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ORIGINAL ARTICLE

Acid Stress Reduces the Function of Na^+-K^+-ATPase in Superior Mesenteric Artery of *Capra hircus*

Subash Chandra Parija, Ipsita Mohanty

Department of Pharmacology and Toxicology, Faculty of Veterinary Sciences, Orissa University of Agriculture and Technology, Bhubaneswar, Odisha, India

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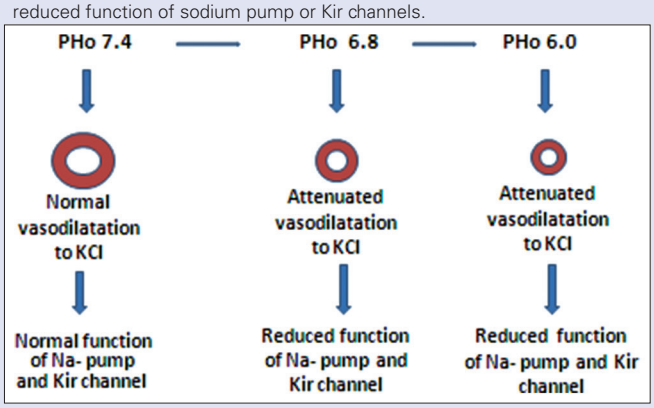
ABSTRACT

Context: Extracellular hydrogen ion concentration (pH_o) is an important physiological regulator of vascular tone, maintained within 7.35–7.45 and any change in it leads to complex health problem including maintenance of normal blood pressure. **Aims:** This study aims to examine the altered function of Na^+-K^+ pump and inward rectifier potassium channels (K_{ir}) channels in extracellular acidosis in goat superior mesenteric artery (GSMA). **Subjects and Methods:** Isolated GSMA rings were mounted in an automatic organ bath containing 20-ml modified Krebs–Henseleit solution at pH 7.4/6.8/6.0 and KCl-induced contraction was elicited either in the absence or presence of ouabain, barium (Ba^{2+}), and combination of ouabain and Ba^{2+}. Rings were dilated with potassium chloride either in the absence or presence of ouabain, Ba^{2+} and combination of ouabain and Ba^{2+} while maintaining at acidic pH. The responses were recorded isometrically by highly sensitive isometric force transducer connected to Powerlab and analyzed using LabChart 7.1.3 software. **Statistical Analysis Used:** Data were analyzed in GraphPad Prism 5 software. **Results:** K^+ vasorelaxation response in K^+-free solution precontracted rings the percent maximal response (93.57 ± 2.57%, 62.60 ± 3.56%, and 53.38 ± 5.41%) was decreased with decrease pH_o (7.4, 6.8 and 6.0). Ouabain, Ba^{2+}, and ouabain and Ba^{2+} inhibited the maximal vasorelaxation of potassium chloride (26.20 ± 3.48%, 17.39 ± 0.54%, 31.92 ± 1.10%) at pH_o 7.4, (42.74 ± 2.48%, 16.12 ± 3.49%, 22.32 ± 1.63%) at pH_o 6.8, and (53.87 ± 2.18%, 25.24 ± 2.90%, 39.71 ± 0.14%) at pH_o 6.0, respectively. **Conclusions:** Attenuated vasodilation in acidosis is due to reduced function or expression of ouabain-sensitive sodium–potassium ATPase (Na^+-K^+-ATPase) and K_{ir} channels. In clinical acidosis, agents augmenting the activity of Na^+-K^+-ATPase and K^+-Channel could improve hypertensive crisis.

Key words: Acidosis, *Capra hircus*, hypotension, K_{ir} channel, mesenteric artery, sodium pump

SUMMARY

- Extravascular reduction of pHo from 7.4 to 6.0 induces cellular acidosis in GSMA model.
- Acidosis causes hypertention which may be due to significant attenuation vasodilatation response to KCl.
- The underlying mechanism of acidosis–induced hypertension is due to reduced function of sodium pump or Kir channels.



