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Complementary Vascular-Protective Actions of Magnesium and Taurine: A Rationale for Magnesium Taurate

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Abstract — By a variety of mechanisms, magnesium functions both intracellularly and extracellularly to minimize the cytoplasmic free calcium level, $[Ca^{2+}]_i$. This may be the chief reason why correction of magnesium deficiency, or induction of hypermagnesemia by parenteral infusion, exerts antihypertensive, anti-atherosclerotic, anti-arrhythmic and antithrombotic effects. Although the amino acid taurine can increase systolic calcium transients in cardiac cells (and thus has positive inotropic activity), it has other actions which tend to reduce $[Ca^{2+}]_i$. Indeed, in animal or clinical studies, taurine lowers elevated blood pressure, retards cholesterol-induced atherogenesis, prevents arrhythmias and stabilizes platelets – effects parallel to those of magnesium. The complex magnesium taurate may thus have considerable potential as a vascular-protective nutritional supplement, and might also be administered parenterally, as an alternative to magnesium sulfate, in the treatment of acute myocardial infarction as well as of pre-eclampsia. The effects of magnesium taurate in diabetes deserve particular attention, since both magnesium and taurine may improve insulin sensitivity, and also may lessen risk for the micro- and macrovascular complications of diabetes.

Role of magnesium in vascular health

There is considerable suggestive evidence, primarily from epidemiological as well as animal studies, that magnesium nutrition has an important impact on vascular health, and that poor magnesium status may be associated with increased risk for hypertension, atherogenesis, coronary spasm, sudden-death (non-occlusive) cardiac arrhythmias, insulin resistance and diabetic complications (1–7). Magnesium's impact in this regard may be primarily reflective of its role in modulating ion movements across cell membranes – in particular, calcium transport. Poor magnesium status tends to promote increased cellular calcium uptake and increased intracellular free calcium levels ($[Ca^{2+}]_i$) by several mechanisms.

Intracellular magnesium is an essential cofactor (usually in a complex with ATP) for numerous enzymes, including energy-dependent membrane transport proteins such as the Na/K-ATPase and the Ca-ATPase (8). Significant intracellular magnesium deficiency impairs the activity of these transporters,

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resulting in decreased intracellular levels of potassium, and increased intracellular levels of sodium and calcium (1,5,8–11). Reduced activity of the sodium pump (Na/K-ATPase) indirectly increases $[Ca^{2+}]_i$ by decreasing the transmembrane sodium gradient; this impedes calcium extrusion via sodium-calcium countertransport. Additionally, in excitable tissues that express voltage-gated calcium channels (such as cardiac myocytes and vascular smooth muscle cells), reduced sodium pump activity can increase calcium influx through these calcium channels by decreasing membrane polarization. Animal studies indicate that a relatively moderate degree of dietary magnesium deficiency can have a significant adverse impact on sodium pump function in heart cells (11). The role of magnesium in support of sodium pump function may explain the clinical observation that potassium supplementation often fails to remedy potassium deficiency until concurrent magnesium deficiency is addressed with supplemental magnesium (12,13). Intracellular magnesium may be viewed as a permissive factor for ion transport enzymes; thus, once a modest 'adequate' magnesium concentration is achieved, increasing magnesium concentration further will not further activate these enzymes.

Extracellularly, magnesium functions much like a calcium channel blocker, reducing calcium influx (8,14); the nature of the calcium channels which magnesium blocks is still not well defined. When resistance arteries are perfused in vitro with a physiological calcium solution, a high magnesium concentration in the perfusate blocks calcium uptake and induces vasodilation; conversely, a low magnesium concentration promotes vasoconstriction. A similar phenomenon can be demonstrated in perfused coronary arteries (suggesting a role for hypomagnesemia in some cases of coronary vasospasm) (15). These effects occur virtually immediately, and thus are not mediated by a change in intracellular magnesium content. Since calcium influx plays an important role in cardiac automaticity, it is not surprising that hypermagnesemia – like calcium channel blockers – as clinically useful anti-arrhythmic activity (9,10,16). Hypermagnesemia also stabilizes platelets and increases clotting times (17–19). Clinically, induction of hypermagnesemia by slow i.v. infusion of magnesium salts has been shown to be useful in managing acute myocardial infarction (10,20,21), intractable arrhythmias (16,22) and hypertensive crises (notably in eclampsia) (23). Magnesium infusion is of particular importance in acute MI, since hypomagnesemia develops as a consequence of the stress response (24); increased lipolysis can lead to the precipitation of magnesium in soaps (25,26). Magnesium therapy of acute MI has been shown to reduce the subsequent incidence of arrhythmias and left ventricular failure, and to improve survival (10,20,21).

