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Compared myocardial and vascular effects of captopril and dihydralazine during hypertension development in spontaneously hypertensive rats

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1 When administered to young spontaneously hypertensive rats (SHRs), dihydralazine (25 mg kg^{-1}, daily) and captopril (100 mg kg^{-1}, daily) prevent with the same efficacy genetic hypertension development (GHD).

2 Dihydralazine treatment increased vascular mesenteric compliance, as shown by a significant decrease in the stiffness of the vessels (−27%), and induced slight reductions in contractility (−12%) and in wall to lumen (W/L) ratio (−15%). After treatment withdrawal, all these parameters returned to control values within 7 weeks, as did blood pressure.

3 Captopril treatment also strongly increased the mesenteric vessels compliance, vessel stiffness being decreased by 16%, and reduced their contractility (−15%) and their W/L ratio (−30%). These effects as well as those exerted on blood pressure persisted up to 7 weeks after treatment ceased although there was a slight trend to a progressive reduction in the intensity of both phenomena.

4 These experiments show that captopril but not dihydralazine has a long-lasting effect in opposing the functional and morphological vascular alterations occurring during GHD in SHRs and this phenomenon probably contributes to a large extent to the sustained preventive effects of the drug against GHD.

Introduction

When administered chronically to young spontaneously hypertensive rats (SHRs) during their growth, captopril strongly inhibits genetic hypertension development (GHD) (Ferrone & Antonaccio, 1979; Giudicelli, Freslon, Glasson & Richer, 1980) and limits myocardial hypertrophy (Antonaccio, Rubin, Horovitz, Laffan, Goldberg, High, Harris & Zaidi, 1979; Giudicelli *et al.*, 1980; Sen, Tarazi & Bumpus, 1980). Furthermore, the preventive effect of captopril against GHD persists for at least up to 12 weeks after treatment ceases and during this period there is, as previously shown (Giudicelli *et al.*, 1980), a close parallelism between the evolution of systolic blood pressure (SBP) and heart weight/body weight ratio (HW/BW), which exhibit a tendency to increase slowly and simultaneously.

In contrast, dihydralazine, a vasodilator drug also effective in preventing GHD in SHRs (Sen, Tarazi, Khairallah & Bumpus, 1974; Hamilton, 1975; Giudicelli, Richer & Freslon, 1981) has no limiting effect on myocardial hypertrophy (Sen *et al.*, 1974; Giudicelli *et al.*, 1981) and no longer opposes GHD as soon as treatment is interrupted (Giudicelli *et al.*, 1981).

Thus, these two compounds, which prevent GHD to the same extent during treatment, differ from each other regarding (a) their effects on myocardial hypertrophy, one of the physiopathological complications occuring in SHRs during GHD (Takatsu & Kashii, 1972; Pfeffer & Frohlich, 1973; Bianchi, Fox & Imbasciati, 1974) and (b) the duration of their efficacy after treatment withdrawal. These differences together with the above-mentioned parallel evolution of SBP and HW/BW after captopril withdrawal suggest that limitation of the pathophysiological complications accompanying GHD in SHRs might be involved in the long-lasting effect of this drug against GHD. Another of these complications occurs at the vascular level and consists in vascular wall thickening and vascular compliance reduction (Folkow, Hallbäck, Lundgren, Sivertsson & Weiss, 1973; Mulvany, Hansen & Aalkjaer, 1978). The present study was

thus designed to determine whether captopril and dihydralazine do also exert differential effects at the vascular level, as they do at the cardiac one, which could explain the differences between their effects vs GHD after treatment ceases.

Methods

Animals

Four-week old male SHRs of the Okamoto Aoki strain were obtained from Charles River France; 120 animals were randomly divided into three groups of 40 each, the rats being housed together in subgroups of 10 animals. They were fed *ad libitum* with standard diet and drank tap water.

Treatments

On their 42nd day of age, 10 animals were randomly selected from each group and immediately used for general, haemodynamic and vascular functional parameters (see below for details) determinations at the age of 6 weeks. Thus, these animals received no treatment.

The remaining 30 animals of groups I, II and III were then assigned the following treatments: group I, distilled water, 1 ml $100g^{-1}$; group II, dihydralazine, 25 mg kg^{-1}, 1 ml $100g^{-1}$ of an aqueous solution; group III: captopril, 100 mg kg^{-1}, 1 ml 100 g^{-1} of an aqueous solution, which were started on the 42nd day of age and pursued up to the 20th week of age.

