Carotid sinus baroceptor functions in the spontaneously hypertensive rat

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NOSAKA, SHOICHIRO, AND S. C. WANG. Carotid sinus baroceptor function in the spontaneously hypertensive rat. Am. J. Physiol. 222(5): 1079-1094. 1972.--Carotid sinus baroceptor function in the spontaneously hypertensive rat (SHR) was studied by isolating and perfusing the sinuses at various perfusion pressures and recording the systemic arterial pressure responses. Under steady-state conditions for systemic arterial and carotid sinus perfusion pressures, the threshold pressure to elicit a hypotensive response was significantly higher in SHR (120-140 mm Hg) than in normotensive controls (60-100 mm Hg). Higher perfusion pressures were required to elicit maximum hypotensive responses in SHR (200-240 mm Hg in SHR; 140-160 mm Hg in normotensive controls). Baroceptor sensitivity was also evaluated by stepwise increases of the sinus pressure. In normotensive controls, blood pressure responses to steps of 20 mm Hg were greater at the basal perfusion pressure of 100 mm Hg than at 60 or 160 mm Hg. In the SHR, baroceptor responsiveness to equivalent steps was minimal at 100 mm Hg basal perfusion pressure, but it increased remarkably at 160 mm Hg. Electrophysiological studies showed that these differences were due mostly to the altered function of the carotid sinus baroceptors. It was concluded that baroceptor sensitivity (both transient and steady-state) in SHR is shifted toward higher pressure levels. Possible mechanisms of these functional baroceptor differences are discussed.

Experimental neurogenic hypertension has been produced in dogs by surgical disruption of the sinoaortic nerves (5). However, many investigators have denied the role of the sinoaortic regulatory system in the pathogenesis of essential hypertension because hemodynamic changes in the latter differ from those found in experimental neurogenic hypertension (1). Indeed, Kezdi (8) demonstrated unequivocally that the receptors of the carotid sinus nerves are not disrupted in essential hypertension and their regulatory mechanism acts normally at the higher blood pressure level. In 1956, McCubbin et al. (15) showed that in chronic experimental renal hypertension the carotid sinus baroceptors are reset to regulate at an elevated blood pressure level and they tend to maintain rather than prevent the hypertension. This reset phenomenon has since been confirmed by Kezdi and Wennemark (11) and Kezdi (9).

Spontaneously hypertensive rats develop hypertension on a genetic basis and are regarded as a good model for the study of human essential hypertension (17). In the present experiments, the systemic arterial responses and baroceptor discharges to changing carotid sinus pressure were investigated in these rats and compared with those of normotensive animals.

**METHODS**

Twenty-three spontaneously hypertensive male rats (SHR), 6-8 months of age, were used in these experiments. An equal number of normotensive male rats (Wistar strain) of the same age were used as controls.

Animals were anesthetized with α-chloralose, 60 mg/kg iv. The left femoral artery was cannulated for recording systemic blood pressure. The trachea was intubated and the animal was allowed to respire spontaneously or was artificially respired when gallamine was administered.

Isolation and perfusion of carotid sinuses. Both carotid sinuses were exposed by removing the sternocleidomastoid and mandibular biventer muscles, the hyoid bones, and hypoglossal nerves. The common and external carotid arteries were cannulated for perfusion. All other branches were ligated. The carotid sinus was perfused with oxygenated Tyrode solution (pH adjusted to 7.4) at variable perfusion pressures (see Fig. 1). Both cervical vagosympathetic trunks were cut. Experiments were started 30 min after these procedures were completed when the systemic blood pressure was stabilized.

Blood pressure responses to carotid sinus perfusion pressure changes. The systemic blood pressure and carotid sinus perfusion pressure were monitored from the left femoral artery and from a branch in the perfusion system close to carotid sinuses, respectively. These were recorded via Statham P23A pressure transducers on a Grass model 7A polygraph.