Good magnesium status thus restrains the influx of calcium while supporting the activity of transporters that remove calcium from the cytoplasm. The increased $[Ca^{2+}]_i$ consequent to poor magnesium status can be expected to increase the susceptibility of protein kinase C (PKC) to activation by agonists or metabolic conditions (such as hyperglycemia or high-fat diets) that promote diacylglycerol synthesis (27,28). Increased $[Ca^{2+}]_i$ also activates calmodulin-dependent signalling pathways which, in conjunction with PKC activation, promote vasoconstriction, smooth muscle hyperplasia or hypertrophy (as in atherogenesis or hypertensive medial hypertrophy), platelet aggregation, insulin resistance and possibly diabetic microangiopathy (29–35). Increased calcium influx in cardiac pacemaker cells will promote automaticity and thus increase risk for arrhythmias. These considerations clarify the overriding importance of good magnesium nutrition for vascular health.

Clinical implications of magnesium deficiency

Although fatty, over-refined modern diets tend to be relatively poor sources of magnesium (in comparison to more 'primitive' diets or recommended dietary intakes), the development of physiologically significant magnesium deficiency may usually be dependent on additional factors which compromise magnesium absorption or retention. These factors include long-term diuretic use, very-high-sodium diets, and diabetes (7,36–40). Diuretics, high sodium intakes and the glucosuria consequent to poor diabetic control all tend to impair renal magnesium retention (36,37,40). In addition, suboptimal insulin activity may impede both magnesium absorption and intracellular magnesium transport (7,39). High calcium intakes, in the context of a low-magnesium diet, may also inhibit magnesium absorption (1) – an important consideration in light of recent recommendations for supplemental calcium. The stress response can increase magnesium requirements by a variety of mechanisms (25,26). Feasible doses of oral magnesium are unlikely to produce sustained increases of plasma magnesium in subjects with adequate baseline magnesium status (induction of osmotic diarrhea places a practical limit on the dosages that can be administered orally). Thus, whereas induction of hypermagnesemia with parenteral magnesium can be expected to lower blood pressure and peripheral resistance, independent of pre-existing magnesium status, the antihypertensive efficacy of oral

magnesium may be confined to those individuals who are meaningfully magnesium deficient. This may explain why magnesium supplements have been found to reduce elevated blood pressure in studies enrolling subjects who are long-term diuretic users or who consume very-high-sodium Japanese diets (41–44), but have not reduced blood pressure in several other studies (45–47). The impact of magnesium supplementation on hypertension associated with diabetes merits study.

On the other hand, epidemiological studies suggest that modest ambient variation in magnesium intake may have a significant impact on risk for sudden-death cardiac arrhythmias. Increased magnesium intake has been offered as an explanation for the reduced incidence of such arrhythmias noted in areas supplied by hard water (2,48–50). Since most victims of sudden-death arrhythmias are not predisposed to overt magnesium deficiency by complicating factors (such as diabetes, diuretic use, etc.), it is unlikely that this apparent protective effect of magnesium is contingent on subnormal magnesium status.

Healthy cardiac myocytes show a higher free intracellular magnesium concentration than do other cells, maintaining a concentration gradient by active transport (8,51); presumably, there is a physiological rationale for this increased concentration. The ischemic myocardium tends to lose magnesium, perhaps owing to impaired bioenergetics (8,52). Thus, a tissue-specific cardiac magnesium deficiency may develop in ischemic heart disease. It is also possible that the myocardial magnesium content is more reflective of magnesium intake than is the magnesium content of other tissues. The putative protective effects of hard water/magnesium suggest that cardiac magnesium deficiency is an important risk factor for sudden-death arrhythmias, and that increased oral magnesium intakes act to prevent or remedy cardiac magnesium deficiency. Various lines of evidence support this thesis (2,48–50). Unfortunately, the large and lengthy clinical studies required to demonstrate conclusively that increased magnesium intakes can indeed reduce the incidence of sudden-death arrhythmias, have not been done.

