Mechanism of Impaired Baroreflex Control in Prehypertensive Dahl Salt-Sensitive Rats

Frank J. Gordon and Allyn L. Mark

SUMMARY. Dahl salt-sensitive rats fed a low salt diet demonstrate functional impairment in baroreflex control of cardiovascular function prior to the development of hypertension. The purpose of this study was to identify the mechanism(s) responsible for impaired baroreflex control in prehypertensive Dahl salt-sensitive rats. To examine the central and efferent portions of the baroreflex arc, we electrically stimulated the aortic depressor nerve of urethane anesthetized Dahl salt-sensitive and Dahl salt-resistant rats while recording arterial pressure, heart rate, and sympathetic nerve activity. Aortic nerve stimulation produced equivalent responses in both groups, indicating that central and efferent mechanisms could not account for functional baroreflex impairment. In separate groups of Dahl rats, multifiber afferent aortic baroreceptor discharge was recorded while arterial pressure was increased with phenylephrine. Prehypertensive Dahl salt-sensitive rats demonstrated significantly less baroreceptor activation than Dahl salt-resistant rats, indicating that impaired baroreceptor discharge is the mechanism responsible for baroreflex abnormalities. Aortic arch distensibility was not different between Dahl strains, suggesting that impaired baroreceptor discharge in Dahl salt-sensitive rats is probably not due to abnormalities in vessel wall distensibility. Since arterial pressure of both Dahl strains was in the normotensive range and did not differ significantly between Dahl salt-sensitive and salt-resistant rats, baroreceptor impairment appears to be a primary defect in Dahl salt-sensitive rats, rather than being secondary to hypertension. We speculate that this impairment in baroreceptor function in Dahl salt-sensitive rats prior to any elevation in arterial pressure may contribute to the Dahl salt-sensitive rat's genetic propensity to develop hypertension.

RECENTLY, there has been a resurgence of interest in the role of the baroreflexes in the pathogenesis of both experimental and human hypertension (Zanchetti, 1979; Sleight, 1980; Jones and Sleight, 1981). Since the original report by McCubbin et al. (1956), it has been established that the baroreceptors, as well as the integrated response of the baroreflex arc, are reset, and that baroreflex sensitivity is reduced in association with hypertension. These abnormalities generally have been thought to be secondary to elevated arterial pressure, since baroreflex impairment has never been shown to precede hypertension.

In contrast, recent studies from this laboratory (Gordon et al., 1981; Gordon and Mark, 1983) have shown that impairment in baroreflex control of heart rate and vascular resistance is evident prior to hypertension in a genetic model of hypertension, the Dahl salt-sensitive rat. The Dahl strain provides an unusual opportunity to examine abnormalities in baroreflex control in rats genetically predisposed to develop hypertension prior to any elevation in arterial pressure. Although impaired baroreflex control of cardiovascular function has been demonstrated in prehypertensive Dahl S rats, the mechanism(s) responsible for this abnormality have not been identified. Abnormalities in baroreflex control could reside at any level of the baroreflex arc, including the baroreceptors, the vessel wall in which they are embedded, the central nervous system, efferent autonomic pathways, or any combination of these. The purpose of the present study was to identify the loci and mechanisms responsible for baroreflex impairment in prehypertensive Dahl salt-sensitive rats.

Methods

Animals

Female Dahl salt-sensitive (DS) and salt-resistant (DR) rats were purchased from Brookhaven National Laboratories. Dahl rats were fed a low salt (0.13% NaCl) diet (ICN Pharmaceuticals) from a few days postweaning until the time of experimentation during the 5th week of the diet.

In all experiments, Dahl rats were anesthetized with urethane (1.0-1.5 g/kg ip), and catheters were placed in the right femoral artery and vein for measurement of arterial pressure and injection of drugs, respectively. Heart rate (beats/min) was measured by a cardiostachometer (Beckman 9857B) triggered from the arterial pulse pressure signal.

