Br. J. Pharmacol. (1991), **104**, 296–300

Differences in inositol phosphate production in blood vessels of normotensive and spontaneously hypertensive rats

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1 Total inositol phosphate formation was measured in labelled femoral and iliac arteries and veins of 14 week-old spontaneously hypertensive rats (SHR) and age-matched Wistar Kyoto (WKY) controls, either unstimulated or in the presence of noradrenaline.

2 Basal levels of [^{3}H]-inositol phosphates and [^{3}H]-phosphatidylinositol were significantly enhanced in SHR femoral artery, but not in the other 3 vessels, compared with WKY.

3 Noradrenaline stimulated phosphoinositide hydrolysis in all four vessels of SHR and WKY. Pretreatment with prazosin (10^{-7}–10^{-6} M) but not with yohimbine (10^{-7} M), inhibited the noradrenaline-induced inositol phosphate formation indicating an α_1-adrenoceptor-mediated response.

4 In the femoral artery of SHR compared to WKY, [^{3}H]-inositol phosphate accumulation induced by noradrenaline (10^{-7}–10^{-5} M) was significantly reduced when expressed relative to basal values although the response to higher concentrations (10^{-4}–10^{-3} M) was not altered. In contrast, a significant reduction of inositol phosphates was seen only with 10^{-7} M noradrenaline when absolute values were compared. In the other three vessels, no difference in noradrenaline-induced [^{3}H]-inositol phosphate formation was observed between strains.

5 These data suggest that phosphoinositide hydrolysis-mediated by α_1-adrenoceptors may be reduced in some but not all blood vessels of adult SHR.

Keywords: α_1-adrenoceptors; hypertension; phosphoinositide hydrolysis; noradrenaline

Introduction

Essential hypertension is characterized by an increase in peripheral vascular resistance (Webb & Vanhoutte, 1979; Webb, 1984). Abnormal responses to a variety of vasoconstrictor and vasodilator agents have been shown in vascular smooth muscle from different animal models of hypertension, including the spontaneously hypertensive rat (SHR) (Holloway & Bohr, 1973; Berecek *et al.*, 1980; Whall *et al.*, 1980). Contractions of helical strips of the aorta from SHR have been found to decrease (Shibata *et al.*, 1973; Aidulis *et al.*, 1990) or not change (Hallback *et al.*, 1971) in response to noradrenaline, as compared with normotensive animals. Further, the sensitivity to noradrenaline is not modified in femoral small arteries, is decreased in rat tail artery (Mulvany *et al.*, 1982) and is increased in mesenteric vessels (Mulvany *et al.*, 1980) of SHR compared to Wistar Kyoto rats (WKY) if the uptake of noradrenaline by the nerve terminal is inhibited.

It is extensively accepted that the sympathetic nervous system controls vascular tone predominantly through α_1-adrenoceptors. The stimulation of these receptors by agonists activates a phosphodiesterase, phospholipase C, and leads to hydrolysis of membrane phosphatidylinositol-4,5-bisphosphate to generate two second messengers, inositol 1,4,5,trisphosphate and 1,2-diacylglycerol. Inositol-1,4,5-trisphosphate is known to release calcium from intracellular stores of smooth muscle cells leading to contraction (Somlyo *et al.*, 1985).

The differences in vascular contraction observed in a variety of animal models of high blood pressure compared to normotensive animals have led to the suggestion that they may be ascribed to differences in the cellular processes linked to activation of α_1-adrenoceptors or to differences in the number of receptors. In that sense, several authors have demonstrated changes in vascular inositol phosphate formation in various rat models of hypertension. Eid & De Champlain (1988) showed that in the femoral and mesenteric arteries of DOCA-salt hypertensive rats the noradrenaline-induced inositol phosphate production was increased compared to controls. However Heagerty *et al.* (1986) demonstrated that in the aorta of 5-week old SHR, before major blood pressure and vascular changes have occurred, both basal and noradrenaline-induced inositol phosphate formation in the presence of lithium was increased compared with age-matched WKY rats. This suggests that in the early stages of hypertension the system was overactive. In the same study at 19 weeks of age, when hypertension was established, the noradrenaline-induced inositol phosphate accumulation was reduced in SHR compared with age-matched WKY rats. In addition, Ek *et al.* (1989) have reported that phosphoinositide turnover was impaired in the aorta of 12–16 week-old SHR while Eid & De Champlain (1988) have demonstrated an increase in basal and noradrenaline-stimulated inositol monophosphate production in atria and ventricles of DOCA-salt hypertensive rats. However, the importance of all these findings in relation to our understanding of hypertension remains unclear. The aim of this study was to measure basal and stimulated levels of [^{3}H]-inositol phosphate formation in the femoral and iliac arteries and veins of adult SHR and WKY rats.

