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

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

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.

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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 glomeru-

lopathy. 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 insulindependent 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 extracellularsuperoxide dismutase by ameliorating endoplasmic reticulum stress induced by homocysteine (68), a wellknown 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 Ca²⁺ transport and protein synthesis and reduces angiotensin II signaling, because taurinedepleted 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 NO₂ (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 receptormediated 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 highfat 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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REFERENCES

- 1. Huxtable, R. J. 1992. Physiological actions of taurine. Physiol. Rev. 72:101–163.
- Hayes, K., Rabin, A., and Berson, E. 1975. An ultrastructure study of nutritionally induced and reversed retinal degeneration in cats. Am. J. Path. 78:505–509.
- 3. Hayes, K. and Sturman, J. A. 1981. Taurine in metabolism. Annu. Rev. Nutr. 1:401–425.
- Geggel, H. S., Ament, M., Heckenlively, J. R., Martin, D. A., and Kopple, J. D. 1985. Nutritional requirement for taurine in patients receiving long-term parenteral nutrition. N. Engl. J. Med. 312:142–146.
- Heller-Stilb, B., van Roeyen, C., Rascher, K., Harting, H. G., Huth, A., Seeliger, M., Warskulat, U., and Haussinger, D. 2001. Disruption of the taurine transporter gene (taurinet) leads to retinal degeneration in mice. FASEB J. 10.1096/fj01-0691fje.
- Reccia, R., Pignalosa, B., Grasso, A., and Campanella, G. 1980.
 Taurine treatment in retinitis pigmentosa. Acta. Neurol. (Napoli) 2:132–136.
- Pasantes-Morales, H., Quiroz, H., and Quesada, O. 2002. Treatment with taurine, diltiazem and vitamin E retards the progressive visual field reduction in retinitis pigmentosa: A 3 years follow-up study. Metab. Brain Dis. 17:183–197.
- Pion, P. D., Kittleson, M. D., Rogers, Q. R., and Morris, J. G. 1987. Myocardial failure in cats associated with low plasma taurine: A reversible cardiomyopathy. Science 237:764–768.
- Pion, P. D., Sanderson, S. L., and Kittelson, M. D. 1998. The effectiveness of taurine and levocarnitine in dogs with heart disease. Vet. Clin. North Am. Small Anim. Pract. 28:1495–1514.
- Lake, N. 1993. Loss of cardiac myofibrils: Mechanism of contractile deficits induced by taurine deficiency. Am. J. Physiol. 264: H1323–H1326.
- vom Dahl, S., Monnighoff, I., and Haussinger, D. 2000. Decrease of plasma taurine in Gaucher disease and its substained correction during enzyme replacement therapy. Amino Acids 19: 585–592.
- Franconi, F., Bennardini, F., Mattana, A., Miceli, M., Ciuti, M., Mian, M., Gironi, A., Bartolomei, G., Anichini, R., and Seghieri, G. 1995. Plasma and platelet taurine are reduced in subjects with insulin-

- dependent diabetes mellitus: Effects of taurine supplementation. Am. J. Clin. Nutr. 61:1115–1119.
- Franconi, F., Miceli, M., Fazzini, A., Seghieri, G., Caputo, S., Di Leo M. A. S., Lepore, D., and Ghirlanda, G. 1996. Taurine and diabetes mellitus: Human and experimental models. Adv. Exp. Med. Biol. 403:579–582.
- 14. De Luca, G., Calpona, P. R., Caponetti, A., Romano, G., Di Benedetto, A., Cucinotta, D., and Di Giorgio, R. M. 2001. Taurine and osmoregulation: Platelet taurine content, uptake, and release in type 2 diabetes mellitus. Metabolism 50:60–64.
- Airaksinen, E. M., Airaksinen, M. M., Sihvola, P., and Marnela, K.-M. 1981. Decrease in the uptake and concentration of taurine in blood platelets of retinitis pigmentosa patients. Metab. Pediatr. Ophthalmol. 5:45–48.
- Hansen, S. H. 2001. The role of taurine in diabetes mellitus and development of diabetic complications. Diabetes Metab. Res. Rev. 17:330–346.