Abbreviations used: Ba^{2+}: Barium; E_{max}: Percent maximal response; E_{Bmax}: Percent maximal response in presence of antagonist; K_{ATP}: Adenosine triphosphate-sensitive potassium channel; K_{ir}: Inward rectifier potassium channels; K_{Ca}: Calcium-activated potassium channels; Na^+-K^+-ATPase: Sodium–potassium ATPase; NO: Nitric oxide; pH_i: Intracellular hydrogen ion concentration; pH_o: Extracellular hydrogen ion concentration; VSMCs: Vascular smooth muscle cells.

Correspondence:

Dr. Subash Chandra Parija,
Department of Pharmacology and Toxicology,
Faculty of Veterinary Science and Animal Husbandry,
Orissa University of Agriculture and Technology,
Bhubaneswar - 751 003,
Odisha, India.
E-mail: profscparijaouat4691@gmail.com

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INTRODUCTION

Extracellular hydrogen ion concentration (pH_o) is generally maintained within a narrow range of 7.35 and 7.45, but local or systemic acidifications may cause some pathological conditions such as ischemia, hypoxia, metabolic disorders, gastrointestinal disorders, and renal dysfunctions.[1] Extracellular acidosis promotes vasodilation mediated by nitric oxide and/or K^+ channels such as adenosine triphosphate-sensitive potassium channel (K_{ATP}) and calcium-activated potassium channels (K_{Ca}) in vascular bed.[2,3] The vasodilatory effects of acidosis have been well described in animals both *in vivo*[4] and *in vitro*.[5,6] Acidosis-induced vasodilatory effect is influenced with respect to the agonist employed,[7] species,[8] genetic strain,[9] vascular location and caliber, [4,10] and experimental model.[5,11]

Modulation of vascular contractility affecting the activities of ion channels and pumps in acidic pH has been reported in several vascular beds. In bovine pial and porcine coronary arteries, an increase in intracellular hydrogen ion concentration (pH_i) potentiated the Ca^{2+} currents through L-type channels.[10] In addition, acidosis influences Ca^{2+}-activated K^+ channels in the porcine coronary artery smooth muscle cells[11-13] and ATP-sensitive K^+ channels in rat thoracic aorta.[3] Information vasorelaxation of the mesenteric artery under altered pH_o

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is almost limited to rat. In rat mesenteric artery, K^+-induced relaxation in SMCs is mediated by Kir2.1 channels and this channel expression increases as diameter decreases. An increase in pH_o potentiates and a decrease in pHo inhibits inward rectifier potassium channels (K_{ir}) currents and Na $^+$-K^+-ATPaseactivity.[14] Na^+-K^+-ATPase plays an important role in generation and maintenance of electrochemical gradient by extrusion of three sodium ions and influx of two potassium ions across the cell membrane by utilizing the energy derived from ATP hydrolysis. Similarly, ouabain-sensitive α_2 and α_3 subunits isoforms of sodium–potassium ATPase (Na^+-K^+-ATPase) have been reported to contribute K^+ vasorelaxation in rat mesenteric myocyte. The phenylephrine-induced elevation of intracellular Ca^{2+} stimulates K^+ efflux, predominantly through BK_{Ca} that lead to an extracellular K^+ "cloud," and this prevents any further activation of ouabain-sensitive Na^+-K^+-ATPase in response to elevation of extracellular K^+.[15] Recent study from our laboratory indicates that adrenergic stimulated contractile response was decreased with increase in extracellular pH_o and that is due to reduced function and expression of α_{1D}-adrenoceptor in the superior mesenteric artery (SMA) of *Capra hircus*.[16] Our previous study revealed that vasorelaxation of goat mesenteric artery is mediated by endothelial ouabain-sensitive Na $^+$-K^+-ATPase.[17] Thus, we hypothesize that in goat mesenteric artery increase in extracellular pH_o could reduce the function of ouabain-sensitive Na^+-K^+-ATPase. The present work examines how does mesenteric vascular bed responds to acidic pH (acidosis) and what is the relative contribution of Na^+-K^+ pump and K_{ir} channels in acidosis-induced altered vasorelaxation in this vascular bed.

SUBJECTS AND METHODS

Ouabain (Sigma (USA) and barium (Ba^{2+}) chloride (Qualigens India) were employed for isometric contraction study. All the solutions were prepared in deionized distilled water. This work has been approved by the Institutional Animal Ethical Committee (Registration No: 433/CPCSEA/20/06/2001) vide ID.No. 130/CVS/dt. 31.03.2015 for conducting randomized animal tissue experiments.

