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Heterogeneity of endothelial dysfunction in hypertension

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The endothelium may play a role as a target and mediator of hypertension. Due to its anatomical position, it is very exposed to mechanical forces; as a source of vasoactive material it may participate in increasing peripheral vascular resistance and in promoting local ischaemia in the heart and brain. Morphological and functional changes in the endothelium occur in experimental and human hypertension. However, the severity of the defect and the mechanisms involved among vascular beds and models of hypertension are heterogeneous. Endothelium-dependent relaxations are impaired in the aorta, carotid artery and in cerebral and mesenteric arterioles in hypertension. In the coronary circulation the defect is less pronounced. The mechanisms involve a reduced formation of nitric oxide, an enhanced production of prostaglandin H_2 and an impaired responsiveness of vascular smooth muscle to nitric oxide. The role of endothelin in hypertension is controversial; circulating levels appear unaltered except in the presence of renal failure or atherosclerosis. The local vascular production of endothelin, however, may still be increased. The potentiating effects of threshold concentrations of endothelin on the vasoconstrictor response to noradrenalin are enhanced in hypertension.

Thus, subtle and distinct endothelial function defects occur in hypertension, but not all vascular beds are similarly affected and different mechanisms contribute. Endothelial dysfunction may contribute to increased peripheral resistance, tissue ischaemia and cardiovascular complications.

Introduction

Hypertension is characterized by altered haemodynamic balance, in particular increased peripheral vascular resistance, as well as increased incidence of cardiovascular complications, such as myocardial infarction and stroke. The vasculature contributes both as a regulator of peripheral vascular resistance and as a target of high blood pressure. The latter alterations induced by hypertensive disease in certain vascular beds is a crucial event in the development of myocardial infarction and stroke. The primary structure of the blood vessel wall, which is most exposed to high blood pressure and hence develops early morphological and functional alterations, is the endothelium. The discovery that endothelial cells also secrete potent vasoactive substances[1-3] which appear to play an important role in the local regulation of vascular tone such as nitric oxide[4,5], prostacyclin[6], endothelin[3] and cyclooxygenase-derived contracting factors[7] further supports the concept that the endothelial organ may play an important role in hypertension both as a mediator and target of the disease.

Endothelium-derived vasoactive mediators

L-ARGININE/NITRIC OXIDE (NO) PATHWAY

In isolated blood vessels, the relaxation evoked by acetylcholine is abolished by removal of the endothelium and mediated by nitric oxide (NO) formed from L-arginine (Fig. 1[1,2,4,5,8]). The enzyme, nitric oxide synthase, is calcium- and calmodulin-dependent. The release of NO can be triggered by shear stress (flow), the calcium ionophore A23187, and a number of autocoids, including bradykinin, histamine, noradrenaline, substance P, vasopressin (in certain arteries), thrombin, and platelet-derived products (adenosine di- and triphosphate (ADP and ATP) and serotonin[1-9]). NO has a dual action and not only evokes relaxation of vascular smooth muscle, but also inhibits platelet adhesion and aggregation[10]. Both effects require the activity of soluble guanylate cyclase, which leads to an increase in the intracellular levels of cyclic 3',5'-guanosine monophosphate (cGMP) (Fig. 1[11]). The L-arginine pathway can be blocked by various N^G-substituted derivatives of L-arginine, such as L-N^G-monomethyl arginine, L-N^G-nitroarginine methyl ester, or L-N-iminoethyl ornithine, which compete with the precursor of NO[5,8].

PROSTACYCLIN (PGI_2)

Endothelial cells are a rich source of PGI_2 which relaxes coronary arteries, increases coronary flow, and inhibits platelet aggregation[6]. The mechanism of action of PGI_2 involves an increase in cyclic 3',5'-adenosine monophosphate (cAMP). The production of PGI_2 is stimulated by shear stress, hypoxia, and autacoids, which release EDRF. However, PGI_2 contributes very little to endothelium-dependent relaxations[2,8].

