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Regulation of renal artery smooth muscle tone by α_1-adrenoceptors: role of voltage-gated calcium channels and intracellular calcium stores

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Abstract The ischemia induced vasospasm of the renal arterial blood vessels mediated by α_1-adrenoceptors is of importance for the loss of kidney function. This is based on reduced perfusion of the kidney cortex occuring in kidney transplant and organ preserving surgery. The present study considered the intracellular mechanism of the norepinephrine (NE) induced renal artery vasospasm by using swine renal artery smooth muscle ring. Norepinephrine and phenylephrine (PE) induced dose-dependent and fully reversible isometric contractions with a threshold concentration of 10 nM ($n = 7$) and 10 nM ($n = 4$), and an EC_{50} of 0.3 μM and 1 μM, respectively. The receptor was identified as α_{1A}-subtype. The contraction was completely inhibited by verapamil ($IC_{50} =$ 1.51 μM; $n = 11$) and diltiazem ($IC_{50} = 9.49$ μM; $n = 8$) and 85% by nifedipine ($IC_{50} =$ 0.13 μM; $n = 21$). Blockade of the intracellular inositol-1,4,5-trisphosphate (IP_3)-sensitive Ca^{2+} store by thapsigargin (1 μM, $n = 7$) or suppression of Ca^{2+} release from the intracellular Ca^{2+}-sensitive Ca^{2+} store by ryanodine (100 μM, $n = 4$) inhibited the PE induced contraction by 39.5% and 47.6%, respectively. The results suggest a key role of voltage-dependent Ca^{2+} channels and intracellular Ca^{2+} stores in the α_{1A}-adrenoceptor induced contraction of the renal artery.

Key words Renal ischemia · Renal artery myocytes · Calcium channels · Calcium stores

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Introduction

Surgical manipulation of the main renal artery during kidney explantation and nephron-sparing surgery induces norepinephrine (NE) secretion from sympathetic nerve endings that leads to renal vasospasm [34]. Onset of renal ischemia by clamping the main renal artery evokes further NE secretion from intravasal sympathetic nerve terminal ends. The lack of oxygen and ATP leads to a decreased activity of various energy-dependent enzymes (e.g. Na^+/K^+-exchanger, Ca^{2+}-ATPases). These events result in an intracellular Ca^{2+} overload maintaining renal vasoconstriction. Activation of Ca^{2+}-dependent proteases, interstitial acidosis and membrane destruction by oxygen radicals damage the nephron and cause acute tubular necrosis (ATN) which might explain depressed post surgical organ function. From a pathophysiological viewpoint free cytoplasmic Ca^{2+} concentration ($[Ca^{2+}]_i$) plays a key role in the development of renal ischemia and in the regulation of smooth muscle contractility [34]. Elevation of $[Ca^{2+}]_i$ activates the Ca^{2+}-calmodulin dependent protein kinase. This protein kinase phosphorylates the myosin light chain kinase leading to myofilamental crossbridging with consecutive smooth muscle contraction [5, 14, 29, 31]. The intracellular Ca^{2+} concentration is determined by voltage-dependent Ca^{2+} channels, capacitative Ca^{2+} entry, intracellular Ca^{2+} pools and Ca^{2+} extrusion systems [5, 12, 15, 25, 29, 31]. In smooth muscle tissue at least two different voltage-dependent Ca^{2+} channels can be distinguished due to their electrophysiological and pharmacological properties [21, 35]. The T-type Ca^{2+} channel is transient and fast inactivating, whereas the L-type is a slowly inactivating Ca^{2+} channel with the more importance in the regulation of smooth muscle tone [21, 35]. The L-type Ca^{2+} channel opens on depolarization above −30 mV (threshold) and is maximally open at around 0 mV [16, 17, 21, 35]. Another class of calcium channels constitutes storage-operated channels. These open on depletion of calcium stores

