Neurogenic and Humoral Factors Controlling Vascular Resistance in the Spontaneously Hypertensive Rat

By Lyman T. Lais, Richard A. Shaffer, and Michael J. Brody

ABSTRACT

The mechanism of sustained hypertension in spontaneously hypertensive rats has not been elucidated. In the present investigation, vasoconstrictor responses to a variety of neurogenic and humoral interventions were studied in the perfused hindquarters of Okamoto spontaneously hypertensive rats and normotensive Wistar rats. In addition, central sympathetic electrical discharge was measured. Vasoconstrictor responses in the hindquarters to lumbar sympathetic nerve stimulation were unchanged or reduced in the spontaneously hypertensive rats, but the responses to intra-arterially administered norepinephrine and epinephrine were enhanced. Vascular responses to intra-arterially administered tyramine, angiotensin, and barium chloride were also greater in the spontaneously hypertensive rats. Vascular resistance was significantly higher in the spontaneously hypertensive rats, and this difference remained following bilateral lumbar sympathectomy. Despite elevated systemic blood pressure, integrated nerve activity at rest was not different in the spontaneously hypertensive rats. The inverse relationship between arterial blood pressure and sympathetic nerve discharge was not different between spontaneously hypertensive and control rats when pressure was either raised or lowered. Changes in efferent sympathetic discharge produced by activation of chemoreceptors (asphyxia) were somewhat less in the spontaneously hypertensive rats. The contribution of low-pressure baroreceptors (45° tilt) to activation of sympathetic vasmotor tone was not different in the spontaneously hypertensive rats despite a greater decline in systemic blood pressure during the procedure. These data demonstrate that established hypertension in the spontaneously hypertensive rat does not derive from either enhanced central adrenergic discharge or altered central integration of afferent information from peripheral sensory receptors but may result from humoral (e.g., increased reactivity to vasoconstrictors) or structural factors.

KEY WORDS

vascular reactivity  adrenergic vasmotor tone

catecholamines  central vasmotor control

sympathetic nervous system  chemoreceptors

sympathectomy

The spontaneously hypertensive rat was isolated as a pure inbred strain by Okamoto and Aoki (1). In these rats, the hypertensive state develops without provocation and is readily apparent soon after weaning age (2). The pathophysiology underlying the development and the maintenance of hypertension in the spontaneously hypertensive rat has not been elucidated. Of the many factors that could contribute to the maintenance of hypertensive state, only the renin-angiotensin pressor system seems to be excluded from participation (3, 4). Some investigators (5–7) have suggested that the hypertensive state is maintained by an increase in neurogenic vasoconstrictor influences which should theoretically be associated with an increase in the turnover of catecholamines (8). However, a growing body of reports indicates a decrease in catecholamine turnover in peripheral tissues from spontaneously hypertensive rats (9–13). Other investigators (5, 14, 15) have suggested that the hypertension derives from increased reactivity to normal vasoconstrictor influences. The participation of a third mechanism involving structural changes has also been proposed (14, 15). According to this hypothesis, increased arterial wall thickness causes a high basal vascular resistance and changes in the responsiveness to vasoconstrictor stimuli.

Since the spontaneously hypertensive rat is thought to be the best available model for the investigation of human essential hypertension (16), it is desirable to define more clearly the contribution of the aforementioned mechanisms to the pathogenesis of the spontaneous hypertension. The purpose of the present study was to determine directly if a high level of sympathetic discharge to the hind-
quarter vasculature contributes to the maintenance of the established hypertensive state in spontaneously hypertensive rats and to examine a variety of reflexogenic, neurogenic, and humoral interventions in the perfused hindquarters of these rats to see if an alteration in any of these factors which regulate vascular resistance contributes to the pathogenesis of the spontaneous hypertension.

**Methods**

**ANIMALS**

The spontaneously hypertensive rats used in this investigation were from the F2 and F3 generations of a rat colony raised in our laboratory. The rats were inbred descendants of the hypertensive Wistar strain developed by Okamoto and Aoki (1), and they corresponded to the descendants of the hypertensive Wistar strain developed by Okamoto and Aoki (1). They were anesthetized with sodium pentobarbital (30 mg/kg, ip). A midline incision was then made in the cervical region, and a tracheal cannula was inserted. One external jugular vein was cannulated for systemic injections. The carotid artery on the same side was cannulated for continuous recording of systemic blood pressure. Pressure was measured using a Statham P23A pressure transducer and a Beckman type RM pen recorder.

