Rapid Baroreceptor Resetting in Dahl Salt-Sensitive Rats

Mingyong Yang and Michael C. Andresen

Dahl salt-sensitive (DS) rats rapidly develop high blood pressure when exposed to a high salt diet, but Dahl salt-resistant (DR) rats maintain normal blood pressure on this diet.1 Baroreceptor reflex control of blood pressure is abnormal in DS rats even on a low salt diet.2-3 Aortic nerve recordings suggest that the function of arterial baroreceptor afferents is impaired in prehypertensive DS rats on a low salt diet.4-6 This afferent defect probably accounts for the low sensitivity of baroreceptor reflexes in DS rats during low salt treatment.4

Chronic adjustments in baroreceptor threshold and sensitivity occur during development, aging, and hypertension.3-5 However, since rapid resetting is a quantitatively important determinant of baroreceptor threshold,10 differences in the short-term adaptability of DS rat baroreceptors might contribute to the measured differences in baroreceptor properties. Although the mechanism of rapid resetting is not known, recent studies suggest that characteristics of the baroreceptor itself and not vessel wall mechanical properties might be responsible.11-16 If the baroreceptor defect in DS rats is genetic, it might affect the ability of baroreceptors to rapidly reset. The present study compares the ability of baroreceptors in DS and DR rats on high and low salt diets to rapidly reset.

Methods

Male DR and DS rats were obtained from Harlan Sprague Dawley, Inc., Indianapolis, Ind., at 4 weeks of age. Each rat strain was divided randomly into two groups, one of which was placed on a low salt (0.15% NaCl) chow diet and the other on a high salt (8.0% NaCl) chow diet. Thus, four experimental groups of rats were formed: DR rats on low salt, DR rats on high salt, DS rats on low salt, and DS rats on high salt diet. The rats were housed in the same room, given food and distilled water ad libitum, and maintained on a fixed 12-hour light/dark cycle. Tail systolic blood pressure (SBP) was measured by the indirect method.6 Experiments were performed on rats at 8-12 weeks of age.

Seventy-two rats were studied in two phases (18 rats per treatment group). In the first phase, the two shipments of rats were part of a larger study to survey the steady-state discharge properties of aortic baroreceptors and the aortic mechanical properties.
in Dahl rats. Only a relatively small proportion (less than 10%) of the baroreceptors in that population survey could be studied successfully over the prolonged time period required for the rapid resetting protocol. Thus, a second phase of baroreceptor studies was initiated to complete the resetting work using a third shipment of rats and identical diet treatments. Approximately half of the baroreceptors in each group belonged to the second phase of the study (21 of 46 baroreceptors).

The discharge properties of single aortic baroreceptors were studied using an in vitro aortic arch-aortic nerve preparation. Methods for testing baroreceptors have been described in detail previously and were in accordance with institutional guidelines. Briefly, while the animal was under pentobarbital sodium anesthesia (30-50 mg/kg i.p.), the aortic arch and the aortic nerve were exposed. Stainless steel-tipped cannulas were placed in the innominate artery and the descending aorta. Ligatures were placed on the ascending aorta, left common carotid, and left subclavian arteries. The aortic arch and nerve were then removed and transferred to a temperature-regulated (37±0.5°C) perfusing bath where the vessel was fixed to approximate its in situ length and shape. The lumen of the aortic arch was perfused with Krebs-Henseleit solution equilibrated with 95% O2-5% CO2 gas mixture. The preparation was perfused at a fixed conditioning mean arterial pressure (cMAP) of 80 mm Hg and was covered with warm mineral oil.

Measurement of Baroreceptor Discharge Characteristics

We used methods for measuring single-fiber baroreceptor discharge identical to those described previously in detail. In brief, after a regularly discharging single-fiber baroreceptor had been isolated, perfusion was halted, and MAP was reduced to 20 mm Hg. After 30 seconds at 20 mm Hg, pressure was increased in a slow ramp (less than 2 mm Hg/sec) from 20 mm Hg to 200 mm Hg using a shaker driver-bellows system. After completion of the test ramp, cMAP was then set at the control or a new conditioning level. Each test ramp generated a complete pressure-discharge relation and the baroreceptor discharge and pressure were recorded on analog FM magnetic tape for further analysis.

Tests of Rapid Resetting

Rapid resetting test protocols were similar to those used previously. After isolation of a single-fiber baroreceptor, the baroreceptor pressure-discharge curve was tested every 5 minutes for at least 15 minutes. Using this in vitro preparation, pressure-discharge curves measured at constant cMAP are very stable. Spontaneous curve shifts are generally less than 2 mm Hg. After the initial period testing at the control level (80 mm Hg), cMAP was stepped to a new level. The order of change in cMAP was random. The step magnitudes of cMAP changes varied from steps of 20 mm Hg to steps of 100 mm Hg across experiments. The absolute values of cMAP varied from as low as 50 mm Hg to as high as 150 mm Hg in different experiments and were chosen to span a range that might be encountered in vivo. Both increases and decreases in cMAP were tested. The duration of the cMAP steps was constant within a given experiment, generally 15 minutes. Test ramps of pressure were repeated every 5 minutes at each level of cMAP. The minimum requirement for a successful baroreceptor resetting experiment was completion of at least three test ramps at each of at least three different levels of cMAP. By using multiple measurements over at least three cMAP levels, we could assess both response stability and the linearity of rapid resetting with confidence in all baroreceptors.

