Taurine and vascular tone modulation

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ABSTRACT

Taurine, an ubiquitary amino acid in the organism, has important physiological functions like bile salt formation, neuronal excitability regulation, immunomodulation, electrolytes homeostasis preservation, osmoregulation, membrane stabilisation, apoptosis inhibition and cell protection. This review article is focusing on the complex vasoactive influence of the sulphur-amino acid and on the possibly involved mechanisms that may underline these effects. Acting on endothelial and smooth muscle cells in the vessels, it regulates blood pressure and delays atherogenesis process, having an increased therapeutic potential that needs to be further explored.

Key words: taurine, vascular tone, vascular reactivity, nitric oxide, vascular smooth muscle cells

INTRODUCTION

Taurine (2-aminoethanesulfonic acid) is the most abundant intracellular free amino acid in the organism, found both in cytosol and plasma, mostly at the level of the myocardium, brain, skeletal muscles, retina, neutrophils and platelets (1,2). Taurine is considered a semi-essential amino acid, because even if is synthesized in the liver from cysteine or methionine in a vitamin B6-dependent manner, its major source is the diet, being predominantly found in meat, eggs and sea food (3). Taurine has been intensively studied in the past years, for its clinical applications as supplemented pharmaconutrient, or as a conditionally-essential amino acid in some subjects in need for long-term parenteral nutrition (3).

Taurine is involved in many physiological processes like bile acids conjugation, regulation of neuronal excitability, immunomodulation, cellular cations homeostasis preservation, osmoregulation, membrane stabilisation, apoptosis inhibition and cell protection (1,4). Taurine has beneficial systemic or

organ-focused effects on the brain, liver, kidney, eye and cardiovascular system (1).

This review focuses on the complex vascular effects of taurine. At this level, it acts in different key points, lowering different risk factors for cardiovascular disease. Thus, it has been shown that taurine can prevent atherosclerosis development by ameliorating lipid profile (5), lowering homocysteine plasmatic concentration (6), reducing intima inflammation and oxidative stress (7,8), decreasing endothelial dysfunction, modulating vascular reactivity and inhibiting vascular muscle cells proliferation (9). More than that, taurine has a protective role in diabetes mellitus (10), reduces blood pressure (11) and modulates haemostasis, especially platelet function (12).

Overall, through its complex positive actions and the lack of adverse effects, taurine is a good candidate for therapeutic use as dietary supplement in cardiovascular disease prevention (8).

Taurine effects on vascular reactivity

Taurine lowers blood pressure by reducing vascular resistance (13,14) and plasma levels of endothelin, neuropeptide Y and thromboxane B₂ (15,16). It also regulates kinin-kalikrein system and brings down plasmatic concentration of norepinephrine and epinephrine after long-term administration in rats (17) and humans (18-20). Other mechanisms by which taurine may influence blood pressure and delay the onset and progression of the atherosclerosis process may be linked to its action on endothelial cells or on the vascular smooth muscle cells (VSMCs), as it will be further presented.

Taurine effects on induced-vasoconstriction

There are several lines of evidence regarding protective effects of taurine in exogenous induced-vasoconstriction. Therefore, taurine administration in endothelial cell cultures from the human umbilical vein (HUVEC) incubated in a conditionally monocytes environment from smokers, brought to normal nitric oxide (NO) and endothelin-1 levels (16). *In vivo* taurine administration reduced the inhibition of the endothelial-dependent vasodilator response induced by a single low-density lipoprotein (LDL) injection. *In vitro* studies on HUVEC exposed to oxidized-LDL and incubated with taurine showed a reduced inhibition of NO formation and a reduced increase of the level of alpha tumor-necrosis factor (α -TNF), malondialdehyde (MDA), lactate dehydrogenase (LDH) and ADMA (the endogenous competitive inhibitor of NO synthase). Through all these effects taurine proved to be efficient

in providing protection against induced endothelial dysfunction (21).

However, most of the information regarding taurine's action on vascular reactivity comes from animal studies. Chronic oral supplementation of the sulphur-amino acid in drinking water showed an *ex-vivo* diminished contractile response to norepinephrine and KCl of endothelium-free or endothelium-intact aortic rings isolated from WKY rats (22). On the other hand, taurine had no effect on the contractile response determined by norepinephrine *in vitro*, although it reduced KCl-induced contraction in arteries isolated from rabbit ears (23). Long-term taurine administration attenuated epinephrine induced vasoconstriction of the mesenteric artery rings in spontaneously hypertensive stroke prone (SHRSP) rats (24). Taurine showed an *in vitro* vasodilating response on porcine coronary arteries vasoconstricted by serotonin, KCl, CaCl₂, U46619 (a TBX A₂ analogue), in a dose dependent manner (25). It also demonstrated an *in vitro* inhibitory effect on norepinephrine / KCl - induced vasoconstriction, when rat aortic rings have been incubated with both high (26) and low taurine doses (27).