(capacitative calcium entry) [12, 25]. Furthermore two different intracellular Ca^{2+} stores can be distinguished: a Ca^{2+}-sensitive Ca^{2+} store which releases Ca^{2+} in response to increasing $[Ca^{2+}]_i$ and an IP_3-sensitive pool which liberates Ca^{2+} in response to IP_3 binding [2, 3]. The Ca^{2+}-sensitive Ca^{2+} pool plays an essential role in excitation-contraction coupling [20] whereby Ca^{2+} entering the cytoplasm via voltage-dependent Ca^{2+} channels triggers the release of Ca^{2+} from this pool (Ca^{2+}-induced Ca^{2+} release) [10, 19, 27, 30, 32, 33]. The IP_3-sensitive Ca^{2+}-store is under the control of various membrane receptors which activate phospholipase C (PLC) converting phosphadityl-inositol-4,5-bisphosphate (P_1P_2) into diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP_3) [2, 3, 5, 19]. Depending on the cell type, the IP_3-sensitive pool amounts up to 60% of the intracellular stored Ca^{2+} and is probably located in the sarcoplasmic reticulum [2, 3, 19]. To prevent intracellular Ca^{2+} overload, Ca^{2+} is pumped into the intracellular pools by Ca^{2+}-ATPases and transported out of the cell by the Na^+/Ca^{2+} exchanger. Thus the balanced activity of these systems enables the optimal control of the cellular Ca^{2+} homeostasis and contractility [1, 18, 31].

As the α_1-adrenoceptor mediated Ca^{2+} overload in renal artery myocytes during renal surgery plays a major role in post surgical organ dysfunction, this study suggests what are the intracellular mechanisms of adrenergically induced vasoconstriction. A knowledge of these cellular mechanisms facilitates an intelligent development of new pharmacological strategies in renal protection.

In the present study the role of voltage-dependent Ca^{2+} channels, capacitative Ca^{2+} entry and intracellular Ca^{2+} stores for the α_1-adrenoceptor induced contraction of swine renal artery smooth muscle tissue is investigated.

Material and methods

Preparation of renal arteries

Swine kidneys were freshly obtained from the slaughterhouse and transported in cold calcium-free tyrode solution (140 mM NaCl, 5.4 mM KCl, 1 mM $MgCl_2$, 10 mM glucose, 10 mM HEPES, pH 7.4 with NaOH) to the laboratory. There the organ was freed from fat, decapsulated and interlobar arteries were prepared and removed.

Organ bath experiments

Contractile properties of swine renal artery smooth muscle rings were studied in the Schuler organ bath FMI IOA-5301 (Föhr Medical Instruments, Seeheim, Germany) (Fig. 1). In all experiments, isometric contractions of the tissue were registered on a FMI GM-2 force displacement transducer (Föhr Medical Instruments, Seeheim, Germany) and stored digitally on a pentium II IBM computer. A pre-tension of 20 mN has been established which is in line with the observation in canine aorta [11, 19]. Contractions were evoked by application of the α_{1A}-adrenoceptor selective agonists PE and NE (10^9 –10^4 M). Dose–response curves for agonists and various blocking agents were obtained. To determine PE and NE dose–response curves, the muscle rings were superfused noncumulatively with increasing agonist concentrations whereby the maximal contractility of an individual muscle ring was counted as 100%. Dose–response curves of inhibitory agents where determined by comparing the remaining contractility after three control contractions (mean 100%) induced by 10 μM PE. The incubation time for all inhibitory drugs was 30 min with a minimum wash-out period of 20 min.

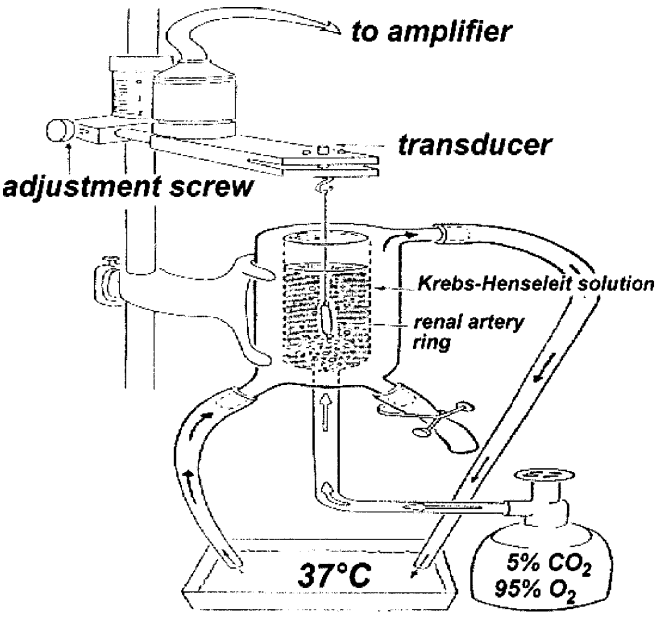

Fig. 1 Scheme of a Schuler organ bath where isometric contractions are recorded. The output of the transducer is connected to the amplifier. The pre-tension of the renal artery ring is adjusted manually to 20 mN at the preadjustment screw

