAU metabolism. TAU-conjugated compounds such as bile acids are also excreted through GI. Compounds such as H_2S could be re-absorbed from GI and have a tremendous physiological effect on other organs (*e.g.*, heart and vessels). Finally, it should be noted that several studies mentioned that TAU could protect GI in various pathological conditions (*e.g.*, xenobiotics-induced GI damage). In the current chapter, a brief review of the absorption, metabolism, and excretion of TAU is provided. Then, the importance of TAU metabolites in the GI and other organs is highlighted. Finally, the effects of TAU on GI complications are discussed, focusing on the effects of this amino acid on oxidative stress biomarkers and mitochondrial impairment. These data could give a new concept of the physiological roles of TAU as well as its effects on GI complications.

Keywords: Absorption, Gastrointestinal disease, Peptic ulcer, Sulfur-containing chemicals, Taurine metabolism.

INTRODUCTION

Taurine (TAU) is readily synthesized from the amino acids methionine and cysteine in the liver of many species (*e.g.*, dogs and rats) [1 - 4]. However, many other species, including humans, depends on the dietary sources of TAU [5 - 8]. TAU is readily absorbed from our gastrointestinal (GI) tract [1]. Some TAU transporters have been identified for TAU in our GI. The SLC35A1 and Na^+/Cl^--dependent transporters are the most investigated TAU transporters in the human intestine [1, 9]. The affinity and capacity of these transporters for TAU are different, but they efficiently transport TAU from the intestine to the bloodstream [1, 9, 10]

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An exciting feature of the connection between TAU and the GI is the metabolism of this amino acid. Actually, no metabolic pathway (enzyme) has been identified for TAU in the human body to date. On the other hand, it is well-known that several GI-resident bacteria are able to metabolize TAU and convert this amino acid into sulfur-containing chemicals [11]. Most interestingly, some of these TAU metabolites, such as H_2Scould have profound biological activities in the GI and may be absorbed into the bloodstream and affect other vital organs [11]. Interestingly, some investigations mentioned that long-term TAU supplementation could change the gut microbiome favoring beneficial microbes and improving GI function [12]. The role of gut bacteria in TAU metabolism and its relevance to human diseases are discussed in the current chapter.

Several studies tested the protective properties of TAU against GI disorders and/or xenobiotics-induced GI injury [13 - 15]. In some cases, it seems that the effects of TAU on mitochondrial function and oxidative stress biomarkers play a role in its positive effects on these disorders. The impacts of TAU on GI disease and xenobiotics-induced GI disturbances are also discussed herein.

TAURINE IN THE DIGESTIVE SYSTEM: ABSORPTION, METABOLISM, AND EXCRETION

As mentioned in previous chapters (refer to chapter one for more information), the capacity of the human liver for TAU synthesis is negligible, and we receive a considerable amount of our body TAU from exogenous sources [3, 5 - 8, 16]. Several transporting systems have been identified in the gastrointestinal (GI) tract for taurine (TAU) absorption. Among these transporters, the Na^+/Cl^--dependent taurine transporter (TauT) and PAT1 (SLC36A1) are well-known transporters identified for TAU absorption from GI [10]. It has been found that TauT has a low capacity but a high affinity for TAU uptake and transport from the small intestine brush border [9]. On the other hand, another TAU transport system has been identified in GI. This transport system has a very high capacity for TAU transport from the GI [9, 17]. Therefore, these transporters, such as TauT and PAT1, are expressed in the intestinal brush border and abundantly found in organs such as the brain, heart, skeletal muscle, reproductive organs, and the liver [9, 18 - 20]. Actually, when TAU reaches the bloodstream by intestinal TauT and PAT1, it is rapidly uptaken by different organs [21, 22]. It has been found that some organs, such as skeletal muscle, express a very high level of TAU transporters [23 - 28]. Thus, it is unsurprising that this tissue contains a massive amount of this amino acid [1, 26, 29, 30]. Other tissues, such as the heart, also express a high level of TAU transporters [27, 31, 32]. Tissues such as the liver have a relatively low level of TAU transporter [2, 33]. As mentioned in Chapter 1, when TAU enters an organ through transporters such as TauT, it compartmentalizes in

various organelles (*e.g.*, mitochondria) and induces physiological/pharmacological actions.

