Effects of des-aspartate-angiotensin I on the actions of angiotensin III in the renal and mesenteric vasculature of normo- and hypertensive rats

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Abstract

An earlier study showed that des-aspartate-angiotensin I (DAA-I) attenuated the pressor action of angiotensin III in aortic rings of the spontaneously hypertensive rat (SHR) but not the normotensive Wistar Kyoto (WKY) rat. The present study investigated similar properties of DAA-I in isolated perfused kidneys and mesenteric beds of WKY and SHR. In the renal vasculature, angiotensin III induced a dose-dependent pressor response, which was more marked in the SHR than WKY in terms of significant greater magnitude of response and lower threshold. DAA-I attenuated the pressor action of angiotensin III in both the WKY and SHR. The attenuation in SHR was much more marked, occurring at doses as low as 10^{-15} M DAA-I, while effective attenuation was only seen with 10^{-9} M in WKY. The effects of DAA-I was not inhibited by PD123319 and indomethacin, indicating that its action was not mediated by angiotensin AT_2 receptors and prostaglandins. However, the direct pressor action of angiotensin III in the SHR but not the WKY was attenuated by indomethacin suggesting that this notable difference could be due to known decreased response of renal vasculature to vasodilator prostaglandins in the SHR. Pressor responses to angiotensin III in the mesenteric vascular bed was also dose dependent, but smaller in magnitude compared to the renal response. The responses in the SHR, though generally smaller, were not significantly different from those of the WKY. This trend is in line with the similar observations with angiotensin III and II by other investigators. In terms of the effect of DAA-I, indomethacin and PD123319 on angiotensin III action, similar patterns to those of the renal vasculature were observed. This reaffirms that in the perfused kidney and mesenteric bed, where the majority of the vessels are contractile, femtomolar concentrations of DAA-I attenuates the pressor action of angiotensin III. The attenuation is not indomethacin sensitive and does not involve the angiotensin AT_2 receptor. The findings suggest that DAA-I possesses protective vascular actions and is involved in the pathophysiology of hypertension.
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Keywords: Des-aspartate-angiotensin I; Angiotensin III; Renal perfusion; Mesenteric; SHR; WKY

1. Introduction

Des-aspartate-angiotensin I (DAA-I), a nine-amino acid endogenous angiotensin peptide, has been shown to attenuate the actions of angiotensin III. It attenuated the contractile response to III in the aortic rings of the rabbit [1] and the spontaneously hypertensive rats (SHR) [2]. Intracerebroventricular administration of DAA-I attenuated dose-dependently the central pressor actions of angiotensin II and III in the SHR and Wistar Kyoto (WKY) rats [3,4]. Although attenuation of the actions of one angiotensin peptide by another is not a new phenomenon, such attenuations often occurs either by receptor antagonism, e.g., [Sar¹,Ile⁸]-angiotensin II and angiotensin-(1–7) block the angiotensin receptor and the actions of angiotensin II [5,6], or by acting on a different angiotensin receptor to produced opposite responses, e.g., angiotensin-(1–7) acts on the putative angiotensin-(1–7) receptor and counteracts most of the actions of angiotensin II in the vascular system [7]. Data obtained from electrically contracted endothelium-denuded rabbit pulmonary arteries showed that DAA-I acted as an agonist on the AT_1 receptor in the pulmonary end of the artery to cause contraction, and via the same receptor at the cardiac end to cause relaxation [8,9]. The latter response was indomethacin sensitive and indicated that DAA-I accessed the AT_1 receptor-coupled prostaglandin second messenger pathway to initiate the inhibitory action. This is a unique action and suggests that

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the different second messenger pathways that are coupled to the AT_1 receptor exhibit ligand specificity. The present study investigated further the effects of DAA-I on the pressor actions of angiotensin III in the renal and mesenteric vasculature of the SHR and WKY. The rationale for the study is the absence of information on the actions of angiotensin III in these two vascular beds and on the effects of DAA-I in contractile vessels. In the present study, angiotensin II was used as a positive control as it has been reported to cause enhanced pressor response in renal vasculature of the SHR [10–12].

2. Materials and methods

2.1. Animals

Male Wistar–Kyoto (WKY) rats and spontaneously hypertensive rats (SHRs) weighing 250–300 g (11–13 weeks) were obtained from the Animal House in the University of Malaya Medical Centre. The animals were fed standard rat chow and tap water ad libitum.

