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REVIEW ARTICLE

Potential role of taurine in the prevention of diabetes and metabolic syndrome

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Abstract Metabolic syndrome is characterized by the cluster of a number of metabolic abnormalities in the presence of underlying insulin resistance. The prevalence of metabolic syndrome has steadily increased in all populations worldwide. Taurine (2-aminoethanesulfonic acid) is a sulfur-containing amino acid that is involved in a variety of physiological functions. Clinical and experimental studies show that taurine intake may be beneficial in the prevention of metabolic syndrome including diabetes, obesity, dyslipidemia, and hypertension. This article reviews the effect of taurine on all of the components of metabolic syndrome. In addition, the possible mechanisms by which taurine prevents diabetes and metabolic syndrome are also discussed. Further study is needed to determine the role of taurine in the development of metabolic syndrome in humans, because there is presently limited clinical data available.

Keywords Taurine · Diabetes · Metabolic syndrome

Introduction

Taurine is the most abundant (~millimolar concentration) free amino acid and accounts for approximately 0.1 % of total human body weight. Taurine is involved in many fundamental biological functions such as anti-oxidation, Ca^{2+} transport regulation, osmoregulation, and anti-inflammation (Huxtable 1992; Schaffer et al. 2010). In humans, the main source of taurine is diet, and the rate of endogenous synthesis is relatively low. The amount of daily taurine intake is estimated to range from 40 to 400 mg (Wójcik et al. 2010).

Diabetes is a major risk factor for developing cardiovascular disease. Many reports indicate that taurine participates in the development of diabetes. Epidemiological study demonstrated that higher dietary intakes of taurine are associated with lower cardiovascular risks (Yamori et al. 2009). Similarly, plasma taurine concentrations are found to be low in patients with diabetes (Franconi et al. 1995; De Luca et al. 2001), thus suggesting that diabetes can be considered to be a taurine-deficient condition. Taurine deficiency in diabetic patients can be explained by the observation that the intestinal absorption rates of taurine are low and the renal excretion rates of taurine are high in these patients (Merheb et al. 2007). In addition, declines in the taurine levels are observed in the liver of diabetic animals (Nandhini et al. 2005). This can be explained by two published reports, i.e., a report that the activities of taurine transporters are inhibited in high glucose conditions (Shi et al. 2003) and another report which shows intracellular taurine to be depleted in response to the intracellular accumulation of sorbitol (Hansen 2001). Therefore, the bioavailability of taurine is low in patients with diabetes and taurine deficiency may be one reason that diabetes development.

Metabolic syndrome, also called syndrome X or insulin resistance syndrome, is currently receiving considerable attention due to its increasing prevalence. Metabolic syndrome represents a cluster of metabolic disorders that are

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related to the risk of developing cardiovascular disease (Grundy et al. 2004). Diagnostic criteria for metabolic syndrome have been defined by several organizations such as the International Diabetes Federation (IDF), World Health Organization (WHO), and National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III). The common components of these criteria include abdominal obesity, hyperglycemia, dyslipidemia, and hypertension. Insulin resistance, the decreased ability of tissues to respond to insulin, causes glucose/lipid dysmetabolism and blood vessel dysfunction, which thus leads to the development of metabolic syndrome.

The hypoglycemic and anti-metabolic syndrome actions of taurine have been intensely studied in the last few decades. Underlying mechanisms have also been identified. The purpose of this review is to highlight the effects of taurine on the development of diabetes and metabolic syndrome.

