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Impaired function of alpha-2 adrenoceptors in smooth muscle of mesenteric arteries from spontaneously hypertensive rats

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1 The α_2-adrenoceptor function in mesenteric arteries of spontaneously hypertensive rats (SHR) was investigated by comparing membrane potential changes in response to adrenergic agonists in preparations from female SHR, Wistar-Kyoto (WKY) and normotensive Wistar rats (NWR).

2 Resting membrane potential was found to be less negative in mesenteric arteries from SHR than in those from NWR and WKY. Apamin induced a decrease in the membrane potential of mesenteric artery rings without endothelium from NWR and WKY, but had no effects in those from SHR. Both UK 14,304 and adrenaline, in the presence of prazosin, induced a hyperpolarization that was significantly lower in de-endothelialized mesenteric rings from SHR than in those from NWR and WKY. In mesenteric rings with endothelium, however, similar hyperpolarization was observed in the three strains.

3 In NWR mesenteric rings with endothelium the hyperpolarization induced by activation of α_2-adrenoceptors was abolished by apamin, whereas in intact SHR mesenteric rings this hyperpolarization was slightly reduced by apamin and more efficiently reduced by N^{ω}-nitro-L-arginine.

4 It is concluded that the activity of potassium channels coupled to α_2-adrenoceptors is altered in the smooth muscle cells of SHR mesenteric arteries, contributing to their less negative membrane potential. On the other hand, the endothelial α_2-receptors are functioning in mesenteric vessels from SHR and their stimulation induces a hyperpolarization mainly through the release of nitric oxide.

Keywords: Alpha-2 adrenoceptors; mesenteric arteries; endothelium; spontaneously hypertensive rats; potassium channels; membrane potential

Introduction

There are many reports in the literature showing that the vascular reactivity to different stimuli is altered in spontaneously hypertensive rats (SHR) (Bohr & Webb, 1988; Kishi & Inoue, 1990). Studies in animal models of genetic hypertension, as well as investigations in hypertensive patients, have provided evidence of a hyperactivity of the central and peripheral sympathetic system, which is mediated through specific alpha- and beta-adrenoceptors (Michel *et al*., 1990). In addition, endothelium-mediated relaxations may be impaired in some vessels of adult SHR due to an increased release of endothelium-derived cyclo-oxygenase-dependent contractile factors (Fu-Xiang *et al*., 1992) and also due to an altered production of endothelium-derived hyperpolarizing factor, EDHF and NO (Mantelli *et al*., 1995).

Noradrenaline and adrenaline are known to induce arterial vasoconstriction through interaction with a mixed population of postjunctional vascular α_1- and α_2-adrenoceptors. Although the α_2-adrenoceptor and its different subtypes have been identified in several tissues by radioligand binding and by selective antagonists (Bylund *et al*., 1994), the physiological role of these adrenoceptors is not fully understood (Ruffolo *et al*., 1993).

Alpha-2 adrenergic agonists are reported to induce either an increase or a decrease in vascular tone, depending on the kind of vessel and also on the location of these receptors. In several vessels, such as the rat aorta, mesenteric and tail arteries, a contractile effect is observed upon stimulation of α_2-receptors in the muscular layer (Carrier & White, 1985; Tsai *et al*., 1993; Kanagy, 1997), whereas a relaxant response occurs in rings from rat mesenteric arteries when the endothelium is present (Bockman *et al*., 1996). However, most of these reports refer to agonists such as clonidine which, in consequence of their relative selectivity, can act synergistically with other vasoconstrictors to facilitate contraction (Tsai *et al*., 1993; Xiao & Rand, 1989) probably through α_1-adrenoceptor activation (Kong *et al*., 1991; Silva *et al*., 1996a). These observations might also explain the controversial results concerning the contribution of postjunctional α_2-receptors in hypertension (Medgett *et al*., 1984). Since the presence of α_2-receptors in smooth muscle of mesenteric arteries from normotensive rats was directly demonstrated by electrophysiological experiments (Silva *et al*., 1996a), in the present work we used membrane potential measurements to evaluate the functional contribution of these receptors in mesenteric arteries from SHR. Also, since in some vessels the stimulation of α_2-adrenoceptors was shown to promote the release of endothelium relaxing factors (Carrier & White, 1985; Bockman *et al*., 1996), the contribution of endothelium-derived relaxing (EDRF NO) and hyperpolarizing (EDHF) factors to the membrane potential were also evaluated.

