



In vitro study of the relaxant effect of doxazosin in the activity of smooth muscles in isolated goat renal artery

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Abstract

Doxazosin is a competitive, short-acting, selective alpha 1-adrenoceptor antagonist. Selective alpha 1-blockers dilate blood vessels in the veins and arteries. The specificity for alpha-adrenoreceptors causes the smooth muscle of the blood vessels to relax. The findings of the recording and analysis demonstrate that doxazosin generates an endothelium-dependent relaxation of renal artery rings that had been pre-contracted with a high amount of KCl (60 mM) or phenylephrine (PE) (10^{-5} M). Additionally, doxazosin shows strong inhibitory effects on PE and weaker effects on contractions induced by KCl. Pre-incubating renal artery rings with 4-aminopyridine (4-AP), indomethacin, potassium (K^+) channels blocker (TEA), barium chloride ($BaCl_2$), prostaglandin I_2 (PGI₂) inhibitor (Indomethacin), and nitric oxide (NO) synthase inhibitor (L-Name), significantly affects the relaxation brought on by doxazosin. Contrarily, neither glibenclamide (GLIB) nor clotrimazole, show any effect on the relaxation caused by doxazosin. Doxazosin's role suggests that a Ca^{++} channel blocking mechanism has a relaxing impact on the smooth muscles of the renal artery. The relaxing effect of doxazosin is thus concluded from these findings to involve both potassium and calcium channels, potentially through the blockage of K_V , K_{Ca} , K_{Ir} , endothelium/NO, PGI₂, and voltage-dependent calcium channels.

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Introduction

Doxazosin is a competitive, short-acting, selective alpha₁-adrenoceptor antagonist (1). It is the second alpha₁-blocker approved by the Food and Drug Administration (FDA) for the treatment of symptomatic Benign Prostatic Hyperplasia (BPH) (2,3). Selective alpha₁-blockers act as vasodilators, both on arteries and veins. The specificity of alpha-adrenoreceptors is that it induces relaxation of the vascular smooth muscle (4,5). Also, the selective alpha_{1A},_{1D}-adrenergic receptor antagonist improves stone passage rates in patients with distal ureteral stones (6,7). Various alpha₁-AR antagonists that are available in clinics, e.g., alfuzosin, doxazosin, tamsulosin, and silodosin, exhibit inhibitory effects on contractions in isolated ureters of a variety of species (8-10), including humans (11,12). Results

obtained from randomized controlled trials suggest that alpha₁-AR antagonists may be used in patients to facilitate the passage of ureter stones (13,14). Doxazosin treatment in rats increased blood flow to the bladder and reduced the severity of the response to partial outlet obstruction (15). Alpha-blockers in MET have a proven role to promote stone passage and reduce the need for minimally invasive surgery for distal ureteral stones (16). Medical expulsive therapy (MET) is defined as the use of medication to facilitate ureteral stone passage before surgical intervention. The two classes of medications generally accepted for use as medical expulsive therapy are alpha-blockers and calcium channel blockers (17). Currently, the two most common drug classes used in medical expulsive therapy are calcium channel blockers and alpha₁-adrenoceptor antagonists, and both are thought to act by inducing relaxation of the smooth muscle

in the most common location of stone formation, the distal ureters, and the pelvic-ureteric junction in order to allow stone passage to the bladder (18). The α_1 -receptor antagonists inhibit basal tone and decrease peristaltic frequency and amplitude. Consequently, intraurethral pressure might decrease and fluid transport might increase, according to some studies (19). Recent studies implicated the α -adrenoceptor as the mediator of prostate smooth muscle contraction (3).

This current study aims to provide a helpful guide to further understand the underlining mechanisms of doxazosin vascular actions, and its use as medication or stone passing by testing it on a goat's renal smooth muscle cells with emphases on the role of endothelium/NO, PGI₂ and EET, Ca⁺⁺ and K⁺ channels in its relaxant effects.