Preparation of superior mesenteric artery and tension recording

After careful exposure of goat intestinal mesentery, a branch of SMA adjacent to the duodenum and jejunum just before its branching into inferior branch was dissected out and placed in cold aerated modified Krebs–Henseleit saline (MKHS) solution of the following composition: (mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 11.9, KH_2PO_4 1.2, and dextrose 11.1 (pH 7.4). The solution was adjusted to either pH_o 7.4, 6.8, or 6.0 using 1 N HCl. Then, these arterial rings were cleared of fascia and subcutaneous fat, cut into 1.5–2 mm long circular rings and further employed for isometric contraction studies. Na^+-K^+-ATPase activity was studied by assessing K^+-induced relaxation (1 μM–0.1 mM) on K^+ free MKHS-induced contractile response in goat SMA (GSMA). KCl induced vasorelaxation in the absence or presence of ouabain (1 μM) or Ba^{2+} (30 μM) or ouabain (1 μM) and Ba^{2+} (30 μM) at different pH_o. The change of isometric tension was measured by a highly sensitive isometric force transducer (Model: MLT0201, AD instrument, Australia) and analyzed using LabChart 7.1.3 software (ADInstruments Pty Ltd, New South Wales, Australia). Vasodilatation effects were expressed as the percentage of maximal response considering plateau tension induced by K^+ free as 100%.

Statistical analysis

The concentration related contractile response curve was analyzed using GraphPad Prism5 and percent maximal response/E_{max} in the presence of antagonist (E_{max}/E_{Bmax}) (%), pD_2 were compared using unpaired Students *t*-test using GraphPad Software Quick Calcs (San Diego, CA, U. S. A). $P < 0.05$ was considered statistically significant.

RESULTS

GSMA rings exposed to K^+-free MKHS maintained at different pH_o (7.4, 6.8, and 6.0) induced a slow phasic contraction followed by sustained (plateau) contractile response. The mean peak and plateau tension at pH_o 7.4 (1.43 ± 0.27 g; 1.32 ± 0.25 g, n = 22) was reduced (0.99 ± 0.11 g; 0.97 ± 0.14 g, n = 16) at pH_o 6.8 and (0.64 ± 0.07 g; 0.63 ± 0.07 g, n = 10) at pH_o 6.0, respectively. The proportionality of mean peak tension (1: 0.71: 0.45) did not differ from the mean plateau tension (1: 0.72: 0.47) at different pH_o (7.4, 6.8, 6.0).

KCl (1 mM) reduced the plateau contraction induced by K^+-free MKHS by 83.58 ± 2.87% (pH_o 7.4), 57.19 ± 3.88% (pH_o 6.8), and 34.60 ± 4.41% (pH_o 6.0), respectively [Figures 1 and 2]. The concentration-related vasorelaxation response curve of KCl (1 μM–10 mM) at pH_o 7.4 (E_{max} 93.57 ± 2.57%, pD_2 3.82 ± 0.12) was shifted to the right with significant ($P < 0.05$) decrease in E_{max} and pD_2 (62.60 ± 3.56%, 4.16 ± 0.12) at pH_o 6.8 and (53.38 ± 5.41%, 4.21 ± 0.14) at pH_o 6., respectively [Table 1 and Figure 3]. The maximal relaxation responses to K^+ were inhibited at acidic pH.

