Taurine, a sulfur-containing amino acid (Figure), has been termed a functional nutrient that could be used to protect against, among others, diabetes mellitus and atherosclerosis. Indeed, an increasing body of literature supports the use of taurine supplements. Because taurine has very diverse functions, notably, intracellular osmoregulation and bile acid formation, and is abundantly present in several organs, multiple pathways could be involved. Some of these are discussed in this editorial.

Of the 20 canonical amino acids, 18 are composed of carbon, hydrogen, nitrogen, and oxygen only. The remaining 2, methionine and cysteine, also contain 1 atom of sulfur. Because sulfur is not as electronegative as oxygen, the sulfur-containing amino acids play a key role in protein structure and synthesis. Methionine and cysteine also play important roles in cell metabolism. For instance, methionine serves as a substrate for S-adenosylmethionine, which is vital for methylation of nucleic acids, proteins, lipids, etc. In proteins, cysteine easily forms double bonds with other cysteine residues, thus determining tertiary structure and binding sites. Moreover, cysteine is substrate for glutathione, an important intracellular antioxidant, and H$_2$S, a gas that can induce endothelial-dependent relaxation. Cysteine is considered a nonessential amino acid because it is synthesized from the essential amino acid methionine. However, because homocysteine lies in the pathway between methionine and cysteine, excess methionine induces hyperhomocysteinemia, a risk factor for atherosclerosis.

Dietary hypercholesterolemia leads to coronary atherosclerosis in rabbits, and maternal hypercholesterolemia can even lead to fatty streaks in the aorta of the human fetus. Dietary methionine induced hyperhomocysteinemia in rabbits, but this in itself does not induce atherosclerosis in the coronary artery. However, coronary atherosclerosis induced by dietary hypercholesterolemia was exacerbated by dietary methionine in rabbits, and this combination also induced cardiac fibrosis.

In this issue of Hypertension, Zulli et al present data showing in this model that dietary taurine, a downstream metabolite of methionine and cysteine, can ameliorate coronary atherosclerosis and also prevent hyperhomocysteinemia and ameliorated hypermethionemia. This observation raises a number of questions: 1) is there negative feedback by taurine on its own metabolic pathway; 2) if so, is the protective effect of taurine dependent on a reduction in homocysteine; 3) does taurine have antiatherosclerotic effects that are not related to its metabolic pathway; and 4) is dietary taurine supplementation always safe. In our opinion, answers to these questions are required before taurine supplementation can be tested in a controlled clinical trial.

Direct effects of taurine on its own metabolic pathway have not been described. However, taurine inhibits methionine uptake in intestinal Caco-2 cells. This inhibitory effect occurs because taurine and methionine share the B$_0$AT1 transporter. This may explain why the high plasma methionine levels induced by dietary methionine in the rabbits studied by Zulli et al were initially reduced by dietary taurine. Because this inhibitory effect occurs on the apical side of the intestine, this could occur without an increase in plasma taurine. Indeed, dietary taurine had practically no effect on plasma taurine levels. Furthermore, after 4 weeks of dietary cholesterol plus methionine (and taurine), plasma levels of methionine and homocysteine had normalized, suggesting that, by the end of the experimental period, methionine uptake was completely inhibited by taurine.

High methionine intake can lead to hyperhomocysteinemia-induced toxicity. Tenfold increases in homocysteine levels lead to myocardial mitochondrial injury and hepatitis. Both effects can be reversed by taurine but, surprisingly, without any effect on these very high plasma homocysteine levels. These studies suggest that, even if high methionine intake leads to severe hyperhomocysteinemia, protective effects of taurine can occur, presumably via intracellular events that are not dependent on a reduction of homocysteine levels. Apparently protective effects of taurine need not be related to direct effects on its own metabolic pathway. Hence, the normalization of high methionine-induced hyperhomocysteinemia by dietary taurine observed in rabbits by Zulli et al may be a coincident phenomenon not related to the antiatherosclerotic effect of taurine.

