ELSEVIER

European Journal of Pharmacology 455 (2002) 135–141

www.elsevier.com/locate/ejphar

The role of angiotensin II in hypertension due to adenosine receptors blockade

Manuela Morato, Teresa Sousa, Serafim Guimarães, Daniel Moura, António Albino-Teixeira*

Institute of Pharmacology and Therapeutics, Faculty of Medicine of Porto and IBMC, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal

Received 25 July 2002; received in revised form 8 October 2002; accepted 11 October 2002

Abstract

The renin–angiotensin system may be involved in hypertension induced by adenosine receptors blockade with 1,3-dipropyl-8-sulfophenylxanthine (DPSPX). Contractions of the mesenteric vasculature to angiotensin II, noradrenaline and potassium chloride were studied in DPSPX-induced hypertension. Male Wistar rats received infusions of saline or DPSPX (90 μg kg^{-1} h^{-1}, i.p.) for 3 or 7 days. Blood pressure was determined by the tail-cuff method. On days 3 or 14, concentration–response curves were obtained on mesenteric arteries and veins. Plasma angiotensin II levels, measured by radioimmunoassay, were higher in DPSPX-hypertensive rats. The maximum contractile effect of angiotensin II was lower in vessels from DPSPX-hypertensive rats while that for noradrenaline was higher. Potassium chloride-induced contractions were larger in veins from DPSPX-hypertensive rats but similar in arteries, when compared with control rats. We conclude that raised angiotensin II levels and altered vascular reactivity are consistent with a renin–angiotensin-mediated hypertension.

Keywords: Adenosine receptors blockade; Hypertension; Angiotensin II; Vascular reactivity

1. Introduction

The prolonged infusion of 1,3-dipropyl-8-sulfophenylxanthine (DPSPX), a water-soluble nonselective antagonist of adenosine receptors, causes an hypertensive state (Albino-Teixeira et al., 1991) that lasts for at least 7 weeks even after the administration of the drug is stopped. It is also known that DPSPX treatment induces marked structural changes in the cardiovascular system: hypertrophy of smooth muscle cells and proliferation of intima cells, occasionally forming buttons of smooth muscle cells in the intima protruding into the lumen of renal, mesenteric and caudal arteries (Albino-Teixeira et al., 1991). These structural changes are similar to those found when subpressor amounts of angiotensin II are infused in the rat (McCubbin et al., 1965). The mechanisms underlying the development and maintenance of this hypertensive state are not well characterized. Other alterations have already been documented in this experimental model of hypertension: prejunctional α_2-adrenoceptor-mediated responses of the tail artery are enhanced, while postjunctional adrenoceptor-mediated responses are not changed (Guimarães et al., 1994); adrenergic regulation of the cardiac function is altered resulting in reduced responses of atrial and ventricular myocardium to endogenous as well as exogenous noradrenaline (Rubino and Burnstock, 1995); perivascular neurotransmission in the rat tail artery is enhanced (Karoon et al., 1995); mesenteric sensorimotor vasodilation is increased (Ralevic et al., 1996); the facilitatory effect of isoprenaline on noradrenaline release from the tail artery is enhanced (Guimarães et al., 1995). Although it changed the time-course of the rise of the blood pressure, sympathetic denervation with 6-hydroxydopamine was not able to prevent the increase in blood pressure in this model (Sousa et al., 2002); hence, one cannot conclude that these changes in the modulation of the neurotransmitter release observed in DPSPX-hypertensive rats are the cause of the hypertensive state. The reported alterations in neurotransmission, although suggesting some participation of sympathetic neuroeffector control of blood pressure, cannot be the main factor responsible for the hypertensive state generated by DPSPX administration. Since angiotensin II is a potent vasoconstrictor and can produce structural changes in blood vessels that are similar to those referred to above,

* Corresponding author. Tel.: +35-122-509-5694; fax: +35-122-550-2402.

E-mail address: albinote@med.up.pt (A. Albino-Teixeira).

0014-2999/02/$ - see front matter © 2002 Elsevier Science B.V. All rights reserved.
PII: S0014-2999(02)02587-6

Table 1
Plasma angiotensin II levels (pg/ml) and systolic and diastolic blood pressure (mm Hg) in control and DPSPX-hypertensive rats

	Plasma angiotensin II (pg/ml)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Control	100.8 ± 4.5	115 ± 0.3	85 ± 0.8
Day 3	137.8 ± 13.0[a]	135 ± 0.5[a]	100 ± 0.9[a]
Day 14	240.6 ± 17.3[b]	144 ± 0.7[b]	107 ± 0.9[b]

Shown are the means ± S.E.M.
[a] Significantly different from control ($P<0.05$; $n=7–10$ rats).
[b] Significantly different from control and day 3 ($P<0.05$; $n=7–10$ rats).