Materials and methods

Ethical approve

Renal artery samples collected from freshly slaughtered goat in Koya slaughter house in Koya city, Iraq. The technique and research methodology of the research approved by Koya technical institute/ Erbil polytechnic university. Of course, we did not any experimental animals in this research. By approval letter with no. 4161 in 20/10/2022.

Goat renal artery

This research was carried out at Health and Science Research Centre, Koya University. Forty male goats' renal arteries are employed throughout this investigation, and after they are slaughtered and weighed nearly 20kg with the age ranging 12-18 months, at Koya slaughterhouse, their kidneys are promptly collected. Then, they were submerged in a freshly made Krebs's solution at 37°C, the which has a pH of 7.4, and is exposed to the air with 95% O₂ and 5% CO₂ (17). The stock solution of doxazosin (Abcam, UK, ab120754), was prepared by dissolving 0.4515 gm of doxazosin in 1 ml of 0.9% NaCl. The solution was kept in the refrigerator and warmed to 37°C just before use. From the stock solution, the necessary serial dilution was made using a 0.9% NaCl solution.

Renal artery preparation

The isolated renal artery was cleared of adhering fat and blood. Then, the dissected artery was cut into several rings (2-4 mm) in length and kept in the physiological saline before starting the experiments. To evaluate the vascular reactivity in the isolated renal artery (20). To measure the isometric tension of the isolated renal artery rings, two stainless steel wires were carefully inserted into the lumen of the artery rings; one of them was attached to a glass organ bath, and the other wire was connected to a force transducer, coupled to the trans bridge amplifier, and operated by an AD

Instrument Power Lab 26T Data Acquisition system with a computer running LabChart Version8 chart software.

Data record by organ bath

The temperature of the organ bath was fixed to 37°C before the experiment started, and it was filled with double-distilled water (60-90 min), followed by the addition of (10 ml) of Krebs's solution (in mM/L: 118 NaCl, 4.7 KCl, 25 NaHCO₃, 1.2 KH₂PO₄, 1.2 MgSO₄, 2.4 CaCl₂, 11 Glucose, and 0.03 EDTA) or Free Calcium Krebs's solution to each organ bath channel (18,21). The preparation was oxygenated continuously with (95% O₂ and 5% CO₂). As for temperature of the solution inside the organ bath, it was maintained at 37 °C by circulating water through a water jacket from a circulating water bath set at 37 °C (Thermo circulator LabTech DAIHAN LABTECH CO., LTD.). The primary tension was set at (2 gm) weight. Renal artery rings were given 1 to 1.5 hours to equilibrate, with buffer solution changes every (15 min). KCl was used to ensure the prepared artery segments' functional integrity (60 mM) (22), and a standard percentage contractile response was employed with the largest contraction produced being taken into account. After the maximum contraction by KCl was reached to plateau, the renal artery rings were washed and restabilized at the optimum tension for at least (30 min) before applying any vasoactive substances (23). Constructing concentration-response curves (CRCs) for PE (1 10⁻⁵ M) and KCl (60 mM) against induced contraction was done after tension had isometrically stabilized before the studies could begin.

Experimental procedure

The experimental process entails observing the normal mechanical activity of the smooth muscles in the renal arteries and examining the effects of potassium chloride (KCl), phenylephrine (PE), and free Ca⁺⁺ Krebs's solution on the smooth muscles in the renal arteries of goats. Then, the role of endothelial nitric oxide (NO), prostaglandin I₂ (PGI₂), and EET in the association with vasorelaxation induced by different doses of the doxazosin (1×10⁻³ -10⁻⁸ M) was studied, then followed by incubating intact renal artery rings for (10 min) separately with each of NO synthase inhibitor (L-Name (3×10⁻⁴ M)), PGI₂ inhibitor (Indomethacin (3×10⁻⁵ M)) and EET (Clotrimazole (3×10⁻⁵ M)) and contracted with PE (1×10⁻⁵ M). Also, the roles of Potassium channels (K⁺ channel) and calcium channels (Ca⁺⁺ channel) in the development of vasorelaxation induced by different doses of doxazosin (1×10⁻³ - 10⁻⁸ M), were also studied by preincubating the renal artery rings separately with each of the following potassium channel blockers, K_{Ca} channel blocker (TEA (1 mM)), K_{ATP} channel blocker (GLIB (1×10⁻⁵ M)), K_{IR} channel blocker (BaCl₂ (1mM)) and K_V channel blocker (4-AP (1 mM)), and contracted with PE (1×10⁻⁵ M). Then, in the free Ca⁺⁺ solution, the α_1 -AR antagonist doxazosin, Doxa. 1×10⁻⁵ and 3×10⁻⁵ M, were used to test the role of the Ca⁺⁺ channels.