Effect of pH_o (7.4 or 6.8 or 6.0) on KCl-induced vasorelaxation in K^+-free MKHS in the absence or presence of ouabain (1 μM) or Ba^{2+} (30 μM) or ouabain (1 μM) and Ba^{2+} (30 μM), Table 1 represents the influence of pH_o (7.4–6.0) on vasotonic effect of ouabain or Ba^{2+} or ouabain and Ba^{2+}- on K^+-induced vasorelaxation in GSMA rings. Ouabain (1 μM) caused rightward shift of KCl-induced concentration-related vasorelaxation curve with significant ($P < 0.05$) decrease in E_{Bmax} and pD_2 at pH_o 7.4 (26.20 ± 3.48%, 4.30 ± 0.19), pH_o 6.8 (42.74 ± 2.48%, 5.07 ± 0.13), and pH_o 6.0 (53.87 ± 2.18%, 4.70 ± 0.11) [Figure 4]. In the presence of Ba^{2+} (30 μM), the K^+-induced concentration-related vasorelaxation curve was shifted to right with a significant ($P < 0.05$) decrease in E_{Bmax} and pD_2 (17.39 ± 0.54%, 4.59 ± 0.07) at pH_o 7.4, (16.12 ± 3.49%, 4.64 ± 0.08) at pH_o 6.8, and (25.24 ± 2.90, 1.95 ± 0.24) at pH_o 6.0 [Figure 5]. A combination of ouabain (1 μM) and Ba^{2+} (30 μM) caused rightward shift of KCl-induced concentration-related vasorelaxation curve with a significant ($P < 0.05$) decrease in E_{Bmax} (31.92 ± 1.10%) and decrease in pD_2 (3.55 ± 0.12) at pH_o 7.4, increase in E_{Bmax} (22.32 ± 1.63%) and decrease in pD_2 (2.88 ± 0.07) at pH_o 6.8, and increase in E_{Bmax} (39.71 ± 3.76%) and decrease in pD_2 (3.34 ± 0.08) at pH_o 6.0 [Figure 6].

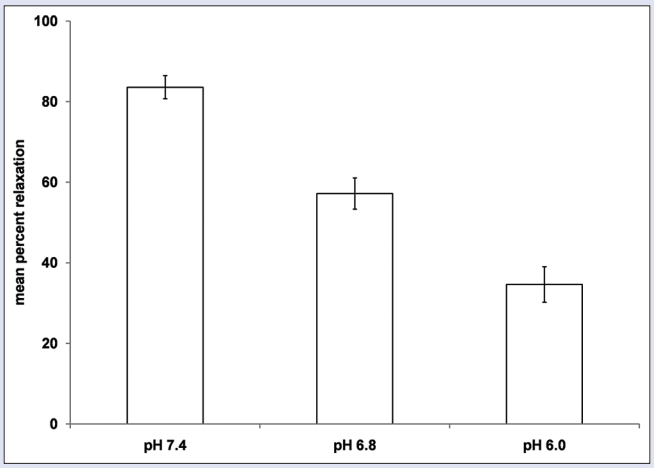

Figure 1: KCl (1 mM)-induced concentratile response in goat superior mesenteric artery incubated with K^+-free modified Krebs–Henseleit saline maintained at pH 7.4, 6.8, and 6.0

DISCUSSION

This study provides evidence to indicate that the Na^+-K^+ pump and K_{ir} channels participate in the pH_o dependent control of vascular contractility and membrane Na^+-K^+-ATPase may have a secondary role in K-induced relaxation in the goat mesenteric artery. The major observations are as follows: A decrease in pH_o (7.4–6.0), (1) decreased maximal vasotonic response to K^+-free medium, (2) progressively attenuated vasorelaxation to KCl, (3) reduced ability of ouabain to inhibit K^+-induced vasorelaxation that could be due to reduced activity or expression of ouabain-sensitive Na^+-K^+ pump, and (4) attenuated inhibitory effect of Ba^{2+} that could be due to reduced function or densities K_{ir} channels.

There was proportionate decrease in both mean peak tension (1: 0.71: 0.45) and mean plateau tension (1: 0.72: 0.47) with reduction of pH_o (7.4, 6.8, and 6.0) on incubation of GSMA rings in K^+-free medium. The reduction of both peak and plateau tensions were in identical proportion. Vasocontractility arising from the removal of K^+ extracellular medium is due to the basal influx of Ca^2+.[16,18] Hence, the progressive reduction of vasotonic response to K^+-free medium in acidosis could be attributed in part to decrease in Ca^{2+} influx.