Several intracellular effects of taurine are potentially protective. Taurine reduces oxidative stress induced by binding hypochlorite. A novel hypothesis is that taurine conjugates to mitochondrial transfer RNA and, thus, prevents formation of mitochondrial superoxide. Taurine can inhibit homocysteine-induced stress of the endoplasmic reticulum of vascular smooth muscle cells and so restore expression and secretion of extra-cellular superoxide dismutase. How this works is unknown, but one possibility is intracellular conjugation of taurine to other molecules. For instance, taurine-conjugating ursodeoxycholic acid increases the water solubility of this bile acid.
This conjugate, tauroursodeoxycholic acid, has been used to reduce endoplasmic reticulum stress–induced apoptosis in liver and other tissues in hyperglycemic mice. Thus, the lowering effect of taurine on CCAAT/enhancer binding protein homologous protein, a marker of endoplasmic reticulum stress, in the study by Zulli et al may “simply” have been attributed to the water solubility of intracellular taurine conjugates and may have had nothing to do with the methionine-taurine pathway. Supplementation of taurine to hamsters increased taurine content in liver and in urine but did not affect plasma taurine. This shows that the absence of an effect of taurine supplements on plasma taurine levels possibly does not exclude an increase in taurine levels in extravascular or intracellular compartments. Thus, as is the case for arginine, there may also be a “taurine paradox.”

The mechanisms by which taurine reduced atherosclerosis in the study by Zulli et al are unknown. Although taurine has been reputed to reduce plasma cholesterol by stimulating cholesterol excretion into bile acids, there were no beneficial effects on lipid profiles or endothelial function. If anything, the lipid profile deteriorated, because low-density lipoprotein-high-density lipoprotein ratios were transiently increased. Antithrombogenic effects of taurine have been described in hypercholesterolemic apolipoprotein E–deficient mice and Watanabe heritable hyperlipidemic rabbits. It would have been interesting to know whether rabbits with dietary hypercholesterolemia without methionine would also have been protected by taurine. Unfortunately, such a group was not included.

Taurine has antihypertensive effects in diverse rodent models of hypertension. A central sympatholytic effect appears to be a common pathway. However, because blood pressure was not measured by Zulli et al, this factor cannot be evaluated. Dietary taurine supplements are considered nontoxic, because excess taurine, being highly water soluble, is excreted by the kidney. Hyperhomocysteinemia in patients with chronic renal failure may be attributed to a reduction in sulfur excretion proportional to the loss of renal function, because, among other factors, metabolism of homocysteine to cysteine may be reduced by the accumulation of sulfates. In patients with end-stage renal disease, taurine supplements (100 mg/kg per day, equivalent to ∼7 cans of Red Bull), lead to extremely high plasma and muscle taurine levels and dizziness. Thus, renal failure is probably a contraindication for taurine supplements. Taurine supplements protect the endocrine pancreas from deficiency during fetal protein malnutrition and may, thus, prevent the development of type 2 diabetes mellitus in later life. In spontaneously hypertensive rat offspring, we have observed persistent antihypertensive effects of micronutrient supplements, including taurine, administered during pregnancy and lactation. In the kidney there were no persistent effects on differential gene expression, but in silico analysis of transcription factor–binding sites suggested reduced involvement of ELK-1. Whether, in the presence of maternal hypercholesterolemia, dietary taurine can prevent the development of fatty streaks in the fetus has not yet been investigated.

Thus, as is the case for other micronutrients, eg, vitamin E and folic acid, a myriad of beneficial effects have been ascribed to taurine. However, we should be cautious. Meta-analysis convincingly failed to show beneficial effects of both vitamin E and folic acid on all-cause or cardiovascular mortality and nonfatal myocardial infarction. The study by Zulli et al suggests that, in patients with one or more adequately treated cardiovascular risk factor, it may be worthwhile to study the effects of supplementary taurine in a controlled fashion. A simple “off taurine-on taurine-off taurine” design should suffice. Obvious surrogate end points include blood pressure, lipid levels, glycemic control, intracellular antioxidants (red cell glutathione), microalbuminuria, and markers of inflammation.

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