2.2. Isolation of kidney and mesenteric vascular bed

Rats were anaesthetized with sodium pentobarbitone (60 mg/kg, i.p.). The right kidney was exposed by midline laparotomy. The renal artery was cannulated with a catheter (PET-50) via the superior mesenteric artery, and perfusion was started in situ. The right renal vein and ureter were cut. The right kidney was excised and placed in a water-jacketed chamber maintained at 37 °C and perfused with an oxygenated (95% O_2 and 5% CO_2) Kreb's solution by means of a peristaltic pump (Minipuls 3 Model 312, Gilson Villiers Le Bel, France) at a rate of 5 ml/min. In order to isolate the mesenteric arterial bed, the remaining length of the superior mesentery artery was cannulated with a catheter according to the method of McGregor [13]. The mesentery was carefully excised from the intestine and placed in a water-jacketed chamber maintained at 37 °C and perfused with an oxygenated Kreb's solution by means of a peristaltic pump at a rate of 5 ml/min. The composition of the Kreb's solution was as follows (mmol/l): NaCl, 136.9; KCl, 5.4; $CaCl_2$, 1.5; $MgCl_2$, 1.0; $NaHCO_3$, 23.8; EDTA, 0.01; and glucose, 5.5. Changes in perfusion pressure were measured by means of a pressure transducer (Model P23XL, Ohmeda Medical Devices Division,USA) and recorded via a MacLab data acquisition system (AD instruments, Australia).

2.3. Angiotensin and drug administration

After an equilibration period of 20 min, the preparation (renal or mesenteric) was preconstricted with phenylephrine (PE, 10^{-5} M), and the increase in perfusion pressure was recorded until a 5-min plateau was observed. This contractile response to phenylephrine was taken as unity, and responses to other pressor compounds were normalized against this unit. The preparation was then perfused with a Kreb's solution that contained 30 μM captopril. Following 30 min of perfusion, various concentrations (10^{-10}–10^{-6} M) of angiotensin III were used to produce a dose response. Angiotensin III was administered as a single bolus injection of 20 μl into the perfusion system. The minimum time interval between successive bolus injections was 10 min, or the time until the basal pressure was again recorded. For the renal preparation, a dose response to angiotensin II was similarly obtained as a positive control.

The effects of various concentrations (10^{-15}–10^{-9} M) of DAA-I on the response to angiotensin III were studied with the following protocol. This concentration range was based on the findings of an earlier study showing that DAA-I attenuated the pressor action of angiotensin III at a concentrations as low as 10^{-11} M [2]. The preparation was first perfused with Kreb's solution containing 30 μM captopril and a concentration of DAA-I for 30 min, prior to initiating a dose response to angiotensin III. Each concentration of DAA-I was studied using a different preparation. The same protocol was used to study the direct effect of indomethacin or PD123319 on the responses to two doses of angiotensin III. The effect of PD123319 or indomethacin on the attenuation of angiotensin III pressor response by DAA-I was studied by perfusing the preparation with DAA-I and PD123319 (or indomethacin) for 30 min prior to bolus injections of angiotensin III.

2.4. Drugs

Captopril, angiotensin II, angiotensin III and indomethacin were purchased from Sigma. Des-aspartate-angiotensin
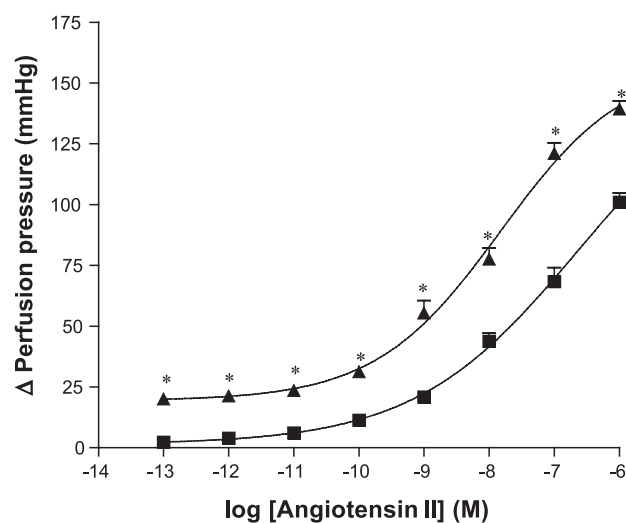

