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Effects of taurine on contractions of human internal mammary artery: a potassium channel opening action

K. KARABACAK[1], E. KAYA[1], K.G. ULUSOY[2], M. SEYREK[2], M. KURTOGLU[4], S. DOGANCI[1], V. YILDIRIM[3], O. YILDIZ[2], U. DEMIRKILIC[1]

[1]Department of Cardiovascular Surgery, Gulhane Faculty of Medicine, Ankara, Turkey
[2]Department of Medical Pharmacology, Gulhane Faculty of Medicine, Ankara, Turkey
[3]Department of Anesthesiology, Gulhane Faculty of Medicine, Ankara, Turkey
[4]Department of Cardiovascular Surgery, Guven Hospital, Ankara, Turkey

Abstract. – OBJECTIVE: Taurine is an abundant amino acid that is widely distributed in human and animal tissues. Pharmacodynamic studies show that taurine has hypotensive and myocardial protective effects. Studies in isolated tissue baths show that taurine relaxes precontracted arteries. This study aimed to show the effects of taurine on human internal mammary artery (IMA) *in vitro* and to explain the mechanisms of its effects.

METHODS: The response in the IMA was recorded isometrically by a force displacement transducer in isolated organ baths. Taurine (20, 40, 80 mM) was added to organ baths after precontraction with KCl (45 mM) or serotonin (5-HT, 30 μM). Taurine-induced relaxations were also tested in the presence of the cyclooxygenase inhibitor indomethacin (10 μM), the nitric oxide synthase inhibitor L-NAME (100 μM), the large conductance Ca^{2+}-activated K^+ channel inhibitor tetraethylammonium (TEA, 1 mM), the ATP-sensitive K^+ channel inhibitor glibenclamide (GLI, 10 μM), the voltage-sensitive K^+ channel inhibitor 4-aminopyridine (4-AP, 1 mM) and the inward rectifier K^+ channel inhibitor barium chloride ($BaCl_2$, 30 μM).

RESULTS: Taurine did not affect the resting tone of IMA. However, it produced relaxation in the 5-HT and KCl-precontracted preparations. The relaxation to IMA was not affected by GLI, 4-AP, $BaCl_2$, indomethacin and L-NAME. But, TEA inhibited taurine-induced relaxations significantly ($p < 0.05$).

CONCLUSIONS: The preincubation of IMA with taurine antagonized KCl and 5-HT induced contractions in a concentration dependent manner, while it did not affect the resting tone. The relaxations to taurine were significantly antagonized by pretreatment with TEA.

These results suggest that mechanism of vasodilator effect of taurine in IMA may be the activation of large conductance Ca^{2+}-activated K^+ channels.

Key Words:
Taurine, Internal mammary artery, Vasodilation, Potassium channel.

Introduction

Taurine is a sulphur-containing intracellular β-amino acid found in large quantities not only in brain but also in peripheral tissues such as heart, muscle and blood. In some tissues, the concentrations of taurine exceeds 10 mM, and it may even be higher locally because large amount of taurine may be released in to the neighbouring interstitial tissue, i.e. heart, neurons, when cells are damaged[1-3]. It has been suggested that taurine plays important roles in neuromodulation, thermoregulation, osmoregulation, calcium regulation, antioxidant defence, apoptosis, and vascular functions[4-9]. Several pharmacodynamic studies have shown that taurine has hypotensive effect following acute and long-term administration. Previously, Franconi et al[10] showed that taurine relaxed high potassium and noradrenaline precontracted rabbit ear artery. Additionally, Ristori and Verdetti[11] showed that taurine, at physiological concentrations, relaxes rat aorta precontracted with high potassium and noradrenaline. The vasodilator effect of taurine was independent of endothelium and extracellular calcium in rat aorta[11]. Furthermore Li et al[12] reported that taurine relaxed norepinephrine -precontracted mesenteric arteries from spontaneous hypertensive rats, but not from normotensive rats *in vivo* and *in vitro*. Recently Liu et al[13] have reported that taurine antagonizes and relaxes the contractions of the porcine coronary artery via activation of some

Corresponding Author: Oguzhan Yildiz, MD; e-mail: oyildiz@gata.edu.tr

potassium channels. To our knowledge, little is known about the mechanism of vasodilator effect of taurine in human vasculature.