- Bustamante, J., Lobo, M. V. T., Alonso, F. J., Mukala, N. T. A., Ginè, E., Solis, J. M., Tamarit-Rodriguez, J., and Martin del Río, R. 2001. An osmotic-sensitive taurine pool is localized in rat pancreatic islet cells containing glucagon and somatostatin. Am. J. Physiol. Endocrinol. Metab. 281:E1275–E1285.
- Cherif, H., Reusens, B., Dahri, S., Remacle, C., and Hoet, J. J. 1996. Stimulatory effects of taurine on the insulin secretion of fetal rat islets cultured in vitro. J. Endocrinol. 151:501–506.
- Cherif, H., Reusens, B., Ahn, M. T., Hoet, J. J., and Remacle, C. 1998. Effects of taurine on the insulin secretion of rat fetal islets from dams fed a low-protein diet. J. Endocrinol. 159:341–348.
- Goodman, H. O. and Shihabi, Z. K. 1990. Supplemental taurine in diabetic rats: Effect on plasma glucose and triglycerides. Biochem. Med. Metab. Biol. 43:1–9.
- Stevens, M. J., Lattimer, S. A., Kamijo, M., Van Huysen, C., Sima, A. A. F., and Green, D. A. 1993. Osmotically-induced nerve taurine depletion and the compatible osmolyte hypothesis in experimental diabetic neuropathy in the rat. Diabetologia 36:608–614.
- Trachtman, H., Futterweitt, S., and Bienkowski, R. S. 1993. Taurine prevents glucose-induced lipid peroxidation and increased collagen production in cultured rat mesangial cells. Biochem. Biophys. Res. Commun. 191:759–565.
- Trachtman, H., Futterweitt, S., Maesaka, J., Ma, C., Valderrama, E., Fuchs, A., Tarectecan, A. A., Rao, P. S., Sturman, J. A., Boles, T. H., Fu, M. X., and Baynes, J. 1995. Taurine ameliorates chronic streptozotocin-induced diabetic nephropathy in rat. Am. J. Physiol. 269:F429–F438
- Kamata, K., Sugiura, M., Kojima, S., and Kasuya, Y. 1996. Restoration of endothelium-dependent relaxation in both hyper-cholesterolemia and diabetes mellitus by chronic taurine. Eur. J. Pharmacol. 303:47–53.
- Nanami, K., Oda, H., and Yokogoshi, H. 1996. Antihypercholesterolemic action of taurine on streptozotocin-diabetic rats or on rats fed a high cholesterol diet. Adv. Exp. Med. Biol. 403: 561–568.
- Lim, E., Park, S., and Kim, H. 1998. Effect of taurine supplementation on lipid formation and the activities of glutathione related enzymes in the liver and islet of type I and type II diabetic model mice. Adv. Exp. Med. Biol. 442:99–104.
- You, J. S. and Chang, K. J. 1998. Effect of taurine supplementation on lipid peroxidation, blood glucose and blood lipid metabolism in streptozotocin-induced diabetic rats. Adv. Exp. Med. Biol. 442:163–168.
- Mochizuki, H., Takido, J., Oda, H., and Yokogoshi, H. 1999.
 Improving effect of dietary taurine on marked hypercholesterolemia induced by a high-cholesterol diet in streptozotocin-induced diabetic rats. Biosci. Biotechnol. Biochem. 63:1984–1987.
- Ha, H., Yu, M. R., and Kim, K. H. 1999. Melatonin and taurine reduce early glomerulopathy in diabetic rats. Free Radic. Biol. Med. 26:944–950.
- 30. Obrosova, I. G. and Stevens, M. J. 1999. Effect of dietary taurine supplementation on GSH and NAD(p)-redox status, lipid

- peroxidation, and energy metabolism in diabetes precataractous lens. Invest. Ophthalmol. Vis. Sci. 40:680–688.
- Mitton, K. P., Linklater, H. A., Dzialoszynski, T. S., Sanford, E., Starkey, K., and Trevithick, J. R. 1999. Modelling cortical cataractogenesis 21: In diabetic rat lenses taurine supplementation vitro reduction of damage in model diabetic is due to its antioxidant activity? Exp. Eye Res. 69:279–289.
- Kilic, F., Bhardwaj, R., Caulfeild, J., and Trevithick, J. R. 1999.