Fig. 1. Perfusion pressure response to angiotensin II in the kidney of the WKY (■) and SHR (▲). Each point is the mean ± S.E.M. of four to six individual determinations. *Indicates significant difference from the WKY.
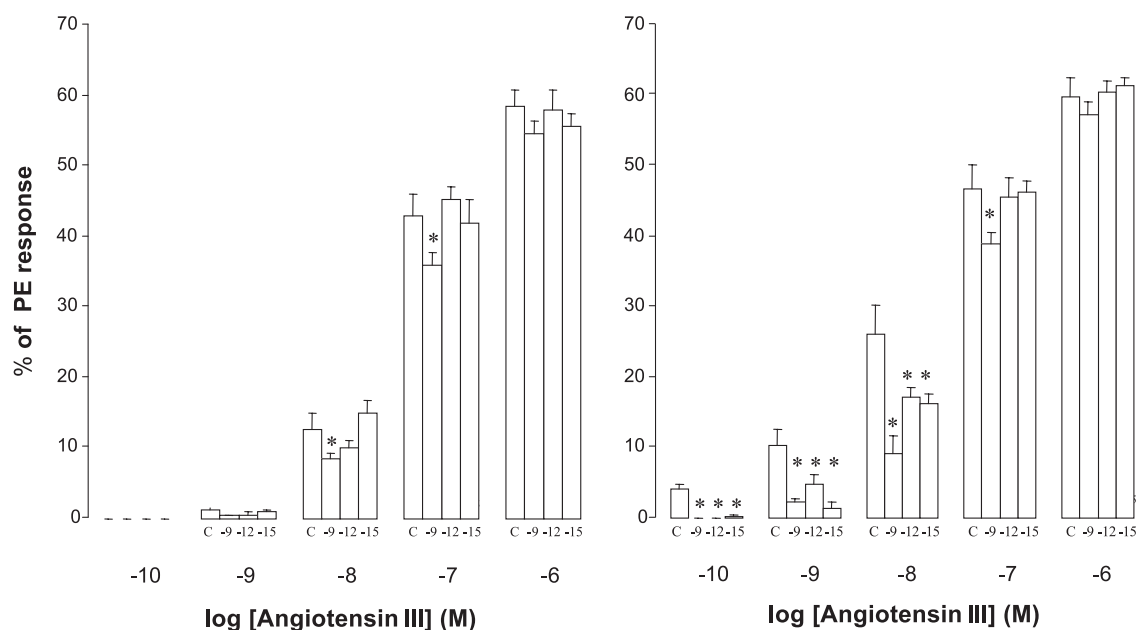
Fig. 2. Effect of DAA-I on the angiotensin III-induced pressure response in the kidney of the WKY (left histograms) and SHR (right histograms). Alphabet and numbers immediately below histograms: C, control (not treated); -9, pretreated with 10^{-9} M DAA-I; -12, pretreated with 10^{-12} M DAA-I; -15, pretreated with 10^{-15} M DAA-I. Each histogram and bar represent the mean $\pm$ S.E.M. of four to six separate preparations. *Indicates significant difference from the control.

I was purchased from BACHEM, Bubendorf, Switzerland. PD123319 was a generous gift from Parke-Davis Pharmaceutical Research, MI, USA. All other reagents used were of analytical grade.

2.5. Statistical analysis

Data are presented as mean $\pm$ S.E.M. Significant difference ($p < 0.05$) between means was evaluated using Stu-
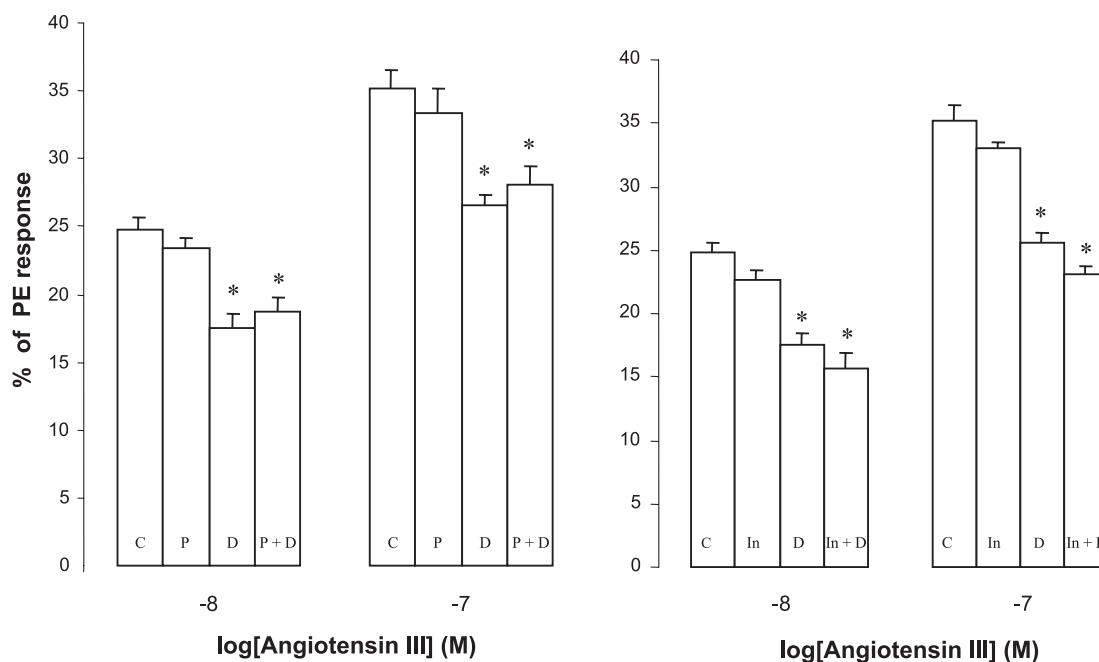