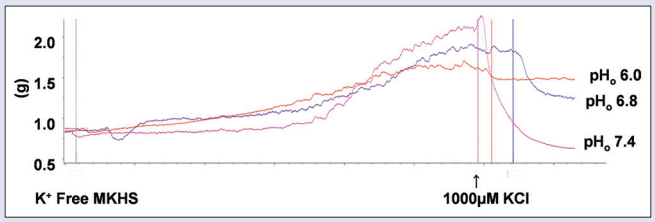

Figure 2: Tracings indicating KCl (1 mM)-induced vasorelaxation in goat superior mesenteric artery incubated with K^+-free modified Krebs–Henseleit saline maintained at pH 7.4, 6.8, and 6.0

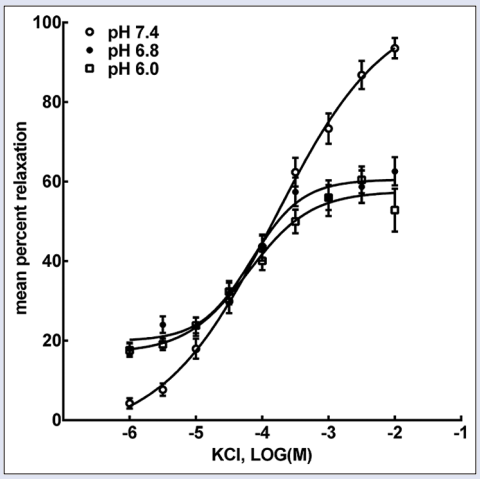

Figure 3: KCl-induced concentration-related contractile response curve in goat superior mesenteric artery incubated with K^+-free modified Krebs–Henseleit saline at extracellular hydrogen ion concentration 7.4, 6.8, and 6.0

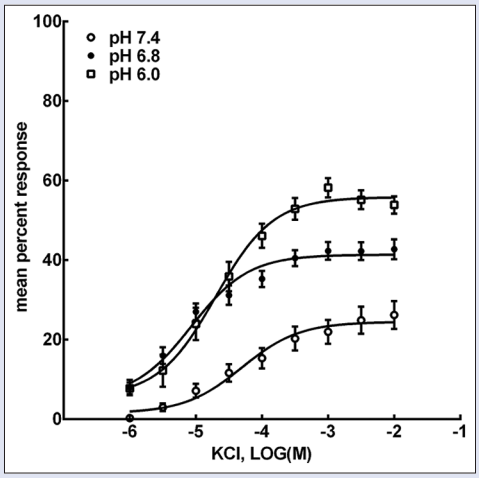

Figure 4: Effect of extracellular hydrogen ion concentration (7.4 or 6.8 or 6.0) on KCl-induced vasorelaxation in K^+-free modified Krebs–Henseleit saline in the presence of ouabain (1 μM)

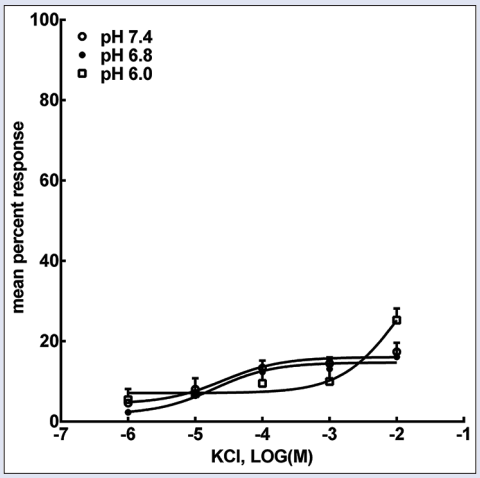

Figure 5: Effect of extracellular hydrogen ion concentration (7.4 or 6.8 or 6.0) on KCl-induced vasorelaxation in K^+-free modified Krebs–Henseleit saline in the presence of barium (30 μM)

Table 1: Comparison of E_{max} / EB_{max} or pD_2 of KCl (1μM to 10mM)-induced vasorelaxation at different pH_o (7.4, 6.8 and 6.0) either in absence or presence of Ouabain (1μM), Barium (30μM), Ouabain (1μM) and Barium (30μM) in GSMA rings. All values are expressed as mean±SEM, *n*=8 (KCl and Ouab); *n*=4 (Ba and Ouab +Ba)

pH_o	E_{max}/EB_{max} (%)			pD_2		
	7.4	6.8	6.0	7.4	6.8	6.0
KCl	93.57±2.57	62.60±3.56[a]	53.38±5.41[a]	3.82±0.12	4.16±0.12[a]	4.21±0.14[a]
Ouabain	26.20±3.48[c]	42.74±2.48[a,c]	53.87±2.18[a,b]	4.30±0.19[c]	5.07±0.13[a,c]	4.70±0.11[b,c]
Ba	17.39±0.54[c]	16.12±3.49[c]	25.24±2.90[a,b,c]	4.59±0.07[c]	4.64±0.08[a,c]	1.95±0.24[a,b,c]
Ouabain + Ba	31.92±1.10[c]	22.32±1.63[a,c]	39.71±3.76[b,c]	3.55±0.12	2.88±0.07[a,c]	3.34±0.08[b,c]