Coronary artery bypass grafting (CABG), is the most reasonable and reliable treatment in multivessel coronary artery disease patients[14]. The internal mammary artery (IMA) is the graft of choice in CABG operations to replace diseased coronary vessels, because of its greater long-term success that is related to graft patency. But, as with any other vessel, it has a tendency to spasm during operation, and early postoperative period[15]. Several studies have reported some vasoactive drugs altering IMA graft flow[16,17]. However, there is no study related to effects of taurine on IMA.

The present study was designed to elucidate the effects of taurine on IMA and to explore its vasodilator mechanism by studying the effects of different specific inhibitors and endothelial denudation on the effect of taurine.

Methods

Tissue Preparation

IMA preparations were obtained from patients undergoing CABG. Approval to use discarded IMA tissue was granted by the Ethics Committee of Gulhane Faculty of Medicine (KAEK-14038), and this investigation conforms to the principles outlined in the Declaration of Helsinki (2013). IMA preparations were put immediately in cold (4°C) Krebs-Henseleit solution (NaCl, 118 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM; KH_2PO_4, 1.2 mM; $MgSO_4$, 1.2 mM; glucose, 10 mM; and $NaHCO_3$, 25 mM; pH 7.4) and transferred immediately to the laboratory where the preparations were dissected from adhering fat and connective tissue and then cut into 3- to 4-mm length rings. The rings were mounted in an organ bath containing 10 mL of Krebs-Henseleit solution, on an L-shaped brace for tension measurement along the former circumferential axis. The solution was gassed with 95% O_2 and 5% CO_2 at 37°C. Changes in arterial tensions were recorded isometrically by a force-displacement transducer (model FT03, Grass Instruments, Astro-Med Inc, West Warwick, RI, USA) and recorded continuously on a multichannel recorder polygraph (model P122, Grass Instruments, Astro-Med Inc, West Warwick, RI, USA) by using computer software (Polyview, version 2.0, Grass Instruments, Astro-Med Inc, WestWarwick, RI, USA). The segments were allowed to equilibrate under final resting force of 2.0 g for at least 2 hours and were washed every 30 minutes before one of the following four protocols being undertaken.

Experiments on Effects of Taurine on Basal Tone and After Precontraction with KCl and 5-HT

After the equilibration period IMA rings were challenged with 45 mM KCl to test their viability. The rings that were contracted more than 2 g were included in the experimental protocol. The tissues were washed every 10 minutes during a 30-minutes additional equilibration period.

Thereafter, cumulative concentrations (20, 40, 80 mM) of taurine were added to organ bath to test its effect on basal tone. In another set of experiments, taurine (20, 40, 80 mM) was added to organ bath before contraction with KCl (45 mM) and 5-HT (30 μM). Additionally, the rings were challenged with 5-HT (30 μM) after incubation with taurine (20, 40, 80 mM) for 20 minutes. In another set of experiments, the contractions to KCl (11, 22, 45, 68 mM) were tested in the absence and presence of taurine (80 mM).

Experiments on Effects of Taurine on Contractions Induced by Calcium Chloride ($CaCl_2$)

In another set of experiments, antagonistic effect of taurine on contractions to $CaCl_2$ was investigated by obtaining concentration-response curves to $CaCl_2$ (10 μM to 10 mM) in the absence and presence of taurine (20, 40, 80 mM) as described previously[17]. After the equilibration period, the rings were washed three times at 15-min intervals with Ca^{2+} free Krebs solution containing 1 mM ethylenediaminetetraacetic acid (EDTA, disodium salt). Then, the rings were bathed with Ca^{2+}free (containing 1 mM EDTA), 45 mM KCl Krebs solution with or without taurine for 20 min.

Effect of Endothelial Denudation on Taurine Responses

In this group of experiments, endothelial layers of some IMA segments were removed by mechanical rubbing. After arterial strips were precontracted with 45 mM KCl, the relaxation to acetylcholine (ACh, 1 μM) was used to test the success of endothelial denudation. In these preparations, taurine (20, 40, 80 mM) was added to organ bath after precontraction with KCl (45 mM), and the relaxations to taurine were compared with control taurine responses.

Experiments with Inhibitors of NOS, Cyclooxygenase, and K^+ Channels

In some experiments, after the equilibration period, IMA rings were challenged with 45 mM KCl to test their viability. Then, the tissues were washed every 10 minutes during a 30-minute additional equilibration period. The rings were incubated with cyclooxygenase inhibitor indomethacin (10 μM), nitric oxide synthase inhibitor L-NAME (100 μM), nonselective large-conductance Ca^{2+}-activated and voltage-sensitive K^+ channel inhibitor TEA (1 mM), ATP-sensitive K^+ channel inhibitor glibenclamide (10 μM), and voltage-sensitive K^+ channel inhibitor 4-AP (1 mM), inward rectifier K^+ channel inhibitor $BaCl_2$ (30 μM) for 30 minutes, before precontraction with depolarizing agent KCl (45 mM), and the relaxations to taurine (20, 40, 80 mM) were recorded.