Fig. 3. Effect of PD123319 (left histograms) and indomethacin (right histograms) on the inhibitory effects of DAA-I on the angiotensin III-induced pressure response in the kidney of the WKY. Alphabets inside histograms: C, control (not treated); P, pretreated with 10^{-5} M PD123319; D, pretreated with 10^{-9} M DAA-I; P+D, pretreated with PD123319 and DAA-I; In, pretreated with 10^{-5} M indomethacin; In+D, pretreated with indomethacin and DAA-I. Each histogram and bar represent the mean $\pm$ S.E.M. of four to six separate preparations. *Indicates significant difference from the control.
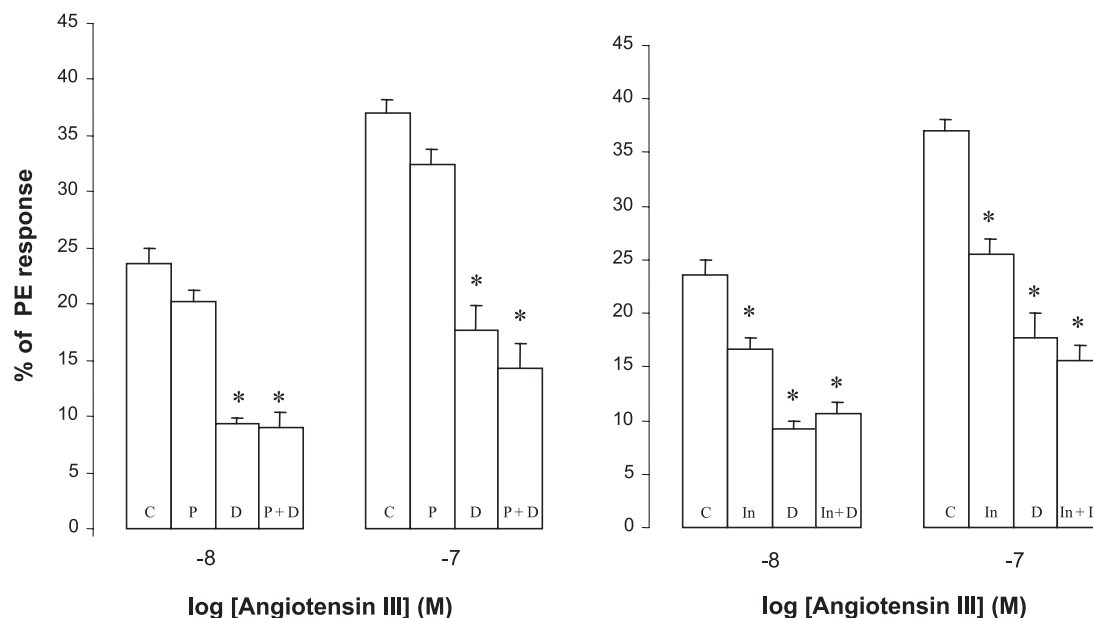
Fig. 4. Effect of PD123319 (left histograms) and indomethacin (right histograms) on the inhibitory effects of DAA-I on the angiotensin III-induced pressure response in the kidney of the SHR Alphabets inside histograms: C, control (not treated); P, pretreated with 10^{-5} M PD123319; D, pretreated with 10^{-9} M DAA-I; P+D, pretreated with PD123319 and DAA-I; In, pretreated with 10^{-5} M indomethacin; In+D, pretreated with indomethacin and DAA-I. Each histogram and bar represent the mean $\pm$ S.E.M. of four to six separate preparations. *Indicates significant difference from the control.

dent's *t*-test when comparing two groups. When more than two groups were compared and for the comparison of the dose–response curves, data were evaluated by two-factor analysis of variance (ANOVA) followed by Newmann–Keul's post hoc test. Results with $p < 0.05$ were considered statistically significant.

