Pathogenesis of Hypertension in the Sinoaortic-Denervated Spontaneously Hypertensive Rat

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The present study was performed to examine the relation between the gain of the baroreceptor reflex and the pathogenesis of hypertension in the spontaneously hypertensive rat. Spontaneously hypertensive or Wistar-Kyoto rats underwent either sinoaortic baroreceptor denervation or sham denervation at 28–35 days of age. Four months later these rats were chronically instrumented for measurements of arterial pressure and heart rate. Sixty-minute computerized measurements of arterial pressure showed no difference between spontaneously hypertensive sham (163±5 mm Hg) and spontaneously hypertensive baroreceptor-denervated (166±5 mm Hg) rats, or Wistar-Kyoto sham (114±3 mm Hg) and Wistar-Kyoto baroreceptor-denervated (121±4 mm Hg) rats. The gain of baroreceptor reflex control of heart rate was assessed by measuring maximal heart rate responses to changes in arterial pressure elicited by bolus injection of phenylephrine and nitroprusside (gain=slope of linear regression equation of change in heart rate versus change in arterial pressure). Baroreceptor reflex gain was significantly higher in Wistar-Kyoto sham rats (—2.10 beats/min/mm Hg) than spontaneously hypertensive sham rats (—0.94 beats/min/mm Hg). Baroreceptor denervation significantly decreased baroreceptor reflex gain in both Wistar-Kyoto (—0.26 mm Hg) and spontaneously hypertensive (—0.22 beats/min/mm Hg) groups. Since baroreceptor denervation did not exacerbate the development of hypertension in adult spontaneously hypertensive rats or lead to hypertension in Wistar-Kyoto rats, we conclude that a primary dysfunction in the baroreceptor reflex alone is not responsible for the development of hypertension in this model. (Hypertension 1991;18:475–482)

Increased activity of the sympathetic nervous system has long been suspected to contribute to the pathogenesis of hypertension in the spontaneously hypertensive rat (SHR).1–4 The mechanism responsible for increased sympathetic nerve activity is not known. One possibility is that a primary defect in the baroreceptor reflex leads to chronic increases in the activity of the sympathetic nervous system. In support of this hypothesis, several laboratories have demonstrated that the gain of the baroreceptor reflex in adult SHR is significantly less than Wistar-Kyoto (WKY) control rats.5–8 However, since alterations in the baroreceptor reflex may be secondary to changes in arterial pressure, it is not possible to make definitive conclusions in regard to cause and effect by correlating baroreceptor reflex gain and arterial pressure in the established phase of hypertension. However, recent studies have demonstrated that chronic administration of the converting enzyme inhibitor captopril prevents the development of hypertension in the SHR as well as normalizes the gain of the baroreceptor reflex.5,6 This effect of captopril has been shown to be mediated by its actions on the central nervous system.5,9 These observations have led to the hypothesis that the development of hypertension in SHR may be due to initial impairment of baroreceptor reflex control of sympathetic nerve activity as a result of increased activity of the brain renin-angiotensin system.6 Again however, these studies cannot exclude the possibility that normalization of baroreceptor reflex gain by captopril was secondary to the prevention of hypertension.

The hypothesis that a primary deficit in the baroreceptor reflex leads to chronic neurogenic hypertension has been investigated in several laboratories by studying the effects of baroreceptor denervation on long-term regulation of arterial pressure. The results are controversial. Although some groups have reported that baroreceptor denervation does indeed...
result in chronic hypertension,\textsuperscript{10,12} this has not been confirmed by other laboratories.\textsuperscript{13-15} Studies in this laboratory\textsuperscript{16} and others\textsuperscript{17,18} have shown that denervation of high pressure baroreceptors does not result in a chronic elevation of arterial pressure in the adult Sprague-Dawley rat. However, these studies may not be comparable with those in SHR since they were conducted in adult rats of a different strain. It is possible that the development of hypertension in SHR is dependent on impairment of the baroreceptor reflex at a young age. In addition, full expression of the hypertension may also depend on responses of renal and vascular effectors that are genetically different in SHR compared with WKY and Sprague-Dawley rats.

