Effect of phenylephrine and endothelium on vasomotion in rat aorta involves potassium uptake

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Abstract Vasomotion is defined as the rhythmic contractions in blood vessels, consisting of two components: vasoconstriction and oscillations of the plasma membrane potential. To determine whether vasomotion is associated with changes in $K^+$ uptake, we measured the effect of phenylephrine (PE) and acetylcholine (ACh) on the $K^+$ uptake and vascular reactivity in rat aortic rings. We found that the incubation of aortic rings with $10^{-7}$ M PE ($210 \pm 28$ mg maximum amplitude), and $10^{-6}$ M ACh ($177 \pm 6$ mg maximum amplitude) produced the highest rhythmic contractions. Both $10^{-7}$ M PE and $10^{-6}$ M ACh significantly increased $K^+$ uptake in endothelium-intact aorta versus control (121 % PE, 117 % ACh). Removal of the endothelium blunted rhythmic contractions and decreased $K^+$ uptake in presence of vasoactive substances (88 % PE, 81 % ACh). The inhibition of nitric oxide synthase with $10^{-4}$ M L-NNA significantly reduced the rhythmic contractions, and it was reversed in the presence of $10^{-8}$ M sodium nitroprusside (SNP; a nitric oxide donor). Also, we found that $10^{-4}$ M l-NNA significantly decreased the effect of $10^{-7}$ M PE on $K^+$ uptake in aortic rings (104 % PE + l-NNA vs. control). The incubation of endothelium-denuded rings with $10^{-8}$ M SNP significantly increased the $K^+$ uptake (116 % SNP vs. control), similar to those observed in the presence of $10^{-6}$ M ACh. The inhibition of protein kinase G with KT-5823 blocked SNP-mediated increase in $K^+$ uptake. In conclusion, these data suggest that a certain range of $K^+$ uptake is necessary to induce the rhythmic contractions in response to vasoactive substances.

Keywords Vasomotion · Potassium uptake · Aorta · Rat

Introduction

Vasomotion involves rhythmic oscillations in vascular tone, contraction and relaxation. Rhythmic contractions are a local mechanism to regulate the vascular resistance in microcirculation [1, 2]. Furthermore, it is considered as a compensatory mechanism in hypertension [3, 4] or type 2 diabetes mellitus patients [5].

Although the mechanisms contributing to vasomotion are not well known, the changes of vascular tone are generated by calcium oscillations in the cytosol of vascular smooth muscle cells [6]. The Koenigsberger vasomotion model postulates three states of contraction in blood vessels with different levels of calcium: small contraction, medium contraction, and tonic contraction, and showed that only the medium contraction produces rhythmic contractions [7]. To regulate the cytosolic calcium oscillations, the membrane oscillator model considers the participation of $Ca^{2+}$ channels, calcium-activated $K^+$ channels, $Na^+/Ca^{2+}$ exchange, plasma membrane $Ca^{2+}$-ATPase, and the $Na^+,$ $K^+$-ATPase [8].

It has been described that rhythmic contractions occur in arteries in vitro either in response to agonist or spontaneously [9]. The response to agonist is explained because some of these arteries have a highly negative resting
membrane potential (−60 mV) [10]. In these cases, rhythmic contractions are preceded by a state of hyperpolarization of the plasma membrane, which is caused by the opening of calcium-activated K⁺ channels [11, 12]. For example, rhythmic contractions in response to phenylephrine (PE) occurs by plasma membrane depolarization, and Ca²⁺ influx by opening of the voltage-dependent Ca²⁺ channels [10, 13].

The endothelial regulation of rhythmic contractions is still controversial. Although it is known that endothelial nitric oxide (NO) modulates the rhythmic contractions through calcium-activated K⁺ channels and calcium oscillations of vascular smooth muscle cells [1, 14], little is known about the role of K⁺ uptake on rhythmic contractions.