Hypoglycemic effects of taurine observed in clinical and animal studies

Type 1 diabetes

The effects of taurine on type 1 diabetes have been reported in clinical and animal studies. In a single-arm clinical trial, supplementation with taurine (0.5 g of taurine twice a day for 30 days) improved carbohydrate metabolism in type 1 diabetic patients who were receiving insulin (Elizarova and Nedosugova 1996). The effects of taurine on type 1 diabetes have also been evaluated in experimental animals. Type 1 diabetes is usually induced by administering either streptozotocin or alloxan, both of which destroy pancreatic β cells. Treatment with taurine has been shown to improve hyperglycemia in streptozotocin-treated rats (Chang and Kwon 2000; El-Batch et al. 2011), alloxan-treated rats (Gavrovskaya et al. 2008; Das et al. 2012), and alloxan-treated rabbits (Tenner et al. 2003; Winiarska et al. 2009). Moreover, taurine has been shown to improve alloxan-induced declines in the number and the size of pancreatic islets (Gavrovskaya et al. 2008).

Type 2 diabetes

Some clinical trials have been conducted to test the hypoglycemic effects of taurine on type 2 diabetes; however, no reports exist that demonstrate such effects in humans (Chauncey et al. 2003; Brøns et al. 2004). On the other hand, the hypoglycemic actions of taurine have been demonstrated in type 2 diabetic animals. In Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model of type 2 diabetes and obesity, supplementation with 3 % taurine in drinking water for 9 weeks ameliorated high blood glucose levels and improved insulin resistance (Harada et al. 2004). Similar results have been demonstrated in rats fed a high-fructose diet. Consuming high doses of fructose leads to glucose intolerance, hyperglycemia, and hyperinsulinemia, while the administration of taurine improves these conditions (Nandhini et al. 2005; El Mesallamy et al. 2010).

Hypoglycemic mechanisms of taurine

Insulin sensitivity and insulin secretion

One clinical study was conducted on overweight/non-diabetic males. In this study, a state of insulin resistance was established by infusing intravenous intralipid (fat emulsion) and heparin. Taurine supplementation at 3 g/day for 2 weeks was found to significantly improve the fatty acid-induced impairment of the insulin sensitivity and beta cell function (Xiao et al. 2008).

Similar results have also been demonstrated in mice supplemented with 2 % taurine in drinking water for 30 days (Carneiro et al. 2009). The taurine-supplemented mice showed low blood glucose levels, and taurine supplementation enhanced both basal and insulin-stimulated tyrosine phosphorylation of the insulin receptors in the skeletal muscle and liver. The mice in both groups showed glucose-induced insulin release; however, the mice in the taurine group showed higher levels of insulin secretion compared with that in the control group. The expression levels of the genes involved in the stimulus secretion of insulin, i.e., glucose transporter 2 (Glut-2), glucokinase, sulfonylurea receptor-1, and pancreatic duodenal homeobox-1 (Pdx-1), were also elevated in the mice of the taurine group.

The mechanisms underlying the improvement of peripheral insulin sensitivity have been analyzed by several groups. For example, the improving effects of taurine on hepatic insulin sensitivity have been demonstrated by Wu et al. (2010). In this study, rats were injected with intralipid and heparin to induce insulin resistance, and the effects of taurine on insulin signal pathways were analyzed. The infusion of intralipid and heparin created an insulin-resistant state, i.e., increased levels of Jun N-terminal kinase 1 (JNK-1) and insulin receptor substrate 1/2 (IRS-1/2) serine phosphorylation and reduced levels of IRS-1/2 tyrosine and Akt serine phosphorylation. Supplementation with taurine improved these states of deteriorated phosphorylation. Other papers have shown that taurine supplementation stimulates glycogen synthesis in the liver and glucose uptake in peripheral tissues such as the liver and skeletal muscle (Kulakowski and Maturo 1984; Haber et al. 2003).

Moreover, taurine supplementation has been shown to enhance glucose uptake in response to insulin in vitro studies (Lampson et al. 1983; Ragheb et al. 2009). In this way, taurine improves insulin resistance in peripheral tissues and throughout the entire body. Maturo and Kulakowski (1988) has reported that taurine specifically and reversibly binds to purified human insulin receptor, which suggests that taurine may improve the insulin resistance by the direct interaction with insulin receptor.