Methods

Animals

Experiments were carried out using female Okamoto & Aoki (1963) spontaneously hypertensive rats (SHR) and their Wistar-Kyoto normotensive controls (WKY) derived from an original colony supplied by the National Institutes of Health, Bethesda, MD, U.S.A. Normotensive Wistar rats (NWR) from the Wistar Institute, Philadelphia, PA, U.S.A., inbred at Escola Paulista de Medicina, SP, Brazil, were also used. The rats aged 20–30 weeks and weighed 200–220 g.

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Membrane potentials

Microelectrodes were constructed as previously described (Harvey & Kernan, 1984) by pulling capillaries in a horizontal puller (Narishige model PN3). The pipettes were filled with 2 M KCl and had tip resistances of 20–40 MΩ. The electrodes were mounted in Ag/AgCl half-cells on a micromanipulator (Leitz) and connected to an electrometer (WP Instruments, model FD 223). The signals were recorded in a potentiometric chart recorder (ECB, model RB102).

Rings of 1 cm length were cut from the superior mesenteric artery and some of them were everted for endothelium removal by gentle rubbing with a plastic tube wrapped in cotton. The rings were placed in a 2 ml perfusion chamber and superfused at a rate of 3 ml min^{-1} with Krebs solution of the following composition (in mM): NaCl 137; $NaHCO_3$ 5.9; $KHCO_3$ 5.9; $CaCl_2$ 2.3; $MgCl_2$ 1.2; glucose 11.8. The solution was bubbled with 5% CO_2–95% O_2 gas mixture and maintained at 37°C, pH 7.4. The impalements were made directly in the smooth muscle cells from the intimal side in everted rings, and also from the adventitial side in rings with intact endothelium. We have previously observed that the membrane potentials measured in normal and everted mesenteric rings from normotensive rats present similar values (Silva *et al*., 1996a).

Membrane potentials were measured as previously described (Frediani-Neto *et al*., 1991; Silva *et al*., 1994). The successful implantation of the electrode was evidenced by a sharp drop in voltage upon entry into a cell, a stable potential (±3mV) for at least 1 min after impalement, a sharp return to zero upon exit, and minimal change (<10%) in microelectrode resistance after impalement. All measurements reported in this paper were made with unloaded preparations since no significant differences were found between membrane potentials measured in unloaded mesenteric arteries and those submitted to an 1 g load for 1 h, as described in the literature for both strains (Fujii *et al*., 1992).

Since we used only female rats, measurements of membrane potential were made in mesenteric rings from NWR and SHR during different phases of the oestrus cycle. Although during oestrus a significant increase in MP was observed in rings with and without endothelium from NWR and SHR, this increase was similar in preparations from both strains. Thus, the values of membrane potential reported in this paper have been measured without regard to the phase of the oestrus cycle.

Measurements of membrane potential of mesenteric rings were obtained in Krebs solution before and after stimulation of the vessels with noradrenaline (6.4 μM), adrenaline (1 μM) or 5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine, UK 14304 (8 nM), both in the absence and in the presence of prazosin (20 nM for 10 min), apamin (100 nM for 10 min) and N^{ω}-nitro-L-arginine (30 μM for 20 min). The time of contact of the agonists with the preparations before the impalements was about 5 min. No blockers of cathecholamine uptake were used since it has been shown that the neuronal uptake of norepinephrine is indistinguishable between mesenteric arteries from SHR and normotensive rats (Hano & Rho, 1989; Head *et al*., 1984).

Drugs

The inorganic salts were products of the highest analytical grade from Merck Darmstadt. Noradrenaline hydrochloride (NA), adrenaline bitartrate (Ad), prazosin (Pz), apamin (Apa) and N^{ω}-nitro-L-arginine (L-NNA) were obtained from Sigma Chemical Co., St. Louis, MO, U.S.A. 5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine (UK 14,304) was obtained from Research Biochemicals International, Natick, MA, U.S.A.

