Arterial Baroreceptor Reflex Control of Sympathetic Nerve Activity in the Spontaneously Hypertensive Rat

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SUMMARY The combined and individual carotid sinus and aortic baroreceptor control of sympathetic nerve activity (SNA) and mean arterial pressure (MAP) were studied by direct measurement in groups of spontaneously hypertensive rats (SHR) and normotensive Kyoto Wistar rats (WKY) of 5 to 40 weeks of age. The SHR showed a significantly greater SNA and resultant MAP increase as a function of age compared to that of the WKY rats. Both SHR and WKY rats showed a significant rise in SNA and MAP with ablation of all four major baroreceptors. The proportionate change of SNA and MAP after ablation was greater in the younger SHR than in the younger WKY groups and the change in these decreased as a function of age in the SHR. The reflex inhibition of SNA via baroreceptor stimulation also decreased as a function of age in the SHR, due to a 43% loss of aortic inhibitory function; no significant loss of carotid sinus function was found in either the SHR or WKY. The decrement in aortic function occurred after the rapid phase of blood pressure development; therefore baroreceptor dysfunction cannot be the cause of the high SNA and MAP observed in young SHR. An upward resetting of central sympathetic centers was evaluated via the baroreceptor deafferentation; and, it appears that the hyperactive sympathetic nervous system and resultant hypertension in the SHR is due to central resetting of sympathetic centers rather than baroreceptor dysfunction.

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KEY WORDS • arterial baroreceptor • hypertension • sympathetic nervous system • spontaneously hypertensive rat

The sympathetic nervous system has been shown to be hyperactive in the spontaneously hypertensive rat (SHR), and to be a significant factor in the development and maintenance of high blood pressure in this genetic model of hypertension. The factors responsible for the elevated sympathetic nerve activity (SNA) in the SHR are unknown. Historically, it was hypothesized that in experimental renal hypertension a loss of carotid sinus and aortic reflex inhibitory control of SNA resulted in an increase in SNA which in turn produced the hypertensive condition. However, in such studies, the arterial baroreceptors have been shown to adapt or reset during hypertension, such that they have an increased stimulus pressure threshold, a normal firing frequency, and an extended operational range.

Studies in which the aortic and carotid sinus baroreceptor involvement in the development and maintenance of high blood pressure in the SHR have been investigated are few and conflicting. In vitro studies of the isolated carotid sinus of the SHR have shown that these receptors reset to a higher pressure threshold, but have a receptor firing frequency equal to that of normotensive rats.

One group has reported that the aortic baroreceptors of the SHR are also reset to a higher stimulus pressure threshold and have a normal firing frequency. However, another group was unable to show that the firing frequency of the receptors was normal. They demonstrated a significant decrease in aortic baroreceptor activity over an extended pressure range in older SHR. In vivo studies using young SHR during the developmental phase of hypertension have shown that sino-aortic denervation results in a greater mean arterial pressure rise in the SHR than in normotensive rats. These authors concluded that a primary defect or dysfunction of the arterial baroreceptors was not involved in the pathogenesis of spontaneous hypertension. Recently, it has been shown that the arterial baroreceptors are less effective in reflexly inhibiting
SNA of older SHR in which the hypertension was stable compared to normotensive rats of comparable age. A loss of functional control by these receptors seems to increase with age.

In view of the conflicting reports between in vitro and in vivo observations concerning the role of the carotid sinus and aortic baroreceptors in the development and maintenance of the hypertensive process, and since quantitative data showing the combined and individual inhibitory influences of these arterial receptors on SNA in SHR of different ages are not available, the present study was conducted.

