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Invited Review

# Prophylactic role of taurine and its derivatives against diabetes mellitus and its related complications

Poulami Sarkar, Priyanka Basak, Sumit Ghosh, Mousumi Kundu, Parames C. Sil*

*Division of Molecular Medicine, Bose Institute, P-1/12, CIT Scheme VII M, Kolkata-700054, India*

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ABSTRACT

Taurine is a conditionally essential amino acid present in the body in free form. Mammalian taurine is synthesized in the pancreas via the cysteine sulfinic acid pathway. Anti-oxidation and anti-inflammation are two main properties through which it exerts its therapeutic effects. Many studies have shown its excellent therapeutic potential against diabetes mellitus and related complications like diabetic neuropathy, retinopathy, nephropathy, hematological dysfunctions, reproductive dysfunctions, liver and pancreas related complications etc. Not only taurine, a number of its derivatives have also been reported to be important in ameliorating diabetic complications. The present review has been aimed to describe the importance of taurine and its derivatives against diabetic metabolic syndrome and related complications.

## 1. Introduction

Diabetes mellitus refers to a group of metabolic disorders characterized by high blood sugar level over a prolonged period of time with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action or both (American Diabetes Association, 2014). According to WHO, it is the most common endocrine disease and in 2014 about 422 million people suffered from it worldwide. About 43% of all deaths occur due to high blood glucose before the age of 70 (WHO, 2016). Diabetes is classified into different categories. Among them, Type 1 diabetes mellitus (T1DM) or insulin dependent diabetes mellitus (IDDM) (formerly known as juvenile diabetes) and Type 2 diabetes mellitus (T2DM) or non-insulin dependent diabetes mellitus (NIDDM) (formerly known as adult diabetes) are the main types. T2DM encompasses the most prevalent form of the disease. Gestational diabetes, protein-deficient pancreatic diabetes, impaired glucose tolerance and drug-induced diabetes are other minor types of diabetes (American Diabetes Association, 2014). Owing to the overwhelming occurrence of diabetes worldwide, the quest for hypoglycemic agents with ameliorative effects and minimal adverse effects has become a necessity as the antihyperglycemic drugs popular in the market are beset with various significant side effects (Bhattacharya et al., 2013; Manna et al., 2009b, 2010b; Manna and Sil, 2012; Pal et al., 2014; Rashid and Sil, 2015a, b). As diabetes is always accompanied with an increased production of free radicals, especially reactive oxygen species (Santos-Silva et al.) and weak antioxidant defenses (Chowdhury et al., 2016a; Ghosh et al., 2017, 2015a, 2015b; Rashid et al., 2017), a new therapeutic vision through antioxidant supplementation is popular now-a-days (Das and Sil, 2012; Manna et al., 2009a, 2010a, b; Pal et al., 2014).

Taurine is widely distributed in animal tissues and is also an important naturally occurring antioxidant. It is a major constituent of bile and can also be found in the electrically excitable tissues (heart and brain), retina, platelets, large intestine and secretary structures

*Abbreviations:* ACC, Acetyl-CoA carboxylase; AChE, acetylcholinesterase; AIF, apoptosis-inducing factor; AMPK, AMP-activated protein kinase; ATF, activating Transcription Factor; CHOP, CCAAT/Enhancer-Binding Protein Homologous Protein; CYP17, cytochrome P450 17-hydroxylase; CYP2E1, Cytochrome P450 2E1; DKA, diabetic ketoacidosis; FOXO1, Forkhead box protein O1; GABA, gamma-aminobutyric acid; $GABA_AR$, $GABA_A$ receptor; GAD, glutamate decarboxylase; GAD, glutamic acid decarboxylases; GHb, glycated hemoglobin; GLAST, glutamate transporter; GLUT, glucose transporter1; GnRH, gonadotropin-releasing hormone; GPBAR, G protein-coupled bile acid receptor; GRP78, 78 kDa glucose-regulated protein; GS, glutamine synthetase; GSh-Px, glutathione-peroxidase; GSIS, glucose-stimulated insulin secretion; HDL, high density lipoprotein; HO-1, heme Oxygenase-1; HRMEC, human retinal microvascular endothelial cells; ICAM-1, intercellular adhesion molecule-1; iNOS, inducible nitric oxide synthase; INS, insulin-secreting cell lines; JAK, Janus kinase; lncRNA TGU1, Long noncoding RNA taurine-upregulated gene 1; LOX-1, lipoxygenase-1; LPO, lactoperoxidases; MafA, v-maf musculoaponeurotic fibrosarcoma oncogene family, protein A; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MPC, model predictive control; mTOR, mammalian target of rapamycin; NeuroD, neurogenic differentiation; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B; Ngn3, neurogenin 3; NKHS, nonketotic hyperosmolar syndrome; NMDA, N-methyl D-aspartate; nNOS, neuronal nitric oxide synthase; Nrf2, Nuclear factor (erythroid-derived 2)-like 2; OLETF, Otsuka Long-Evans Tokushima fatty; PKB, Protein Kinase B; $PPAR\gamma$, Peroxisome proliferator-activated receptor γ; SST, somatostatin; STAT, signal transducer and activator of transcription; TauT, taurine transporter; TRPM, transient receptor potential ion channels ("M" stands for "melastatin"); TSH, thyroid stimulating hormone; TUDCA, tauroursodeoxycholic acid; VCAM-1, vascular cell adhesion molecule-1

