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Effects of high sodium intake diet on the vascular reactivity to phenylephrine on rat isolated caudal and renal vascular beds: Endothelial modulation

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Abstract

High salt intake is involved in the genesis of hypertension and vascular changes in salt-sensitive patients. Although many mechanisms have been proposed, the underlying mechanisms of these alterations in healthy rats are not completely elucidated. The aim of this study was to investigate if male Wistar rats fed a high salt diet, NaCl 1.8% in drinking water for 4 weeks, develop changes in the pressor reactivity of isolated tail and renal vascular beds. Salt treatment increased mean arterial pressure (SALT = 124 ± 2.2 vs. CT = 111 ± 3.9 mmHg; $p < 0.01$) and urinary sodium excretion in the absence of changes in sodium plasma levels. Pressor reactivity was generated in isolated tail and kidney vascular beds as dose–response curves to phenylephrine (PHE = 0.01 to 300 μg). SALT increased the reactivity (E_{max}: SALT = 378 ± 15.8 vs. CT = 282 ± 10 mmHg; $p < 0.01$) without changing the sensitivity (pD_2) to PHE in the tail vascular bed. However, these parameters did not change in the renal bed. In subsequent studies on the isolated caudal vascular bed, we found that endothelial damage, but not L-NAME (100 μM) or indomethacin (10 μM), abolished the increment in E_{max} to PHE induced by SALT. On the other hand, losartan (100 μM) reduced E_{max} in SALT to CT values. Additionally, local angiotensin-converting enzyme activity in segments from tail artery increased by 95%. In conclusion, 4 weeks of high salt diet increases blood pressure and induces specific territorial vascular changes in response to PHE. Results also suggest that the increment in E_{max} in the tail vascular bed from SALT rats was endothelium-dependent and was mediated by the activation of the local renin–angiotensin system.

Keywords: Salt-diet; Hypertension; Endothelium; Renin–angiotensin system; Vascular reactivity

Introduction

Hypertension is a highly prevalent cardiovascular disease and an independent risk factor (Joint, 2003). The results of many studies in humans and laboratory animals showed a clear relation between high salt intake and the development of hypertension (Dahl et al., 1962; Luscher et al., 1987; INTERSALT, 1988; Stamler et al., 1991; Kassab et al., 1998; Huang and Johns, 2000). A reduction or "normalization" of arterial pressure can be achieved by changes in life style and/or antihypertensive therapy. Among the changes in life style, dietary salt restriction is often recommended to protect against the increase in blood pressure (Houston, 1986; Chrysant, 2000; Joint, 2003).

Many mechanisms by which high salt intake can initiate the development and maintenance of hypertension have been reported. There are changes in vascular reactivity (Mulvany et al., 1978; Adegunloye and Sofola, 1997; Nishida et al., 1998; Lenda et al., 2000), in sympathetic reflexes (Miyajima and Bunag, 1985; Ferrari and Mark, 1987), on calcium mobilization, in Na^+, K^+-ATPase activity (Obiefuna et al., 1991a; Li et al., 1994), on endogenous sodium pump ligands levels (Fedorova et al., 2001), and in the balance between blood volume and cardiac output (Simchon et al., 1991).

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A high sodium intake might be related to an increment in vascular reactivity that leads to an increased peripheral vascular resistance. A variety of factors appear to contribute to an augmented vascular reactivity to α-adrenoceptor agonists reported in laboratory animals (Nishida et al., 1998; Sofola et al., 2002). There is an increased generation of reactive oxygen species (Lenda et al., 2000) and a down-regulation of nitric oxide synthase (NOS) subtypes (Ni and Vaziri, 2001). In spontaneously hypertensive rats (Kagota et al., 2001) and in Dahl salt-sensitive rats (Luscher et al., 1987; Nishida et al., 1998), a high salt intake produced an impaired endothelium-dependent relaxation.