Statistical analysis

All data are expressed as means ± s.e.means. The Student *t*-test was employed to compare results in mesenteric arteries from NWR and SHR. One-way analysis of variance followed by the Newman-Keuls test was used for the comparisons among different conditions. A probability of $P<0.05$ was considered significant. Where more than one impalement was made on the same mesenteric ring from the same rat these were averaged and considered as $n=1$.

Results

Membrane potential measurements

To evaluate the relative contributions of α_1- and α_2-adrenoceptors to the responses of the mesenteric artery to adrenergic agents, the effects of agonists and antagonists on the vascular smooth muscle membrane potential were measured in arterial rings with and without endothelium.

Rings without endothelium

The resting membrane potential (RMP) was measured through impalements from the intimal side in everted rings of superior mesenteric arteries, after endothelium removal. Figure 1 shows that the rings from SHR were depolarized (RMP = −33.4 ± 0.8 mV) when compared with those from WKY (RMP = −41.9 ± 3.4 mV) and from NWR (RMP = −44.7 ± 1.8 mV).

To determine whether dysfunctional calcium-dependent potassium channels could be responsible for the depolarized state of the SHR mesenteric arteries, the effect of apamin was studied. Whereas this blocker of calcium-dependent potassium channels induced a significant depolarization in rings from NWR (ΔMP = 8.0 mV) and WKY (ΔMP = 7.6 mV) mesenteric arteries, it did not significantly affect the membrane potential of SHR preparations (ΔMP = 1.0 mV) (Figure 1).

The role of α_1- and α_2-adrenoceptors was investigated by determining the effect of adrenergic agents upon the membrane

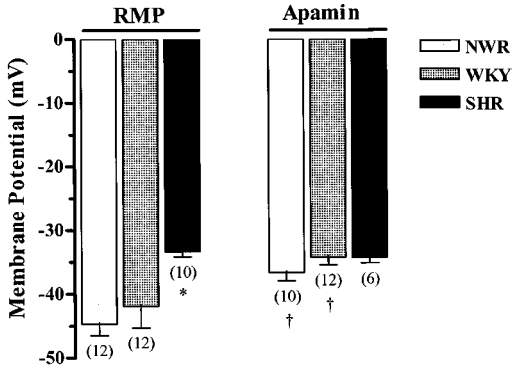

Figure 1 Membrane potential measured in everted rings (without endothelium) of mesenteric arteries from NWR, WKY and SHR in the absence (RMP) and in the presence of 100 nM apamin. For each mesenteric ring obtained from individual rats, the number of which is shown in parentheses below the bars, 3–7 cells were impaled and the average of the respective measurements was used to obtain the mean ± s.e.mean. *Significantly different from NWR and WKY. †Significantly different from the respective RMP.

potential (MP) in de-endothelialized rings from NWR (Figure 2). Noradrenaline (6.4 μM) induced a depolarizing effect (from -44.7 ± 1.8 to -30.5 ± 1.1 mV) which was significantly reduced in the presence of the α_1-antagonist prazosin (MP = -39.3 ± 1.1 mV). Prazosin alone did not cause significant change in the resting membrane potential (MP = -44.2 ± 1.7 mV, $n=6$). Adrenaline (1 μM) depolarized the membrane (from -44.7 ± 1.8 to -28.9 ± 1.2 mV) to a similar extent as noradrenaline, but in the presence of prazosin it induced a significant hyperpolarization (MP = -53.3 ± 0.9 mV). This hyperpolarizing response was mimicked by the α_2-adrenergic agonist UK 14,304 (8 nM) (from -44.7 ± 1.8 to -71.3 ± 2.1 mV), whose effect was abolished by 10 min preincubation with 100 nM apamin (MP = -49.0 ± 2.8 mV) (Figure 2) and potentiated by 20 nM prazosin (MP = -83.8 ± 2.0 mV) (Figure 3). The addition of L-NNA did not affect the resting membrane potential (from -44.7 ± 1.8 mV to -49.1 ± 1.4 mV) or the hyperpolarization induced by UK 14,304 (Figure 2). The concentrations of apamin and L-NNA that were used are those that have been described as effective to block endothelium-dependent responses of vascular tissues (Shimokawa *et al*., 1996; Petersson *et al*., 1997).