Peak vascular responses were measured in isolated, perfused hindquarters of control and spontaneously hypertensive rats by the technique of Brody et al. (18). The aorta was doubly cannulated. Blood from the proximal aorta was diverted through Tygon tubing to the isolated hindquarter above the level of the bifurcation of the abdominal aorta. Constant flow through the hindquarter was maintained by a Sigma motor pump inserted in the external circuit. At constant flow, changes in perfusion pressure reflect proportional changes in vascular resistance. Mean pressure changes were used in all calculations of alterations in vascular resistance. Blood flow to the hindquarter was adjusted so that the perfusion pressure closely approximated the existing systemic blood pressure. Drugs were injected intra-arterially into a rubber cuff just proximal to the caudal cannulation site. Injections were made in volumes of 5 or 6 μl with a 50-μl syringe (Hamilton Co., Inc.). Vasocostrictr agents tested in this study included norepinephrine bitartrate and epinephrine hydrochloride (doses of both are expressed as the free base), tyramine hydrochloride, synthetic 1-L-asparagyl-5-L-valine-angiotensin II amide (Ciba), and barium chloride. The lumbar sympathetic chains were isolated and electrically stimulated at L3, using small bipolar stainless steel electrodes with square-wave pulses generated by a Grass S4D stimulator.

**HINDQUARTER PERFUSION STUDIES**

Both male and female rats (five male and five female spontaneously hypertensive rats) were used in this study; all of them were 6-7 months of age. The rats were anesthetized with a Dial-urethane solution (0.65 ml/kg, ip) (each milliliter of solution contained 100 mg of allobarbitral, 400 mg of urethane, and 100 mg of monoethylyurea) and ventilated artificially using a Harvard small-animal respirator (model 820). Decamethonium bromide (1 mg/kg, iv) was injected to eliminate spontaneous respiratory movement during the course of the experiment. Supplemental doses of this drug were given as necessary.

The lumbar sympathetic chains were exposed by a midline abdominal incision. Both chains, which run side by side, were placed on a bipolar stainless steel electrode (1 mm wide at the tip). The isolated nerves were transected distal to the recording site. The nerves and the electrode were covered with lightweight mineral oil, and the preparation was placed in a grounded Faraday cage. Nerve activity was amplified using a Tektronix model 122 low-level preamplifier. The amplified nerve activity was visualized on both a Tektronix model 502 oscilloscope and a Beckman type RM dynograph. Integration of the sympathetic nerve activity was achieved by passing the output of the Beckman preamplifier into a Beckman 9873B integrating coupler. Nerve activity is expressed in arbitrary units. In several of the preparations, the nerve was crushed proximal to the recording site in order to eliminate background noise level. When this noise was subtracted and analyzed separately, identical results were obtained.

The femoral artery was cannulated and used for monitoring systemic arterial blood pressure. Pressures were measured using a Statham P23A pressure transducer and a Beckman type RM pen recorder. A cannulated femoral vein was used for systemic administration of drugs. The following interventions were tested in random order: increased blood pressure induced by norepinephrine bitartrate (10 μg/kg, iv), decreased blood pressure induced by acetylcholine bromide (25 μg/min), and asphyxia. Following these procedures, the whole body was tilted to 45° (head up) for 1 minute. Integrated nerve activity was recorded over a 30-second period during the peak blood pressure change produced by the drugs, between 45 and 75 seconds after the onset of asphyxia (respirator turned off) and during the last 30 seconds of the tilting procedure. After these procedures had been completed, hexamethonium chloride (10 mg/kg, iv) was administered.
and the preparation allowed to stabilize; then nerve activity was again integrated.

**STATISTICAL ANALYSES**

Linear regression was computed by the method of Snedecor (19). The six-point bioassay of Finney (20) and Student's group t-test (21) were also used.