In healthy normotensive rats the effects of sodium loading are not consistent with respect to changes in arterial pressure or in vascular reactivity. Matrougui et al. (2001) reported changes in pressure–flow relationships in mesenteric resistance arteries without changes in arterial pressure. Other investigators reported a moderate elevation of blood pressure (Miyajima and Bunag, 1985; Kassab et al., 1998; Yu et al., 1998; Contreras et al., 2000; Lenda et al., 2000). Additionally, different effects on the vascular function were reported, such as no change (Barton et al., 1998; Giardina et al., 2001) or reduction of vasodilation induced by acetylcholine (Obiefuna et al., 1991b; Lenda et al., 2000) and an increased compensatory vasodilation produced by the endothelium-derived hyperpolarizing factor (Sofola et al., 2002).

A high sodium intake might also be related to changes in the renin–angiotensin system. The expression of angiotensin type 1 (AT_1) receptors is altered in high salt diet; but this is dependent on the vessel and animal studied. It is enhanced in arteries from Dahl salt-sensitive or -resistant rats and in Wistar rats (Wang and Du, 1998; Strehlow et al., 1999; Wang et al., 2003). In contrast, it is down-regulated in renal and aortic arteries from Dahl salt-sensitive rats during high salt diet independently of blood pressure levels (Strehlow et al., 1999).

These apparently conflicting results about high salt diet may be due, in part, to the use of different vessels, models and animals. Thus, the goal of the present study was to evaluate the effect of a high sodium intake in Wistar healthy normotensive rats on the blood pressure and vascular reactivity of the tail and kidney vascular beds, particularly the alterations of vascular function and its endothelial modulation. The kidney is an important organ involved in the regulation of sodium plasma levels and changes in the vascular renal resistance modify renal function. In addition, it is already known that the tail vascular bed is a representative resistance vascular bed with high contractile response that can contribute to the maintenance of the total vascular resistance in the rat. Based on these facts, we performed experiments to evaluate the vascular reactivity to α-agonist on these two vascular beds.

Materials and methods

Experimental animals and treatment

Male Wistar rats, 8 weeks old (180–200 g), were used. All experiments were conducted in compliance with the guidelines for biomedical research as stated by the Brazilian Societies of Experimental Biology. During the study, rats were housed at a constant room temperature and humidity and at a 12-h light/dark cycle. Rats had free access to tap water and were fed with standard rat chow ad libitum. The animals were randomly divided into two treatment groups: Control (CT) and high salt intake (NaCl 1.8%, SALT) group. NaCl was administered for 30 days in drinking water ad libitum.

Arterial pressure, heart rate and body weight determinations

On the day before the experiments, the rats were anesthetized with ether. The left carotid artery was catheterized with a polyethylene catheter (PE-50 with saline plus heparin) that was exteriorized in the mid-scapular region. On the day of the experiments, 24 h after the surgery, body weight, arterial pressure and heart rate were measured in conscious animals.

Arterial blood pressure was measured by a pressure transducer (model 1050BP, UFI, Inc., Morro Bay, CA, USA) and recorded using an interface and software for computer data acquisition (model MP100A, BIOPAC Systems, Inc., Santa Barbara, CA, USA). Heart rate was determined from the pulse pressure intervals.

Urinary and plasmatic sodium measurement

Samples of urine and blood from animals were collected to measure the concentration of sodium. Briefly, the rats were anesthetized with sodium pentobarbital (65 mg/kg, i.p.) and, after loss of the righting reflex, heparin (500 UI, i.p.) was administered. After this, a blood sample was collected from the left ventricle. The sample was centrifuged at $3000 \times g$ for 10 min and a sample of plasma was collected and frozen. Urine was collected directly from the bladder prior to the beginning of the experiment and frozen. Sodium was measured by the sodium, potassium and chloride methods (Roche© ISE SnapPak, São Paulo, SP, Brazil). The sodium, potassium and chloride measurement methods used the direct sensing Integrated Multisensor Technology (IMT) to develop an electrical potential proportional to the activity of each specific ion in the sample.