DPSPX-induced changes might be related to an increased production of angiotensin II. This putative mechanism of action finds support in the known inhibitory role of adenosine as regulator of renin release from the juxtaglomerular cells (Jackson, 1991). In rats treated with DPSPX, plasma renin activity is increased which suggests that the renin–angiotensin system is involved in the development of the hypertensive state in these rats (Sousa et al., 2002). In good agreement with this suggestion is the fact that the angiotensin-converting enzyme inhibitor captopril (100 mg kg^{-1} day^{-1}) prevented not only the development of the hypertension but also the hypertrophic changes induced by DPSPX in arteries and heart (Guimarães and Albino-Teixeira, 1996). Experimental and human hypertension is associated with marked alterations in vascular reactivity. Having in mind these facts, it seemed of interest to measure plasma angiotensin II levels and to compare responses to angiotensin II, noradrenaline and potassium of the mesenteric vasculature (arteries and veins) of control and DPSPX-hypertensive rats, not forgetting the importance of the regulatory role of the venous compartment and the known differences in the reactivity to various agonists of the two components of the mesenteric bed.

2. Materials and methods

2.1. Experimental groups

Male Wistar rats (250–300 g) were used. The animals were kept under constant photoperiod conditions (12 h dark, 12 h light) at 23 °C temperature and 60% relative humidity. Standard laboratory rat chow and water were available ad libitum. Alzet osmotic minipumps (model 2ML1; Alza, Palo Alto, CA, USA), intraperitoneally implanted (day 0) under pentobarbitone sodium anaesthesia (60 mg kg^{-1}, i.p.), were used for continuous infusion of DPSPX (90 μg kg h^{-1}) or saline (vehicle). This dose was chosen because the induced hypertension and morphological changes persist for at least 7 weeks after the infusion of DPSPX is stopped (Albino-Teixeira et al., 1991). A lower dose (30 μg kg^{-1} h^{-1}) also causes an increase in blood pressure and marked morphological changes, but both effects are reverted when the infusion of DPSPX stops (Albino-Teixeira et al., 1991). Three groups of rats were included in this study. The control group received an infusion of saline i.p., the second group was treated with DPSPX (90 μg kg h^{-1}) for 3 days and killed on day 3, and the third group received an infusion of DPSPX (90 μg kg h^{-1}) for 7 days and was killed on day 14. Systolic and diastolic blood pressure were measured by the tail-cuff method (LE 5000, Letica, Barcelona, Spain) in conscious animals. The animals were trained during 7 days before the study started to get used to the procedure. Five determinations were made each time during the training period, on day 0 and at the end of the study, and the means used for further calculation.

2.2. Radioimmunoassay

Rats were anaesthetized with pentobarbitone sodium (60 mg kg^{-1}, i.p.). Blood was withdrawn from the left ventricle into ice-cold tubes containing 0.1M EDTA and centrifuged (3000 rpm, 15 min, 4 °C) immediately. Plasma samples were stored at −80 °C until assayed for the angiotensin II measurement. Angiotensin II was extracted from plasma samples by solid phase extraction using C18 cartridges (Sep-pack, Waters, Milford, MA, USA) and a speed vacuum concentrator. The cartridges were activated with 5 ml methanol and 5 ml of distilled water. Subsequently, samples were passed through the cartridges, washed twice with 5 ml of distilled water and the peptide eluted with 2 ml of 80% methanol (v/v). The eluate was then evaporated to dryness using a nitrogen stream and angiotensin II levels determined by radioimmunoassay (Peninsula Laboratories, Belmont, CA, USA).

Table 2
Maximum effect (mN/mg) and pD_2 values for angiotensin II (Ang II), noradrenaline (NA) and potassium chloride (KCl) on mesenteric arteries from control and DPSPX-hypertensive rats

	Maximum effect (mN/mg)			pD_2		
	Ang II	NA	KCl	Ang II	NA	KCl
Control	0.66 ± 0.07	2.40 ± 0.06	2.01 ± 0.02	8.42 ± 0.13	6.30 ± 0.05	1.29 ± 0.01
Day 3	0.24 ± 0.05[a]	2.17 ± 0.13	2.00 ± 0.03	8.51 ± 0.26	6.43 ± 0.12	1.31 ± 0.01
Day 14	0.47 ± 0.04[a,b]	2.86 ± 0.21[a,b]	2.06 ± 0.03	8.50 ± 0.11	5.90 ± 0.14[a,b]	1.15 ± 0.01[a,b]

Shown are the means ± S.E.M.
[a] $P<0.05$ vs. control for the same agonist ($n=6–12$).
[b] $P<0.05$ vs. day 3 for the same agonist ($n=6–12$).