Lumbar Sympathetic Nerve Recording

A midline incision was made in the abdomen, and the viscera were retracted to expose the aorta and vena cava below the renal bifurcations. These vessels were carefully...
freed from surrounding connective tissue and gently re-
ttracted to expose the paired lumbar sympathetic chains at
the approximate level of L3 to L5. One member of the
chain was cut distally, the nerve sheath was removed, and
the nerve was split into two filaments. Each filament was
placed over one pole of a bipolar Ag-AgCl hook electrode.
The nerve then was covered with a viscous mixture of
mineral oil and petroleum jelly to prevent tissue drying.
Spontaneous multifiber sympathetic nerve activity was
amplified with a Grass P511 differential preamplifier with
the lower and upper bandpass filters set at 30 and 10,000
Hz, respectively. The signal from the preamplifier was
visualized on a Tektronix 564B storage oscilloscope and
was passed to a nerve traffic analyzer (University of Iowa
Bioengineering Facility) equipped with a window discrimi-
nator and a microprocessor based counter and frequency
meter capable of resolving interpulse intervals ≥0.1 msec.
The oscilloscope sweep speed was adjusted until gaps
between bursts of nerve activity could easily be discerned,
and the cursor of the window discriminator was set just
above the remaining activity so that only nerve action
potentials exceeding this level were counted for subse-
quent analysis. At the conclusion of all experiments, the
nerve was crushed proximal to the recording electrode. In
most cases, the magnitude of the remaining noise was
virtually identical to that determined during active nerve
recording. In those instances where noise remaining after
erve crush exceeded the voltage threshold of the window
discriminator, these values were small, comprising less
than 10% of total recorded activity, and were subtracted
from all measurements prior to data analysis. Multifiber
sympathetic nerve activity was quantified as impulses/
sec, employing 1-second time bins, and displayed on a
pen-writing recorder (Beckman type RM) as a time-fre-
quency histogram in real time.

Assessment of the Central and Efferent Components
of the Reflex Arc

To assess the central and efferent components of the
baroreflex arc, we employed graded electrical stimulation
of the cut central end of the left aortic depressor nerve,
while simultaneously recording arterial pressure, heart
rate, and multifiber lumbar sympathetic nerve activity in
baroreceptor-denervated Dahl rats. The aortic nerve was
chosen for these studies since it contains exclusively bar-
oreceptor afferents (Sapru and Kreiger, 1977).

DR and DS rats were prepared with arterial and venous
catheters as described. A ventral midline incision was
made in the neck, and the trachea was cannulated. The
region of the carotid bifurcation was exposed bilaterally,
and the vagus, superior laryngeal, cervical sympathetic,
and aortic depressor nerves were identified (Sapru and
Kreiger, 1977). The carotid baroreceptor afferents were
destroyed on the right side by stripping the carotid bifur-
cation of nervous and connective tissue. In addition, the
cervical ganglion was removed. This procedure was re-
peated on the left side, except that the aortic depressor
nerve was cut as it exited the vagal sheath leaving a 4- to
10-mm section of nerve that was placed across bipolar
stainless steel stimulating electrodes and covered with
mineral oil and petroleum jelly. Efficacy of baroreceptor
denervation was confirmed by noting the absence of reflex
reductions in heart rate and sympathetic nerve activity
when systemic arterial pressure was raised by 40–60 mm
Hg with a bolus injection of phenylephrine.

Reflex-mediated decreases in arterial pressure, heart
rate, and lumbar sympathetic nerve activity were pro-
duced by electrical stimulation for 60 seconds of the cut
central end of the left aortic depressor nerve at graded
frequencies ranging from 0.5 to 64 Hz. In preliminary
experiments, it was found that the voltage necessary to
produce observable decreases in arterial pressure and sym-
pathetic nerve activity ranged between 0.05 and 0.2 V at
a pulse duration of 2.0 msec and stimulation frequency of
50–100 Hz. Maximal responses were always obtained at
stimulation intensities ranging between 1.0 and 3.0 V.
These results are similar to those reported by Sapru et al.
(1981). In all of the reported experiments, stimulation
voltage and pulse duration were held constant at supra-
maximal values of 5.0 V and 2.0 msec, respectively, while
stimulation frequency was systematically varied. These
stimulation parameters would be expected to activate both
A and C fibers of the aortic nerve (Aars et al., 1978).