Drugs and solutions

Krebs-Henseleit solution (KH) was prepared and consisted of the following: 118 mM NaCl, 24.9 mM $NaHCO_3$, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.6 mM $MgSO_4$, 1.2 mM KH_2PO_4, 5.6 mM glucose, 1 mM sodium pyruvate, pH 7.4 with NaOH, temperature 37.0 °C. The solution was aerated with 5% CO_2 and 95% O_2.

The following drugs were used: phenylephrine, norepinephrine, EGTA, HEPES, sodium pyruvate, $LaCl_3$, nifedipine, prazosin, verapamil, urapidil, WB4101 (all from Sigma-Aldrich GmbH, Deisenhofen, Germany), thapsigargin, ryanodine, phenoxybenzamine (all from Calbiochem-Novabiochem, Bad Soden, Germany). All other chemicals were from Merck, Darmstadt, Germany.

Statistical analysis

Standard statistical tests such as Student's *t*-test, Mann Whitney and chi-square were used for statistical analysis; correlations among different variables were calculated. P values < 0.05 were considered significant. Results are expressed as mean values ± SEM, whereby the number of experiments is given in brackets.

Results

Phenylephrine and norepinephrine-induced contraction of renal artery smooth muscle rings

Since vascular tissue is composed of muscular and elastic components it was necessary to determine the pre-tension by establishing the corresponding length(–)tension

curve of the renal artery ring. The length–tension curve is depicted in Fig. 2. Lengthening of renal artery rings above 2.5 mm corresponding to a pre-tension of 20 mN resulted in elastic tissue resistance being overcome. The development of almost a linear force above a pre-tension of 20 mN was observed. This is a necessary precondition to avoid ineffective tissue contraction according to the isometric principle in organ bath experiments [5]. Thus in the present experiments a pre-tension of 20 mN was used and neither NE or the selective α_1-adrenoceptor agonist PE were administered to elicite isometric contractions. Figure 3 illustrates the time course of an original trace of isometric contraction in response to

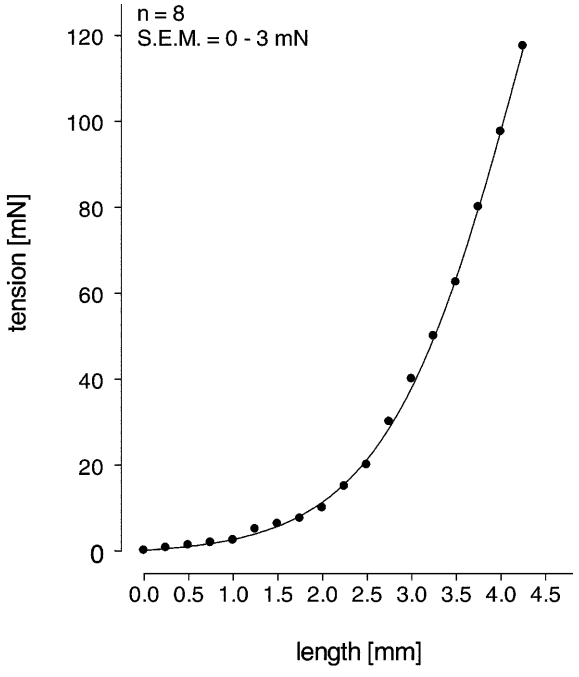

Fig. 2 Length–tension curve of the renal artery smooth muscle ring. The increase in passive elongation is plotted versus the mean tension developed by the tissue ($n = 8$)