2.3. Functional studies

Vehicle- or DPSPX-treated animals were killed by decapitation on day 3 or day 14. The superior mesenteric artery and vein were removed and immediately placed in cold modified Krebs–Henseleit solution (Guimarães and Osswald, 1969) of the following composition (mM): NaCl, 118.6; KCl, 4.70; $CaCl_2$, 2.52; KH_2PO_4, 1.18; $MgSO_4$, 1.23; $NaHCO_3$, 25.0; glucose, 10.0; EDTA, 0.027; ascorbic acid, 0.57. Each vessel was dissected free from fat and connective tissue, and rings of about 5 mm length were obtained and mounted in 15 ml baths containing aerated modified Krebs–Henseleit solution at 37 °C. Two stainless steel wires (diameter 0.05 mm) introduced into the lumen were used to stretch the vessel wall until a resting tension of about 4.9 mN was reached. One of the wires was fixed to the bottom of the bath while the other was connected to an isometric transducer. The mechanical responses were recorded on a polygraph (Letica Unigraph 2000-5.6). After a stabilization period of 2 h, the vessels were primed twice with noradrenaline (1 μM) to check for viability and stabilization. Then, concentration–response curves were obtained for increasing concentrations of angiotensin II (1–81 nM), noradrenaline (30 nM to 19 μM) and potassium chloride (25–200 mM). Angiotensin II concentration–response curves were obtained by single additions separated by 40 min washout periods, to avoid tachyphylaxis; the concentration–response curves to other agents were cumulative.

2.4. Data and statistical analysis

The concentration–response data were analysed by non-linear regression and best curve fitting obtained using GraphPad software. For each agonist, results were expressed by the maximum contractile effect (mN tension/mg tissue) and by the pD_2 value, which represents the negative logarithm of the molar concentration of the agonist that causes 50% of the respective maximal contraction.

All data are expressed as means ± S.E.M., where n equals the number of rats. Statistical analysis of the data was by analysis of variance (ANOVA) followed by Newman–Keuls test. P values of less than 0.05 were considered significant.

2.5. Drugs

All drugs were from Sigma (St. Louis, MO, USA), except for potassium chloride (Merck, Darmstadt, Germany).

3. Results

3.1. Plasma angiotensin II

DPSPX treatment caused an increase of both blood pressure (systolic and diastolic) and plasma levels of angiotensin II. Both increases reached maximum levels at day 14 (Table 1). There was a positive correlation between the increases in blood pressure and plasma levels of angiotensin II ($r^2 = 0.79$).

3.2. Responses to angiotensin II, noradrenaline, and potassium chloride during the development of the hypertensive state caused by DPSPX

3.2.1. Mesenteric artery

Under control conditions, angiotensin II, noradrenaline, and potassium chloride caused concentration-dependent contractions of the mesenteric artery rings, which were not parallel. In spite of that, comparing pD_2 values of the three

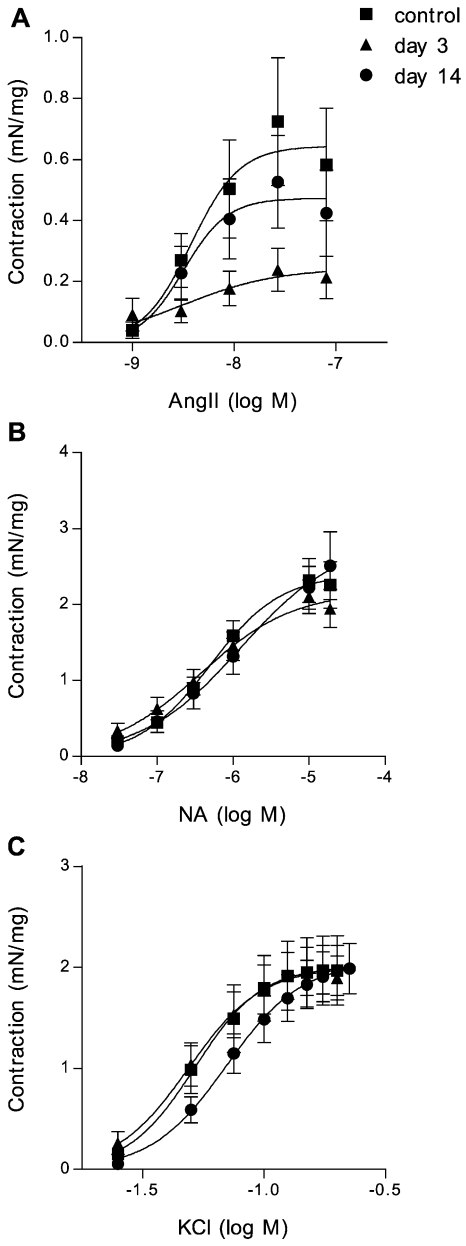

Fig. 1. Concentration–response curves to angiotensin II (A), noradrenaline (B) and potassium chloride (C) in mesenteric arteries from control and DPSPX-hypertensive rats (day 3 and day 14). Values are means ± S.E.M.; $n = 6–12$ rats in each group.