Meanwhile, the effects of taurine on insulin secretion have also been studied in several groups. Intravenous infusion of oleate in rats has been shown to decrease glucose-induced insulin secretion, and the protective effects of co-infusion of taurine have been observed (Oprescu et al. 2007). A similar effect of taurine is also observed in MIN6 pancreatic β cells, which may be mediated by the anti-oxidant properties of taurine (Oprescu et al. 2007). On the other hand, the stimulatory effects of taurine on insulin secretion have also been observed in conditions that are independent of oxidant states (Cherif et al. 1996). This can be explained by the observation that taurine inhibits ATP-sensitive K^+ channels by interacting with the benzamido-binding sites of sulfonylurea receptor 1 in β cells (Park et al. 2004). These results suggest that the hypoglycemic properties of taurine are mediated by the modulation of insulin sensitivity and insulin secretion.

Anti-oxidation

Oxidative stress results from the increased generation of reactive oxygen species (ROS) and is involved in the pathogenesis of diabetes through the induction of pancreatic β cell dysfunction and insulin resistance (Lamb and Goldstein 2008). Mitochondria are the major source of ROS, and leakage of superoxide during the process of mitochondrial respiration is a trigger for the development of diabetes (Victor et al. 2011). Taurine has been shown to inhibit lipid peroxidation in genetically hyperlipidemic animals including apoE-deficient mice (Kondo et al. 2002) and Watanabe heritable hyperlipidemic (WHHL) rabbits, a model of human familial hypercholesterolemia (Murakami et al. 2002a). As mentioned above, taurine improves β cell dysfunction through the anti-oxidant property (Oprescu et al. 2007).

The inhibition of mitochondrial superoxide generation by taurine has been reported in mice, thus suggesting that the anti-oxidant properties of taurine are mediated by mitochondrial pathways (Parvez et al. 2008). The molecular mechanisms involved in this process have been evaluated in in vitro studies by depleting mitochondrial taurine levels. The depletion of taurine in mitochondria causes a decline in the biosynthesis of mitochondrial-encoded proteins ND5 and ND6, which leads to the impairment of complex I and III activities. The reduction of complex I and III activities results in the excess production of superoxide (Jong et al. 2012). Moreover, it is speculated that the first step of the ROS-generating process is mediated by the modification of mitochondrial tRNA by taurine, according to a report that taurine is directly incorporated into mitochondrial tRNA (Suzuki et al. 2002). The lack of taurine incorporation leads to a decline in mitochondrial-encoded protein synthesis (Kirino et al. 2004). Therefore, taurine functions as an indirect anti-oxidant which may help to prevent diabetes.

In addition to hypoglycemic effect, taurine has been shown to ameliorate diabetic complications such as diabetic nephropathy, retinopathy, and neuropathy (Hansen 2001; Ito et al. 2011). Taurine supplementation attenuates renal damages and suppresses the increase in blood urea nitrogen (BUN) and serum creatinine in diabetic rats (Wang et al. 2008). Taurine improves the increase in glia fibrillary acid protein (GFAP), a marker of gliosis, in retina (Zeng et al. 2009). Taurine attenuates hyperalgesia and abnormal calcium signaling in sensory neurons of diabetic rats (Li et al. 2005). It is well documented that oxidative stress is the initiator of the development of diabetic complications (Brownlee 2001). The beneficial effects of taurine on diabetic complications have been accompanied by improvement of oxidative status (Li et al. 2005; Wang et al. 2008; Zeng et al. 2009). Therefore, anti-oxidant action may be involved in the prevention of diabetic complications by taurine.

Anti-inflammation

Inflammation is considered to be the root cause of diabetes, i.e., the destruction of pancreatic β cells by inflammatory processes (type 1 diabetes) and the infiltration of macrophages into adipose tissue participates (type 2 diabetes) (González-Chávez et al. 2011).