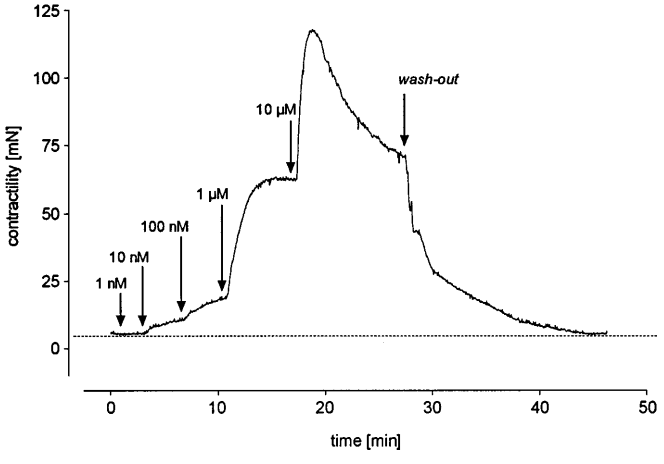

Fig. 3 Time course of an original trace of renal artery smooth muscle contraction in response to increasing concentrations of phenylephrine (PE)

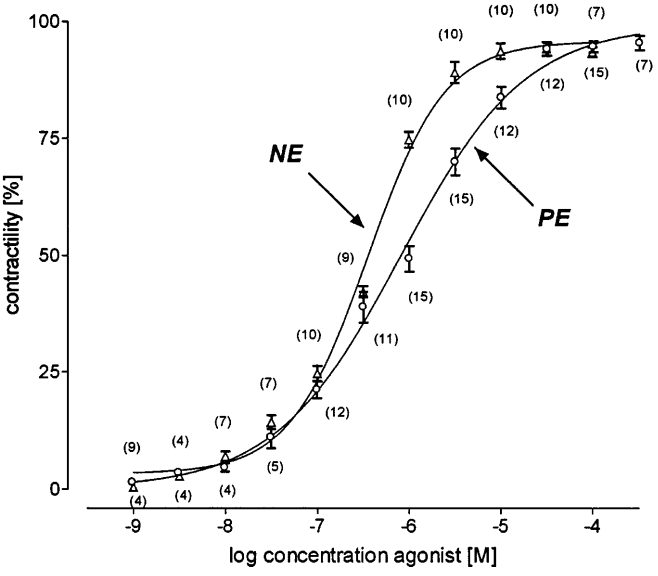

Fig. 4 Dose–response curve of the norepinephrine (*NE*) and phenylephrine (*PE*)-induced contraction of renal artery smooth muscle rings. The concentration of the agonist in logarithmic scale is plotted versus the mean contractility, expressed as percentage of the maximal contraction (100%). The number of experiments is given in *parentheses*, whereby the *bars* represent the standard error of the mean

cumulatively increasing concentrations of PE. The threshold concentration was 10 nM with maximal contractions in the micromolar range. The force of the contractions was dose-dependent; the contractions were fully reversible and showed no desensitization. The peak contraction was reached within 4.1 min ($n = 4$). The dose–response curves of the PE and NE induced contractions are depicted in Fig. 4. Using a logarithmic scale the concentration is plotted versus the mean contractility whereby the maximal contraction was calculated as 100%. Note the slight right-shift of the PE curve (EC_{50} 804 nM) indicating a higher affinity of NE (EC_{50} 353 nM) towards renal artery α_1-adrenoceptors.

Characterization of renal artery α_1-adrenoceptor

In order to identify the renal artery α_1-adrenoceptor subtype, the α-adrenoceptor blockers phenoxybenzamine, prazosin, urapidil and WB4101 were used [4, 6, 11]. The corresponding dose–response curves which were obtained non-cumulatively, i.e., the next higher concentration was applied after several wash-outs, are presented in Fig. 5. The used antagonists fully suppressed the contractions induced by 10 µM PE. The effect of phenoxybenzamine was not reversible within 4 h. The renal artery α_1-adrenoceptor was identified as α_{1A}-subtype since the selected α_{1A}-adrenoceptor blocker WB4101 showed the highest affinity (Table 1).

Role of transmembranous Ca^{2+} influx

The force of contraction depended on the extracellular Ca^{2+}-concentration. Withdrawal of external calcium

Table 1 Comparison of IC_{50} concentrations of the investigated α_1-adrenoceptor blockers

	WB4101	Prazosin	Phenoxybenzamine	Urapidil
IC_{50} [M]	6.11×10^{-9}	1.19×10^{-8}	2.46×10^{-8}	2.43×10^{-7}