Chemicals

KCl, TEA and $BaCl_2$ were purchased from Merck Co (Darmstadt, Hessen, Germany). Taurine, glibenclamide, indomethacin, and Nω–nitro-L-arginine methyl ester (L-NAME) were purchased from Sigma Chemical Co (St Louis, MO, USA). 4-Aminopyridine (4-AP) was purchased from Acros Organics (Thermo Fischer Scentific, New Jersey, NJ, USA).

Statistical Analysis

Taurine-induced relaxations were expressed as percent of KCl (45 mM) contraction as arithmetic mean ± SEM. Taurine-induced relaxations in the presence and absence of the K^+ channel inhibitors were expressed as the percentage of the maximum KCl (45 mM) response in each corresponding tissue. Comparison among multiple groups was made by using a one-way ANOVA followed by Scheffe's procedure post hoc to determine significant differences among the means of the data groups. When needed, statistical significance between two groups was evaluated by Student's *t*-test for paired data. A probability of $p < 0.05$ was accepted as significant difference. In all experiments, n equals number of patients from whom the arteries were obtained.

Results

KCl (45 mM) produced a marked and sustained contraction of upon the basal resting tone of IMA preparations. However, incubation with taurine (20, 40, 80 mM) for 30 min did not significantly change the basal resting tone (n=6, data not shown).

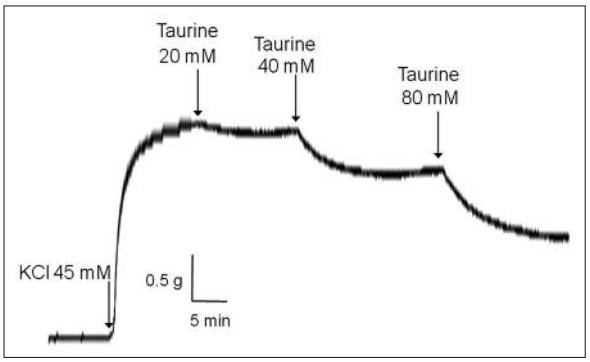

Figure 1. Original tracing of KCl (45 mM) – precontracted human internal mammary artery rings showing relaxation to taurine (20, 40, 80 mM).

In other set of experiments, taurine (20, 40, 80 mM) induced significant relaxations after precontraction of KCl ($p < 0.05$) (Figures 1, 2). In addition, the contractions to KCl (11, 22, 45, 68 mM) were significantly antagonized by taurine (80 mM) ($p < 0.01$) (Figure 3).

5-HT (30 μM) induced a marked and reproducible contraction in IMA. After incubation with taurine (80 mM) 5-HT-induced contractions were significantly decreased ($p < 0.05$). Additionally the contractions to 5-HT, in the presence of 80 mM taurine, were significantly lower than that in the presence of 20 mM taurine ($p < 0.05$) (Figure 4).

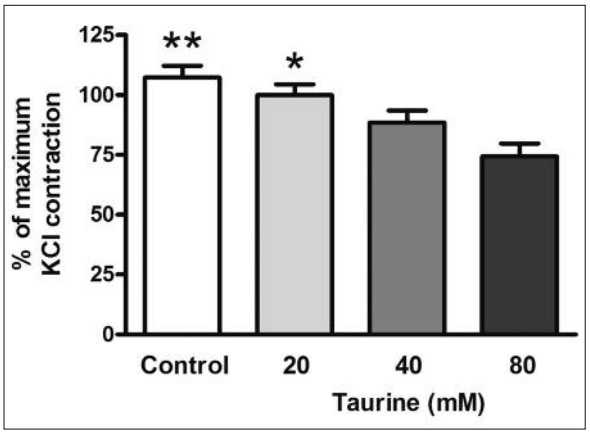

Figure 2. The inhibitory effects of 30 min preincubation with taurine (20, 40, 80 mM) on contractions induced by KCl (45 mM) in human internal mammary rings (n = 6). Data are expressed as percentage of the previous KCl (45 mM) contraction obtained in the same ring. Each value is mean ± SEM. Vertical bars represent SEM. *$p < 0.05$, **$p < 0.005$ compared with taurine 80 mM.

