Baroreceptor Function in Spontaneously Hypertensive Rats

Effect of Preventing Hypertension

MICHAEL C. ANDRESEN AND ARTHUR M. BROWN

SUMMARY In the previous paper we showed that baroreceptor resetting in spontaneously hypertensive rats (SHR) resulted from an incomplete matching of increased receptor strain sensitivity with reduced vessel wall distensibility. Here SHR and Wistar-Kyoto controls were treated with antihypertensive drugs in their drinking water (reserpine, hydrochlorothiazide, and hydralazine) from 5 weeks of age so that we might examine the role of blood pressure in the SHR vessel wall-receptor mismatch. Radius and receptor properties were measured using the in vitro aortic arch-aortic nerve preparation at 8, 14, 20, and 30 weeks. We found that baroreceptors from SHR with normal blood pressures had normal pressure thresholds and suprathreshold pressure sensitivities. However, the treated SHR receptors still had lower strain thresholds and the aortas still were less distensible than were the normal. Now, however, the increased receptor sensitivity was sufficient to normalize the relationship between baroreceptor function and arterial blood pressure. We conclude that, although blood pressure may be restored to normotensive levels by therapy, vascular abnormalities may continue to develop.


IN THE previous paper we showed that baroreceptor resetting in spontaneously hypertensive rats (SHR) resulted from an incomplete matching of increased receptor strain sensitivity with reduced vessel wall distensibility. This mismatch becomes greater as the rats get older. In normal animals [Wistar-Kyoto strain (WKY)], the large changes in vessel wall properties that occur during development and aging are matched by changes in the transduction properties of the receptor sufficient to prevent changes in the pressure threshold. An obvious question that arises is the role of increased blood pressure in the mismatch that occurs in SHR. We have examined this question by using antihypertensive drugs to normalize SHR blood pressure. We found that baroreceptors from SHR with normal blood pressures had normal pressure thresholds and suprathreshold sensitivities but that aortic wall distensibility was still reduced while the receptors had increased their strain sensitivity. Now, however, the increased receptor sensitivity was sufficient to normalize the relationship between baroreceptor function and arterial blood pressure. An important conclusion, therefore, is that, whereas normalization of blood pressure can be accomplished in this way, development of vessel wall abnormalities may proceed.


Methods

Fifty normotensive WKY and 50 SHR (Okamoto-Aoki strain) were obtained from Taconic Farms, Inc. All animals were 4 weeks of age upon receipt and were part of a larger group of WKY and SHR which was used for the preceding series of experiments (Andresen et al., 1980). Antihypertensive drugs were added to 1 liter of drinking water for 5-week-old animals in the following amounts: hydralazine, 80 mg; reserpine, 1.4 mg; and hydrochlorothiazide, 100 mg (Freis et al., 1972). Animals receiving drug treatment will be designated with a T. Animals receiving tap water only and described in the preceding report (Andresen et al., 1980) will be designated with a U. All four groups, WKYU, WKYT, SHRU, and SHRT, were fed otherwise identical diets and housed in the same room. Blood pressure and body weight were measured as described in the preceding paper (Andresen et al., 1980).

The experimental methods for in vitro isolation of aortic baroreceptors and for the vessel wall measurements were identical to those described in the preceding paper (Andresen et al., 1980). Only steady state properties of regularly discharging single unit baroreceptor fibers were studied. Each receptor was characterized by its threshold pressure ($P_{th}$), the sensitivity of the receptor to suprathreshold pressures ($S_{th}$), the threshold strain ($e_{th}$), and suprathreshold strain sensitivity ($S_{e}$), as previously defined (Andresen et al., 1980). The following mechanical properties of the aortic segment, external and internal radii ($R_{e}$ and $R_{i}$), vessel wall thickness ($h$), circumferential wall strain ($e$), wall stress ($\sigma$), and incremental elastic modulus ($E_{inc}$) were calcu-
lated as previously defined (Andresen et al., 1980).