 Modelling cortical cataractogenesis 22: Is in vitro reduction of damage in model diabetic is taurine due to its antioxidant activity? Exp. Eye Res. 69:291–300.
- Wu, Q. D., Wang, J. H., Fennesy, F., Redmond, H. P., and Bouchier-Hayes, D. 1999. Taurine prevents high-glucose-induced human vascular endothelial cell apoptosis. Am. J. Physiol. 277: C1229–C1238.
- Militante, J. D., Lombardini, J. B., and Schaffer, S. W. 2000. The role of taurine in the pathogenesis of the cardiomyopathy of insulin-dependent diabetes. Cardiovasc. Res. 393:393–400.
- Pop-Busui, R., Sullivan, K. A., Van Huysen, C., Cao, Towns, X., and Stevens, M. J. 2001. Depletion of taurine in experimental diabetic neuropathy: Implications for nerve metabolic and functional deficits. Exp. Neurol. 168:259–272.
- Obrosova I., Minchenko, A. G., Marinescu, V., Fathallah, L., Kennedy, A., Stockert, C. M., Frank R. N., and Stevens, M. J. 2001. Antioxidants attenuate early up regulation of retinal vascular endothelial growth factor in streptozotocin-diabetic rat. Diabetologia 44:1102–1110.
- Obrosova, I., Fathallah, L., and Stevens, M. J. 2001. Taurine counteracts oxidative stress and nerve growth factor deficit in early experimental diabetic neuropathy. Exp. Neurol. 172: 211–219.
- 38. Di Leo, M. A. S., Santini, S. A., Cercone, S., Marra, G., Lepore, D., Caputo, S., Antico, L., Giardina, B., Pitocco, D., Franconi, F., and Ghirlanda, G. 1999. Dose-dependent effects of taurine in the prevention of Na,K-ATPase impairment and lipid peroxidation in the retina of streptozotocin-diabetic rats. Diabetologia 42(Suppl. 1):A315.
- 39. Di Leo, M. A. S., Santini, S. A., Cercone, S., Marra, G., Lepore, D., Gentiloni Silveri, N., Caputo, S., Greco, A. V., Giardina, B., Franconi F., and Ghirlanda, G. 2002. Chronic taurine supplementation ameliorates oxidative stress and Na⁺K⁺-ATPase impairment in the retina of diabetic rats. Amino Acids 23:401–406.
- Di Leo, M. A. S., Ghirlanda, G., Gentiloni Silveri, N., Giardina, B., Franconi, F., and Santini, S. A. 2003. Potential therapeutic effect of antioxidants in experimental diabetic retina: A comparison between chronic taurine and vitamin E plus selenium supplementations. Free Radic. Res. 37:323–330.
- Nakaya, Y., Minami, A., Haradica, N., Sakamoto, S., Niwa, Y., and Ohnaka, M. 2000. Taurine improves insulin sensitivity in the Otsuka Long-Evans Tokushima fatty rat, a model of spontaneous type 2 diabetes mellitus. Am. J. Clin. Nutr. 71:54–58.
- Odetti, P., Pesce, C., Traverso, N. Menini, S., Pesce Manieri, E., Cosso, L., Velentini, S., Patriarca, S., Cottalasso, D., Marinari, U. M., and Pronzato, M. A. 2002. Comparative trial of N-acetyl-cysteine, taurine, and oxerutin on skin and kidney damage in long-term experimental diabetes. Diabetes 52:499–505.
- 43. Franconi, F., Di Leo, M. A. S., Santini, S. A., Gentiloni Silveri, N., Caputo, S., Giardina, B., and Ghirlanda, G. 2002. Taurine supplementation prolongs the survival and reduces glycemia in streptozotocin-induced diabetic rats. Taurine in the 21st century, September 20–23, Radisson Kauai Beach Resort, Hawaii.
- Movassat, J. and Portha, B. 1999. Beta-cell growth in the neonatal Goto-Kakisaki rat and regeneration after treatment with streptozotocin at birth. Diabetologia 42:1098–1096.
- 45. Trachtman, H., Futterweitt, S., Prenner, J., and Hanon, S. 1994. Antioxidants reverse the antiproliferative effect of high glucose and advanced glycosylation end products in cultured rat mesangial cells. Biochem. Biophys. Res. Commun. 199:346–352.