Subsequent stimulation periods were not initiated until all
of the measured variables had returned to prestimulation
baseline values, usually within 2–5 minutes. Baseline con-
trol measurements were collected for 10 seconds imme-
diately preceding each stimulation period. Peak responses
occurred rapidly and were taken as the mean values
obtained during the first 3 seconds of stimulation. Steady
state responses were taken as the mean values recorded
during the last 10 seconds of the 60-second stimulation
period.

Aortic Nerve Recording

To determine whether the responsiveness of the arterial
baroreceptor afferents might differ between DR and DS
rats, in a separate group of animals we recorded multifiber
activity from the cut peripheral end of the left aortic
depressor nerve while varying arterial pressure. The rats
used in these studies were prepared as described previ-
uously, except that the left aortic nerve was cut near its
junction with the superior laryngeal nerve and placed
across Ag-AgCl recording electrodes. The remaining bar-
oreceptor afferents were not cut in this group of animals.
Instead, reflex responses and efferent sympathetic activity
were abolished by intravenous infusion of 5 mg/kg of the
ganglionic blocking drug, chlorisondamine (Ecolid, Ciba).
Abolition of reflex responses was confirmed by noting the
lack of reflex bradycardia following bolus injections of
phenylephrine. Ganglionic blockade was used in these
studies to lower arterial pressure below resting levels so
that blood pressure could then be increased through the
point of maximal baroreceptor gain. In addition, gangli-
onic blockade abolished rapid reflex-mediated changes in
heart rate, as well as efferent sympathetic activity.

The response characteristics of the aortic baroreceptors
were assessed under two conditions. First, systolic arterial
pressure was increased from approximately 80 to 180 mm
Hg over a period of 1–2 minutes as a continuous ramp by
increasing the rate of intravenous phenylephrine infusion
from 2.5 to 150 µg/kg per min while recording arterial
pressure, heart rate, and multifiber afferent aortic nerve
activity. Next, after return to baseline, steady state re-
sponses were obtained by intravenous infusions of seven
doses of phenylephrine (2.5–150 µg/kg per min) for a
period of 3 minutes each. At the end of each 3-minute
infusion, all of the measured variables were allowed to
return to baseline before the next dose of phenylephrine
was administered.

Raw values for aortic nerve discharge were normalized
by converting them to percent change to avoid any bias
that might result from differences in recording techniques
in DS vs. DR rats. Aortic baroreceptor discharge sensitivity
was determined by fitting a linear regression equation
through the dependent variables, percent change in aortic nerve activity vs. change in systolic arterial pressure, for individual animals. The slope of this relationship during both the ramp and steady state conditions was taken as an index of baroreceptor discharge sensitivity for each animal.

Aortic Arch Distensibility

To determine the distensibility of the aortic arch in these animals, we constructed pressure-volume curves on the isolated arch of each rat in situ. A saline-filled polyethylene catheter (PE-50) connected to a pressure transducer was inserted into the right common carotid artery and threaded toward the heart for a distance of approximately 1–1.5 cm. The chest then was opened and the tip of the carotid catheter was advanced and tied into place at the juncture of the right innominate artery with the aortic arch. The aorta then was ligated at its exit from the left ventricle, and the left carotid and subclavian arteries were occluded at their juncture with the arch. The descending aorta was catheterized with a saline-filled PE-50 catheter connected to a 100-μl microsyringe. The catheter tip was advanced rostrally to the level of the left subclavian artery and tied into place. Pressure in the arch was adjusted to 0 mm Hg, and saline was injected into the isolated arch in 0.01-ml increments while aortic arch pressure was recorded via the right carotid catheter over the volume range of 0.01–0.08 ml.