Methods

Experiments were carried out on 14 week-old male SHR and WKY rats (Harlan Olac, Bicester, U.K.).

Assay for total inositol phosphates

The animals were killed by a sharp blow to the head and the blood vessels (femoral and iliac arteries and veins) were removed, cleaned of adherent tissue and immediately placed on ice. The vessels were incubated for 30 min at 37°C in Krebs solution (composition, mM: NaCl 118.3, KCl 4.7, $CaCl_2$ 0.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25.0 and glucose 11.1) with 1.5% bovine serum albumin (BSA) continuously bubbled with 5% CO_2:95% O_2. The Krebs solution was changed every 10 min. Subsequently, the blood vessels were transferred

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and incubated for a further 15 min in Krebs solution containing 10^{-2} M LiCl and 2×10^{-6} M imipramine. Two vessels were transferred to each assay tube containing 450 μl of Krebs solution with 10^{-2} M LiCl and 2×10^{-2} M imipramine. Each sample was weighed, 0.5 μCi of [^{3}H]-myoinositol added and incubated at 37°C for 3 h under an atmosphere of 95% O_2:5% CO_2.

Noradrenaline (10^{-7}–10^{-3} M) or the vehicle ascorbic acid (0.1%) was added 30 min before stopping the reaction. Antagonists were added 15 min before noradrenaline. Blank tubes lacking only tissue, and control tubes lacking agonist were assayed simultaneously with all experiments. The reaction was terminated by the addition of $CH_3OH/CHCl_3/HCl$ (40:20:1 V/V/V) and the sample sonicated for 45 min. After the addition of 0.63 ml of $CHCl_3$ and 1.26 ml distilled water, the samples were centrifuged at 2500 g for 10 min to facilitate phase separation. The aqueous layer was removed from the tubes for assay of inositol phosphates. Each sample was neutralized and run through a column containing Dowex anion exchange resin in the formate form. The columns were washed with 15 ml of unlabelled *myo*-inositol (5 mM). The total [^{3}H]-inositol phosphates were eluted by washing with 0.1 M formic acid in 1 M ammonium formate. The eluant was collected in scintillation vials and scintillant added. Samples were counted in a liquid scintillation counter.

Assay for phosphoinositides

The lipid layer remaining after removal of the aqueous phase was used for measurement of the [^{3}H]-phosphoinositides: 3 ml of $CHCl_3/CH_3OH$ (2:1, V/V) and 2 ml of CH_3OH/KCl (1 M)-*myo*-inositol (0.01 M) (1:1, V/V) were added to each sample, mixed and centrifuged at 250 g for 5 min. The aqueous layer was removed and discarded. The washing process with CH_3OH/KCl-*myo*-inositol was repeated twice. The lipid phase was then removed and placed in a scintillation vial and left to evaporate overnight. Scintillant was added and the samples counted in a liquid scintillation counter.

Drugs and isotopes

[^{3}H] *myo*-inositol was purchased from Amersham International plc and ECOSCINT scintillant fluid from National Diagnostics. All other materials were obtained from the Sigma Chemical Company.

Analysis of results

Basal [^{3}H]-inositol phosphates were calculated as counts per minute (c.p.m.) per mg of tissue and stimulated [^{3}H]-inositol phosphates as a percentage of unstimulated values. Due to the small size of the vessels used, each sample belongs to a different animal. Therefore group sizes varied and are given in the tables and figures which describe the results. In all the studies n is the number of samples, with every sample being the mean of two duplicates except for the body and tissue sample weight where n is the number of animals used. Comparisons between hypertensive and normotensive rats were carried out by use of ANOVA and Student's t test with a Bonferroni correction for multiple comparisons. Two-sample and unpaired t tests were used to analyse the differences between normotensive and hypertensive basal inositol phosphates, body and tissue weights, respectively. All values are expressed as mean ± s.e.mean.