The vascular consequences of overt magnesium deficiency in animals are readily predictable based on the known actions of increased $[Ca^{2+}]_i$. Thus, magnesium-deficient animals develop increased peripheral resistance and hypertension, are more prone to lipid-induced atherogenesis and to arterial calcinosis provoked by vitamin D toxicity, and are more susceptible to arrhythmias and to coronary spasm (1,4,8,53,54). It is notable that these effects are all diametrically opposite to those exerted by calcium channel blocker drugs. Indeed, one researcher has dubbed magnesium 'nature's physiological calcium blocker' (46).

Magnesium in diabetes

As implied by the foregoing, the broadest benefits of supplemental magnesium are likely to be achieved in individuals predisposed to magnesium deficiency. Diabetics are of particular interest in this regard, as they typically display reduced intracellular, plasma and bone levels of magnesium (7,38,39,56). Most of the pertinent studies in this regard pertain to type I diabetics, but more limited evidence establishes magnesium deficiency in type II diabetics as well. Regardless of the etiology of the diabetes, the degree of magnesium deficiency tends to correlate with indices of hyperglycemia such as glycated hemoglobin (38,56). This suggests that poor diabetic control exacerbates magnesium deficiency, as is predictable from the known adverse effect of glycosuria and deficient insulin function on renal retention, intestinal absorption and intracellular uptake of magnesium. However, the converse proposition – that magnesium deficiency impairs diabetic control – also deserves consideration.

Indeed, several studies demonstrate that RDA-level magnesium supplementation improves insulin sensitivity in both type I and type II diabetics, as well as in elderly insulin-resistant subjects (6,57,58). In the magnesium-supplemented type II diabetics, improved β cell function was also noted (6). The mechanism of magnesium's favorable influence on insulin sensitivity is not clear, although it may be noted that increased $[Ca^{2+}]_i$ has been shown to impair insulin function in some tissues (32), and that enhanced protein kinase C activation consequent to increased $[Ca^{2+}]_i$ (27,28) could also be expected to decrease insulin activity (33).

Several reports indicate that the extent of magnesium deficiency is greater in diabetics with retinopathy (59,60). The most parsimonious interpretation of this is that the magnesium deficiency and the retinopathy are both reflective of poor diabetic control. However, it has also been suggested that magnesium depletion may play a pathogenic role in the development of retinopathy (7). Since the increased activity of protein kinase C documented in poorly controlled diabetes has been proposed as an etiologic factor in diabetic microangiopathy (34,35), it is not unreasonable to hypothesize that magnesium deficiency could increase risk for retinopathy and nephropathy in diabetics.

With respect to the macroangiopathic complications of diabetes – atherogenesis and hypertension – it is pertinent to recall that magnesium depletion induces

hypertension and increases susceptibility to atherosclerosis and arterial calcinosis in experimental animals, and that, conversely, calcium channel blockers tend to reduce elevated blood pressure and retard progression of atherogenesis, both clinically and in animal models (61–63). There is growing evidence that subnormal insulin activity tends to increase $[Ca^{2+}]_i$ in vascular smooth muscle (64,65) – an effect that could play a fundamental pathogenic role in the increased risk for macroangiopathy observed in both diabetes and insulin resistance. Concurrent magnesium depletion could be expected to amplify the increase of $[Ca^{2+}]_i$ in vascular smooth muscle, and thus presumably intensify macroangiopathic risk.

In light of these considerations, large, long-term studies are warranted to assess the impact of effective magnesium supplementation on glycemic control and on development of macrovascular and microvascular complications in diabetics – particularly those who are poorly controlled. Such supplementation would be contraindicated in diabetics experiencing renal failure.

In summary, there is suggestive evidence – admittedly far from conclusive – that effective magnesium supplementation may reduce risk for sudden-death arrhythmias in individuals with coronary atherosclerosis, and may have a favorable influence on hypertensive and atherogenic disease in diabetics and other groups predisposed to magnesium deficiency. Additionally, there is reason to hope that correction of magnesium deficiency associated with diabetes could both aid glycemic control and help retard or prevent the onset of microvascular complications. A substantial and expensive clinical effort will be required to evaluate these possibilities. Improved control of $[Ca^{2+}]_i$ may be the chief biochemical mechanism underlying the suspected benefits of magnesium supplementation. With respect to parenteral administration, the utility of intravenous magnesium salts in the treatment of acute myocardial infarction, intractable arrhythmias and hypertensive crises, can be considered established.