In SHR de-endothelialized rings (Figure 2), neither noradrenaline nor adrenaline induced depolarization. Moreover, no hyperpolarizing effect was induced by adrenaline in the presence of prazosin, as observed in NWR rings (Figure 2). Furthermore, UK 14,304 (8 nM) induced only a small hyperpolarization in the presence of prazosin (from -33.4 ± 0.8 to -43.8 ± 0.9 mV, Figure 3). The addition of L-NNA did not alter the resting membrane potential (from -33.4 ± 0.8 mV, $n=10$ to -35.1 ± 1.0 mV, $n=3$).

Rings with endothelium

Since stimulation of endothelial α_2-adrenoceptors has been reported to cause release of endothelium relaxing factors (Miller & Vanhoutte, 1985; Bockman *et al*., 1996), mesenteric arteries in which the endothelium was preserved were also examined in this study. The resting membrane potentials, measured by inserting the electrodes from the adventitial side of the arterial rings (Figure 3), were also significantly lower in SHR (-36.2 ± 1.2 mV) than in WKY (-46.6 ± 1.2 mV) and in NWR (-50.4 ± 1.7 mV).

Apamin, as observed in de-endothelialized rings, did not affect the resting membrane potential in SHR rings with endothelium (Figure 5). Similar results were observed in some experiments in which apamin was added on top of L-NNA (not shown).

This result could be attributed to the depolarized state of the SHR rings. Therefore, in some experiments, rings from SHR were hyperpolarized by using 10^{-6} M acetylcholine. In these conditions the membrane potential of SHR mesenteric arteries was -52.6 ± 1.0 mV, $n=4$ and the addition of apamin had no effect (MP = -50.8 ± 1.0 mV, $n=4$).

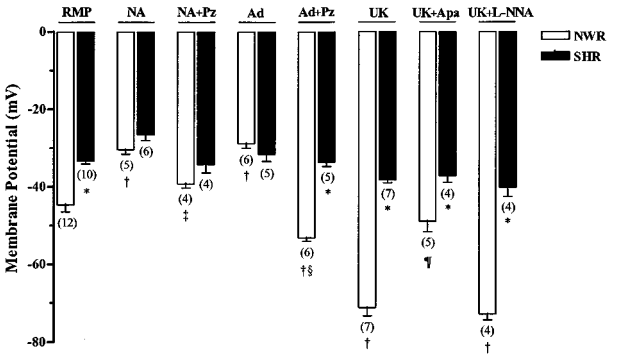

Figure 2 Membrane potential measured in everted rings (without endothelium) of mesenteric arteries from NWR and SHR in the absence (RMP) and in the presence of 6.4 μM noradrenaline (NA), NA plus 20 nM prazosin (Pz), 1.0 μM adrenaline (Ad), Ad plus Pz, 8 nM UK 14,304 (UK), UK plus 100 nM apamin (Apa) and UK plus 30 μM N^{ω}-nitro-L-arginine (L-NNA). For each mesenteric ring obtained from individual rats, the number of which is shown in parentheses below the bars, 2–7 cells were impaled and the average of the respective measurements was used to obtain the mean$\pm$s.e.mean. *Significantly different from NWR. †Significantly different from the respective RMP. ‡Significantly different from the membrane potential measured in the presence of NA. §Significantly different from the membrane potential measured in the presence of Ad. ¶Significantly different from the membrane potential measured in the presence of UK.

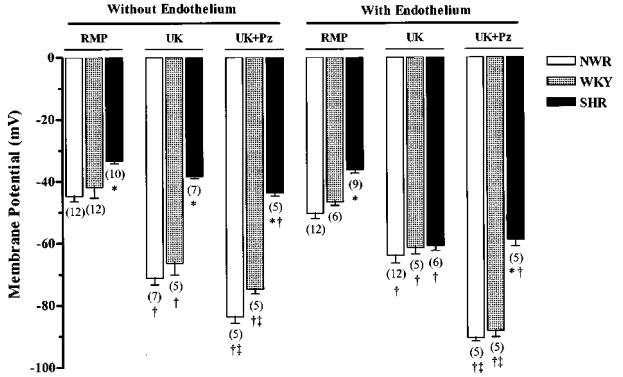

Figure 3 Membrane potential measured in everted rings (without endothelium) and intact rings (with endothelium) of mesenteric arteries from NWR, WKY and SHR in the absence (RMP) and in the presence of 8 nM UK 14,304 (UK) and UK plus 20 nM prazosin (Pz). For each mesenteric ring obtained from individual rats, the number of which is shown in parentheses below the bars, 3–7 cells were impaled and the average of the respective measurements was used to obtain the mean$\pm$s.e.mean. *Significantly different from NWR and WKY. †Significantly different from the respective RMP. ‡Significantly different from the membrane potential measured in the presence of UK.