Results

The mean body weight and the mean tissue sample weight for normotensive and hypertensive rats are shown in Table 1. Body weight was significantly greater in SRH compared to age-matched WKY rats. However, the mean sample weight for each vessel was not significantly different between strains.

Basal and noradrenaline (10^{-5} M)-stimulated levels of [^{3}H]-inositol phosphates, expressed as c.p.m.mg^{-1}, in the four vessels are shown in Table 2. In the femoral artery the unstimulated basal value was significantly higher ($P < 0.05$) in SHR compared to WKY rats but no difference was observed between basal values in the other vessels studied.

Noradrenaline (10^{-5} M) induced a significant increase in [^{3}H]-inositol phosphate accumulation in all four vessels of SHR and WKY (Table 2). The type of α-adrenoceptor involved in this activation is addressed in Figures 1 and 2. As shown, pretreatment of the tissues with the selective α_1-adrenoceptor antagonist prazosin (10^{-7}–10^{-6} M) dramatically inhibited the inositol phosphate accumulation induced by noradrenaline (10^{-5} M), whereas pretreatment with the selective α_2-adrenoceptor antagonist, yohimbine (10^{-7} M), resulted in no significant inhibitory effect. The selectivity of this blockade indicates an α_1-adrenoceptor-mediated response in both strains of rats.

Figure 3 illustrates the concentration-response curve to noradrenaline for phosphoinositide metabolism in the femoral artery and in the femoral vein from SHR and WKY rats. Concentrations of 10^{-7}–10^{-5} M noradrenaline elicited significantly smaller responses (expressed as % of unstimulated basal values) in the femoral artery of SHR compared to femoral arteries of WKY rats. No significant differences were observed with higher doses of agonist (10^{-4} and 10^{-3} M). When the results obtained in the femoral artery were expressed as absol-

Table 1 Mean body weight (g) plus mean of tissue sample weights (2 vessels/sample)

	n	*Body weight*	*FA*	*FV*	*IA*	*IV*
WKY	108	278 ± 28	5.24 ± 1.2	5.07 ± 0.9	8.15 ± 0.12	6.14 ± 0.12
SHR	113	298 ± 25*	5.07 ± 1.0	4.84 ± 0.9	7.90 ± 0.09	5.73 ± 0.13

n = number of animals; FA = femoral artery; FV = femoral vein; IA = iliac artery; IV = iliac vein. * $P < 0.05$ by unpaired Student's t test.

Table 2 Basal and noradrenaline (10^{-5} M)-stimulated [^{3}H]-inositol phosphate formation, expressed as c.p.m.mg^{-1}, in 14 week-old SHR and WKY rats

	WKY				*SHR*			
	n	*Basal*	n	*NA*	n	*Basal*	n	*NA*
Femoral artery	20	169 ± 17	11	679 ± 87.1***	19	229 ± 22†	10	684 ± 91.8***
Femoral vein	19	249 ± 30.3	9	357 ± 36.5**	18	285 ± 35.6	11	393 ± 46.4**
Iliac artery	21	117 ± 17	10	166 ± 21.3*	20	114 ± 14.5	10	192 ± 22.8**
Iliac vein	21	190 ± 20.6	10	278 ± 26.8**	20	182 ± 33	11	278 ± 41.4**

*** $P < 0.001$; ** $P < 0.02$; * $P < 0.05$ within strains; † $P < 0.05$ between strains by two-sample Student's t test; n = number of samples.

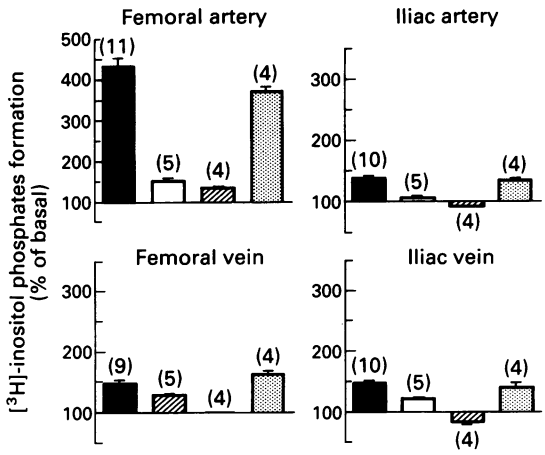

Figure 1 Effect of α-adrenoceptor blockade on noradrenaline (10^{-5} M)-induced accumulation of [^{3}H]-inositol phosphates in several blood vessels of 14 week-old WKY rats. The solid columns represent control, the open columns in the presence of prazosin (10^{-7} M), the hatched columns in the presence of prazosin (10^{-6} M) and the stippled columns in the presence of yohimbine (10^{-7} M). Results are expressed as mean ± s.e.mean. Values for each treatment are expressed as a percentage of the unstimulated value. The number of samples is indicated in parentheses.