Isolated rat tail and kidney vascular bed preparation

Ten minutes after the anesthesia and administration of heparin, 1 cm strip of the tail artery was dissected and cannulated with an intracath (Nipro 24G 3/4, Sorocaba, SP, Brazil) near the base of the tail. After laparotomy, the left renal artery was dissected and cannulated with a polyethylene catheter (PE-10 with buffer). The tail and kidney were then severed from the body and placed in a tissue bath and perfused with Krebs–Henseleit buffer (KHB in mM) (120 NaCl, 5.4 KCl, 1.2 $MgCl_2$, 1.25 $CaCl_2$, 2.0 NaH_2PO_4, 27 $NaHCO_3$, 11 glucose and 0.03 EDTA) bubbled with 5% CO_2 and 95% O_2 at 36±0.5 °C. The tail and kidney were

Table 1
Effects of 30 days Salt-treatment on systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP), heart rate (HR), body weight (BW) and urinary and plasmatic sodium concentration

	Control	N	Salt	N
SAP (mmHg)	134±3.6	7	146±2.9*	18
DAP (mmHg)	98±4.8	7	109±2.4*	18
MAP (mmHg)	110±4.0	7	124±2.2*	18
HR (bpm)	335±8.2	7	345±11.4	18
BW (g)	282±7.6	7	262±4.2	18
Na^+ urinary (mmol/L)	50±17.1	7	383±72.1*	7
Na^+ plasmatic (mmol/L)	144±1.3	7	149±1.9	7

Values are means±S.E.M. for *N* animals.
* $p < 0.05$ vs. control, unpaired *t*-test.

perfused with a constant flow of 2.5 and 5 mL/min, respectively, with a peristaltic pump (Milan, Colombo, PR, Brazil). Mean perfusion pressure (MPP) was measured by using a pressure transducer (TPS-2, InCor, São Paulo, SP, Brazil) and the data was recorded using an interface and software for computer data acquisition (model MP100A, BIOPAC Systems, Inc., Santa Barbara, CA, USA) with a sample rate of 500 Hz per channel. Because a constant flow was maintained, changes in the perfusion pressure represented changes in vascular resistance.

After 30–45 min equilibration period, the vascular reactivity to phenylephrine was evaluated in both the caudal and renal vascular preparations. Dose–response curves to phenylephrine (PHE, 0.00001 to 0.3 mg) were administered as bolus injections of 100 μL. Because we found no effects of salt loading on the actions of PHE on the kidney vasculature, all subsequent evaluations of vascular reactivity were done with the isolated tail vascular bed preparation.

Acetylcholine was used to evaluate endothelium-dependent relaxation in the isolated caudal vascular bed. Vasoconstriction was induced by perfusion of KHB containing 45 mM KCl. KCl produced approximately 60% to 80% of the contraction induced by PHE (100 μg). Once a plateau was attained, dose–response curves to graded concentrations of acetylcholine (10^{-10} to 10^{-3} M) were generated, each one infused for 4 min.

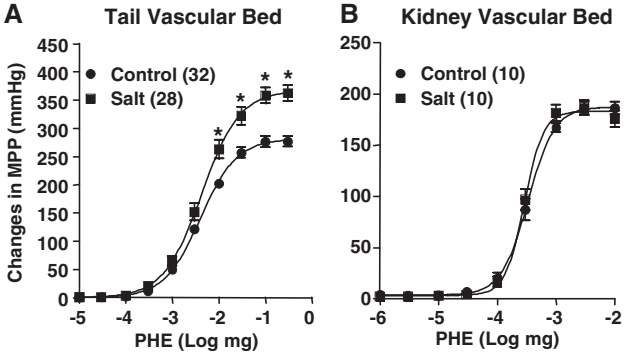

Fig. 1. Dose–response curves to phenylephrine (PHE) in isolated rat tail (A) and kidney (B) vascular beds from Control and Salt groups. Symbols represent means±S.E.M. of changes in mean perfusion pressure (MPP). *$P < 0.01$, Salt vs. Control, 2-way ANOVA, completely randomized.