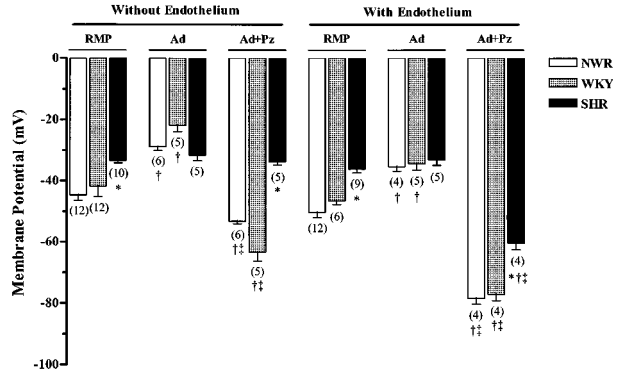

Figure 4 Membrane potential measured in everted rings (without endothelium) and intact rings (with endothelium) of mesenteric arteries from NWR, WKY and SHR in the absence (RMP) and in the presence of 1.0 μM adrenaline (Ad) and Ad plus 20 nM prazosin (Pz). For each mesenteric ring obtained from individual rats, the number of which is shown in parentheses below the bars, 2–7 cells were impaled and the average of the respective measurements was used to obtain the mean$\pm$s.e.mean. *Significantly different from NWR and WKY. †Significantly different from the respective RMP. ‡Significantly different from the membrane potential measured in the presence of Ad.

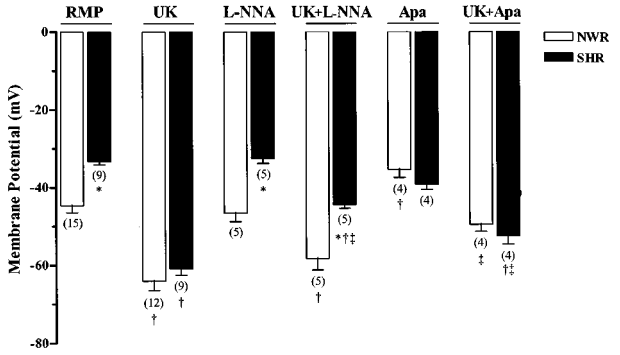

Figure 5 Membrane potential measured in intact rings (with endothelium) of mesenteric arteries from NWR and SHR in the absence (RMP) and in the presence of 8 nM UK 14,304 (UK), 30 μM N^{ω}-nitro-L-arginine (L-NNA), UK plus L-NNA, 100 nM apamin (Apa) and UK plus Apa. For each mesenteric ring obtained from individual rats, the number of which is shown in parentheses below the bars, 2–7 cells were impaled and the average of the respective measurements was used to obtain the mean ± s.e.mean. *Significantly different from NWR. †Significantly different from the respective RMP. ‡Significantly different from the membrane potential measured in the presence of UK.

The membrane potential of mesenteric rings from SHR after the addition of UK 14,308 was similar (MP = -60.9 ± 1.6 mV) to that observed in mesenteric rings from WKY (MP = -61.5 ± 2.1 mV) and NWR (MP = -64.1 ± 2.4 mV, Figure 3). The hyperpolarization induced by UK 14,304 in SHR, but not in WKY and NWR, was higher in mesenteric arteries with endothelium than in those without endothelium (Figure 3). The presence of prazosin (20 nM) did not alter the hyperpolarizing effect induced by UK 14,304 in SHR rings, but potentiated that observed in rings from WKY and NWR. The hyperpolarization induced by UK 14,304 in the presence of prazosin in the three strains was higher in rings with preserved endothelium than in de-endothelialized preparations (Figure 3). Adrenaline (1 μM) in the presence of 20 nM prazosin induced hyperpolarization in SHR rings with endothelium, which was not observed in de-endothelialized rings. In addition, a greater hyperpolarizing effect was evoked by adrenaline plus prazosin in WKY and NWR rings with endothelium (Figure 4).