Results

Blood Pressure

Drug treatment reduced the blood pressure (BP) of both WKYT and SHRT rats below levels for their respective untreated controls of the same age (Fig. 1). As in the untreated animals, BP rose with age until reaching a relatively stable, adult level. At 6 weeks of age, after 1 week of therapy, both treated groups had BP well below the WKYU level of 109 mm Hg (WKYT, 91.8 ± 3.0 mm Hg; SHRT, 98.8 ± 2.2 mm Hg) and BP increased up to about 8-10 weeks of age. SHRT remained generally stable at a BP of about 125 mm Hg from 10 weeks until the end of the study and were not significantly different from WKYU. In contrast, the WKYU BP progressively declined after the 10th week, and at the 15th week the BP at 100 was significantly lower than the BP of normotensives, WKYU, and SHRT (P < 0.001). Water consumption of the two treated groups was compared periodically and was at no time different, so that both treated groups received the same quantity of drugs. The group BP rankings remained constant from 6 weeks of age onward and were: SHRU > WKYU > SHRT > WKYT. Body weights were ranked from highest to lowest: WKYU, SHRU, WKYT = SHRT. All animals were healthy, alert, and continued to gain weight throughout the study period.

Effects of Treatment on Vessel Wall Development

Treatment of SHR was very effective in reducing the differences in vessel wall properties found between SHRU and WKYU (Andresen et al., preceding paper). \( R_E, R_i, h, \sigma \) for the SHRT group were not significantly different at all ages from 8 to 30 weeks, than those of the WKYU group at both 100 mm Hg (Figs. 2 and 3) and at systolic BP (Figs. 4 and 5). Treatment also shifted wall strain for the SHRT group to greater values, nearer those of WKYU, but beyond 8 weeks of age at both 100 mm Hg and at systolic BP, SHRT values remained significantly lower (\( P < 0.008; \) Figs. 3 and 5). With the prevention of a hypertensive BP, \( E_{\text{inc}} \) in SHRT was less than in WKYU at the prevailing BP (Fig. 6) though the difference was not significant.

Treatment of WKY with the antihypertensive program produced hypotension which was accompanied by a number of vessel wall changes. \( R_E \) and \( R_i \) at 100 mm Hg distending pressure were significantly increased beyond 14 weeks, and \( h \) was significantly reduced when compared with WKYU (Fig. 2). Wall stress, \( \sigma \), was increased due to the increase in radius and decrease in \( h \), while total wall strain was unchanged (Fig. 3B). Plots of these parameters at systolic BP, however, show that the WKYU operates at similar radii to WKYU and the other differences referred to were also eliminated (Figs. 4, 5, and 6).
Baroreceptor Function during Treatment

The steady state discharge characteristics of 71 SHRT and 75 WKYT single unit baroreceptors were recorded. The threshold pressure ($P_{th}$) for SHRT baroreceptor activation was variable with age but not significantly greater than for WKYU receptors after age 8 weeks (Fig. 7A). Treatment lowered $P_{th}$ for both WKY and SHR baroreceptors. In WKYT receptors, by 30 weeks of age, $P_{th}$ had fallen far below normal approaching a mean of 75 mm Hg. Treatment increased the sensitivity of WKYT baroreceptors to suprathreshold pressures, $S_{th}$, above that for WKYU (Figure 7B). Initially SHRT receptors were less pressure sensitive than WKYU, but, with age and treatment, $S_{th}$ increased in the SHRT group so that beyond 14 weeks of age, $S_{th}$ for SHRT was equivalent to that for WKYU.

Despite normalization of receptor responses to pressure by treatment of SHR's significant differences in the wall distortion-receptor transduction sequence remain. Figure 8A shows that, even with a normotensive BP and the accompanying normal development of most wall properties, SHRT receptors beyond 8 weeks of age have markedly lower strain thresholds, $e_{th}$, and these are also more stable with age. By 30 weeks, $e_{th}$ for SHRT was equivalent.

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**Figure 3** Relationships of the circumferential wall stress, $\sigma$ (A) and wall strain $\epsilon$ (B) at 100 mm Hg with age. Points are means of four animals. * designates significant differences between SHRT and WKYU ($P < 0.05$).

**Figure 4** Relationship of aortic radius at the prevailing systolic blood pressure with age. Points are means of four rats. There are no significant differences among the three groups.

**Figure 5** Relationships of aortic wall thickness, $h$ (A), circumferential wall strain, $\epsilon$ (B), and wall stress, $\sigma$ (C) at the prevailing systolic blood pressure with age. Points are means of four rats.

