Renal Denervation Normalizes Pressure and Baroreceptor Reflex in High Renin Hypertension in Conscious Rats

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High renin hypertension is usually accompanied by impairment of the baroreceptor reflexes. This feature has been mostly ascribed to overactivity of the renin-angiotensin system. However, renal nerves could also modulate the baroreceptor reflexes. In the present experiments, the effect of renal denervation on the depressed baroreceptor reflexes was studied in rats subjected to aortic ligation between the renal arteries. Renal denervation of the ischemic kidney was performed at the same time as aortic ligation. The resulting effects on arterial pressure, heart rate, plasma renin activity, and baroreceptor reflex control of heart rate were studied 10–12 days after ligation and denervation. Aortic ligation induced high levels of mean arterial pressure (166±6 versus 110±3 mm Hg in controls), heart rate (380±9 versus 352±8 beats per minute in controls), and plasma renin activity (44±5 versus 6±1.2 ng angiotensin I/ml/hr). The baroreceptor reflex sensitivity for bradycardia and tachycardia was significantly reduced (−0.18±0.04 and −0.18±0.05, respectively, versus −2.3±0.01 and −2.4±0.1 beats per minute per mm Hg in controls). Denervation of the ischemic kidney attenuated the development of hypertension in aortic-ligated rats (122±3 mm Hg), lowering heart rate (319±8 beats per minute) and normalizing baroreceptor reflex sensitivity to bradycardia (−2.0±0.2 beats per minute per mm Hg) and to tachycardia (−4.0±0.1 beats per minute per mm Hg). Plasma renin activity was also normalized (4.3±2.4 ng angiotensin I/ml/hr). Baroreceptor reflex sensitivity assessed 10 days after unilateral renal denervation in three control rats showed no alteration when compared with baroreceptor reflex sensitivity assessed before denervation in the same rat. Because normalization of the baroreceptor reflexes after complete renal denervation was accompanied also by normalization of plasma renin activity, this effect could be mostly explained by the well-known action of angiotensin II on baroreceptor reflex function. (Hypertension 1992;19[suppl II]:II-17–II-21)

The participation of neurogenic mechanisms in the pathogenesis of renal hypertension has been established in several studies. The depletion of central catecholamines by intraventricular or cisternal administration of 6-hydroxydopamine prevents or reverts the development of renal hypertension.2 Centrally acting angiotensin II has also been accounted for in the development of renal hypertension, because lateral ventricular administration of a competitive angiotensin antagonist significantly lowered arterial blood pressure in high renin hypertension by aortic coarctation. An important component of the central effect of angiotensin II leading to hypertension is the well-demonstrated inhibition of the baroreceptor reflexes.4–5 Consistent with this idea, we have shown an impairment of baroreceptor reflex control of heart rate4 and renal sympathetic nerve activity5 in high renin hypertension. On the other hand, studies of complete renal denervation in several experimental forms of hypertension suggest the participation of the renal nerves in hypertension.6 Both efferent and afferent renal nerve activity have been related to cardiovascular homeostasis. The former modulates the secretion of renin,7 the excretion of sodium and water, and the arterial resistance in renal vessels,8 whereas the latter projects to the central nervous system9–12 and to hypothalamic areas where the regulation of norepinephrine stores and the control of peripheral sympathetic activity occurs.13,14 Afferent renal activity could also regulate the function of baroreceptor reflexes, as suggested by an increased baroreceptor reflex sensi-
tivity in renal-deafferented spontaneously hypertensive rats.15 Because total renal denervation was shown to produce attenuation of the hypertension even though plasma renin activity remained elevated,13,14 the present experiments were undertaken to study the effects of complete renal denervation on baroreceptor reflex control of heart rate in high renin hypertension. As in previous studies,4,5 aortic ligation between renal arteries was used as a model of high renin hypertension.

Methods

Male Wistar rats weighing 200–250 g were used. Aortic ligation between the renal arteries16 was performed with rats under ether anesthesia with periaortic dissection to avoid hind limb paresis.17 Renal denervation was accomplished through a flank incision by stripping the renal artery adventitia and painting the renal artery with 20% phenol in ethanol, simultaneously with aortic ligation. Sham-operated control rats received only a flank incision with neither aortic ligation nor denervation. One day before the experiment, the animals were instrumented under ether anesthesia with carotid artery and jugular vein catheters exteriorized through the back of the rat for pressure measurements and drug injection, respectively. The arterial cannula was connected to a strain-gauge transducer (P23Db, Gould-Statham, Oxnard, Calif.). Rats were studied 10–12 days after surgery and were conscious and allowed to move freely during the experiments.