Captopril and dihydralazine dosages were chosen on the basis of pilot experiments showing that captopril, 100 mg kg^{-1} daily, and dihydralazine, 25 mg kg^{-1} daily (both given orally) were the lowest doses of these drugs that could completely oppose GHD and stabilize SBP at the same level (Giudicelli *et al.*, 1981).

General, haemodynamic and vascular functional parameters

The above parameters were measured: at 6 weeks of age in the 30 animals which received no treatment; at 8 weeks of age, i.e. two weeks after starting the treatment, on 10 animals randomly selected from groups I, II and III; at 20 weeks of age, i.e. after 14 weeks of treatment, on the same number of animals; at 27 weeks of age, i.e. 7 weeks after treatment ceased, in the remaining 10 animals from groups I, II and III. It has previously been shown (Giudicelli *et al.*, 1981) that at this stage SBP of animals previously treated with dihydralazine no longer differs from that of controls while SBP of rats previously treated with captopril is still significantly lower than that of controls.

During treatment periods (8th and 20th weeks of age) parameters were measured 16 h after the last drug administration. The parameters investigated were as follows: (1) general parameter: body weight (BW); (2) haemodynamic parameters: (blood pressure and heart rate) under light ether anaesthesia, a catheter (PE50 and PE10) was inserted into the femoral artery. After complete recovery from anaesthesia, mean blood pressure (MBP) was measured in the conscious state and under light contention. Heart rate (HR) was obtained from the pressure signals (HP 1280 transducer, HP 7702 B recorder, HP 5307 A counter). (3) Vascular functional parameters: after MBP and HR measurements were completed, the animals were immediately anaesthetized with pentobarbitone (50 mg kg^{-1} *i.p.*). After laparotomy, the vascular mesenteric bed was gently spread out and a segment, approximately 0.8 mm in length, of an arterial resistance vessel was removed from the first branches of mesenteric arcades (Ichijima, 1969). This vessel was threaded onto two parallel tungsten wires tied on two supports of a myograph as previously described (Mulvany & Halpern, 1976). During this process, which lasted about 30 min, the vessel was kept cool (15 °C) in Ringer solution. After mounting, the vessels were equilibrated for 1 h before experimentation in a modified Ringer solution containing (mM): NaCl 119, $NaHCO_3$ 14.9, KCl 4.7, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 2.5 and glucose, 5.5. This solution was adjusted to pH 7.4, oxygenated externally with 93% O_2 – 7% CO_2 and circulated around the vessel at 2.5 ml/min at a temperature of 37 ± 0.3 °C.

In a first set of experiments, the passive elastic properties of the vessel were determined by constructing the resting wall tension-internal circumference relationship (see below, definition of parameters) and the normalized internal diameter (NID, see below) was calculated. In a second set of experiments, the active contractile properties of the vessel were then investigated by constructing a dose-contractile response relationship to noradrenaline, from which the noradrenaline ED_{50} and the effective active pressure (EAP, see definition of parameters) were calculated.

Heart and vascular morphological parameters

These parameters were measured at 20 and 27 weeks of age in the same animals in which general, haemodynamic and vascular functional parameters had been determined. The procedure was as follows: after ligation of the mesenteric area, two catheters were inserted in the carotid artery and in the jugular vein respectively for histological preparation. A washing solution followed by a fixation solution (4% formalin and 1% glutaraldehyde in 0.17M phos-

phate buffer) were successively perfused into the carotid artery. The perfusate was allowed to drain through the catheterized jugular vein. Perfusion was non pulsatile from pressurized reservoirs. Perfusion pressure in each rat was maintained at the level of its blood pressure previously measured in the conscious state. Following perfusion, the heart, the aorta and a mesenteric vessel were removed. The heart was cleaned, blotted and weighed. Results are expressed as HW/BW ratio ($mg\,g^{-1}$). The aorta was cleaned and gently stripped along its long axis. Length and weight of the strip were determined and results expressed as the ratio AW (aorta weight, mg)/AL (aorta length, mm). The mesenteric vessel, removed from an area as close as possible to that from which the vessel used for the functional study had been taken, was dehydrated by being placed successively in a graded series of acetone solutions and embedded in Epoxy resin. Transverse sections (0.5 μm thick) were cut with glass knives, mounted on glass slides and stained with toluidine blue. For each vessel, the length of the internal elastic lamina and the cross sectional area were determined for calculation of the wall/lumen ratio according to the method previously described by Furuyama (1962).

Definition of parameters (Figure 1)

Passive wall tension, (PWT): calculated as PWT ($mN\,mm^{-1}$) = F (mN)/2l (mm) where F is the force exerted by the vessel on the tension transducer and l the length of the vessel. Thus PWT expresses circumferential wall force per length unit.