**Figure 6** Relationship of the incremental elastic modulus, $E_{inc}$ at the prevailing systolic blood pressure with age.
FIGURE 7 Relationships of the baroreceptor pressure-response characteristics with age. Points are means of n numbers of regularly discharging, single fiber baroreceptors. A: Pressure threshold, P lh. SHRT n: 14, 8 weeks; 24, 14 weeks; 13, 20 weeks; and 20, 30 weeks. WKYT n: 19, 8 weeks; 17, 14 weeks; 15, 20 weeks; and 24, 30 weeks. B: Suprathreshold pressure sensitivity, S lh (see text) for same receptors as A.

to the level for SHR. Treatment of WKY appears to lower εth, although there is great variability in the results. The suprathreshold strain sensitivity, S th, was significantly increased in treated SHR at 14 and 20 weeks but was not significantly altered in treated WKY (Fig. 8B).

In general, changes in systolic BP were accompanied by changes in P th. Figure 9 shows that for either group (WKY or SHR), when T and U animals are taken together, there is a positive correlation between systolic BP and P th (r² = 0.804 and r² = 0.557, respectively). The slope of the relationship between BP and P th for WKY receptors is roughly twice that for SHR (0.39 mm Hg P th/100 mm Hg of systolic BP and 0.17 mm Hg P th/100 mm Hg of systolic BP, respectively). Pressure threshold for WKY receptors appears to be more sensitive to changes in blood pressure than pressure threshold for SHR receptors.

Factors other than BP may be important to the determination of P th, especially in SHR. SHRT BP was a constant 125 mm Hg from 8 to 30 weeks, yet P th varied over nearly 20 mm Hg during this period (Fig. 9B, lower panel). In SHRU from 20 to 30 weeks, BP remained at its adult plateau of about 200 mm Hg, yet P th continued to increase. If εth is plotted against ε at the systolic blood pressure, εBP, (Fig. 10), the correlation improves (WKYU and WKYT, r² = 0.935; SHRU and SHRT, r² = 0.627) and the large difference in slopes in Figure 9, A and B, is reduced (WKYU and WKYT, 0.609; SHRU and SHRT, 0.517). SHR are offset to slightly higher strains at prevailing BP, and the range of strains associated with systolic BP, εBP, is smaller. As we have already noted, WKY experience a greater range of wall strains than SHR (Andresen et al., 1980), and this is true for treated animals as well. The match between strain threshold and strain produced by systolic BP is also much better for WKY. It appears that the functional properties of baroreceptors may be more closely related to the total circumferential wall strain to which the receptors are subjected than to BP per se.

Discussion

Since baroreceptors are distortion receptors (Hauss et al., 1949), discussion of their pressure transduction characteristics must include a consideration of vessel wall distensibility. Any pressure input to the baroreceptors is transformed into distortion via the distensibility properties of the vessel. This distension of the vessel wall is then encoded by the receptor process according to its mechanotransduction properties. Thus, distensibility plays the intermediary role between pressure input and receptor output. These studies have sought to quantify the interplay between pressure, distensibility, and receptor mechanotransduction.

In the normal course of the development of baroreceptor discharge properties, it appears that the burst in WKYU vessel wall growth and increase in distensibility during early adolescence are offset by a fall in the distortion sensitivity of the receptor.
Baroreceptors of Normotensive SHR

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Figure 9 Relationships of the baroreceptor pressure threshold, $P_{th}$, at various ages to the prevailing systolic blood pressure. Part A shows the WKY data; unfilled squares are WKYU, and filled squares are WKYT. The solid line is a least squares fit of the data points with a slope of 0.39 mm Hg $P_{th}$/mm Hg BP and $r^2 = 0.804$. Part B shows the SHR data; unfilled circles are SHR and filled circles are SHRT. The solid line is a least squares fit of the data points with slope of 0.17 mm Hg $P_{th}$/mm Hg BP and $r^2 = 0.557$. Notice the differences in axis scales between A and B.

and an increase in the minimum wall strain required for activation. These opposing processes result in a constant WKYU pressure threshold (Andresen et al., 1980). In hypertension, SHR vessel wall growth may be impaired and distensibility remains at low, juvenile levels. SHR baroreceptors develop lower threshold strains and have greater strain sensitivity than WKY baroreceptors. In the early stages, the increases in $e_{th}$ may compensate for the reductions in $e$, and pressure threshold may not be significantly increased. In later stages, compensation is inadequate and pressure threshold is increased.