**Results**

**HINDQUARTER PERFUSION STUDIES**

Figure 1 illustrates the preoperative systolic blood pressures determined by tail plethysmography. The average systolic blood pressure in the spontaneously hypertensive rats was significantly greater than that in the control rats. Following surgical preparation and cannulation, the mean blood pressures of the spontaneously hypertensive rats were not statistically different from those of the control rats. At this time, mean pressure in the spontaneously hypertensive rats was 110 ± 8 mm Hg compared with 100 ± 5 mm Hg in the control rats. Hindquarter vascular resistances were determined at the beginning of each experiment when the hindquarters were innervated. Vascular resistance in the spontaneously hypertensive rats was 63 ± 12 mm Hg/ml min⁻¹, a value significantly higher than the control group resistance of 39 ± 4 mm Hg/ml min⁻¹ (Fig. 1). Thus, hindquarter vascular resistance in the spontaneously hypertensive rats was 161% of that in the control rats. Flow rates averaged 1.7 ± 0.1 ml/min in the spontaneously hypertensive rats vs. 2.9 ± 0.2 ml/min in the control rats.

Reflexly initiated vasoconstrictor responses should be enhanced if sympathetic nervous system hyperactivity exists in the spontaneously hypertensive rats. Figure 2 illustrates the results obtained when rats were maintained at a 45° tilt, head up, for 1 minute. Tilting the control rats resulted in a moderate decline in mean systemic blood pressure, but hindquarter vascular resistance was maintained. The fall in systemic blood pressure was significantly greater in the spontaneously hypertensive rats. In contrast to the control rats and in contrast to what would be predicted on the basis of the reflex response to more severe hypotension, hindquarter vascular resistance in the spontaneously hypertensive rats fell significantly.

To assess the contribution of the sympathetic nervous system to the control of vascular resistance in the spontaneously hypertensive rats, vascular responses to bilateral lumbar sympathetic nerve stimulation and to injected tyramine were examined (Fig. 3). Tyramine acts primarily by releasing noradrenaline from adrenergic nerve terminals; typical responses to a single acute injection are rapid in onset and brief in duration. The average constrictor responses to injected tyramine were significantly greater in spontaneously hypertensive rats than they were in control rats. Vasoconstrictor responses to nerve stimulation in the spontaneously hypertensive rats were consistently lower than but not significantly different from those in the control rats.

Figure 4 illustrates the hindquarter vasoconstrictor responses to intra-arterially injected norepinephrine and epinephrine. At each dose tested, for both amines, significantly greater vasoconstric-
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SYMPATHETIC NERVE STIMULATION

FIGURE 3
Vasoconstrictor responses during sympathetic nerve stimulation and following intra-arterial administration of tyramine in hindquarters of spontaneously hypertensive (SHR) and normotensive (C) rats. The parallel-line bioassay was calculated using ten responses per frequency per group. Values for the responses to nerve stimulation were not significantly different between the two groups. The bars on the right denote the mean of ten responses to tyramine. Brackets represent the standard errors. The asterisk denotes a significant difference from control (P < 0.05).

FIGURE 4
Effects of intra-arterially administered norepinephrine and epinephrine on vascular resistance in the constant flow-perfused hindquarters of spontaneously hypertensive (SHR) and normotensive Wistar (C) rats. Each plotted point represents the mean of ten responses. Brackets indicate the standard errors. Asterisks mark values that are significantly different from control (P < 0.05).

FIGURE 5
Effects of intra-arterially administered angiotensin and barium chloride on vascular resistance in constant flow-perfused hindquarters of spontaneously hypertensive (SHR) and normotensive (C) rats. Bars represent mean values for ten rats. Brackets indicate the standard errors. Asterisks mark values that are significantly different from control (P < 0.05). Left: Responses to angiotensin prior to sympathectomy. Right: Responses to barium chloride following bilateral lumbar sympathectomy.

Vascular responses to two nonadrenergic vasoconstrictor agonists were also measured. Responses to angiotensin (0.5 μg) and to barium chloride (1 mg) following intra-arterial administration are illustrated in Figure 5. Both agents produced significantly greater increments in vascular resistance in the spontaneously hypertensive rats.

All of the responses described in this section, with the exception of the responses to barium chloride, were obtained prior to surgical sympathectomy. The effects on vascular resistance of acute bilateral sympathectomy at L3 are illustrated in Figure 6. Sympathectomy resulted in a significantly greater fall in vascular resistance in the control group. The right section of Figure 6 illustrates the level of hindquarter vascular resistance remaining following sympathectomy; in the acutely denervated state, the vascular resistance of the spontaneously hypertensive rats was still significantly elevated over that of the control rats.