The objective of the present study was to further investigate the relation between baroreceptor reflex function and the development of hypertension in SHR. Our hypothesis was that the pathogenesis of hypertension in this strain was dependent on a genetic impairment of the baroreceptor reflex. We tested this hypothesis by removing the afferent limb of the arterial baroreceptor reflex (sinoaortic denervation [SAD]) in young (4–5 week) SHR and WKY rats. Sham-operated SHR and WKY rats served as controls. Studies were then conducted 4 months later in conscious, chronically instrumented adult SHR and WKY rats to examine the relation between the gain of the baroreceptor reflex and the pathogenesis of hypertension. Based on previous reports, we predicted that SHR would exhibit an impaired baroreceptor reflex\textsuperscript{2,5-8} and that further impairment of this reflex by SAD would exacerbate the development of hypertension in this model.

**Methods**

**General Procedures**

Male SHR and WKY rats were purchased at 25–30 days of age from Sasco Inc., Omaha, Neb., and were housed in small groups in a temperature- and light-controlled animal housing facility until the time of study. Standard rat chow and water were provided ad libitum. All procedures were approved by the institutional Animal Care Committee and were conducted in accordance with institutional and National Institutes of Health guidelines.

**Experimental Procedures**

Sinoaortic and sham denervation of young SHR and WKY rats. Between 28 and 35 days of age, SHR and WKY rats were randomly selected to undergo either SAD or sham SAD (SHAM). SAD was performed as described by Krieger.\textsuperscript{19} Briefly, rats were anesthetized with pentobarbital (50 mg/kg) and atropinized (0.4 mg/kg) with a single intraperitoneal injection. A ventral midline neck incision was made and the sternocleidomastoid muscles were retracted. Aortic baroreceptors were denervated by sectioning bilaterally the cervical sympathetic trunks (caudal to the superior cervical ganglion), the superior laryngeal nerves, and when positively identified, the aortic depressor nerve. There were no identifiable differences in baroreceptor reflex sensitivity between rats in which the aortic depressor nerve was not positively identified and sectioned (approximately 30% of the animals) and those in which the nerve was located and sectioned. Denervation of the carotid baroreceptors was performed by stripping the region of the carotid sinus. SHAM surgery consisted of a midline incision and retraction of the sternocleidomastoid muscles bilaterally. After SAD or SHAM surgery, antibiotic was administered (50,000 units penicillin G i.m.). Rats were subsequently housed in a quiet isolated laboratory with a 12-hour light/dark cycle and were weighed on a weekly basis. Standard rat chow and water were provided ad libitum. Four months later, cardiovascular studies (see below) were conducted in this same laboratory to insure that the rats had acclimated to the laboratory environment.

Instrumentation for cardiovascular studies. SHR and WKY rats were instrumented with chronic indwelling arterial and venous catheters 16–17 weeks after SHAM or SAD. Rats were atropinized (0.4 mg/kg i.p.), anesthetized (sodium pentobarbital, 50 mg/kg i.p.), and placed on a heated surgical table. Arterial and venous catheters (Dural Plastics, Dural, Australia) were advanced to the abdominal aorta and vena cava, respectively, from the femoral vessels. The distal ends of these lines were tunneled subcutaneously to the head where they were secured to the surface of the skull with stainless steel screws and dental acrylic. The distal ends of the catheters were then passed through a lightweight flexible spring connected to a swivel. The incisions were closed, antibiotic was administered (100,000 units penicillin G i.m.), and the rats were kept on the heated surgical table until they were mobile. Rats were then placed in individual stainless steel cages with the swivel mounted above. This allowed the animals complete freedom of movement about the cage and permitted handling of the catheters with minimal disturbance. Three days were permitted for recovery from surgery and for acclimatization to the environment. Studies were conducted while the rats rested in their home cage.