3. Results

3.1. Renal vasculature

A 10^{-5} M concentration of PE caused an average increase in perfusion pressure of 250 ± 20 mm Hg in
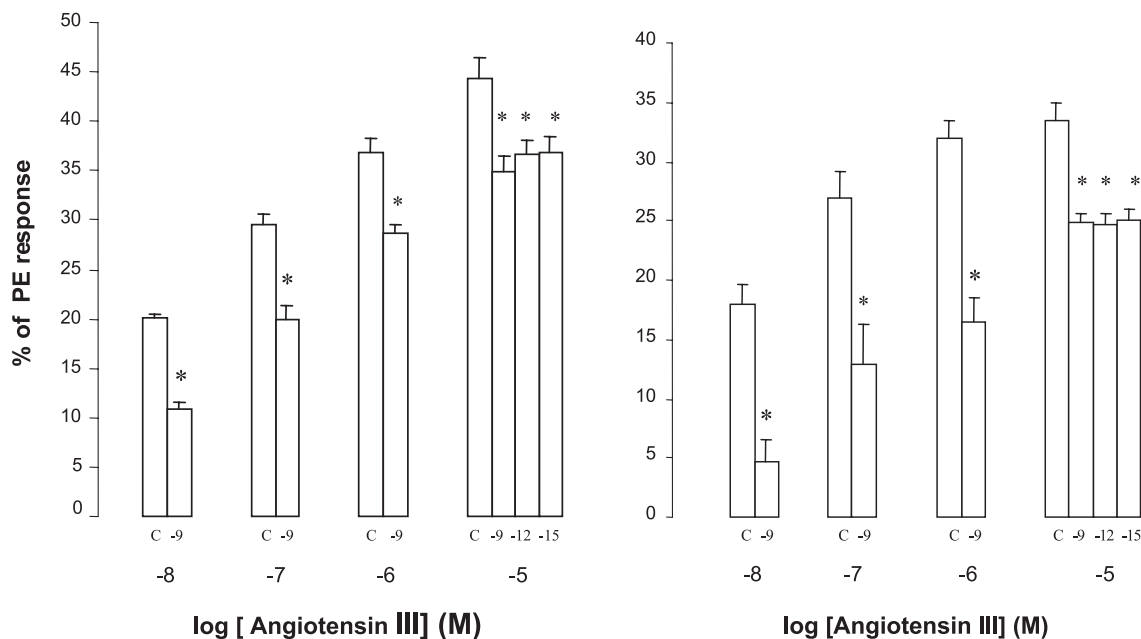

Fig. 5. Effect of DAA-I on the angiotensin III-induced pressure response in the mesenteric vascular bed of the WKY (left histograms) and SHR (right histograms). Alphabet and numbers immediately below histograms: C, control (not treated); -9, pretreated with 10^{-9} M DAA-I; -12, pretreated with 10^{-12} M DAA-I; -15, pretreated with 10^{-15} M DAA-I. Each histogram and bar represent the mean $\pm$ S.E.M. of four to six separate preparations. *Indicates significant difference from the control.
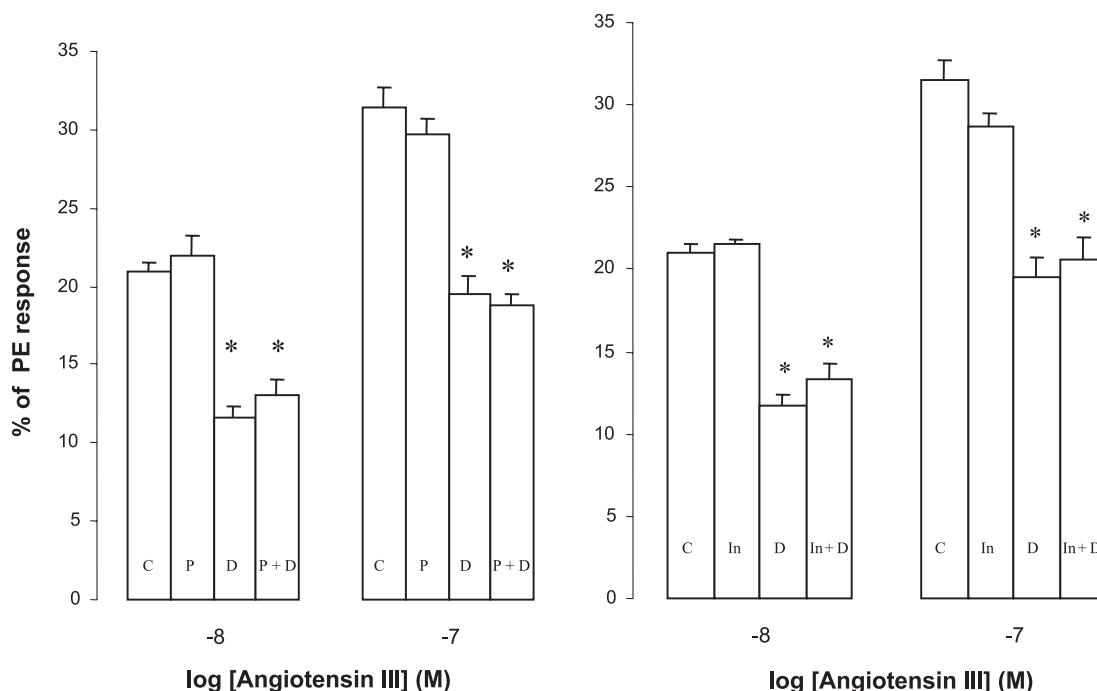
Fig. 6. Effect of PD123319 (left histograms) and indomethacin (right histograms) on the inhibitory effects of DAA-I on the angiotensin III-induced pressure response in the mesenteric vascular bed of the WKY. Alphabets inside histograms: C, control (not treated); P, pretreated with 10^{-5} M PD123319; D, pretreated with 10^{-9} M DAA-I; P + D, pretreated with PD123319 and DAA-I; In, pretreated with 10^{-5} M indomethacin; In + D, pretreated with indomethacin and DAA-I. Each histogram and bar represent the mean ± S.E.M. of four to six separate preparations. *Indicates significant difference from the control.