- Kirpichnikov, D. and Sowers, J. R. 2001. Diabetes mellitus and diabetes associated vascular disease. Trends Endocrinol. Metab. 12:225–429.

- Baynes, J. W. and Thorpe, S. R. 1999. Role of oxidative stress in diabetic complications: A new perspective on an old paradigm. Diabetes 48:1–9.
- 48. Wright, C. E., Tallan, H. H., and Lin, Y. Y. 1986. Taurine: Biological update Annu. Rev. Biochem. 55:427–453.
- Pasantes-Morales, H. and Cruz, C. 1984. Protective effect of taurine and zinc on peroxidation induced damage in photoreceptor outer segments. J. Neurosci. Res. 11:303–311.
- Pasantes-Morales, H. and Cruz, C. 1985. Taurine and hypotaurine inhibit light induced lipid peroxidation and protect rod outer segment structures. Brain Res. 330:154–157.
- Alvarez, J. G. and Storey, B. T. 1983. Taurine, hypotaurine, epinephrine and albumin inhibit lipid peroxidation in rabbit spermatozoa from O₂ toxicity due to lipid peroxidation. Biol. Reprod. 28:1129–1136.
- Dawson, R., Tang, E., Shib, D., Hern, H., Hu, M., Baker, D., and Eppler, B. 1998. Taurine inhibition of iron-stimulated catecholamine oxidation. Adv. Exp. Med. Biol. 442:155–162.
- Schuller-Levis, G. B., Gordon, R. E., Park, E., Pendino, K. J., and Laskin, D. L. 1995. Taurine protects rat bronchioles from acute ozone-induced lung inflammation and hyperplasia. Exp. Lung Res. 21:877–888.
- Milei, J. R., Ferreira, R., Llesuy, S., Focarda, J., Covarrubias, J., and Boveris, A. R. 1992. Reduction of reperfusion injury with preoperative rapid intravenous infusion of taurine during myocardial revascularization. Am. Heart J. 123:339–345.
- Tadolini, B., Pintus, G., Pinna, G., Bennardini, F., and Franconi, F. 1995. Effect of taurine and hypotaurine on lipid peroxidation. Biochem. Biophys. Res. Commun. 213:820–826.
- Weiss, S. J., Klein, R., Slivka, A., and Wei, M. 1982. Chlorination of taurine by human neutrophils: Evidence for hypochlorous acid generation. J. Clin. Invest. 70:598–607.
- Zglinczynski, J. M., Stelmaszynka, T., Domasnski, J., and Ostrowski, W. 1971. Chloramines as intermediate of oxidation reaction of amino acids by myeloperoxidase. Biochim. Biophys. Acta 233:419–424.
- Cantin, A. 1994. Taurine modulation of hypochlorous acid-induced lung epithelial cell injury in vitro. J. Clin. Invest. 93:606–614.
- Kearns, S. and Dawson, R. 2000. Cytoprotective effect of taurine against hypochlorous acid toxicity to PC12 cells. Adv. Exp. Med. Biol. 483:563–570.
- Raschke, P., Massoudy, P., and Becker, B. F. 1995. Taurine protects the heart from neutrophil-induced reperfusion injury. Free Radic. Biol. Med. 19:461–471.
- Omi, H., Okayama, N., Shimizu, M., Okouchi, M., Ito, S., Fukutomi, T., and Itoh, M. 2002. Participation of high glucose concentrations in neutrophil adhesion and surface expression of adhesion molecules on cultured human endothelial cells: Effect of antidiabetic medicines. Diab. Compl. 16:201–218.
- 62. Zhang, R., Brennan, M. L., Fu, X., Aviles, R. J., Pearce, G. L., Penn, M. S., Topol, E. J., Sprecher, D. L., and Hazen, S. L. 2001. Association between myeloperoxidase levels and risk of coronary artery disease. J. Am. Med. Ass. 286:2136–2142.
- 63. Brennan, M, Anderson, M. M., Shih, D. M., Qu, X., Wang, X., Mehta, A. C., Lim L. L., Shi, W., Hazen, S. L., Jacob, J. J., Crowley, J. R., Heinecke, J. W., and Lusis, A. J. 2001. Increased atherosclerosis in myeloperoxidase-deficient mice. J. Clin. Invest. 107:419–430.