In this study the combined and individual carotid sinus and aortic baroreceptor control of SNA was investigated in SHR of various ages. The results indicate that there was a significant loss of baroreceptor sinus and aortic baroreceptor control of SNA was investigated in SHR of various ages. The results indicate that there was a significant loss of baroreceptor control of SNA in the maintenance phase, but not in the developmental phase of the hypertension. A baroreceptor defect does not appear to be the major cause of the hyperactive sympathetic nervous system and the resultant hypertension in young SHR, but may be one of the factors responsible for the maintenance of the sympathetic nerve activity and blood pressure in older SHR.

**Methods**

Experiments were conducted using groups of various ages of male SHR (Okamoto Strain) and normotensive male Kyoto Wistar (WKY) rats, the parent strain of the SHR (Cox Laboratory Animal Supply). All rats were anesthetized with sodium pentobarbital (20 mg/kg, i.p.). A light level of anesthesia was maintained with supplemental doses of 2.5 mg/kg given intravenously as needed. The trachea was exposed through a midline incision, intubated, and the rats were placed on a rodent respirator (Model 680, Harvard Apparatus, Inc., Millis, MA). The vagal-sympathetic trunks were bilaterally isolated from the carotid arteries and a loose ligature was placed around each trunk. A snare occluder was then placed around each carotid below the sinus area.

Arterial pressure was measured at the level of the lower thoracic aorta by means of a pressure transducer (Model P23-Dd, Statham Instruments, Oxnard, CA) connected to a polyethylene tube (PE-50, wall) filled with heparinized saline. This catheter was inserted through the abdominal aortic wall below the kidneys and positioned in the lower thoracic aorta. Mean arterial pressure (MAP) was derived using an electronic averaging circuit. The right femoral vein was cannulated (PE-60 tubing) for the administration of supplemental anesthetic doses.

Sympathetic nerve activity (SNA) was recorded from the renal nerves coursing along the left renal artery. A left lateral incision was made exposing the left kidney, its blood supply, sympathetic nerves and the abdominal aorta. A small bundle of postganglionic nerve fibers was separated from the renal plexus using microscopic assistance (Model 644051, Carl Zeiss). The connective tissue coverings were removed and the nerve bundle was placed across a pair of fine stainless steel electrodes for recording purposes. The nerve bundle and electrodes were bathed in a pool of 37°C mineral oil to prevent tissue drying. The efferent elecetrograms were processed and recorded as previously described. The efferent signals were detected with an AC differential preamplifier (Model P-15, Grass Instrument Co., Quincy, MA) with a time constant of 3 msec. The amplified nerve spikes were displayed on an oscilloscope (Model R103N, Tektronix Inc., Beaverton, OR) for visualization and photographing (Tektronix Camera, Model C-12). These signals were further amplified, then rectified using a full-wave rectifier circuit and integrated continuously with an RC integrator (time constant 20 msec). The integrated signals were averaged using an RC network with a time constant of 1 second. The nerve data presented in this paper are expressed as mean renal sympathetic nerve activity (RSNA) and are calibrated in microvolts (µV) above noise level. The noise level was determined by shorting the input electrodes, and this value, for each experiment, was electronically subtracted from the electroneurogram by adjusting the zero bias level on the recording system. All analog and electronically averaged signals were recorded on a Beckman Type R Dynograph (Beckman Instruments, Inc., Fullerton, CA). To summarize for graphic presentation, mean RSNA was determined by measuring the area under the electronically derived curve over a period of 10 to 30 seconds. Data collection began 15 to 30 minutes after experimental preparations were completed.

To compare the levels of MAP and mean RSNA of the WKY with that of the SHR during the development and maintenance phases of the hypertension, separate groups of six rats at 5, 10, 15, 24, and 40 weeks of age were tested. In these same rats, the combined and individual reflex inhibitory effects of the aortic and carotid sinus baroreceptors were determined. In addition, the SNA and MAP rise in response to the removal of each of the two groups of baroreceptors in turn was measured to gain information concerning the involvement of the central nervous system in the genesis of the hyperactive sympathetic nervous system and resultant hypertension in the SHR. In these experiments one would expect to see the SNA increase to the same level in the SHR and WKY groups of similar age if indeed no upward resetting of the central sympathetic centers was involved. If, however, an upward resetting of the central sympathetic centers was present, then there should be a difference between the maximum uninhibited static sympathetic outflow between the SHR and WKY groups.

