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INFLUENCE OF ANTI-HYPERTENSIVE DRUG TREATMENT ON VASCULAR REACTIVITY IN SPONTANEOUSLY HYPERTENSIVE RATS

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1 The effect of prolonged anti-hypertensive drug treatment on the blood pressure of conscious spontaneously hypertensive rats (SH-rats), and of age-matched normotensive Sprague-Dawley rats was determined during the development of hypertension in SH-rats and in the early stages of established hypertension. A comparison of the vascular reactivity to noradrenaline (NA) and 5-hydroxytryptamine (5-HT) was also made in isolated perfused mesenteric artery preparations from treated and control SH- and Sprague-Dawley rats.

2 Chronic treatment from age 4 to 16 weeks with hydrallazine alone, or a combination of hydrallazine/hydrochlorothiazide/reserpine, *ad libitum* in the drinking water, prevented the development of hypertension in SH-rats and also reduced the vascular reactivity to NA and 5-HT in isolated vessel preparations from treated compared to control rats.

3 Similar drug treatments started in early established hypertension reduced blood pressure in SH-rats over the 12 week treatment period (from age 8 to 20 weeks) without affecting vascular reactivity to NA and 5-HT in the isolated vessel preparation.

4 Drug treatments had little effect on blood pressure of age-matched Sprague-Dawley rats and no effect on vascular reactivity to NA and 5-HT in the isolated perfused mesenteric artery preparation from treated compared to control rats.

5 These results indicate that the development of increased vascular reactivity and of hypertension in SH-rats occurs simultaneously and, therefore, the vascular changes may be a consequence of the structural changes induced by the raised blood pressure.

6 In established hypertension, no regression of vascular changes was observed despite prolonged reduction of blood pressure. The rôle of an increased vascular reactivity in the maintenance of hypertension is therefore questionable.

Introduction

Folkow, Grimby & Thulesius (1958) suggested that the raised peripheral vascular resistance in essential hypertension in man may be largely due to structural changes in the resistance vessels. The raised blood pressure may induce these adaptive structural changes so that an increased wall/lumen ratio develops and is responsible for the increased vascular reactivity to vasoconstrictor stimuli in hypertensive, compared to normotensive, states (Folkow, 1956; Folkow *et al.*, 1958; Folkow & Sivertsson, 1968; Folkow, Hallbäck, Lundgren & Weiss, 1970a; Hallbäck, Lundgren & Weiss, 1974).

Experimental data support these theoretical derivations and demonstrate that an increased vascular reactivity to vasoconstrictor stimuli exists in clinical hypertension (Conway, 1963; Sivertsson & Oleander, 1968) and in different types of experimental hypertension in rats whether in the whole animal preparation (Folkow *et al.*, 1970a) or in perfused hindquarters (Folkow, Hällback, Lundgren & Weiss, 1970b) or isolated perfused mesenteric artery preparation (Haeusler & Haefely, 1970; Haeusler & Finch, 1972). However, the work of others (Bandick & Sparks, 1970; Bohr & Sitrin, 1970; Harris, 1972; Holloway & Bohr, 1973) suggests that the adaptive structural changes lead to the individual smooth muscle cells becoming supersensitive to vasoconstrictor stimuli.

More recently it has been shown that interference with the development of hypertension in spontaneously hypertensive rats (SH-rats) by immunosympathectomy (Folkow, Hällback, Lundgren & Weiss, 1972), anti-hypertensive drugs (Weiss, 1974; Weiss, Lundgren & Folkow, 1974) or by the production of regional hypotension by aortic clipping (Folkow, Gurevich, Hällback, Lundgren & Weiss, 1971) alters the vascular activity of the perfused hindquarters to noradrenaline; in renal hypertensive rats, removal of the renal artery clip results in a fall in blood

pressure and regression of vascular changes (Lundgren, 1974). However, in established hypertension, the work of Weiss (1974) and of Weiss *et al.* (1974) indicates that the regression of vascular changes is less likely and none was observed in deoxycorticosterone acetate (DOCA)/saline hypertensive rats after short-term anti-hypertensive treatment (Finch, 1974).