Pharmacokinetic studies have also been conducted on TAU in humans. In a study by Ghandforoush-Sattari *et al.,* the pharmacokinetics of TAU in healthy volunteers was evaluated [34]. They found that the administration of 4 g of TAU solution to fasting volunteers (in the morning) gave a peak plasma of the amino acid, C_{max}) of 86.1±19.0 mg/L after 1.5±0.6 h after TAU administration [34]. They also found that the plasma elimination half-life ($T_{1/2}$) of TAU was 1±0.3h and its clearance/bioavailability was 21.1±7.8 L/h [34]. These pharmacokinetic data are precious for drug development studies and TAU application for therapeutic purposes. In another study by Rodella *et al*., they claimed that TAU is well absorbed in its crystal solution [35]. All these studies give vital clues about TAU formulation for future therapeutic purposes.

An exciting finding of the TAU and GI system relates to TAU metabolism. There is no TAU metabolizing enzyme in human cells. However, TAU is metabolized by gut bacteria to sulfur-containing compounds (Fig. **1**) [11, 36]. TAU acts as an organic sulfonate substrate in the gut [11]. Some gut bacteria have been identified using TAU as a substrate to produce sulfite [11, 36]. Sulfite acts as an electron donor for the anaerobic bacteria to respirate and produce energy [11, 36]. Sulfite respiration (Fig. **1**) is a phenomenon in anaerobic bacteria that finally leads to the release of H_2S [11, 36]. Sulfite is reduced to H_2S by the bacterial sulfite reductase enzyme [11, 36]. The produced H_2S might also be oxidized to bio-sulfur compounds by other sulfide-oxidizing bacteria [11, 36]. Acetaldehyde is another product made by TAU metabolism by gut bacteria (Fig. **1**). It is believed that acetaldehyde is further metabolized to acetyl-CoA by bacterial dehydrogenase enzymes [11, 36] (Fig. **1**).

Interestingly, recent studies identified some bacteria in the human intestine responsible for TAU metabolism [11]. *Bilophila wadsworthia* is an opportunistic pathogen in the human GI [37]. *B. wadsworthia* presents a very low abundance in the healthy human colonic microbiota [37]. The abundance of *B. wadsworthia* is less than 0.01% of whole gut microbiota in healthy subjects [37]. Some investigations revealed that a high level of *B. wadsworthia* in the GI is associated with several human diseases such as appendicitis and colorectal cancer [38, 39]. The conditions such as hypoxia might also increase *B. wadsworthia* population because of the death of other normal flora [37 - 39]. Other microorganisms have also been identified for TAU metabolism and the production of sulfite and H_2S in GI [36]. *Clostridium butyricum* and *Anaerostipes hadrus* are also TAU metabolizing bacteria in the human GI tract [36].

CHAPTER 10

The Role of Taurine in the Reproductive System: A Focus on Mitochondria-related Mechanisms

Abstract: The cytoprotective features of taurine (TAU), including anti-programmed cell death, membrane stabilization, antioxidant, anti-inflammation, osmoregulation, and intracellular calcium homeostasis regulation, have been well addressed in the literature. TAU has also been considered a potent agent for diminishing various xenobiotics-caused by physiological and pathophysiological alterations through its antioxidant action in reproductive and non-reproductive organs. Hence, exogenous TAU administration is the topic of many in-depth investigations. Several studies revealed that the antioxidative effect, anti-cellular death, and anti-inflammatory effects of TAU are involved in inhibiting xenobiotics-induced reproductive toxicity. Hence, the exact targets of TAU during the intracellular routes related to mitochondrial functionality (such as mitochondria-mediated oxidative stress and cell death) triggered by xenobiotics are discussed in this chapter. The data collected in this chapter suggest that TAU could be highly protective against various kinds of xenobiotics-induced gonadotoxicity, spermatotoxicity, and steroidogenotoxicity (hormonal steroids' genotoxicity) *via* its antioxidative, anti-inflammatory, and anti-cell death features. Furthermore, this amino acid also acts as an anti-apoptotic and anti-autophagic molecule by modifying the regulation of some related genes and proteins and inflammatory and mitochondrial-dependent signaling molecules.