SHR and 210 ± 25 mm Hg in WKY. The limits of detection of the system were 5–350 mm Hg. Fig. 1 shows the dose response of renal perfusion pressure to angiotensin II in WKY and SHR. The responses to the eight increasing doses of angiotensin II were significantly greater in the SHR than

WKY. Fig. 2 shows the dose response of renal perfusion pressure to angiotensin III in the WKY and SHR. Similar greater responses to the lower doses (10^{-9} and 10^{-8} M) of angiotensin III were seen with the SHR (10.1, 25.6% vs. 1.2, 25.6%, $p < 0.05$). SHR also exhibited a lower threshold
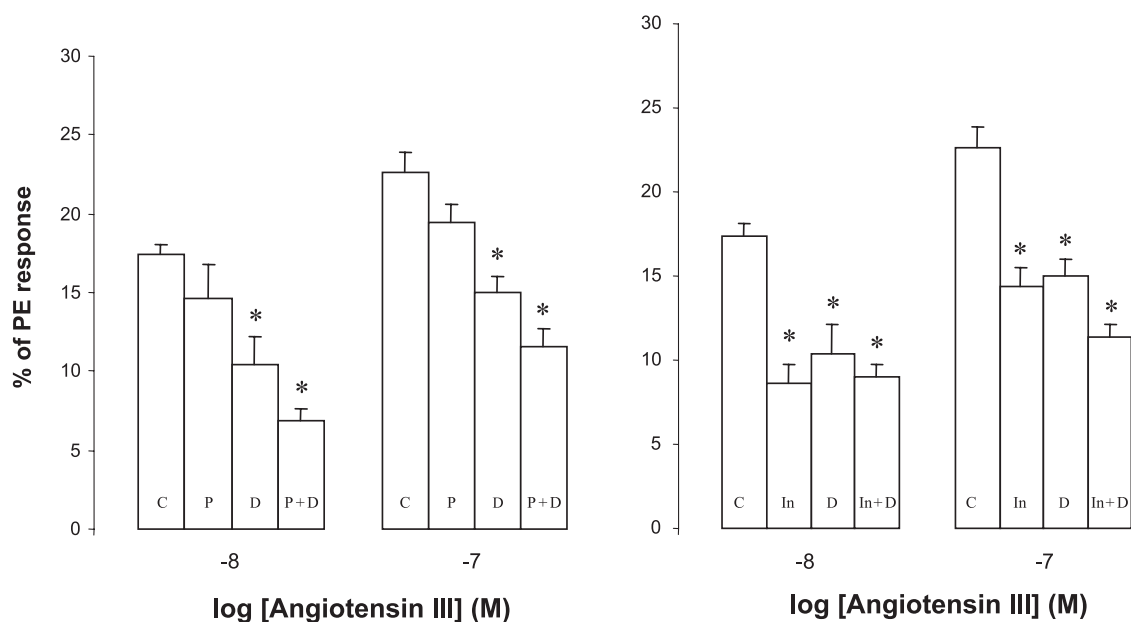