n=Number of experiments, [a]*P*<0.05 versus pH 7.4, [b]*P*<0.05 versus pH 6.8, (data were compared between subcolumns, within rows under E_{max}/EB_{max} and pD_2), [c]*P*<0.05 versus respective control (data were compared between rows, within subcolumn under E_{max}/EB_{max} and pD_2). All values are expressed as mean±SEM, *n*=8 (KCl and ouabain); *n*=4 (Ba and ouabain+Ba). SEM: Standard error of mean; E_{max}: Percent maximal response; EB_{max}: Percent maximal response in presence of antagonist

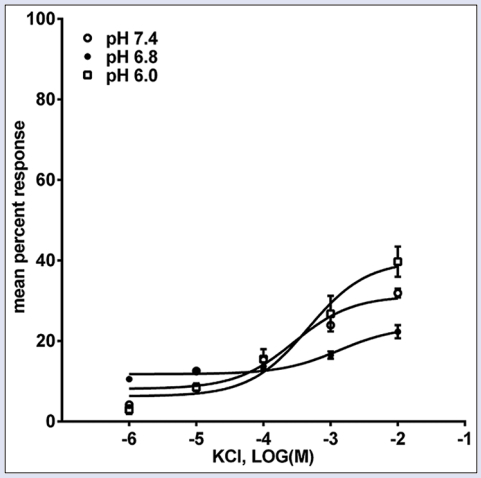

Figure 6: Effect of extracellular hydrogen ion concentration (7.4 or 6.8 or 6.0) on KCl-induced vasorelaxation in K^+-free modified Krebs–Henseleit saline in the presence of ouabain (1 μM) and barium (30 μM)

KCl-induced relaxation in vascular smooth muscles may involve several independent mechanisms, such as activation of sarcolemmal Na^+-K^+-ATPase and/or activation of inwardly rectifying K^+-channels.[19] K^+-induced dilation of the small renal artery attributed to the activation of smooth muscle Na^+-K^+-ATPase with no role for K_{ir} channel.[20] Similarly, K^+ vasorelaxation in goat ruminal artery is predominantly mediated by ouabain-sensitive Na^+-K^+-ATPase has been reported from our previous study.[21] One of the distinguishing features of vascular relaxation by K^+ involving Na^+-K^+-ATPase is that the extracellular concentration of K^+ is <5 mM, whereas K_{ir}-channels primarily mediate K^+-induced relaxation above the physiological K^+-concentration (>5 mM).[22] In addition, $(K^+)_o$ elevation increases K_{ir}-channel conductance and activates Na^+-K^+ pump, thus hyperpolarize membrane potential. This hyperpolarization inhibits voltage-gated Ca^{2+} channels and relaxes the vascular smooth muscle. In contrast, vascular smooth muscle contracts in response to $(K^+)_o$ elevation to <25 mM and 12 or 15 mM K^+ may be enough to evoke K^+-induced relaxation.[20] Na^+-K^+ pump and K_{ir} channels maybe the main contributor in K^+-induced relaxation as Kir2.1 gene has been expressed in arterial smooth muscle.[21] In SMA rings of *Capra hircus*, K^+ (1 μM-10 mM)-induced vasorelaxation was increased dose dependently and attained E_{max}(>95%) at pH_o 7.4. This findings clearly demonstrate that Na^+-K^+ pump and K_{ir}-channels are main contributors in K^+-induced relaxation in SMA rings of *Capra hircus* as observed in rat mesenteric arterial rings.[15] In contrast, with a decrease in pH_o from 7.4–6.0, K^+-induced maximal vasorelaxation was attenuated by about 31% and 40% at pH_o 6.8 and 6.0, respectively. The decrease in pH_o in isolated rat SMA from 7.8–6.4 significantly reduced apparent affinity (pD_2) to norepinephrine (NE) and maximal contraction by NE, which were more prominent in larger-diameter arteries and also reduced Ba^{2+}-sensitive K^+-induced relaxation in the first branch and inhibited Kir currents in cultured smooth muscle cells of SMA.[15] In the present finding, we observed that K^+ (1 μM)-induced vasorelaxation in GSMA was reduced with reduction of pH_o from 7.4 to 6.0, with a clear-cut rightward shift of K^+-induced concentration-related vasorelaxation curve. Concisely, at pH_o 6.8 and 6.0, K^+-induced vasorelaxation was significantly attenuated with increased affinity and reduced efficacy as compared to pH_o 7.4 that is identical to the observation obtained in rat mesenteric artery.[15]