Statistical Analysis

Statistical analyses were performed by Student’s t-test when a unitary measure was collected for each animal (e.g., baseline blood pressure, heart rate, baroreceptor discharge sensitivity, etc.). Factorial experiments were analyzed by two-way analysis of variance, with significance statements relating to differences between groups over the range of treatments tested. Multiple pairwise comparisons among means were performed by Dunn's procedure for planned orthogonal comparisons, Tukey’s test for post-hoc analysis, and Dunnett’s test for comparison of control and treatment means (Kirk, 1968). The criterion for statistical significance was set at the 0.05 level. Numerical values cited in the text refer to the mean ± SEM.

Results

Central and Efferent Components of the Reflex Arc

Baseline mean arterial pressure (MAP) and heart rate were similar prior to sinoaortic denervation (SAD) in this group of urethane-anesthetized Dahl rats (MAP: DR = 89 ± 2 vs. DS = 89 ± 2 mm Hg; heart rate: DR = 353 ± 15 vs. DS = 342 ± 12 beats/min). After SAD, MAP increased in both groups to the same level (DR = 97 ± 5 vs. DS = 96 ± 3 mm Hg). Heart rate was significantly higher in DR rats following SAD (DR = 396 ± 9 vs. DS = 360 ± 11 beats/min, P < 0.05). Lumbar sympathetic nerve activity was not measured until after the SAD procedure had been completed. After SAD, baseline sympathetic nerve activity (impulses/sec) was 177 ± 7 for DR rats and 163 ± 7 for DS rats.

Mean arterial pressure, heart rate, and sympathetic nerve activity were reduced in a frequency-dependent fashion by electrical stimulation of the aortic nerve in both groups of Dahl rats (Fig. 1). As shown in Figure 2, graded stimulation of the aortic nerve produced similar decreases in blood pressure for DR and DS rats during the first 3 seconds and last 10 seconds of stimulation. No significant difference was observed in the magnitude of these changes between DR and DS animals. Aortic nerve stimulation produced marked decreases in sympa-
Afferent Aortic Baroreceptor Discharge

Since no differences were observed between Dahl strains during electrical stimulation of the central end of the aortic nerve, the response characteristics of the aortic baroreceptor afferents were examined in a separate group of Dahl rats.

In these animals, arterial pressure did not differ significantly between urethane-anesthetized DR and DS rats prior to ganglionic blockade. Systolic and diastolic arterial pressure averaged 123 ± 4 and 72 ± 4 mm Hg, respectively, for DR rats, and 117 ± 4 and 66 ± 4 mm Hg for DS rats. Heart rate was also similar for the two groups (DR = 330 ± 17 vs. DS = 308 ± 19 beats/min). After ganglionic blockade, blood pressure was reduced in both groups (P < 0.001), but no significant difference was observed between groups for either systolic (DR = 79 ± 2 vs. DS = 75 ± 2 mm Hg) or diastolic (DR = 51 ± 2 vs. DS = 49 ± 1 mm Hg) arterial pressure. Heart rate

**Figure 2.** Decreases in mean arterial pressure (mean ± SEM) in baroreceptor deafferented prehypertensive Dahl rats during graded electrical stimulation of the left aortic nerve (5.0 V, 10 msec). Peak responses usually were observed during the first 3 seconds of stimulation (left panel). Steady state responses were recorded during the last 10 seconds of the 60-second stimulation period (right panel). Baseline mean arterial pressure and decreases in arterial pressure produced by aortic nerve stimulation did not differ significantly between Dahl R and Dahl S rats. The number of animals in each group is shown in parentheses.

