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Is Taurine Beneficial in Reducing Risk Factors for Diabetes Mellitus?*

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Taurine is a semiessential amino acid, and its deficiency is involved in retinal and cardiac degenerations. In recent years, it was found that diabetes mellitus (DM) is associated with taurine, and many *in vivo* experimental studies showed that taurine administration is able to reduce the alterations induced by DM in the retina, lens, and peripheral nerve, although its effects on diabetic kidney are dubious. Interestingly, long-term taurine supplementation reduces the mortality rate in diabetic rats. The mechanisms by which taurine exerts beneficial effects in DM are discussed below. Recently, it has been suggested that taurine deficiency may alter the endocrine pancreas "fetal programming," increasing the risk of insulin resistance in adult life. The bulk of experimental data suggests that taurine administration could be useful in the treatment of type 1 DM and in the prevention of insulin resistance.

KEY WORDS: Taurine; diabetes mellitus; oxidative stress; insulin resistance.

INTRODUCTION

Taurine is a sulphonic amino acid that is present in especially high concentrations in the heart, retina, brain, and skeletal muscle; high levels are also found in white blood cells and platelets (1). The physiological role of taurine has received considerable attention because reports showing that cats fed with a taurine-free diet develop retinal degeneration (1,2). Similar, but less severe, changes have been found in primates raised with taurine-free diet (3); children parentally fed with taurine-free diet developed retinogram alterations that were reversed by taurine administration (4). The importance of this amino acid in retina has been recently confirmed in mice with disruption of the gene coding for Na^+-dependent taurine transporters. In fact, they developed a progressive retinal degeneration (5) together with a marked alteration in reproductive fitness, a lower body mass, and lower tissue taurine levels. The pattern of retinal degeneration resembled that seen in human retinitis pigmentosa. However, in these patients, taurine administration has given contradictory results (6,7). In cats, the deficit of taurine induces also the so-called feline dilated myocardiopathy, which is reverted by taurine administration (8). Cardiomyopathy induced by taurine deficiency is not unique in the cat, because it also has been reported in foxes (1) and in some dogs, such as the American cocker spaniel (9). Interestingly, the heart of depleted rats presents a loss of myofibrillar bundles (10), and this alteration could be the basis of cardiomyopathy seen in deficient animals.

Cats, like humans, have only low levels of the enzyme cysteinsulphinic decarboxylase, which synthesizes taurine *de novo* (1). Nevertheless, in adult humans, unlike cats, are not prone to taurine deficiency because the former have renal and hepatic mechanisms that permit the conservation

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of this amino acid when it is low or absent in the diet (1). However, vegans, patients with Gaucher disease or retinitis pigmentosa, patients receiving long taurine-free parenteral nutrition, and diabetic patients in good metabolic state have low taurine levels (1,11–15). Patients with poorly controlled diabetes mellitus (DM) have a high urinary excretion rate of this aminoacid (16). Although dietary taurine has not been proven to be essential for adult humans, it can be regarded as an essential amino acid during fetal life and in newborns because they have a very low capability, if any, to produce it and conserve it (1,3).

DISCUSSION

Taurine and Glucose Metabolism

In pancreas, taurine is mainly localized in most of glucagons-positive cells and in some somatostatin-positive cells, whereas it is absent in insulin-positive cells (17). The role of taurine in pancreas is not clearly understood. Although a hypoglycemic effect of taurine was firstly seen in the 1930s (16) until the 1990s only few studies investigated the possible role of taurine in the regulation of glucose metabolism (16). The amino acid seems to increase glyconeogenesis, glycolysis, and glucose oxidation and glucose uptake in the liver and heart of adult rats. A few reports indicate that taurine increases insulin activity (16), probably through the binding to insulin receptors (16). However, the effect of taurine on endocrine pancreas appears to be age-dependent because in adults it seems to reduce insulin secretion (14), whereas in fetal pancreas it stimulates the insulin release induced by leucine and arginine (18,19).