Taurine reacts with hypochlorous acid to produce taurine chloramine which exhibits anti-inflammatory activities. Taurine chloramine suppressed the secretion of TNF-α and monocyte chemoattractant protein 1 (MCP-1) expression levels and inhibits the activity of NF-κB, a key factor in inflammation pathways (Park et al. 1993; Liu and Quinn 2002; Barua et al. 2001). There is no direct evidence from in vivo studies that taurine improves diabetes through anti-inflammatory actions; however, it is possible that taurine chloramine improves diabetes by attenuating the destruction of pancreatic β cells (type 1 diabetes) or by suppressing macrophage activity (type 2 diabetes).

Improvement of metabolic syndrome

Metabolic syndrome is a cluster of risk factors that include abdominal obesity, dyslipidemia, hypertension, and

diabetes. The WHO-CARDIAC study, a worldwide cross-sectional epidemiological survey, demonstrated that high urinary taurine levels, as a marker of the dietary taurine intake, are associated with low values of body mass index (BMI), blood pressure, cholesterol, and atherogenic index, raising the possibility that dietary taurine may thus be important for the prevention of metabolic syndrome (Yamori et al. 2010).

Obesity/dyslipidemia

Taurine has been demonstrated to have beneficial effects on obesity and lipid profiles in clinical trials. The administration of 3 g of taurine per day for 7 weeks has been shown to improve plasma triglyceride levels, total cholesterol levels, body weight, and atherogenic index in overweight/non-diabetic subjects (Zhang et al. 2003). Mizushima et al. (1996) also demonstrated the hypolipidemic effects of taurine. In this study, healthy young men were given experimental high-fat and high-cholesterol diets for 3 weeks. Six grams per day of taurine was administered and the subjects' lipid profiles were analyzed. Taurine supplementation attenuated the elevation of total cholesterol and LDL cholesterol levels induced by the experimental diet.

The anti-obesity effects of taurine have also been demonstrated in genetically diabetic KK mice (Fujihira et al. 1970), OLETF rats (Harada et al. 2004), and high-fat diet fed rats (Tsuboyama-Kasaoka et al. 2006). A mechanism speculated to be involved in the anti-obesity effects of taurine is the enhancement of oxygen consumption rates. Dietary taurine has been shown to induce the expression levels of energy expenditure-related genes such as transcription factors (PPAR α, PPAR γ, PGC-1 α and nuclear respiratory factor 2α) and their target genes (lipoprotein lipase, acyl-coA oxidase, acyl-CoA synthetase and medium-chain acyl-CoA dehydrogenase) in adipose tissue (Tsuboyama-Kasaoka et al. 2006). Similarly, Pina-Zentella et al. (2011) also reported that taurine enhances lypolysis rates in isolated adipocytes by stimulating protein kinase A (PKA) activity.

The hypolipidemic effects of taurine have also been investigated in stroke-prone spontaneously hypertensive rats (SHRSP) fed a high-cholesterol diet (Murakami et al. 1996), a high-cholesterol diet mice (Chen et al. 2004), rats fed a high-cholesterol diet (Choi et al. 2006), and ovariectomized rats (Kishida et al. 2003). Many mechanisms underlying the hypocholesterolemic effects of taurine have been demonstrated. In rats fed a high-cholesterol diet, the expression level of CYP7A1, the rate-limiting enzyme of bile acid synthesis, is upregulated by taurine and the fecal excretion of bile acid is increased (Murakami et al. 1996; Yokogoshi et al. 1999). Enhancement of cholesterol 7α-hydroxylase (CYP7A1) mRNA expression by taurine has also been observed in HepG2 cells (Lam et al. 2006). The activation of CYP7A1 decreases the cholesterol pool in liver causing some secondary changes. For example, taurine enhanced the hepatic low-density lipoprotein (LDL) receptor activity and the binding of LDL to LDL receptor (Stephan et al. 1987; Murakami et al. 2002b). Other mechanisms have been reported such as the inhibition of very low-density lipoprotein (VLDL) secretion from the liver (Yamamoto et al. 2000; Chen et al. 2004; Yanagita et al. 2008), the suppression of hepatic acyl-CoA:cholesterol acyltransferase (ACAT) activity (Murakami et al. 1996; Murakami et al. 2002b), and the inhibition of the absorption of bile acid from the intestinal tract (Nishimura et al. 2009). Therefore, taurine improves obesity and dyslipidemia through multiple mechanisms.