Fig. 7. Effect of PD123319 (left histograms) and indomethacin (right histograms) on the inhibitory effects of DAA-I on the angiotensin III-induced pressure response in the mesenteric vascular bed of the SHR. Alphabets inside histograms: C, control (not treated); P, pretreated with 10^{-5} M PD123319; D, pretreated with 10^{-9} M DAA-I; P + D, pretreated with PD123319 and DAA-I; In, pretreated with 10^{-5} M indomethacin; In + D, pretreated with indomethacin and DAA-I. Each histogram and the bar represent the mean ± S.E.M. of four to six separate preparations. *Indicates significant difference from the control.

response to angiotensin III, i.e., 10^{-10} M as compared to 10^{-9} M for the WKY.

The responses to angiotensin III were attenuated by DAA-I. Responses in the SHR were more markedly attenuated, especially with the lower doses of angiotensin III (see Fig. 2). DAA-I, by itself, did not affect the basal perfusion pressure when used up to a dose of 10^{-9} M (data not shown). Figs. 3 and 4 show that the actions of DAA-I on the response to angiotensin III in the renal vasculature of the WKY and SHR, respectively, were not affected by PD123319 and indomethacin. However, the direct contractile action to angiotensin III in the renal vasculature of the SHR, but not WKY, was attenuated by indomethacin (Fig. 4).

3.2. Mesenteric vasculature

A 10^{-5} M concentration of PE caused an average increase in perfusion pressure of 100 ± 25 mm Hg. This was smaller than the increase recorded with the renal vasculature. Similarly, the response to angiotensin III was also smaller, and the threshold dose was 10^{-8} M. Fig. 5 shows the dose response of mesenteric perfusion pressure to angiotensin III in WKY and SHR. Except for the maximum dose, the responses in SHR (though generally smaller) were not significantly different from those of WKY. DAA-I attenuated the angiotensin III response in both the WKY and SHR. The attenuation was seen with all doses of angiotensin III and was more marked in SHR than WKY and seen . In addition, 10^{-15} M DAA-I was effective in attenuating the response to the maximum dose of angiotensin III. The action of DAA-I on angiotensin III-induced increase in perfusion pressure was not affected by either PD123319 or indomethacin (Figs. 6 and 7). However, as seen with the renal vasculature, the direct contractile action of angiotensin III in the mesenteric vasculature of the SHR, but not WKY, was attenuated by indomethacin (Fig. 7).

4. Discussion

4.1. Renal vasculature

Angiotensin II produced a greater pressor response in the renal vasculature of SHR than WKY. This finding is in line with similar findings reported by earlier investigators [10–12] and served as a good positive control for the present study. Angiotensin III, the immediate metabolite of angiotensin II, induced similar dose–response increases in renal perfusion pressure in both the WKY and SHR. The response was enhanced in the SHR in terms of a lower threshold dose and greater magnitudes of pressor action at lower doses. Plasma levels of angiotensin III in the WKY and SHR are less than 10^{-10} M [14], and the lower threshold seen in the SHR would suggest that its renal vasculature is under the pressor action of the heptapeptide in vivo. The importance of this constant pressor action in the development of

hypertension in SHR remains to be investigated. Of related interest are the findings by Healy and Song [15] showing that aminopeptidase A, the principal enzyme that hydrolyzes angiotensin II to angiotensin III, was significantly higher in the kidneys of SHR than WKY. Under this scenario, angiotensin III could have contributed to the observed enhanced response to angiotensin II in the SHR. Such a possibility requires further study with aminopeptidase A inhibitors as has been carried in the brain to establish that angiotensin III is the active central angiotensin peptide [16]. The SHR is not a high renin hypertension model, and plasma renin activity and plasma renin substrate were not significantly different from the WKY [17]. Plasma ACE activity [18], angiotensin II level [14,19] and angiotensin III level [14] were also found not to be significantly different from the WKY. These findings rule out changes in circulating level of the heptapeptide and its precursors as causes of hypertension and hyperresponsiveness to angiotensin III in the SHR. Various mechanisms such as deficiency in the action of endogenous vasodilator prostaglandins [10] or their release [20], genetically determined enhanced responsiveness [11], greater negative influence on phosphodiesterase-induced increase in cAMP [21], upregulation of angiotensin II receptors [22] and augmented cross-talk in the renal microcirculation between the G_i signal transduction pathway and the signal transduction pathway used by angiotensin II [23] have been alluded to cause hyperresponsiveness to angiotensin II. These open up avenues for further investigation on the mechanisms of angiotensin III hyperresponsiveness and the likelihood of sharing similar mechanisms with angiotensin II.