ENDOTHELIUM-DERIVED HYPERPOLARIZING FACTOR (EDHF)

In addition to NO, the endothelium releases a hyperpolarizing factor, at least in certain blood vessels. In canine coronary arteries, acetylcholine causes an endothelium-dependent hyperpolarization of smooth muscle cells that is mediated by a diffusible substance[12].

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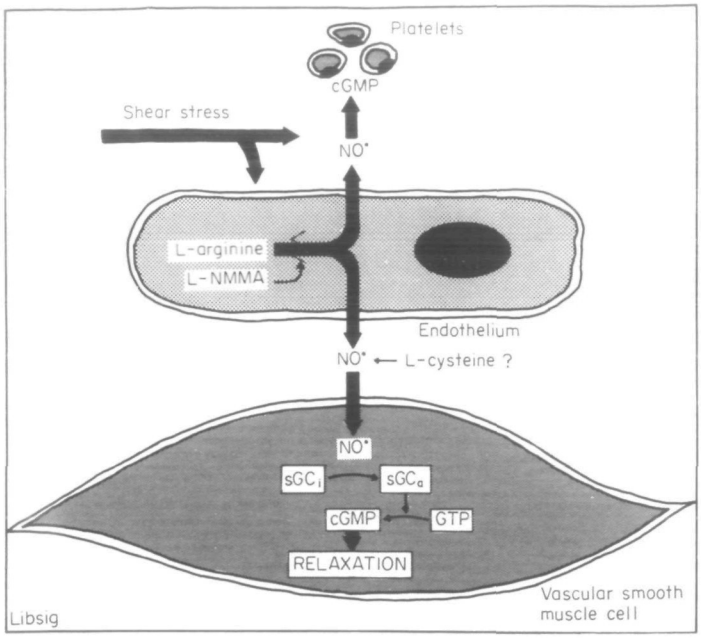

Figure 1 The endothelial L-arginine nitric oxide (NO) pathway: NO is formed from L-arginine via the activity of NO synthase, a calcium- and calmodulin-dependent enzyme which can be inhibited by analogues of L-arginine such as L-L-N^G-monomethyl arginine (L-NMMA). sGC = soluble guanylate cyclase, cGMP = cyclycGMP. Reproduced with permission[2].

Similarly, in porcine coronary arteries, L-NMMA blocks the response to serotonin but not that to bradykinin[13]. Debate continues, however, whether at least under certain conditions, NO or nitrovasodilators can hyperpolarize smooth muscle cells[14]. The endothelium-dependent hyperpolarization may contibute to the relaxation and/or reduce the sensitivity of vascular smooth cells of vasoconstrictor substances.

ENDOTHELIN

Endothelial cells also produce the potent vasoconstrictor peptide, endothelin (Fig. 2[3]). The 21-amino-acid peptide is produced and released by endothelial cells (on the basis of de novo protein synthesis rather than release of stored peptide) upon stimulation with thrombin, transforming growth factor-beta, norepinephrine, phorbol ester, and the calcium ionophore A23187 (Fig. 2 [1,3,15]). Three isoforms exist: endothelin-1, endothelin 2, and endothelin 3. Endothelial cells appear to produce primarily endothelin-1. In vascular smooth muscle, endothelin-1 binds to specific receptors, activates phospholipase, increases intracellular calcium and causes long-lasting contractions for renin[16]. The peptide has a greater vasoconstrictor potency than the other cardiovascular hormones. In vivo, the circulating levels of the peptide are extremely low. Threshold concentrations, however, potentiate contractions evoked by norepinephrine and serotonin (Fig. 3[17]). In most, but not in all preparations, NO or nitrovasodilators are able to inhibit contractions induced by endothelin-1[18,19]. In addition, EDRF or nitrovasodilators inhibit the release of endothelin from intact porcine aorta[15].