In the present study the relationship between the level of blood pressure in SH-rats and vascular reactivity to noradrenaline and 5-hydroxy-tryptamine in the isolated mesentery preparation has been investigated by preventing the development of hypertension in these rats by continuous anti-hypertensive drug therapy; in addition SH-rats were subjected to similar therapy in the early stages of established hypertension to determine whether the structural changes regressed after reduction of the elevated blood pressure to approximately normotensive levels for 12 weeks.

Methods

Age-matched female spontaneously hypertensive rats (SH-rats) (Japanese strain; Okamoto & Aoki, 1963) and female Sprague-Dawley rats were used for these studies.

Isolated perfused mesenteric artery preparation

For the determination of vascular reactivity to noradrenaline (NA) and 5-hydroxytryptamine (5-HT) in this preparation, rats were anaesthetized with ether and after cannulation of the superior mesenteric artery the mesentery was isolated as described by McGregor (1965).

The isolated preparation was floated on the surface of a 50 ml organ bath filled with Krebs-Henseleit solution at 37° C and bubbled with 95% O_2 and 5% CO_2 (Haeusler & Haefely, 1970). The preparation was perfused through the cannulated mesenteric artery with Krebs-Henseleit solution at a constant flow rate of 6-8 ml/min (to give a basal perfusion pressure of approximately 40 mmHg); perfusion pressure was recorded with a Statham P23Db pressure transducer.

Dose-response curves to NA and 5-HT were obtained by injecting these drugs into the perfusion system just anterior to the cannulated artery. Single injections (10 μl) were given at 2 min intervals and the maximum increase in perfusion pressure was recorded.

Indirect measurement of blood pressure

Before the *in vitro* experiments, and during the course of anti-hypertensive treatment described below, systolic blood pressure was measured in the conscious rat by the indirect tail cuff method, using the appropriate size of sensor and pressure cuff (W + W recorder); body weight was also recorded before the *in vitro* study.

Anti-hypertensive drug treatment

Preliminary studies showed that the blood pressure of female SH-rats rose from normotensive levels of 130 mmHg at an age of 5 weeks to 180 mmHg at 8 weeks of age and that from 9 to 20 weeks of age blood pressure was maintained at 200 mmHg.

Table 1 Effect of anti-hypertensive drug treatment on the development of hypertension in spontaneously hypertensive rats and on the blood pressure of age-matched normotensive Sprague-Dawley rats

Animals	*Treatments*	*Blood pressure (mean ± s.e. mean) (mmHg) at age (weeks)*		
		7	*13*	*16*
Spontaneously hypertensive rats	Water (n = 16)	180.7 ± 3.3	207.9 ± 3.8	196.6 ± 2.6
	Hydrallazine/reserpine/ hydrochlorthiazide (n = 7)	150 ± 2.7 ($P < 0.001$)	144.4 ± 1.9 ($P < 0.001$)	132.6 ± 4.6 ($P < 0.001$)
	Hydrallazine (n = 7)	152 ± 6 ($P < 0.001$)	162 ± 7.2 ($P < 0.001$)	138.6 ± 5.1 ($P < 0.001$)
Normotensive Sprague-Dawley rats	Water (n = 16)	127 ± 1.8	–	130 ± 1.8
	Hydrallazine/reserpine/ hydrochlorthiazide (n = 16)	130 ± 2.6 ($P > 0.05$)	–	110 ± 4.4 ($P < 0.001$)
	Hydrallazine (n = 8)	135 ± 3.5 ($P > 0.05$)	–	131.6 ± 3 ($P > 0.05$)

Treatment was started at age 4 weeks; for details of treatments see Methods section; n is the number of rats per group; P values indicate significant difference from water-treated control group.

Drug treatments were started at an age of 4 weeks, i.e. before the development of hypertension and at an age of 8 weeks, i.e. in the early stages of established hypertension.

Groups of SH-rats aged 4 weeks, received the following combination of anti-hypertensive drugs *ad libitum* in their drinking water: hydrallazine 80 mg/l, hydrochlorothiazide 100 mg/l, reserpine 1.0 mg/l or hydrallazine 80 mg/l alone. Treatment was continued for 12 weeks (to 16 weeks of age); control groups received water alone. Age-matched Sprague-Dawley rats were subjected to the same treatment or received water alone. Groups of SH-rats and Sprague-Dawley rats, aged 8 weeks, received the same treatments as the younger rats for a period of 12 weeks (to 20 weeks of age).