Taurine and Diabetes Mellitus

Only recently it has been shown that taurine has beneficial effects in adult experimental models of DM (20–41). In early experimental studies, the beneficial effect of taurine occurs without any significant change in blood glucose. However, two long-term studies showed that taurine supplementation for more than 6 months finally reduced blood glucose levels in streptozotocin rats (42,43). No clear explanations are available for this taurine effect; probably it enhances the spontaneous pancreas regeneration that occurs after the injection of streptozotocin (44). Moreover, in the already mentioned Odetti's study (42), taurine administration does not modify advanced glycosylation end products in kidney and skin (42) and does not reduce glomerulopathy. This is in contrast with other studies that have shown that taurine partially prevents diabetic glomerulopathy (23,45). However, Trachtman et al. (45) showed that taurine failed to inhibit *in vitro* albumin glycation and an inhibitory effect of renal accumulation of advanced glycosylation end products. In the retina of streptozotocin-injected rat the effects of taurine are compared with those of vitamin E plus selenium. Interestingly, the decrease in lipid peroxidation and the preservation of sodium pump activity induced by taurine supplementation are longer-lasting than in vitamin E plus selenium treated groups (40).

Considering that the treatment of diabetic patients leads to a lower incidence of diabetic complications and, ultimately, to a lower mortality, we investigated whether taurine decreases mortality rates in streptozotocin-induced diabetic rats in comparison with vitamin E plus selenium. Whereas supplementation of the latter did not decrease mortality rate, the former significantly increased the survival rate (43). The main cause of mortality and morbidity associated with DM and insulin-resistant state are long-term vascular complications (46); thus taurine could reduce cardiovascular mortality.

Clinically, in insulin-dependent and insulin-independent DM patients, taurine was decreased in plasma and platelets (12–14). In addition, an inverse correlation between the log of plasma taurine and glycosylated hemoglobin has been found (12). Moreover, in insulin-dependent diabetic patients, taurine supplementation decreased platelet aggregability, restored its own plasma and platelet levels (12), and abolished the inverse correlation between log plasma taurine and glycosylated hemoglobin. However, in a double-blind trial of 1-year duration, taurine failed to improve kidney complications associated with type 2 DM (16), which is in accordance with the findings of Odetti et al. (42). Therefore the effect of taurine in DM could be tissue specific.

How Does Taurine Act in Diabetes Mellitus?

Antioxidant Effects of Taurine. Oxidative stress has been implicated in the pathogenesis of many diabetic complications (47), and taurine functions as an antioxidant in many biological systems (1,39–41,45,48–54). The antioxidant effect of this amino acid has been also described in humans, in whom its preoperative administration during myocardial revascularization reduces reperfusion injury (54). Chemically, taurine reacts poorly with superoxide, peroxide, and hydroxyl radicals (55), but it reacts 1:1 with HOCl-generating taurochloramines which are a scavenger of the acid (1,56). Consequently,

taurine reduces the cytotoxicity of HOCl in many cell types (57–60). The direct scavenging properties appear essential, because if taurine is applied after the acid, the damage cannot be reverted, therefore the availability of an HOCl scavenger is useful because hyperglycaemia-mediated vascular inflammation is associated with an increased production of HOCl (61), and because myeloperoxidase has been considered an inflammatory marker in coronary artery diseases (62). However, myeloperoxidase-deficient mice present a 50% elevation in atherosclerotic lesions (63).

In vitro, taurine reacts with aldehydes (64); nevertheless the results of *in vivo* studies are contradictory (22,23,43,65,66). Interestingly, taurine supplementation attenuated the age-related increase of oxidative damage by decreasing carbonyl group production (67). This point requires further investigation because the enhanced formation of glycosylated proteins observed in DM may be the result of an overload of detoxification mechanisms (47); if taurine is a glycation scavenger, the intracellular taurine depletion seen in some tissues could promote the accumulation of reactive carbonyl and advanced glycosylation end products.