Internal circumference As the vessel was found to be flat between the wires, the internal circumference L was calculated as: $L = (\pi+2)\,d+2f$ where d is the diameter of the wires (25 μm) and f is the distance between the inner edges of the wires (μm).

Resting tension-internal circumference relationship The vessel immersed in the above-mentioned solution, was stretched in steps of 20 μm until the wall tension was 4.5 $mN\,mm^{-1}$. It was maintained at each circumference (L) for a period of 2 min at the end of which the PWT was measured as the wall tension at the internal circumference concerned. For each vessel the experimental curve could be closely fitted with an exponential equation, $PWT = PWTo.e^{\beta L/2\pi}$, where PWTo ($mN\,mm^{-1}$) and β (μm^{-1}) are constants. The β constant reflects the degree of non-linearity of the curve and is in direct relationship to the stiffness or in inverse relationship to the compliance of the vessel.

Normalized internal diameter (NID): NID was defined as the internal diameter corresponding to the point of the fitted exponential curve at which the effective transmural pressure was equal to the MBP in the conscious animal. This point was the intersection of the extension curve and of a line of equation $T = P \times L/2\pi$ (Laplace's equation), where P is MBP

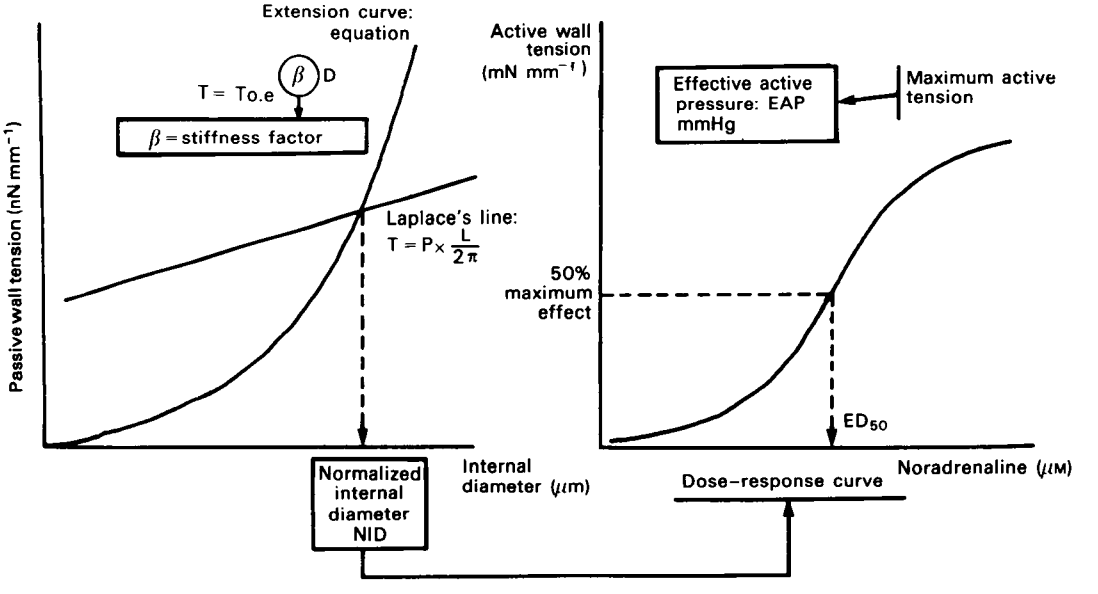

Figure 1 Definitions of parameters used for determination of vascular compliance (extension curve, left panel) and vascular reactivity (dose-response curve, right panel) on mesenteric arterioles.

expressed in mN mm^{-2} and L is expressed in mm.

Thus NID is an estimate of the lumen diameter the vessel would have *in situ* when relaxed and under a transmural pressure equal to MBP (Halpern, Mulvany & Warshaw, 1978).

Dose-response relationship This relationship has been established in the vessel at its NID value by adding increasing concentrations of noradrenaline (ranging from 1.5×10^{-7} to 1.5×10^{-5} M) in the bath. The corresponding values of contractile responses were plotted on a curve with a computer programme using least squares method. The 50% response concentration (effective dose, ED_{50}, and the maximum active wall tension (AWT) at its NID were calculated.

The contractility was normalized by using Laplace's equation to determine the intraluminal pressure against which the vessel would be able to contract when developing its maximum active wall tension. This effective active pressure (EAP) was given by:

$$\text{EAP (mN mm}^{-2}) = \frac{\text{AWT (mN mm}^{-1})}{\text{NID (mm)}/2}$$

Since 1 mN mm^{-2} = 7.5 mm Hg,

$$\text{EAP (mm Hg)} = \frac{\text{AWT (mN mm}^{-1}) \times 15}{\text{NID (mm)}}$$

Drugs

The drugs used were captopril (Squibb) and dihydralazine sulphate (Ciba). Doses are expressed in terms of the salt for dihydralazine.