Keywords: Antioxidant, Apoptosis, Autophagy, Fertility, Inflammatory response, Oxidative stress.

INTRODUCTION

Having a healthy and efficient reproductive system guarantees the survival of generations of different species. This is also vital in humans. Defects in the reproductive system's function and cumulative damage to the reproductive indices could lead to the birth of babies with various abnormalities. This issue also imposes many social and psychological burdens on families and society. Therefore, identifying the mechanisms of injury of reproductive systems (*e.g.*, induced by diseases or xenobiotics) and using substances that effectively protect the reproductive attributes in both males and females could have tremendous clinical value. Also, finding such materials could be of great importance to developing biological banks for specimens for future applications.

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Mitochondria are vital organelles that control the normal, forward movement of sperm by producing large amounts of energy (ATP). This ensures that sperm reaches the egg cell easily and can fertilize it. On the other hand, humans receive all the mitochondria of their cells (also the sperm mitochondria) from the egg (mother). Therefore, protecting this vital cell could play an essential role in the generation's survival and prevent various abnormalities in human generations.

Taurine (TAU) is a sulfur-containing amino acid that has been extensively researched for its biological effects. In the field of research on the impacts of TAU on the reproductive system, it has been found that this amino acid could robustly protect sperm and eggs against a wide range of xenobiotics or diseases and protect them in both *in vitro* and/or *in vivo* models. It has also been observed that the level of ATP in TAU-exposed sperm is higher than that of control groups. This point could confirm that these sperms could be more efficient in fertilizing eggs. Numerous studies revealed the protective effects of TAU on damage caused by xenobiotics to sperm, eggs, and various components of the male and female reproductive systems. It has also been shown that the administration of TAU could alleviate the damage caused by multiple human diseases.

This chapter discusses the effects of TAU on fertility parameters, sperm and egg health, and finally, the use of this safe substance in treating human fertility disorders. Attempts have been made in different sections to pay special attention to the effect of this amino acid on other mitochondrial functions and their application as potential therapeutic points of intervention.

THE HISTORY OF TAURINE/HYPOTAURINE ON REPRODUCTIVE PARAMETERS

There are two kinds of antioxidants in the reproductive system, including enzymatic and non-enzymatic antioxidants. **A:** Enzymatic antioxidants (natural antioxidants) include glutathione reductase, glutathione peroxidase, catalase, and superoxide dismutase. **B:** Non-enzymatic antioxidants (synthetic antioxidants or dietary supplements) consist of reduced glutathione (GSH), α-tocopherol (vitamin E), β-carotene (carotenoids), urate, ubiquinone, ascorbic acid (vitamin C), selenium, zinc, hypo taurine (hTAU), and taurine (TAU).

The last non-enzymatic antioxidant, TAU (2-aminoethanesulfonic acid; as the most critical intracellular free beta-amino acid), is present in most tissues of mammals. It has been shown that male motile and immotile gametes might contain various intercellular levels of TAU and hTAU. These chemicals' biological and physiological roles through their antioxidant activities have been assessed in the last century [1 - 4]. However, there is a considerable contradiction among these observations. This chapter aims to cover all those discrepancies.

In-depth investigations have recommended that these vital compounds (TAU and hTAU) play a crucial role in spermatozoa physiology, probably through osmoregulation, neurotransmission, and/or ion modulation [5 - 7]. About fifty years ago, considerable concentrations of both TAU and hTAU have been frequently recorded in male and female reproductive-related organs, gametes, and fluids of various species [1, 8 - 14]. However, as mentioned earlier, there are contradictions about their concentrations in these tissues and cells; for instance, the levels of these elements were equal in the gametes extracted from hamsters and guinea pigs [8]. Holmes *et al.* (1992) highlighted the crucial roles of TAU and hTAU in sperm motility and fertility.

They have also shown that male gametes TAU ranged from 17 to 348 nmol/mg DNA, and hTAU was in the range of 0 to 251 nmol/mg DNA, whereas seminal fluid encompassed 319 to 1590 μmol/L TAU, but no detectable hTAU [4]. They also reported that the average level of hTAU in fertile men (n = 8) was higher, four times that of the gametes from infertile men (n = 9), 149 ± 92 nmol/mg DNA as compared with 35 ± 19 nmol/mg, respectively. In their study, the sperm values for TAU were significantly lower in fertile men (83 ± 33 nmol/mg DNA) than in infertile men (168 ± 119 nmol/mg DNA) [4]. In view of seminal fluid TAU levels, the concentrations were identical in both trial studied groups.