Treating rats with beta-alanine (a frequently used substance for endogenous taurine deprivation) produced an enhancement of norepinephrine and KCl induced vasoconstriction on the endothelium-free aortic rings (28) and a higher contractile response to angiotensin II (29).

Taurine effects on induced-vasodilatation

Except for inhibiting vasoconstriction in response to different exogenous substances, taurine also exerts a positive influence on substance-induced vasodilatation. Short-term (14 days) and low doses (1.5 g/day) administration of the sulphur-amino acid in diabetes type I patients normalized arterial rigidity and showed a positive effect on flux-mediated vasodilatation (30). The same dose of taurine, but administered in a shorter period (5 days) on young smokers led to an ultrasonographic improvement of the endothelial-dependent vasodilatation (16).

Chronic taurine administration in WKY rats led to a better acetylcholine-induced vasodilatation in endothelium-intact aortic rings (22). A similar endothelial-dependent effect was registered in diabetic and hypercholesterolemic rats, in which taurine augmented the acetylcholine-induced aortic rings relaxation (31). Also, incubating isolated vascular tissue, like aortic rings from streptozocin-treated diabetic rats with taurine amplified the acetylcholine-stimulated vascular relaxation (32).

Endogenous taurine deficiency determined by beta-alanine administration, led to reduced vasodilator response of the rat endothelium-intact aortic rings, when exposed to supramaximal acetylcholine levels. Beta-alanine treatment also produced a lower sensitivity of the endothelial - denuded aortic rings to sodium nitroprusside (28). Taurine depletion led to a similar effect on the endothelium-intact or endothelium-free aortic rings, reducing the 2-chloride-adenosine and 5'-N-ethyl-carboxyamino-adenosine (adenosine receptors agonists) induced relaxation. Same action of the sulphur-amino acid was obtained when 2-chloride adenosine (but not 5'-N-ethyl-carboxyamino-adenosine) has been used to induce vasodilatation in the superior mesenteric artery rings, suggesting that its vasoactive influence is independent on the artery type, but dependent on type of adenosine receptors agonist involved (33). On the other hand, *in vitro* endogenous taurine deprivation by beta-alanine administration didn't change the influence of some vasoactive agents on vascular reactivity (29).

Taurine and endothelial NO release

Available data regarding the influence of taurine on NO endothelial release are conflictual, despite a considerable number of findings suggesting a stimulatory effect of the sulphur-amino acid on NO production.

Upregulation of NO endothelial release, with consecutive vasodilating effects, has been observed both in human and animal studies. Therefore, either *in vivo* taurine supplementation in humans after a single injection of native LDL-cholesterol, or *in vitro* taurine incubation of HUVEC exposed to oxidized LDL, led to a lower raise of ADMA and a lower NO decrease induced by endothelial dysfunction (21). A similar protective role of taurine in endothelial dysfunction has been shown after oral administration of the sulphur-amino acid in young smokers, determining a lower inhibitory effect on vasodilatation induced by vasoactive agents, while *in vitro* taurine incubation with HUVEC exposed to a conditional monocyte environment from smokers, normalized NO levels (16). Taurine also showed a stimulatory effect on nitrite/nitrate (NOx) production, as stable end-products of NO metabolism, when administered in HUVEC cultures (34). The same results regarding taurine's effect on NO production have been noticed in lab animals. Supplementation of the sulphur-amino acid in drinking water determined an improvement of NO bioavailability in post-weaning protein restriction rats, and partially prevented blood pressure increase (35). Additionally, endogenous taurine deficit induced by beta-alanine in L-NAME rats, was shown to

produce a lower NO synthesis (33).

However, other studies noted a lack of any effect of taurine on the nitric oxide production. *In vitro* administration of the NO - synthase inhibitor L-NAME did not modify aortic rings relaxation when incubated with taurine, indicating that the vasodilating effect of the sulphur-amino acid is not NO-dependent (26). An *ex-vivo* study on taurine treated rats (1% in drinking water) showed a neutral effect on both blood pressure and NO, respectively NO-synthase (NOS) plasma levels (15). Moreover, oral administration of taurine prevented blood pressure raise and plasma NO decrease in cyclosporine treated rats, but without reaching the statistical significance (36). Taurine given in the same concentration (1% in drinking water) led to a significant increase in NO and NOS plasma levels, but this effect wasn't confirmed by taurine deprivation with beta-alanine (37). Even if intraperitoneal supplementation of taurine limited NO metabolites production in Wistar rats fed with a high fructose diet and induced insulin resistance syndrome, it had no significant influence on their plasma concentration when was administered in healthy animals (38).