The amino acid also seems to have indirect antioxidant effects. In vascular smooth muscular cells, taurine restores the secretion and expression of extracellular-superoxide dismutase by ameliorating endoplasmic reticulum stress induced by homocysteine (68), a well-known risk factor of cardiovascular disease. Moreover, it preserves the intracellular redox state, enhancing the antioxidant activity of other molecules (69). *In vivo* and *in vitro,* taurine is antihypoxic (1,71,72) and this activity may contribute to its beneficial effect in DM. In fact, in the pathogenesis of diabetic complications, the injury related to the mechanism within ischemia-reperfusion perfused and nonperfused tissue seems to play a role in increasing the production of reactive oxygen species (ROS). Finally, taurine attenuates the actions of angiotensin II on Ca^{2+} transport and protein synthesis and reduces angiotensin II signaling, because taurine-depleted animals are more sensitive to the effects of angiotensin II (72,73). Angiotensin II generates ROS (74); thus a reduced activity of angiotensin II may decrease the generation of ROS. In this context, in rat kidney proximal tubular cells, taurine prevents the overexpression of the angiotensinogen gene induced by ROS generated by hyperglycemia (75).

Antiinflammatory Activity of Taurine. Taurine seems to protect against tissue damage induced by inflammation including atherosclerosis (see below). The anti-inflammatory effects depend on tauchloramine (76), which downregulates the expression of some gene products, such as nitric oxide synthase 2, tumor necrosis factor-α, and cyclooxygenase 2, all involved in inflammatory reactions (78–80). Furthermore, tauchloramines affect leukocyte function by inhibiting the oxidative burst and decreasing the release of inflammatory cytokines (78,80–82) and also the production of IL-6 and IL-8 in cells isolated from patients with rheumatoid arthritis (82). In this context, taurine protects against lung injury induced by bleomycin, ozone, and acute NO_2 (83,84) and reduces the damage of ischemia-reperfusion (53,60) and rheumatoid arthritis (77,85). These antinflammatory effects of taurine-taurinechloramine systems could be important in preventing cardiovascular diseases and hyperglycaemia-induced damage.

Antiatherosclerotic Effects of Taurine. Diabetic subjects are most prone to atherosclerosis. In some experimental models of atherosclerosis and DM, taurine has hypolipidemic effects (20,24–28,86–89). However, the reports on the hypocholesterolemic effects of taurine are not univocal (90). As already mentioned, the best-known taurine function is the formation of bile salts, which participate in fat absorption and cholesterol excretion. Taurocholates in comparison with glycholate and unconjugated bile salts are more active in favoring the excretion and degradation of cholesterol (28,89) and in the neonate taurine prevents cholestasis. In addition, bile salts influence lipoprotein metabolism. In hamsters the cholesterol-lowering effects of taurine seem to be mediated by an upregulation of the low-density lipoprotein (LDL) receptor and by the subsequent increase in receptor-mediated LDL turnover (91).

There are only a few reports on the effects of taurine on the initiation and progression of atherosclerosis. Taurine slowed the progression of atherosclerosis without reducing total cholesterol in rabbit fed a cholesterol-rich diet (90). In addition, in C57BL/61 mice fed with a high-fat diet and in apolipoprotein E–deficient mice, taurine reduced aortic lipid accumulation (87,92). Furthermore, in the Watanabe rabbit with heritable hyperlipidemia, it prevented aortic accumulation of cholesteryl ester, and reduced acyl-CoA, cholesterol acyltransferase, and malonyldialdehyde generation, both in serum and aorta, thereby decreasing the susceptibility of LDL to oxidation (93). Such data suggest that the effect of taurine on the progression of atherosclerosis depends on its antioxidant effect. All these studies were performed in small animals—rabbits, mice, and rats, in which the rate of free radical generation is very high, reflecting their higher metabolic rate (94). LDL oxidation is associated with the rate of generation of ROS, thus the small animals, which generate more oxidized LDL, should benefit more than humans from antioxidant treatment. In this regard it is

important to note that a recent worldwide epidemiological study revealed an inverse correlation between the levels of taurine excretion and ischemic heart disease (95).

Antiaggregating Effects of Taurine. The increased activity of platelets in DM patients is considered to be a contributing factor to diabetic complications, including retinopathy. It is also possible that the beneficial effect of taurine could depend on its antiaggregating activity. It has been reported that taurine reduces platelet aggregation in diabetic patients (12,13). Interestingly, the effects of taurine supplementation were of long duration and still present after 60 days of washout (13). In healthy individuals, taurine reduced thromboxane synthesis (96).