It is known that K⁺ uptake represents major influx of K⁺ into the cell through Na⁺,K⁺-ATPase, and Na⁺-K⁺-2Cl⁻ cotransporter. In the early 1970s, it was stated that K⁺ uptake via Na⁺,K⁺-ATPase is insaturable because efflux of K⁺ (the pump-leak hypothesis) [15, 16]. However, in the presence of ouabain, a specific inhibitor of Na⁺,K⁺-ATPase, K⁺ uptake is saturable through the cotransporter Na⁺-K⁺-2Cl⁻ [17]. It was postulated that the opening of calcium-activated K⁺ channels inhibits the K⁺ uptake via Na⁺,K⁺-ATPase [18, 19], but not K⁺ uptake via cotransporter Na⁺-K⁺-2Cl⁻, in vascular smooth cells [20].

Vasomotion is consisted of two components: rhythmic oscillations of plasma membrane potential and vasoconstriction [21]. The purpose of this study was to determine whether rhythmic contractions are associated with changes in K⁺ uptake of vascular smooth muscle cells. We studied the effect of different vasoactive substances (PE, ACh, a NO donor) on aortic rings. Female rat aortas were used because their endothelium releases a greater amount of endothelial relaxing factors, such as NO, than male rat endothelium [22–24].

Methods

Animals

Female Sprague–Dawley rats (1 month old; 100–140 g) from the breeding colony at the University of Antofagasta were used. All rats were housed in groups of three in a temperature-controlled, light-cycled (0800–2000 hours) room with ad libitum access to drinking water, and standard rat chow (Champion, Santiago de Chile). All rats drank water from the time of weaning. The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996), and the local animal research committee approved the experimental procedure used in the present study.

Isolation of aortic rings

Rats were killed by cervical dislocation. The thoracic aorta was quickly excised and placed in a cold (4 °C) physiological Krebs–Ringer bicarbonate (KRB) buffer containing (in mM): 4.2 KCl, 1.19 KH₂PO₄, 120 NaCl, 25 Na₂HCO₃, 1.2 MgSO₄, 1.3 CaCl₂, and 5 D-glucose (pH 7.4). Rings (3–5 mm and 2–4 mg) were prepared after connective tissue was dissected from the aorta, taking special care to avoid endothelium damage. Aortic rings were equilibrated for 40 min at 37 °C by constant bubbling with a gas mixture of 95 % O₂ and 5 % CO₂.

Vascular reactivity experiments

In each experiment, we studied 4–8 adjacent aortic rings from the same animal, using the method for isometric tension measurements [25]. The rings were mounted on two 25-gauge stainless steel wires; the lower one was attached to a stationary glass rod and the upper one was attached to an isometric transducer (Radnoti Glass Technology, Monrovia, CA, USA). The transducer was connected to converter (MP100) and amplifier (DA100) for continuous recording of vascular tension using the AcqKnowledge 3.9.1.6 computer program (BioPac Systems, Santa Barbara, CA, USA). After the equilibration period, the aortic rings were stabilized by 3 successive near-maximum contractions with KCl (60 mM) for 10 min. The passive tension on aorta was 1.4 g, which was determined to be the resting tension for obtaining maximum active tension induced by 60 mM KCl. The vascular reactivity was studied in different concentrations of PE (10⁻⁸ to 10⁻⁵ M). In another experiment, 10 min after the contraction with 10⁻⁶ M PE, the different concentrations of acetylcholine (ACh) were added to the medium (ACh 10⁻⁸ to 10⁻⁵ M). This protocol was repeated in different conditions: intact aortic rings, endothelium-denuded aortic rings; relaxation with sodium nitroprusside (SNP) (10⁻⁹ to 10⁻⁵ M), or pre-incubated for 30 min with L-NAME (10⁻⁴ M). To test the role of K⁺ on rhythmic oscillations in rat aorta, vascular reactivity experiments were carried out in different concentrations of K⁺ (10–30 mM) or in the presence of K⁺ channel blockers alone [5 mM tetraethylammonium (TEA) and 5 mM BaCl₂]. To study the role of extracellular calcium, experiments were realized with a calcium-free KRB buffer for 10 min, and then the aortic rings were contracted with 10⁻⁷ M PE.