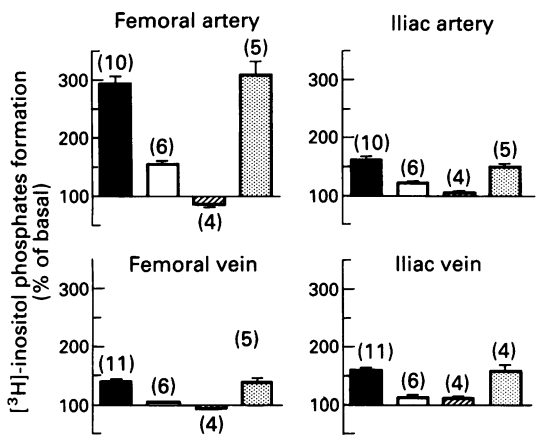

Figure 2 Effect of α-adrenoceptor blockade on noradrenaline (10^{-5} M)-induced accumulation of [^{3}H]-inositol phosphates in several blood vessels of 14-week-old SHR. The solid columns represent control, the open columns in the presence of prazosin (10^{-7} M), the hatched columns in the presence of prazosin (10^{-6} M) and the stippled columns in the presence of yohimbine (10^{-7} M). Results are expressed as mean ± s.e.mean. Values for each treatment are expressed as a percentage of the unstimulated value. The number of samples is indicated in parentheses.

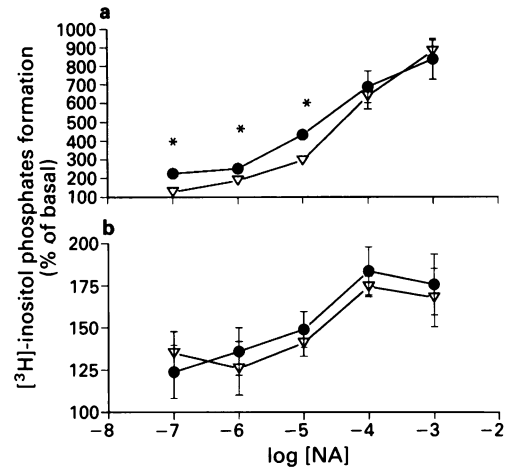

Figure 3 Concentration-response curve for noradrenaline-induced accumulation of [^{3}H]-inositol phosphate formation in the femoral artery (a) and femoral vein (b) of 14 week-old SHR (●) and WKY (▽) rats. Results are expressed as mean with s.e.mean shown by vertical bars. * $P < 0.05$ by ANOVA with a Bonferroni correction.

ute values (Table 3) no difference was observed except with the lowest dose of NA (10^{-7} M) where the value obtained in the WKY rats was greater than in age-matched SHR. In the femoral vein (Figure 3b) as well as in the iliac artery and vein (results not shown) neither the concentration-response curve to noradrenaline nor the absolute values showed difference between SHR and age-matched WKY rats.

Table 4 shows the unstimulated levels of [^{3}H]-phosphoinositides in the four vessels. In the femoral artery, but not in the other three vessels from SHR, [^{3}H]-phosphoinositide values were greater ($P < 0.05$) than in age-matched WKY.