Statistical analysis

The data of this study were expressed as $M \pm SE$. The effective mean concentrations (IC_{50} and EC_{50}) were presented as geometric means with (95% confidence intervals) and the potency values were described as the negative logarithms ($-\log IC_{50} = pIC_{50}$ and $-\log EC_{50} = pEC_{50}$) of the mean of individual values for each tissue. Two-way analysis of variance (Two-way ANOVA) (24), backed by Sidak's multiple comparisons test, was used to compare the means of the two groups, and non-linear regression was employed to analyze the concentration-response curve. A Probability of less than 0.05 ($P < 0.05$) was considered statistically significant, in all figures and tables, the symbols *, **, ***, and **** indicate that the difference between means is significant at 0.05, 0.01, 0.001, and < 0.0001 levels, respectively. GraphPad Prism software for Windows, version 7.04, was used to construct all the graphs, calculations, and statistical analyses (GraphPad Software, USA). The maximal amplitude response obtained in concentration effects for the relaxant substance was referred to as the maximum effect of relaxation (E_{max}) (18).

Results

Effect of doxazosin on renal artery rings

The doxazosin (1×10^{-8} - 1×10^{-3} M) exerts a relaxing action on contractions produced by KCl and PE, with the PE having a stronger relaxing effect (10^{-5} M) compared to its relaxing impact on precontracted renal artery rings treated with KCl (60 mM) (Figure 1). The pIC_{50} , ($\log IC_{50}$ of CI 95%) and E_{max} are shown in (Table 1). Doxazosin produced a highly effective inhibitory action on PE-and KCl-induced contractions in renal artery rings with a pIC_{50} of 7.72 mg/mL, ($\log IC_{50}$ of CI 95% between -8.027 to -7.342) and 7.879 mg/mL ($\log IC_{50}$ of CI 95% between - 8.199 to -7.479), respectively. The E_{max} (%) ring contractions in the renal arteries caused by PE dropped to only 96.245 ± 3.566 %, while in renal artery rings precontracted with KCl, the increased contraction tone showed that the relaxation response was reduced. 86.8 ± 4.203 %.

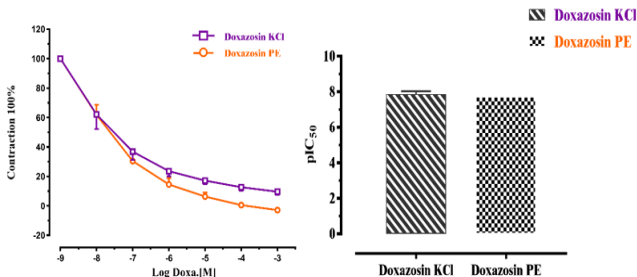


Figure 1: Cumulative dose-response curve of the effects of doxazosin on PE (10^{-5}) and KCl (60mM) precontracted renal artery rings. Left panel: lines represent 4 parameters logistic curve, which calculate the variable, pIC_{50} and E_{max} .

Table 1: The pIC_{50} , $\log IC_{50}$ of CI 95%, and E_{max} (%) \pm SEM for the effects of doxazosin on PE- and KCl precontracted renal artery rings

Parameters	Doxazosin + PE	Doxazosin + KCl
pIC_{50}	7.72	7.879
$\log IC_{50}$ of CI 95%	-8.027 to -7.432	-8.199 to -7.479
E_{max} (%) Mean \pm SE	96.245 \pm 3.566	86.8 \pm 4.203

pIC_{50} : Potency value, $\log IC_{50}$ of CI 95%: Geometric mean with 95% confident interval, E_{max} : Maximum effect of relaxation.