Drugs used were hydrallazine hydrochloride (Ciba), hydrochlorothiazide (MSD), 5-hydroxytryptamine creatinine sulphate (5-HT), noradrenaline bitartrate (NA) and reserpine (Koch-Light). Doses of hydrochlorothiazide, 5-HT and NA are expressed as base.

Results

Effect of anti-hypertensive drug therapy on the development of hypertension in SH-rats

Table 1 shows that each drug treatment effectively prevented the development of hypertension in SH-rats whilst blood pressure rose over the same 12 week period in SH-rats drinking water alone. Three weeks after treatment started (7 weeks of age) the blood pressure of each treated group was in the region of 150 mmHg compared to a value of 180 mmHg in the untreated control group; after 12 weeks treatment (16 weeks of age) the blood pressure of the hydrallazine/hydrochlorothiazide/reserpine group was 60 mmHg lower than that of the control group whilst that of the hydrallazine alone group was 60 mmHg lower than that of the untreated SH-rats.

Apart from a significant reduction, at 16 weeks of age, of 20 mmHg in the hydrallazine/hydrochlorothiazide/reserpine group, the blood pressure of Sprague-Dawley rats subjected to drug therapy did not differ from that of Sprague-Dawley rats drinking water alone.

Effect of anti-hypertensive drug therapy on the blood pressure of SH-rats with established hypertension

Throughout the 12 week treatment period each drug treatment significantly lowered the blood pressure of SH-rats compared with that of untreated SH-rats (Table 2). After 12 weeks treatment (age 20 weeks) the blood pressure of the hydrallazine/hydrochlorothiazide/reserpine group was approximately 100 mmHg lower than that of control rats drinking water whereas that of the hydrallazine group was approximately 90 mmHg lower than that of the control rats.

After 12 weeks of similar treatments the blood pressure of treated normotensive Sprague-Dawley rats was not significantly different from that of control Sprague-Dawley rats (Table 2).

Table 2 Effect of anti-hypertensive drug treatment on the blood pressure of spontaneously hypertensive rats in the early stages of established hypertension and on the blood pressure of age-matched normotensive Sprague-Dawley rats

Animals	*Treatments*	*Blood pressure (mean ± s.e. mean) (mmHg) at age (weeks)*			
		7 (pre-dose)	*10*	*16*	*20*
Spontaneously hypertensive rats	Water ($n = 8$)	190 ± 5	197 ± 2.5	195 ± 5.2	209 ± 5
	Hydrallazine/reserpine/ hydrochlorthiazide ($n = 9$)	189 ± 4.6 ($P > 0.05$)	149 ± 3.4 ($P < 0.001$)	116 ± 3 ($P < 0.001$)	111 ± 4.3 ($P < 0.001$)
	Hydrallazine ($n = 8$)	–	151 ± 5 ($P < 0.001$)	128 ± 4.2 ($P < 0.001$)	129 ± 5.9 ($P < 0.001$)
Normotensive Sprague-Dawley rats	Water ($n = 8$)	–	127 ± 2.6	131 ± 3	125.7 ± 3.1
	Hydrallazine/reserpine/ hydrochlorthiazide ($n = 9$)	–	140 ± 4.3 ($P < 0.02$)	135 ± 7 ($P > 0.05$)	126 ± 7.6 ($P > 0.05$)
	Hydrallazine ($n = 8$)	–	137.3 ± 3.3 ($P < 0.02$)	133 ± 5 ($P > 0.05$)	128 ± 3.2 ($P > 0.05$)

Treatment was started at age 7 weeks; n is the number of rats per group; P values indicate significant difference from water-treated control group.