To determine the combined reflex inhibitory effect of the carotid sinuses and aortic baroreceptors on mean RSNA, arterial pressure was abruptly increased in the receptor areas by occlusion of the abdominal aorta at the base of the diaphragm using a snare occluder to arrest flow for only 15 seconds. The reflex reduction of mean RSNA associated with the central pressure rise was measured between the 5th and 15th seconds of the occlusion. The aortic baroreceptor...
reflex influence was determined after bilateral carotid artery occlusion to remove these receptors from the system; the carotid arteries were occluded 15 to 20 seconds before stimulating the aortic receptors. The carotid baroreceptor effects were determined after removing the aortic receptors from the system by bilateral vago-sympathetic trunk sectioning. The sequence of baroreceptor testing used in this study was: 1) both groups, aortics only; 2) both groups, carotids only; and 3) neither group. In order to test the contribution of the two baroreceptor groups independently in the same animal, the above sequence was necessary. With all four baroreceptor pathways ablated or opened (bilateral carotid occlusion and vago-sympathetic trunk sectioning), the basal buffering influence of these receptors on MAP and SNA was determined by the fractional change in each. To test for completeness of the “open loop” system, MAP was again increased by aortic occlusion. The relative control of the combined or individual baroreceptors was determined by calculating the percent decrease in mean RSNA from the initial pre-occlusion level for each respective baroreceptor configuration.

Three reflex experiments were done in each rat for every operative baroreceptor configuration with appropriate recovery periods between each. The SNA responses of the three experiments were averaged for each rat and from these a group mean ± SE was calculated. The differences between group mean values were determined statistically using Student’s t test.

Results

Influence of Age on Sympathetic Nerve Activity and Blood Pressure

As has been well documented in other studies, the MAP in the SHR increased significantly with age.3-11 The hypertension occurred in two phases (fig. 1A): a rapidly developing phase between 5 and 24 weeks of age (MAP = 118 ± 3.6 and 163 ± 6.8 mm Hg, respectively), and a maintenance phase thereafter, during which blood pressure increased slightly. In the WKY controls, MAP also increased significantly (p < 0.05) between 5 and 24 weeks of age (MAP = 108 ± 2.8 and 122 ± 5.8 mm Hg, respectively), and was maintained at a constant level thereafter (fig. 1A). The absolute group mean MAP level at each age tested and the change in pressure between age groups for the SHR was greater than that of the WKY groups (p < 0.05).

Mean RSNA in the SHR increased rapidly between 5 and 24 weeks of age as well (RSNA = 20 ± 2.5 and 56 ± 3.8 μV, respectively) paralleling the increase in MAP (fig. 1B). Similarly, mean RSNA of the WKY increased significantly between 5 and 24 weeks of age (RSNA = 13 ± 2.4 and 23 ± 3.2 μV, respectively); however the magnitude of change at each age group was significantly less (p < 0.05) than that of the same age SHR groups. Although RSNA increased in both the SHR and WKY rats as a function of age, the mean change between the youngest and oldest groups was 4 times greater (RSNA = 46 vs 11 μV) in the hypertensive model than in the WKY. Figure 1A and B show a positive relationship between sympathetic nerve activity and blood pressure in the SHR as previously reported.3

Influence of the Number of Operative Baroreceptors on Sympathetic Nerve Activity and Blood Pressure

Removal of all Four Major Baroreceptor Pathways

When the number of baroreceptors was reduced from four to zero by bilateral vago-sympathetic trunk sectioning and carotid artery occlusion, MAP and mean RSNA increased significantly (p < 0.01) in all the SHR and WKY age groups tested (figs. 2A and B). The MAP and RSNA increases paralleled the initial resting (“closed loop” configuration) levels. In all age WKY groups, the “open loop” MAP levels exceeded the initial “closed loop” levels of the respective SHR groups; however, these values were still significantly less (p < 0.01) than the “open loop” levels of the same age SHR groups (fig. 2A).