On the other hand, a good body of literature demonstrates that among various mammalian tissues, the reproductive-related organs are unique in containing high levels of hTAU [1, 4, 8, 11 - 14]. Finally, Holmes *et al.* (1992) claimed a close and positive relationship between the concentration of hTAU with some sperm parameters, including sperm morphology, motility, and attention [4]. In contrary to the recent popular belief, they claimed these indices were negatively correlated with the sperm concentration of TAU. Fascinatingly, the high levels of hTAU, which varied in a hormone-dependent manner, were also recorded in the oviducts of the ewe [11] and the reproductive fluids of the rodents, monkeys, and cow [8]; which implies the crucial role of hTAU in the reproductive tissues of females as well. To sum up, it sounds that hTAU, a well-known antioxidant, can play a vital role in mitigating oxidative stress action by inhibiting reactive oxygen species (ROS) formation in the male gametes. On the other hand, the higher observed levels of TAU in the infertile men's gametes in their study were interpreted that the recorded abnormalities in sperm parameters might be induced by accelerated oxidation of hTAU to TAU. Several studies have mentioned that hTAU oxidation is involved in the generation of TAU [1 - 3]. This hypothesis is contrary to the views of modern research indicating the high protective role of TAU on reproductive-related parameters [15, 16].

CHAPTER 11

Role of Taurine Supplementation in Obesity: Stimulating Fats to Burn in Cellular Power Plants

Abstract: With changes in lifestyle and eating habits, obesity is a significant health issue, especially in developed countries. Obesity could be induced by an imbalance between energy expenditure and energy intake. Obesity harms several body organs' functions by causing impairments in vital intracellular organelles such as mitochondria. Meanwhile, it has been found that chronic inflammation and oxidative stress could induce mitochondrial impairment in various tissues of obese individuals. On the other hand, it has been revealed that there is a negative correlation between obesity and taurine (TAU) biosynthesis. In the current chapter, we tried to present a good body of evidence on the role of mitochondria in various types of fatty tissues, including white adipose tissues (WAT), brown adipose tissues (BAT), and beige/brite/inducible/brown-like adipose tissues (bAT). We also highlighted the effects of TAU on mitochondria related signaling in adipocytes. The data collected in this chapter could help develop new strategies for preventing and treating obesity and its associated complications.

Keywords: Antioxidant, Lipid peroxidation, Mitochondrial impairment, Oxidative stress, Overweight.

INTRODUCTION

Obesity is a significant health issue worldwide that imposes a considerable cost on the healthcare system annually. It is estimated that the annual fee for obesity-related comorbidities exceeds $150 billion annually in the united states [1]. In 2008, approximately 1.5 billion adults were estimated to have a body mass index (BMI) greater than 25 [2]. Changes in dietary habits, especially in developing countries, lead to the obesity crisis. Consuming many fast foods, fructose, and trans fatty acid-rich diets in combination with decreased physical activity have been identified as contributing factors in the obesity crisis [1].

Obesity is a body mass index (BMI) greater than 30 kg/m^2 [3]. Extremely obese patients have a BMI greater than 40 kg/m^2 [1, 3]. It is well-known that obesity is associated with a higher incidence of significant health complications such as metabolic syndrome, diabetes, cardiovascular disease, and cancer [3]. Hence, obesity is considered a major threat to public health, especially in developed

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countries, and significantly influences people's quality of life [3 - 5]. Based on these data, developing strategies to treat and/or prevent obesity is essential.

Obesity is a chronic condition; thus, managing this complication requires a continuous and integrated approach. The strategies for managing obesity could differ among health care systems worldwide. However, it generally includes changing lifestyle and eating habits and, if necessary, adding medications or even surgical operations [6]. Surgical procedures are often used in morbidly-obese patients [2].