Taurine and Calcium Homeostasis. As shown by several authors, taurine also functions as a modulator of intracellular calcium homeostasis (97–99). Taurine appears to affect calcium homeostasis through a biphasic effect that depends on calcium concentrations. Taurine has been also found to prevent the cell injury mediated by intracellular calcium (1,98–100). It is well known that oxidative stress produces an increase in intracellular calcium. Taurine, scavenging HCIO, and modulating intracellular calcium may interrupt the vicious circle between lipid peroxidation and calcium overload, blunting the ability of prooxidants to increase intracellular calcium. It is important to note that taurine, at least in the retina of diabetic rats, preserves the activity of the sodium pump (38–40) and also preserves the enzyme activity in red cells exposed to ozone (101). This could be important because the lower pump activity and lipid peroxidation can be interrelated in a vicious circle. In fact, the decrease in sodium ATPase activity can generate calcium overload, which in turn induces lipid peroxidation, further decreasing the ATPase activity.

Osmoregulation. Taurine is also an osmolyte (1), and in "isotonic" hyperglycemia a huge sorbitol accumulation may cause compensatory depletion of taurine. In DM it is decreased in some tissues, such as the retinal pigment epithelium, platelets, nerve, and lens (12,14,32, 102–104), but increased in skeletal muscle and heart of diabetic animals (16). Thus, unequivocal data have been obtained in DM (16). The difference in experimental results may reflect differences in the duration of hyperglycemia and in metabolic status. Dietary treatment with taurine increased serum taurine concentrations and restored taurine in platelets (12). Therefore taurine supplementation seems to be able to reduce or overcome taurine depletion in some diabetic tissues. It is generally believed that taurine transport plays an important role in maintaining intracellular taurine levels (2,105). At least in cultured cells of retinal pigmented epithelium, glucose downregulates taurine transport, modulating transcription, mRNA stability, and perhaps other posttranscriptional or posttranslational mechanisms (103).

Taurine and "Fetal Programming" for Development of Type 2 Diabetes Mellitus

It is hypothesized that alterations in the "programming" of the pancreatic endocrine system in fetal life and early life persists throughout life, elevating the risk for later development of type 2 DM (106). Numerous data suggest that taurine is important for fetal development, including pancreas function (107). Fetuses are supplied by mothers, and when the activity of placental transporters is reduced, fetal tissues are depleted of taurine (108). In dams a low-protein diet reduced the taurine level in the fetus (19) and induced maternal DM, alterations in fetal endocrine pancreas (109,110), and impaired glucose tolerance in adult offspring (109). Cultured fetal pancreatic islets obtained from undernourished fetuses showed an impaired insulin secretion (19) that was not restored by *in vitro* exposure to taurine, but could be restored by supplementing mothers with taurine (19), confirming that taurine has an impact on fetal beta cell maturation. Maternal taurine supplementation reduced the rate of apoptosis induced by IL-1 in fetal pancreas islets (111) and acted on DNA synthesis, preventing an abnormal development of the endocrine pancreas (112). Plasma taurine levels were low in diabetic pregnant rats and in their offspring throughout life and in the fetuses of the next generation (113). The above findings suggest that it is time to perform detailed investigations on taurine involvement in "fetal programming" so as to determine whether this amino acid must be supplemented during gestation to avoid insulin resistance and other metabolic damages in adult life and in the second generations.

CONCLUSION

It has been demonstrated that tight glycemic control alone cannot mitigate atherosclerosis in type 2 DM, thus reducing the incidence of macrovascular diabetic complications. New therapies able to prevent vascular complications of DM are needed. Based on animal trials, one of these treatments could be taurine supplementation. Acting as a relatively specific antioxidant with ancillary properties, it may reduce oxidative stress and inflammatory response. It has also been reported that taurine administration in young smokers restores endothelial-dependent vasodilatation (114). However, at the beginning of third

millennium, the evidence of beneficial effects of taurine from human studies is not sufficient. Even though the use of taurine supplements is an interesting possibility, the reported health-promoting effects and the safety of such supplementation awaits further confirmation. Another important point is the possibility to supplement taurine during pregnancy in view of its preventive role in reducing alterations in pancreas programming that may in turn favor the onset of type 2 DM in the offspring, adult life, and second generation.

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