The mean RSNA “open loop” levels of the 5- and 15-week-old WKY rats exceeded the initial “closed loop” levels of the respective SHR groups. After 15 weeks of age, however, RSNA levels of the WKY
groups were less than in the SHR groups (fig. 2B). The "open loop" RSNA levels of all the SHR groups were significantly greater ($p \leq 0.05$) than those of the WKY groups of the same age. Although the absolute magnitude of MAP and mean RSNA in the "four open loops" condition was greater in the SHR groups, examination of the change in these two variables in response to the loss of all four baroreceptors provides a different picture (fig. 3).

The change in MAP in the 5-, 10- and 15-week-old SHR and WKY groups was approximately the same; however, that of the 24- and 40-week-old SHR groups were significantly ($p < 0.05$) less than that of the corresponding WKY groups (fig. 3A). The mean RSNA changes of the 5- and 10-week-old SHR groups were significantly ($p < 0.05$) greater than those of the same age WKY groups, whereas that of the 24- and 40-week-old SHR rats were significantly ($p < 0.05$) less than those of the respective WKY rats (fig. 3B).

**Removal of the Carotid or Aortic Baroreceptors**

When the carotid or aortic baroreceptors were individually removed from the inhibitory control system, MAP and mean RSNA increased in all SHR and WKY groups tested. However, the responses were less than those observed in the "four open loops" condition. Examples of such experiments in a 10- and a 40-week-old SHR are shown in figures 4A and 5A. Since the response characteristics of both MAP and RSNA of the 10- and 40-week-old WKY rats was similar to those of the 10-week-old SHR, examples of these are not shown. In Part A of figures 4 and 5, each panel (left to right) shows the initial baseline MAP and RSNA, and the subsequent response of these to a 15-second aortic occlusion for the respective operative baroreceptor groups. Part B represents the initial MAP, and Part C the initial RSNA level at each of the following baroreceptor configurations: all four baroreceptors operative (A and C), only the carotids operative (C), only the aortics operative (A), and

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**Figure 2.** Initial (I) and "open loop" (O) mean arterial pressure (A) and mean renal nerve activity (B) levels in groups of seven spontaneously hypertensive rats (SHR) and normotensive Kyoto Wistar controls (WKY) of different ages. Values represent means ± se. All SHR "open loop" (O) mean values are significantly greater than the WKY values of the same age at the $p < 0.05$ level. The shaded area represents the difference between the SHR and WKY groups in the "open loop" condition.

**Figure 3.** Mean arterial pressure (A) and mean renal sympathetic (B) response (change) to removing all four major arterial baroreceptors ("open loop" condition) in groups of seven spontaneously hypertensive rats (SHR) and normotensive Kyoto Wistar controls (WKY). Values represent means ± se. Values marked with an asterisk are significantly different at the level of $p < 0.05$. The shaded areas represent the difference between SHR and WKY responses.
neither group of baroreceptors operative (N). Part D of these figures depicts the percent reflex inhibition of RSNA in response to an abrupt 50 to 60 mm Hg rise in MAP (taken from Part A).

In the 10-week-old SHR (figure 4B), MAP increased from an initial level of 126 to 140, 143, and 178 mm Hg, respectively, when the carotids, aortics, and both of these baroreceptor groups were made inoperative. Mean RSNA (figure 4C) had a similar pattern of change increasing from 26 to 30, 34, and 65 μV. Deletion of the carotid and aortic baroreceptors had approximately the same effect on MAP and RSNA in the 10-week-old SHR, but the characteristics of the response were different in the 40-week-old SHR (fig. 5). Although both MAP and RSNA increased with removal of each of the baroreceptors, a greater change occurred with exclusion of the carotids (figs. 5B and C). Another feature of these figures is that the magnitude of MAP and RSNA change, with all four major baroreceptor pathways inoperative, was less in the 40-week-old SHR; i.e., MAP increased 38 mm Hg and RSNA 31 μV in the 10-week-old SHR compared to 25 mm Hg and 23 μV in the 40-week-old SHR. Experiments such as these for each age group are summarized in figures 6 (MAP) and 7 (RSNA).