CYCLOOXYGENASE-DEPENDENT CONTRACTING FACTORS

In certain blood vessels, endothelium-dependent increases in tension can be obtained with arachidonic acid, acetylcholine, serotonin and other agonists (see[1,16]). Most of these responses can be prevented by cyclooxygenase inhibitors, such as indomethacin or meclofenamate, suggesting that they are mediated by a cyclooxygenase-dependent contracting factor (Fig. 2). Depending on the blood vessels and agonists studied, the responses also can be prevented by thromboxane synthetase inhibitors, thromboxane receptor antagonists or scavengers of oxygen-derived free radicals. These pharmacological data support the notion that the cyclooxygenase pathway can produce mediators causing endothelium-dependent contractions such as thromboxane A_2, prostaglandin H_2 or superoxide anions[16].

Although a distinct endothelium-derived contracting factor released during hypoxia has been proposed, more recent evidence strongly suggests that endothelium-dependent contractions to hypoxia are due to removal of nitric oxide (the production of which is oxygen-dependent) rather than due to the release of contractile material[20].

Heterogeneity of endothelial dysfunction in hypertension

In isolated arteries obtained from hypertensive animals with different forms of hypertension, alterations of endothelial function have been documented by numerous groups[1]. Similarly, in human hypertension endothelial dysfunction occurs[21,22]. However, in

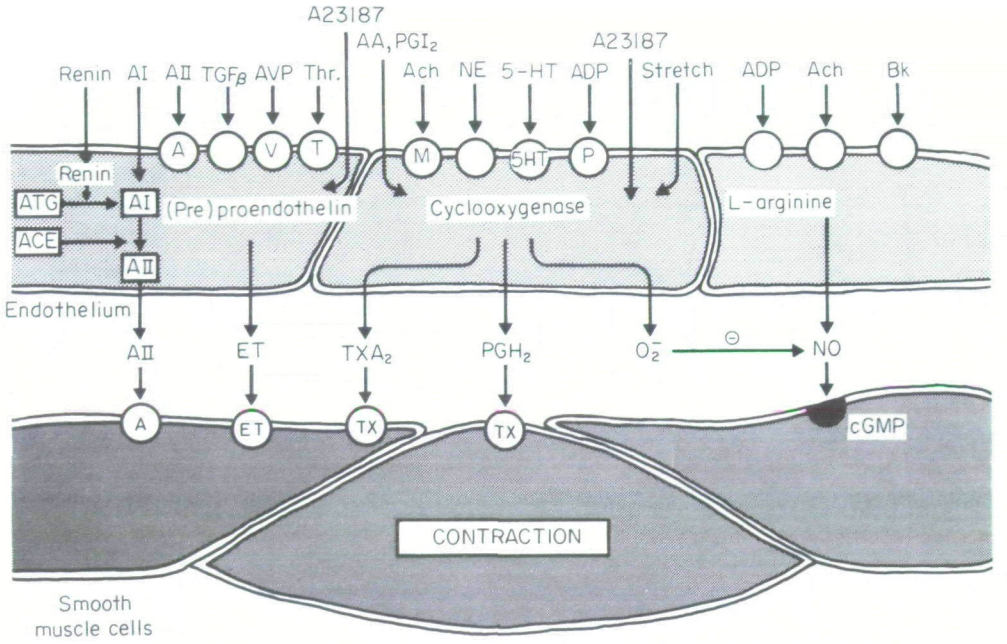

Figure 2 Endothelium-dependent contractions: The endothelium is a source of numerous contracting factors such as endothelin-1 (ET), thromboxane A_2 (TXA_2), prostaglandin H_2 (PGH_2) and possibly also of angiotensin II (AII). The cyclooxygenase pathway is also a source of superoxide anions (O_2^-) which is able to break down nitric oxide (NO). O = receptors; AA = arachidonic acid; ACE = angiotensin converting enzyme; Ach = acetylcholine; ATG = angiotensinogen; ADP = adenosine diphosphate; AVP = arginine vasopressin; Bk = bradykinin; 5HT = serotonin (5-hydroxytryptamine); NE = norepinephrine; PGF-beta = transforming growth factor beta; Thr = thrombin. Reproduced with permission from the American Heart Association[16].

experimental hypertension, it appears that endothelial dysfunction is particularly prominent in certain, but not in all, vascular beds and in addition may be related to different mechanisms in different vascular beds as well as in different models of hypertension.