Discussion

Extensive studies have been made of phosphatidylinositol turnover in many tissues including the rat aorta but few detailed studies in small blood vessels have been described. The present study demonstrates that noradrenaline increases phosphoinositide hydrolysis in femoral and iliac arteries and veins of 14 week-old SHR and WKY rats via α_1-adrenoceptors. The population of α-adrenoceptors mediating contraction in the rat femoral artery has been well characterized as exclusively of the α_1 subtype on the basis of the affinity for agonists and antagonists, but in femoral veins both α_1- and α_2-adrenoceptors subtypes seem to be involved

Table 3 Noradrenaline-induced [^{3}H]-inositol phosphate accumulation, expressed as c.p.m.mg^{-1} of tissue, in the femoral artery of 14 week SHR and WKY rats

	Noradrenaline (M)				
	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}
SHR	281 ± 18.6* (6)	391 ± 7.1 (6)	684 ± 91.8 (10)	1458 ± 157 (6)	2008 ± 160 (6)
WKY	380 ± 31.9 (6)	433 ± 34.7 (6)	679 ± 36.5 (11)	1160 ± 143 (6)	1409 ± 322 (6)

Number of experiments in parentheses. * $P < 0.05$ between strains by two-sample Student's t test.

Table 4 Basal [^{3}H]-phosphoinositides, expressed as c.p.m.mg^{-1}, in 14 week-old SHR and WKY rats

	WKY	n	*SHR*	n
Femoral artery	1123.8 ± 137.3	9	1987 ± 293*	9
Femoral vein	761 ± 42	4	563 ± 89.5	4
Iliac artery	455.6 ± 69.9	4	590 ± 69.2	4
Iliac vein	351.9 ± 33	4	268 ± 46	4

n = number of experiments. * $P < 0.05$ between strains.

(Edvinsson *et al.*, 1989). It has also been demonstrated, in the femoral veins of Wistar rats, that phosphoinositide turnover is linked to activation of α_1- but not α_2-adrenoceptors (Stubbs *et al.*, 1988). These results are in good agreement with those obtained in this study which confirms that contraction induced by α_1-adrenoceptor stimulation in the femoral artery and vein is associated with phosphoinositide turnover. In the vas deferens and caudal artery (Fox *et al.*, 1985) noradrenaline appears to be more potent in activating [^{3}H]-*myo*-inositol metabolism than in activating contraction possibly due to a greater receptor reserve for contraction than for inositol phosphate formation. The femoral artery of Sprague-Dawley rats (Edvinsson *et al.*, 1989) contracts in response to noradrenaline (10^{-7}–10^{-3} M) with the maximum contraction obtained between 10^{-4} M and 10^{-3} M. These results correlate well with the results of this study. The concentration-response curve for formation of [^{3}H]-inositol phosphates to noradrenaline (10^{-7}–10^{-3} M) shows a maximum response between 10^{-4} and 10^{-3} M. However, Edvinsson *et al.* (1989) found that the femoral vein had a greater affinity for noradrenaline than the femoral artery. Therefore when compared to the concentration-response curve for inositol phosphate accumulation, noradrenaline seems to be less potent for activation of [^{3}H]-*myo*-inositol metabolism than contraction in the rat femoral vein. Nevertheless when the α_2-adrenoceptor antagonist rauwolscine (10^{-6}–10^{-5} M) was present, the contractile concentration-response curve was clearly shifted to the right and the maximum obtained was again at 10^{-3} M (Edvinsson *et al.*, 1989). Taking account that [^{3}H]-inositol phosphate accumulation induced by noradrenaline in the femoral vein is exclusively mediated via α_1-adrenoceptor stimulation, the results obtained in the femoral vein agree with those obtained in the contractile studies when rauwolscine was present. To date no one has reported, either the subtype of α-adrenoceptors or the cellular response involved in the contractile response of iliac artery and vein in response to noradrenaline. A study carried out using the iliac artery of Wistar rats demonstrated that prazosin but not yohimbine produced a shift to the right of the contractile concentration-response curve of noradrenaline (Vila, Daly & McGrath, unpublished results) suggesting that the population of postjunctional α-adrenoceptors in this vessel belong to the α_1-adrenoceptor subtype. These results agree with those obtained in the present study and demonstrate that the contraction induced by α_1-adrenoceptors in the iliac artery is associated with phosphoinositide turnover. In addition the fact that noradrenaline induced an increase of [^{3}H]-inositol phosphates in the iliac vein, which was blocked by prazosin, suggests that this vessel contains a population of α_1-adrenoceptors linked to phosphoinositide metabolism.