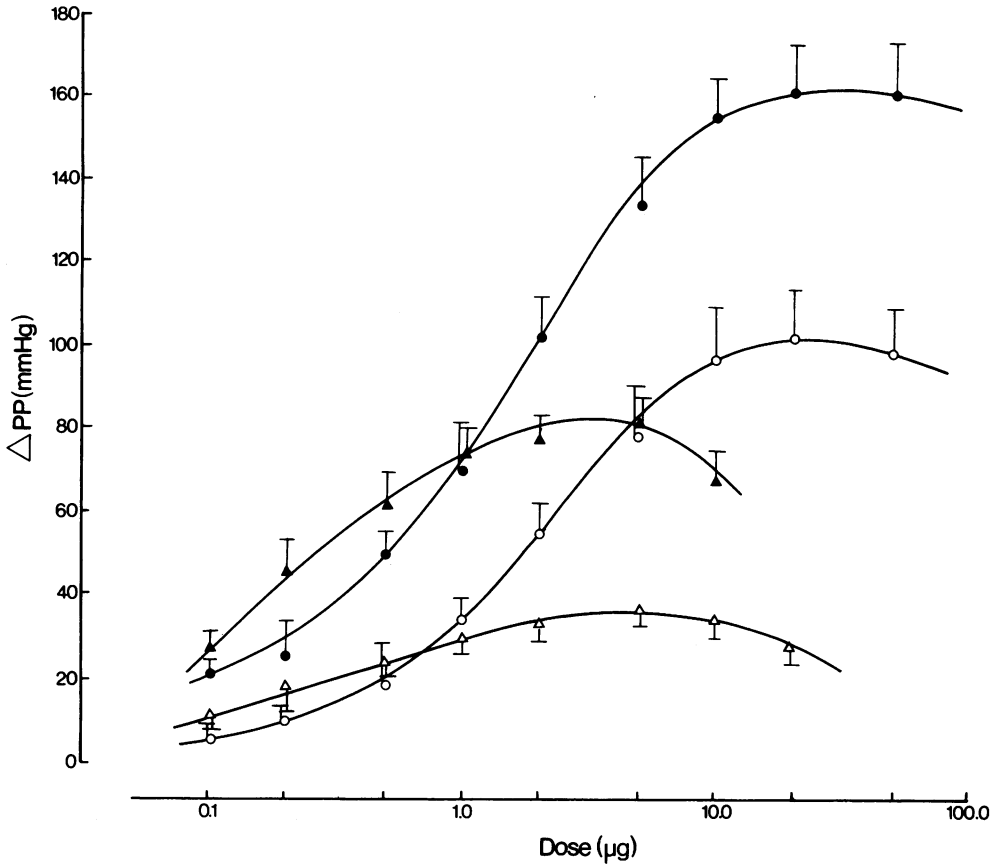

Figure 1 Dose-response curves for the increase in perfusion pressure (△PP) (mmHg) produced by noradrenaline (NA) and 5-hydroxytryptamine (5-HT) in isolated perfused mesenteric artery preparations from age-matched spontaneously hypertensive rats drinking water (controls) or treated with water containing hydrallazine/hydrochlorothiazide/reserpine, from age 4 to 16 weeks. From control rats, for NA responses (●) $n = 8$, BP = 206 ± 5.2 mmHg, body weight = 207 ± 3 g and for 5-HT responses, (▲) $n = 8$, BP = 196 ± 4.2 mmHg, body weight = 205.5 ± 3 g. From treated rats, for NA responses (○) $n = 8$, BP = 125 ± 8.2 mmHg, body weight = 196 ± 4.5 g and for 5-HT responses (△) $n = 8$, BP = 127 ± 7.5 mmHg, body weight = 191 ± .3 g. Mean values with s.e. mean are shown or quoted.

Vascular reactivity to noradrenaline and 5-hydroxytryptamine in isolated perfused mesentery preparation

Since Sprague-Dawley rats were used as controls, and not rats of the Wistar strain from which the Japanese strain of SH-rats were originally derived, no attempt is made to compare the vascular reactivity to NA and 5-HT of preparations from SH-rats with that of Sprague-Dawley rats. The Sprague-Dawley rats were considered to serve as adequate controls for the determination of any effect of the drug treatments *per se* on vascular reactivity to NA and 5-HT

Effect of prevention of development of hypertension in SH-rats on vascular reactivity