Table 3
Maximum effect (mN/mg) and pD_2 values for angiotensin II (Ang II), noradrenaline (NA) and potassium chloride (KCl) on mesenteric veins from control and DPSPX-hypertensive rats

	Maximum effect (mN/mg)			pD_2		
	Ang II	NA	KCl	Ang II	NA	KCl
Control	5.20 ± 0.13	1.01 ± 0.05	3.72 ± 0.02	8.65 ± 0.04	6.84 ± 0.07	1.52 ± 0.01
Day 3	2.85 ± 0.02[a]	2.03 ± 0.09[a]	8.11 ± 0.33[a]	8.40 ± 0.01[a]	6.96 ± 0.07	1.57 ± 0.03
Day 14	2.78 ± 0.07[a]	1.71 ± 0.04[a,b]	4.54 ± 0.02[a,b]	8.52 ± 0.04[a,b]	6.47 ± 0.04[a,b]	1.61 ± 0.01[a]

Shown are the means ± S.E.M.
[a] $P<0.05$ vs. control for the same agonist ($n=6-12$).
[b] $P<0.05$ vs. day 3 for the same agonist ($n=6-12$).

agonists, the ranking order of potency was angiotensin II>noradrenaline>potassium chloride, while that for the intrinsic efficacy was noradrenaline>potassium chloride>angiotensin II (Table 2 or Fig. 1).

At day 3, the maximal response to angiotensin II was markedly reduced (to about 36%), whereas those to noradrenaline and potassium chloride were not changed. Regarding pD_2 values, there was no pronounced change for any of the three agonists (Table 2 or Fig. 1).

At day 14, i.e. 7 days after the administration of DPSPX had been stopped, the maximum response to angiotensin II was still significantly smaller than the control value, although larger than that observed at day 3, while that to noradrenaline was slightly increased and that to potassium chloride was not changed. The pD_2 values for angiotensin II were not changed, whereas those for noradrenaline and potassium chloride were slightly reduced (Table 2 or Fig. 1).

3.2.2. Mesenteric vein

As shown in Table 3, under control conditions, angiotensin II was not only the most potent agonist but also the one causing the largest maximum effect. In the mesenteric vein, the ranking order of potency for the three agonists was angiotensin II>noradrenaline>potassium chloride, while that for the intrinsic efficacy was angiotensin II>potassium chloride>noradrenaline (Table 3 or Fig. 2).

At day 3, there was a marked reduction of the maximal response to angiotensin II and marked increases in those to noradrenaline and potassium chloride. The potency (pD_2 values) of angiotensin II was slightly decreased whereas those for noradrenaline and potassium chloride were not changed (Table 3 or Fig. 2).

At day 14, while the marked reduction of the maximum response to angiotensin II remained, the increase of that to noradrenaline and potassium chloride was smaller than at day 3. The potencies of angiotensin II and noradrenaline were slightly decreased whereas that for potassium chloride was slightly increased (Table 3 or Fig. 2).

4. Discussion

The present results show that in the rat under control conditions, angiotensin II, as a contracting agent, is almost as potent on the mesenteric artery as on the mesenteric vein. However, the magnitude of the maximum contraction caused by angiotensin II is much larger at the venous than at the arterial side of the mesenteric vasculature, the opposite occurring with noradrenaline, although in this case the difference is not so marked. This differential effectiveness of angiotensin II and noradrenaline in the mesenteric artery and vein has already been reported (Warner, 1990; Konishi et al., 1997).

DPSPX treatment leads to a hypertensive state (Albino-Teixeira et al., 1991), which is accompanied by an increase in plasma renin activity (Sousa et al., 2002). Since the renin–angiotensin system is an important regulator of blood pressure, the increase in plasma renin activity occurring in DPSPX-hypertensive animals may be involved in the development of the hypertensive state. The marked cardiovascular morphological changes typical of DPSPX-hypertensive rats (Albino-Teixeira et al., 1991) which are similar to those caused by subpressor doses of angiotensin II (McCubbin et al., 1965) strongly support this hypothesis. Furthermore, not only the angiotensin-converting enzyme inhibitor captopril (Sousa et al., 2002) but also the angiotensin II AT_1 selective antagonist losartan prevent the arterial blood pressure increase and the morphological alterations as well, whereas the selective β_1-adrenoceptor antagonist atenolol prevented the blood pressure increase only (Morato et al., 2002). In this study, there was a marked increase in plasma levels of angiotensin II in DPSPX-hypertensive rats, which further stresses the involvement of the renin–angiotensin system in the development and/or maintenance of this experimental model of hypertension.