Effects of Baroreceptor Stimulation on Sympathetic Nerve Activity

Simultaneous Carotid and Aortic Baroreceptor Stimulation

With both carotid and aortic baroreceptors operative, a 50 to 60 mm Hg MAP rise (aortic occlusion) reflexly inhibited mean RSNA as shown in figures 4A and 5A. This reflex was apparent in all animals tested. However, a differing response character and magnitude of change was seen between the young and old SHR groups. Part D of figures 4 and 5 shows the relative inhibitory control of all four major baroreceptors in RSNA. In these examples, 95% of the initial (pre-MAP rise) mean RSNA was reflexly inhibited in the 10-week-old SHR, whereas in the 40-week-old SHR only 63% of the initial mean RSNA was inhibited by the same procedure (fig. 5A and D). Experiments such as these delineating the

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**Figure 4.** Basal mean arterial pressure and mean renal sympathetic nerve activity and the changes in these during descending aortic occlusion in a 10-week-old SHR. Panel A: Initial levels and responses for various operative baroreceptor configurations. Panel B: Steady-state mean arterial pressure levels at each operative baroreceptor configuration. Panel C: Steady-state mean renal sympathetic nerve activity at each operative baroreceptor configuration. Panel D: Percentage of baroreceptor reflex inhibition of renal sympathetic nerve in response to an increase in MAP for the respective operative baroreceptors (A and C = both aortic and carotid; C = only carotids; A = only aortics; and N = neither carotids nor aortics). The actual sequence of baroreceptor testing was aortic before carotid as described in the Methods section. For clarity of presentation the carotid effects were presented before the aortic response in figures 4–7. The time indication at the top of Part A represents 1-second intervals.
total inhibitory control of all four major baroreceptors mean RSNA are summarized in figure 8A.

In the WKY groups, no significant difference in the reflex inhibition of RSNA occurred as a function of age (fig. 8A); the inhibition ranged from 98 ± 4.2% at 5 weeks of age to 96 ± 6.2% at 40 weeks. In the 5- and 10-week-old SHR groups, the RSNA inhibition was similar to that of the WKY groups (97 ± 4.8 and 96 ±
4.2%, respectively), however, after 15 weeks of age, the RSNA inhibition progressively decreased as a function of age from 82 ± 4.4% at 15 weeks to 56 ± 7.6% at 40 weeks (fig. 8A). This loss of total reflex inhibitory control of RSNA between the young and older (24 and 40 weeks) rats was significant (p < 0.01), as was the difference between the SHR and WKY at 24 and 40 weeks of age.

**Individual Carotid or Aortic Baroreceptor Stimulation**

An abrupt increase in MAP reflexly decreased mean RSNA when only the carotid or aortic baroreceptors were operative as shown in figures 4A and 5A. In the examples shown, carotid baroreceptor stimulation reflexly decreased mean RSNA 51% of the control level in the 10-week-old SHR (fig. 4A and D) and 50% in the 40-week-old SHR (fig. 5A and D).

The carotid sinus baroreceptor reflex decrease of RSNA was proportionately similar for all SHR and WKY age groups (fig. 8B). The magnitude of RSNA inhibition ranged from 48 ± 5.3% at 10 weeks of age to 44 ± 6.0% at 40 weeks in the WKY groups, and from 48 ± 5.6% at 5 weeks to 40 ± 5.0% at 40 weeks in the SHR groups. Although the relative inhibitory control of the carotids over RSNA decreased as a function of age, the difference between the oldest and youngest groups (8 μV) was not significant.