Experimental protocol. Mean arterial pressure (MAP), the lability of MAP, and heart rate were measured over a 60-minute period between the hours of 8:30 AM and noon. MAP was measured by connecting the arterial catheter to a pressure transducer coupled to a polygraph (Grass Instruments, Inc., Quincy, Mass.). The pulsatile pressure signal was input to a second amplifier with a low-pass filter to acquire an electrical mean of arterial pressure. The filtered analog signal was digitized with an analog/digital converter (model DT2801A, Data Translation Inc., Marlboro, Mass.) and was sampled at 0.5 Hz using an IBM AT compatible computer and commercial data acquisition and analysis software (ASYSTANT +, MacMillan Software Co., New York).
The average and standard deviation of MAP was then calculated from the 1,800 data points for each 60-minute recording period. The standard deviation of MAP was used as an index of the lability of arterial pressure.20 Heart rate was measured three to four times throughout the recording session by increasing the chart speed and counting peaks on the pulsatile pressure tracing.

On completion of the arterial pressure recording, the sensitivity of baroreceptor reflex control of heart rate was tested by measuring the heart rate response to acute increases and decreases of arterial pressure. Arterial pressure was elevated by bolus injection of one to two doses of phenylephrine (0.1–1.0 μg/kg, Winthrop-Breon Laboratories, New York), and decreased by bolus injection of one to two doses of sodium nitroprusside (0.1–1.0 μg/kg, Elkins-Sinn, Inc., Cherry Hill, N.J.). Responses were measured as the peak change in MAP and heart rate. Because of the increased lability of MAP after SAD, special care was taken to insure that injections were not made until MAP was stable. Both vasoactive agents were dissolved in sterile 0.9% saline. The volume of injections ranged from 0.1 to 0.3 ml.

Two to three hours after the baroreceptor reflex test, the contribution of the sympathetic nervous system to the maintenance of MAP was assessed by measuring the depressor response to administration of the ganglionic blocking agent hexamethonium (20 mg/kg i.v.). MAP was monitored by computer for 30 minutes before and 30 minutes after hexamethonium administration. Computerized monitoring of MAP was begun 5 minutes after ganglionic blockade when MAP had stabilized. Direct recordings of sympathetic nerve discharge have shown that this dose of hexamethonium effectively blocks ganglionic transmission over this period of time.3

Statistical Analysis

Analysis of variance for nonrepeated measures was used for comparisons of cardiovascular variables among the four groups (SHR-SHAM, SHR-SAD, WKY-SHAM, and WKY-SAD). A significant F ratio (p<0.05) was followed by Duncan’s Multiple Range test to establish statistical differences among the four groups. The sensitivity of the baroreceptor reflex was determined by linear regression analysis using the least-squares method. The slope of the regression equation was used as an indicator of the "gain" of baroreceptor reflex control of heart rate. Statistical significance for all tests was set at p<0.05. All values are reported as the mean±SEM.

Results

Shown in Figure 1 are the body weights for the four experimental groups in this study. Although the SHR and WKY rats were age-matched, body weights were significantly different between the two groups. Body weight before SAD or SHAM surgeries averaged 61.9±3.8 and 57.7±1.6 in the SHR-SHAM (n=9) and SHR-SAD (n=6) groups, respectively. Both WKY rat groups had significantly higher body weights than the SHR groups (WKY-SHAM, 88.6±4.0 g, n=9; WKY-SAD, 89.2±0.2 g, n=7). This difference between SHR and WKY rats persisted after SHAM or SAD surgeries. SAD had no apparent effect on growth in WKY rats but appeared to attenuate growth rate slightly in the SHR.

There were significant differences among groups with respect to the gain of the baroreceptor reflex (Figure 2, Table 1). The slope of the relation between changes in heart rate in response to changes in MAP, was greatest in WKY-SHAM rats. The slope was significantly less in SHR-SHAM rats. Baroreceptor reflex control of heart rate was significantly attenuated but not abolished (statistically different...
from slope=0) in both WKY-SAD and SHR-SAD groups. There was no significant difference in the baroreceptor reflex gain between WKY-SAD and SHR-SAD groups.