**Figure 3.** Decreases in lumbar sympathetic nerve activity (mean ± SEM) in baroreceptor deafferented Dahl rats during graded electrical stimulation of the aortic nerve. Sympathetic responses are expressed as percent change from initial baseline activity recorded prior to each 60-second stimulation period. Aortic nerve stimulation produced similar decreases in sympathetic nerve activity for Dahl R and S rats during both measurement periods.
in anesthetized DR animals was higher than that for DS rats following ganglionic blockade (DR = 348 ± 4 vs. DS = 325 ± 10 beats/min; P < 0.05).

**Ramp Increases in Arterial Pressure**

Baseline aortic nerve activity (impulses/sec) before the ramp infusion of phenylephrine was 29 ± 5 for DR rats and 26 ± 5 for DS rats. As seen in Figure 4, aortic nerve activity increased markedly as arterial pressure was raised as a ramp by iv phenylephrine. As seen in Figure 5, DS rats demonstrated significantly impaired aortic baroreceptor discharge (P < 0.05) at all levels of systolic arterial pressure above 80 mm Hg. Moreover, analysis of variance revealed that the slope or sensitivity of aortic baroreceptor discharge was significantly reduced in DS animals (F(5, 115) = 2.98, P < 0.05).

At the higher infusion rates of phenylephrine, heart rate started to increase (Fig. 4). This increase was similar for both DR and DS rats, averaging approximately 7% for both groups at a systolic arterial pressure of 180 mm Hg. However, marked changes in arterial pressure and aortic nerve activity occurred well before any changes in heart rate (Fig. 4). Heart rate did not increase significantly from baseline levels in either group until systolic arterial pressure reached 160 mm Hg (P < 0.05; Dunnett's test), by which time aortic nerve activity had already increased several hundred percent from baseline control levels, and marked differences in baroreceptor discharge between DR and DS rats were already apparent (Fig. 5). Intravenous phenylephrine infusion also significantly (P < 0.001) increased pulse pressure, as well as arterial pressure in both groups of Dahl rats (Fig. 4). No significant difference in pulse pressure was observed between DR and DS rats at any time during phenylephrine infusion (F(1, 23) = 1.77, P > 0.1).

**Steady State Increases in Arterial Pressure**

Results similar to those seen during ramp increases in arterial pressure were observed when arterial pressure was held at a constant level by 3-minute infusions of graded doses of phenylephrine. Baseline values for arterial pressure were not different between DR and DS rats during this protocol. Systolic and diastolic arterial pressure averaged 84 ± 3 and 50 ± 2 mm Hg, respectively, for DR rats. The values recorded for DS animals were 83 ± 2 mm Hg for systolic and 49 ± 2 mm Hg for diastolic arterial pressure. Baseline heart rate (DR = 326 ± 7 vs. DS = 312 ± 12 beats/min) and aortic nerve
discharge (DR = 40 ± 4 vs. DS = 36 ± 6 impulses/sec) were also similar for the two groups.

The increases in aortic nerve activity for a given increase in pressure were smaller during steady state (Fig. 5, right panel) than during ramp (Fig. 5, left panel) increases in pressure. However, during steady state, as well as ramp increases in pressure, DS rats demonstrated impaired baroreceptor discharge compared to DR rats (Fig. 5). Pressor responses to sustained infusions of phenylephrine in the ganglionically blocked animals were not significantly different between the two groups over the range of doses tested (Fig. 6), and although pulse pressure increased significantly (P < 0.001) with the larger doses of phenylephrine, no significant difference in pulse pressure was observed at any time between the two Dahl strains (F(1, 23) = 0.83, P > 0.1). Heart rate tended to increase at the higher doses of phenylephrine. This increase was somewhat greater for DS than for DR animals (P < 0.05). The maximal increase in heart rate occurred at the 150 µg/kg per min dose of phenylephrine for both groups, and averaged 26 ± 2% for DR rats and 32 ± 3% for DS rats.