Toward optimal magnesium supplementation

Although magnesium oxide is the magnesium source most commonly provided in nutritional supplements, there is evidence that certain soluble organic complexes of magnesium are better and more reliably assimilated – examples include magnesium aspartate, citrate and glycinate (66). A drawback with these preparations is that magnesium represents only 8–12% of their weight, necessitating the daily ingestion of 4 g or so of material if RDA-level magnesium supplementation is to be achieved.

Since the counteranion in these soluble magnesium complexes represents approximately 90% of the weight of the complex, it would be advantageous to use a counteranion which itself has nutritional utility, and which, if feasible, complements the vascular-protective actions of magnesium. I suggest that the amino acid taurine may satisfy these criteria.

Physiological role of taurine

Although not used in protein synthesis, taurine is usually described as an amino acid. Humans and most other animals (but not cats) can synthesize it from cysteine in a reaction pathway that involves decarboxylation and multiple oxidations of the sulfhydryl group (67). However, capacity for endogenous synthesis is limited in humans (particularly infants), with the result that the majority of body taurine stores usually derive from food sources. Meats and fish are rich in taurine, dairy products are comparatively low and foods of vegetable origin are devoid of taurine. For this reason, vegans are dependent on up-regulated synthesis and efficient renal retention to maintain adequate taurine levels. Typical American diets provide 40–400 mg taurine daily (68). Cats are absolutely dependent on exogenous taurine, and develop retinopathy and cardiomyopathy when placed on low-taurine diets.

Intracellular taurine levels are especially high in electrically active or secretory tissues, i.e. those in which $[Ca^{2+}]_i$ has an important signalling function (67). Whereas plasma taurine concentrations typically fall in the range of 50–200 μM, the intracellular taurine content of taurine-rich tissues is maintained at 10–30 mM, implying a roughly 100-fold transmembrane taurine gradient that is achieved by active transport. Inhibitors of this active transport, such as β-alanine, can be administered to rats to achieve intracellular taurine deficiency, and thereby elucidate the physiological role of taurine (69).

Taurine research has suffered from a twin handicap. Since taurine is a non-patentable nutrient, the pharmaceutical industry has been indifferent. Since taurine is not considered an essential nutrient (rather like coenzyme Q or carnitine, it is a 'conditionally essential' nutrient or 'metavitamin'), most nutritionists have shown little interest. Lacking encouragement from either the drug industry or nutritionists, most clinical researchers are only dimly aware of taurine's existence. Fortunately, physiologists have taken up the slack, devoting considerable effort over the last two decades to defining the physiological role and pharmacological actions of this fascinating nutrient.

Wading through the research literature on taurine is

no easy task, as a bewildering variety of actions – many of them tissue-specific and often seemingly contradictory – have been described. This diversity of actions may reflect the fact that taurine has an important modulatory impact on membrane structure and function (67). It is now believed that intracellular taurine interacts electrostatically with the head groups of neutral phospholipids (primarily phosphatidylcholine and phosphatidylethanolamine) in the inner plasma membrane and in intracellular membranes (67,70). This interaction has a direct effect on membrane permeability and fluidity, influences the susceptibility of membranes to covalent modification (inhibiting phosphorylation of certain membrane proteins, blocking methylation of phosphatidylethanolamine and reducing membrane peroxidation) (67,71,72), and modulates the structure and function of a range of membrane-bound proteins, including hormone receptors, transport proteins, ion channels, G proteins and enzymes. As membrane binding sites for taurine are not saturated by ordinary intracellular taurine levels, and as taurine transport is not saturated at ordinary plasma taurine levels, it is not surprising that the oral or parenteral administration of taurine can exert a variety of physiological effects. In interpreting in vitro studies with taurine, it should be noted that high extracellular taurine concentrations (e.g. ~10 mM) may alter the external plasma membrane in a manner that cannot be achieved in vivo except by high-dose intravenous infusion.

Taurine's effects on the heart, neurons and skeletal muscle have received the most research attention; its impact on vascular smooth muscle – most germane to the current discussion – has received relatively little study. Its effects on neurons and skeletal muscle may be primarily traceable to activation of chloride channels (67,73), which induces membrane hyperpolarization and thus has a 'depressor' effect on myoneural function. This may account for the possible clinical utility of taurine in the treatment of epilepsy, alcohol withdrawal syndrome and myotonia, as suggested by a few clinical studies (68,74,75).