In order to assess the possible contribution of EDRF and EDHF to the hyperpolarizing effect induced by UK 14,304, rings with endothelium were pretreated for 20 min with the NO-synthesis inhibitor, N^{ω}-nitro-L-arginine (30 μM), or with the K^+ channel blocker apamin (100 nM for 10 min). Whereas preincubation with N^{ω}-nitro-L-arginine had no effect on the hyperpolarization induced by UK 14,304 in NWR (from -64.1 ± 2.4 to -58.3 ± 2.9 mV) (Figure 5) or WKY (not shown), it efficiently reduced the responses to this agonist in rings from SHR (from -60.9 ± 1.6 to -44.5 ± 0.9 mV) (Figure 5). On the other hand, apamin was more effective in reducing the hyperpolarization induced by UK 14,304 in NWR (from -64.1 ± 2.4 to -49.6 ± 1.8 mV) than in SHR arteries (from -60.9 ± 1.6 to -52.6 ± 2.1 mV) (Figure 5).

Discussion

Vascular tone is regulated by several factors, including circulating cathecholamines. A vasoconstrictor effect of adrenergic agonists is observed in response to stimulation of α_1-receptors (Vargas & Gorman, 1995), whereas the stimulation of α_2-adrenoceptors can induce either an increase or a decrease in vascular tone, depending on the kind of vessel and on the animal strain as well as on the physiological condition (Medgett *et al*., 1984; Bockman *et al*., 1996).

The role of postsynaptic α_2-adrenoceptors in regulating arterial pressure is still undetermined and there is evidence either supporting or refuting their contribution to the pathogenesis of hypertension. Thus, whereas Van Zwieten *et al*. (1987) did not observe differences in α_2-adrenoceptors-mediated forearm blood flow in normotensive and hypertensive patients, Medgett *et al*. (1984) reported that, in the smooth muscle, α_2-adrenoceptors mediate vasoconstrictor responses to exogenous norepinephrine and sympathetic stimulation to a greater extent in SHR than in WKY rat tail arteries.

In the present work we observed that the hyperpolarization induced by activation of the smooth muscle α_2-adrenoceptors with adrenaline in the presence of prazosin (α_1-antagonist) was much smaller in SHR than in WKY or NWR de-endothelialized mesenteric arteries.

Moreover, in SHR rings the reduced hyperpolarizing response induced by UK 14,304 was not affected by the addition of apamin. These results might indicate a decreased density and/or sensitivity of α_2-adrenoceptors as previously demonstrated in the brain of SHR (Olmos *et al*., 1991), or an impairment of the calcium-dependent potassium channels coupled to these receptors (Silva *et al*., 1996a), as already demonstrated in other SHR smooth muscles such as duodenum (Feres *et al*., 1992) and uterus (Silva *et al*., 1996b).

In addition, in agreement with Fujii *et al*. (1992), we observed that the membrane potential was less negative in mesenteric arteries from female SHR than in those from WKY and NWR. A less negative membrane potential has also been observed in other vascular smooth muscle from SHR such as the caudal artery (Hermsmeyer *et al*., 1982). This may account for the enhancement of vascular responsiveness observed by several authors (Asano *et al*., 1988). Also, the membrane potential of mesenteric arteries from SHR was not affected by apamin as observed in normotensive animals suggesting, again, that the activity of apamin-sensitive K^+ channels is reduced in SHR mesenteric arteries. The activity of the apamin-sensitive potassium channels has been shown to be independent of the membrane potential (Edwards & Weston, 1990; Blatz & Magleby, 1986).

We have also measured the resting membrane potential of mesenteric rings from NWR, WKY and SHR in which the endothelium was present. The membrane potential values measured in these rings did not differ from those obtained in the de-endothelialized mesenteric arteries from the three strains, in agreement with Fujii *et al*. (1992). These findings suggest that the endothelium does not affect the resting membrane potential and that the degree of membrane depolarization observed in SHR is related to the impairment of K^+ channels located in the arterial smooth muscle. This hypothesis is reinforced by the observation that apamin had no effect even in SHR rings in which the resting membrane potential was normalized by addition of a hyperpolarizing agonist (acetylcholine). In normotensive rats these K^+ channels may serve as a negative feedback pathway to control the degree of membrane depolarization and vasoconstriction.