SYMPATHETIC NERVE RECORDINGS
Spontaneously hypertensive rats exhibited significantly elevated systolic pressures (measured in-
SYMPATHECTOMY

POST SYMPATHECTOMY

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SHR</th>
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<tbody>
<tr>
<td>Pressure (mm Hg)</td>
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</tr>
<tr>
<td>Unanesthetized</td>
<td>132 ± 1</td>
<td>199 ± 4*</td>
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<tr>
<td>Preabdominal</td>
<td>92 ± 7</td>
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<tr>
<td>Postoperative</td>
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<tr>
<td>Prehexamethonium</td>
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<tr>
<td>Posthexamethonium</td>
<td>80 ± 6</td>
<td>85 ± 9</td>
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<tr>
<td>Integrated nerve activity (units/30 sec)</td>
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<tr>
<td>Initial</td>
<td>508 ± 57</td>
<td>521 ± 21</td>
</tr>
<tr>
<td>Prehexamethonium</td>
<td>520 ± 72</td>
<td>536 ± 54</td>
</tr>
<tr>
<td>Posthexamethonium</td>
<td>375 ± 67</td>
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Values are means ± SE. The number of rats per group is indicated in parentheses. * Significantly different from control, P < 0.05.

The changes in sympathetic nerve activity expressed as a function of the changes in mean arterial blood pressure are shown in Figure 7C. Nerve activity changes in response to either an increase or a decrease in mean arterial blood pressure were not different when they were calculated as a function of pressure. Figure 8 illustrates sympathetic discharge as a function of arterial blood pressure. The slope of the regression line for the responses in spontaneously hypertensive rats is not significantly different from that for control rats. These data suggest that resetting of sympathetic discharge is relatively constant over a wide range of mean arterial blood pressures. It should be emphasized that this figure is only a schematic depiction of the expected relationship between pressure and central discharge; the slopes may not be exact. For example, a maximum increase in discharge could have occurred at a higher arterial blood pressure (i.e., smaller depressor response) than was actually observed. It seems quite likely however that the scheme does accurately reflect the phenomenon of resetting in the spontaneously hypertensive rat.

The possible contribution of receptors other than the arterial baroreceptors which could be involved in enhanced neurogenic vasomotor tone was also investigated. Responses to asphyxia and a 45° tilt are presented in Figure 9. The decline in mean arterial blood pressure during asphyxia was significantly less in the spontaneously hypertensive rats. Since arterial pressure fell in the control rats, the increment in discharge may well not be caused solely by chemoreceptor activation. If the change in discharge seen in control rats is
Reflex changes in lumbar sympathetic nerve activity produced by alterations in arterial blood pressure. Bars indicate mean responses in each group. Brackets indicate the standard errors. Asterisks mark values that are statistically different from control (P < 0.05). n = number of rats per group. A: Arterial blood pressure changes produced by acetylcholine (ACh) and norepinephrine (NE). B: Changes in the level of sympathetic activity determined during the peak alteration in arterial blood pressure. C: Changes in nerve activity expressed as a function of the change in mean arterial blood pressure. SHR = spontaneously hypertensive rats.

Schematic representation of the expected relationship of central sympathetic outflow to mean arterial blood pressure. Solid circles = control rats and open circles = spontaneously hypertensive rats (SHR). Points indicate the average sympathetic discharge at the average systemic blood pressure at rest (INITIAL) and after administration of acetylcholine (ACh) and norepinephrine. Vertical and horizontal bars indicate standard errors of integrated nerve activity and mean arterial blood pressure respectively. Numbers of rats per group is given in parentheses. b denotes the calculated slope and its 95% confidence interval (in parentheses) for each group.