Expression of results and statistical analysis

Values in Tables 1 and 2 and Figure 2 are expressed as means ± s.e.mean ($n = 10$).

For each parameter, a 2-way analysis of variance was performed using a Tektronix statistical computer programme (2 way-analysis of variance with balanced data). The significance of the differences is

Table 1 Evolution at different periods of the physiological parameters [body weight (BW), mean blood pressure (MBP) and heart rate (HR)] and of the heart and vascular morphological parameters [heart weight to body weight ratio (HW/BW), aortic weight to aortic length ratio (AW/AL) and wall to lumen ratio (W/L)] in the control (C), dihydralazine- (D) and captopril (Cap) -treated rats

	Group	*Age (weeks)*				*ANOVA (P)*		
		6	8	20	27	Age	Treatment	Interaction
			⊢—— Treatment ——⊣					
BW (g)	C	94 ± 9	165 ± 4	321 ± 6	359 ± 5			
	D	113 ± 12	170 ± 4	320 ± 8	355 ± 7	< 0.001	NS	NS
	Cap	103 ± 12	160 ± 5	317 ± 6	353 ± 2			
MBP (mmHg)	C	113 ± 3	120 ± 2	160 ± 2	163 ± 2			
	D	112 ± 5	106 ± 2***	117 ± 3***	156 ± 3	< 0.001	< 0.001	< 0.05
	Cap	115 ± 5	106 ± 2***	117 ± 2***	135 ± 3***			
HR (beats min^{-1})	C	455 ± 16	417 ± 7	434 ± 6	447 ± 8			
	D	432 ± 22	461 ± 14	460 ± 4	454 ± 4	NS	NS	NS
	Cap	430 ± 22	449 ± 13	425 ± 17	436 ± 8			
HW/BW (mg g^{-1})	C			2.83 ± 0.06	2.92 ± 0.05			
	D			2.70 ± 0.04	2.85 ± 0.05	NS	< 0.05	NS
	Cap			2.65 ± 0.05*	2.73 ± 0.05*			
AW/AL (mg mm^{-1})	C			0.47 ± 0.01	0.55 ± 0.01			
	D			0.42 ± 0.01*	0.55 ± 0.01	< 0.001	< 0.001	NS
	Cap			0.40 ± 0.01***	0.49 ± 0.02*			
W/L (10^{-2})	C			8.9 ± 0.4	10.4 ± 0.6			
	D			7.6 ± 0.8	9.0 ± 0.1	NS	< 0.05	NS
	Cap			6.3 ± 0.6**	8.2 ± 0.5*			

Values show mean ± s.e.mean. Significance of differences between groups is shown by *P*-age, *P*-treatment and *P*-interaction. Values significantly different from respective controls: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

indicated in the tables by giving the values of *P*-treatment and *P*-age. When a significant *P*-treatment value is obtained, a comparison of the values measured at a given age in the three groups is performed by means of Student's *t* test. For *P*-interaction, a significant value of this factor (*P*-interaction <0.05) indicates that the concerned parameter develops differently with age in each group of animals.

Results

General and haemodynamic parameters

Table 1 illustrates the evolution of body weight (BW), mean blood pressure (MBP) and heart rate (HR) at the four investigated periods in the three groups of animals. Body weight was not affected by treatment.

While MBP significantly increased with age in the control group (*P*-age <0.001), its evolution was strongly treatment-affected (*P*-treatment <0.001) but in a different way for each drug (*P*-interaction <0.05). Thus, if dihydralazine and captopril strongly opposed (almost to the same extent) the age-related increase in MBP, this effect no longer persisted after treatment withdrawal in the dihydralazine-treated group, while in the captopril-treated group, MBP remained significantly lowered as compared to the 27 weeks old controls.

HR showed no evolution with age in the control group. Captopril and dihydralazine had no effect on HR although there was a slight but not significant increase in this parameter in the dihydralazine-treated group.

Functional vascular parameters

For vascular passive properties, Table 2 shows the evolution of the stiffness factor β and of normalized internal diameter (NID) values in the three groups of animals.

The stiffness factor β showed a progressive and significant increase with age in the control group ($P<0.01$). Dihydralazine induced as early as after 2 weeks of treatment (8th week of age) a slight but significant reduction of this parameter (−14%). At 20 weeks of age, the reduction was even more marked (−27%) but after treatment withdrawal (27th week of age), β value no longer differed from the corresponding control value. In contrast, after two weeks of treatment, there was no difference between the values of the stiffness factor β in the vessels of captopril-treated and control rats. But after 14 weeks of treatment, captopril induced a significant decrease in this parameter (−18%) and this effect was fully maintained seven weeks after treatment discontinuation (−24%).