Examples of the reflex effects of the aortic baroreceptors on RSNA are shown for the 10- and 40-week-old SHR in figures 4 and 5, respectively. In the 10-week-old SHR, aortic receptor stimulation decreased mean RSNA 48% of the initial value (fig. 4D), whereas in the 40-week-old rat, only a 32% reduction occurred (fig. 5D). A summary of the aortic baroreceptor stimulation effects on mean RSNA in the various SHR and WKY age groups is shown in figure 8C.

The reflex inhibition of RSNA by the aortic or carotid baroreceptors did not change as a function of age in the WKY groups, nor was there a significant difference between baroreceptor groups at any age tested in these normotensive rats (fig. 8B and C). Aortic inhibition of RSNA ranged from 42 ± 4.6% at 5 weeks of age to 39 ± 3.8% at 40 weeks in the WKY rats. In the SHR groups, the aortic baroreceptor inhibitory control of RSNA decreased as a function of age (fig. 8C). Although the contribution by the aortic baroreceptors was less than that of the carotids at all ages, only that of the 24- and 40-week-old groups was significantly different (p < 0.01). Similarly, only the difference between the 24- and 40-week-old SHR and WKY groups was significant (p < 0.01). The range of aortic inhibition of RSNA for the SHR was from 42 ± 5.0% at 5 weeks of age to 23 ± 4.4% at 40 weeks. Thus, the loss of aortic baroreceptor control of RSNA was 45% and 48% in the 24- and 40-week-old groups, respectively, when compared with that of the 5- and 10-week-old groups. Compared to the same age WKY groups, a 49% and 43% loss of inhibitory influence by these receptors was observed for the 24- and 40-week-old SHR groups, respectively.

**Discussion**

The present study clearly shows that SNA increases in the SHR as a function of age and that the sym-
Hypertensive nervous system of this strain is hyperactive compared to that of the normotensive Kyoto-Wistar strain (fig. 1). The MAP and mean RSNA for the various SHR age groups are comparable to those previously reported. The MAP and RSNA of the various WKY age groups also agree with those of other normotensive control rats that were genetically related to the SHR. The significantly greater MAP and RSNA in the 5-week-old SHR suggests that the mechanisms responsible for the hyperactive sympathetic nervous system and resultant hypertension are operative at a very young age.

Even though the role of the arterial baroreceptors in the development of hypertension in the SHR has been previously investigated, their influence on the maintenance of the hypertensive state has not been examined. In addition, the combined and individual buffer actions of the carotid and aortic baroreceptors on SNA in the SHR and WKY rats of different ages have not been quantitatively defined. Although several other baroreceptor regions are known to exist in various sites in the heart and arteries, the two carotid and aortic baroreceptors constitute the major high pressure afferent pathways to the medullary vasomotor center. The possible role of the cardiopulmonary low-pressure mechanoreceptors in this study was not evaluated. Afferent pathways from these receptors ascend to the CNS via the vago-sympathetic trunk and should play some role in renal SNA control when these pathways are intact. However, in testing only the carotid baroreceptors, no contribution by the cardiopulmonary receptors should have occurred, since these afferent pathways were cut. In testing the aortic baroreceptor or both buffer groups simultaneously, some low-pressure receptor inhibition might have occurred. However, without knowing the changes in central venous pressure or cardiac volumes, assessments of cardiopulmonary influences in these experiments cannot be made. The dominance of the high-pressure baroreceptors is clearly demonstrated for the rat in the "four open loops" condition by the resultant increase in MAP and RSNA (fig. 2), and the abolition of the reflex inhibitory effect of these receptors on SNA after their removal from the sympathetic control system (figs. 4D and 5D).