When the sensitivity of the mesenteric vessels to the different agonists is compared during the development of the hypertensive state, some important differences can be detected. While the maximum contraction to noradrenaline increases (slightly in the artery and markedly in the vein) and that to potassium increases only in the vein, the maximum contraction to angiotensin II clearly decreases both in the artery and in the vein. This increase in the responses to noradrenaline, as the decrease in the response to angiotensin II, may be ascribed to the increased levels of circulating angiotensin II in DPSPX-hypertensive animals. In fact, it has been reported that angiotensin II in subthreshold concentrations (concentrations unable to cause con-

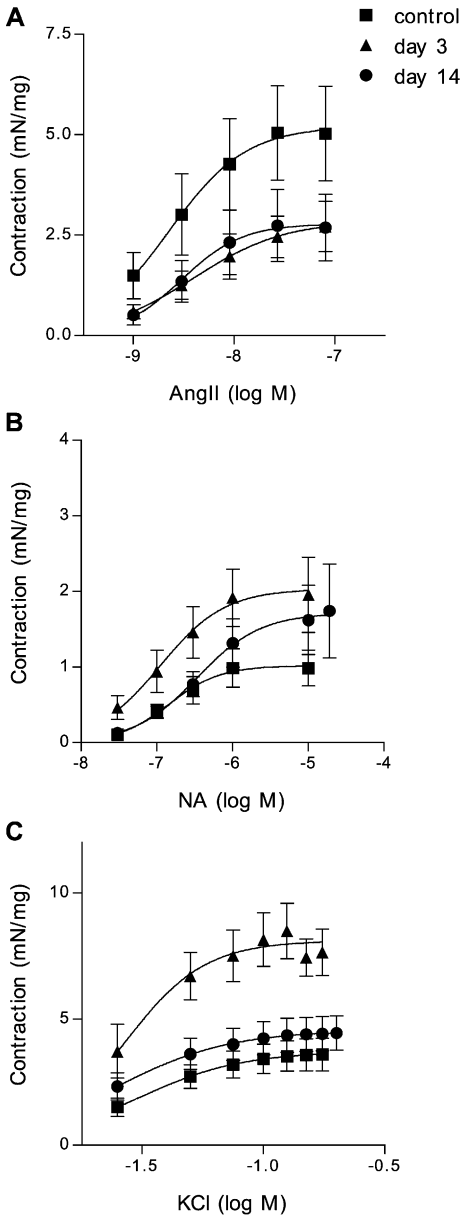

Fig. 2. Concentration–response curves to angiotensin II (A), noradrenaline (B) and potassium chloride (C) in mesenteric veins from control and DPSPX-hypertensive rats (day 3 and day 14). Values are means ± S.E.M.; $n = 6–12$ rats in each group.

traction) enhances the responses to other vasoactive agents like noradrenaline both in vivo and in vitro. In vivo, angiotensin II enhances phenylephrine-induced tone in the rat mesenteric bed (Qiu et al., 1994; Dowell et al., 1996) and potentiates the vasoconstriction of the coronary vessels caused by sympathetic nerve stimulation in humans (Saino et al., 1997). In vitro, it was shown that not only the responses to exogenous noradrenaline (Vanhoutte et al., 1981; Henrion et al., 1992a,b), but also those to sympathetic nerve stimulation (Day and Moore, 1976; Duckles, 1981; Weber et al., 1989) were enhanced by angiotensin II. These enhancing effects of angiotensin II occur at concentrations relatively lower than those required to cause a direct constrictor effect, which in turn, are relatively high compared with the endogenous levels, even under pathological conditions characterized by high plasma renin levels. The levels of circulating angiotensin II reported in the present study for DPSPX-hypertensive rats, which are more than two times higher than those of control rats, are still in the subconstrictor range and may well be the enhancing factor of noradrenaline-induced contractions. Moreover, increased adrenergic vasoconstrictor responses can also occur if factors that modulate vasoconstriction, namely endothelial factors, are changed. Nitric oxide has been reported to oppose noradrenaline-induced vasoconstriction in hypertension (Hayakawa and Raji, 1997; Nishida et al., 1998). The renin–angiotensin system has also been implicated in endothelial dysfunction (Laragh et al., 1972; Hoshino et al., 1994). In DPSPX-hypertensive rats, the endothelium-dependent relaxant effects of carbachol but not the endothelium-independent relaxations to sodium nitroprusside are decreased (Paiva et al., 1997), suggesting that endothelial function is impaired. The possibility that this fact contributes to our results cannot be excluded since noradrenaline-induced contractions can be increased by impairment of endothelial relaxation. The reduction of the response to angiotensin II may also be due to the increased plasma level of the circulating angiotensin II in DPSPX-hypertensive animals. It is well established that continued stimulation of cells with agonists generally results in desensitization or down-regulation of receptors such that the effect that follows subsequent exposure to the same agonist is diminished. Responses to angiotensin II have been reported to be unaffected (Tschudi and Lüscher, 1995; Boonen et al., 1993; Moreno et al., 1996), enhanced (Collis and Alps, 1975; Endemann et al., 1999; Cawley et al., 1995) or reduced (Sitzmann et al., 1990). Decreased expression of angiotensin II AT_{1A} receptor mRNA has been reported in both kidneys of 2-Kidney,1-Clip-hypertensive rats, an experimental model of hypertension also characterized by high plasma levels of both renin and angiotensin II (Haefliger et al., 1995). The high level of angiotensin II in the plasma of DPSPX-hypertensive rats may well have desensitized or down-regulated angiotensin II AT_1 receptors causing the maximum effect of angiotensin II to be reduced. A direct antagonistic effect of DPSPX on angiotensin II receptors could also explain the decreased responses to angiotensin II observed in the vessels of DPSPX-hypertensive rats. However, in the in situ perfused mesenteric vascular bed, blockade of adenosine receptors with DPSPX did not alter the ability of angiotensin II to constrict vascular smooth muscle, regardless of whether the angiotensin II was administered directly into the mesenteric artery or into the jugular vein (Holycross and Jackson, 1989). In preliminary experiments (data not shown), we have also observed that incubation with DPSPX of the isolated mesenteric artery and vein of control rats did not alter the subsequent responses to angiotensin II. These facts suggest that DPSPX has no angiotensin II receptor blocking activity. Furthermore, in this study, the decrease of angioten-