The treatment-induced variations in NID were qualitatively similar to those of the stiffness factor β. Thus dihydralazine induced an early increase in NID which disappeared when treatment ceased. Con-

Table 2 Evolution at different periods of the functional vascular parameters: passive properties [stiffness factor (β) and normalized internal diameter (NID)] and active properties [ED_{50} and effective active pressure (EAP)] in the control (C), dihydralazine- (D) and captopril (Cap) -treated rats

	Group	*Age (weeks)*				*ANOVA (P)*		
		6	8	20	27	Age	Treatment	Interaction
			⊢——Treatment——⊣					
β	C	8.0±0.8	8.6±0.2	8.9±0.4	9.9±0.5			
($\mu m^{-1} \times 10^{-3}$)	D	7.6±1.1	7.4±0.5*	6.5±0.5**	8.8±0.5	<0.01	<0.05	NS
	Cap	7.8±1.1	8.5±0.3	7.3±0.3**	7.5±0.7*			
NID	C	220±16	220±7	250±8	241±8			
(μm)	D	218±22	241±7*	285±11*	247±11	<0.001	<0.05	NS
	Cap	236±22	222±9	276±7*	294±11***			
ED_{50}	C	1.40±0.12	1.00±0.01	2.08±0.07	2.15±0.10			
(μM)	D	1.30±0.10	1.14±0.03	1.80±0.11	1.90±0.15	<0.001	NS	NS
	Cap	1.35±0.06	1.20±0.01	2.23±0.03	2.20±0.08			
EAP	C	197±10	172±8	273±12	281±15			
(mmHg)	D	208±8	190±15	240±6*	260±13	<0.001	<0.05	NS
	Cap	207±9	180±14	234±8*	239±17			

Values show mean ± s.e.mean. Significance of differences between groups is shown by *P*-age, *P*-treatment and *P*-interaction. Values significantly different from respective controls: $*P<0.05$; $**P<0.01$; $***P<0.001$.

versely, the captopril-induced elevation of NID developed only after 14 weeks of treatment but persisted up to seven weeks after treatment withdrawal.

Figure 2 illustrates the extension curves determined in the three groups of animals at 8, 20 and 27 weeks of age respectively. It is clear from this figure that dihydralazine induces an early shift to the right of the control extension curve, which is not the case for captopril (8th week of age, Figure 2a). At 20 weeks of age, both drugs induce a similar shift to the