As mentioned, obesity is connected with serious health issues and significantly influences people's quality of life [4, 5]. Several pharmacological interventions have also been developed to manage obesity on overweight. These strategies are usually used as adjuvant therapies when patients' lifestyle changes are insufficient. Most of these medications are centrally-acting agents that affect eating habits (*e.g.*, suppressing appetite). Some other drugs prevent the absorption of food fats. On the other hand, these medications have several adverse effects and low patient compliance. Therefore, finding effective and safe agents to manage obesity is still essential.

Taurine (TAU) is one of the most abundant sulfur-containing free amino acids in various excitable tissues. This amino acid (AA) is evaluated as 0.1% of the total live bodyweight [7], obtained from two sources, including extracellular resources (*i.e.*, active uptake from the diet) and intracellular resources through biosynthetic routes of other sulfur-containing AAs such as cysteine and methionine. Until today, various functions are considered for this vital AA, including membrane stabilizing properties, anti-inflammatory, and anti-oxidative properties. Meanwhile, it has been well shown that TAU can considerably enhance metabolic-related maladies (through improving insulin resistance to control glucose metabolism) [8]. However, it should be highlighted that TAU, as a component of reformed uridine, has a particular function in conjugating mitochondrial tRNAs for two crucial AAs (*e.g.*, leucine and lysine). Meanwhile, the ameliorative role of TAU in the pathologies of mitochondrial myopathy, lactic acidosis, encephalopathy, stroke-like episodes (MELAS), myoclonic epilepsy, and ragged-red fiber syndrome (MERRF) has been well reported. TAU also mitigates plasma and liver cholesterol levels caused by high energy/cholesterol foods, possibly related to bile acid homeostasis [9 - 13].

In the current chapter, the efficacy of the amino acid TAU on several parameters involved in fatty acid metabolism focuses on the effect of this amino acid on mitochondrial function in various forms of fat tissue. Several clinical trials revealed that TAU could control obesity with no significant adverse effects.

TYPES OF ADIPOCYTES AND THEIR RELEVANCE TO ENERGY METABOLISM AND STORAGE

Generally, mammals have two types of adipose tissues with opposite functions, including white adipose tissue (WAT) and brown adipose tissue (BAT). In another classification, three types of fat cells, adipocytes, have been identified in the human body [14, 15]. White, brown, and beige/brite/inducible/brown-like adipocytes form adipose tissue, abbreviated to WAT, BAT, and bAT, respectively [14, 15]. Different adipocytes' morphological and functional activity and their role in the development of obesity and the weight loss process are different [14, 15]. For instance, emerging evidence from the literature demonstrated a close relation between BAT activation and further physiological alterations (*i.e.*, a significant decrease in blood sugar content resulting in an increment of resting energy expenditure and consequently reduced weight).

The WAT is the energy-storing tissue [15] and saves extra energy as a form of triglyceride (TG). This type of adipocyte could go under the “browning” process by different stimuli and produce BAT [15, 16].

As mentioned above, BAT has an opposite function compared to WAT. The BAT is specified in the overindulgence of energy by generating heat to keep the body's temperature and energy consumption. Different stimulations, such as thermal changes, hormones, and cytokines, could cause BAT production [15, 17]. The BAT is a fatty tissue that expends energy and is considered the central place of non-shivering thermogenesis in mammals [15, 17]. Some in-depth animal studies claimed that the thermogenic activity of this type of fatty tissue might protect against obesity. Humans have shown that BAT primarily comprises these inducible adipocytes in adults. However, new studies claimed the classical BAT persistence in certain anatomical spots. Hence, they showed that BAT activity might be negatively related to obesity. The brown-like adipose tissue is formed within WAT after browning and is called bAT (beige/brite/inducible/brown-like adipocytes) [17] and emerges in reaction to particular environmental signals. The bAT has the agonistic functions of BAT and the antagonistic roles of WAT [18]. In general, bAT acts as WAT; nevertheless, as soon as the body receives the signal that heat production is required *via* energy consumption (such as cold stimulation), this type of adipocyte exhibits a function and morphology like those in BAT [19].