Role of potassium channel in the vasorelaxant effect of doxazosin

The rings have been preincubated for 10 minutes separately with: TEA (1mM), Glib (10^{-5}), $BaCl_2$ (1mM), and 4-AP (1mM), which are the blockers of K_{Ca} , K_{ATP} , K_{IR} , and K_V channels, to study the involvement of potassium channels in the vasorelaxant effect of doxazosin in the renal artery rings. They were observed to have relaxing effects. Dose-response curves for doxazosin's effects on PE-induced contractions and its pre-incubation with potassium channel blockers are displayed in (Figures 2-5). Pre-treatment of renal artery rings with Glib remained unaltered, while 4-AP and TEA revealed a slight shift to the right and $BaCl_2$ significantly shifted to the right. doxazosin concentrations (10^{-8} to 10^{-3} M) caused a potent relaxation on PE (10^{-5} M) precontracted the goat renal artery rings. Table2 shows, the pIC_{50} , ($\log IC_{50}$ of CI 95%) and E_{max} for the effect of K^+ channel inhibitors on the relaxant response to doxazosin in the rings. Pre-treatment of renal artery rings with 4-AP, TEA, and $BaCl_2$ significantly reduced the relaxation, with pIC_{50} 7.107 ± 0.2629 mg/ml, 6.884 ± 0.1504 and 6.606 ± 0.1527 ($\log IC_{50}$ of CI 95% between -7.916 to -5.993, -7.227 to -6.471 and -7.028 to -6.327), and also, it reduced the percentage of relaxation to 73.13 ± 2.083 %, 91.939 ± 1.948 and 81.897 ± 1.024 , compared to the control, which was 96.245 ± 2.566 %.

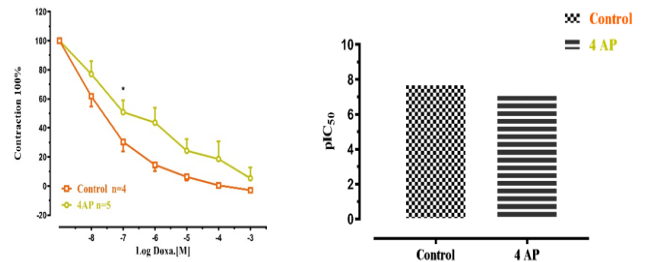


Figure 2: Cumulative dose-response curves of the vasorelaxant effects of Doxa. On control and preincubated renal artery rings with 4AP (1mM), precontracted with PE (1×10^{-5} M). Left panel: lines represent 4 parameters logistic curve which calculate the variable, pIC_{50} and E_{max} .

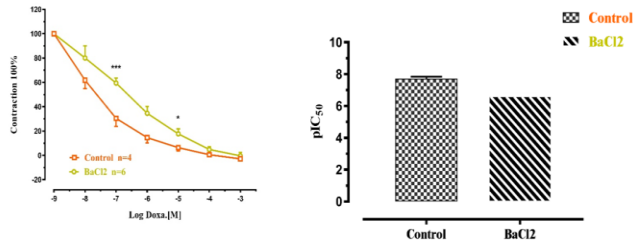


Figure 3: Cumulative dose-response curves of the vasorelaxant effects of doxazosin on control and preincubated renal artery rings with BaCl₂ (1mM), precontracted with PE (1×10⁻⁵ M). Left panel: lines represent 4 parameters logistic curve, which calculate the variable, pIC₅₀ and E_{max}.

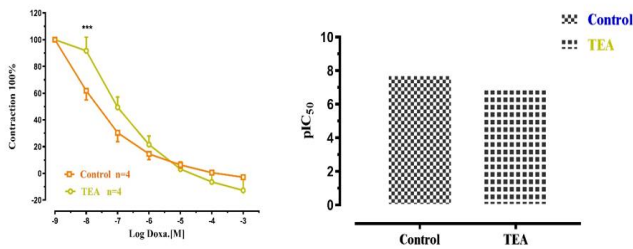


Figure 4: Cumulative dose-response curves for the vasorelaxant effects of doxazosin on control and preincubated renal artery rings with TEA (1mM), precontracted with PE (1×10⁻⁵ M). Left panel: lines represent 4 parameters logistic curve, which calculate the variable, pIC₅₀ and E_{max}.