Cardiac actions of taurine

The effects of taurine on the heart are fascinating but confusing. As we shall see, many of the effects of taurine and magnesium on cardiovascular and platelet function are parallel and possibly complementary, and presumably indicative of improved control of $[Ca^{2+}]_i$. However, taurine exerts a positive inotropic effect on heart function that is quite distinct from the actions of magnesium, and in fact involves an amplification of systolic calcium transients. Taurine enhances the sensitivity of calcium-activated calcium channels in the sarcoplasmic reticulum, resulting in a more vigorous release of calcium from the sarcoplasmic reticulum during the systolic action potential (76,77). However, the membrane effects of taurine also promote the activity of transport enzymes – notably the sarcolemma Ca-ATPase and Na/Ca-countertransporter (69,77,78) – which remove calcium from the cytoplasm during diastole, promoting rapid diastolic relaxation. In effect, taurine enables the calcium signal for contraction to snap on and snap off quite vigorously, resulting in efficient pump function. Taurine also somehow enhances the sensitivity of cardiac myofilaments to calcium, such that a slightly lower $[Ca^{2+}]_i$ is required to achieve a given degree of force generation (79); the maximal calcium-activated force generation is not altered.

Beta-adrenergic stimulation of the heart increases cardiac taurine transport through a cAMP-mediated mechanism (80). Thus, intracellular cardiac taurine levels are regulated to modulate inotropic activity. Not surprisingly, cardiac taurine levels are elevated in congestive failure (81); however, taurine administration elevates these levels further and promotes a greater inotropic effect. In oral doses ranging from 3 to 6 g daily, taurine has been shown to improve cardiac efficiency in congestive heart failure (82–84); confirmatory data is provided by a rabbit model of congestive failure (85). Unlike positive inotropes which inhibit the sodium pump or elevate cAMP levels, taurine does not increase arrhythmic risk or the heart rate. Indeed, parenteral pre-administration of taurine in animals has been reported to reduce their sensitivity to a range of arrhythmia-inducing stimuli (86–88); in this respect, taurine's action is parallel to that of hypermagnesemia. These considerations are of some importance, as there is fear that traditional inotropic therapy of congestive failure may sometimes actually increase mortality owing to greater cardiac oxygen demand and an increased incidence of arrhythmias (89).

As noted briefly above, taurine has a membrane-stabilizing antioxidant activity. Although taurine has little value as a free radical quencher, it nevertheless protects membrane lipids from peroxidative damage, presumably because of a steric effect on membrane structure (67). This may explain the observation that taurine perfusion (1–20 mM) protects guinea-pig hearts from reperfusion injury after 30 min of hypoxia; the taurine treatment decreased ventricular arrhythmias, enhanced recovery of electrical and mechanical function, reduced calcium overload and decreased LDH release (90). (The ability of taurine to protect the heart from calcium overload has been demonstrated in other experimental models as well (77).) More recently,

intravenous infusion of taurine (5 g) prior to coronary artery bypass surgery reduced the peroxidative damage to cardiac membranes (as assessed by chemiluminescence) measured after 10 min of reperfusion; the structural integrity of cardiac mitochondria was also protected by the taurine infusion (91). The membrane-stabilizing action of taurine is complemented by its ability to nucleophilically cleave hypochlorite, an inflammatory mediator released by activated macrophages (92); this suggests anti-inflammatory potential for taurine.

The ability of taurine to reduce reperfusion damage, prevent arrhythmias and promote efficient pump function (while minimally increasing cardiac oxygen demand), suggests that it would have value in the prevention or acute treatment of myocardial infarction. Another effect of taurine which could be beneficial in this regard is platelet stabilization. This stabilizing effect has been demonstrated both in vitro, and ex vivo after oral administration of 400–1600 mg taurine daily to human volunteers (93–96). Cyclooxygenase inhibitors such as aspirin interact synergistically with taurine in this regard (94). The little work that has been done to define a mechanism of action suggests that taurine blunts the $[Ca^{2+}]_i$ response to platelet-activating agonists (96). Supplemental taurine may be especially beneficial for platelet function in diabetics, as the taurine level of platelets from diabetics is lower than that measured in the platelets of age-matched controls (95); perhaps this has a bearing on increased platelet aggregability reported in diabetics.