Although SAD significantly depressed the gain of the baroreceptor reflex control of heart rate in SHR, there were no significant differences in basal MAP (Figure 3) or heart rate (Figure 4) between SHR-SHAM and SHR-SAD rats. Similarly, there were no significant differences in MAP or heart rate between WKY-SHAM and WKY-SAD groups. Both SHR groups were hypertensive compared with the WKY controls. There were no differences in heart rate among the four groups.

Although SAD did not result in differences among groups in resting MAP, the lability of MAP was significantly higher in baroreceptor-denervated rats (Figure 5). There was no significant difference in arterial pressure lability between WKY-SHAM (7.0±0.5 mm Hg) and SHR-SHAM (7.3±0.3 mm Hg) groups. Similarly, the WKY-SAD (14.4±1.0 mm Hg) and SHR-SAD (13.7±2.2 mm Hg) groups were not different from each other.

The contribution of sympathetic vasoconstrictor activity to the maintenance of arterial pressure was assessed by measuring the depressor response to ganglionic blockade with hexamethonium (Figure 6). Hexamethonium administration resulted in depressor responses in WKY-SHAM (−29.4±5.2 mm Hg), WKY-SAD (−41.3±3.0 mm Hg), and SHR-SHAM (−34.5±4.3 mm Hg) groups that were not statistically different from each other. The depressor response to hexamethonium in the SHR-SAD group...
afferents as well as baroreceptor afferents, which is pathophysiologically. It is therefore conceivable that angiotensin II impairs baroreceptor reflex control of the circulation.21

In the present study, we found no correlation between baroreceptor reflex gain and arterial pressure in SHR or WKY rats. Similar to previous investigations, baroreceptor reflex control of heart rate was impaired in hypertensive SHR compared with normotensive WKY rats. However, further impairment of this reflex by removal of the afferent limb of the baroreceptor reflex arc (SAD) did not exacerbate the development of hypertension. Similarly, although SAD at 4–5 weeks of age resulted in reduced baroreceptor reflex gain, it did not result in hypertension in adult WKY rats. Finally, although the greatest difference in baroreceptor reflex gain was between WKY-SHAM and WKY-SAD rats, there was no difference in arterial pressure between these two groups. Taken together, these results suggest that a primary decrease in baroreceptor reflex gain alone cannot account for the development of hypertension in SHR.

This conclusion is based on the assumption that sinoaortic denervation is an appropriate model of decreased baroreceptor sensitivity induced pathophysiologically. Although there is no question that sinoaortic denervation decreases sensory input to the central nervous system, this approach is limited since it results in complete loss of arterial baroreceptor input, rather than the attenuated input likely to occur pathophysiologically. It is therefore conceivable that SAD may result in alterations in central neural pathways (plasticity) or enhancement of cardiopulmonary reflexes, which would not occur under pathophysiological states of an attenuated baroreceptor reflex. Furthermore, SAD removes chemoreceptor afferents as well as baroreceptor afferents, which is not necessarily true in pathological states of decreased baroreceptor reflex sensitivity. However, despite these limitations, it is clear from the present study that baroreceptor denervation impaired reflex control of the circulation and that this impairment had no effect on either the development of hypertension in SHR or basal levels of arterial pressure in WKY rats.

Development of hypertension in SHR begins at 3–4 weeks of age,22 progresses rapidly over the next 4–6 weeks, and reaches a plateau at 3–4 months of age.23 Since in the present study, there were no differences in arterial pressure between 5–6-month-old SHAM-SHR and SAD-SHR, we conclude that the steady state or maintenance phase of hypertension was not affected by baroreceptor denervation in SHR. Since arterial pressure was not measured serially in this study, it is not possible to determine if baroreceptor denervation altered the rate of development of hypertension in SHR. It is known from other studies that SAD accelerates the development of renovascular hypertension without affecting the steady-state level of arterial pressure.24,25 These findings are most likely explained by progressive adaptation of baroreceptors to chronic elevations of arterial pressure.24 This results of the present study in SHR support this hypothesis.