After treatment from age 4 to 16 weeks with a combination of hydrallazine/hydrochlorothiazide/reserpine, during which time the development of hypertension in SH-rats was prevented (Table 1), the vascular reactivity to NA and 5-HT of 16-week-old SH-rats was significantly reduced compared to that of water-treated SH-rats (Figure 1). However, the vascular reactivity to those amines of preparations from treated and control Sprague-Dawley rats did not differ (Figure 2). Similarly anti-hypertensive therapy by hydral-

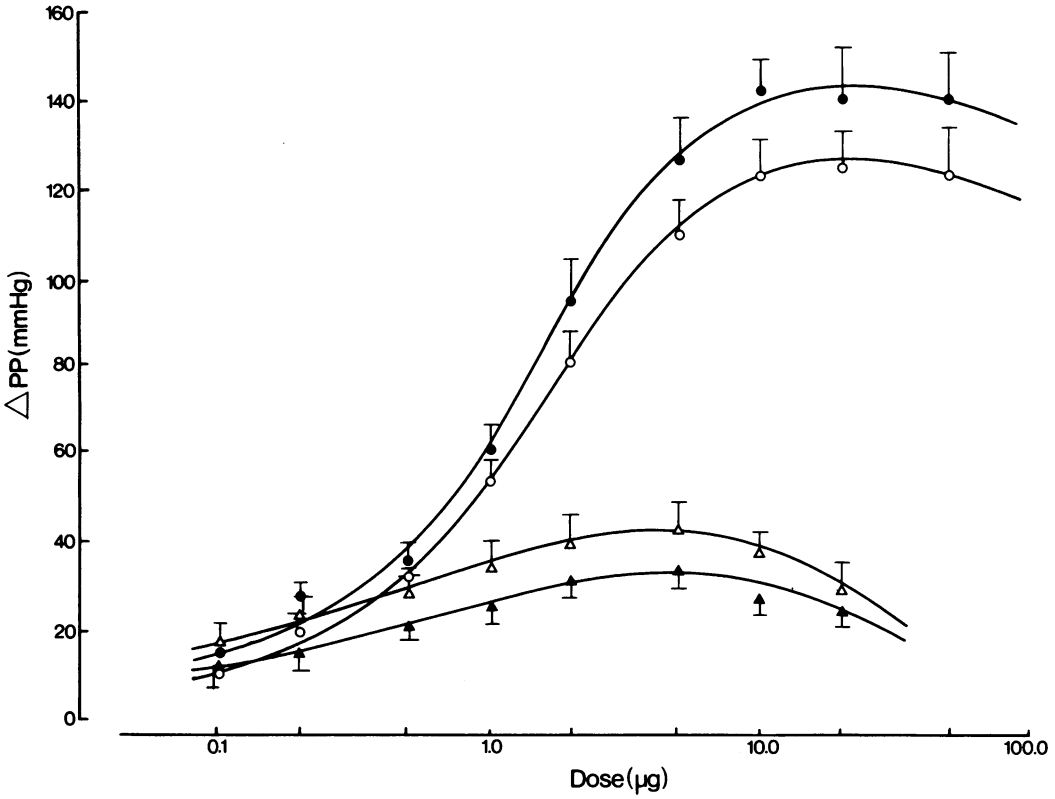

Figure 2 Dose-response curves for the increase in perfusion pressure (△PP) (mmHg) produced by noradrenaline (NA) and 5-hydroxytryptamine (5-HT) in isolated perfused mesenteric artery preparations from age-matched normotensive Sprague-Dawley rats drinking water (controls) or treated with water containing hydrallazine/hydrochlorothiazide/reserpine, from 4 to 16 weeks. From control rats, for NA responses (●) n =7, BP = 128 ± 3 mmHg, body weight = 235 ± 3.2 g and for 5-HT responses (▲) n = 7, BP = 129 ± 3 mmHg, body weight = 246 ± 5.5 g. From treated rats, for NA responses (△) n = 7, BP = 105 ± 4 mmHg, body weight = 233 ± 6.99 g and for 5-HT responses (△) n = 7, BP = 99 ± 3.4 mmHg, body weight = 228 ± 5 g. Mean values with s.e. mean are shown or quoted.

lazine alone reduced the vascular reactivity to NA and 5-HT of 16 week SH-rats but did not affect those of similarly treated Sprague-Dawley animals.