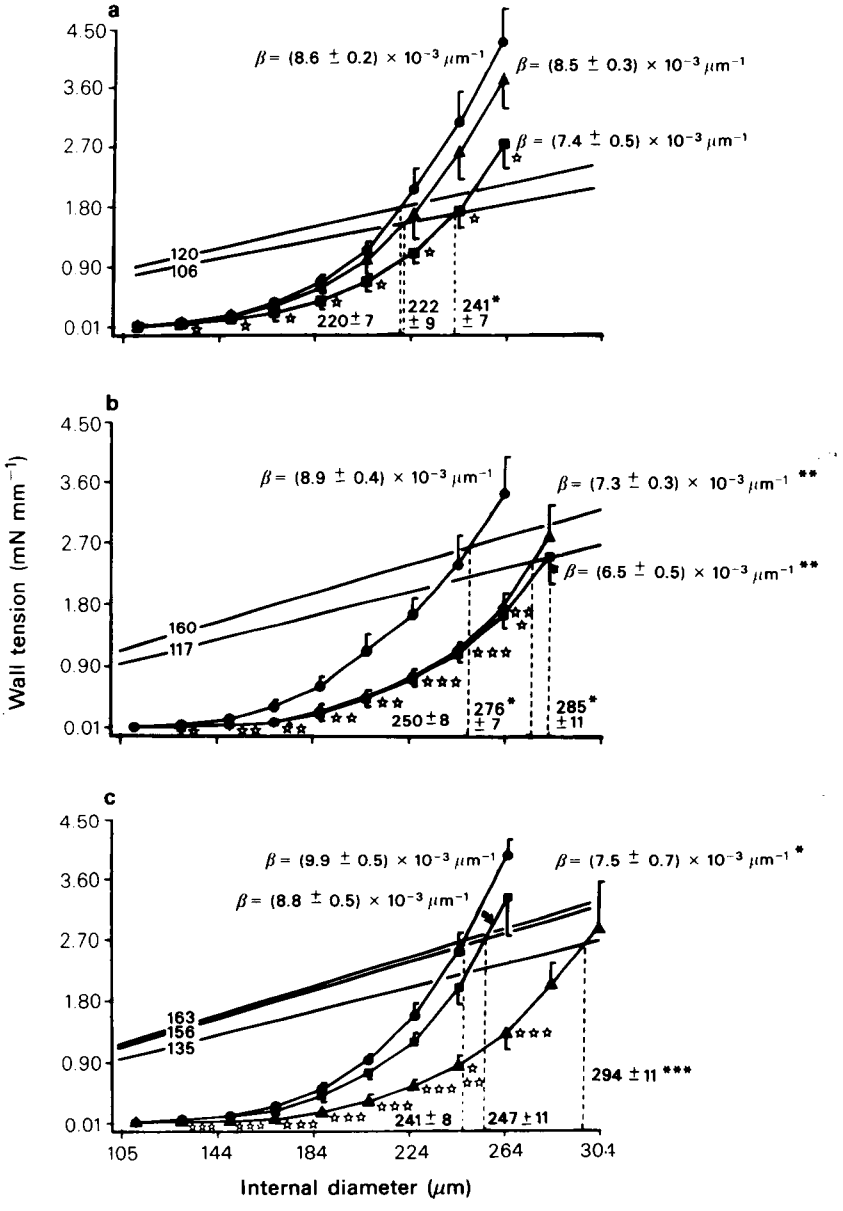

Figure 2 Passive extension curves of control (●), dihydralazine- (■) and captopril-treated (▲) spontaneously hypertensive rats' mesenteric arteries at the 8th week of age (after 2 weeks of treatment, a), at the 20th week of age (after 14 weeks of treatment, b) and at the 27th week of age (7 weeks after treatment withdrawal, c). In each panel, values are indicated for the stiffness factor (β) and normalized internal diameters (NID). Numbers within lines give values of intraluminal pressure (mmHg) from which the equations of the lines have been calculated, using Laplace's law. Values significantly different from control: $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

right of the extension curve (Figure 2b) but after 7 weeks of treatment withdrawal, only the captopril-induced shift is maintained (Figure 2c)

Regarding vascular active properties, Table 2 shows the evolution of the ED_{50} and effective active pressure (EAP) values in the three groups of animals.

ED_{50}s and EAPs tended to increase with age in the control group. In the dihydralazine- and captopril-treated groups, ED_{50}s were not modified during or after treatment. In contrast, after 14 weeks of treatment, both captopril and dihydralazine significantly reduced EAPs as compared to controls, but this effect had disappeared 7 weeks after treatment withdrawal.

Morphological parameters

Table 1 illustrates the evolution of heart weight-body weight ratio (HW/BW), aorta weight-aorta length ratio (AW/AL) and wall to lumen ratio in the three groups of animals, at the 20th and 27th weeks of age.

HW/BW ratio in captopril-treated rats was significantly decreased not only during treatment but also up to 7 weeks after treatment withdrawal. Conversely, this parameter remained unaffected by dihydralazine.

AW/AL ratio was significantly reduced by both dihydralazine (−10%) and captopril (−15%) after a 14-week treatment period; 7 weeks after treatment ceased, this effect disappeared in the dihydralazine-treated group but persisted in the captopril-treated group.

The wall to lumen ratio was significantly decreased by captopril during treatment but also up to 7 weeks after treatment ceased. Dihydralazine had no effect on this parameter. Furthermore, in the captopril-treated group, a slight but significant reduction in the wall to lumen ratio was still present up to 7 weeks after treatment ceased.

Discussion

Our results confirm that adequate oral dosing of SHRs with either captopril (100 mg kg^{-1}, daily) or dihydralazine (25 mg kg^{-1}, daily) is able to prevent genetic hypertension development (GHD) up to the 20th week of age, maintaining blood pressure at very low and approximately similar levels (117 ± 2 mmHg for captopril and 117 ± 3 mmHg for dihydralazine). As previously shown (Ferrone, Heran & Antonaccio, 1980; Giudicelli *et al.*, 1980; Koike, Katsuaki, Miyamoto & Nishino, 1980; Giudicelli *et al.*, 1981), both drugs exert their preventive effect mainly by opposing the progressive increase in peripheral resistance which normally develops in SHRs during their growth (Tobia, Lee & Walsh, 1974). However, after treatment ceased while blood pressure of previously captopril-treated SHRs is still significantly lower than in controls up to 7 weeks after treatment withdrawal, in the previously dihydralazine-treated SHRs blood pressure is at the same time no longer significantly different from that of controls. These results, together with the differential effects of the two drugs on HW/BW (Giudicelli *et al.*, 1980; 1981), suggest that the mechanisms by which they oppose GHD are different and prompted us to investigate whether the differences previously observed at the cardiac level could also be found at the vascular one. Therefore, we have compared in SHRs during and after captopril- and dihydralazine-treatments the evolution of (a) the passive extension properties and (b) the active contractile properties of small resistance vessels, namely the mesenteric arteries, by using the technique described by Mulvany & Halpern (1976). At the same time, the morphological changes which occurred in the aorta and the mesenteric arteries were also investigated.