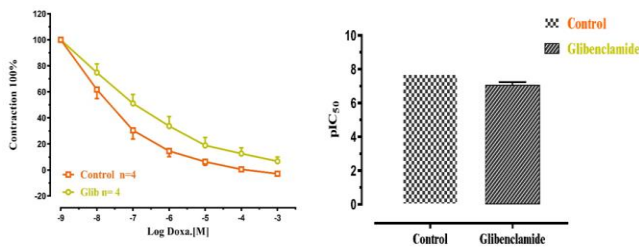


Figure 5: Cumulative dose-response curves for the vasorelaxant effects of doxazosin on control and preincubated renal artery rings with Glib (1mM), precontracted with PE (1×10⁻⁵ M). Left panel: lines represent 4 parameters logistic curve, which calculate the variable, pIC₅₀ and E_{max}.

Role of endothelium/NO, PGI₂, and EET in the vasorelaxant effect of doxazosin

Comparing renal artery rings preincubated with L-Name and slightly with Indomethacin to control rings, the percentage of relaxation, pIC₅₀, and (LogIC₅₀ of CI 95%) for

the doxazosin-induced relaxant response were very significant (Figures 6-8), with pIC₅₀ 5.935 M, and (LogIC₅₀ of CI 95% between -6.387 to -5.476) and 6.814M (withLogIC₅₀ of CI 95% between -7.267 to -6.245) and E_{max} were 84.412±0.888 and 70.95±1.555, respectively. Although pre-treatments with Clotrimazole seemed to no effect on the relaxation brought on by doxazosin (Table 2).

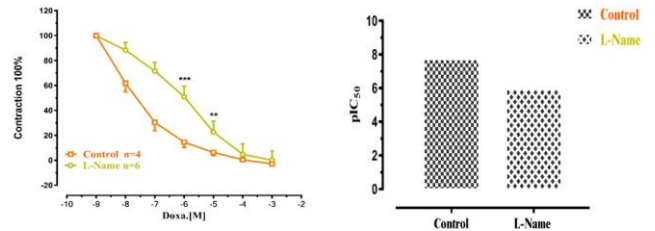


Figure 6: Cumulative dose-response curve for the vasorelaxant effects of doxazosin on control and preincubated renal artery rings with L-Name (3 ×10⁻⁵ M), precontracted with PE (10⁻⁵ M). Left panel: lines represent 4 parameters logistic curve, which calculate the variable, pIC₅₀ and E_{max}.

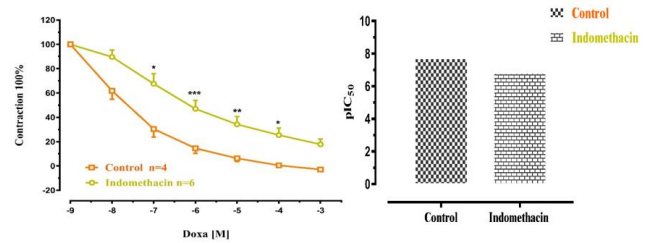


Figure 7: Cumulative dose-response curve for the vasorelaxant effects of doxazosin on control and preincubated renal artery rings with Indomethacin (3×10⁻⁵ M), precontracted with PE (10⁻⁵ M). Left panel: lines represent 4 parameters logistic curve which calculate the variable, pIC₅₀ and E_{max}.