The influence of endothelium, endogenous nitric oxide, cyclooxygenase (COX) pathway, and angiotensin II on the contractile activity of PHE were evaluated. Dose–response curves to PHE (0.0001 to 0.1 mg, as bolus injections, 100 μL) were generated before and 30 min after endothelium damage (CHAPS, 0.8 mg in bolus), blockade of nitric oxide production (L-NAME, 10^{-4} M), cyclooxygenase (indomethacin, 10^{-5} M) or angiotensin receptor AT_1 (losartan, 10^{-4} M) added to the KHB.

Determination of angiotensin-converting enzyme activity

Angiotensin-converting enzyme activity was determined in the tail artery of SALT and Control rats by a method described by Oliveira et al. (2000). Briefly, tissues were homogenized in sucrose and borate buffer (sucrose 320 mM and sodium borate 400 mM; pH 7.2) (10 ml buffer/1 g tissue). Homogenates were centrifuged (3000×*g* for 10 min) and the supernatants were used for the fluorometric assay of angiotensin-converting enzyme activity. Supernatants from homogenized tissues (20 μl) were incubated with 480 μl of assay buffer containing 5 mM Hip–His–Leu (Sigma Chemical, St. Louis, USA) in 400 mM sodium borate buffer with 0.1% Triton X-100 with 900 mM NaCl, pH 8.3 for 30 min at 37 °C. The reaction was stopped by the addition of 1.2 ml of 0.34 N NaOH. The product, His–Leu, was measured fluorometrically at 365-nm excitation and 495-nm emission with a fluoro-colorimeter (luminescence spectrometer, SLM-AMINCO, Rochester, NY, USA) as follows. *O*-phthaldialdehyde (100 μl, 20 mg/mL, Sigma Chemical) in methanol was added and after 10 min the solution was acidified with 200 μl 3 N HCl and centrifuged at 3000×*g* for 10 min at room temperature. To correct for the intrinsic fluorescence of the

Table 2
Dose–response parameters for the contractile actions of phenylephrine on the isolated perfused tail vascular bed preparation

Group	E_{Max} (ΔmmHg)	pD_2	N
CT	282±10	2.41±0.04	32
SALT	378±15.8*	2.33±0.07	28
CT E+	297±12.4	2.02±0.29	10
CT E−	383±28.6**	2.62±0.37**	10
SALT/E+	410±36.1*	2.38±0.13	6
SALT/E−	313±27.6**	2.96±0.12**	6
CT E+	291±12.2	2.28±0.10	7
CT E+/LN	293±25.9	3.05±0.08**	7
SALT E+	360±35.7*	2.28±0.11	7
SALT E+/LN	381±37.7*	2.81±0.14***	7
CT E+	247±21.0	2.43±0.07	10
CT E+/INDO	222±16.5	2.62±0.05	10
SALT E+	344±25.5*	2.28±0.11	8
SALT E+/INDO	316±28.4*	2.75±0.14***	8
CT E+	281±20.8	2.49±0.07	7
CT E+/LOS	282±32.3	2.70±0.17	7
SALT E+	378±21.2*	2.42±0.20	7
SALT E+/LOS	295±10.3	2.40±0.09	7

* $P < 0.05$, unpaired *t*-test.
** $P < 0.01$, one-way ANOVA followed by Tukey's post-hoc test.
*** $P < 0.05$, one-way ANOVA followed by Tukey's post-hoc test.