In spite of the great amount of information available on basal and noradrenaline-induced inositol phosphate levels in the aorta of SHR and WKY rats only a few reports on phosphoinositide turnover in small blood vessels of hypertensive and normotensive rats are available. Basal values of inositol phosphates in the femoral artery, but not in the other three vessels studied, were significantly higher in the SHR than in age-matched WKY rats. These results partly agree with the enhanced basal activity of the phosphatidylinositol cycle demonstrated in the heart but not in the femoral artery (Eid & De Champlain, 1988) or the mesenteric artery (Takata *et al.*, 1989) of DOCA-salt rats compared to controls. In the aorta of 5 week-old SHR the basal activity was higher than in age-matched WKY rats but this difference was no longer apparent when the hypertension was established (Heagerty *et al.*, 1986). Our results concerning the basal values of inositol phosphates could be explained by the fact that unstimulated [^{3}H]-phosphatidylinositol levels in the femoral artery but not in the other three vessels were higher in the SHR than in control animals. However we cannot exclude the possibility of a greater phosphoinositide turnover in the femoral artery of 14 week-old SHR. Since the studies in all the blood vessels were always carried out in parallel, we do not have any explanation for the higher basal [^{3}H]-*myo*-inositol incorporation into lipid membrane of the SHR femoral but not the iliac artery or the veins other than different blood vessels behave in a different way. Our results are partly in accord with those of Durkin *et al.* (1989) who, using a highly sensitive method to measure the tissue levels of phospholipids in rat resistency arteries, showed that radiolabelled phospholipids but not inositol phosphates were greater in the resting state of 12 week-old SHR rats. In contrast Ek *et al.* (1989) did not see any difference between adult SHR and WKY either in the incorporation of ^{32}P into aortic inositol lipid or [^{3}H]-*myo*-inositol into inositol phosphates.

The stimulation of inositol phosphate accumulation induced by noradrenaline was similar in both strains of rats except in the femoral artery where the results obtained varied depending on the mode of analysis used. When the agonist-induced inositol phosphate accumulation is expressed relative to the basal value the results obtained seem to suggest a decrease in noradrenaline-induced [^{3}H]-inositol phosphate accumulation in adult SHR compared to age-matched WKY. Alternatively, if absolute values for noradrenaline-stimulated tissue are compared (Table 3) a significant difference is only apparent at the lowest concentration. Ek *et al.* (1989) failed to show an increase of [^{3}H]-inositol phosphates by noradrenaline in SHR whereas labelling was increased 219% in the aorta of WKY. Furthermore, a decrease of inositol phosphate accumulation induced by noradrenaline was reported in the aorta of 19 week-old but not in 5 week-old SHR (Heagerty *et al.*, 1986). In addition, isometric contractions of aortic rings as well as incorporation of ^{32}P-phosphate into phosphatidic acid induced by noradrenaline was greater in WKY than in age-matched SHR (Ek *et al.*, 1989; Aidulis *et al.*, 1990). In another study carried out in neuronal cells in primary culture from the hypothalamic brainstem areas of 1 day-old normotensive and hypertensive rat brain it has been observed that noradrenaline-induced phosphoinositide turnover was significantly lower in SHR neuronal cultures than in WKY cultures pointing to a difference genetically determined not secondary to hypertension (Crews *et al.*, 1988). In contrast Eid & De Champlain (1988) have reported that there is an increase of inositol phosphate accumulation in the femoral arteries of DOCA-salt hypertensive rats following noradrenaline-stimulation. Similarly, the results in precapillary resistance arteries from 5 and 12 week-old SHR and WKY rats reveal that the level of 1,4,5-inositol trisphosphate was increased in SHR (Durkin *et al.*, 1990).

In summary, our results demonstrate that in the femoral and iliac arteries and veins of SHR and WKY phosphoinositide hydrolysis is linked to α_1-adrenoceptors. In addition, enhancement in the basal levels of inositol phosphates as well as in [^{3}H]-phosphoinositides was observed in the femoral artery of SHR, indicating a greater incorporation of [^{3}H]-*myo*-inositol into the membrane lipid in this femoral vessel. The significant difference in basal levels of inositol phosphates between strains complicate the analysis and interpretation of agonist-stimulated results. However, irrespective of the way results are calculated, there is evidence of a reduced response in the femoral artery of SHR suggesting a reduced α_1-adrenoceptor-mediated phosphoinositide response in some but not all blood vessels of adult SHR.

E.V. was supported by a Fleming award (British Council/M.E.C., Spain) and I.M.M. is supported by the British Heart Foundation.

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(Received January 30, 1991
Revised May 13, 1991
Accepted June 4, 1991)