ANATOMICAL HETEROGENEITY

Most studies have been performed in large conduit arteries, such as the aorta, where reduced endothelium-dependent relaxations have been described in all rat models of hypertension. Similarly, in the carotid as well as the cerebral microcirculation, impaired endothelium-dependent relaxations or vasodilatation respectively have been documented in the spontaneously hypertensive rat (Fig. 4[23,24]). Similarly, endothelium-dependent relaxations are impaired in the mesenteric resistance circulation[25]. In contrast, although endothelium-dependent contractions occur in the spontaneously hypertensive rat in the renal circulation, the responses differ very little from those obtained in normotensive Wistar Kyoto rats, at least up to an age of 30 weeks[23]. In isolated epicardial coronary arteries of the spontaneously hypertensive rat, endothelium-dependent relaxations do not differ from those obtained in Wistar Kyoto rats up to an age of 60 weeks (Fig. 4[26]). Hence, although altered endothelium-dependent responses occur in experimental hypertension of the rat, certain vascular beds, in particular large coronary and renal arteries, appear to be protected from the defect, while in other arteries marked endothelium dysfunction can be noted.

HETEROGENEITY OF SPECIES

Endothelial function has been investigated in experimental hypertension of the rat, rabbit and mouse as well as in human essential hypertension[1]. In all rat models of hypertension, impaired endothelium-dependent relaxations have been observed, while in the rabbit (which does develop less pronounced hypertension) very little

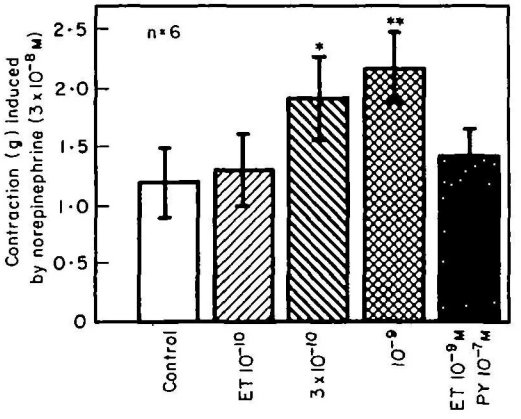

Figure 3 Potentiating effects of low and threshold concentrations of endothelin-1 (ET) in the human internal mammary artery. In the presence of minute amounts of ET, the response to norepinephrine is enhanced, an effect which is prevented by the dihydropiridine calcium antagonist PY (darodipine). Reproduced with permission from the American Heart Association[17].

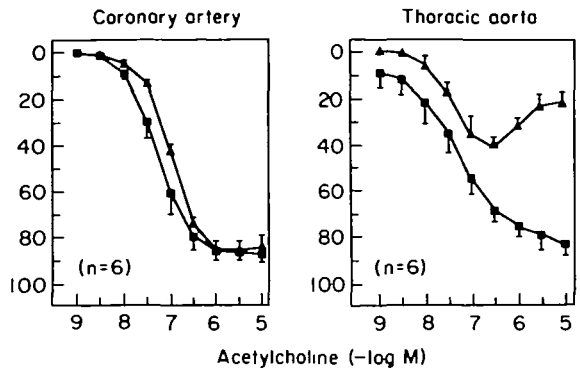

Figure 4 Heterogeneity of endothelial dysfunction in experimental hypertension. In the thoracic aorta of the spontaneously hypertensive rat (▲), endothelium-dependent relaxations to acetylcholine are markedly reduced as compared to normotensive Wistar-Kycto rats (■) (right panel), while in the coronary artery of the same animals, the responses are well maintained (left panel). Data reproduced from[7,23].