Considering that the Na^+-K^+-ATPase activity is ouabain-sensitive in several vascular beds and ouabain-inhibited K^+-induced vasorelaxation, we incubated the GMSA rings with ouabain before eliciting K^+-induced vasorelaxation at different pH. Our present results showed that ouabain inhibited the KCl-induced vasorelaxation with a decrease in E_{Bmax} by about 66%, 19%, and 0% and in pD_2 by about 0.5, 1.0, and 0.5 log units at pH_o 7.4, 6.8, and 6.0, respectively. Thus, attenuation of K^+-induced vasorelaxation by ouabain is maximum at pH_o 7.4 and minimum at pH_o 6.8 and almost abolished at pH_o 6.0. This could be due to a graded reduction of ouabain-sensitive Na^+ efflux and K^+ influx arising from reduced function or activity of Na^+-K^+-ATPase in the acidic pH_o. This proportional inhibition of Na^+-K^+-ATPase by H^+ ion accumulation during acidosis is not fully understood as such observed in mouse ventricular cells[22] and rat SMA.[14]Endogenous ouabain increases vasotonic response indirectly by increasing the intracellular calcium through depolarization and reducing intracellular calcium buffering mechanism during cellular acidosis.[12]In squid giant axon, influence of pH_o and pH_i on sodium pump fluxes over the pH range of 6.0–8.6 revealed that changes of pH_i (but not pH_o) resulted in a graded inhibition of ouabain-sensitive Na^+ efflux and K^+ influx in both acidic or alkaline direction which was maximum at pH_i of 7.2–7.4 and any variations away from this optimal pH_i resulted in a graded inhibition of ouabain-sensitive Na^+ efflux and K^+ influx in either the acidic or alkaline direction.[23] Basing on above functional evidence on ouabain-induced vasotonic response physiological and altered pH_o (acidic/alkaline), the reduced sensitivity to ouabain due to acidosis in GSMA could be attributed to interference with the intracellular calcium buffering mechanism arising from reduced activity of Na^+-K^+-ATPase. It could be possible that the reduction in the binding ability of ouabain to active sites of Na^+-K^+-ATPase is interfered by acidic pH that results in nonreversal of K^+ vasorelaxation in GSMA under acidosis. Na^+-K^+-ATPase exists in the plasma membrane as a heterodimer consisting of a catalytic α-subunit and a glycosylated β-subunit.[24] In vascular smooth muscle, the occurrence of α_1, α_2, and α_3 subunits has been reported in rat mesenteric artery,[14] rat aorta myocytes,[25] rat thoracic, superior mesenteric, and tail arteries.[26] Consistent with the expression of the sodium pump isoforms in rodents, studies on gene-targeted mice emphasize a significant role of the α_2 isoform in regulating contractility of blood vessels *in vitro* and regulation of blood pressure *in vivo*.[27] The α_1 isoform has been found to be having a "housekeeping role" in mouse aorta, and α_2 isoform has been shown to possess a high affinity to low (submicromolar) concentrations of ouabain[28] in the pulmonary vasculature. Thus far, there is no information on the physiological roles of α_1 and α_2 isoforms in goat mesenteric artery; the present functional study suggests that α_2 isoform may have a major role in regulating contractility of this vasculature and acidosis could be substantially reducing its affinity to ouabain. Conversely, the shift of balance between vasotonic and vasorelaxation in reduced pH_o may be due to decreased expression of α_2 isoform of Na^+-K^+-ATPase in this vasculature.