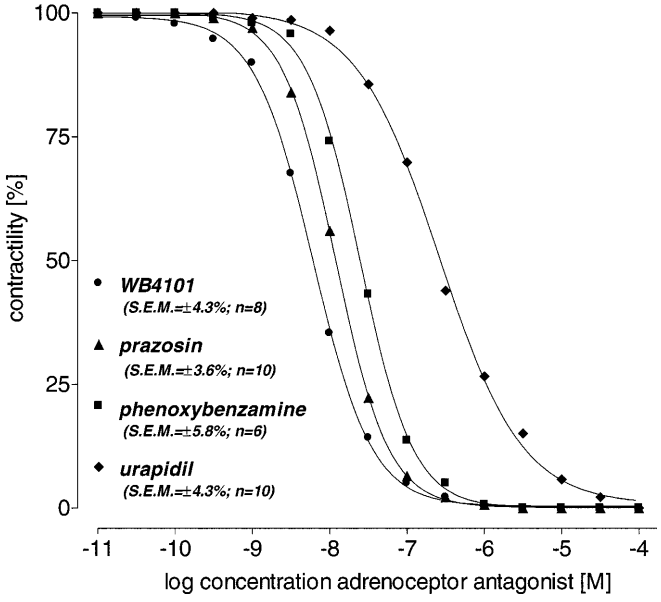

Fig. 5 Characterization of the renal artery α_1-adrenoceptor subtype by various α_1-receptor-blockers. Dose–response curves of WB4101, prazosin, phenoxybenzamine and urapidil whereby the concentration in logarithmic scale is plotted versus the mean contractility evoked by 10 μM PE (100%). Since WB4101 has the highest affinity towards the renal α_1-adrenoceptor, the receptor subtype is identified as α_{1A}-subtype

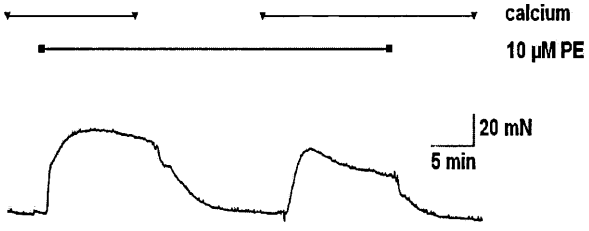

Fig. 6 Time-dependent reduction of contraction in Ca^{2+}-free solution. Arterial rings were incubated either in KH containing 2.5 mM $CaCl_2$ or in Ca^{2+}-free KH containing 1 mM EGTA for the time indicated and then stimulated by 10 μM phenylephrine (*PE*)

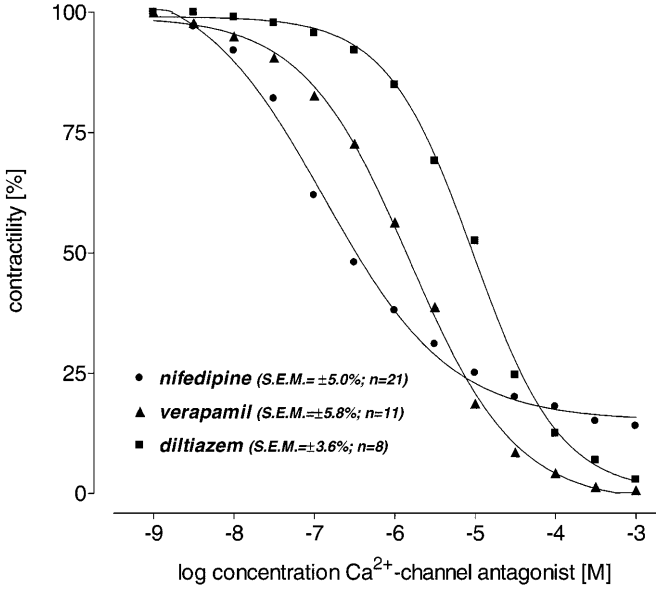

Fig. 7 Inhibition of PE contraction by various blockers of the voltage-dependent L-type Ca^{2+}-channel. PE contraction is fully suppressed by the antagonists diltiazem and verapamil, whereas nifedipine only blocks the contraction by 85% and exerts the highest affinity to L-type Ca^{2+}-channels. Using a logarithmic scale the concentration of the antagonists is plotted versus the mean contractility evoked by 10 μM PE. Standard error of the mean and numbers of experiments are given in *brackets*