As described in Methods, the sensitivity of aortic baroreceptor discharge for individual animals was taken as the slope of the relationship between changes in aortic nerve activity and systolic arterial pressure. This relationship was highly linear as evidenced by the mean correlation coefficients of 0.98 ± 0.01 for DR rats and 0.97 ± 0.01 for DS rats during ramp increases in arterial pressure, and 0.94 ± 0.01 and 0.85 ± 0.03 for DR and DS rats, respectively, during steady state elevations in blood pressure. Virtually identical correlations were obtained when changes in mean or diastolic arterial pressure were compared with changes in aortic nerve activity. These results are similar to those of Arndt et al. (1977). Figure 7 shows that prehypertensive DS rats had significantly (P < 0.05) impaired aortic baroreceptor discharge sensitivity during both ramp and steady state increases in arterial pressure.

**Aortic Arch Pressure-Volume Curves**

When aortic arch distensibility was assessed by constructing pressure-volume curves on the isolated aortic arch of these animals, no significant difference in distensibility was observed between the two strains over the range of volumes required to produce aortic arch pressures ranging from approximately 30 to 200 mm Hg (F(1, 21) = 2.41, P > 0.1; Fig. 8). Post-hoc analysis of these data (Tukey’s test)
indicated that aortic arch pressure in DS rats was significantly greater (P < 0.05) than DR animals only at the 0.08-ml volume which produced aortic arch pressures of 180 ± 8 mm Hg in DR rats and 223 ± 17 mm Hg in DS animals, respectively.

Discussion

The purpose of this study was to identify the mechanisms responsible for impaired baroreflex function in prehypertensive Dahl salt-sensitive rats. Previous studies from this laboratory have shown that DS rats fed a low salt diet demonstrate functional impairment in baroreflex control of both heart rate and vascular resistance prior to significant elevation in arterial pressure (Gordon et al., 1981; Gordon and Mark, 1983). These abnormalities could not be accounted for by differences in end organ response between the two Dahl strains (Takeshita and Mark, 1978; Gordon et al., 1981; Gordon and Mark, 1983), a finding that led us to examine in more detail the neural portions of the reflex arc.

Abnormalities in baroreflex control could reside at any level of the baroreflex arc in DS rats. Possible loci for baroreflex impairment in DS animals could include abnormalities in the baroreceptors themselves (Brown et al., 1976; Andresen et al., 1978), the vessel wall in which the sensory fibers are embedded (Angell-James, 1973; Sapru and Wang, 1976), the central nervous system (Gonzales et al., 1983), efferent autonomic pathways, or any combination of these. In examining the response of the central and efferent portions of the baroreflex arc, the central end of the left aortic nerve was electrically activated at graded frequencies, while blood pressure, heart rate, and lumbar sympathetic nerve activity were simultaneously recorded. The aortic nerve was chosen for study in these experiments, in the rat, this nerve appears to contain exclusively baroreceptor afferents (Sapru and Kreiger, 1977).

Electrical stimulation of the aortic nerve produced frequency-dependent decreases in blood pressure, heart rate, and sympathetic nerve activity in both strains of Dahl rats. The magnitude of these responses was not significantly different between DR and DS rats during either the early or late stage. These results indicate that the integrated response of the central nervous system to afferent baroreceptor input does not differ between prehypertensive DR and DS rats. Interestingly, this observation is different from that reported for another model of genetic hypertension, the spontaneously hypertensive rat (SHR), where stimulation of the aortic nerve produced significantly less sympathoinhibition in SHR, compared with Wistar-Kyoto control animals (Gonzales et al., 1983). This result suggests that, whereas abnormalities in central integration of afferent baroreceptor information may play a role in baroreflex impairment in SHR, this mechanism does not appear to contribute significantly to baroreflex dysfunction in the prehypertensive stage in the Dahl strain.