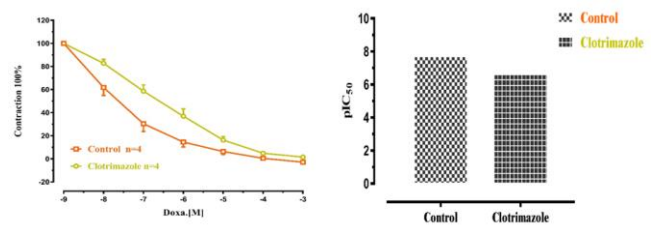


Figure 8: Cumulative dose-response curve for the vasorelaxant effects of doxazosin on control and preincubated renal artery rings with Clotrimazole (3×10⁻⁴ M), precontracted with PE (10⁻⁵ M). Left panel: lines represent 4 parameters logistic curve which calculate the variable, pIC₅₀ and E_{max}.

Table 2: The pIC₅₀, Log IC₅₀ of CI 95%, and E_{max} (%) ± SEM for the effects of doxazosin after incubation of renal artery with K⁺ channel blockers, clotrimazole, indomethacin, and L-Name

Groups	No.	pIC ₅₀	LogIC ₅₀ of CI 95%	E _{max} (%) Mean ± SE
Control	4	7.72±0.1268	-8.027 to -7.342	96.245±2.566
TEA	4	6.884±0.1504	-7.227 to -6.471	91.939±1.948**
Glib	4	7.067±0.1714	-7.57 to -6.568	76.97±2.04
BaCl ₂	6	6.606±0.1527	-7.018 to -6.317	81.897±1.024***
4AP	5	7.107±0.2629	-7.916 to -5.993	73.13±2.085*
Clotrimazole	4	6.618±0.138	-7.012 to -6.152	82.312±0.953
Indomethacin	6	6.814±0.1891	-7.267 to -6.2445	70.95±1.555***
L-Name	6	5.935±0.1741	-6.387 to -5.476	84.412±0.888***

pIC₅₀: Potency value, Log IC₅₀ of CI 95%: Geometric mean with 95% confident interval, E_{max}: Maximum effect of relaxation.

Role of Ca²⁺ channels in doxazosin: The vasorelaxant effect of CaCl₂-induced contraction

Both doxazosin dosages (1×10⁻⁵ and 3×10⁻⁵ M) produced highly significant (P<0.0001) vasoconstriction effects on CaCl₂-induced dose-dependent contraction in renal artery rings pre-incubated with doxazosin as compared to the control (Figure 9). The pEC₅₀, (LogEC₅₀ of CI 95%) and the maximum contraction are shown in (Table 3). Both doxazosin doses (1×10⁻⁵ and 3×10⁻⁵ M) showed highly significant effects on CaCl₂ contracted goat artery rings with pEC₅₀ 2.386 M (LogEC₅₀ of CI 95% between -2.609 to -2.13) and 2.845 M (LogEC₅₀ of CI 95% between -3.112 to -2.56), along with the greatest contraction (62.155 ± 5.499) and (53.346 ± 3.183), respectively.

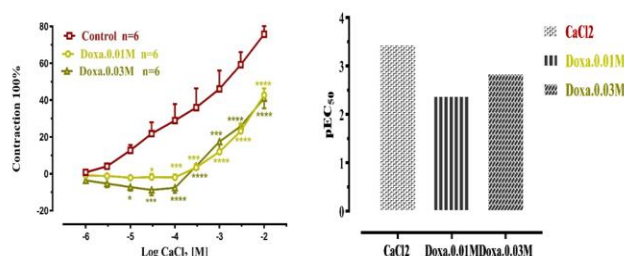


Figure 9: Cumulative dose-response curves of CaCl₂ in renal artery rings pre-incubated with different doses of doxazosin (1×10⁻⁵ mg/ml - 3×10⁻⁵ mg/ml). Left panel: lines represent 4 parameters logistic curve, which calculate the variable, pEC₅₀ and E_{max}.

Table 3: The pEC₅₀ (Log EC₅₀ of CI 95%) and E_{max} (%) ± SEM for the effects of doxazosin and Nifedipine on preincubated renal artery rings with CaCl₂

Parameters	Control	Doxazosin	
		0.01 M	0.03 M
No.	6	6	6
pEC ₅₀	3.442±0.2037	2.386±0.1107	2.845±0.1296
LogEC ₅₀ of CI 95%	-4.074 to -2.827	-2.609 to -2.13	-3.112 to -2.56
E _{max} (%) Mean ± SE	+61.402±2.318	62.155±5.499 ****	53.346±3.186****

pEC₅₀: Potency value, Log EC₅₀ of CI 95%: Geometric mean with 95% confident interval, E_{max}: Maximum effect of relaxation.