In vivo, taurine may also act to stabilize platelets by an indirect mechanism: taurine promotes arterial prostacyclin production, as demonstrated both in vivo and in vitro with rat aortas (97). This latter action may reflect taurine's ability as an antioxidant to decrease lipid peroxide-mediated inhibition of prostacyclin synthetase.

Taurine and vascular smooth muscle

I am able to find only two studies which address the direct effects of taurine on vascular smooth muscle function. Recently, French researchers, working with perfused aortic rings from rats, noted that taurine perfusion (1–10 mM) reduced basal tone and had a relaxant effect on rings preconstricted with KCl or norepinephrine (98). This effect was not mediated by endothelium or by muscarinic or adrenoreceptors, and thus probably represented a direct effect of taurine on vascular smooth muscle cells. Although this study did not define the mechanism of taurine's vasorelaxant action, the authors suggest that taurine may be minimizing $[Ca^{2+}]_i$ by enhancing the activity of calcium-transporting enzymes. This suggestion is credible in light of evidence that taurine stimulates Ca-ATPase and Na/Ca-countertransport in cardiac sarcolemma. In a previous study, taurine perfusion was shown to relax KCl-preconstricted rabbit ear arteries, but did not significantly influence the tonic phase of norepinephrine-mediated contraction (99). Since KCl-mediated contraction (but not that induced by norepinephrine) results from calcium influx through voltage-gated calcium channels, these data suggest that taurine may reduce the open-probability of these channels, much like calcium channel-blocker drugs. In cardiac myocytes, taurine inhibits the rise in $[Ca^{2+}]_i$ induced by α-agonists (100); it would be of interest to determine whether taurine has an analogous effect on G_q-linked receptors mediating vasoconstriction in vascular tissue. Clearly, more work is required to define the impact of taurine on calcium transport mechanisms in vascular smooth muscle; in any case, the net effect of these actions appears to be a reduction of $[Ca^{2+}]_i$.

These findings cast some light on the ability of dietary taurine to prevent or delay the onset of hypertension in various rat models of this disease; the benefit ranges from modest to substantial, depending on the model examined (100–104). There are also several reports from Japanese clinicians, dating as far back as 1967 (105), that chronic oral administration of taurine reduces elevated blood pressures. In one such study, eight essential hypertensives received 6 g/day of taurine orally for 6 weeks; initial average blood pressure of 174/103 fell to 148/91, with a drop in mean blood pressure of 19 mmHg (106). These authors also reported that urinary taurine excretion was markedly subnormal in untreated hypertensives. In a later controlled study enrolling young subjects whose systolic pressure was slightly elevated, systolic and diastolic readings fell significantly by 9/4 mmHg, respectively, after 1 week of 6 g taurine/day; no change was noted in those receiving placebo (107). In general, the authors of reports demonstrating taurine's antihypertensive activity have suggested hormonal modulation – in particular, suppression of sympathetic activity – as its mode of action; while such effects might indeed play a part, the data cited above suggest that taurine is also directly influencing the responsiveness of vascular smooth muscle to vasoconstrictor agonists.

Intracellular signalling pathways triggered by $[Ca^{2+}]_i$ and protein kinase C also play a role in the hyperplasia of intimal smooth muscle that is the fundamental basis of atherogenesis (31); the anti-atherogenic action of calcium channel blocker drugs illustrates this principle. It is therefore reasonable to suspect that taurine might have a beneficial influence on the atherogenic process. In fact, inclusion of taurine in the drinking water (0.2–0.5%) of cholesterol-fed rabbits

significantly reduced the area of atherosclerotic plaque by 20–30%; blood pressure also fell significantly at the higher taurine intake (108). In mice subjected to arterial calcinosis by joint administration of high dose vitamin D and nicotine, taurine pre-treatment substantially prevented arterial calcium deposition and enhanced survival; diltiazem had a comparable effect (109). Since neither taurine nor diltiazem significantly influenced the vitamin D-induced hypercalcemia, these agents apparently functioned to block stimulated calcium influx in vascular smooth muscle cells. Good magnesium nutrition has a comparable protective effect in arterial calcinosis (1).