Two other points arising from these experiments deserve comment. First, electrical stimulation of the aortic nerve consistently produced a two-component response pattern. This pattern was characterized by rapid sympahto-inhibition, accompanied by a fall in heart rate and blood pressure. Peak responses were observed during the first few seconds of stimulation, after which all of the measured variables tended to recover toward prestimulation control levels, despite continued stimulation of the aortic nerve. This partial recovery cannot be attributed to compensatory responses mediated by other arterial baroreflex pathways (Kardon et al., 1973), since all of the remaining arterial baroreceptor afferents were severed, and the efficacy of deafferentation was confirmed by noting the failure of increases in arterial pressure to reduce sympathetic nerve activity and heart rate. It seems unlikely that cardiopulmonary baroreceptors with vagal afferents contributed to these compensatory responses, since previous studies from this laboratory (Gordon and Mark, 1983) have indicated that these afferents play little or no role in sympathetically mediated responses during baroreceptor activation produced by raising arterial pressure with phenylephrine. Instead, these observations would support the view that partial recovery of sympathetic nerve activity, blood pressure, and heart rate during aortic nerve stimulation may be due to central nervous system adaptation to afferent baroreceptor input, a finding consistent with results reported by other investigators (Richter et al., 1970; Gonzales et al., 1983).

Second, no attempt was made in these studies to differentially activate various afferent fiber types of the aortic nerve. The parameters chosen for aortic nerve stimulation (voltage and pulse duration) were selected to activate both A and C fibers (Aars et al., 1975), while the frequency of stimulation was systematically varied. Although no difference in reflex responses was observed between prehypertensive DR and DS rats, our data do not entirely exclude the possibility that subtle differences in response between Dahl strains might be observed if A and C fibers were activated separately.

Since no differences were observed between Dahl strains when baroreflex function was assessed by electrical stimulation of the aortic nerve, the response characteristics of the afferent aortic baroreceptors were examined in a separate group of Dahl rats.

Baroreceptor discharge was measured from the aortic nerve in ganglionically blocked Dahl rats during both ramp and steady state increases in arterial pressure. Prehypertensive Dahl S rats had significantly less baroreceptor discharge at equivalent levels of arterial pressure during both ramp and steady state increases in pressure. The magnitude of the
arterial pressure pulse, as well as the level of arterial pressure has been shown to influence the discharge rate of aortic baroreceptors (Brown et al., 1978). Since pulse pressure did not differ between DR and DS rats at any level of arterial pressure produced by phenylephrine infusion, differences in pulse pressure cannot account for impaired baroreceptor discharge in prehypertensive DS rats. Moreover, when aortic baroreceptor sensitivity was calculated for individual animals, DS rats were found to have significantly impaired aortic baroreceptor discharge sensitivity, compared with DR animals. These results indicate that impaired baroreceptor discharge is the mechanism responsible for previously observed (Gordon et al., 1981; Gordon and Mark, 1983) functional deficits in baroreflex control in prehypertensive Dahl S rats.

No attempt was made in these studies to differentiate the response patterns of myelinated vs. unmyelinated aortic baroreceptor afferents in the Dahl rats. Although the rat aortic nerve contains predominantly unmyelinated fibers (Krauhs, 1979), our recording procedure did not allow for discrimination of these fibers from myelinated ones. Whole nerve recordings measure population activity of baroreceptor afferents without discriminating fiber type and would be reflective of baroreceptors with different thresholds, spontaneous and activated responses, and adaptation characteristics. Whether impaired aortic baroreceptor discharge in DS rats is due to abnormalities in myelinated or unmyelinated afferents will require further investigation.

Great care was taken to standardize our recording procedures between animals, and percent change scores were used to quantify aortic nerve activity to avoid any bias that might result from between-animal differences in recording technique. The observation that untransformed baseline nerve activity and variability were similar between Dahl strains suggests that extraneous variables contributing to our measurements were randomly distributed across both populations. This observation would also suggest that errors in sampling did not contribute to the group differences we observed, and that our measurements of aortic nerve activity accurately reflected the population of receptors we recorded.