WAT contains a large amount of lipid, usually a single droplet, which occupies a large proportion of cell volume [15, 17] (Fig. **1**). However, it should be highlighted that a few numbers mitochondria are found in WAT. On the other hand, the number of mitochondria in BAT is very high, and the size of lipid

CHAPTER 12

The Importance of Appropriate Taurine Formulations to Target Mitochondria

Abstract: As repeatedly mentioned in the current book, taurine (TAU) is a very hydrophilic molecule. Hence, the passage of this amino acid through the physiological barriers (*e.g.*, blood-brain barrier; BBB) is weak. In this context, experimental and clinical studies that mentioned the positive effects of TAU on CNS disorders administered a high dose of this amino acid (*e.g.*, 12 g/day). For example, in an animal model of hepatic encephalopathy, we administered 1 g/kg of TAU to hyperammonemic rats to preserve their brain energy status and normalize their locomotor activity. In some cases, where anticonvulsant effects of TAU were evaluated; also, and a high dose of this amino acid was used (150 mg/kg). In other circumstances, such as investigations on the reproductive system, the blood-testis barrier (BTB) could act as an obstacle to the bioavailability of TAU. On the other hand, recent studies mentioned the importance of targeted delivery of molecules to organelles such as mitochondria. These data mention the importance of appropriate formulations of this amino acid to target brain tissue as well as cellular mitochondria. Perhaps, TAU failed to show significant and optimum therapeutic effects against human disease (*e.g.*, neurological disorders) because of its inappropriate drug delivery system. Therefore, targeting tissues such as the brain with appropriate TAU-containing formulations is critical. The current chapter discusses possible formulations for bypassing physiological barriers (*e.g.,* blood-brain barrier; BBB or BTB) and effectively targeting subcellular compartments with TAU. These data could help develop effective formulations for managing human diseases (*e.g.*, CNS disorders or infertility issues in men).

Keywords: Amino acid, Drug delivery, Drug therapy, Mitochondria, Mitochondria-targeted antioxidants, Oxidative stress.

INTRODUCTION

As mentioned in several parts of this book, studies on the therapeutic potential of TAU against various human disorders usually administered very high doses (*e.g.*, 6-12 g/day) of this amino acid [1 - 4]. On the other hand, it is well known that TAU transporters such as TauT effectively facilitate the uptake of this amino acid by organs such as the skeletal muscle and the heart [5 - 11]. However, as TAU is a very hydrophilic compound, its transport to tissues with physiological barriers

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(*e.g.*, brain and testis) could be complex. Interestingly, the investigations that used very high doses of TAU were those conducted on CNS complications (*e.g.*, seizure) [12 - 14].

Another critical issue after increasing TAU's tissue (cellular) level is its appropriate mitochondria targeting. As mentioned in different chapters of this book, the acceleration of mitochondria-mediated ROS generation, decreased oxidative phosphorylation, and reduced ATP metabolism play a pivotal role in the pathogenesis of many human diseases [15 - 19]. These events could be related to a disturbed mitochondrial redox environment, indicating that endogenous mitochondrial antioxidants are insufficient to encounter excess ROS [15 - 19]. Many studies show that TAU effectively decreases mitochondria-mediated ROS formation and improves mitochondria antioxidant capacity [20 - 43]. Moreover, as noted in previous chapters, TAU acts as a buffering agent for the mitochondrial matrix [44, 45]. It is well-known that the activity of many mitochondria-embedded enzymes involved in energy metabolism is significantly increased by TAU [33, 45]. TAU also enhanced mitochondrial membrane potential ($\Delta\Psi_m$), a driving force for ATP metabolism [20 - 31, 42, 46 - 49]. It is also well-known that TAU robustly inhibits mitochondria-mediated cell death by preventing the induction of mitochondrial permeabilization [50]. All these data indicate that TAU should be effectively targeted to mitochondria; thus, the maximum benefit of this precious amino acid will be achieved in managing mitochondria-related disorders.

In the following parts, some novel strategies for targeting mitochondria are explained, and their relevance to the delivery of TAU to mitochondria is highlighted.