Reflex activation of sympathetic vasomotor tone by chemoreceptors and low-pressure baroreceptors. Bars indicate the average response for each group. Brackets indicate the standard errors. An asterisk marks the value that is statistically different from control (P < 0.05). Number of rats per group is given in parentheses at the bottom of the figure. Left: Alterations in systemic arterial blood pressure during asphyxia and 45° tilt. Right: Changes in central sympathetic discharge during asphyxia and tilting in spontaneously hypertensive (SHR) and normotensive Wistar control rats.
corrected for the amount of increase expected from the fall in pressure (see Fig. 7C), it still appears that asphyxia produces greater increases in sympathetic discharge in control rats than it does in spontaneously hypertensive rats.

Tilting resulted in a significantly greater decline in mean arterial blood pressure in the spontaneously hypertensive rats. Although the fall in arterial blood pressure was eightfold greater in the spontaneously hypertensive rats, the change in integrated nerve activity was not different from that in the control rats. Even though low-pressure baroreceptor activation in the spontaneously hypertensive rats appears to be equally effective in augmenting neurogenic vasomotor discharge, arterial blood pressure falls more.

Administration of the ganglionic blocker hexamethonium resulted in a decline in both mean arterial blood pressure and integrated sympathetic nerve activity (Table 1). The changes in pressure and nerve activity were not different in spontaneously hypertensive and control rats. This finding indicates that similar levels of centrally mediated sympathetic discharges were recorded in both groups. The drug reduced sympathetic discharge 28% in control rats and 12% in spontaneously hypertensive rats. These reductions, which were not significantly different from each other, indicate that on the average 80% of the discharge is central in origin in both groups. Another point worth emphasizing is that, although arterial blood pressure changed during the course of the experiment (a slight increase in normotensive rats and a decrease in spontaneously hypertensive rats), these pressure changes did not appear to be due to a change in adrenergic discharge, since the level of nerve activity did not change between the beginning of the experiment and the time at which hexamethonium was administered.

Discussion
The pathogenesis of hypertension in the spontaneously hypertensive rat is not yet known. It has been reported that cardiac output is not enhanced and may even be slightly depressed during the chronic established phase of this hypertensive state (22, 23). Since arterial blood pressure is a function of both cardiac output and peripheral resistance, the hypertensive state must derive from elevated peripheral resistance in the spontaneously hypertensive rat. In the present investigation, vascular resistance in the perfused hindquarter was elevated more than 50% in spontaneously hypertensive rats compared with normotensive Wistar control rats.

These data confirm previous reports of elevated resistance in the perfused whole body (14) and in several isolated vascular beds (24, 25). It appears that a large part, if not all, of the hypertension seen in adult spontaneously hypertensive rats is the result of alterations in peripheral vascular beds.

It has been suggested that the elevated vascular resistance results from increased reactivity to normal vasoconstrictor influences (5, 24, 25). It is evident from the present results that the smooth muscle of the hindquarter vasculature is hyperresponsive to a variety of vasoconstrictor agents. Resistance changes were greater in the spontaneously hypertensive rats when the response was mediated through specific receptors (i.e., epinephrine and norepinephrine) and when it involved direct interaction with smooth muscle elements (i.e., barium chloride). The observed responses to two doses of epinephrine and norepinephrine suggest that the dose-response relationships for these agents are steeper in the spontaneously hypertensive rats. A similar shift in the response to norepinephrine has been reported by Folkow et al. (14, 24), who have suggested that this shift in response is a result of altered vascular dimensions (i.e., a greater wall-lumen ratio). If the hyperresponsiveness of the vasculature of spontaneously hypertensive rats were due entirely to structural alterations, one would predict similarly enhanced responses to all vasoconstrictor agents. Increases in resistance in response to catecholamines were five- to tenfold greater in spontaneously hypertensive rats but responses to angiotensin II and barium chloride were only two to threefold greater. These data suggest that the hyperresponsiveness of hindquarter vasculature does not derive entirely from structural alterations. Although a portion of the hyperresponsiveness appears to be nonspecific, the results indicate that a substantial specific alteration in the responses to catecholamines occurs in spontaneously hypertensive rats. Haefuser and Haeffely (25) have reported that cocaine does not enhance the supersensitivity of the vascular smooth muscle of spontaneously hypertensive rats to injected norepinephrine, suggesting a defect in the amine uptake mechanism of noradrenergic nerves. The present results demonstrated differential changes in responsiveness, indicating that the enhanced vascular responsiveness in spontaneously hypertensive rats may well be caused by more than simple structural alterations within the vascular system.