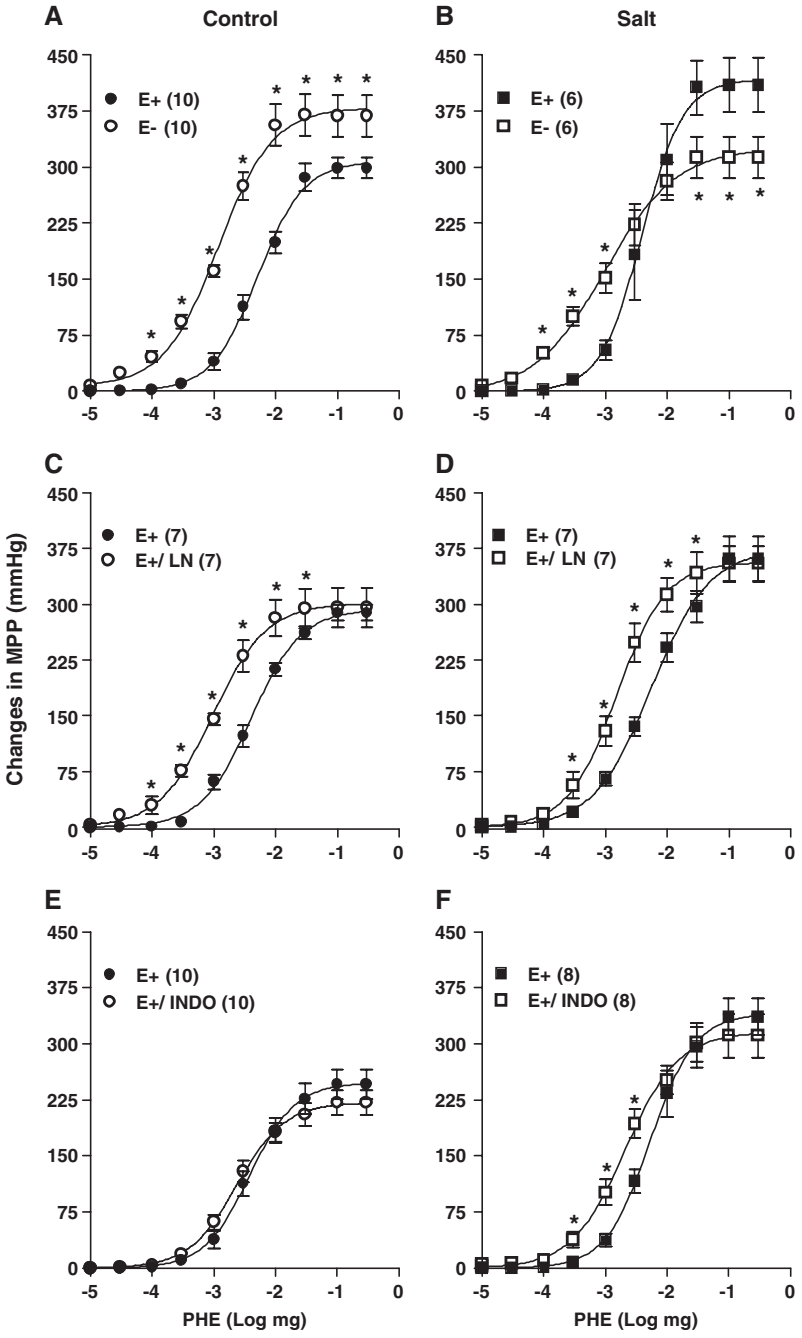

Fig. 2. Effects of endothelial damage (E−), acute perfusion with L-NAME 10^{-4} M (LN) or indomethacin 10^{-5} M (INDO) on the contractile response to phenylephrine (PHE) in tail vascular beds from Control (A, C and E) and Salt (B, D and F) groups. Results are presented as means ± S.E.M. of changes in mean perfusion pressure (MPP). *$P < 0.01$, after vs. before experimental handlings, 2-way ANOVA, repeated measures.

tissues, time zero blanks were prepared by adding tissue after NaOH. All assays were performed in triplicate. Protein was measured by the Bradford method using bovine albumin as a standard. Activity calculations were based on Michaelis–Menten first-order kinetics.

