Increased vascular sensitivity to serotonin and methysergide in hypertension in rats

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Summary
1. The effect of the hypertensive process on vascular sensitivity to serotonin and methysergide was studied.
2. Isometric contractions were recorded from arteries isolated from spontaneously hypertensive (SHR), Kyoto-Wistar normotensive (WKY), deoxycorticosterone acetate (DOCA)-hypertensive and Sprague-Dawley normotensive rats.
3. Arteries from hypertensive rats (except SHR aorta) were more sensitive (lower ED₃₀) to noradrenaline, serotonin and methysergide relative to those from controls.
4. The magnitude of the leftward shift in ED₃₀ was similar for the three agonists in mesenteric and tail arteries from DOCA rats, whereas the shift in ED₃₀ for serotonin and methysergide in aortae exceeded that to noradrenaline. In SHR, the shift in ED₃₀ for serotonin and methysergide in tail and mesenteric arteries was greater than that to noradrenaline; SHR aortae did not differ from WKY aortae.
5. Arteries from hypertensive rats (except SHR aorta) developed a greater maximal contraction to methysergide than those from controls; maximal contractions to noradrenaline and serotonin were either less than or similar to those of controls.
6. The agonistic action of methysergide in DOCA rats paralleled the development of high arterial pressure. Low sodium diet abated the high pressure in DOCA rats and reduced vascular sensitivity to all agonists.
7. These observations support the view that in hypertension there is a generalized increase in vasoconstrictor sensitivity. The major finding is that, in two hypertensive models, there is a uniquely greater increase in vascular responsiveness to the agonistic action of methysergide.

Key words: aorta, arteries, DOCA hypertension, spontaneous hypertension, vascular smooth muscle.

Introduction
Recent evidence establishes that variability in the vasoconstrictor response to serotonin in different vascular beds is due (1) to differences in receptor distribution and (2) to the presence of different receptor types [1, 2]. As a generalization, it appears that although most vascular beds respond to serotonin through its action on classical receptors which are competitively blocked by methysergide, cyproheptadine or lysergic acid diethylamide, there are some vascular beds in which the serotonin receptors differ in that methysergide acts as an agonist. This paper studies the effect of the hypertensive process on these two types of serotonin receptors.

Methods
Male spontaneously hypertensive rats (SHR), Kyoto-Wistar normotensive (WKY) rats and Sprague-Dawley rats (250-300 g) were used. Half of the Sprague-Dawley rats were uninephrectomized and received subcutaneous implantations of deoxycorticosterone acetate (DOCA, 200 mg/kg). These DOCA rats were given 1% NaCl/0.2% KCl in their drinking water. Three weeks after implant, six DOCA rats and six controls were placed on a low sodium diet for 2 weeks before termination [tap water; synthetic diet (Purina, 0.02% sodium)]. All other animals were maintained on standard rat chow (Purina, 0.36% sodium).

The rats were killed by cervical dislocation and
thoracic aortae and mesenteric and tail arteries were excised. Standard muscle bath techniques were used to measure isometric contractions from strips of these vessels.

**Results**

The mean systolic blood pressures of DOCA rats and SHR were significantly higher than those of their respective controls (DOCA, 4–5 weeks post-implant = 168 ± 5 mmHg; normotensive = 118 ± 2 mmHg; SHR = 178 ± 3 mmHg; WKY rats = 126 ± 3 mmHg).

Addition of noradrenaline, serotonin or methysergide (10^{-12}–10^{-5} g/ml) to the muscle bath produced contractions in all arteries. To allow interpretation in terms of vascular sensitivity, the responses of each artery were normalized to its maximum and the agonist concentration producing a 30% maximal response (ED_{30}) was determined. Arteries from hypertensive rats (except SHR aortae) were more sensitive to the three drugs than those from controls. In DOCA rats the magnitude of the leftward shift in ED_{30} was similar for the three agonists in mesenteric and tail arteries, whereas the shift for serotonin and methysergide in aortae exceeded that to noradrenaline (Fig. 1a). In SHR, the shift in ED_{30} for serotonin and methysergide in tail and mesenteric arteries was greater than that to noradrenaline; SHR aortae were not different from WKY rat aortae (Fig. 1b).