eliminated the PE-mediated response, pointing to a Ca^{2+} influx as an essential step in the cellular mechanism of the α_1-adrenoceptor induced contraction (Fig. 6). In order to study the mechanism of Ca^{2+} entry, blockers of the voltage-dependent Ca^{2+} channels were administered. Figure 7 shows the dose–response curves of nifedipine, diltiazem and verapamil induced inhibition of PE mediated contraction and in Table 2 the corresponding IC_{50} concentrations are listed. In concentrations lower than 1 μM, nifedipine was the strongest and diltiazem the weakest inhibitor. However, in contrast to verapamil and diltiazem, at concentrations higher than 10 μM nifedipine did not fully depress the contraction (85 ± 5.0%; $n = 21$). The blocker of Ca^{2+} release activated current (I_{crac}), $LaCl_3$, [12, 25], inhibited the PE-induced contraction by 21.0 ± 9.0% ($n = 7$). The results suggest that voltage-dependent Ca^{2+} channels and capacitative Ca^{2+} entry play an important role in PE-induced contraction.

Role of intracellular Ca^{2+} stores

Besides external Ca^{2+} entry through membrane integrated Ca^{2+} channels, $[Ca^{2+}]_i$ may increase by being released from intracellular Ca^{2+} pools. At least two distinct Ca^{2+} stores can be differentiated [2, 3]. An IP_3-sensitive Ca^{2+} store which releases Ca^{2+} in response to IP_3 and a Ca^{2+}-sensitive Ca^{2+} store which liberates Ca^{2+} in response to increasing $[Ca^{2+}]_i$ are distinguished [2, 3, 10, 12, 19]. Pretreating the vascular rings with thapsigargin (1 μM), a substance that is known to deplete IP_3-sensitive Ca^{2+} stores by inhibiting Ca^{2+} reuptake by blockade of the Ca^{2+}-ATPase [5, 19, 27, 30, 32, 33], inhibited the PE contraction by 39.5 ± 12.5% ($n = 7$) (Fig. 8). Ryanodine (10 μM) depleted the Ca^{2+}-sensitive Ca^{2+} stores by arresting the sarcoplasmic

Table 2 Comparison of IC_{50} concentrations of the investigated Ca^{2+}-channel blockers

	Nifedipine	Verapamil	Diltiazem
IC_{50} [M]	1.33×10^{-7}	1.51×10^{-6}	9.49×10^{-6}

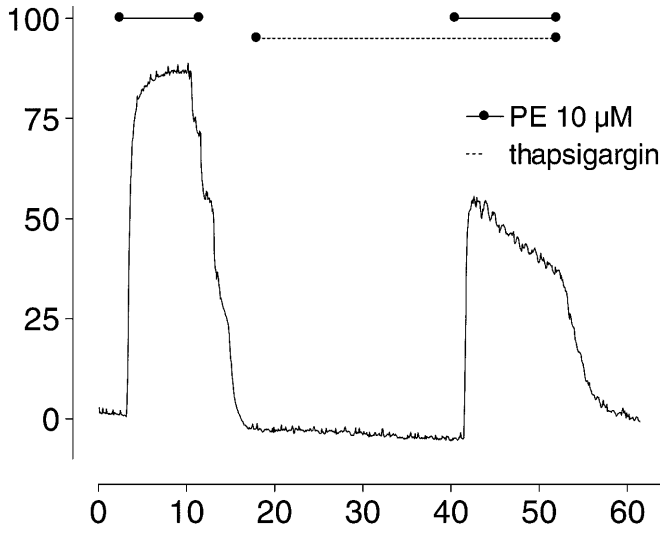

Fig. 8 An original trace showing the time course of the inhibition of renal artery smooth muscle contraction by thapsigargin (1 µM). The effect of thapsigargin was irreversible within 240 min

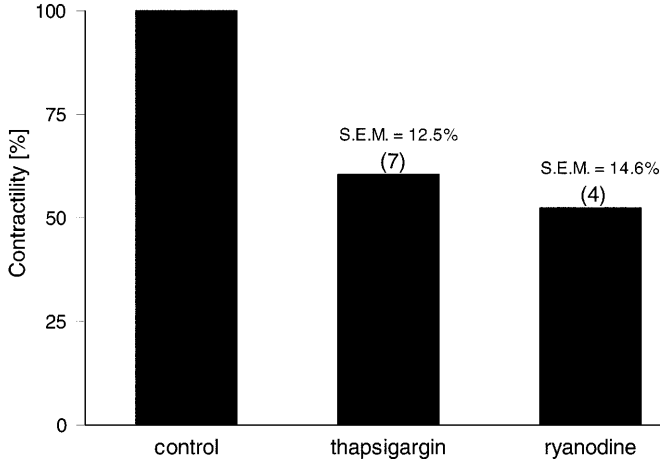

Fig. 9 Statistical comparison of the ryanodine and thapsigargin induced inhibition of the phenyleprhine contraction of renal artery smooth muscle ring. The number of experiments and the SEM are indicated in the figure