K⁺ uptake in the rat aorta

The K⁺ uptake was measured by ⁸⁶Rb⁺/K⁺ uptake into aortic rings according to Palacios et al. [25]. The thoracic aorta was quickly excised and placed in cold (4 °C) KRB.
buffer. Then, the aortic rings were equilibrated for 40 min in KRB buffer (37 °C), and triplicate samples were incubated in 2 mL of KRB buffer containing 86Rb (0.1 mCi mL⁻¹). Transferring the aortic rings into iced KRB buffer stopped the reaction. The tissue was then quickly washed in cold buffer and gently blotted. Sample radioactivity was determined by Cerenkov radiation in a liquid scintillation counter in the presence of 0.1 % Tween 20 (4 mL). K⁺ uptake was measured from the total 86Rb⁺ uptake. The results are expressed as nanomoles of 86Rb⁺/K⁺ min⁻¹ (g aorta)⁻¹. The K⁺ uptake on aorta rat was studied in different concentrations of vasoactive substances: PE (10⁻⁷ and 10⁻⁵ M), ACh (10⁻⁶ and 10⁻⁵ M), PE (10⁻⁷ M) + ACh (10⁻⁶ M), and 10⁻⁸ M SNP; PE (10⁻⁷ M) + 1-NNA (10⁻⁴ M), and SNP (10⁻⁵ M) + KT-5823 (10⁻⁶ M). In some cases, these protocols were repeated in different conditions: intact aortic rings or endothelium-denuded aortic rings.

Drugs and solutions

The following drugs were used in this study: Rubidium chloride (86Rb; Comisión Chilena de Energía Nuclear, Santiago de Chile), l-phenylephrine hydrochloride (PE; Sigma-Aldrich, St. Louis, USA), ACh chloride (Sigma-Aldrich, Munich, Germany), l-NNA (Aldrich Chemical, Sheboygan Falls, WI, USA), SNP (Merck, Darmstadt, Germany), EGTA tetrasodium (Sigma-Aldrich), KT-5823 (Fermentek, Israel); TEA (Sigma-Aldrich); BaCl₂ (Merck). Drugs were dissolved in distilled de-ionized water. The solutions in KRB buffer were freshly prepared before each experiment.

Analysis

The amplitude of rhythmic contractions was measured from the average maximum of 5 cycles for 1 min, and 5 min after the contractile response to agonist. Values are expressed as mean ± standard error of the mean; n denotes the number of rings studied. One-way analysis of variance (ANOVA) was carried out to detect significant differences, followed by Student–Newman–Keuls test to compare all groups. A P value of <0.05 was considered statistically significant.

Results

Effect of PE and ACh on rhythmic contractions in rat aortic rings

The first experiments on the aorta were designed to analyze the rhythmic contractions in response to agonist. Vascular reactivity experiments were carried out in the presence of PE alone (10⁻⁸ to 10⁻⁵ M) or ACh (10⁻⁸ to 10⁻⁵ M) following 10⁻⁶ M PE. As shown in Fig. 1a, b, we observed rhythmic contractions in the intact aortic rings of rat with both vasoactive substances. These responses were dose-dependent and reversible after washing. We found that 10⁻⁷ M PE (210 ± 28 mg maximum amplitude) and 10⁻⁶ M ACh (177 ± 6 mg maximum amplitude) produced the highest rhythmic contractions (Fig. 1c, d; Table 1). We determined that there was an optimal vascular tone to produce the maximum amplitude of oscillation: 1.60 ± 0.10 g for 10⁻⁷ M PE, 1.34 ± 0.03 g for 10⁻⁶ M ACh, and 1.46 ± 0.02 g for 10⁻⁷ M ACh (Fig. 1c, d).

