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VASCULAR REACTIVITY OF PERFUSED VASCULAR BED IN SPONTANEOUSLY HYPERTENSIVE AND NORMOTENSIVE RATS

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1 Hypertensive and normotensive rats of the same age group were isolated from an inbred colony of spontaneously hypertensive rats.

2 The perfused hindquarter and mesenteric artery preparations obtained from hypertensive and normotensive rats exhibited an increased reactivity to noradrenaline (NA) and angiotensin II.

3 Dose-response curves to NA obtained from hypertensive and normotensive rats exhibited a steeper slope and higher maximum than those from control rats.

4 These findings suggest that increased vascular reactivity of blood vessels is independent of the development or maintenance of elevated blood pressure.

Introduction

Vascular reactivity to different pressor agents has been extensively studied in different types of experimental hypertension in animals, either in the whole animal preparation (Folkow, Hällback, Lundgren & Weiss, 1970a) or in isolated organ preparations (Folkow, Hällback, Lundgren & Weiss, 1970b; Haeusler & Finch, 1972). The underlying mechanism for this hyper-responsiveness and its role in the development of hypertension is not clear. However, it has been suggested that elevated blood pressure may induce adaptive structural changes in the vessel walls, resulting in an increased wall/lumen ratio. This might be responsible for increased vascular reactivity to vasoconstrictor stimuli (Folkow, Grimby & Thulesius, 1958).

Recently it has been shown that in hypertensive rats the increased reactivity to vasoconstrictor agents persisted even after the blood pressure had been normalized by antihypertensive treatment (Finch, 1974; 1975; Wayyes & Paterson, 1975). These authors have suggested that adaptive/structural changes are not entirely responsible for the increased reactivity of the blood vessels and that hyper-responsiveness is only secondary to hypertension.

In our laboratory we have succeeded in isolating rats from an inbred colony of spontaneously hypertensive rats differing in their blood pressure and which are classified as hypertensive (SH) and normotensive (NSH). These rats were used for investigating the relationship between blood pressure levels and vascular reactivity to noradrenaline (NA) and angiotensin II in vascularly isolated but neurologically intact hindquarter and mesenteric artery preparations.

Methods

Age-matched, male spontaneously hypertensive rats used in these studies were direct descendants of the original strain developed by Okamoto & Aoki (1963). At the time of the experiment the animals were 20–24 weeks old. The blood pressures of the conscious animals were measured regularly from their twelfth week onwards at two weekly intervals by the indirect tail cuff method. At the end of the twentieth week the animals with systolic blood pressures of 170 mmHg and above were considered hypertensive (SH) and those with 110–130 mmHg were considered normotensive (NSH). Male rats of Wistar strain (NW) with blood pressure between 100–130 mmHg were used as control for comparison.

Perfused hindquarter preparation

Animals were anaesthetized with a combination of sodium pentobarbitone (20 mg/kg, i.p.) and urethane (500 mg/kg, i.p.). The hindquarters of the rats were perfused at constant flow as described by Beck (1961). Blood was forced from the proximal to the distal part of the abdominal aorta by a peristaltic pump (DESAGA). Heparin 10 mg/kg was administered intravenously to all the animals, before cannulation of the aorta. The blood pressure and perfusion pressure

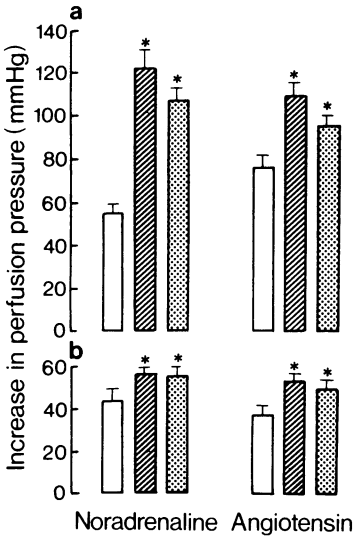

Figure 1 Effect of noradrenaline and angiotensin II on (a) perfused mesenteric artery and (b) hindquarters preparations from age-matched normotensive Wistar (NW) rats (open columns) spontaneously hypertensive (SH) rats (cross-hatched columns) and normotensive rats from a spontaneously hypertensive colony (NSH) (dotted columns). The mean values are shown; vertical bars indicate s.e. mean. ($n = 10$ for each group).
* significantly different from control, $P < 0.01$ Student's t test).

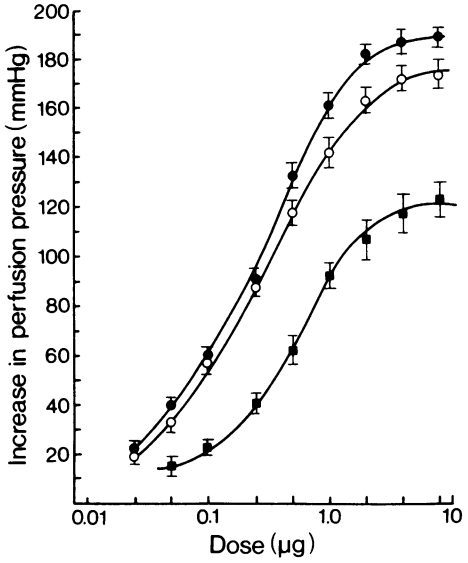

Figure 2 Dose-response curves for the increase in perfusion pressure produced by noradrenaline (NA) in perfused mesenteric artery preparations from age matched (■) normotensive Wistar (NW) rats, (●) spontaneously hypertensive rats (SH) and (○) normotensive rats from a spontaneously hypertensive colony (NSH). The mean values are shown; vertical bars indicate s.e. mean. ($n = 8$ for each group).

were measured with Statham P23Db pressure transducers and recorded on a two-channel Hellige physiological recorder. The pump speed was initially set in such a way that the perfusion pressure was the same as the systemic blood pressure. Local intra-arterial injections into the hindquarters were given by needle puncture into the rubber tubing leading to the distal part of the aorta.