Data Analysis

The analog magnetic tape was played back for microcomputer digitization. Action potentials were detected directly with a simple Schmitt-trigger voltage level detector for single-fiber baroreceptor recordings, or 2) sorted from recordings of two baroreceptors in the same filament using a pair of time-voltage amplitude window discriminators to detect (sort) unitary action potentials. Discharge rate was calculated as the reciprocal of the interspike interval (i.e., the instantaneous frequency). From the ramp responses, a pressure-discharge relation was constructed by plotting the instantaneous frequency of discharge against pressure for each baroreceptor. Typically, these relations have a distinct minimum pressure at which discharge begins (pressure threshold) and a suprathreshold region in which increases in discharge are quite linearly related to increases in pressure above pressure threshold. The suprathreshold linear region was fit by least-squares regression, and the slope was used as an index of receptor gain or sensitivity to pressure.

The rapid resetting process uniformly resulted in parallel shifts in the baroreceptor pressure-response curve along the pressure axis in the direction of the change in cMAP. Because the shifts in the baroreceptor pressure-response curves were proportional to the changes in cMAP, plots of pressure threshold versus cMAP were generally used to represent quantitatively the rapid resetting relation. When threshold values were used, the first 10 points were averaged to avoid basing this important measure on the location of a single spike. These resetting relations were fitted with a linear function by least-squares regression. Resetting relations were well described by this linear function ($r^2$ generally exceeded 0.9). The slopes of the rapid resetting relations ($\Delta Pth/\Delta cMAP$, where $Pth$ is pressure threshold) were used as a measure of the ability of a given baroreceptor to rapidly reset. Pressure threshold, slope, and resetting slopes were compared by analysis of variance. Values of $p<0.05$ were considered significant.
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Figure 1. Bar graph showing baroreceptor pressure threshold values measured at an initial conditioning mean arterial pressure (cMAP) of 80 mm Hg for each treatment group. Results are displayed as mean±SEM. Mean pressure threshold (Pth) of Dahl salt-sensitive rat group on high salt diet was significantly greater than other groups (see text). DS, Dahl salt-sensitive rats; DR, Dahl salt-resistant rats; LS, low salt diet; HS, high salt diet.

Results

Basic Discharge Properties

Forty-six single-fiber baroreceptor experiments met or exceeded our minimum criteria for a successful characterization of rapid resetting (See Methods). Fourteen of these baroreceptors were recorded from DR rats on a low salt diet, 13 from DR rats on a high salt diet, 8 from DS rats on a low salt diet, and 11 from DS rats on a high salt diet. The basic properties of the baroreceptors from this study showed much the same trends as those of the larger, previous study of this age group. Mean pressure threshold values were similar among both DR rat groups and the DS rat low salt group (Figure 1) but were increased for the DS rat high salt group (p<0.004). The variability of pressure threshold values for the DS rat low salt group was much lower than the other groups (Figure 1). However, since only one pressure threshold was included in this average per animal, it is difficult to place much weight on observation. The numerical averages for pressure sensitivity were similar to the previous study (Figure 2), but with the smaller numbers of baroreceptors, there were no significant differences among the four groups (p<0.05). Thus, the basic discharge properties of the baroreceptors studied followed similar trends as those of the larger population study. Similarly, when tail blood pressures were measured in most animals, DS rats on a high salt diet had the highest blood pressures, as was found in previous reports (mean±SD: DR rats on low salt, 144.7±6.0 [n=6]; DR rats on high salt, 145±3.8 [n=4]; DS rats on low salt, 147.5±7.0 [n=5]; and DS rats on high salt diet, 162.7±7.8 [n=4]).

Rapid Resetting

Rapid baroreceptor resetting developed and stabilized within 5–10 minutes of a change in cMAP in all baroreceptors tested. Rapid resetting was characterized as a shift in the baroreceptor pressure-discharge curve with no change in suprathreshold gain. Rapid resetting relations plotting pressure threshold versus cMAP were quite linear (mean r=0.933, r ranging from 0.793–0.987) for each of the 46 baroreceptors over a pressure range that included what in vivo would be hypotensive (cMAP of 50 mm Hg) and hypertensive (cMAP 150 mm Hg) blood pressures. We found a wide range of resetting ratios—the slopes of the resetting relations, ΔPth/ΔcMAP—in

Figure 2. Bar graph showing baroreceptor pressure sensitivity values for each treatment group. Results are displayed as mean±SEM. There were no significant differences among means of these groups. Sth, slope; DS, Dahl salt-sensitive rats; DR, Dahl salt-resistant rats; LS, low salt diet; HS, high salt diet.