sin II-induced contraction on the arterial side of the mesenteric circulation was more marked in the initial phase of hypertension, while on the venous side, both groups of DPSPX-hypertensive rats showed a similar degree of hyporresponsiveness to angiotensin II. Collis and Alps (1975) proposed that in the perfused mesenteric artery, a previous exposure to angiotensin II might possibly potentiate the direct response to a second stimulation, once the tachyphylaxis had passed off. A similar effect may account for our results. The mesenteric artery, but not the mesenteric vein, may have mechanisms to counteract the consequences of increased angiotensin II levels, namely desensitization or down-regulation of the receptors, which result in decreased responses. In the mesenteric artery, there was no difference between the maximum responses to potassium chloride obtained in control and DPSPX-hypertensive animals. It is not easy to explain the marked increase of the maximum response of the mesenteric vein to potassium chloride at day 3, as well as the relatively small increase of the maximum response to this agonist at day 14. Since potassium acts to produce membrane depolarization, these results suggest that in DPSPX-induced hypertension, the efficacy of the intracellular excitation–contraction mechanisms and/or the contractile machinery is not modified on the arterial side of the mesenteric circulation but it is somehow increased in the mesenteric vein. Preliminary experiments have shown that the marked increase in potassium chloride-induced responses was not due to a putative direct potentiating effect of the DPSPX per se. Furthermore, this increase in potassium chloride-induced contraction was not observed in the femoral vein, where the pattern of response was different (data not shown). Having in mind the morphological changes that characterize the vascular tissues of DPSPX-hypertensive animals, namely the hypertrophy of smooth muscle cells of the mesenteric and tail arteries (Albino-Teixeira et al., 1991), which are minimal at day 3 and exuberant at day 14, it is tempting to look at these morphological changes as playing some role in the development of these alterations in the sensitivity. However, if the morphological changes were the cause of this supersensitivity to potassium chloride, they should have been more marked on day 14 than on day 3 and they would affect noradrenaline and angiotensin II as well, and they did not.

Changes in vascular responsiveness to various stimuli are frequently associated with hypertension. While contradictory data are reported for one and the same vasoactive agent, this has been ascribed to be due to differences between hypertensive models, to the developmental phase of the hypertension considered for investigation, to the vascular territory under study and also to technical variations.

Changes other than those related to the renin–angiotensin system may also play a role in the development of this kind of hypertension. In fact, it has been shown that: (1) denervation with 6-hydroxydopamine changes the time-course and magnitude of the increase in blood pressure (Sousa et al., 2002); (2) the responses of atrial and ventricular myocardium to endogenous as well as exogenous noradrenaline are reduced (Rubino and Burnstock, 1995); (3) perivascular neurotransmission in the rat tail artery is enhanced (Karoon et al., 1995); (4) mesenteric sensorimotor vasodilation is increased (Ralevic et al., 1996). Also, the α_2-mediated auto-inhibition of noradrenaline release from sympathetic nerve terminals is decreased in DPSPX-hypertensive rats (Guimarães et al., 1994) while the facilitatory effect of isoprenaline on noradrenaline release is enhanced (Guimarães et al., 1995). Although it remains to be clarified whether these changes are responsible for the hypertension induced by DPSPX, it is likely that they also contribute to the development and/or maintenance of the hypertension induced by DPSPX.

