Vascular reactivity in the pathogenesis of spontaneous hypertension

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Summary
1. Alterations in vascular reactivity were assessed in isolated artificially perfused kidneys from stroke-prone spontaneously hypertensive (spSH) rats at different stages of hypertension and after neonatal sympathectomy with 6-hydroxydopamine (6-OHDA).

2. During the pre-hypertensive stage, and the early and chronic stages of hypertension, the responses to noradrenaline, vasopressin, serotonin and angiotensin II were enhanced in renal vascular beds from spSH animals compared with age- and sex-matched Wistar-Kyoto (WK) rats; dose-response curves were shifted to the left, had steeper slopes, greater maximal responses and decreased thresholds.

3. With increasing severity and duration of hypertension, renal vascular resistance at maximal vasodilatation increased, the slopes of the dose-response curves were steeper and maximal responses were greater.

4. Neonatal sympathectomy with 6-OHDA greatly attenuated but did not prevent the eventual development of hypertension; furthermore, this treatment had no effect on the enhanced resistance or reactivity in renal vascular beds from spSH rats.

5. The appearance of enhanced resistance and reactivity in the early stages of hypertension and the inability to prevent these vascular changes by neonatal sympathectomy suggest that these alterations are a primary pathogenic mechanism in spSH rats.

Key words: 6-hydroxydopamine, neonatal sympathectomy, perfused kidneys, renal vascular reactivity, stroke-prone spontaneously hypertensive rats.

Abbreviations: 6-OHDA, 6-hydroxydopamine; spSH, stroke-prone spontaneously hypertensive.

Introduction
The sympathetic nervous system is thought to participate in the development of spontaneous hypertension in rats. Treatment of spontaneously hypertensive rats in the early stages of hypertension with peripheral sympathectomy (Provoost & De Jong, 1978) markedly attenuates the development of hypertension but does not prevent its eventual occurrence. Therefore it is necessary to look for other factors that have a greater dominance in the pathogenesis of spontaneous hypertension. One factor could be increased reactivity of the resistance vessels. The present study examines changes in vascular reactivity in perfused kidneys from spSH rats at different stages of hypertension and the effect of neonatal sympathectomy on these changes.

Methods
Male, Okamoto spontaneously hypertensive rats of the stroke-prone (spSH) substrain were compared with age- and sex-matched Wistar-Kyoto control (WK) rats. Hypertensive rats were studied at three phases: the pre-hypertensive (4–6 weeks), the early (2 months) and the chronic (4 months) hypertensive phases. In a second series of experiments spSH and WK rats were sympathectomized by using subcutaneous injections of 6-hydroxydopamine (6-OHDA; 100 \( \mu \text{g day}^{-1} \text{g}^{-1} \)) for the first 10 days after birth. Sympathectomized rats were studied at 8 weeks of age. Systolic blood pressure was monitored by tail-cuff plethysmography.
Vascular reactivity to noradrenaline, vasopressin, serotonin and angiotensin II was assessed in isolated, perfused kidneys. Surgical isolation and perfusion of the kidneys was carried out by using modifications of the techniques described by Hofbauer, Zschiedrich, Rauh & Gross (1973). The right kidney was perfused through a catheter placed into the distal aorta and advanced to the origin of the right renal artery. The kidney was perfused at constant flow (5–6 ml min⁻¹ g⁻¹) with a modified Krebs–Henseleit solution containing Ficoll (70 000 mol. wt., 35 g/l). The medium was gassed with O₂ + CO₂ (95:5) and maintained at a temperature of 37°C and pH of 7.4. Perfusion pressure was recorded from the side arm of the perfusion cannula and perfusate flow was recorded by a drop counter placed at the end of the renal venous catheter. Drugs were injected intraarterially in bolus amounts from subthreshold to maximum doses (volume per dose was 10 μl).

**Results**

At all ages studied the systolic blood pressure of the spSH rats was significantly greater than that of

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**Fig. 1.** Dose–response relationships in the isolated, perfused kidney preparation from 2 month old spSH (●) and WK (■) rats treated from birth with 6-OHDA, compared with untreated, age-matched spSH (○) and WK (⊗) animals to (a) noradrenaline and (b) vasopressin. On the abscissae the doses of the vasoconstrictors (g/10 μl injection volume) are shown. At all doses of noradrenaline or vasopressin the responses of renal vascular beds from kidneys of treated and untreated spSH rats were significantly greater (P < 0.005) than the responses of treated and untreated WK animals respectively.
the WK animals. Furthermore, in kidneys of spSH rats vascular resistance at maximal vasodilatation (papaverine HCl) was greater and there was enhanced reactivity to all drugs tested. Dose–response curves of kidneys from spSH animals were characterized by significant leftward shifts, steeper slopes and greater maximal responses as well as decreased thresholds. With increasing severity and duration of hypertension, renal vascular beds from kidneys of spSH rats showed increasingly steeper dose–response curve slopes and greater maximal responses for all drugs. Moreover, resistance at maximal vasodilatation increased.

Neonatal sympathectomy with 6-OHDA slowed the rate of growth of both spSH and WK animals. The body weights of both groups at 2 months of age were 81% of that of untreated, age-matched groups. The mean systolic blood pressure of treated WK rats (93.1 ± SEM 2.4 mmHg) was slightly, but not significantly, less than that of untreated WK animals (98.5 ± 3.1 mmHg). In contrast, the blood pressure of treated spSH rats (110.9 ± 2.5 mmHg) was substantially less than that of untreated spSH animals (147.7 ± 6.2 mmHg). The renal vascular beds of treated spSH and WK rats showed denervation hypersensitivity to exogenous noradrenaline (Fig. 1a); however, reactivity of treated spSH rats was still greater than that of treated WK animals. Sympathectomy had little effect on the enhanced renal vascular reactivity of treated spSH rats to other drugs with the exception that maximal responses to vasopressin (Fig. 1b), serotonin and angiotensin II were decreased, as well as the steepness of the slopes of the dose–response curves, compared with those of untreated spSH animals.

Discussion

Vascular beds of kidneys from spSH rats show changes in both the structure of the wall of the resistance vessels (Folkow, Hallback, Lundgren & Weiss, 1970), as signified by increased resistance at maximal vasodilatation, steeper dose–response curve slopes and greater maximal responses, as well as in vascular smooth muscle function (Bohr, 1977), as signified by decreased thresholds. With increasing severity and duration of hypertension there is a greater resistance at maximal vasodilatation, increased steepness of the slopes of the dose–response curves and greater maximal responses, suggesting that structural vascular changes are enhanced by the increase in arterial pressure and, in turn, make a greater contribution to the increased reactivity in vascular beds of spSH rats.

Although neonatal sympathectomy with 6-OHDA markedly attenuated the rise in arterial pressure in spSH rats, this treatment did not prevent the eventual development of hypertension (Schömig, Dietz, Rascher, Ebser, Voss & Gross, 1979), nor was it able to prevent or reverse changes in vascular reactivity. The decreases in maximal response and steepness of the dose–response curves in kidneys from treated spSH rats is probably attributable to a decrease in the pressure load on the vascular wall with a consequent decrease in the hypertrophy of the muscle cells in the wall. Nevertheless, vascular reactivity of treated spSH animals to all vasoconstrictor drugs was greater than that of treated or untreated WK rats.

The early appearance of increased reactivity and the inability to prevent or reverse it by sympathectomy suggests that structural and functional changes in the resistance vessels are a primary pathogenic mechanism in stroke-prone spontaneously hypertensive rats.

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References