Altered Dilator Responses to Heptanol and Octanol in Aorta from Renal Hypertensive Rats

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= Abstract =

**Background**: Cells rely on gap junctions for intercellular communication, which is important for growth and contractility. The present study was conducted to test the hypothesis that contractile responses in aortic rings from two-kidney, one clip (2K1C) hypertensive rats are more dependent on gap junctional communication compared to those from normotensive rats.

**Methods**: 2K1C hypertension was induced by clipping the left renal artery and age-matched rats received a sham operation. Heptanol and octanol were used as inhibitors of gap junctional activity.

**Results**: The contraction induced by phenylephrine or KCl was completely reversed by either heptanol or octanol, and the relaxant response to inhibitors was more enhanced in 2K1C hypertensive rats compared to sham-operated rats. Vessels from hypertensive rats also relaxed more to nifedipine when precontracted with KCl, although it did not differ in aortic segments contracted with phenylephrine in between normotensive and hypertensive rats.

**Conclusion**: These results suggest that gap junctional communication and voltage-operated calcium channels are differentially regulated in 2K1C renal hypertension.

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**Introduction**

Vascular responsiveness to multiple contractile agonists is often increased in hypertension\(^1\). In two-kidney, one clip (2K1C) renal hypertensive rats, for example, vasoconstrictor responses to norepinephrine, phenylephrine, serotonin and phorbol ester in isolated aortae are exaggerated compared with those in normotensive rats\(^2,3\). Although enhanced contractile responses in hypertension may be attributed to some changes in individual agonist signal transduction pathways\(^4\), a more global change in signal transduction may occur that can explain the seemingly indiscriminate change in vascular reactivity.

Alterations in both the structure and the function
of the blood vessel wall contribute to the increased peripheral vascular resistance characteristic of hypertension in humans and animals. The observed morphologic changes, such as increased wall thickness and lumen encroachment, provide a mechanical advantage for reducing lumen diameter during smooth muscle contraction and limit minimal blood flow resistance. Functional vascular changes in hypertension are variable and complex. One type of functional vascular change that characterizes many forms of experimental and clinical hypertension is the increased occurrence of oscillatory contractile events in isolated and intact vascular preparations. Presumably, this coordinated contractile activity reflects an abnormality in intercellular communication via gap junctions. An alteration in gap junction activity may contribute to the increased vascular reactivity characteristic of hypertension. Indeed, the immunoreaction for the gap junction protein is increased in aortic homogenates from mineralocorticoid hypertensive rats, and the increased vascular responsiveness to the contractile agonist in aortic strips of hypertensive rats is inhibited by the gap junctional antagonist, heptanol.

Enhanced cell-to-cell communication via gap junction may provide one explanation both for the occurrence of oscillatory contractions in vascular smooth muscle from hypertensive subjects and for the increased sensitivity of vascular smooth muscle from hypertensive subjects to contractile stimuli. Gap junctional plaques are larger and more numerous in the aortic media of 2K1C renal hypertensive rats. In addition, helical strips of vessels of renal hypertensive rats display spontaneous oscillations, and we have also observed that isolated aortic rings from 2K1C renal hypertensive rats are more dependent on gap junctional communication compared to those from normotensive rats. The experimental approach was pharmacological, using heptanol and octanol, which are known inhibitors of gap junctional activity.

Methods

1. Induction of 2K1C renal hypertension

Renal hypertension was induced in rats following the 2K1C Goldblatt model. Briefly, male Sprague-Dawley rats, weighing 160 to 180 g, were anesthetized with sodium thiopental (40 mg/kg, IP). Under antiseptic conditions, an incision was made on the left flank to provide access to the left renal artery which was separated from the renal vein and cleaned of the connective tissue. A u-shaped solid silver clip with an internal diameter of 0.2 mm was applied on the exposed renal artery, resulting in partial occlusion of renal perfusion. The contralateral kidney remained untouched and the wound was closed. A group of age-matched rats received a sham treatment and served as control: they were operated as in 2K1C rats except for that no clip was made. All animals were fed normal chow and were given tap water. Six weeks after surgery, the systolic arterial pressure was measured in a conscious state by use of tail cuff method. It is established that in this phase of hypertension neither the renin nor the angiotensin converting enzyme activities are increased in plasma and/or aorta of 2K1C rats. The experiments were performed in this phase of hypertension to rule out a major interference of the renin–angiotensin system on our results. Rats were considered to be hypertensive when systolic pressure was more than 160 mmHg.

2. Tissue preparation

At the time of experimentation, the thoracic aorta between the aortic arch and diaphragm was carefully removed and placed in cold, standard phys-