Discussion

Effect of doxazosin's vasorelaxant on isolated renal artery rings

This study is the first in-depth examination of how doxazosin relaxes the renal artery in a concentration-dependent approach. Several scientific studies examined the use of α₁A/D-selective alpha-blockers and demonstrated their advantages in improving stone removal. A recent study revealed that doxazosin produced a significant increase in maximum urinary flow rate (1). Doxazosin is a clinically effective α₁-adrenergic antagonist used in the treatment of symptomatic benign prostatic hyperplasia (BPH). Notwithstanding, the major therapeutic effect of the agent is

believed to occur on the smooth muscle components of the prostate by reducing prostatic urethral resistance and thus improving emptying (15,25). The results of this study showed that doxazosin added cumulatively had a more relaxing effect on contractions brought on by PE than by KCl. With KCl-induced vasoconstriction, doxazosin's vasorelaxant effects became less effective. The constriction brought on by PE reduced the doxazosin-induced vasodilation, which is supported by Nickel (26), which states the effective phenylephrine concentration for a rabbit. Therefore, phenylephrine promotes maximal contraction and was chosen as the effective concentration used in the experiment. Karadeniz (27) showed that when PE binds to α₁A-adrenoceptors, Phospholipase C is activated, which

releases the second messenger IP_3 and causes the release of calcium ions from IP_3 -sensitive stores. When calcium ions rise, there is a subsequent increase in $[Ca^{2+}]_i$ as a result of Ca^{2+} being released from Ca^{2+} -sensitive Ca^{2+} pools and increased Ca^{2+} entry through L-type.

The role of potassium channels in the doxazosin relaxing action

Pre-treatment of renal artery rings with potassium channel blockers, 4-AP, TEA, and $BaCl_2$ showed significant enhancement in the vasorelaxant effect of doxazosin, while there were no changes in the vasorelaxation effect of doxazosin in pre-treated with Glib. The finding of the study disagrees with Eckert (28), which stated that TEA and $BaCl_2$ did not affect biochanin-A-induced relaxation in the goat coronary arterial rings. While Brede (18) and Kumar (29) revealed that 4-AP has significant enhancement in renal artery relaxation. In addition, Novakovic (30) stated that $BaCl_2$ has a significant effect on broncho dilators. Doxazosin's dose-dependent vasodilation with 4-AP, TEA, and $BaCl_2$ was statistically proven in the current study's findings. These results demonstrate that the vasodilatory effects of doxazosin are mediated via a negative function of K_v , K_{Ca} , and K_{Ir} channels.

The effect of doxazosin on relaxation is influenced by NO, PGI_2 , and EET

Renal artery rings were pre-incubated with L-Name, indomethacin, or clotrimazole to investigate the roles of endothelium/NO, PGI_2 , and EET, the three key enzymes responsible for the release of relaxant substances in the vascular beds. The impact of doxazosin was then assessed. According to the current study's findings, doxazosin causes vasodilation in precontracted renal artery rings with PE, which is mediated by indomethacin, L-Name, but not by Clotrimazole. Otherwise, Clotrimazole has a significant effect when preincubated by herbal medicine, which acts as an alpha blocker (31,32). In addition, Hassan (33) revealed the role of PGI_2 , as a potent vasodilator substance, which mediated through activation of Adenylate Cyclase in VSMCs. Furthermore, the result of our study can be supported by Valero (34) and Kwon (35), which found that after treatment with L-NAME, the vasorelaxant effect was significantly diminished and relaxations on the endothelium-denuded rings were nearly entirely eliminated. We demonstrate a specific beneficial effect of doxazosin on endothelium-dependent vasodilation. This may be due to a direct effect on NO levels both by increasing nitric oxide synthase (NOS) activity, thus potentially enhancing NO synthesis, and also by reducing NO degradation. Conversely, the endothelial function may have been enhanced by the reduction in blood pressure per se rather than a specific action of doxazosin (36).