Effect of anti-hypertensive drug treatment on vascular reactivity in established hypertension

After treatment from age 8 to 20 weeks with hydrallazine/hydrochlorothiazide/reserpine the vascular reactivity to NA and 5-HT of 20-week-old SH-rats was not significantly different from that of water-treated controls (Figure 3). The vascular reactivity to NA and 5-HT of preparations from age-matched Sprague-Dawley rats did not differ from that of water-treated controls. Similarly, treatment with hydrallazine alone did not affect vascular reactivity to NA and 5-HT in preparations from either SH-rats or Sprague-Dawley rats.

Discussion

As shown by others (Okamoto & Aoki, 1963; Freis, Regan, Pillsbury & Matthews, 1972) the development of hypertension in spontaneously hypertensive rats occurred from birth until the animals were 3-4 months of age. This growth period is therefore critical for the development of raised blood pressure and for this reason chronic anti-hypertensive therapy intended to prevent the development of hypertension was started at 4 weeks of age; other workers (Freis *et al.*, 1972; Weiss *et al.*, 1974) considered that starting drug treatment at 10 weeks of age was adequate.

The hydrallazine/hydrochlorothiazide/reserpine drug combination used as anti-hypertensive therapy in the present investigation was found, as reported by Freis *et al.* (1972), to prevent the