alteration has been noted[27] and in psychosocial hypertension in the mouse an enhanced response to endothelium-dependent agonists has even been reported[28]. In the human forearm circulation of patients with essential hypertension, two independent research groups have reported impaired endothelium-dependent vasodilation to acetylcholine with a preserved or only slightly altered responsiveness to sodium nitroprusside (Fig. 5[21,22]).

HETEROGENEITY OF MECHANISMS

An alteration in endothelium-dependent regulation of vascular tone can involve the endothelial vasodilator as well as vasoconstrictor systems. In the case of endothelium-dependent relaxations, a reduced response could involve a specific defect in all or certain receptor-operated pathways, an impaired production of nitric oxide

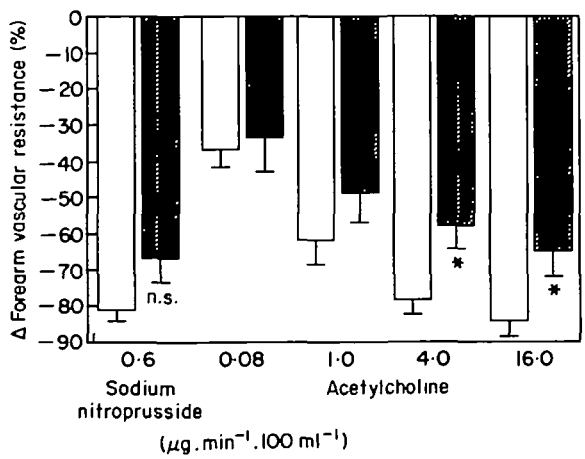

Figure 5 Impaired endothelium-dependent vasodilation in human essential hypertension. Infusion of acetylcholine in the brachial artery causes marked decreases in forearm vascular resistance, an effect which is impaired in hypertensives (▨; n = 8) as compared to normotensives (□; n = 8). * $P = < 0{\cdot}05$. Reproduced with permission from the American Heart Association[21].

from L-arginine, a reduced smooth muscle responsiveness to the endogenous nitrovasodilator and/or a concomitant formation of a contracting factor interfering with the effects of NO.

All of these disturbances have been observed under certain conditions, but are not uniformly found in all models of hypertension or all vascular beds studies. Although an increased medial thickness commonly occurs in hypertensive arteries, both in conduit vessels as well as in the resistance circulation, a reduced responsiveness to NO donors such as sodium nitroprusside or SIN-1 is particularly prominent in the aorta and the carotid artery of the hypertensive rat[23,29], while in mesenteric resistance arteries and in large renal arteries the response to the nitrovasodilators is well maintained[30]. Even in the presence of an impaired responsiveness to NO, this alteration does not fully explain the reduced endothelium-dependent relaxations, as the response to acetylcholine commonly is much more impaired than that to nitrovasodilators[30]. Hence, different endothelial mechanisms must be altered under these conditions.

In the spontaneously hypertensive rat, endothelium-dependent relaxations are impaired to certain but not all agonists, although all of them activate specific receptors linked to the formation of relaxing factors[1]. Indeed, in the aorta of these animals, the response of acetylcholine is markedly reduced, while that to thrombin is fully maintained and that to histamine may actually be enhanced[1,7]. This suggests that defects may be quite specific and must not necessarily involve all pathways activating endothelial cells.