In spite of the hyperresponsiveness of vascular smooth muscle to exogenous norepinephrine, vas-
cicular responses to graded lumbar sympathetic nerve stimulation were not different in the spontaneously hypertensive rats. These data suggest that less transmitter may be liberated per impulse from noradrenergic nerve terminals in spontaneously hypertensive rats. Alternatively one might suggest that barriers have been interposed to restrict diffusion of norepinephrine from nerve terminals to smooth muscle. The failure of neurogenically induced vasoconstriction in the isolated hindquarter to increase in parallel with the response to exogenous norepinephrine is different from results reported on mesenteric vasculature perfused in vitro (25). There are two possible explanations for this difference. First, appreciable differences may exist between various vascular beds because of the specialized functions which these beds subserve. Second, in the in vitro mesenteric vascular preparation, a synthetic perfusion medium was employed; thus, humoral modulators of sympathetic nervous system activity that may be present in spontaneously hypertensive rats were excluded.

Increased reactivity of the hindquarter vasculature of spontaneously hypertensive rats to tyramine is not necessarily inconsistent with the view that the elevated peripheral resistance in these rats does not derive from enhanced sympathetic nervous system activity. Partial preservation of tyramine responses in immunosympathectomized rats indicates that a component of the tyramine response in rats may derive from a direct stimulating action on vascular smooth muscle (26). Any direct component would be enhanced by either deficient uptake mechanisms (25) or interposed diffusion barriers. The major component of the action of tyramine probably results from nerve terminal release of norepinephrine. The norepinephrine released by tyramine could be from a different transmitter pool than that released by nerve action potentials; any norepinephrine liberated by tyramine should produce a greater than normal response, since the vessels of the spontaneously hypertensive rat are much more sensitive to this agent.

One of the questions considered in this investigation was whether the noradrenergic vasomotor system is in a hyperactive state in the spontaneously hypertensive rat. We found no evidence that vascular tone of neurogenic origin was augmented in these rats. Bilateral lumbar sympathectomy revealed a smaller component of neurogenic vasoconstrictor tone in the perfused hindquarters of the spontaneously hypertensive rats. In addition, basal vascular resistance was approximately twofold greater in the spontaneously hypertensive group than it was in the normotensive group. The lesser neurogenic component, measured in response to sympathectomy, is different from that seen by Nosaka et al. (5), but the reasons for the difference are not clear. The present results however are in agreement with the generally lower rate of norepinephrine turnover which has been reported in several tissues with sympathetic innervation (9–13) in the spontaneously hypertensive rat.

The postulate that the high peripheral resistance seen in spontaneously hypertensive rats is derived from enhanced sympathetic vasoconstrictor tone is also not supported by the results on lumbar sympathetic nerve discharge. Basal sympathetic nerve activity was essentially the same in hypertensive and control groups in this experiment, even in the face of a significantly higher systemic arterial blood pressure in the hypertensive rats. Although anesthesia may have obliterated any enhancement of neurogenic activity in the spontaneously hypertensive rats, this possibility becomes less likely when the effects of these procedures on arterial blood pressure are compared in the two groups. It is reasonable to assume that the similar changes in pressure following anesthesia and carotid cannulation, approximately 40%, were not due to grossly different effects on neuronal activity in the two groups. The impact of laparotomy and dissection of the lumbar sympathetic nerves is unclear. Whether the arterial blood pressure changes following this manipulation are the result of neurogenic, humoral, or physical factors is not known.

Recording of sympathetic nerve traffic in the intact, unanesthetized spontaneously hypertensive rat has not been accomplished. Thus, the contribution of sympathetic vasoconstrictor tone to the maintenance of hypertension under normal conditions is not known. Despite this fact, the similar degree of hypotension induced by anesthesia and the equivalent sympathetic nerve traffic in the face of elevated systemic blood pressure in the spontaneously hypertensive rat provide no evidence that the hypertension seen in spontaneously hypertensive rats is the result of enhanced neurogenic vasoconstrictor discharge.