We conclude that: (1) chronic blockade of adenosine receptors with DPSPX causes an hypertensive state which is accompanied by an increase of plasma levels of angiotensin II; (2) DPSPX-induced hypertension is associated with alterations of vascular reactivity; (3) these facts are consistent with a renin–angiotensin-mediated hypertension.

References

Albino-Teixeira, A., Matias, A., Polónia, J., Azevedo, I., 1991. Blockade of adenosine receptors causes hypertension and cardiovascular structural changes in the rat. J. Hypertens. 9 (Suppl. 6), S196–S197.

Boonen, H.C., Daemen, M.J., Eerdmans, P.H., Fazzi, G.E., van Kleef, E.M., Schiffers, P.M., De Mey, J.G., 1993. Mesenteric small artery changes after vasoconstrictor infusion in young rats. J. Cardiovasc. Pharmacol. 22 (3), 388–395.

Cawley, T., Geraghty, J., Osborne, H., Docherty, J.R., 1995. Effects of portal hypertension on responsiveness of rat mesenteric artery and aorta. Br. J. Pharmacol. 114, 791–796.

Collis, M.G., Alps, B.J., 1975. Vascular reactivity to noradrenaline, potassium chloride, and angiotensin II in the rat perfused mesenteric vasculature preparation, during the development of renal hypertension. Cardiovasc. Res. 9, 118–126.

Day, M.D., Moore, A.F., 1976. Interaction of angiotensin II with noradrenaline and other spasmogens on rabbit isolated aortic atrips. Arch. Int. Pharmacodyn. 219, 29–35.

Dowell, F.J., Henrion, D., Benessiano, J., Poitevin, P., Levy, B., 1996. Chronic infusion of low-dose angiotensin II potentiates the adrenergic response in vivo. J. Hypertens. 14, 177–182.

Duckles, S.P., 1981. Angiotensin II potentiates responses of the rabbit basilar artery to adrenergic nerve stimulation. Life Sci. 28, 40–47.

Endemann, D., Touyz, R.M., Li, J.-S., Deng, L.-Y., Schiffrin, E.L., 1999. Altered angiotensin II-induced small artery contraction during the development of hypertension in spontaneously hypertensive rats. Am. J. Hypertens. 12, 716–723.

Guimarães, S., Albino-Teixeira, A., 1996. Hypertension due to chronic blockade of P_1-purinoceptors. J. Auton. Pharm. 16, 367–370.

Guimarães, S., Osswald, W., 1969. Adrenergic receptors in the veins of the dog. Eur. J. Pharmacol. 5, 133–140.

Guimarães, S., Paiva, M.Q., Moura, D., Vaz-da-Silva, M.J., Albino-Teixeira, A., 1994. Long-term administration of 1,3-dipropyl-8-sulfophenylxanthine (DPSPX) alters α_2-adrenoceptor-mediated effects at the pre- but not at the postjunctional level. Naunyn-Schmiedeberg's Arch. Pharmacol. 350, 692–695.

Guimarães, S., Albino-Teixeira, A., Paiva, M.Q., 1995. Hypertension and enhanced beta-adrenoceptor-mediated facilitation of noradrenaline release produced by chronic blockade of adenosine receptors. Br. J. Pharmacol. 114 (8), 1595–1598.

Haefliger, J.-A., Bergonzelli, G., Waeber, G., Aubert, J.-F., Nussberger, J., Gavras, H., Nicod, P., Waeber, B., 1995. Renin and angiotensin II receptor gene expression in kidneys of renal hypertensive rats. Hypertension 26 (5), 733–737.

Hayakawa, H., Raji, L., 1997. The link among nitric oxide synthase activity, endothelial function, and aortic and ventricular hypertrophy in hypertension. Hypertension 29 (Part 2), 235–241.

Henrion, D., Laher, I., Laporte, R., Bevan, J.A., 1992a. Angiotensin II amplifies arterial contractile response to norepinephrine without increasing $^{45}Ca^{2+}$ influx: role of protein kinase C. J. Pharmacol. Exp. Ther. 261, 835–842.

Henrion, D., Laher, I., Laporte, R., Bevan, J.A., 1992b. Further evidence from an elastic artery that angiotensin II amplifies noradrenaline-induced contraction through activation of protein kinase C. Eur. J. Pharmacol. 225, 13–20.

Holycross, B.J., Jackson, E.K., 1989. Adenosine–angiotensin II interactions: Part I. Role of adenosine in regulating angiotensin II-induced potentiation of noradrenergic neurotransmission and angiotensin II-induced vasoconstriction. J. Pharmacol. Exp. Ther. 250 (2), 433–441.

Hoshino, J., Sakamaki, T., Nakamura, T., Kobayashi, M., Kato, M., Sakamoto, H., Kurashina, T., Yagi, A., Sato, K., Ono, Z., 1994. Exaggerated vascular response due to endothelial dysfunction and role of the renin–angiotensin system at early stage of renal hypertension in rats. Circ. Res. 74, 130–138.