Baroreceptor Mechanotransduction in Normotensive SHR

Treatment of SHR from an early age prevented baroreceptor resetting through 30 weeks of age. Sapru and Krieger (1979) have shown that the effect continues through 1 year of age. The treatment of SHR reported here successfully eradicated some but not all SHRU-WKYU vessel wall differences. With normotensive BP, SHRT showed near-normal growth patterns of radius and wall thickness. Total wall strain, however, remained significantly lower in SHRT although it was shifted toward normal values. As noted, treatment success-fully prevented receptor resetting (Sapru and Wang, 1976; Sapru and Krieger, 1979), and $P_{th}$ for SHRT was not different from WKYU values. Nevertheless, significant differences persisted in receptor strain transduction. Beyond 8 weeks, $e_{th}$ remained significantly below normal and normalization of baroreceptor discharge and blood pressure resulted from an appropriate and timely matching of reduced strain threshold to reduced wall distensibility. Put another way, when compared to values for WKYU “normals,” the strain sensitivity was increased while the wall distensibility was reduced.

Blood pressure in SHRT never rose above adult normotensive pressures. WKYT blood pressure was significantly lower than SHRT after 18 weeks. The smallest difference between WKYT and SHRT for the 6- to 30-week period of measurement occurred at 6 weeks of age and was 18.5 mm Hg. At 5 weeks, when treatment began, BP was not different between SHRU and WKYU (Andresen et al., 1980). In the case of the SHR, BP in treated animals had dropped significantly below BP in untreated animals by 6 weeks of age. In the following discussion, we assume that BP was normotensive throughout in the SHRT group and that normalization of the systolic BP is equivalent to normalization of the systemic diastolic pressures and, hence, mean and pulse pressures.
Role of Blood Pressure in Baroreceptor Mechanotransduction

These studies clearly indicate that the functional characteristics of baroreceptors, namely, their discharge in relation to blood pressure, result from the interaction of vessel wall distensibility with receptor mechanotransduction. Direct information about both phenomena is necessary for the interpretation of the resulting pressure responses. Recently, it was suggested that distensibility of SHRT and WKYU aorta was identical based on pressure-volume relationships (Sapru and Krieger, 1979). These pressure-volume measurements, however, were averaged over a large segment of artery, including the entire aortic arch and segments of the common carotid and subclavian arteries. With the great variability in vessel wall composition and distensibility of these various vessels, this technique may not provide sufficient specificity to measure differences in distensibility for the region of interest. Our measurements, in the region of aortic baroreceptor innervation, reveal that the prevention of resetting results not simply from the increases in distensibility associated with treatment and normotension but from the appropriate matching of receptor mechanotransduction with treated, normotensive vessel wall strain characteristics. Thus, neither wall strain nor receptor strain threshold is completely normalized by treatment and restoration of normal blood pressure. A comparison between SHRT and WKYU baroreceptors shows that $e_{th}$ is higher and $S_t$ is lower for WKYU. The comparison also holds for SHRU baroreceptors. Since distensibility is higher in WKYU than in SHRT, the resulting output of the baroreceptors may be very similar at the prevailing BP of the animal due to the opposing interactions of wall distensibility and receptor sensitivity. For SHRU baroreceptors however, the increase in strain sensitivity does not offset the reduction in wall distensibility, and pressure resetting of the baroreceptors is the result. It appears to be the degree of compensation of transduction for structural changes brought about either by growth and development or by blood pressure that results in resetting or constancy of $P_{th}$. The relatively poorer correlation coefficients of SHR $P_{th}$ with systolic BP and $e_{th}$ with $e$ at systolic BP suggest that untreated SHR may be less capable of compensating for changes in distensibility.

The implication of these results for our understanding of hypertension seems significant. It is possible that normalization of blood pressure and blood pressure variability in treated hypertensives is due in part to compensatory changes in baroreceptors of the type we have shown to occur in treated SHR. In this situation, the blood vessels remain abnormal. The heart also may remain abnormal (Sen et al., 1976). Perhaps therapy should be reconsidered since it might be necessary to lower the blood pressure of hypertensives below normal levels. Whatever the relevance for human hypertension may be, the hypertension of SHR clearly needn’t be fundamental, but may result from a number of widely dispersed membrane and biochemical defects of genetic origin which lead secondarily to an elevated blood pressure.

References

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