Drugs and reagents

The following drugs were used: L-NAME, acetylcholine chloride, l-phenylephrine hydrochloride, losartan, Tris ((hydroxymethyl)aminomethane), sodium nitroprusside, and CHAPS (3,3-chloamidopropyldimethylammonium-1-propanesulfonate) were purchased from Sigma (St. Louis, MO, USA), indomethacin from Merck (Whitehouse Station, NJ, USA), heparin from Roche (São Paulo, SP, Brazil), and sodium pentobarbital from Fontoveter (São Paulo, SP, Brazil).

All stock solutions of the compounds used were dissolved in bidistilled water, except indomethacin that was previously dissolved in Tris. All solutions were freshly prepared before use and protected from light.

Data analysis and statistics

Results of perfusion pressure measurements are presented as changes in the mean perfusion pressure (MPP) subtracting peak pressure from the baseline pressure and are expressed as mmHg. Relaxation responses to acetylcholine were expressed as a percentage of relaxation in relation to precontracted MPP. Phenylephrine dose–response curves were expressed as log of phenylephrine in mg.

Dose–response curves were analyzed by nonlinear regression analyses (GraphPad Prism software, San Diego, CA, USA) to estimate the maximal response, E_{max} produced by the drug and the dose that produces one-half maximal response, $\log ED_{50}$. In the text, values for $-1 \cdot \log ED$ (pD_2) are used.

Results are expressed as means ± standard error of the mean (S.E.M.) and were compared by using an unpaired *t*-test and one- or two-way analysis of variance (ANOVA), repeated measures or completely randomized, followed by Tukey's post-hoc test. Statistical significance was established at $p < 0.05$.

Results

Arterial pressure, heart rate, body weight and plasmatic and urinary sodium concentration

Salt overload induced an increase in systolic, diastolic and mean arterial pressures (Table 1) when compared to the control group. No differences in body weight or heart rate were observed among the groups (Table 1). Sodium loading produced an increased urinary excretion of Na^+ and no changes in the concentration of Na^+ in plasma (Table 1).

Effects of high salt intake on the phenylephrine-induced response of tail and kidney vascular beds

Fig. 1A and Table 2 show that salt-treatment increased significantly the E_{max} value for PHE, without changing pD_2. In the perfused kidney, we found no differences between groups as shown in the Fig. 1B. Therefore, in all subsequent experiments, we used only the isolated tail vascular bed preparation.

Effect of high salt intake on the endothelial-dependent relaxation produced by acetylcholine

The endothelial-dependent vascular relaxation to acetylcholine in isolated tail vascular bed preparations was not altered by sodium loading. There were no changes in the maximal response (SALT = 80 ± 2.1% vs. CT = 80 ± 2.7% relaxation; $p > 0.05$) or sensitivity (SALT = 5.08 ± 0.25% vs. CT = 4.97 ± 0.27%; $p > 0.05$).

Role of endothelium, nitric oxide, COX-pathway and angiotensin II on the phenylephrine response in tail vascular bed from salt-treated rats

In the control group, endothelial damage by CHAPS (E−) increased both E_{max} and pD_2 values for PHE (Fig. 2A and Table 2). In contrast, E_{max} value for PHE was reduced but pD_2 value was increased in the SALT group following endothelial damage (Fig. 2B and Table 2).

The acute inhibition of NOS by L-NAME (Fig. 2C, D and Table 2) produced an increase in the pD_2 value for PHE in both CT and SALT groups without changing E_{max} value.

Inhibition of COX by indomethacin increased the pD_2 for PHE only in the SALT group without changes in E_{max} (Fig. 2F and Table 2). No effects of indomethacin were observed in preparations from the CT group (Fig. 2E and Table 2).

Blockade of AT_1 receptors with losartan resulted in E_{max} reduction for PHE in the tail vascular bed from the SALT group without changing its pD_2 value (Fig. 3A and Table 2). In CT group losartan had no effect both on E_{max} or pD_2 values for PHE (Fig. 3A and Table 2).