Much is understood about the relationship of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) to metabolic syndrome and diabetes. Taurine has been reported to improve NASH and NAFLD in clinical and animal studies (Obinata et al. 1996; Chen et al. 2006). However, the mechanisms underlying the improvement of these diseases are not fully understood and further studies are expected.

Blood pressure

The hypotensive effect of taurine has been widely studied. Treatment with 6 g of taurine administered for 7 days resulted in significant decrease in both systolic and diastolic blood pressure in young patients with borderline hypertension (Fujita et al. 1987). The hypotensive effects of taurine have also been tested in Tibetans. Both systolic and diastolic blood pressures were significantly decreased by consuming 3 g of taurine per day for 2 months (Yamori et al. 1996).

Basic research on the hypotensive effects of taurine has been conducted using spontaneously hypertensive rats (SHR) (Nara et al. 1978), rats fed a high-fructose diet (Nandhini et al. 2004), and deoxycorticosterone acetate (DOCA)-salt hypertensive rats (Sato et al. 1991). Many mechanisms are associated with the hypotensive effects of taurine. The activation of the renin-angiotensin-aldosterone system (RAAS) is the primary event in the development of hypertension (Hsueh and Wyne 2011). Angiotensin II is an important hormone in the RAAS and many drugs that inhibit the angiotensin II activity are used to treat hypertension. Taurine has been demonstrated to antagonize the effects of angiotensin II activity in cell cultures (Takahashi et al. 1997; Azuma et al. 2000).

The renal sympathetic nervous system plays a critical role in the development of hypertension (Malpas et al. 2006). Taurine has been shown to affect the sympathetic

Table 1 The beneficial effects of taurine and its underlying mechanisms

Physiological effect	Mechanisms	Detailed mechanisms
Hypoglycemic action	Improvement of insulin sensitivity	By modulating phosphorylation states of IRS-1, IRS-2, Akt and JNK-1 in peripheral tissues, and/or by interacting with insulin receptor directly (Maturo and Kulakowski 1988; Wu et al. 2010)
	Stimulation of insulin secretion	By upregulating the expression levels of genes involved in the stimulus secretion of insulin, and/or by inhibiting ATP-sensitive K^+ channels (Park et al. 2004; Carneiro et al. 2009)
	Anti-oxidantion	By protecting the mitochondrial excessive superoxide generation through the conjugation with the key uridine moiety of mitochondrial tRNALeu (Jong et al. 2012)
	Anti-inflammation	By suppressing the secretion of diabetes related Cytokines including TNF-α and MCP-1) (Park et al. 1993; Liu and Quinn 2002)
Anti-obesitic action	Enhancement of oxygen consumption rate	By upregulating the expression levels of energy expenditure-related genes in adipose tissue (Tsuboyama-Kasaoka et al. 2006)
Hypolipidemic action	Enhancement of cholesterol degradation	By stimulating the gene expression level of CYP7A1 and bile acid production in the liver (Murakami et al. 1996; Yokogoshi et al. 1999)
	Enhancement of LDL uptake from blood	By stimulating the binding of LDL to LDL receptor and/or by stimulating LDL uptake (Stephan et al. 1987; Murakami et al. 2002b)
	Inhibition of cholesterol release from liver	By enhancing cholesterol elimination from liver, and/or by suppressing the ACAT activity in the liver (Murakami et al. 1996; Yamamoto et al. 2000; Yanagita et al. 2008)
	Suppression of bile acid absorption from intestine	By modulating rate of bile acid conjugation (Nishimura et al. 2009)
Hypotensive action	Suppression of renin-angiotensin-aldosterone action	By antagonizing renin-angiotensin-aldosterone activity through the modulation of calcium homeositasis (Takahashi et al. 1997; Azuma et al. 2000)
	Augmentation of kallikrein activity in blood and peripheral tissues	By upregulating the gene expression level of kallikrein (Ideishi et al. 1994)
	Suppression of renal sympathetic nervous system	By lowering the epinephrine and norepinephrine levels (Yamamoto et al. 1985; Mizushima et al. 1996)
	Diuretic and natriuretic action	By suppressing renin-angiotensin-aldosterone activity, and/or by suppressing renal sympathetic nerve activity (Mozaffari et al. 2006)
	Vasorelaxant action	By opening potassium channel (Niu et al. 2008)