The technique of Mulvany & Halpern (1976) allows investigations on small resistance arteries of 100 μm internal diameter, i.e. those mostly involved in peripheral resistance (Mulvany & Halpern, 1977). Another advantage of this method is that vessels' passive and active wall tensions are measured in a functional configuration which is closely related to the circumferential orientation of the smooth muscle cells at this level, thus allowing application of Laplace's law (Mulvany & Halpern, 1977).

The passive stress-strain relationship which we studied with this model closely fitted with theoretical exponential curves of equation $PWT = PWTo.e^{\beta L/2\pi}$, as demonstrated previously on larger vessels (Roach & Burton, 1957) and small mesenteric arteries (Mulvany & Halpern, 1977; Mulvany & Warshaw, 1979). The β constant was used to quantify the stiffness of the extension curve, which is inversely related to the compliance of the vessel. Normalization of its internal diameter was performed according to Mulvany & Halpern (1977) but at an intraluminal pressure identical to that which the vessel was exposed to *in vivo*. The aim of this procedure was to obtain wall tensions and internal diameters as close as possible to those the vessel has *in vivo*.

It appears from our results that there are at least three types of clear-cut differences between the vascular effects of captopril and dihydralazine.

First, regarding the evolution of the small mesenteric arteries compliance, dihydralazine induced as early as after two weeks an increase in this parameter which persisted during the whole treatment period (Table 2, Figure 2, a and b) but had disappeared 7 weeks after treatment withdrawal (Table 2, Figure 2, c). Results in the literature are conflicting concerning the effects of hydralazine on vascular extensibility.

Thus our experimental data are in agreement with those of Greenberg (1980) who observed a dose-related decrease in passive stiffness of mesenteric arteries taken from hydralazine-treated SHRs but conflict with those of Seidel, Allen & Bowers (1980) who found no effects of the drug either on the passive elastic properties or on arterial elastin and collagen content. But it must be emphasized that these authors used lower dosages than those of Greenberg (1980) and than ours. On the other hand, captopril exerted a delayed but sustained action on the vessels' passive elastic properties. Vascular compliance was still increased 7 weeks after treatment discontinuation (Table 2, Figure 2c) and at this stage, its value was not different from that observed at the end of the captopril-administration period (Table 2), thus demonstrating that the drug is able to induce long-lasting changes in the mechanical properties of SHRs' mesenteric vasculature.

Second, regarding the evolution of vascular active contractile properties, it appears that dihydralazine did not affect the mesenteric vascular sensitivity to noradrenaline (Table 2), in agreement with the data published by Seidel *et al.* (1980). After 14 weeks of treatment, dihydralazine significantly reduced effective active pressure, and this effect was related to both a decrease in AWT and an increase in NID. These data fit with those of Greenberg (1980) and Seidel *et al.* (1980) who observed a reduction in maximum contractile tension with hydralazine. But it must be emphasized that this effect did not persist when treatment was interrupted (Table 2). Captopril also did not affect the mesenteric vascular sensitivity to noradrenaline in our *ex vivo* experiments, although it has previously been shown to affect post-junctionally vascular α-adrenoceptor responsiveness both *in vitro* (Okuno, Kondo, Konishi, Saruta & Kato, 1979; Casellas, Mimran, Dupont & Chevillard, 1980; Collis & Keddie, 1981) and *in vivo* (Antonaccio & Kerwin, 1981; Spertini, Brunner, Waeber & Gavras, 1981; Timmermans, Wilffert, Kalkman, Thoolen, Van Meel, De Jonge & Van Zwieten, 1982). The captopril-induced decrease in EAP (Table 2) was mainly due to a decrease in AWT and hence to an increase in NID. This result is in agreement with *ex vivo* and *in vitro* data from Kikta & Fregly (1980; 1982) but conflicts with the *ex vivo* data published by Antonaccio, Rubin & Kotler (1981). The reasons for the above mentioned discrepancies are unknown but it may be speculated that the reduced EAP observed is related to the decrease of the vascular wall hypertrophy as supported by the evolution of the wall-lumen ratio in the captopril-treated group (Table 1).