In each animal, carotid sinus pressure was varied in two ways. First, the sinus pressure was elevated 20 mm Hg each time in a staircasewise manner. Each elevation in the sinus pressure was kept for 50 sec or longer until changes in the systemic arterial pressures were stabilized. The steady-state relationship was obtained by plotting these stabilized blood pressure levels against sinus pressures. Secondly, the sinus pressure was elevated rapidly from the basal perfusion pressure and then returned to the basal level in a stepwise fashion. Each step or increment was 20 mm Hg greater than the preceding one. After a maximum fall in the arterial pressure was reached, sinus perfusion pressure was lowered to the original level. The smallest increment was 20 mm Hg and the largest was 160 mm Hg. The maximum fall in
arterial pressure for each increment was used to evaluate baroceptor sensitivity. These responses were studied with different basal sinus pressures.

Recording of carotid sinus baroceptor activities. In another group of animals, activities of afferent fibers from the carotid sinus baroceptors were recorded. Since the carotid sinus nerve in the rat is very short (3-4 mm in total length), a unipolar recording electrode was placed on the glosso-pharyngeal nerve. Portion of glosso-pharyngeal nerve between 2 arrows was used for recording. Approximate scale is given for 1 cm of actual size.

RESULTS

Systemic arterial blood pressure responses to carotid sinus perfusion pressures. The average systolic blood pressure of normotensive controls was 119 ± 3 mm Hg (mean ± SE), the diastolic pressure 90 ± 3 mm Hg, and the mean pressure 100 ± 3 mm Hg. The corresponding values for SHR were 187 ± 3 mm Hg, 148 ± 3 mm Hg, and 164 ± 3 mm Hg, respectively. The steady-state relationship between systemic arterial pressure and carotid sinus perfusion pressure showed an inverted sigmoid curve. The arterial pressure started to fall at certain sinus perfusion pressure (threshold). As the perfusion pressure increased, the arterial pressure showed a greater fall until a maximum hypotensive level was reached (Fig. 3 and Table 1). In most cases, as the sinus pressure was further elevated beyond the pressure for the maximal fall, the hypotensive response became less pronounced. In the normotensive group, the threshold sinus pressure was between 60 to 100 mm Hg (60 mm Hg in two, 80 mm Hg in three, and 100 mm Hg in two), whereas in SHR it was 120 and 140 mm Hg (120 mm Hg in four and 140 mm Hg in six). The sinus pressure to bring about maximum hypotensive levels was also higher in SHR (200 mm Hg in five, 240
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mm Hg in three, not determined above 200 mm Hg in one, and above 240 mm Hg in one), while in normotensive controls, the corresponding values were 120 mm Hg in one, 140 mm Hg in three and 160 mm Hg in three.

Responses to transient stepwise increase of sinus pressure were studied at three different basal perfusion pressures 60, 100, and 160 mm Hg (Fig. 4A and Table 2). When the basal perfusion pressure was 100 mm Hg in normotensive rats, an increment of 20 mm Hg elicited a sizable fall in the systemic arterial pressure, and in every case a maximum response was brought about with an increment of 60–80 mm Hg. However, when the basal perfusion pressure was lowered to 60 mm Hg, the response to the increment of 20 mm Hg was negligible. At this level, a pressure elevation greater than 100 mm Hg was necessary to elicit a maximum response. If the basal perfusion pressure was raised to 160 mm Hg, the response was greatly reduced for all subsequent increments.

On the other hand, when the basal perfusion pressure in SHR was set at 100 mm Hg (Fig. 4B and Table 2), an increment of 20 mm Hg elicited a small response or none at all. An increment of 100 mm Hg or more was required to obtain a maximum response. However, when the basal perfusion pressure was elevated to 160 mm Hg, an increment of 20 mm Hg gave a substantial response and an increment of 60 or 80 mm Hg, a maximum response.

Carotid sinus baroceptor firing and carotid sinus perfusion pressures. Carotid sinus baroceptors in the rats, like those in cats and dogs, showed firing with bursts and pauses synchronous to heart beats when the sinus was not isolated from the body circulation. After isolation of carotid sinus and perfusion with a constant pressure, the sinus nerve showed a continuous firing pattern.