Ganglionic blockade was employed in these studies for three reasons. First, autonomic blockade lowered arterial pressure below baseline levels so that aortic baroreceptor activity could be examined while arterial pressure was raised through the point of maximal baroreflex gain, at or near the level of baseline blood pressure. Second, we sought to avoid rapid reflex-mediated changes in heart rate, since the magnitude of reflex bradycardia is always less in DS compared to DR rats for any given increase in arterial pressure (Gordon et al., 1981; Gordon and Mark, 1983). Third, since sympathetically mediated reflex responses are also impaired in DS animals (Gordon and Mark, 1983), possible strain differences in efferent sympathetic effects on the aortic baroreceptors (Brattstrom et al., 1980) would also be eliminated by ganglionic blockade.

The use of ganglionically blocked animals in these experiments permitted us to measure aortic baroreceptor discharge over a wide range of arterial pressure. However, this procedure was not wholly successful in preventing heart rate changes since, at higher doses of phenylephrine, tachycardia was observed in both strains of Dahl rats. This was apparently due to stimulation of cardiac β-adrenergic receptors, since subsequent experiments indicated that β-blockade with propranolol virtually eliminated the tachycardic effect of phenylephrine. β-Adrenergic blockade was not used in the present experiments, since previous studies have shown that this treatment can influence aortic baroreceptor discharge (Angell-James and Bobik, 1979).

There are several reasons why these unanticipated changes in cardiac rate do not mitigate our conclusion that prehypertensive Dahl S rats have impaired baroreceptor sensitivity. First, marked differences in aortic nerve discharge between DR and DS rats were observed prior to any significant change in heart rate. Second, although heart rate did increase, it did not appreciably influence baroreceptor activity, which appeared to be responsive primarily to changes in arterial pressure, independent of cardiac rate. This observation is consistent with the results of other investigators (Brown et al., 1978), who have shown that the frequency of aortic baroreceptor discharge (impulses/sec) remains constant when pressure is held steady, even though pulse frequency may vary widely. Third, during ramp increases in arterial pressure, DS rats had significantly impaired baroreceptor discharge, even though heart rate changes for the two groups were not different. Moreover, during steady state elevations in blood pressure, DS rats demonstrated less baroreceptor activation than DR animals even though their tachycardic response to phenylephrine was greater than that observed for the DR animals.

It has been suggested that α-adrenergic agonists may influence baroreceptor or baroreflex sensitivity, either by a direct action on the baroreceptors themselves (Goldman and Saum, 1980), or by constricting the arterial muscle in which the receptors are embedded (Peveler et al., 1983). Although, in the present studies, we raised arterial pressure with the α-agonist, phenylephrine, we have previously demonstrated impaired baroreflexes in DS rats when vasopressin was employed as the pressor agent (Matsuguchi et al., 1981). Moreover, arterial muscle contraction provoked by adrenergic stimulation either in vitro (Abel et al., 1981) or in vivo (Takeshita and Mark, 1978; Fink et al., 1980) does not differ between DR and DS rats fed low salt, and systemic pressor responses produced by phenylephrine in ganglionically blocked animals do not differ significantly between the two Dahl strains (Fig. 6; Gordon
relative proportion of medullated vs. nonmedullated afferents in DR and DS rats. Conclusive evidence bearing on these possible mechanisms will require further electrophysiological and morphological investigation.

In summary, this study has demonstrated that the sensitivity of aortic nerve baroreceptor discharge is reduced in prehypertensive Dahl salt-sensitive rats. This impairment probably derives from genetic factors and not from elevated arterial pressure, since blood pressure did not differ between the two Dahl strains. The impaired baroreceptor discharge was not explained by differences in aortic distensibility, which suggests that it may be related to abnormalities in the baroreceptors themselves or in their coupling to the vessel wall. Furthermore, abnormalities in afferent baroreceptor discharge, rather than alterations of central mechanisms, appear to be responsible for functional impairment in baroreflex control of cardiovascular function in Dahl S rats, since electrical stimulation of the aortic nerve produced equivalent reductions in blood pressure, heart rate, and sympathetic nerve activity in both Dahl strains. We speculate that genetic abnormalities in baroreflex function might predispose the Dahl S rats to develop hypertension during the stress of high salt diet.

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