- 64. Ogasawara, M., Nakamura, T., Koyama, I., Remoto, M., and Yoshida, T. 1994. Reactivity of taurine with aldehydes and its physiological role. Adv. Exp. Med. Biol. 359:71–78.
- Li, H., Li, J. C., Jiang, S. S., Du, H., and Gu, X. P. 1996. Inhibiting effect of taurine on nonenzymatic glycosylation on aortic collagen in diabetic rats. Chin. Pharmacol. Bull. 12:445–447.
- Devanmanoharan, C., Ali, P. S., and Varna, A. H. 1997. Prevention of lens protein glycation by taurine. Mol. Cell. Biochem. 177:245–250.
- 67. Eppler, B. and Dawson, R. 2001. Dietary manipulations in aged male Fishers 344 rat tissue: Taurine concentration, taurine biosynthesis, and oxidative markers. Biochem. Pharmacol. 62:29–39.

- 68. Nonaka, H., Tsujino, T., Watari, Y., Emoto, N., and Yokoyama, M. 2001. Taurine prevents the decrease in expression and secretion of extracellular superoxide dismutase induced by homocysteine: Amelioration of homocysteine-induced endoplasmic reticulum stress by taurine. Circulation 104:1165–1170.
- Keys, S. A. and Zimmerman, W. F. 1999. Antioxidant activity of retinol, glutathione, and taurine in bovine photoreceptor cell membranes. Exp. Eye Res. 68:693–702.
- Franconi F., Stendardi I., Failli P., Matucci R., Baccaro C., Montorsi L., Bandinelli R., and Giotti, A. 1985. The protective effects of taurine on hypoxia (performed in the absence of glucose) and on reoxygenation (in the presence of glucose) in guineapig heart. Biochem. Pharmacol. 34:2611–2620.
- Malcangio, M., Bartolini, A., Ghelardini, C., Bennardini, F., Malberg-Aiello, P., Franconi, F., and Giotti, A. 1989. Effect of I.C.V. taurine on the impairment of learning, convulsion and death caused by hypoxia. Psycopharmacology 98:316–320.
- Schaffer, S. W., Lombardini, J. B., and Azuma, J. 2000. Interaction between the actions of taurine and angiotensin II. Amino Acids 18:305–318.
- Mozaffari, M. S. and Abebe, W. 2000. Cardiovascular responses of the taurine-depleted rat to vasoactive agents. Amino Acids 19: 625–634.
- Seshiah, P. N., Weber, D. S., Rocic, P., Valppu, L., Taniyama, Y., and Griendling, K. K. 2002. Angiotensin II stimulation of NAD(P)H oxidase activity: Upstream mediators. Circ. Res. 91: 406–413.
- Hsieh, T. J., Zhang, S. L., Filep, J. G., Tang, S. S., Infelfinger, J. R., and Chan, S. D. 2002. High glucose stimulate angiotensinogen gene expression via reactive oxygen species generation in rat kidney proximal tubular cells. Endocrinology 143:2975–2985.
- Cunningham, C., Tipton, K. F., and Dixon, H. B. F. 1998. Conversion of taurine into N-chloramine (taurine chloramine) and sulphoacetaldehyde in response to oxidative stress. J. Biochem. 330:939–945
- Marcinkiewicz, J., Grabowska, A., Bereta, J., and Stelmaszynska, T. 1995. Taurine chloramines, a product of activated neutrophils, inhibits the generation of nitric oxide and other macrophage inflammatory mediators. J. Leukoc. Biol. 58:667–674.
- Liu, Y., Tonna-DeMaise, M., Park, E., Schuller-Levis, G., and Quinn, M. R. 1998. Taurine chloramine inhibits production of nitric oxide and prostaglandin E2 in activated C6 glioma cells by suppressing inducible nitric oxide synthase and cyclooxygenase-2 expression. Mol. Brain Res. 59:189–195.
- Park, E., Jia, J., Quinn, M. R., and Schuller-Levis, G. 2002. Taurine chloramine inhibits lymphocyte proliferation and decreases cytokine production in activated human leukocytes. Clin. Immunol. 102:179–184.