Blood pressure was recorded during a 1-hour period (Hewlett-Packard tape recorder, model 7754A, San Diego, Calif.) and further analyzed on a beat-to-beat basis (120 Hz) to obtain averaged arterial pressure, heart rate, and their variability using an analog-to-digital converter board (CAD10/16 Lynx, Sao Paulo, Brazil) coupled to a microcomputer (model PC-XT, Itautec, Sao Paulo, Brazil).

Rats were separated into three groups: control (sham-operated, n=6), aortic-ligated (n=9), and aortic-ligated with denervation of ischemic kidney (n=6). Reflex changes in heart rate were produced by acute changes of mean arterial pressure elicited by administration of phenylephrine (0.25–4 μg) and sodium nitroprusside (6–25 μg) by bolus injection to produce at least four pressure responses ranging from 5 to 40 mm Hg. Maximum heart rate changes in mean arterial pressure were used to calculate the respective sensitivities of the bradycardic and tachycardic responses using linear regression analysis of heart rate and mean arterial pressure data for each rat. The value of the mean for a group was calculated from the slopes of the regression lines of each rat. In three rats of the control group, we assessed baroreceptor reflex sensitivity before and after denervation (10 days) in the same animal. During the experiments, the animals were housed under standard laboratory conditions (constant temperature of 21°C, a 12-hour light/dark cycle, standard rat food and tap water ad libitum).

Plasma renin activity was measured by radioimmunoassay of a blood sample (1 ml) collected 1 day after the recording period and baroreceptor reflex sensitivity test to avoid the interference of arterial pressure changes induced by phenylephrine and sodium nitroprusside.

Results are expressed as mean±SEM. One-way analysis of variance and Tukey’s studentized range (honestly significant difference) test were used to compare slopes of the relations between control and experimental animals, as well as arterial pressure and heart rate. Statistical significance was assumed at a value of p<0.05.

Results

Arterial Pressure and Heart Rate

Ten to 12 days after aortic ligation, mean arterial pressure was 50% higher (166±6 mm Hg) than in control rats (110±3 mm Hg; Figure 1, top panel). As shown in Figure 1 (bottom panel), hypertension was accompanied by a significantly higher mean arterial pressure lability (SD changed from 6±0.3 to 10±1.8). Heart rate also was significantly higher in the hypertensive rats than in control rats (380±9 versus 352±8 beats per minute). Heart rate variability (Figure 1, bottom panel) expressed by standard deviation of the mean did not modify in aortic-ligated rats (23±2 versus 29±4 in controls). Interestingly, we observed in aortic-ligated rats a frequent occurrence of dips in the pressure recordings as illustrated in Figure 2 (left panel), which appears to be the cause of the negative skewness seen in the frequency histogram (Figure 2, right panel). Renal denervation of the ischemic kidney resulted in a significant change in the development of hypertension. After aortic ligation plus renal denervation, the average mean arterial pressure (1 hour, beat-to-beat analysis) was significantly lower (122±3 mm Hg) than that of rats with aortic ligation and intact innervation but was not different when compared with control animals (Figure 1, top panel). Mean arterial pressure variability did not change after aortic ligation plus denervation. Heart rate in aortic-ligated and denervated rats was even lower (9%) than in control rats (Figure 1). Heart rate variability did not change.

Baroreceptor Reflex Sensitivity of Heart Rate

The baroreceptor reflex sensitivity for reflex bradycardia (Figure 3) was markedly impaired in aortic-ligated rats (−0.18±0.04 versus −2.3±0.1 beats per minute per mm Hg in controls). After renal denervation, the baroreceptor reflex sensitivity of bradycardic responses returned to normal (−2.0±0.2 beats per minute per mm Hg). The baroreceptor reflex sensitivity of reflex tachycardia was greatly depressed in aortic-ligated rats (−0.18±0.05 versus −2.4±0.1 beats per minute per mm Hg in controls). In aortic-ligated and denervated rats, baroreceptor reflex sensitivity was higher (−4.0±0.1 beats per minute per mm Hg) but not statistically different from controls.
In three control animals, baroreceptor reflex sensitivity was assessed before denervation of the left kidney and 10 days after denervation. Denervation did not modify baroreceptor reflex sensitivity to phenylephrine (−1.53±0.6 versus −1.57±0.6 before) or to sodium nitroprusside (−2.21±0.9 versus −2.88±1.0 before).