K^+-induced vasodilatation following stimulation of Na^+-K^+-ATPase is also mediated by K_{ir} channels or Ba^{2+} sensitive and inwardly rectifying potassium channels mostly localized in the small artery and arterioles.[14,21] $BaCl_2$ has been reported to antagonize both K_{ATP} and K_{ir}-channels at 30 mol/L in rat cerebral arterioles[3,29] and K_{ir} channels at 50 mol/L in rat arterial SMCs.[30] In the present study, Ba^{2+} (30 mM) was employed to assess the role of K_{ir}-channels in K^+ vasorelaxation as influenced by reduced pH_o. K_{ir} channels play an important role in acidosis-mediated vasodilatation in rat coronary and cerebral arteries,[19] rat cerebral arterioles,[3] and rat mesenteric artery.[16] A decrease in pH_o inhibits K_{ir} currents.[15,31] K_{ir}2.3 current inhibition by extracellular acidification started at pH 7.0 and plateaued at pH 6.0 with a pK of 6.7.[32] Similarly, Ba^{2+}-sensitive K_{ir}-induced relaxation was

markedly reduced in rat mesenteric artery at pH_o values of 6.9 and 6.4.[15] Our present work revealed that in the presence of Ba^{2+} (30 μM), K^+-induced vasorelaxation was attenuated with decrease in E_{Bmax} by about 76%, 46%, and 28% at pH_o 7.4, 6.8, and 6.0, respectively. In contrast, pD_2 was increased by about 0.7, 0.5 log units at pH_o 7.4, 6.8 and decreased by 2.2 log units at pH_o6.0. On comparison, Ba^{2+}-sensitive K_{ir}-channel activity did not alter by decreasing pH_o 7.4–6.8, but it was significantly reduced at pH_o 6.0. Further, we observed that ouabain significantly reduced inhibitory effect of Ba^{2+} by about 14% at pH_o 7.4, 6.0 and by about 6% at pH_o 6.8. Hence, it could be inferred that Ba^{2+}-sensitive Kir-channel activity is markedly reduced at pH_o 6.0 but not at pH_o 6.8 when compared with that of pH_o 7.4 which in agreement with functional study obtained in rat coronary and cerebral arteries,[20] rat cerebral arterioles,[3] and rat mesenteric artery.[16]

Based on the evidence gathered on reduced function and expression of K_{ir} channels in other vascular bed including rat mesenteric bed our observation is well in agreement with the fact that in GSMA, decreased K^+ vasorelaxation arising due to reduction of pH_o is due to in part reduced function and expression of K_{ir}-channels. Further, we observed that ouabain significantly reduced inhibitory effect of Ba^{2+} by about 14% at pH_o 7.4, 6.0 and by about 6% at pH_o 6.8. Such a reduction in the sensitivity to Ba^{2+} in the presence of ouabain could be attributed to net combined inhibitory effect on K^+ vasorelaxation arising from shifting of membrane K^+ efflux mechanism to possibly opening of BK_{ca} channels as reported in the rat mesenteric artery.[16] Attenuation of vasorelaxation in GSMA in acidic stress is due to a reduction in function/expression of Na^+-K^+ pump and K_{ir} channels. This reduced vasorelaxation is predominantly mediated by reduction in ouabain-sensitive Na^+-K^+-ATPase activity. In clinical acidosis, it is well predicted that a decreased vascular resistance may be arising from the inability of the vascular bed to dilate that could be due to reduced function of Na^+-K^+ pump in vascular smooth muscle cells.

Brief summary

Activation of ouabain-sensitive Na^+-K^+-ATPase and K_{ir} channels contributes to the K^+-induced vasorelaxation in goat mesenteric artery at normal pH_o. The reduction in K^+-induced vasorelaxation with decrease in pH_o (acidosis) occurs due to the attenuation of function or sensitivity of Na^+-K^+-ATPase and K_{ir} channels could be implicated to one of the possible mechanisms of hypertensive crisis in acidosis.

CONCLUSIONS

Attenuated vasodilation in acidosis is due to reduced function or expression of ouabain-sensitive Na^+-K^+-ATPase and K_{ir} channels. In clinical acidosis, agents augmenting the activity of Na^+-K^+-ATPase and K^+-channel could improve hypertensive crisis.

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Conflicts of interest

There are no conflicts of interest.

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