The conclusion that a primary decrease in baroreceptor reflex gain does not affect chronic regulation of arterial pressure is supported by studies in this laboratory16 and others13-15,17,18 demonstrating that SAD in adult animals does not result in chronic hypertension. This observation, originally made in conscious dogs,13 supports the hypothesis that the sole purpose of the baroreceptor reflex is rapid control of the circulation, whereas the long-term regulation of arterial pressure is not influenced by this system.13 This view, which remains controversial in light of other studies demonstrating chronic hypertension in baroreceptor-denervated animals,10-12 is supported by the fact that the lability of arterial pressure increases dramatically after SAD.11,13,16-18,20 The present study provides additional evidence that baroreceptor denervation does not exert a chronic influence on arterial pressure regulation since SAD at a young age did not significantly affect arterial pressure in the adult rat. This observation suggests that a lifetime of the acute hypertensive and hypertensive episodes (i.e., increased pressure lability), which are characteristic of SAD animals, does not result in adaptive changes in vascular function resulting in chronic hypertension.

Other studies have also revealed a dissociation between gain of the baroreceptor reflex and the development of hypertension in SHR. Direct recordings of renal sympathetic nerve activity have shown that although both arterial pressure and RSNAs were elevated at 5 weeks of age in SHR,2 baroreceptor dysfunction was not apparent until 109 to 15 weeks of age.2 A similar conclusion was reached by examining the effect of acute SAD on arterial pressure in

Discussion
The present study was performed to investigate the relation between the gain of the baroreceptor reflex and the pathogenesis of hypertension in SHR. Several laboratories have shown that baroreceptor reflex control of heart rate is impaired in adult SHR compared with WKY rats.2,5-8 This observation has led to the hypothesis that a primary dysfunction in baroreceptor reflex control of sympathetic activity may be an initiating factor in this model of neurogenic hypertension. This hypothesis is supported by the observation that prevention of hypertension in SHR by chronic blockade of the central renin-angiotensin system is associated with increased gain of the baroreceptor reflex.9 Since these effects appear to be mediated by the brain renin-angiotensin system, it has been proposed that a primary increase in activity of the central renin-angiotensin system impairs the gain of the baroreceptor reflex, leading to increased activity of the sympathetic nervous system.6 This hypothesis is supported by studies demonstrating that angiotensin II impairs baroreceptor reflex control of the circulation.21

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young (30–50 days) and adult (90–120 days) SHR and normotensive rats.27

Although the present study has demonstrated that reduced gain of the baroreceptor reflex does not result in chronic hypertension, a recent study has shown the opposite to be true, that is, an increased baroreceptor reflex gain does not attenuate the development of hypertension in SHR.7 In that study, renal afferents were removed at 4 weeks of age in SHR and WKY rats. Studies were then conducted when the animals reached 16 weeks of age. Renal deafferentation had no effect on arterial pressure, heart rate, or plasma catecholamines compared with sham-operated animals. It is interesting to note, however, that renal deafferentation increased baroreceptor reflex gain without attenuating the development of hypertension.7 The increase in baroreceptor reflex gain was correlated with an attenuated depressor response to hexamethonium in SHR with renal deafferentation.

These results bear a striking resemblance to those of the present study. First, deafferentation of arterial baroreceptors and the kidney at a young age (4 weeks) was associated with changes in the gain of the baroreceptor reflex control of heart rate in adult rats. SAD decreased baroreceptor reflex gain whereas renal deafferentation increased the gain. Second, despite these effects on baroreceptor reflex gain, the development of hypertension was neither exacerbated by SAD or attenuated by renal deafferentation. Finally, in both studies deafferentation was associated with changes in the depressor responses to ganglionic blockade that were inversely correlated with changes in baroreceptor reflex gain in the SHR but not WKY rats. Taken together these findings clearly show that although sinoaortic and renal deafferentation in young SHR result in alterations in baroreceptor reflex gain in adult SHR, the development of hypertension was not affected by these interventions.