The increase in MAP and RSNA, which occurred with all four baroreceptors inoperative (figs. 2, 6 and 7) shows the amount of basal buffering action of these receptors. By use of the following formula:

$$\text{Basal Buffer Effect (\%) = \frac{\text{open loop level} - \text{closed loop level}}{\text{open loop level}} \times 100}$$

the basal buffering action of RSNA in all WKY groups was calculated to be 57% of the "open loop" level; whereas that of the SHR groups decreased as a function of age (57, 57, 40, 29 and 25%, respectively). A similar loss of buffering action on MAP as a function of age occurred in the SHR groups (18, 26, 22, 21 and 17%), but not in the WKY groups (18, 25, 30, 33 and 32%). These data indicate that in the SHR there is a progressive loss of baroreceptor buffering of basal SNA and MAP in the maintenance phase of hypertension. The percentage of basal MAP of the "open loop" level in the three youngest SHR groups agrees with those reported by Thant et al. in response to sinoaortic denervation. The percentage of basal MAP buffering in the mature WKY groups (24 and 40...
weeks) agrees with those reported by Ninomiya and Irisawa who used a similar procedure in normotensive cats.

The reduced MAP response of the two older SHR groups when compared to the WKY (figs. 3A and 8), appears to be directly related to a diminished SNA response. A reduced baroreceptor buffering capability in these older SHR (fig. 7A) would suggest that the basal SNA is set closer to the maximum static outflow of the involved central sympathetic centers. This may account for the observed reduced change in SNA and resultant MAP in the older SHR in the “open loop” condition. If SNA had not been measured in these experiments, the reduced pressure rise could be explained by the secondary morphological changes in resistance vessels as described by Folkow and coworkers. According to these investigators, an increased vessel wall thickness in the SHR makes the arterioles more resistive and closer to their maximum constricted level. When these vessels are exposed to an additional sympathetic stress, the full effectiveness of such may not be seen due to little available constrictor reserve. A combination of elevated basal SNA tone and vascular hypertrophy should position the resistance vessels at a point on their response curve where little constrictor reserve is available. A low basal SNA tone and no vascular hypertrophy could explain the observed MAP responses in the WKY and younger SHR groups. It is challenging to propose a link between the SNA, vascular hypertrophy, and hypertension. The early onset of elevated SNA in the SHR may be a trigger mechanism for both vascular hypertrophy and hypertension in the pressure development phase; whereas a combination may be responsible for the hypertension maintenance.

The mean RSNA and MAP response to removal of the four major baroreceptors should provide information concerning the involvement of the central nervous system (CNS) in the hyperactive sympathetic nervous system of the SHR. If, for example, there were no upward resetting of central sympathetic centers and the increased SNA was only due to a lack of baroreceptor buffer action, then in the “open loop” condition, sympathetic outflow and MAP in both the SHR and WKY groups should be approximately equal. Such was not the case as shown in figure 2A and B. The “open loop” RSNA and MAP of the SHR was significantly greater than that of the WKY in each respective age group. The difference between the SHR and WKY “open loop” levels (shaded area, fig. 2A and B) should represent the contribution or upward resetting of the CNS. From these figures a resetting of 42–57% and a resultant 10–15% change in MAP can be calculated for each age group. Thus, both the magnitude of the basal renal SNA outflow and the change in SNA are suggestive of a major central nervous system involvement in the hypertensive process. This upward central resetting may involve a medullary sympathetic component as well as other sympathetic centers that are additive to the static outflow of the medulla. Although the mechanisms responsible for this upward resetting are unknown, it is clear that the process begins before 5 weeks of age and is almost complete by 15–20 weeks of age.