Plasma Renin Activity

Plasma renin activity was significantly higher in the aortic-ligated group than in the control group (44±5 versus 6±1.2 ng angiotensin I/ml/hr). In the aortic-ligated and denervated rats, plasma renin activity was normal (4.3±2.4 ng angiotensin I/ml/hr).

Discussion

The most important findings of these experiments were that the complete denervation of ischemic kidney performed simultaneously with aortic ligation 1) attenuates the hypertension observed after 10 days of aortic ligation, although normalization of arterial blood pressure was not complete; 2) normalizes plasma renin activity; and 3) normalizes the baroreceptor reflex control of heart rate. These findings strengthen the important role of the renal nerves in cardiovascular homeostasis. In fact, studies of renal denervation in several experimental forms of hypertension have shown the universally important role of renal nerves in attenuating or preventing hypertension. However, the relative role of afferent and efferent renal neural pathways has not been established yet. Recently, direct techniques involving selective interruption of afferent renal nerves have shown that in some experimental models of hypertension, the decrease of blood pressure was associated with the interruption of information being conveyed to the neuraxis by afferent renal nerves.

Our data showed that renal denervation normalizes plasma renin activity 10 days after aortic ligation, reassuring the role of renal nerves in the secretion of renin during decreases in perfusion pressure. Indeed, a low-frequency stimulation rate of renal nerves, which usually causes no changes in renal blood flow or glomerular filtration rate, may...
increase renin secretion during decreases in perfusion pressure.7,9 Our results are in contrast to other studies that showed attenuation of hypertension was still accompanied by high plasma renin activity levels after renal denervation (see References 9, 13, and 14). This difference could be partially due to the fact that in the present study the denervation was performed at the same time as aortic ligation. Alternatively, the denervation was performed in kidneys subjected to a drastic reduction in flow (aortic ligation) and not in kidneys with partial constriction (clip) of the renal artery.13 The normalization of the baroreceptor reflex control of heart rate could also be attributed to normalization of plasma renin activity, because it has been well demonstrated that increased levels of circulating angiotensin II decrease baroreceptor reflex sensitivity in several species.4,5 The negative skewness in the frequency histogram of mean arterial pressure resulting from the contribution of dips to mean arterial pressure lability in aortic-ligated rats is similar to that observed in sinoaortic-denervated rats (Franchini and Krieger, unpublished observations). This represents another indication of decreased baroreceptor reflex sensitivity by high plasma renin activity. A reduced input of afferent renal nerves modifying the baroreceptor reflex sensitivity by altering the central store of catecholamines15,20 or central integration of reflexes changing afferent inputs to the hypothalamus or medulla9,10 could also participate in the observed effect. However, the exact contribution of this mechanism cannot be assessed in the present study because plasma renin activity was reduced simultaneously. In spontaneously hypertensive rats, bilateral sensory denervation of the kidney produced improvement15 or no changes21 in baroreceptor reflex gain, but in our study, unilateral denervation in normal rats per se did not alter baroreceptor reflex sensitivity. On the other hand, we have shown previously22 that overactivity of the renin-angiotensin system rather than the severity of hypertension modifies the pattern of pressure changes during natural sleep in rats, which is a fine index of the functional integrity of the baroreceptor reflex.22 Moreover, we have observed that normalization of renin-angiotensin system activity coincided with normalization of the baroreceptor reflex control of heart rate.4 Therefore, the data of the present study are in agreement with the idea that the impairment of the baroreceptor reflexes observed in high renin hypertension is predominantly caused by angiotensin. The denervation of the left kidney in normal rats did not alter baroreceptor reflex sensitivity, which was indeed normalized after denervation of ischemic kidney in aortic-ligated rats. Normalization of baroreceptor reflex sensitivity was accompanied by normalization of plasma renin activity in aortic-ligated and denervated rats, which could be explained mainly by the well-known blunting role of angiotensin II on baroreceptor reflex.

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**KEY WORDS** • baroreceptors • heart rate • renin-dependent hypertension • renal denervation
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