The failure to find a correlation between baroreceptor reflex control of heart rate and the development of hypertension in SHR may be related to the fact that the method used to quantitate baroreceptor reflex gain in this study and others,6,7 may not accurately assess the efferent sympathetic limb of the reflex arc. Bradycardia induced by bolus injections of phenylephrine is mediated by cardiac vagal rather than sympathetic efferents.28 Although the reflex tachycardia induced by bolus injection of nitroprusside is sympathetically mediated, it has been reported that only the vagal component is impaired in SHR, since baroreceptor reflex responses to decreases of arterial pressure were normal.8 This is not supported by the present study and others6 in which heart rate responses to both pressor and depressor stimuli were impaired. Nonetheless, it may be erroneous to correlate the blunted reflex control of heart rate in SHR, with impaired regulation of sympathetic vasoconstrictor activity. Indeed, several studies have shown a dissociation between baroreceptor reflex control of heart rate and peripheral sympathetic nerve discharge. For example, dietary salt loading in normal rats impairs baroreceptor reflex control of heart rate but not renal sympathetic nerve activity.29 More relevant to the present study, some investigators have shown that baroreceptor reflex control of renal sympathetic activity in anesthetized2 and conscious SHR30 is normal despite impaired regulation of the heart. Although this has not been found by all investigators,31 the present study demonstrated that baroreceptor reflex control of heart rate in SHAM-SHR was impaired but lability of arterial pressure was not different from SHAM-WKY rats. This suggests that if baroreceptor reflex control of vascular resistance is impaired in adult SHR, it is not expressed by an increased lability of arterial pressure as would be expected.

In contrast to studies of baroreceptor reflex control of renal nerve activity, a recent study has shown that the gain of baroreceptor reflex control of lumbar sympathetic nerve activity is blunted in adult SHR.6 It is interesting to note that captopril administration increased the gain of this reflex.6 Taken together, baroreceptor reflex studies of renal and lumbar sympathetic nerve activity suggest differential reflex control of renal and hind limb vascular beds. If this is true, it must be established whether one vascular bed is more critical than the other in the pathogenesis of hypertension in SHR. There is significant evidence, based on both direct nerve recordings2 and renal denervation,32 33 to suggest that increased renal sympathetic nerve activity occurs at an early age in SHR. The fact that renal denervation attenuates the development of hypertension in SHR,32 33 strongly suggests that elevated sympathetic nerve activity to the kidney is an important component in this model.

Primary Versus Secondary Role of the Baroreceptor Reflex in Neurogenic Hypertension

Theoretically, chronic increases in sympathetic nerve activity can result from primary changes in the afferent, central, or efferent components of the baroreceptor reflex arc. This can result from primary changes in the gain (sensitivity) or set-point of these components. Although there is no question that such changes have occurred in the established phase of hypertension in SHR, the question remains whether these changes are the cause or result of hypertension. The present study clearly demonstrates that changes in gain of the entire baroreceptor reflex has no effect on chronic regulation of arterial pressure in either WKY rats or SHR. However, the possibility remains that central resetting of the baroreceptor reflex (with no change in gain) may be the initiating factor in this neurogenic model. However, the present study demonstrated that removal of arterial baroreceptors did not alter the increase in arterial pressure (and presumably sympathetic activity) in SHR. This observation supports the hypothesis that sympathetic hyperactivity in SHR is centrally driven1 27,31 and occurs independent of the baroreceptor reflex. Since an increase in central drive, by definition,
shifts the set-point (central resetting) of the baroreceptor reflex, alterations in the reflex do occur but are secondary to increased central drive, rather than the primary cause of it. A similar analysis may apply to changes in baroreceptor reflex gain. Based on this logic, we propose that alterations in baroreceptor reflex function per se are not the cause of sympathetic hyperactivity in SHR. To the contrary, we conclude that it is a primary increase in central drive, independent of the baroreceptor reflex, that leads to sympathetic hyperactivity and hypertension in SHR. Although the mechanism of increased central drive remains to be determined, increased activity of the brain renin-angiotensin system is one possible mechanism.5,9

Finally, a second interpretation of this study is that the pathogenesis and maintenance of hypertension in SHR is not neurally mediated. Chronic increases in arterial pressure may result from primary defects in renal function36-39 or increased plasma levels of circulating hormones or as yet unidentified circulating factors.40

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