Aortae isolated from DOCA rats at 6 days after implant (mean blood pressure = 138 ± 3 mmHg) had increased sensitivity to methysergide and serotonin, which paralleled the development of high arterial pressure (Fig. 1a). Two weeks on a low sodium diet abated the high blood pressure in DOCA rats (128 ± 4 mmHg) and reduced the increased sensitivity to all agonists (Fig. 1a).

Arteries from hypertensive rats (except SHR aortae) developed a greater maximal contraction to methysergide than did those from controls (68–128% change from control); maximal responses to noradrenaline and serotonin were either less than (−19% to −31% change from control) or similar to those from controls. SHR aortae did not differ from WKY rat aortae in their maximal contractions.

**Discussion**

This study indicates that there is an increase in vascular sensitivity in two types of hypertensive rats. Although, in previous publications [3–6], such an increase in vascular sensitivity has been reported for noradrenaline, serotonin and for many other vasoconstrictors, the finding that greater sensitivity to methysergide exists in hypertension is a novel observation.

The current study has as its goal the characterization of changes in serotonin receptors that occur in hypertension. The criterion of Apperly and associates [1, 2] for differentiating classical receptors from those that elicited a contraction in response to methysergide (M receptors) was used.

The increases in sensitivity that occurred in DOCA hypertension in the mesenteric and tail arteries were equivalent regardless of the agonist. This similarity is compatible with the possibility

![Fig. 1. Increase in vascular sensitivity in hypertension.](image-url)

The magnitude of the leftward shift of the dose–response curves for serotonin, methysergide and noradrenaline for aortae (□) and mesenteric (□) and tail (■) arteries from the hypertensive rats is expressed as the change in ED_{30} relative to that in arteries from normotensive rats. For example, the ED_{30} for methysergide in aortae from normotensive Sprague–Dawley rats was 2 × 10^{-6} g/ml, whereas in aortae from DOCA hypertensive rats (4–5 weeks after implant) was 2 × 10^{-10} g/ml; this difference represents a 100-fold shift to the left in ED_{30}. In (a) □, □ and ■ indicate results from aortae taken from rats 6 days after implant, 4–5 weeks after implant and after 5–6 weeks (with 2 weeks on a low sodium diet) respectively.
that, in these vessels, the change in hypertension reflects a non-specific increase in vascular sensitivity. The changes that occur in aorta of DOCA rats and in mesenteric and tail arteries of SHR are quite different. Here the sensitivity to noradrenaline is only minimally greater in the hypertensive rat; yet these vessels evidence great increases in sensitivity to serotonin and to methysergide. The increased sensitivity to noradrenaline may reflect the modest increase in non-specific sensitivity, whereas the increase in sensitivity to the other two agonists may reflect an increase in number or change in the ratio of the two types of serotonin receptors. Interestingly, the change in responsiveness of these receptors occurs early in the development of DOCA hypertension and their increased sensitivity is reduced by a low sodium diet.

In all vessels from the DOCA rats and in the mesenteric and tail arteries of SHR, the maximal contractile responses to noradrenaline and to serotonin are either the same or less than those of the controls. In sharp contrast, when methysergide is used as an agonist all arteries (except SHR aorta) develop greater maximum force than do these vessels from the controls. Clearly, the vasculature of hypertensive animals evidences a specific increase in response of the M receptor.

It is concluded that there are individualities in the changes that occur in the vascular smooth muscle of different arteries in hypertension. Furthermore, in addition to the general increase in vascular sensitivity that occurs in hypertension, there is a specific increase in its membrane receptors through which methysergide has an agonistic action. Thus it is not surprising that attempts to lower blood pressure by treatment with this blocker of the classical serotonin receptor failed [4].

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References