- Ogino, T., Kobuchi, H., Sen, C. K., Roy, S., Packer, L., and Maguire, J. J. 1997. Monochloramine inhibits phorbol esterinducible neutrophil respiratory burst activation and T cell interleukin-2 receptor expression by inhibiting inducible protein kinase C activity. J. Biol. Chem. 272:26247–26252.
- Park, E., Quinn, M. R., Wright, C. E., and Schuller-Levis, G. 1993. Taurine chloramine inhibits the synthesis of nitric oxide and release of tumor necrosis factor in activated RAW-264.7. J. Leukoc. Biol. 54:119–124.
- Kontny, E., Grabowska, A., Kowalczewski, J., Kurowska, M., Janicka, I., Marcinkiewicz, J., and Maslinski, W. 1999. Taurine chloramine inhibition of cell proliferation and cytokine production by rheumatoid arthritis fibroblast-like synoviocytes. Arthritis Rheum. 42:2552–2560.
- 83. Gordon, R. E., Shaked, A. A., and Solano, D. F. 1986. Taurine protects hamster bronchioles from acute NO₂ induced alteration: A histological, ultrastructural, and freeze fracture studies. Am. J. Path. 125:10404–10413.
- Wang, Q. J., Giri, S. N., Hyde, D. M., and Nakaashima, J. M. 1989. Effects of taurine on bleomycin-induced fibrosis in hamsters. Proc. Soc. Exp. Biol. Med. 190:330–338.

- Davies, J. M., Horwitz, D. A., and Davies, K. J. A. 1993. Potential roles of hypochlorous acid and N-chloramines in collagen breakdown by phagocytic cells in synovitis. Free Radic. Biol. Med. 15:637–643.
- Murakami, S., Yamagishi, I., Asami, Y., Ohta, Y., Toda, Y., Nara, Y., and Yamori, Y. 1996. Hypolipidemic effect of taurine in stroke-prone spontaneously hypertensive rats. Pharmacology 52:303–313.
- Murakami, S., Kondo-Ohta, Y., and Tomisawa, K. 1999.
 Improvement in cholesterol metabolism in mice given chronic treatment of taurine and fed a high-fat diet. Life Sci. 64:83–91.
- Balkan, J., Kanbagli, O., Hatipoglu, A., Kucuk, M., Cevikbas, U., Aykac-Toker, G., and Uysal, M. 2002. Improving effect of dietary taurine supplementation on the oxidative stress and lipid levels in the plasma, liver and aorta of rabbits fed on a high-cholesterol diet. Biosci. Biotechnol. Biochem. 66:1755–1758.
- Yokogoshi, H. and Oda, H. 2002. Dietary taurine enhances cholesterol degradation and reduces serum and liver cholesterol concentrations in rats fed a high-cholesterol diet. Amino Acids 23: 433–439.
- Petty, M. A., Kintz, J., and DiFrancesco, G. F. 1990. The effects of taurine on atherosclerosis development in cholesterol fed rabbits. Eur. J. Pharmacol. 180:119–127.
- Murakami, S., Kondo, Y., Toda, Y., Kitajima, H., Kameo, K., Sakono, M., and Fukuda, N. 2002. Effect of taurine on cholesterol metabolism in hamsters: Up-regulation of low density lipoprotein (LDL) receptor by taurine. Life Sci. 70:2355–2366.
- Kondo, Y., Toda, Y., Kitajima, H., Oda, H., Nagate, T., Kameo, K., and Muratami, S. 2001. Taurine inhibits development of atherosclerotic lesions in apolipoprotein E-deficient mice. Clin. Exp. Pharmacol. Physiol. 28:809–815.
- Murakami, S., Kondo, Y., Sakurai, T., Kitajima, H., and Nagate, T. 2002. Taurine suppresses development of atherosclerosis in Watanabe heritable hyperlipidemic (WHHL) rabbits. Atherosclerosis 163:79–87.
- Steinberg, D. and Witztum, J. L. 2002. Is the oxidative modification hypothesis relevant to human atherosclerosis. Circulation 105:2107–2111.
- Yamori, Y., Liù, L., Ikeda, K., Miura, A., Mizuhushi, S., Miki, T., and Nara Y. 2001. Distribution of twenty-four hour urinary taurine excretion and association with ischemic disease mortality in 24 population 16 countries: Results from WHO-cardiac study. Hypertens. Res. 24:453–461.