On the other hand, in SHR intact rings the hyperpolarizing response induced by UK 14,304 was significantly higher than that observed in rings without endothelium. Also, in the presence of prazosin, adrenaline induced a hyperpolarization in mesenteric rings with endothelium but not in de-endothelialized rings. This could indicate that the α_2-receptors in the SHR endothelium release relaxing factors that

compensate for the impairment of the α_2-adrenoceptors present in the smooth muscle.

Since activation of endothelial α_2-adrenoceptors can induce the release of endothelium relaxing factors (Carrier & White, 1985; Liao & Homey, 1993; Bockman *et al*., 1996), the possible contribution of nitric oxide or hyperpolarizing factor (EDHF) to the hyperpolarizing response to UK 14,304 was investigated by using the NO-synthesis inhibitor N^{ω}-nitro-L-arginine and the potassium channel blocker apamin. Whereas preincubation with N^{ω}-nitro-L-arginine had no effect on the hyperpolarization induced by UK 14,304 in mesenteric rings with endothelium from NWR or WKY, a significant reduction of the SHR response in the same condition was observed. On the other hand, apamin completely inhibited the hyperpolarizing response to UK 14,304 in de-endothelialized NWR rings, but only attenuated the hyperpolarization observed in SHR rings with endothelium. Similar results were found by combined administration of adrenaline and prazosin in intact mesenteric arteries, suggesting that the hyperpolarizing response induced by α_2-adrenoceptors in NWR is mainly mediated by EDHF, whereas in SHR this effect is largely mediated by NO. This observation is in agreement with Adeagbo *et al*. (1994), who demonstrated that NO synthase activity is not impaired in the mesenteric arterial bed of SHR.

Our results are in accordance with those of Mantelli *et al*. (1995) who showed that, in the SHR mesenteric vascular bed, the ability of acetylcholine to relax vessels through EDHF is impaired and that there is a parallel increase in NO release. Furthermore, Kahonen *et al*. (1995) also demonstrated that the nitric oxide synthase inhibitor N^{G}-nitro-L-arginine methyl ester (L-NNAME) inhibited the relaxation induced by acetylcholine in mesenteric artery rings from SHR, whereas this effect was not observed in rings from WKY.

Previous studies also reported interaction between NO and EDHF systems. Thus, McCulloch *et al*. (1997) demonstrated that EDHF activity may become upregulated upon inhibition of NO production and this may compensate for the loss of NO. On the basis of these results, it is likely that the reduced hyperpolarization induced by UK 14,304 in the SHR de-endothelialized vascular smooth muscle, due to the impairment of potassium channels, can also upregulate the production of NO, which could account for the increased hyperpolarization *via* the α_2-adrenergic pathway in SHR intact rings. This compensation of the impaired hyperpolarizing response induced by stimulation of α_2-adrenoceptors in SHR by the endothelial production of NO could not explain the increased vascular resistance observed in this strain. However, the isolated mesenteric arteries used in the present work cannot be considered resistance vessels and there are several reports showing that in the rat mesenteric bed the role of EDHF increases as the vessel size decreases (Hwa *et al*., 1994; Shimokawa *et al*., 1996). Thus, if the impaired function of α_2-adrenoceptors demonstrated in this work is also found in these small vessels, it could account for the elevated vascular resistance observed in hypertension.

In conclusion, the results of the present work confirm the presence of α_2-receptors in the mesenteric vascular smooth muscle (Silva *et al*., 1996a), which appear to be important for the control of muscular tone in resistance vessels. The alterations of apamin sensitive potassium channels, which are also coupled to these α_2-adrenoceptors in SHR mesenteric vessels, could contribute to the decrease of the vascular resting membrane potential and to the greater vasoconstriction in response to alpha-adrenergic agonists, leading to the increased tone and peripheral vascular resistance observed in hypertension.

In addition, our results show that the hyperpolarization induced by α_2-adrenergic agonists in intact mesenteric arteries involves different mediators in NWR and in SHR. Whereas NO, but not EDHF, is involved in the case of SHR, the opposite occurs in NWR.

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