nervous system in animals and humans. For example, taurine suppresses increases in renal sympathetic nerve activity induced by jet-air stress in SHR (Hano et al. 2009). In addition, taurine has been shown to decrease the plasma levels of epinephrine and norepinephrine during short-term shaker stress in SHR (Yamamoto et al. 1985). The clinical study also highlighted the suppressive effects of taurine on the sympathetic nervous system. In this study, healthy volunteers were administrated 6 g of taurine for 3 weeks, and significantly lower levels of urinary norepinephrine excretion were observed (Mizushima et al. 1996).

Water/sodium imbalances in the kidney cause hypertension (Iimura and Shimamoto 1993). Taurine has been shown to have diuretic and natriuretic properties in saline-loaded rats (Mozaffari et al. 2006). Considering that RAAS and renal sympathetic nerve activities are involved in the renal excretion of fluids and sodium (Iimura and Shimamoto 1993), the diuretic and natriuretic properties of taurine may be mediated by the suppression of the RAAS and/or renal sympathetic nerve activity.

Blood vessel reactivity is also associated with hypertension, and taurine has been reported to improve vessel function. In one study, thoracic aortas isolated from rats administered 1 % taurine in drinking water for 8 weeks showed depressed contractile responses to norepinephrine and high potassium nonspecifically, and these responses were partially mediated by the endothelium (Abebe and Mozaffari 2000). In isolated arterial rings, taurine directly relaxes KCl and phenylephrine induced contractions, and that process is ended by potassium channel blocker, tetraethylammonium, suggesting that potassium channel opening may be involved in the vasorelaxant actions of taurine (Niu et al. 2008). Improvement of endothelial dysfunction by taurine has also been observed in a human study (Fennessy et al. 2003). In this study, endothelial function was analyzed using flow-mediated dilatation (FMD), a NO-mediated response. In additional, pretreatment of young smokers with 1.5 g of taurine for 5 days was found to attenuate endothelial dependent vasodilatation. Therefore, the hypotensive effects of taurine are mediated by many mechanisms.

Conclusion

In summary, the beneficial effects of taurine supplementation on diabetes and metabolic syndrome have been reported in several animal models. Multiple mechanisms are reported to be involved (summarized in Table 1). Epidemiological studies also indicated the potential power of taurine to improve diabetes, metabolic syndrome, and cardiovascular events. Nevertheless, the clinical trials conducted to date are very scarce in number and are limited regarding data such as the doses of taurine, the duration of trials, the sample size (power of detection), the severity of diseases, the presence of metabolic syndrome related diseases, the basal level of intake of taurine from foods, the lifestyle factors, and the genetic factors of the subjects. Further studies are needed in which the conditions of the clinical trials are optimized. This will provide important information regarding whether to recommend taurine unequivocally as a nutraceutical for the prevention of diabetes and metabolic syndrome.

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

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