Although clinical and animal data bearing on taurine's effects on arteriopathy are still fragmentary, they are consistent with the possibility that taurine supplementation may retard the progression of both hypertension and atherosclerotic disease. Thus, in addition to its short-term benefits to the ischemic myocardium (anti-arrhythmic, platelet-stabilizing, membrane-stabilizing, improving cardiac efficiency and reducing cardiac afterload by lowering elevated blood pressure), taurine may work in the longer term to retard the development of coronary stenosis.

Taurine and diabetes

In light of magnesium's likely beneficial impact on insulin resistance and the complications of diabetes, it is appropriate to cite data pertaining to taurine's influence in this regard. Since 1935, a number of investigators have reported that taurine enhances insulin sensitivity and glucose tolerance in animals (110–112); this does not result from increased insulin production, as taurine appears to have a direct suppressive effect on β cell function (112). (One recent study noted that oral taurine failed to influence glucose levels in streptozotocin-treated mice (113); however, the administered dose of taurine – 0.1% in drinking water – was so low that plasma taurine levels were actually lower than in the healthy controls.) However, there do not appear to be any published clinical studies regarding taurine's impact on type II diabetes (perhaps because, until recently, there were few diabetics in Japan. Taurine is an extremely popular supplement in Japan, where it is promoted as a hangover remedy!) Taurine has been reported to bind with high affinity to the insulin receptor (114); however, this affinity is so high relative to intracellular or even plasma taurine levels that this binding clearly cannot mediate the modulatory effects of dietary taurine.

The pathogenic effects of hyperglycemia in diabetic microvascular disease may be mediated not only by protein glycation, but also by glucose-catalyzed free radical damage (115). Recent studies show that high extracellular glucose concentrations stimulate collagen synthesis, retard mitosis and promote membrane peroxidation in cultured mesangial cells; taurine – as well as vitamin E – prevents all of these effects, probably by limiting the peroxide-driven production of transforming growth factor-β (72,116,117). Altered mesangial cell function, as well as the resistance of glycation-damaged mesangial matrix to catabolism, appears to be the root cause of diabetic nephropathy (118,119). With respect to retinopathy, there is at least one clinical report that high dose antioxidant therapy may slow its progression (120); presumably, the membrane-stabilizing action of taurine could complement the benefits of other antioxidants in this regard. Also, by restraining $[Ca^{2+}]_i$, taurine might be expected to moderate the activity of protein kinase C; activation of this enzyme is believed to be another mediator of the angiopathic effects of hyperglycemia. Thus, there are various theoretical grounds for suspecting that, independent of any influence on glycemia, taurine might be protective with respect to the microvascular complications of either form of diabetes.

Complementary protection with magnesium and taurine

In overview, it appears that correction of magnesium deficiency, and/or the induction of hypermagnesemia with parenteral magnesium, have a number of effects on cardiovascular/platelet function that are strikingly parallel to those of supplemental taurine: reduction of elevated blood pressure, inhibition of atherogenesis, stabilization of platelets, prevention or correction of arrhythmias, prevention of tissue calcium overload, improvement of insulin sensitivity, and possibly also prevention of diabetic microangiopathy. These parallels are likely to reflect a common underlying mechanism of action: controlling $[Ca^{2+}]_i$ by limiting calcium influx while activating transporter proteins which extrude calcium. The exception to this generalization is taurine's ability to enhance systolic calcium transients in cardiac cells by stimulating calcium-activated calcium channels in sarcoplasmic reticulum – an effect largely responsible for the positive inotropic effect induced by taurine but not by magnesium. (In vascular smooth muscle, the predominant calcium channel of the sarcoplasmic reticulum is opened by inositol triphosphate, rather than cytoplasmic calcium, which may explain why taurine does not induce vasoconstriction (121).)

In a companion publication (122), I have defined a disorder of intracellular signalling – protein kinase C hyperresponsiveness syndrome, or 'PKC syndrome'

for short – which sensitizes vascular smooth muscle (and perhaps other tissues) to a variety of vasoconstrictive and growth factor stimuli, and which is induced by many aspects of our modern diet (as contrasted to the nutritional intakes of our paleolithic forebears). Evidence is adduced that PKC syndrome plays a fundamental pathogenic role in essential hypertension, atherogenesis, insulin resistance, platelet hyperreactivity and possibly the promotion of certain types of cancer. The factors which induce PKC syndrome do so by increasing $[Ca^{2+}]_i$ and/or by increasing production or tissue levels of diacylglycerol – thereby either increasing the baseline activity of PKC or rendering it more sensitive to activation by G_q-linked receptors. Elevated PKC activity, alone or in conjunction with increased $[Ca^{2+}]_i$, is fundamental to vasoconstriction, mitotic signalling, platelet aggregation, and cancer promotion, and may be an important cause of insulin resistance. Magnesium and taurine are likely to be protective with respect to PKC syndrome in many tissues. Other likely protective factors include low-fat, low-sodium diets, ample intakes of omega-3 oils, potassium, calcium, chromium and vitamin E, as well as aerobic exercise training and correction of abdominal obesity.