In mesenteric resistance arteries of the spontaneously hypertensive and 2-kidney-1 clip renovascular hypertension, the relaxations to acetylcholine are impaired although that to endothelium-independent vasodilators such as SIN-1 are normal, suggesting a reduced formation of endothelium-derived NO[25,30,31]. In perfused mesenteric resistance arteries, intraluminal activation of the endothelium by acetylcholine is particularly impaired in hypertension, while extraluminal application of acetylcholine evokes normal responses[25]. This suggests that the intraluminal surface of the endothelium, which is most exposed to high blood pressure, selectively exhibits the defect.

In the aorta of the spontaneously hypertensive rat, but not in that of the Dahl salt-induced hypertensive rat, acetylcholine causes endothelium-dependent contractions mediated by prostaglandin H_2 (Fig. 6[7,16]). In this preparation, antagonists of the thromboxane receptor or inhibitors of cyclooxygenase (which prevent the formation of the vasoconstrictor prostanoids) can normalize the imparied endothelium-dependent relaxations to acetylcholine. Hence, in this particular preparation an increased formation of an endothelium-derived contracting factor derived from the cyclooxygenase pathway (i.e. prostaglandin H_2) is responsible for the impaired relaxations in response to acetylcholine, serotonin and aggregating platelets[16].

The contribution of endothelin in this context remains uncertain[16]. As judged from the circulating levels of the

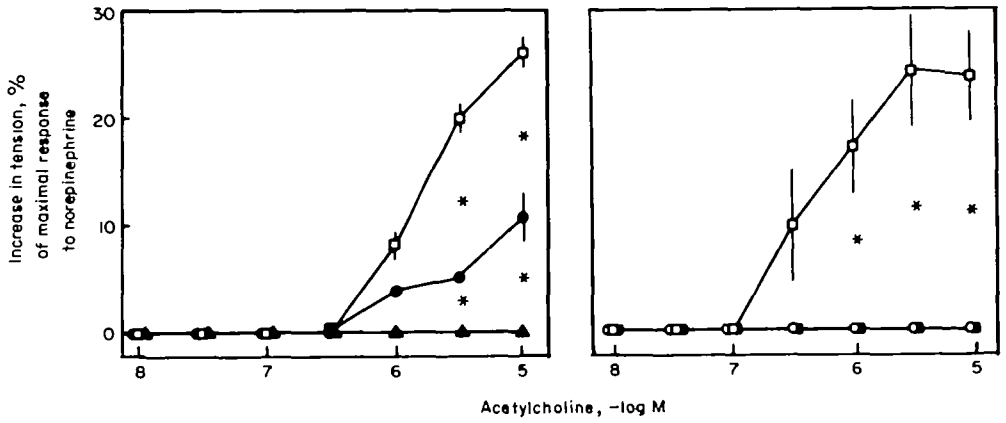

Figure 6 Endothelium-dependent contractors to acetylcholine in the aorta of the spontaneously hypertensive rat. Acetylcholine elicits endothelium-dependent contractions at higher concentrations which are prevented by the phospholipase A_2 quinacrine or the cyclooxygenase inhibitors indomethacin or meclofenomate. * $P<0.05$. □ = control; ● = quinacrine, 10^{-5}M; ▲ = quinacrine, 10^{-4}M; ○ = indomethacin, 10^{-5}M; ■ = meclofenamate, 10^{-5}M. Reproduced with permission from the American Heart Association[7].

peptide in rat and human hypertension it appears that the production of endothelin is not grossly increased (for review see[16]) except in the presence of renal failure or atherosclerosis[32]. However, circulating levels of endothelin may not necessarily reflect the local vascular production of the peptide, particularly since endothelin is preferentially released into the abluminal direction. In addition, the production of the peptide may be increased in certain but not all vascular beds. An interesting effect of endothelin in this context is the fact that the peptide, even at threshold concentrations, can potentiate the response to other vasoconstrictor hormones, suggesting that it may act as a regulator of vascular contractility (see Fig. 3). In ageing and hypertensive rats this indirect potentiating effect of threshold concentrations of endothelin are augmented[33,34]. Angiotensin II expresses endothelin messenger RNA even in the microcirculation (Fig. 7[34]) and stimulation with AII of perfused mesenteric resistance arteries is associated with an endothelium-dependent potentiation of the response to norepinephrine (Fig. 8[34]). As this response is prevented by phosphoramidone, an inhibitor of the endothelin converting enzyme, as well as endothelin antibody, this strongly suggests that angiotensin II is able to stimulate local vascular endothelin production which then in turn augments contractile responses to noradrenaline. If this were to occur in vivo, such response may participate in the pressure effects of very low concentrations of angiotensin II.