Role of Ca^{++} channel blockers in doxazosin relaxant effect

In the study, doxazosin considerably increased the rate of relaxation in renal artery rings. The smooth muscle is effectively relaxed by α_1A -adrenoceptor blockers and Ca^{++} channel blockers. Doxazosin inhibits $\alpha_1A/1D$ receptors in the ureter and bladder, which prevents calcium from entering the cell and relaxes smooth muscle cells (37,38). Alpha antagonists, calcium channel blockers, and steroids have been demonstrated to improve the time to the ejection of distal ureteral stones in adults in several recent researches (39,40). Researchers have demonstrated that Ca^{++} channels allow the passage of extracellular calcium into the cell, restoring normal levels of ureteral peristalsis. Troxel (41) using human caliceal rings that demonstrate how calcium channel blockers can suppress the upper urinary tract's naturally occurring phasic-rhythmic activity. While α -1 adrenergic blockers decreased ureter muscle tone, calcium channel blockers decreased the degree of smooth muscle contractions and reduced ureter spasm (42,43).

Conclusion

The results of the current study revealed that different doses of doxazosin have relaxant actions in the goat isolated renal artery precontracted by PE and KCl. These effects may be countable for their uses as vasodilators and uses as medications for stone passing. Also, we can say the results is the first observation of this drug in the renal artery. Doxazosin also blocks potassium and calcium channels, possibly by inhibiting K_v , K_{Ca} , K_{Ir} , endothelium/NO, PGI_2 , and voltage-dependent calcium channels. With these findings, we came to the conclusion that doxazosin can be utilized as a MET for ureteric stones.

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Conflict of interest

No conflict of interest to declare

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دراسة التأثير الاسترخائي للدوكسازوسين في نشاط العضلات الملساء للشريان الكلوي المعزول من الماعز

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الخلاصة

الدوكسازوسين هو مضاد انتقائي لمستقبلات ألفا 1 الأدرينية قصير المفعول. إذ تعمل حاصرات ألفا 1 الانتقائية على توسيع الأوعية الدموية في الأوردة والشرايين. وتؤدي خصوصية مستقبلات ألفا الأدرينية إلى استرخاء العضلات الملساء في الأوعية الدموية. أظهرت نتائج التسجيل والتحليل أن الدوكسازوسين يسبب ارتخاء معتمد على البطانة الاندوثيليه في حلقات الشريان الكلوي المستحث التقلص مسبقاً بكمية عالية من كلوريد البوتاسيوم أو فينيليفرين. بالإضافة إلى ذلك، أظهر الدوكسازوسين تأثيرات مثبطة قوية على النشاط الانقباضي المحدث بفينيليفرين وتأثيرات أضعف على الانقباضات المحدثه بكلوريد البوتاسيوم. وتظهر الحضانه المسبقة ل حلقات الشريان الكلوي مع 4- أمينوبيريدين، والإندوميثاسين ومثبطات قنوات البوتاسيوم وكلوريد الباريوم، ومثبط البروستاغلاندين إندوميثاسين ومثبط تكوّن أوكسيد النيتريك تأثيراً كبيراً في النشاط الاسترخائي الذي يسببه الدوكسازين. وعلى النقيض من ذلك، لم يظهر جليبينكلاميد ولا كلوتريمازول تأثيراً مثبطاً على الاسترخاء الناجم عن الدوكسازوسين. كما ويشير دور دوكسازوسين إلى أن لآلية تثبيط قنوات الكالسيوم تأثيراً استرخائياً على العضلات الملساء في الشريان الكلوي. وفي ضوء النتائج المتوصل إليها من هذه الدراسة يستنتج أن آلية التأثير الاسترخائي للدوكسازوسين تشمل كلاً من قنوات البوتاسيوم والكالسيوم ويرجح أن يكون ذلك من خلال انسداد قنوات الكالسيوم المعتمدة على الجهد.