- Hayes, K., Pronezn, K. A., Adessa, A. E., and Stephan, Z. F. 1989.
 Taurine modulates platelet aggregation in cats and in humans. Am.
 J. Clin. Nutr. 49:1211–1215.
- Franconi, F., Martini, F., Stendardi, I., Matucci, R., Zilletti, L., and Giotti A. 1982. Effect of taurine on calcium levels and contractility in guinea-pig ventricular strips. Biochem. Pharmacol. 31:3181–3187
- Satoh, H. 1994. Cardioprotective actions of taurine against intracellular and extracellular calcium-induced effect. Adv. Exp. Med. Biol. 359:181–196.
- Militante, J. D. and Lombardini, J. B. 2000. Stabilization of calcium uptake in rat rod outer segments by taurine and ATP. Amino Acids 19:561–570.
- Chen, Y. X. 1995. Protective action of taurine on ischemiareperfusion liver injury in rats and its metabolism. Chin. Med. J. 73:977–986
- Qi, B., Yamagami, T., Naruse Y., Sokejima, S., and Kagamimori, S. 1995. Effect of taurine on depletion of erythrocyte membrane NaKATPase activity due to ozone exposure or cholesterol enrichment. J. Nutr. Sci. Vitaminol. 41:627–634.
- 102. Vilchis, C. and Salceda, R. 1996. Effect of diabetes mellitus on levels and uptake of putative amino acid neurotrasmtitters in rat retina and retinal pigment epithelium. Neurochem. Res. 21: 1167, 1171.
- Stevens, M. J., Hosaka, Y., Masterson, J. A., Jones, S. M., Thomas, T. P., and Larkin, D. D. 1999. Downregulation of the

- human taurine transporter by glucose in cultured retinal pigment epithelial cells. Am. J. Physiol. 277:E760–E771.
- Malone, J. L., Lowitt, S., and Cook, W. R. 1990. Non osmotic diabetic cataracts. Pediat. Res. 27:293–296.
- Franconi, F., Martini, F., Manghi, N., Galli, A., Bennardini, F., and Giotti, A. 1981. Uptake of ³H-taurine into myocardial membranes. Biochem. Pharmacol. 30:77–85.
- Hales, C. N. and Baker, D. J. P. 1992. Type-2 (non-insulin dependent) diabetes mellitus: The thrifty phenotypes hypothesis. Diabetologia 35:595–601.
- Sturman, J. A. 1993. Taurine in development. Physiol. Rev. 73: 119–147.
- Norberg, S., Powel, T. L., and Jansson, T. 1998. Intrauterine growth restriction is associated with reduced activity of placental transporters. Pediat. Res. 44:233–238.
- Dahri, S., Snock, A., Reusens, B., Remacle, C., and Hoet, J. J. 1991. Islet function in offspring of mothers on low protein diet during gestation. Diabetes 40(suppl 2) 115–120.
- 110. Oliver, M. H., Hawkins, P., Breier, B. H., Van Zijl, P. L., Sargison, S. A., and Harding, J. E. 2001. Maternal undernutrition

- during the periconceptual period increases plasma taurine levels and insulin response to glucose but not arginine in the late gestation fetal sheep. Endocrinology 142:4576–4579.
- 111. Merezak, S., Hardikar, A. A., Yajnik, C. S., Remacle, C., and Reusens, B. 2001. Intrauterine low protein diet increases fetal beta-cell sensitivity to NO and IL-1 beta: The protective role of taurine. J. Endocrinol. 171:299–308.
- 112. Boujender, S., Reusens, B., Merezak, S., Ahn, M. T., Arany, E., Hill, D., and Remacle, C. 2002. Taurine supplementation to a low protein diet during foetal and early postnatal life restores a normal proliferation and apoptosis of rat pancreatic islets. Diabetologia 45:856–866.
- 113. Aerts, L. and Van Assche, F. A. 2001. Low taurine, gamma-aminobutyric acid and carnosine levels in plasma of diabetic rats: Consequences for the offspring. J. Perinat. Med. 29: 81–84.
- Fennessy, F. M., Moneley, D. S, Wang, J. H., Kelly, C. J., and Bouchier-Hayes, D. J. 2003. Taurine and vitamin C modify monocyte and endothelial dysfunction in young smokers. Circulation 107:410–415.