* Corresponding author. Division of Molecular Medicine, Bose Institute, P-1/12, CIT Scheme VII M, Kolkata-700054, West Bengal, India.
*E-mail addresses:* parames@jcbose.ac.in, parames_95@yahoo.co.in (P.C. Sil).

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(Huxtable, 1992). It is a conditionally essential amino acid and occurs in the body as a free molecule or in simple peptides (Lodish et al., 1995; Stapleton et al., 1998). It accounts for upto 0.1% of the total weight of the human body (Oudit et al., 2004). It exhibits several important biological functions, such as, osmoregulation, membrane stabilization, modulation of calcium signaling neurotransmission along with anti-apoptotic and antioxidant activity which are emphasized by different studies (Sirdah, 2015). Taurine and its different derivatives also exert protective effect against oxidative stress and various chemical toxin induced pathophysiological conditions as well as hyperglycemia and related complications (Chowdhury et al., 2016b; Das et al., 2012a, b, 2011; 2010a, b, c, 2009a, b, 2008; Das and Sil, 2012; Ghosh et al., 2009, 2014; Sinha et al., 2008).

This review provides new insights and information related to the latest developments in the expedition for understanding the ameliorative role of taurine and its derivatives on diabetic complications.

## 2. Structure and biosynthesis of taurine

Taurine is a byproduct of the sulphurous amino acids cysteine and methionine. Contrary to common belief, it is in itself not an amino acid in the scientific sense, as it does not contain a carboxyl group. It is, therefore, in fact an amino sulphonic acid. As it is not incorporated into the structural building blocks of protein, it is a lesser-known amino acid (Lodish et al., 1995; Ripps and Shen, 2012; Stapleton et al., 1998) (Fig. 1).

The main sources of taurine in vivo are dietary intake and biosynthesis. Endogenously it is derived from cysteine. Mammalian taurine is synthesized in the pancreas via the cysteine sulfinic acid pathway (Jurkowska et al., 2015) (Fig. 2). Endogenous production of taurine is insufficient, so the main source is diet which includes sea foods, meats etc (Sirdah, 2015). It is present in human breast milk in large quantity and is beneficial in infant brain and retinal development (Das et al., 2012b).

## 3. Effect of taurine on diabetes induced metabolic disorders

Taurine deficiency can lead to various tissue dysfunctions which may be the cause of diabetic complications of related tissues (Ito et al., 2012). Several studies have proved that taurine has high potentiality to prevent the progression of diabetic and related metabolic complications, in both type 1 and type 2 diabetes mellitus (Chen et al., 2016; De la Puerta et al., 2010; Fatma El Zahraa et al., 2012; Foda et al., 2016; Imae et al., 2014; McCarty, 2017). According to Santos-Silva et al., taurine supplementation helps in maintaining glucose homeostasis by preventing insulin and glucagon hypersecretion and by controlling α, β and δ cells in genetic obese mice (Santos-Silva et al., 2015). It also has a potent hypoglycemic effect upon glucose homeostasis (Das et al., 2012c). It exerts insulin-like action which enhances glycolysis and glycogenesis (Lampson et al., 1983). Diminished rate of renal gluconeogenesis (Winiarska et al., 2009) and inhibition of oxidative stress (Verzola et al., 2002) can be responsible for its hypoglycemic effect. Study by Cappelli et al. have shown that improvement of taurine induced liver insulin signal transduction and enhancement of whole body glucose tolerance in obese malnourished mice is associated with redox balance and protein phosphatases activity modulation (Cappelli et al., 2014). Translation from autologous adipose derived mesenchymal stem cells (ADMSCs) to islet like cell aggregates (ICAs) is a potential