ACE activity on tail artery

As shown in Fig. 3B, ACE activity was approximately 95% higher in tail arteries obtained from the SALT group as compared to the CT group (SALT = 69.89 ± 5.21 vs. CT = 35.73 ± 5.38 nmol/min/mg protein; $p < 0.01$).

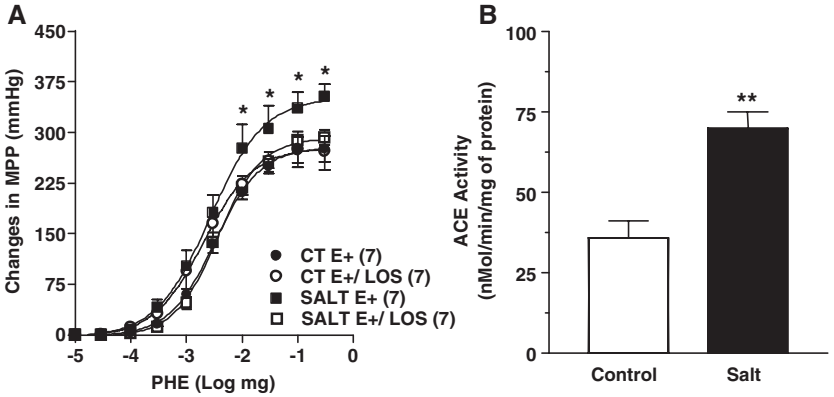

Fig. 3. (A) Effect of acute perfusion of losartan 10^{-4} M (LOS) on the contractile response to phenylephrine (PHE) in tail vascular beds from control (CT) and salt (SALT) groups. Results are presented as mean ± S.E.M. of changes in mean perfusion pressure (MPP). *$P < 0.01$ SALT E+ vs. SALT E+/LOS, 2-way ANOVA, repeated measures. (B) Tissue angiotensin-converting enzyme (ACE) activity of experimental groups. **$P < 0.01$, Salt vs. Control group, unpaired *t*-test.

Discussion

The present study showed that in healthy Wistar rats, an increased salt intake for 30 days enhanced blood pressure and induced specific changes in the vascular pressure response produced by PHE. Salt treatment did not change the reactivity to PHE in kidney vascular beds. However, the vasoconstrictor actions of PHE on the tail vascular bed were enhanced and dependent upon the local renin–angiotensin system in endothelial cells.

Many studies showed that sodium overload results in changes in sympathetic reflexes (Miyajima and Bunag, 1985; Ferrari and Mark, 1987) and changes in vascular reactivity (Mulvany et al., 1978; Adegunloye and Sofola, 1997; Nishida et al., 1998; Lenda et al., 2000). Additionally, there are changes in cardiac structure (Lal et al., 2003), function (Simchon et al., 1991), and volume that result in an increased cardiac output. However, the mechanisms by which a high salt diet causes an increase in the blood pressure in healthy rats are not clear yet. In the present study, we evaluated the effects of a high salt diet on blood pressure and on the reactivity of two different vascular beds, the kidney and the tail, from healthy rats maintained on a high salt diet for 1 month.

Similar to the present results, the increase in arterial blood pressure that occurred in the absence of changes in heart rate also has been previously reported in rats treated with high sodium diet (Miyajima and Bunag, 1985; Kassab et al., 1998; Yu et al., 1998; Contreras et al., 2000; Lenda et al., 2000; Ni and Vaziri, 2001; Lal et al., 2003; Li and Wang, 2003). The elevated blood pressure level can be explained in part by an enhanced reactivity to the activation of α-adrenoceptors seen in some vascular preparations, such as isolated aortic rings (Obiefuna et al., 1991a,b; Adegunloye and Sofola, 1997), perfused mesenteric bed (Sofola et al., 2002), and the perfused tail vascular bed preparations (present study). Additionally, our results show that the enhanced PHE response induced by the salt loading treatment used in the present study is not generalized to all vascular beds. In particular, no effects of the treatment were seen on the renal vascular bed. This result may reflect the selective auto-regulation of the kidney circulation. In addition, Yu and colleagues have demonstrated no changes in renal vascular function after 4 weeks of salt loading beside the development of a considerable renal fibrosis without an increment in blood pressure (Yu et al., 1998). Therefore, maybe a longer treatment would change renal vascular reactivity, as a result of a persistent increment in blood pressure seen in our study, which could affect the vascular function of the kidney (Vaneckova et al., 1999; Vazquez-Cruz et al., 2000; Orea et al., 2002).