Figure 3. Bar graph showing baroreceptor resetting ratio values for each treatment group. Results are displayed as mean±SEM. There were no significant differences among means of these groups. DS, Dahl salt-sensitive rats; DR, Dahl salt-resistant rats; LS, low salt diet; HS, high salt diet.
each group (Figure 3). With the exception of the DS rat group on a low salt diet, our samples of baroreceptors within each group included a wide range of initial pressure thresholds measured at the control cMAP of 80 mm Hg. The DS rat group on a low salt diet had the smallest number of successful experiments ($n=8$) and the narrowest range of initial pressure thresholds. Despite the higher average initial pressure thresholds in the DS rat high salt group, no significant differences in resetting ratio among the four groups were found (Figure 3, $p>0.2$).

**Discussion**

One of the most important determinants of baroreceptor discharge characteristics is the pressure to which they are exposed.\(^{10}\) In chronic hypertension, baroreceptor responsiveness to pressure is decreased: pressure threshold is increased and gain is decreased. These are the classic hallmarks of chronic hypertensive baroreceptor resetting.\(^{22}\) In the short-term, baroreceptors rapidly reset if mean pressure changes, and this rapid resetting effectively shifts pressure threshold selectively without affecting gain.\(^{23-25}\) Although the transition between rapid and chronic baroreceptor resetting and the basic mechanisms involved are unclear, it appears that the majority of the change in pressure threshold occurs in the first minutes and this shift remains constant for up to 6 hours.\(^{13,26,27}\)

From the detailed studies of Gordon, Mark, and associates,\(^{2,4,28}\) the defect in neural cardiovascular control in the DS rat appears to be primarily in the baroreceptor afferents. Aortic baroreceptors in relatively young DS rats maintained on low salt have decreased pressure sensitivities (gain) relative to their DR rat counterparts on low salt and to rats of the Sprague-Dawley strain.\(^{6}\) In older DS rats maintained on low salt diets, the variability of discharge properties from baroreceptor to baroreceptor within each rat was much greater within DS than DR rats.\(^{5}\) This variability was not expressed in younger DS rats.\(^{6}\) Because generally only one baroreceptor per rat was included in the present study, within-rat variability of baroreceptor properties could not be assessed, but we presume that it was similar to that of our larger, previous study of this age class of Dahl rats.\(^{6}\) Although it is very difficult to assess, one recent study\(^{11}\) suggests that rapid resetting may be quite variable across different baroreceptors within the same rat, even for those sharing the same receptive field, similar pressure thresholds, and obviously the same vessel wall properties. At the earliest stages of development, in the prehypertensive phase, the transformation of pressure into mechanical deformation of the baroreceptor endings appears to play a critical role in this abnormal behavior.\(^{6}\) Thus, variability of baroreceptor properties might make it very difficult to demonstrate differences in rapid resetting and thus contribute to our finding that rapid resetting is similar across these four groups of rats.

We hypothesized that since baroreceptors from DS rats have altered discharge properties, they might have altered adaptation ability. One powerful adaptive mechanism is rapid resetting.\(^{10,24,25}\) The results of the present study suggest that short-term adaptation to changes in cMAP is not very different in the two Dahl strains. Furthermore, the level of dietary salt does not appear to affect the ability of baroreceptors to rapidly reset. This general equivalence of rapid resetting in DS and DR rat baroreceptors suggests that short-term mechanisms of adaptation probably do not contribute to the decreased sensitivity of DS baroreceptors. Recent studies of rapid resetting in chronic hypertension of genetic (spontaneously hypertensive rats\(^{11}\)) or renal\(^{29-30}\) origin have found no differences in the rapid resetting process, despite the classical signs of chronic hypertensive resetting (increased pressure threshold and decreased gain). In that study of spontaneously hypertensive rats,\(^{11}\) the higher thresholds and depressed gains compared with Wistar Kyoto rats persisted despite prolonged conditioning at the control "normotensive" cMAP of 80 mm Hg. Based on multifiber recordings, however, others have reported differences in or absence of rapid resetting associated with two hypertensive models: spontaneously hypertensive rats\(^{31}\) and renal hypertensive rabbits.\(^{32}\) Chronic changes in baroreceptor function may reflect processes that include structural or other changes requiring greater time for expression or regression.

The present results, together with our earlier study,\(^{6}\) suggest that elevated pressure threshold is the dominant change in DS rat baroreceptors on high salt diets. Despite this higher set point, the baroreceptors maintain the ability to rapidly reset to higher and to lower pressures when exposed to changes in cMAP. The present findings in Dahl rats reinforce the concept that the rapid resetting process is remarkably resistant to other factors that significantly compromise chronic baroreceptor function.\(^{7,10,12}\)

**References**


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