Taurine also showed a downregulatory action on nitric oxide production, by reducing the final NO products level in certain situations associating their raise. Therefore, it lowered mRNA expression of endothelial NOS on aortic rings of diabetic rats, this suggesting a potential beneficial effect of taurine on endothelial dysfunction induced by diabetes mellitus (39). It has also been shown that taurine may decrease mRNA expression of inducible NOS (iNOS), neuronal NOS (nNOS) and nitrosative stress in human Schwann cells exposed to a hyperglycaemic environment, suggesting a potential treatment in diabetic neuropathy (40). Taurine administered 2% in drinking water had a restorative effect in a rat model of hepatic fibrosis (induced by simultaneous chronic iron load and ethanol), by decreasing the nitrosative stress, raising the thiols level and decreasing the hepatic accumulation of nitrates. Oxidized protein level was also lowered, this being demonstrated by downregulatory action on the antibodies against 4-hydroxinenol and 3-nitrotyroline (41). More than that, taurine has proved efficiency in lowering NO production, oxygen reactive species, apoptosis and isolated hepatocytes necrosis in rats treated with lipopolysaccharides and antioxidant substances, pointing an anti-inflammatory role of the sulphur-amino acid in the systemic inflammatory syndrome (42). Anti-inflammatory and anti-fibrotic roles have also been noted in a pulmonary fibrosis model induced by bleomycin administration in mice. Taurine

and niacin simultaneous oral treatment suppressed bleomycin-induced NO raise, by reducing iNOS gene expression in the lungs (43).

Controversies in the studies regarding the effect of taurine on NO release may have multiple causes: different hypertension models used, different individual pathological conditions in humans which may interfere with the endothelial function assessment, or the still limited number of models used to investigate endothelial dysfunction (L-NAME, ADMA). In order to get a clear view of the real modulator mechanisms, by which taurine exerts its action on endothelial level, concomitant cell cultures and endothelial arterial slices from different vascular sources should be used, and sample collection from intact animals should always be considered. Doses and time administration (acute/chronic) heterogeneity, as well as the different pathways used for drug administration could also explain the large variability of the results.

Taurine influence on vascular smooth muscle cells

Regarding the modulator influence of taurine on vascular tone, it has been shown that the sulphur-amino acid could act also on other mechanisms than the ones previously mentioned, like interference of the vascular smooth muscle cells (VSMCs) proliferation. Unfortunately, data on this topic is rather poor (4). *In vitro* studies based on the assessment of cell number in rat aorta VSMCs culture or (3H) thymidine incorporation in DNA, showed direct antiproliferative effects of the sulphur-amino acid. Indirect effects of taurine on VSMCs proliferation have also been evidenced, by evaluating the PDGF (platelet-derived growth factor) receptor dephosphorylation (44,45). These results are also sustained by ex vivo studies, in which taurine was shown to lower neointimal hyperplasia and proliferation of VSMCs in rats suffering an iatrogenic carotid injury (46). Taurine demonstrated indirect effects on VSMCs proliferation by lowering angiotensin II vascular action and consecutive remodelling (15,47). Moreover, taurine lowered high plasma homocysteine levels induced by exogenous substances and antagonized the pro-oxidative effects of homocysteine on VSMCs (6,48).

The sulphur-amino acid may also influence the atherogenic process by other mechanisms, like prevention of endothelial adhesion and trans-endothelial migration of leucocytes, inhibition of adhesion molecules expression (ICAM-1) or downregulating the endothelial apoptosis (49,50). Taurine proved a beneficial effect on HUVEC in exogenous induced necrosis mediated by neutrophils (51), and also demonstrated a

positive effect on atherosclerosis progression by improving the lipid profile. Therefore, it was shown to lower the LDL-cholesterol oxidation, to stimulate the bile acids production, to reduce cholesterol hepatic reserve and to prevent the raise of plasma triglycerides, total cholesterol, LDL and VLDL, while reducing the HDL levels (2,9). Also, studies focused on vascular disease have noted that taurine can prevent LDL cholesterol oxidation in rodents, by reducing lectin-like receptor for oxidized LDL, along with an attenuation on the endothelial dysfunction and inhibition of the atherosclerotic process (52,53).

CONCLUSION

Despite the conflictual literature data regarding its effect on endothelial function modulation, taurine has been proven to have an overall protective action on blood vessels (34). By integrating available data, we can conclude that taurine has an inhibitory influence on the vessel tone under basal conditions or under vasoactive stimulation, facilitating vasodilatation induced by exogenous substances, and inhibiting the induced vasoconstriction.

Taurine also contributes to a reduction of the smooth muscle cells proliferation in the arterial wall and has a positive effect on lipid profile, slowing down the atherosclerotic process. There are a series of intrinsic elementary mechanisms through which taurine has these complex protective effects. Even though there is a lot of available data in the literature concerning this subject, more studies are necessary to complete knowledge in this field.

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