Perfused mesenteric artery preparation

The general technique was similar to that described for the perfused hindquarters preparation. Blood from the carotid artery was forced by a peristaltic pump into the superior mesenteric artery. In addition, dose-response curves to NA were obtained by injection into the perfusion system. Injections were given at 5 min intervals and the maximum increase in perfusion pressure and 50% of these maximal responses (M_{50}) were calculated as described by Folkow *et al.* (1970b).

The results obtained were analysed statistically by Student's t test.

Results

The body weights of the animals used were 176.7 ± 6.7 g for NW rats, 209.0 ± 4.9 g for SH rats and 206.7 ± 8 g for NSH rats. NSH and SH rats were significantly ($P < 0.01$) heavier than NW rats.

The mean blood pressures of anaesthetized NW, NSH and SH rats as measured in the carotid artery were 107 ± 4.2 mmHg, 117 ± 8.0 mmHg and 182 ± 5.2 mmHg respectively. Blood pressure of SH rats showed a significant ($P < 0.001$) difference compared to NW and NSH rats.

The vasoconstrictor responses to NA (0.5 μg) and angiotensin II (0.5 μg) were determined in the perfused hindquarters and mesenteric artery preparations of NW, NSH and SH rats. These agents, when given intra-arterially, elicited pressor responses in the perfusion pressure without any effect on the systemic blood pressure. The preparations obtained from NSH and SH rats exhibited significantly increased vasoconstrictor responses to NA and angiotensin II compared to NW rats. The responses of these agents

in NSH rats did not differ significantly from those of SH rats. Vascular reactivity to NA and angiotensin II in the perfused mesenteric artery preparation was significantly greater than that in the perfused hindquarter preparation (Figure 1).

In addition, NA produced a dose-dependent vasoconstrictor response in the perfused mesenteric artery preparation. In preparations obtained from NSH and SH rats the dose-response curves produced by NA exhibited steeper slopes and higher maxima as compared with NW rats (Figure 2). The maximal pressor responses to NA in NSH rats (173.3 ± 5.9 mmHg) and SH rats (188.3 ± 4.2 mmHg) were found to be significantly ($P < 0.001$) increased as compared with NW rats (121.7 ± 7.2 mmHg). The M_{50} values for NA in NSH rats (0.24 ± 0.01) and SH rats (0.25 ± 0.01) were also found to be significantly ($P < 0.001$) lower than those of NW rats (0.48 ± 0.024), while there was no significant difference between NSH and SH rats.

Discussion

Previous studies in different types of experimental hypertensive animals have presented conflicting views concerning the relationship between increased vascular reactivity and the development of elevated blood pressure (Folkow *et al.*, 1958; Dupont & Sassard, 1974; Finch, 1975). Since hyper-reactivity can be demonstrated in both whole animal preparations and perfused arteries, the underlying mechanism for the increase in reactivity seems to be located in the blood vessels themselves. In the present study, the vascular reactivity to NA and angiotensin II was studied in perfused hindquarter and mesenteric artery preparations in different strains of rats of 5–6 months' age, since hypertension develops in SH rats at the age of 3–4 months.

The vascular reactivity to NA and angiotensin II was significantly increased in SH rats, compared to that in NW rats. However, it was surprising to find that NSH rats with lower blood pressure also exhibited significantly increased vascular reactivity compared to that of NW rats. The vascular reactivity to NA and angiotensin II has been found to be similar in SH and NSH rats. Finch (1975) has shown that lowering of blood pressure as a result of antihypertensive therapy failed to modify vascular reactivity to vasoconstrictor agents in the isolated perfused mesenteric preparation of DOCA/NaCl hypertensive rats. These results indicate that vascular reactivity to vasoconstrictor agents is not dependent on the blood pressure levels. This is in agreement with the work of Wayyes & Paterson (1975) in SH rats.

In addition it was observed that vascular reactivity in the perfused mesenteric artery preparation was significantly more elevated than that in the perfused hindquarters preparation. The different results obtained in these two preparations could probably be explained by the presence of intact blood vessels, including resistance vessels in the hindquarters but not in the mesenteric artery preparation.

Furthermore in the perfused mesenteric artery preparation from NSH and SH rats, the dose-response curves to NA exhibited steeper slopes and increased maximal responses as compared with NW rats. According to Folkow *et al.* (1970a) an increase of the wall/lumen ratio alters the shape of the dose-response curve for a vasoconstrictor agent.

These findings would suggest that adaptive/structural changes of the blood vessels could be expected not only in SH rats but also in NSH rats.

The results obtained from the present study raise some doubts about the role of increased vascular reactivity of the blood vessels in the development or maintenance of elevated blood pressure in SH rats. It appears that in addition to the hyper-responsiveness of blood vessels some other factor such as neurohumoral or chemical influences may also be responsible in elevating blood pressure in SH rats. Such a speculation can only be examined critically after other genetic changes in these animals have been identified because there is considerable evidence to indicate that hypertension in these animals is a polygenetic trait (Tanase, Suzuki, Ooshima, Yamori & Okamoto, 1972). Since alteration of adrenergic mechanism has been observed in SH rats, the role of central biogenic amines in the development of hypertension in SH rats needs clarification.

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