Third, our morphological data afford additional evidence for the differential effects of the two drugs on heart and vessels. Thus, dihydralazine, after 14 weeks of treatment, did not affect SHRs' myocardial hypertrophy, confirming previous results (Sen *et al.*, 1974; Giudicelli *et al.*, 1981), and induced a moderate reduction in AW/AL. This effect, which has disappeared 7 weeks after treatment ceased, had not been observed by Yamori, Nakada & Lovenberg (1976) who found the drug devoid of any effect on SHRs' heart and aorta weights and by Seidel *et al.* (1980) who reported no changes in average weight, total protein and DNA contents of aortae taken from hydralazine-treated SHRs. However, the duration of treatment in these two studies was much shorter than in our experiments. On the other hand, our results show that captopril simultaneously induces important and long-lasting decreases in myocardial and in aortic wall hypertrophy (Table 1). This effect not only develops during the treatment period (Antonaccio *et al.*, 1979; Sen *et al.*, 1980), but also persists up to 7 weeks after treatment withdrawal, confirming our previous data (Giudicelli *et al.*, 1980). At the mesenteric vascular level, the captopril-induced long-lasting decrease in wall-lumen ratio might partially explain the persistance of an augmented vascular compliance and of a reduced contractile ability, as indicated by the stability of the β stiffness factor between the 20th and 27th weeks of age (Table 2) and the slight, although not significant, reduction of the effective active pressure still present at the 27th week (Table 2).

Thus our experiments show that if dihydralazine and captopril both oppose GHD to the same extent during treatment, these drugs (a) exert differential effects on functional and morphological vascular properties and (b) differ in the duration of their action after treatment discontinuation. These differences could be due to the fact that, while opposing the age-related increase in peripheral resistance, dihydralazine simultaneously augments sympathetic tone (HR remains slightly increased 16 h after the last drug administration, Table 1) and stimulates the renin-angiotensin system, increasing plasma renin activity (Ueda, Yagi & Kaneko, 1968; Pettinger, Campbell & Keeton, 1973; Sinaiko, 1981) while conversely, captopril simultaneously reduces sympathetic activity (Muirhead, Prewitt, Brooks & Brosius, 1978; Giudicelli *et al.*, 1980; Rubin & Antonaccio, 1980) and suppresses angiotensin II synthesis (Rubin & Antonaccio, 1980; Unger, Yukimura, Marin-Grez, Lang, Rascher & Ganten, 1982). Sympathetic activity is known to exert trophic influences on the heart (Sen, Tarazi & Bumpus, 1977; Frohlich & Tarazi, 1979) and on the vascular wall (Yamori *et al.*, 1976; Hart, Heistad & Brody, 1980). These effects are also shared by angiotensin II either directly (Khairallah, Robertson & Davila, 1972) or indirectly by sympathetic activity potentiation (Malik & Nasjletti, 1976). The sympathetic stimulation pro-

voked by the dihydralazine-induced haemodynamic changes probably counteracts permanently the beneficial influences of the inhibition of blood pressure rise with age on heart and blood vessels morphology and function and this could explain why dihydralazine exhibits no long-lasting effects on SHRs' cardiac and vascular tissues. On the other hand, the captopril-induced sustained blockade of angiotensin II formation probably largely contributes to the abolition of the trophic effects exerted by this peptide, particularly since (a) there is in the vascular wall a complete renin-angiotensin system (Gould, Skeggs & Kahn, 1964; Swales, 1979; Re, Fallon, Dzau, Quay & Haber, 1982) which has been claimed to be involved in the local regulation of vascular contractility (Swales, 1979) and in the aetiology and/or maintenance of hypertension (Garst, Koletsky, Wisenbaugh, Hadady & Matthews, 1979; Thurston, Swales, Bing, Hurst & Marks, 1979; Asaad & Antonaccio, 1982) and (b) this system can be reached (Antonaccio & Kerwin, 1981; Asaad & Antonaccio, 1982) and inhibited (Cohen & Kurz, 1982; Velletri & Bean, 1982) by chronically administered captopril. The resulting reduction in vascular wall hypertrophy could explain the captopril-induced long-lasting vascular functional modifications and the duration of the drug's preventive effects against GHD after treatment withdrawal.

In conclusion, all our results clearly demonstrate the importance of (a) dihydralazine- and captopril-induced increases in vascular compliance for the onset and maintenance of GHD preventive effects during treatment and of (b) vascular morphological modifications induced by chronic converting enzyme inhibition on the duration of GHD preventive effects after treatment ceases.

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