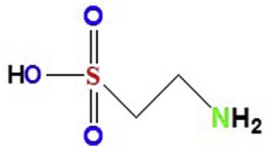


**Fig. 1.** Structure of taurine.

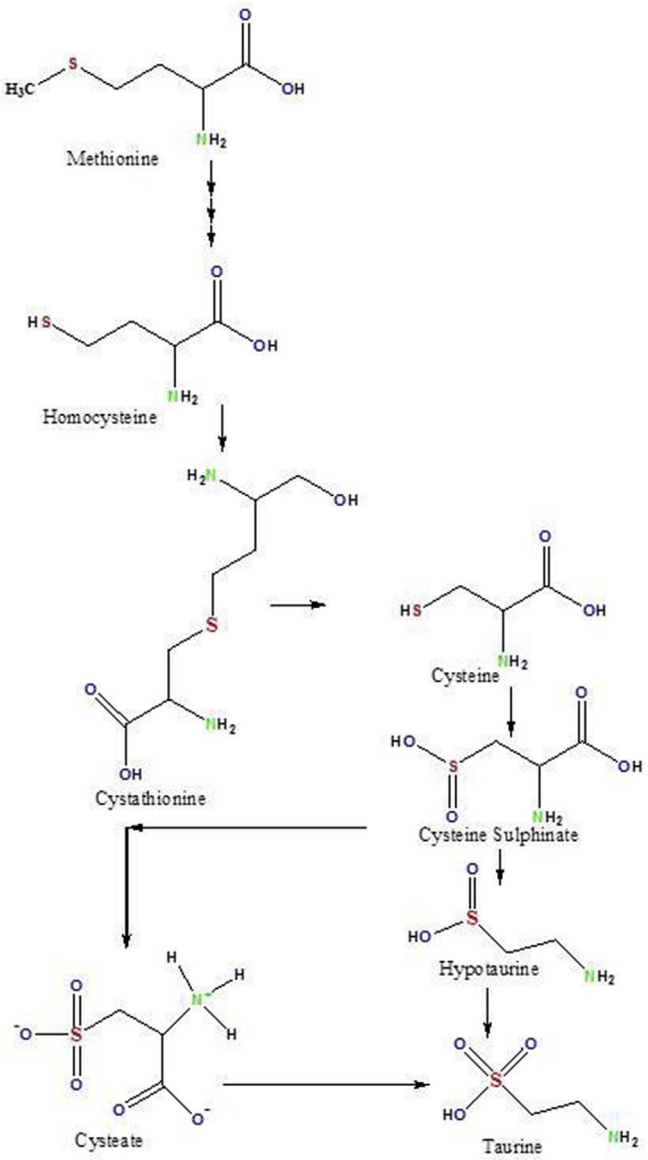


**Fig. 2.** Biosynthesis of taurine.

therapeutic approach against type I diabetes. Taurine produces a large amount of ICA, leading to better glucose control (Thadani et al., 2017).

Another study with taurine transporter knockout mouse model has shown that taurine depletion causes enhanced glucose disposal despite lowering insulin levels and low body weight. Thus taurine is important in maintaining normal metabolism and energy production (Ito et al., 2015). Long term taurine supplementation can also normalize hepatic triglyceride content with improvement in glucose tolerance (Larsen et al., 2013). It enhances the beneficial effects of vanadyl sulfate on the blood glucose and lipid levels in streptozotocin-nicotinamide diabetic rats (Tas et al., 2007). Taurine ameliorates hyperglycemia and dyslipidemia by improving insulin sensitivity and decreasing leptin secretion in Otsuka Long-Evans Tokushima fatty (OLETF) rats with long-term type 2 diabetes (Kim et al., 2012). It acts in the hypothalamus to suppress food intake and locomotor activity and activates signal transduction through the protein kinase B/Forkhead box most important adipostatic messengers, insulin (Solon et al., 2012). Another study by Carneiro et al. have shown that taurine exerts its effect in glucose homeostasis by regulating the expression of genes required for the glucose-stimulated insulin secretion and by enhancing peripheral insulin sensitivity (Carneiro et al., 2009). The exact mechanism of its