THE IMPORTANCE OF ENHANCING TAURINE BIOAVAILABILITY IN SPECIFIC ORGANS

As repeatedly mentioned in the current book, the passage of taurine (TAU) through physiological barriers such as BBB and BTB is challenging due to its hydrophilicity feature [51, 52]. BBB acts as a solid and selective interface between systemic blood flow and neuronal extracellular fluids (Fig. **1**). Therefore, this barrier regulates CNS homeostatic microenvironment [53 - 57]. Several cell types, including tight junctions between the endothelial cells and the interplay between astrocytes, podocytes, and vascular endothelial cells, form the basics of BBB (Fig. **1**). An intact and functional BBB guarantees the normal physiological function of the CNS [53 - 57] (Fig. **1**). BBB acts as a barrier for hydrophilic drugs in the drug delivery system that affects the brain function, and cellular gene expression, protecting many other organs and targeting mitochondria [58 - 77].

This issue highlights the necessity of designing therapeutic strategies for delivering drugs to the CNS to manage a wide range of CNS disorders.

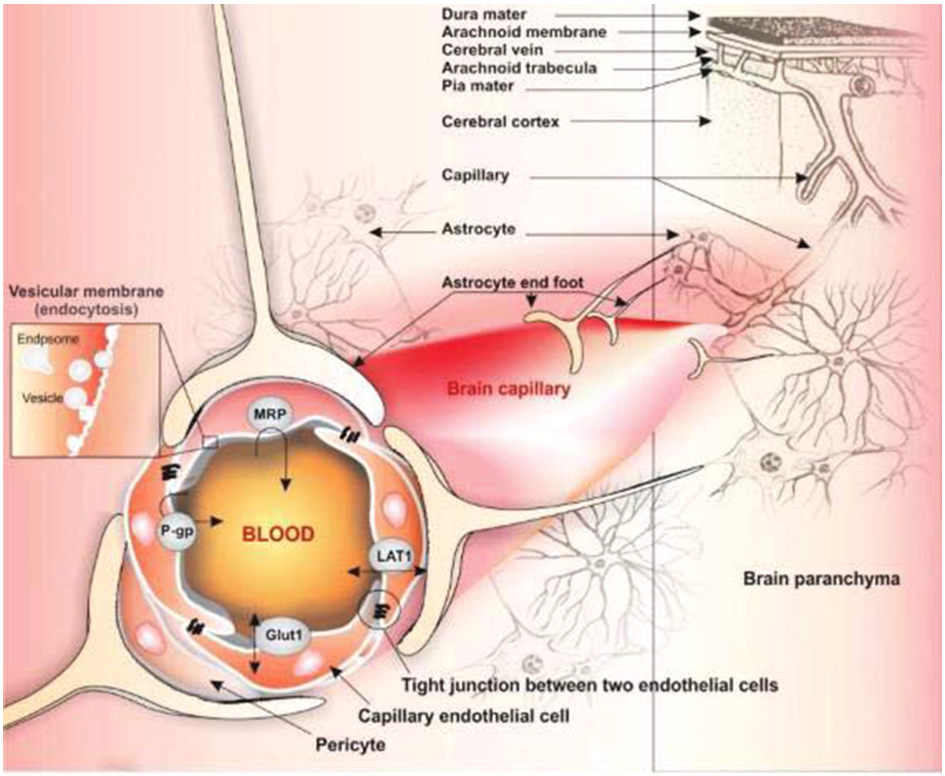

Fig. (1). Schematic representation of blood-brain barrier (BBB). Various cells are involved in BBB and prevent the entry of molecules (*e.g.*, very hydrophilic molecules) into the brain. Designing appropriate formulations of very hydrophilic drugs such as taurine could enhance its delivery to the CNS. MRP: multidrug resistance protein; LAT1: Large amino acid transporter; P-gp: P-glycoprotein; Glut1: Glucose transporter 1. Note: This figure is adapted from " [86]" (CC-BY license).

Several formulations have been designed in the context of bypassing BBB to deliver drugs to the CNS [55, 78 - 85] (Fig. **2**). Nanogels, liposomes, nano-capsules, neosomes, micelles, and nano-spheres are among the most-applied formulations for drug delivery to the CNS [55, 78 - 84] (Fig. **2**). It has been found that these formulations could effectively bypass the BBB and significantly increase the CNS level of drugs [55, 78 - 84]. Therefore, these drug delivery systems could be applied to effectively deliver a significant amount of TAU to the CNS by administrating lower doses of this amino acid (Fig. **2**). Further research on novel TAU formulations could help develop therapeutic strategies to manage a wide range of CNS disorders.

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