Our results suggest that the endothelium participates in the increased response to PHE in the tail vascular bed from SALT animals. In the absence of endothelium, the increased E_{max} for PHE was not observed in treated animals. This result shows that a factor or factors produced by the endothelium leads to the increased vasopressor response produced by PHE. Nitric oxide (NO) is a factor that negatively modulates the activity of contractile agents (Marin and Sanchez-Ferrer, 1990; Luscher and Tanner, 1993). Based on previous reports which show that salt loading can result in an increased superoxide production (Lenda et al., 2000; Sylvester et al., 2002; Bayorh et al., 2004; Zhu et al., 2004) and a down-regulation of NO synthase isoforms (Ni and Vaziri, 2001; Bayorh et al., 2004), it is possible that this treatment decreased NO availability in the tail artery. However, the inhibition of NO synthase by L-NAME produced the same effect in control and SALT groups. This result suggests that in this vascular bed, an alteration of the availability of NO is not the reason for an enhanced vascular responsiveness to PHE.

An increase of COX-derived vasoconstrictor factors released by the endothelium has been associated with the development and/or maintenance of hypertension and vascular dysfunction (Luscher and Vanhoutte, 1986; Carvalho et al., 1997; Taddei et al., 1997; dos Santos et al., 2003). Because the nonselective inhibition of COX by indomethacin did not alter the effects of salt loading on the maximal response to PHE, the participation of a vasoconstrictor prostanoid does not appear to be involved in enhancing the actions of PHE in the tail artery. However, the present results showed that only in salt-treated animals did indomethacin significantly increase the sensitivity to PHE in tail arteries. This suggests that salt treatment caused a compensatory increase (Uehara et al., 1987; Osanai, 1989) in the availability of a vasodilator prostanoid, such as PGI_2, in the tail artery. Collectively, these results suggest that neither the availability of NO nor the COX pathway was responsible for the increased maximal response to PHE in salt-treated animals.

Instead, our results suggest that an increased local availability of angiotensin II in the tail vascular bed enhanced the actions of PHE. This conclusion is supported by our observation that ACE activity in the tail artery increased by 95% in treated animals and by the observation that blockade of AT_1-receptors by losartan prevented the increment in maximal response to PHE. Other observations showed that changes in the local renin–angiotensin system following sodium loading are tissue/vascular bed and strain selective. No changes in the activity of ACE in heart and kidney were found in Wistar–Kyoto rats (Michel et al., 1994) and down-regulation of AT_1-receptors in the aorta and kidney were observed in Dahl salt-sensitive rats (Strehlow et al., 1999) following salt loading. On the other hand, an increased density of AT_1 receptors was described in aorta and mesenteric resistance arteries from Wistar rats (Wang and Du, 1998), brain from Dahl salt-sensitive rats (Strehlow et al., 1999; Wang et al., 2003) and renal cortex from spontaneously hypertensive rats (Stewen et al., 2003) after chronic high salt diet.

In conclusion, we demonstrated that 4 weeks of high salt intake by healthy Wistar rats causes an elevation of blood pressure and increases the activity of PHE in tail vascular bed. However, kidney vascular bed did not present any changes in the vascular reactivity during the 4 weeks of this treatment. The increased response to PHE is mediated by an increment in angiotensin II production resulting from an increased local ACE activity but not by a reduction in nitric oxide availability or by release of an endothelial COX-derived product of the tail vascular bed.

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