Role of K⁺ on rhythmic contractions in rat aortic rings

To test whether K⁺ efflux is involved, vascular reactivity experiments in aortic rings were carried out in different concentrations of KCl (10–30 mM) or in the presence of K⁺ channel blockers. As shown in Fig. 2a, rhythmic contractions were only observed with 20 mM KCl (168 ± 10 mg maximum amplitude). Thereafter, the role of K⁺ efflux was evaluated. The vascular tone increased with both K⁺ channel blockers, 5 mM TEA (a nonselective blocker of calcium-activated K⁺ channel) and 5 mM BaCl₂ (a blocker of inward rectifier K⁺ channel), but rhythmic contractions were only observed with TEA (Fig. 2b).

PE-induced rhythmic contractions are depended of extracellular calcium

To study the role of extracellular calcium on rhythmic contractions in response to PE, experiments were started with a calcium-free KRB buffer. As shown in Fig. 3, the rhythmic contractions appeared after adding increasing doses of calcium to the medium. For example, 0.6 mM Ca²⁺ increased the vasoconstriction and rhythmic contractions (37 ± 7 mg maximum amplitude), and 1 mM Ca²⁺ produced the highest rhythmic contractions (117 ± 22 mg maximum amplitude).

Effect of endothelium on rhythmic contractions in rat aortic rings

To evaluate the role of the endothelium on PE-induced rhythmic contractions, experiments were repeated under the same conditions but after removal of the endothelium. In endothelium-denuded aortic rings, we found that only 10⁻⁸ M PE produced rhythmic contractions (Table 1). In order to confirm the potential role of NO in rhythmic contractions modulation, vascular reactivity experiments were carried out in intact arteries pre-incubated with 1-NNA, and in the presence of SNP. As shown in Fig. 4, the pre-incubation with 10⁻⁴ M 1-NNA reduced rhythmic
contractions in endothelium-intact aortic rings (21 ± 3 mg maximum amplitude with L-NNA). The addition of 10^{-8} M SNP restored the rhythmic contractions in the presence of L-NNA (149 ± 15 mg maximum amplitude; Fig. 4); but other concentrations of SNP (10^{-10}, 10^{-9}, 10^{-7}, and 10^{-6} M) could not.

Role of K^+ uptake on rhythmic contractions in rat aortic rings

With respect to the effect of KCl or K^+ channel blockers on rhythmic contractions, described above, we asked whether K^+ uptake is associated to PE- or ACh-induced...
rhythmic contractions. To check this hypothesis, K⁺ uptake was determined in intact aortic rings incubated with different concentrations of PE alone (10⁻⁷ and 10⁻⁶ M), or ACh alone (10⁻⁶ and 10⁻⁵ M). As shown in Fig. 5, we found that 10⁻⁷ M PE and 10⁻⁶ M ACh significantly increased %K⁺ uptake in endothelium-intact aorta versus control. Increasing the PE concentration 10⁻⁵ M further increased the K⁺ uptake (116 ± 2 % with 10⁻⁷ M PE vs. 136 ± 5 % with 10⁻⁵ M PE; P < 0.01), whereas increasing the ACh concentration to 10⁻⁵ M decreased the K⁺ uptake (116 ± 6 % with 10⁻⁶ M ACh vs. 96 ± 6 % with 10⁻⁵ M ACh; P < 0.05).

On the other hand, we confirmed that K⁺ uptake in the presence of 10⁻⁶ M ACh alone or 10⁻⁶ M ACh following 10⁻⁶ M PE (118 ± 5 % with ACh + PE vs. control) was not significantly different.