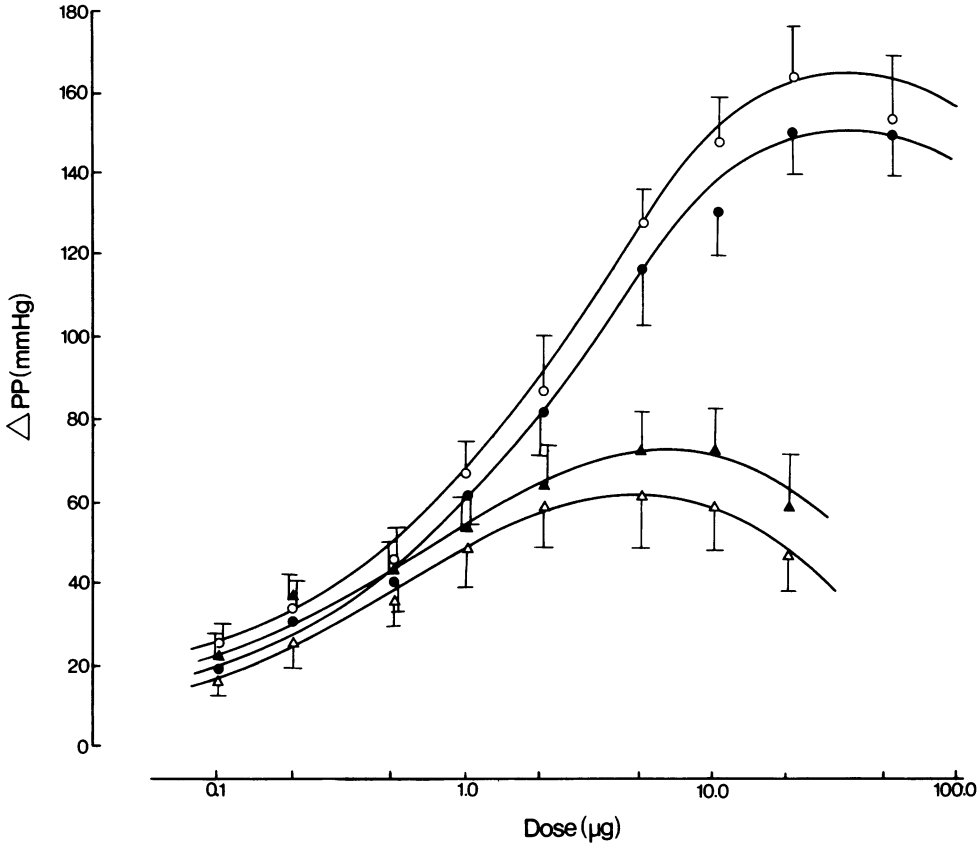

Figure 3 Dose-response curves for the increase in perfusion pressure (△PP) (mmHg) produced by noradrenaline (NA) and 5-hydroxytryptamine (5-HT) in isolated perfused mesenteric artery preparations from age-matched spontaneously hypertensive rats drinking water (controls) or treated with water containing hydrallazine/hydrochlorothiazide/reserpine), from age 8 to 20 weeks. From control rats, for NA responses (●) $n = 8$, BP = 209 ± 5.2 mmHg, body weight = 211 ± 3 g and for 5-HT responses (▲) $n = 8$, BP = 199 ± 2.3 mmHg, body weight = 222.6 ± 4 g. From treated rats, for NA responses (○) $n = 8$, BP = 110 ± 2.8 mmHg, body weight = 186 ± 12 g and for 5-HT responses (△) $n = 8$, BP = 101 ± 8 mmHg, body weight = 191 ± 4.5 g. Mean values with s.e. mean are shown or quoted.

development of hypertension in SH-rats; additionally, hydrallazine alone was also effective in a similar manner. In older SH-rats the administration of hydrallazine alone, or of the drug combination, reduced and maintained the blood pressure of SH-rats to levels approaching those of normotensive rats.

By contrast these drug treatments had little effect on the blood pressure of normotensive Sprague-Dawley rats and moreover these treatments themselves did not significantly alter the vascular reactivity to NA and 5-HT of isolated mesentery preparations from these rats.

The vascular reactivity to NA and 5-HT in preparations from SH-rats treated to prevent the development of hypertension was significantly reduced compared to that in untreated SH-rats. This effect complied with two of Folkow's criteria for reduced vascular reactivity, i.e. less steep dose-response curve and reduced maximum increase in perfusion pressure but threshold doses were less effective in treated SH-rats. However, commencement of similar treatments in SH-rats which were in the early stages of established hypertension failed to reduce vascular reactivity compared to that in untreated SH-rats. These results, therefore, indicate that the critical period for the development of vascular reactivity changes in this preparation is the same as that for the development of hypertension and moreover that

after vascular changes have occurred regression is not obtained after a prolonged period of normalization of the blood pressure.

In DOCA/saline hypertensive rats, Finch (1974) found that similar drug treatment for 4 weeks whilst reducing blood pressure to normotensive levels failed to modify vascular reactivity to NA, 5-HT or adenosine 5′-triphosphate in the isolated mesentery preparation. However, in contrast to these findings, Weiss (1974) found that anti-hypertensive treatment with a hydralazine/guanethidine combination for up to 20 weeks reduced the blood pressure of 8-month-old SH-rats and also caused partial regression of vascular changes in the perfused hindquarters of treated rats. In the renal hypertensive rat Lundgren (1974) found that removal of the renal artery clip after hypertension had developed led to a rapid fall in blood pressure and regression of the increased vascular reactivity in the perfused hindquarters. Additionally, in 8-12-month old SH-rats, Weiss & Hallbäck (1974) reported that partial regression of vascular changes occurred in the hindquarters after regional hypotension was induced by aortic ligation for short periods of time. The different results obtained in rats with established hypertension in this study, from those of Folkow's group, is probably accounted for by the presence of intact blood vessels, including resistance vessels, in the hindquarters, but not the mesentery, preparation.

In contrast to results in established hypertension, prevention of the development of hypertension in SH-rats by immunosympathectomy (Folkow *et al.*, 1972) or by the chronic administration of propranolol (Weiss *et al.*, 1974) also prevented the raised vascular reactivity to NA that occurs in the perfused hindquarters of SH-rats. The present study has shown that anti-hypertensive drug treatment that prevents the development of hypertension in SH-rats also prevents the increased vascular reactivity to NA and 5-HT in isolated mesentery preparations. These results, therefore, support the hypothesis of Folkow and his co-workers that a raised transmural pressure is the main determinant of the structural changes in the wall/lumen ratio of blood vessels and represents a vascular adaptation to the raised perfusion pressure.

Moreover, since the vascular changes did not regress despite prolonged reduction in blood pressure the increased vascular reactivity is of doubtful significance in the maintenance of the elevated blood pressure. It remains possible that reduction in blood pressure for more prolonged periods will result in a reduced vascular reactivity.

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