In contrast to these observations, Okamoto et al. (6) have reported enhanced activity in splanchnic nerves of the spontaneously hypertensive rat. However, in addition to controlling vascular smooth muscle, the splanchnic nerve supplies the adrenal gland with sympathetic innervation. Thus, splanchnic nerve activity may reflect, to a considerable extent, humoral control of vascular resist-
ance through adrenal medullary release of catecholamines. This possibility is supported by the increased adrenal medullary catecholamine turnover which has been reported in spontaneously hypertensive rats (27).

In the present experiments, integrated nerve activity, as would be predicted, was inversely related to the level of arterial blood pressure. Equivalent inverse relationships were demonstrated between spontaneously hypertensive and normotensive Wistar rats during either an increase or a decrease in arterial blood pressure. Since the decline in nerve traffic following ganglionic blockade with hexamethonium was similar in spontaneously hypertensive and normotensive Wistar rats, it is probable that the amount of nerve traffic originating in the central nervous system of the spontaneously hypertensive rat is equivalent to that in the control rat and that the changes in activity produced by alterations in arterial blood pressure are also equivalent. The only difference between the normotensive and the hypertensive rats is in the level of arterial blood pressure yielding the same efferent nerve activity. This central discharge ultimately leads to release of norepinephrine from adrenergic nerve terminals innervating blood vessels. When the lumbar chains were stimulated electrically at the same site from which the nerve activity was recorded, equivalent vasoconstrictor responses were produced in the hindquarters. The conclusion to be drawn from these data is that the high arterial blood pressure and vascular resistance in the spontaneously hypertensive rat cannot derive from either exaggerated central sympathetic discharge or enhanced release of adrenergic transmitter produced by this discharge.

The similarity of efferent discharges probably reflects an alteration of baroreceptor control. Indeed, parallel resetting of afferent activity emanating from aortic and carotid sinus baroreceptors has been reported in spontaneously hypertensive rats (28, 29). Since sympathetic discharge to vascular smooth muscle and baroreceptor afferent traffic both appear to be normal in the face of high pressure, it can be reasoned that there is no alteration in central nervous system integration of afferent information emanating from arterial baroreceptors in spontaneously hypertensive rats. This conclusion does not support an earlier suggestion that the activity of supramedullary brain centers supports a state of augmented neurogenic vascular tone in the spontaneously hypertensive rat (7).

The explanation for the increased ability of the spontaneously hypertensive rat to maintain arterial blood pressure during asphyxia is not readily apparent. The greater increase in nerve activity in the control group appeared to be due largely to chemoreceptor activation, even after correction for the baroreceptor contribution. No attempt was made to produce the asphyxial response at any given point in the respiratory cycle. Although it is possible that a Valsalva-like phenomenon occurred in control rats, random chance alone makes it unlikely that this effect would happen in such an unequal proportion. It appears that the contribution of chemoreceptor activation to sympathetic vasomotor tone is less than optimal in the spontaneously hypertensive rat, an observation which is difficult to reconcile with any hypertensive mechanism.

Tilting usually results in little change in arterial blood pressure or only a slight hypotensive response because of sympathetic nervous system activation. Activation of low-pressure baroreceptors, which is presumably caused by venous pooling, has recently been demonstrated to result in increases in vascular resistance (30). If sympathetic hyperactivity supports the hypertensive state as has been suggested (5, 6), one might expect tilting to elicit more vigorous vascular responses in the spontaneously hypertensive rat. The greater fall in arterial blood pressure and the fall in hindquarter vascular resistance noted in spontaneously hypertensive rats do not support the concept that the high peripheral resistance is derived from hyperactivity of the sympathetic nervous system. In the experiments in which nerve traffic was recorded, increases in sympathetic nerve activity were not different in spite of an eightfold greater decrease in systemic blood pressure in response to tilting in the spontaneously hypertensive rats. These data again do not support the concept of augmented reflex activation of adrenergic vasomotor influences in the spontaneously hypertensive rat. The failure of arterial blood pressure to be supported in spontaneously hypertensive rats by an essentially equal increase in sympathetic activity is suggestive of some sort of defect in the ability of these rats to compensate for changes in "posture." The relationship of an apparent postural hypotension in spontaneously hypertensive rats to the pathogenesis of hypertension is not only unclear but paradoxical. This phenomenon, however, is not restricted to spontaneously hypertensive rats. Similar results have been reported in essential hypertension in man where a significant correlation has been demonstrated between the severity of hypertension and the inability...
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