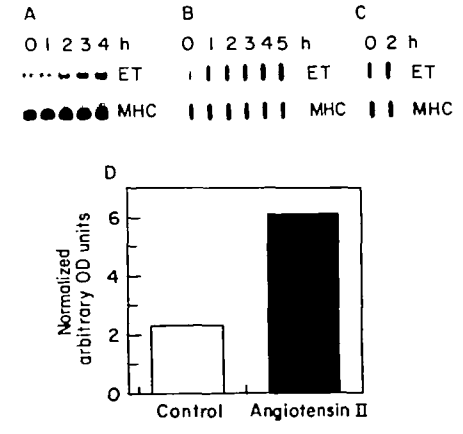

Figure 7 Stimulation of endothelin (ET) messenger RNA by angiotensin II in endothelial cells in culture obtained from the porcine aorta (A), the rat aorta (B) or from freshly obtained endothelial cells of the mesenteric microcirculation (C). The increase in message in the latter cells is quantified in panel D. Reproduced with permission from the American Heart Association[34].

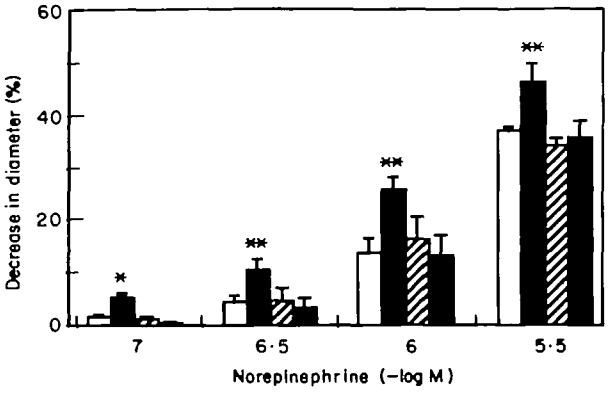

Figure 8 Potentiating effects of angiotensin II (AII 10^{-7}M) in perfused mesenteric resistance arteries with endothelium obtained from the spontaneously hypertensive rat. Perfusion of the vessels with AII for 5 h increases the response to norepinephrine (* $P<0.05$; ** $P<0.01$). This endothelium-dependent potentiation of the response to norepinephrine induced by AII is prevented by either the endothelin converting enzyme inhibitor, phosphoramidone, or an endothelin antibody. □ = control; ■ = AII; ▨ = AII + phosphoraminadone; ▩ = AII + endothelin antibody (n = 5). Reproduced with permission from the American Heart Association[34].

ENDOTHELIAL DYSFUNCTION AND BLOOD PRESSURE

In the Dahl rat, the impairment of endothelium-dependent relaxations to acetylcholine correlates with the degree of blood pressure elevation[29]. Antihypertensive therapy on the other hand, normalizes the response in Dahl salt-hypertensive rats[29]. Similarly, in the spontaneously hypertensive rat, endothelium-dependent relaxations to acetylcholine are impaired in the mesentric resistance circulation of adult (>16 weeks of age) but not of young spontaneously hypertensive rats (6 weeks of age[25]). As antihypertensive therapy with calcium antagonists or drugs interfering with the renin angiotensin system both prevent this defect, it is likely that the impaired endothelium-dependent relaxations are a consequence, rather than a cause, of high blood pressure[25].

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