**Table 1.** Steady-state relationship between systemic arterial pressure and carotid sinus perfusion pressure

<table>
<thead>
<tr>
<th>Carotid Sinus Perfusion Pressure, mm Hg</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
<th>140</th>
<th>160</th>
<th>180</th>
<th>200</th>
<th>220</th>
<th>240</th>
<th>260</th>
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<tbody>
<tr>
<td>Systemic blood pressure response, mm Hg</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Normotensive controls</td>
<td>7</td>
<td></td>
<td></td>
<td>163±16</td>
<td>160±10</td>
<td>159±8</td>
<td>135±5</td>
<td>110±6</td>
<td>96±11</td>
<td>97±13</td>
<td>101±14</td>
<td>120±10</td>
</tr>
<tr>
<td>SHR</td>
<td>10</td>
<td></td>
<td></td>
<td>220±5</td>
<td>218±5</td>
<td>106±6</td>
<td>186±7</td>
<td>166±10</td>
<td>132±10</td>
<td>152±8</td>
<td>151±9</td>
<td>167±9</td>
</tr>
</tbody>
</table>

Values are means ± SE.
Under both steady state and transient state, the results of direct nerve recording were consistent with the blood pressure responses observed under the same conditions. Figure 5 shows the steady-state firing of carotid sinus baroceptors in response to a variety of carotid sinus perfusion pressures. According to count-rate analyses by the computer, the threshold sinus perfusion pressure was higher in SHR (100 mm Hg in one, 120 mm Hg in two, 140 mm Hg in three, and 160 mm Hg in one) than in normotensive controls (60 mm Hg in three, 80 mm Hg in one, and 100 mm Hg in two). The pressure needed to elicit the maximum firing rate was also greater in the SHR (200 mm Hg in one, 220 mm Hg in two, 240 mm Hg in two, and 260 mm Hg in two) than in normotensive controls (120 mm Hg in one, 140 mm Hg in three, 160 mm Hg in one, and 180 mm Hg in one).

At an appropriate basal perfusion pressure, an increase in the sinus pressure caused an instantaneous increase in the baroceptor firing rate (Fig. 6). This increase was greatest in the first few seconds followed by a gradual decrease toward a stable firing rate. When the elevated sinus pressure was brought down to the basal level, the firing rate showed a slight reduction for a short period, and then returned to the initial control rate. Count-rate analyses showed that the increment of 20 mm Hg elicited a much greater increase in baroceptor firing in all normotensive controls at the basal perfusion pressure of 100 mm Hg than at 60 mm Hg or 160 mm Hg. At these latter basal pressures, the corresponding increases in firing were very small (Fig. 7). Also, at the basal perfusion pressure of 100 mm Hg, the baroceptors showed a maximum firing rate with relatively small increments (an increment of 40 mm Hg in one animal, 80 mm Hg in four, and maximum firing rate not reached at 100 mm Hg in two). At the basal pressure of 60 mm Hg, greater increments were necessary to bring about a maximum firing rate (80 mm Hg in one, 100 mm Hg in one, 120 mm Hg in two, and 140 mm Hg in three). When the basal pressure was 160 mm Hg, the baroceptor firing rate did not show much increase to any increment.

The baroceptors of SHR showed only small increases in firing to an increment of 20 mm Hg at the basal perfusion pressure of 100 mm Hg compared with the normotensive responses. They exhibited uniformly greater increases to the same increment at 160 mm Hg basal pressure (all 11 cases). At this basal pressure, maximum firing rate was reached with an increment of 80 mm Hg (40 mm Hg in one, 60 mm Hg in two, 80 mm Hg in seven, and not reached at 100 mm Hg in one). At 100 mm Hg basal pressure, it was reached only at much larger increments (100 mm Hg in one, 120 mm Hg in four, 140 mm Hg in three, and not reached at 160 mm Hg in three).
According to Koch (12) the curve of systemic arterial pressure response versus sinus pressure varied from species to species. In rabbits the responsive range was 25-160 mm Hg and in monkeys it was 20-180 mm Hg. The so-called Blutdruckcharakteristikkurve of these animals was located more to the left compared with that of dogs (53-220 mm Hg), cats (65-230 mm Hg), and hare (40 to above 250 mm Hg). Our results of the baroceptor response to steady sinus pressure showed that the threshold sinus perfusion pressure in Wistar rats was around 80 mm Hg and maximum response was obtained at the sinus pressure of about 160 mm Hg. Thus, it appears that the rat blood pressure response curve may lie between these two groups of animals. However, Koch recorded the blood pressure responses by varying the sinus perfusion pressure for only 5-10 sec. It is doubtful that the steady state was achieved in such a short interval of time.