Ca^{2+}-release channel in a half-open state; in concentrations above 100 µM ryanodine fully blocks the release channel [19, 23]. Ryanodine (100 µM) suppressed the PE contraction by 47.6 ± 14.6% ($n = 4$). Blockers of both intracellular Ca^{2+} sources partially inhibited the PE response (Fig. 9) pointing to a release of intracellular Ca^{2+} as an essential step in the signal transduction pathway of the α_{1A}-adrenoceptor induced contraction.

Discussion

The present study was designed to investigate the cellular mechanism of α_1-adrenoceptor induced smooth muscle contraction of the renal artery that is responsible for vasospasm occuring in kidney transplantation and nephron-sparing surgery. The agonists PE and NE induced dose-dependent and reversible contractions which were mediated by α_{1A}-receptor subtypes. The dose–response curves of PE and NE showed EC_{50} concentrations in the submicromolar range, which is in line with comparable studies in other vascular tissues [13, 22]. Based on the highest affinity of WB4101, a selective α_{1A}-blocker, the receptor has been identified as α_{1A}-subtype [4, 26]. This was the predominant subtype in rat renal artery in radioligand binding experiments [6]. Withdrawal of external Ca^{2+} or application of the Ca^{2+} channel blockers verapamil and diltiazem eliminated the PE response. Interestingly, the Ca^{2+} channel blocker nifedipine did not fully suppress the PE response. This might be explained by there being a lower affinity to L-type Ca^{2+} channel proteins or to technical peculiarities such as light-sensitivity or solubility. The relaxation of smooth muscle tissue by Ca^{2+} antagonists has been observed in a large variety of studies [1, 5, 7, 8, 9, 16, 17, 18, 20, 28, 35]. Clinically, the inhibition of voltage-gated Ca^{2+} channels constitutes a pharmacological rationale for a renoprotective therapy in vascular based renal failure [7, 8, 9, 24, 28]. Moreover the role of extracellular Ca^{2+} for the PE-induced contraction was proven in a series of experiments where reduction of extracellular Ca^{2+} led to a decreased PE response (Fig. 6). Beside Ca^{2+} entry via voltage-dependent Ca^{2+} channel proteins, a capacitative Ca^{2+} entry is involved in the PE response since blockade of non-specific cation channels by $LaCl_3$ reduced the PE contraction significantly [12, 25].

Blockade of intracellular IP_3-induced Ca^{2+} release by thapsigargin reduced the PE contraction and suggests a participation of phospholipase C (PLC) in the signal transduction pathway of the PE response. Moreover suppression of Ca^{2+}-induced Ca^{2+} release by ryanodine inhibited the PE response indicating an involvement of Ca^{2+}-sensitive Ca^{2+} stores. However, sufficient blockade of intracellular Ca^{2+} stores by thapsigargin and ryanodine produced only a partial reduction of the PE contraction. This implies that extracellular Ca^{2+} entry makes a significant contribution to smooth muscle contraction. Intracellular Ca^{2+} release and a Ca^{2+} influx through voltage-dependent Ca^{2+} channels has also been described in the α_1-adrenoceptor induced contraction of prostatic myocytes [5].

In conclusion the following mechanism for PE induced contraction in renal artery myocytes is proposed: binding of PE to α_{1A}-adrenoceptors leads to an activation of the PLC that generates the second messenger IP_3. Intracellular IP_3 causes a release of Ca^{2+} from IP_3-sensitive stores [2, 3, 19]. The rising $[Ca^{2+}]_i$ results in a further increase of $[Ca^{2+}]_i$ due to Ca^{2+} liberation from

the Ca^{2+}-sensitive Ca^{2+} pools [19, 21, 35] and to an augmented Ca^{2+} influx through L-type Ca^{2+} channels [5]. Further studies in isolated myocytes are required to increase the understanding of cellular mechanisms regulating cytoplasmic Ca^{2+} homeostasis in order to develop new pharmacological strategies for renal protection.

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