Effect of endothelium on K⁺ uptake in rat aortic rings

To investigate the effect of the endothelium, K⁺ uptake was measured in endothelium-intact or endothelium-denuded aortic rings incubated with 10⁻⁷ M PE or 10⁻⁶ M ACh. Both vasoactive substances significantly increased K⁺ uptake in endothelium-intact aortic rings. As shown in Fig. 6, 10⁻⁷ M PE increased the K⁺ uptake (control 420 ± 22 vs. 509 ± 14 nmol ⁸⁶⁹⁹Rb/K min⁻¹ g wt tissue⁻¹; P < 0.01), and also 10⁻⁶ M ACh increased the K⁺ uptake (control 433 ± 10 vs. 505 ± 28 nmol ⁸⁶⁹⁹Rb/K min⁻¹ g wt tissue⁻¹; P < 0.01). However, removal of the endothelium significantly reduced the K⁺ uptake with 10⁻⁷ M PE (control 387 ± 26 vs. 448 ± 10 nmol ⁸⁶⁹⁹Rb/K min⁻¹ g wt tissue⁻¹ with PE), and 10⁻⁶ M ACh (control 373 ± 18 vs. 409 ± 19 nmol ⁸⁶⁹⁹Rb/K min⁻¹ g wt tissue⁻¹ with ACh).

To provide some information as to the possible nature of the endothelial factor involved in the K⁺ uptake in response to PE, the vascular rings were incubated with 10⁻⁴ M l-NNa. As shown in Fig. 7a, PE-induced K⁺ uptake was blocked in the presence of l-NNa (480 ± 28
with PE vs. 413 ± 9 nmol 86Rb/K min⁻¹ g wt tissue⁻¹ with PE + l-NNA; P < 0.05).

To study whether protein kinase G is involved in this phenomenon, we used a specific inhibitor of protein kinase G (KT-5823). Experiments were carried out in endothelium-denuded aortic rings incubated with 10⁻⁸ M SNP in the absence or presence of 10⁻⁶ M KT-5823. As shown in Fig. 7b, SNP induced a significant increase in K⁺ uptake (control 332 ± 8 vs. 359 ± 9 nmol 86Rb/K min⁻¹ g wt tissue⁻¹ with SNP; P < 0.05), and KT-5823 blocked SNP-mediated increase in K⁺ uptake (319 ± 12 nmol 86Rb/K min⁻¹ g wt tissue⁻¹).

**Discussion**

The question addressed by the present study was whether the rhythmic contractions were associated with changes in K⁺ uptake in rat aortic rings. The main finding of the study is that rhythmic contractions are dependent of K⁺ uptake in response to vasoactive substances in aortic rings of rats. Moreover, we found that the increase in K⁺ uptake is a direct influence of an endothelial factor.

In this study, we show that rhythmic contractions occurred after adding different doses of PE (10⁻⁸ to 10⁻⁵ M PE) on intact aortic rings of rat. The highest concentration of PE or the continuous PE-stimulation reduced the rhythmic contractions, but aorta regained almost the initial level of rhythmic contractions after washout. PE-induced rhythmic contractions required reaching a threshold of vascular tone, and were mediated through the influx of extracellular Ca²⁺ in aortic rings. Interestingly, ACh following PE also produced rhythmic oscillations of vascular tone. Therefore, these findings suggest that rhythmic contractions require a certain status of vasoconstriction in response to vasoactive substances [26, 27].

To check whether K⁺ is involved with rhythmic contractions, vascular reactivity experiments in aortic rings were performed in different concentrations of KCl (10–30 mM), or in the presence of K⁺ channels blockers. We found that incubation with 20 mM KCl, or inhibition of calcium-activated K⁺ channels by TEA alone in intact aorta produced vasoconstriction, and rhythmic contractions. This is in agreement with the previous studies that show KCl causes rhythmic contractions in aortic rings from normotensive rats [26]. Other authors have shown that inhibition of calcium-activated K⁺ channels by TEA enhanced rhythmic contractions in response to PE in rat
It is known that Na⁺,K⁺-ATPase and Na⁺-K⁺-2Cl⁻ are responsible for the maintenance of K⁺ influx into the vascular cell. We previously observed that the inhibition of Na⁺,K⁺-ATPase with ouabain significantly reduced rhythmic contractions in rat aorta in response to PE (data not shown), a result that agrees with data previously reported by others [30, 31]. While, the inhibition of cotransporter Na⁺-K⁺-2Cl⁻ with bumetanide (a specific inhibitor) significantly increased rhythmic contractions in rat aorta in response to PE (data not shown).