The involvement of the individual baroreceptor groups in the increased SNA and resultant blood pressure in the SHR is well defined in this study. Baroreceptor resetting has been described in the SHR for both aortic and carotid baroreceptors. These studies, in general, investigated only the changes in receptor characteristics associated with the development of hypertension and not their functional ability to control SNA and blood pressure. The carotid and aortic baroreceptors had approximately the same buffer effect on basal SNA and MAP in all WKY age groups and in the 5- and 10-week-old SHR (figs. 6 and 7) as indicated by the same rise in RSNA and MAP when these receptor groups were removed individually. In the 15-, 24- and 40-week-old SHR groups, opening the carotid sinus feedback loops resulted in a greater RSNA and MAP response than occurred with aortic loop opening. This clearly shows that the basal buffering action of the aortic baroreceptors was less than that of the carotids as suggested from the in vitro receptor firing studies of Nosaka and Okamoto and Sapru and Wang. Quantitative estimates of the extended baroreceptor buffer action on RSNA was obtained from the percentage reflex inhibition of nerve activity when MAP was abruptly increased 50 to 65 mm Hg (figs. 4 and 5). Simultaneous stimulation of the aortic and carotid sinuses reflexly inhibited RSNA by 95% to 98% of the initial value in all the WKY age groups and in the 5- and 10-week-old SHR groups (fig. 8A). This finding agrees with that of Ninomiya and Irisawa in cat studies. The progressive loss of baroreceptor buffer action in the three older SHR groups is shown by an 18, 28 and 44% loss of SNA inhibitory function. This observation is consistent with the nonquantitative findings of the authors and other investigators. The SHR baroreceptor group contributing to the decrement observed in figure 8A is undoubtedly the aortic receptors (fig. 8C). This loss was 10, 32 and 43% of the inhibitory capability of the 5-week-old group. The relative inhibitory control of RSNA by the aortic and carotid sinus baroreceptors, when stimulated simultaneously or individually, agrees with that reported by other investigators using different normotensive animals.

The mechanism responsible for the functional loss of aortic receptors was not investigated in this study. It appears that the mechanism is a result of the hypertension, since no functional loss occurred during the rapid phase of development of hypertension (figs. 2 and 8). Hypertension is known to cause vascular hypertrophy and this may be the major cause of the loss of aortic receptor function as described by Sapru and Wang.

The mechanisms responsible for the upward resetting of the sympathetic nervous system and the actual site of the central resetting also remain to be defined. It is interesting that centrally acting antihypertensive drugs, such as clonidine, L-dopa, and alpha-methyl dopa, effectively lower blood pressure in the SHR by...
suppressing SNA centrally (Judy, unpublished data). These compounds presumably stimulate the central alpha adrenergic system, which lowers MAP by reducing peripheral sympathetic activity. Such information suggests that the primary central mechanism may be a loss of higher or lower CNA inhibitory control of sympathetic excitatory centers. Clarification of this possibility remains for future investigations.

In summary, this study has indicated that: 1) the sympathetic nervous system is hyperactive in the SHR compared to that of the derived WKY strain; 2) a functional loss of baroreceptor reflex inhibitory control of SNA occurs with increasing age in the SHR, primarily due to aortic baroreceptor nerve dysfunction; 3) baroreceptor dysfunction does not occur until after the phase of rapid high blood pressure development, and thus cannot be the causative factor for the development of hypertension, although it is probably one of the factors responsible for the maintenance of elevated pressure in the SHR; and 4) an upward resetting of central sympathetic centers appears to be the causative factor for the hyperactive sympathetic nervous system in the SHR and a component of the resultant hypertension. The central location of this upward resetting may involve the medullary vasomotor center and other higher or lower sympathetic centers that are additive to the vasomotor center's SNA outflow. Sympathetic nerve activity and MAP increase at a very early age in the SHR preceding the adaptive changes in baroreceptor function and perhaps vascular morphology that could account for the hypertensive process. It appears that the SHR is a neurogenic hypertension model in which the sympathetic nervous system initiates the hypertensive process and possibly vascular hypertrophy. The excessive SNA may result from a genetically induced CNS lesion. The location and mechanisms involved remain to be clearly defined.

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