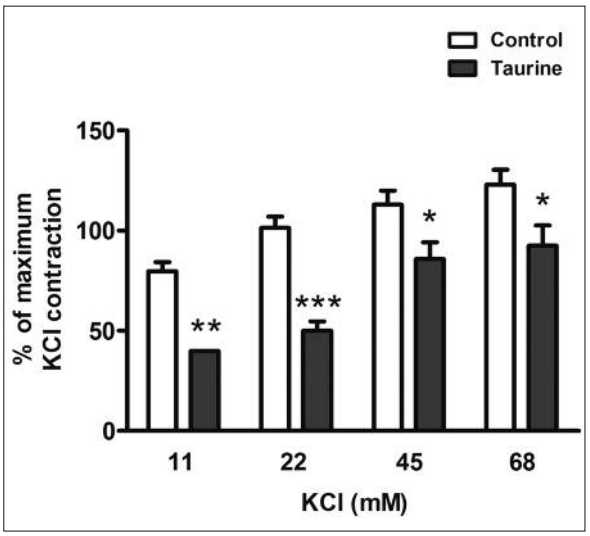

Figure 3. The inhibitory effects of 30 min preincubation with taurine (80 mM) on contractions induced by KCl (11, 22, 45, 68 mM) in human internal mammary rings (n = 5-6). Data are expressed as percentage of the previous KCl (45 mM) contraction obtained in the same ring. Each value is mean ± SEM. Vertical bars represent SEM. *$p < 0.05$, **$p < 0.001$, ***$p < 0.0001$ compared with corresponding control.

In another set of experiments, KCl (45 mM) and $CaCl_2$ (10 μM-10 mM, in calcium free Krebs-Henseleit solution) contracted IMA preparations in a concentrations-dependent manner. Incubation with 20, 40, 80 mM taurine inhibited $CaCl_2$ (10 μM to 10 mM)-induced contractions significantly ($p < 0.001$). Additionally, $CaCl_2$ (10 mM)-induced contractions were significantly inhibited in the presence of taurine (40 and 80 mM) ($p < 0.01$) (Figure 5).

Relaxations to taurine (20, 40, 80 mM) in endothelial-intact preparations were not different when compared to endothelium-denuded IMA segments (n = 4, data not shown).

The relaxation to IMA was not affected by the K^+ channel inhibitors glibenclamide, 4-AP and $BaCl_2$. But, TEA inhibited taurine-induced relaxations significantly ($p < 0.05$) (Figure 6). Indomethacin or L-NAME did not affect taurine-induced relaxations (n = 4, data not shown).

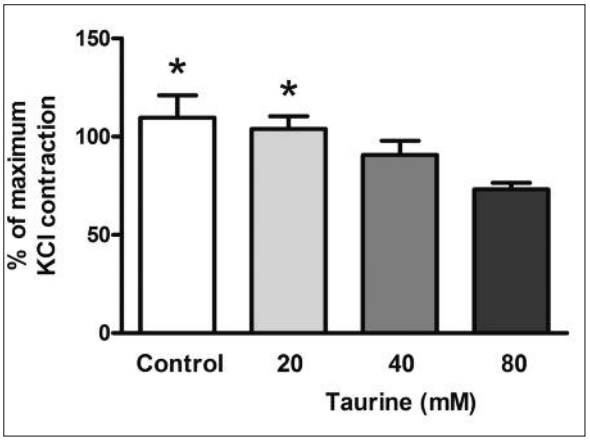

Figure 4. The inhibitory effects of 30 min preincubation with taurine (20, 40, 80 mM) on contractions induced by 5-HT (30 μM) in human internal mammary rings (n = 4-8). Data are expressed as percentage of the previous KCl (45 mM) contraction obtained in the same ring. Each value is mean ± SEM. Vertical bars represent SEM. *$p < 0.05$, compared with taurine 80 mM.