Proposal for magnesium taurate

Clearly, supplemental taurine can be expected to complement many of the vascular-protective benefits of good magnesium status, and moreover may have considerable value in its own right. These considerations encourage the development of magnesium taurate as a supplemental nutrient. This complex has been described once before in the chemical literature – as an intermediate in the synthesis of benzylidene derivatives (123). More recent studies indicate that magnesium taurate occurs both as a salt and as a complex (Sanchez R, Zielinski J, personal communication). The salt is rapidly water soluble; the complex, although insoluble, rapidly breaks down to yield dissolved magnesium ions and free taurine when added to water that is even slightly acidic. Furthermore, the complex appears to be in equilibrium with the salt, such that, when added to water at neutral or alkaline pH, the complex will gradually yield free dissolved ions. Thus, it can be anticipated that either the salt or complex will have good nutritional availability when administered orally, even if gastric acidity is suboptimal. A daily dose providing the full USRDA of magnesium (400 mg) would concurrently provide about 4.1 g taurine – well within the range demonstrated to be therapeutically effective in congestive heart failure. An administration schedule of two tablets, twice daily, would presumably be required to deliver 400 mg of magnesium; if one were to ingest another high-availability source of magnesium plus straight taurine to achieve analogous benefits, eight tablets daily would be needed – hardly optimal from a compliance standpoint. The inclusion of magnesium taurate as a chief source of magnesium in high-quality 'nutritional insurance formulas' would enable these products to provide a significant dose of taurine in addition to the essential vitamins and minerals. Since magnesium and taurine are both very inexpensive, there should be few financial barriers to the widespread use of magnesium taurate.

To date, the studies that have demonstrated the therapeutic benefit of magnesium infusion in the treatment of acute myocardial infarction, have made use of magnesium sulfate. In light of the many effects of taurine that would be protective to the ischemic myocardium – promoting efficient mechanical function and normal electrical activity. reducing oxidant- or calcium-mediated tissue damage, and decreasing thrombotic risk – there may be at least as strong a rationale for taurine infusion as for magnesium. Both objectives could be accomplished by infusion of magnesium taurate – although joint infusion of magnesium sulfate and taurine would also be feasible. (Another nutrient which clearly should be included in such infusion formulas is L-carnitine; such infusion should of course be used as adjuvant to thrombolytic therapy.) The ischemic myocardium tends to lose taurine (124), perhaps owing to failure of energy-dependent active transport; this provides a further rationale for taurine infusion. It is surprising that taurine for treatment of acute myocardial infarction has received little if any previous advocacy; certainly, the work of previous investigators hints strongly at this application (88,90,91).

In light of the well-documented efficacy of parenteral magnesium sulfate for treatment of pre-eclampsia/eclampsia (Sanchez R, Zielinski J, personal communication), it is reasonable to suspect that magnesium taurate could be even more beneficial. This syndrome is characterized by vasospasm, hypertension, increased platelet aggregation and increased free radical activity (124–126), all of which might be favorably influenced by taurine administration. The neurological symptoms often encountered in severe pre-eclampsia or eclampsia (headache, confusion, visual disturbances, paresis and convulsions), may reflect focal cerebral ischemia induced by vasospasm (127,128). It is therefore interesting to note that taurine has been reported to protect transiently hypoxic neurons both in vitro and in vivo, and moreover shows anticonvulsant activity in many although not all animal models, including hypoxia-induced convul-

sions in mice (130–134). Beneficial effects of oral taurine in clinical epilepsy have also been reported, although there is marked inter-individual variability in response (131,133,134). Thus, it can be anticipated that intravenous infusion of magnesium taurate will be a most effective therapy for pre-eclampsia/eclampsia; if administered orally earlier in pregnancy as a component of prenatal supplementation, it might well have preventive value.

References and further reading

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