Jackson, E.K., 1991. Adenosine: a physiological brake on renine release. Annu. Rev. Pharmacol. Toxicol. 31, 1–35.

Karoon, P., Rubino, A., Burnstock, G., 1995. Enhanced sympathetic neurotransmission in the tail artery of 1,3-dipropyl-8-sulfophenylxanthine (DPSPX)-treated rats. Br. J. Pharmacol. 116 (2), 1918–1922.

Konishi, C., Naito, Y., Saito, Y., Ohara, N., Ono, H., 1997. Age-related differences and roles of endothelial nitric oxide and prostanoids in angiotensin II responses of isolated, perfused mesenteric arteries and veins of rats. Eur. J. Pharmacol. 320, 175–181.

Laragh, J.H., Baer, L., Brunner, H.R., Buhler, F.R., Sealey, J.E., Vaughan Jr., E.D., 1972. Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease. Am. J. Med. 52, 633–652.

McCubbin, J.W., DeMoura, R.S., Page, I.H., Olmsted, F., 1965. Arterial hypertension elicited by subpressure amounts of angiotensin. Science 149, 1394–1395.

Morato, M., Sousa, T., Guimarães, S., Moura, D., Albino-Teixeira, A., 2002. Antihypertensive effects of losartan and atenolol on 1,3-dipropyl-8-sulfophenylxanthine (DPSPX)-induced hypertension. Br. J. Pharmacol. 135 (Suppl.), P125.

Moreno, L., Martínez-Cuesta, M.A., Piqué, J.M., Bosch, J., Esplugues, J.V., 1996. Anatomical differences in responsiveness to vasoconstrictors in the mesenteric veins from normal and portal hypertensive rats. Naunyn-Schmiedeberg's Arch. Pharmacol. 354, 474–480.

Nishida, Y., Ding, J., Zhou, M.-S., Chen, Q.-H., Murakami, H., Wu, X.-Z., Kosaka, H., 1998. Role of nitric oxide in vascular hyper-responsiveness to norepinephrine in hypertensive Dahl rats. J. Hypertens. 16, 1611–1618.

Paiva, M.Q., Santos, M.J., Albino-Teixeira, A., 1997. Endothelium-dependent vascular responses in 1,3-dipropyl-8-sulfophenylxanthine (DPSPX)-hypertensive rats. J. Pharm. Pharmacol. 49 (1), 74–77.

Qiu, H.Y., Henrion, D., Levy, B.I., 1994. Endogenous angiotensin II enhances phenylephrine-induced tone in hypertensive rats. Hypertension 24 (3), 317–321.

Ralevic, V., Rubino, A., Burnstock, G., 1996. Augmented sensory-motor vasodilatation of the rat mesenteric arterial bed after chronic infusion of the P_1-purinoceptor antagonist, DPSPX. Br. J. Pharmacol. 118, 1675–1680.

Rubino, A., Burnstock, G., 1995. Changes in sympathetic neurotransmission and adrenergic control of cardiac contractility during 1,3-dipropyl-8-sulfophenylxanthine-induced hypertension. J. Pharmacol. Exp. Ther. 275, 422–428.

Saino, A., Pomidossi, G., Perondi, R., Valentini, R., Rimini, A., Di Francesco, L., Mancia, G., 1997. Intracoronary angiotensin II potentiates coronary sympathetic vasoconstriction in humans. Circulation 96, 148–153.

Sitzmann, J.V., Li, S.S., Wu, Y.P., Groszmann, R., Bulkley, G.B., 1990. Decreased mesenteric vascular response to angiotensin II in portal hypertension. J. Surg. Res. 48 (4), 341–344.

Sousa, T., Morato, M., Albino-Teixeira, A., 2002. Angiotensin-converting enzyme inhibition prevents trophic and hypertensive effects of an antagonist of adenosine receptors. Eur. J. Pharmacol. 441 (1–2), 99–104.

Tschudi, M.R., Lüscher, T.F., 1995. Age and hypertension differently affect coronary contractions to endothelin-1, serotonin, and angiotensins. Circulation 91, 2415–2422.

Vanhoutte, P.M., Verbeuren, T.J., Webb, R.C., 1981. Local modulation of adrenergic neuroeffector interaction in the blood vessel wall. Physiol. Rev. 61, 151–159.

Warner, T., 1990. Simultaneous perfusion of rat isolated superior mesenteric arterial and venous beds: comparison of their vasoconstrictor and vasodilator responses to agonists. Br. J. Pharmacol. 99, 427–433.

Weber, M.A., Purdy, R.E., Stupecky, G.L., Prins, B.A., 1989. Augmentation of sympathomimetic arterial contraction by angiotensin II: a novel mechanism. J. Vasc. Med. Biol. 1, 7–15.