Discussion

The present study is the first to report intracellular amino acid taurine-induced relaxation of a human artery (IMA) *in vitro*. The maximum magnitude of taurine-induced relaxation in human IMA (30-40%) was similar to those observed in animal vessels[11,13]. The acute vasorelaxant effect of taurine is not mediated via endothelium dependent nitric oxide or prostanoid-mediated mechanisms. However, vasorelaxation to taurine seems to be mediated by increasing K^+

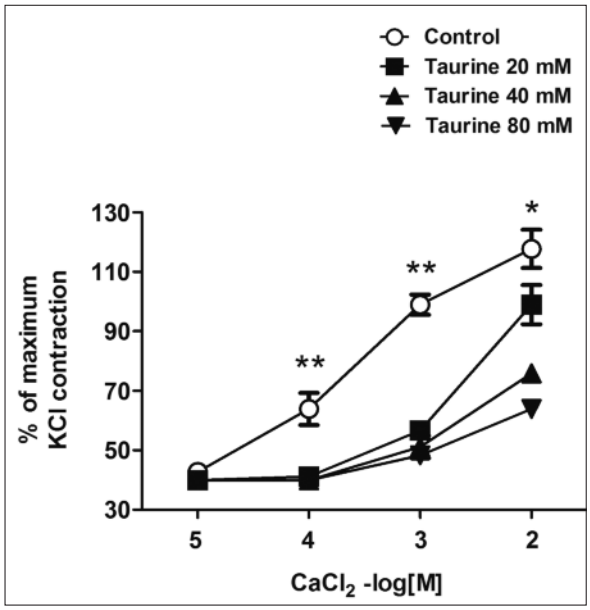

Figure 5. Effects of 30 min preincubation with taurine (20, 40, 80 mM) on contractions induced by $CaCl_2$ (10^{-5} to 10^{-2} M) in human internal mammary rings (n = 6). Data are expressed as percentage of the previous KCl (45 mM) contraction obtained in the same ring. Each value is mean ± SEM. Vertical bars represent SEM. *$p < 0.05$, **$p < 0.0001$ compared with corresponding control.

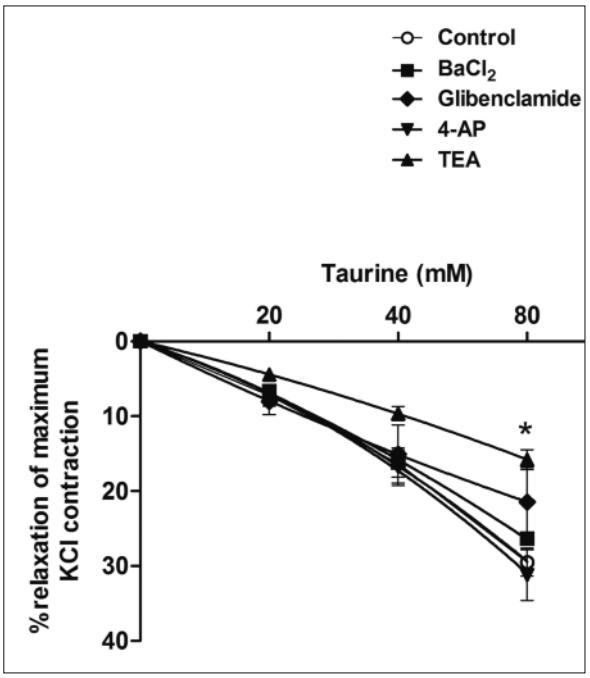

Figure 6. Cumulative relaxation to taurine (20, 40, 80 mM) in human internal mammary artery rings precontration with 45 mM KCl in the presents of tetraethylammonium (TEA, 1 mM), glibenclamide (GLI, 10 μM), 4-aminopyridine (4-AP, 1 mM), barium chloride ($BaCl_2$, 30 μM) (n= 6-10). Data are expressed as percentage of the previous KCl (45 mM) contraction obtained in the same ring. Each value is mean ± SEM. Vertical bars represent SEM. *$p < 0.05$ compared with corresponding control.

efflux through large conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels, but not via ATP-sensitive K^+ (K_{ATP}) or voltage-sensitive K^+ (K_v) channels. Because a BK_{Ca} and Kv channel inhibitor TEA inhibited taurine-induced relaxation and selective Kv channel inhibitor 4-AP did not, the possibility of involvement of Kv channels may be excluded.