DAA-I attenuated the pressor actions of angiotensin III in the WKY at a dose of 10^{-9} M. In the SHR, the enhanced responses to lower doses of angiotensin III (10^{-8}–10^{-10} M) were highly susceptible to attenuation by much lower doses of DAA-I. Remarkably, a dose as low as 10^{-15} M DAA-I significantly attenuated the pressor action of angiotensin III. Contractile responses to femtomolar concentrations of angiotensin II has been reported in the saphenous vein of the dog [24] and endothelium-intact rabbit aortic rings [25]. However, the present finding is the first demonstration of a specific attenuation by femtomolar DAA-I that is seen only in the renal vasculature of SHR but not WKY. SHR has significantly lower plasma level of DAA-I than WKY [14]. In an ex vivo preparation like the perfused isolated kidney, the circulating solution was free of DAA-I. Reintroducing DAA-I at concentrations ranging the circulating level attenuated the pressor action of angiotensin III. Hence, in the in vivo situation, circulating DAA-I modulates the action of angiotensin III in the kidneys. Noting that circulating DAA-I was lower in the SHR and the renal vasculature was more responsive to angiotensin III, the modulation would probably be compromised in the SHR. Both indomethacin and PD123319 were without effect on the action of DAA-I, indicating that the AT_2 angiotensin receptors and prostaglandins were not involved in its

actions. In our earlier findings, indomethacin was also found to have no effect on the actions of DAA-I [2]. A recent study by Badzynska et al. [26] showed that AT_2 receptors were also not involved in the vasoconstriction and vasodilatation induced by angiotensin II in kidneys of the rat.

The direct pressor action of angiotensin III in the SHR but not WKY was attenuated by indomethacin. The exact mechanism for this difference is unknown. However, vasodilator prostaglandins are less effective in reducing the pressor response of constricting agents in renal vasculature of the SHR than WKY. U-46619, the stable thromboxane A_2 agonist, has been shown to increase renal perfusion pressure in indomethacin-treated WKY and SHR, and the vasodilator prostaglandins (PGE_2 and PGI_2) attenuated the increase in WKY but not SHR [27]. Similarly, the ability of PGI_2 to attenuate angiotensin II-induced renal vasoconstriction is reduced in the SHR [28]. Hence, it is possible that indomethacin inhibited the formation of both vasoconstrictor and vasodilator prostaglandins, and the decreased responsiveness to vasodilator prostaglandins in the SHR is reflected as an inhibition of angiotensin III action.

4.2. Mesenteric vasculature

Angiotensin III induced smaller increases in perfusion pressure in the SHR than WKY. However, the differences (except for the maximum dose of 10^{-5} M) were not significantly different. Angiotensin III has also been reported to produce similar magnitude of pressor response in periarterial nerve stimulated-perfused mesenteric vascular bed of the WKY and SHR [29]. Pressor responses to angiotensin II in perfused mesenteric bed of the SHR were also not different from those of the WKY [30,31]. The absence of enhanced response to angiotensin III and II in the SHR contrasted markedly to the enhanced response observed in the renal vascular bed and is a notable difference worthy of further investigation especially where angiotensin II is known to produce differential effect in renal circulation [26]. In terms of the effects of DAA-I, indomethacin and PD123319 on angiotensin III action, similar patterns to those of the renal vasculature were observed. This reaffirms that in the perfused kidney and mesenteric bed, where the majority of the vessels are contractile, femtomolar concentrations of DAA-I attenuates the pressor action of angiotensin III. The attenuation is not indomethacin sensitive and does not involve the angiotensin AT_2 receptor.

The roles of DAA-I in hypertension are not known. Earlier studies on aminopeptidase X, the specific enzyme that converts angiotensin I to DAA-I, showed that the hypothalamus [32], plasma and endothelium [33] of SHR contained higher level of the enzyme. Based on these findings, it was theorized that degradation of angiotensin I in certain critical tissues of the SHR is shunted in favor of DAA-I. In such a scenario, the formation of pressor angiotensin II and III would be curtailed, and the formed DAA-I would further attenuate the action of pressor angiotensins.

However, despite the increase in activity of plasma and endothelial aminopeptidase X in the SHR, its plasma DAA-I level is significantly lower than WKY [14]. These findings support the contention that the causes and responses to hypertension are multifactorial.

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