K⁺ uptake activity regulated rhythmic contractions. In intact aortic rings, 10⁻⁶ M ACh following PE induced rhythmic contractions that were associated with the increase in K⁺ uptake activity; whereas, decreased K⁺ uptake by an increment of ACh dose reduced rhythmic contractions. On the other hand, 10⁻⁷ M PE also increased K⁺ uptake activity and induced rhythmic contractions. But the increased K⁺ uptake, by increasing of PE dose, failed to induce rhythmic contractions.

Whereas several studies have analyzed the regulation of endothelium on vasomotion by the activation of K⁺ channels [12, 30, 32, 33], we have studied the regulation of endothelium on vasomotion by the K⁺ uptake in vascular smooth muscle cells of rat aorta. Stimulatory action of PE or ACh, at the same concentrations used in vascular reactivity experiments, significantly increased the K⁺ uptake in the endothelium-intact aorta of rat; in contrast, removal of the endothelium inhibited the stimulatory action of both vasoactive substances on K⁺ uptake.

The vascular endothelium regulates vasomotion [6, 10, 11]. In fact, the absent of endothelium in rat aorta blunted rhythmic contractions in response to 10⁻⁷ or 10⁻⁶ M PE, but it occurred with 10⁻⁸ M PE. Previous studies in hamster aorta [11] or rat mesenteric arteries [12] showed that rhythmic contractions occurred when the endothelium was present. In other studies, rhythmic contractions were promoted when the endothelium was removed from rat aorta (or the nitric oxide synthase was inhibited) [34]. However, in some situations, the absence or presence of the endothelium did not affect vasomotion in rat aorta [26]. Consequently, these data suggest that endothelium modulates vasomotion, rather than causing inhibition or stimulation [35].

To obtain further insight into the eventual endothelial factor, we have studied K⁺ uptake and rhythmic contractions in the presence of nitric oxide synthase inhibitor or a nitric oxide donor. The inhibition of nitric oxide synthase (NOS) with L-NNA significantly reduced the rhythmic uptake, by increasing of PE dose, failed to induce rhythmic contractions. The increase of SNP-induced K⁺ uptake was blocked by KT-5823, a specific inhibitor of protein kinase G [36]. Moreover, the increase in K⁺ uptake in response to ACh was only observed in intact aortic rings, confirming a direct influence of an endothelial factor. Previous studies show that the relative contribution of the endothelium itself in the K⁺ uptake from intact aortic rings is negligible, hence an endothelial factor is directly involved in K⁺ uptake increase [37, 38].

In summary, we show that rhythmic contractions is associated with a change of K⁺ uptake on vascular smooth muscle cells in rat aortic rings in response to vasoactive substances. As illustrated in Fig. 8, our results are consistent with a putative model in which vasomotion...
phenomenon consists of two components: tonic and phasic vascular response. The tonic response is Ca²⁺-dependent and the phasic response is K⁺-gradient-dependent. The K⁺ gradient is generated by the K⁺ uptake (via Na⁺, K⁺-ATPase and Na⁺-K⁺-2Cl⁻ cotransporter) and K⁺ efflux (via K⁺ channels). In particular, the K⁺ uptake is a direct influence of an endothelial factor, probably nitric oxide, on intact aortic rings of rat. The findings of this study have clinical implications. Vasomotion may be considered as a compensatory mechanism to preserve the pulsation of tissues [39], especially in patients with hypertension [3, 40], type 2 diabetes mellitus [5, 41] or ischemia [42].

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