Previously, the vasorelaxant effects of taurine were reported in rabbit ear artery (REA), the thoracic aorta (RTA), rat mesenteric artery (RMA), and rat renal artery (RRA)[10,12,18-20]. Recently, Liu et al have reported that taurine antagonizes and relaxes the contractions of the porcine coronary artery (PCA)[13]. All of these studies are in accordance that taurine relaxes contracted arteries; however, there are some differences regarding whether taurine affects basal resting tone. It was previously reported that taurine reduced basal tone in RTA[11]; however, it did not significantly affect the basal resting tone in REA and PCA[10,14]. Similarly, in our study, incubation with taurine (20, 40, 80 mM) for 30 min did not significantly change the basal resting tone. Another discrepancy among the previous investigations is the selectivity of the stimuli, namely precontraction induced by various stimuli. Several studies[10-12,19,21] reported that taurine relaxed RTA, RMA, RRA and REA precontracted with KCl (depolarizing substance) and noradrenaline (α-adrenoceptor agonist). The antagonizing effect of taurine to stimuli other than depolarization and α-adrenoceptor agonist was first shown by Liu et al[14] in PCA, in which taurine relaxed histamine, 5-HT, $CaCl_2$ and thromboxane A_2 analog U46619-induced precontractions in a similar fashion. We have shown for the first time that taurine relaxes KCl, 5-HT or $CaCl_2$-precontracted IMA. In our study, taurine has relaxed precontracted IMA segments without remarkable preference among the stimuli.

Vascular contraction may be induced through different mechanisms, and the common activator Ca^{2+} may be generated from different sources. The millimolar concentrations of KCl generates high extracellular K^+ gradient and triggers membrane depolarization with subsequent activation of voltage-operated calcium channels (VOCC). Histamine, 5-HT or U46619 act primarily on their specific receptors gated directly to receptor operated calcium channels (ROCC)[22]. These receptors stimulations rely on both Ca^{2+} influxes through ROCC and Ca^{2+} release from the intracellular stores[22]. Our results, together with previous studies[10-12,14,19,21], show that taurine relaxes depolarizations or several agonist-induced contractions without remarkable preference among the stimuli. It can be concluded that the lack of selectivity of taurine against these tested stimuli could be due to the fact that taurine inhibits the contraction of the arteries studied by interfering with a common pathway.

The mechanism involved in taurine-induced vasodilation has not been clarified. However, some previous studies[24,25] suggested that vasodilator effect of taurine was due to its antioxidant activity, its inhibitory effect on Ca^{2+} transporters, and its osmoregulatuar activity. Some recent researches suggested that TEA-sensitive K^+ channel, namely BK_{Ca}, opening might be involved in the vasodilator effect of taurine in RRA and RTA[19,21]. Involvement of BK_{Ca} was also shown in RRA obtained from either normal or insulin-resistant rats, although taurine-induced vasodilation was altered in insulin resistant rats compared to normal rats. In a more recent study, Liu et al[14] suggested that activation of several K^+ channels, namely K_{IR}, K_{ATP}, and BK_{Ca} might be

involved in taurine-induced relaxation of PCA. In the present study, we have convincingly demonstrated that vasorelaxation to taurine is mediated by increasing K^+ efflux through BK_{Ca} channels, but not via K_{ATP} or K_v channels. Previous studies[26-31] suggested that K_{ATP}, K_V and BK_{Ca} channels are present in IMA.

Taurine may have several physiopathological roles in cardiovascular events, since it plays important roles in neuromodulation, osmoregulation, calcium regulation, antioxidant defence, apoptosis, and vascular function[4-6,8,9,32]. In some tissues, the concentrations of taurine may exceed 10 mM, and it may even be higher locally, because large amount of taurine may be released in to the neighbouring interstitial fluid, when cells are damaged[1-3]. Several of these actions have marked influence on the development of ischemia reperfusion injury. Excessive amounts of K^+ is released from damaged cells during myocardial or other tissue injury. Elevation of extracellular K^+ may lead to membrane depolarization, which eventually results in Ca^{2+} influx and vasoconstriction. Eventually, this contractile status would further reduce blood supply to the ischemic tissue area. Besides, excessive amounts of taurine released from damaged cells may antagonize Ca^{2+} overload and contractile status, and it may even induce vasodilation. Hence, taurine may be an important local endogenous anti-ischemic factor that affects key processes in ischemia-reperfusion mediated cell death. Therefore, the results of the present report may contribute to our knowledge about effects of taurine and its clinical implications in preventing cardiac damage during bypass surgery, heart transplantation and myocardial infarction[33,34].

We would like to underline that we studied IMA only, and we cannot extrapolate our results to other human arteries. Additionally, we have demonstrated that relaxant effect of taurine occurs through activation of BK_{Ca} channels. We have used specific K^+ channel antagonists to reach this conclusion. Further studies, especially with cellular patch-clamp techniques, are essential to make clear the exact mechanism of taurine-induced vasodilation.

Conclusions

Our study is unique to show taurine -induced vasodilation in an human artery, the IMA. The mechanism of vasorelaxant effect of taurine in IMA may be opening of BK_{Ca} channels. Pathophysiological role of taurine in cardiovascular events needs to be explored further.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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