Our experiment revealed that steady-state baroceptor function of the SHR was reset in that the threshold pressure, as well as the entire curve, was shifted to a higher sinus pressure. This finding is in complete accordance with the results of McCubbin et al. (15) and Kezdi (9, 10, 11) on chronic renal hypertensive dogs. This shift in the steady-state baroceptor function is also similar to that reported for the aortic depressor nerve of the SHR (16). Previous reports on nerve recordings have not only dealt with steady-state relationships (3, 13) but have also been concerned with the rate of transient change in pressure (3, 4, 7, 13). The transient blood pressure response of the system has been studied by dynamic stepwise increase and decrease of the sinus perfusion pressure (14, 20). But these studies were carried out in normotensive animals. In our experiments, transient responses to increments (20-100 mm Hg) of sinus perfusion pressure were studied in both normotensive and hypertensive rats. It is important to place emphasis on responses to small increments (20 mm Hg) in evaluating baroceptor sensitivity because larger increments may result in a saturated response.

As clearly shown by our results of systemic blood pressure response to transient increase of sinus perfusion pressure, the baroceptor sensitivity was dependent on the absolute basal perfusion pressure. The baroceptors of the normotensive controls (mean blood pressure at 100 mm Hg) showed the greatest response to a 20 mm Hg increment at the basal perfusion pressure of 100 mm Hg, whereas those of SHR (mean blood pressure at 160 mm Hg) exhibited peak response at a basal pressure of 160 mm Hg. In other words, baroceptor sensitivity in the SHR optimized at a higher sinus perfusion pressure. The above finding is interesting in that baroceptors are known to be most sensitive at their physiological blood pressure level (12).

Although the results from the whole-nerve recordings showed a general agreement with the blood pressure responses, there was an inconsistency in a few experiments. There were two cases in the normotensive group in which a maximum increase in firing was not reached with increments of 100 mm Hg at the basal perfusion pressure of 100 mm Hg, whereas increments of 60-80 mm Hg elicited maximum hypotensive responses without exception. This discrepancy of results might have been due to the fact that these blood...
pressure responses are complex baroceptor functions and represent the responsiveness of the total reflex system. Single-fiber or a few-fiber recordings did not yield absolutely uniform results although most fibers in each group showed the general pattern as described for whole-nerve recordings. This, however, may not be surprising, for the individual end organs may have different characteristics (2, 3, 13). Our results suggest that the difference of overall baroceptor functions between SHR and normotensive controls is due to the shift of characteristics of most, perhaps not all, baroceptor end organs in SHR.

It appears that recording of baroceptor nerve activity has a limited usefulness and yielded no additional information. However, under certain conditions, such as following administration of antihypertensive agents, nerve recording has a distinct advantage over blood pressure response in that the latter is greatly affected by the altered sympathetic activity while the former is not.

There are several possible mechanisms that may play a role in the altered baroceptor function in SHR. One is that these changes are primary and directly operate to increase sympathetic outflow, elevating the blood pressure until it copes with the level preset by these changes. If so, the hypertension thus developed is similar to that induced by baroceptor denervation. However, SHR does not show an increase in heart rate (18) or in cardiac output (19) which characterize the hemodynamics of neurogenic hypertension. On the other hand, hypertension could be primary. Thus, the baroceptors may either adapt or become sensitive only to inactivation of lower threshold fibers. A third possible mechanism is that these changes are due to changed distensibility of the carotid sinus wall. In SHR the baroceptors function as sensitively at a higher basal perfusion pressure as they do in the normotensive controls at their normal pressure. Therefore, a reduction in distensibility of the sinus wall may be the cause of the changed baroceptor function in these animals. We have made preliminary attempts to alter the distensibility of the sinus wall in SHR by means of topical application of drugs, such as papaverine, sodium nitrite, and mephénysaline, which are believed to alter baroceptor activity by altering the arterial wall distensibility (6). However, this is an extremely difficult procedure for the rat, and no convincing results have been obtained. These problems require further investigation.

Whatever the causative mechanism may be, the modified baroceptor function in SHR appears to have a practical meaning. The baroceptors of SHR are definitely reset to operate at an elevated blood pressure level. There is no doubt that these changes contribute to the stability and maintenance of hypertension in SHR, as suggested by McCubbin et al. (15) in the renal hypertension in dogs.

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REFERENCES