HYPERTENSION is among the important risk factors for stroke. However, it is seldom clear why one hypertensive individual has a stroke and another does not. Study of animal models analogous to human essential hypertension, the spontaneously hypertensive rat, (SHR), and the strain of the SHR that is susceptible to stroke as well as hypertension, stroke-prone strain of SHR, decreased cerebral blood flow might result leading to cerebral ischemia and an increased incidence of stroke. However, Ikeda, et al., carried this concept further and postulated that if elevated superior cervical sympathetic nerve activity was present in the stroke-prone strain of SHR, decreased cerebral blood flow might result leading to cerebral ischemia and an increased incidence of stroke. However, Ikeda, et al., did not provide direct evidence to support this concept.

The purpose of this study was to directly measure superior cervical sympathetic nerve activity in SP, SHR and their normotensive controls, Wistar-Kyoto (WKY), during resting conditions and during a maximal sympathetic stimulus. The change in sympathetic nerve activity between these two conditions could contribute to our understanding of the animal's ability to respond to sudden changes in cerebral perfusion pressures and protect against these changes. Such information would further enhance our understanding of stroke.

**Methods**

Twenty-three male animals 16–26 weeks of age were used for this study. They were allowed free access to standard Purina rat chow and water. Nine of the animals were SP (original stock obtained from Carl Hansen at the National Institute of Health), eight were SHR and six were WKY (Charles Rivers, Boston, MA). All rats were anesthetized with sodium pentobarbital (50 mg/kg i.p.). Each rat was artificially ventilated with a respirator and paralyzed with gallamine triethiodide (6 mg/kg). The left femoral artery was catheterized with thin walled PE-50 tubing filled with barbital (50 mg/kg i.p.). Each rat was artificially ventilated with a respirator and paralyzed with gallamine triethiodide (6 mg/kg).
heparinized saline for measurement of blood pressure. The left superior cervical trunk, caudal to the superior cervical ganglia, was then separated from the vagus and aortic depressor nerves. The sympathetic nerve fibers were stripped of their connective tissue covering using 40X magnification (Karl Zeiss, model 64051).

The sympathetic fibers were then suspended from bipolar stainless steel electrodes and bathed in a pool of mineral oil to prevent drying. The nerve activity was detected with an AC differential preamplifier (Grass Instruments, model P-15) with a time constant of three milliseconds. The amplified nerve signals were displaced on a Tektronix oscilloscope (model 5103) for visualization. These signals were further amplified using a high gain operational amplifier, then rectified using a full wave rectifier circuit and integrated continuously with an RC integrator (time constant = 20 milliseconds). This integration method has been previously described by Ninomiya, et al.4 5  The signals were averaged using an RC network with a time constant of one second.

The nerve data presented in this paper is expressed as mean superior cervical sympathetic nerve activity (SNA) above noise level and is calibrated in microvolts (μV). The noise level was determined in each experiment by shorting the input electrodes and recording the noise level. This value (3 to 7 μV) was then subtracted from the raw data obtained in each experiment. The blood pressure and electroneurogram were both recorded on a Beckman type R dynograph.

Within 45 minutes after sedation, superior cervical sympathetic nerve activity was recorded during resting conditions for 15 minutes in all animals. The average sympathetic nerve activity during that period was determined and designated as resting sympathetic nerve activity. A maximal sympathetic discharge6 was obtained through inducing central ischemia produced by rapid hemorrhage of the animals. This was accomplished by cutting out the heart. The mean arterial pressure fell to 0 in less than five seconds.7

**Results**

The mean arterial pressure of the SHR and SP was significantly elevated over the WKY (SHR 191 ± 11*, SP 181 ± 6*, WKY 107 ± 6 mm Hg, *p < .001) during resting conditions (Table 1). Resting superior cervical sympathetic nerve activity of SHR was significantly elevated over SP and WKY (SHR 21 ± 3*, SP 12 ± 1, WKY 10 ± 2 μV, *p < .02) (table 1). SHR peak sympathetic nerve activity (during central ischemia) was significantly elevated over that of SP and WKY (SHR 250 ± 11*, SP 114 ± 12, WKY 114 ± 18, *p < .001) (fig. 1). The increase in superior cervical sympathetic nerve activity of SHR was significantly elevated over the change in SP and WKY (SHR 229 ± 10*, SP 101 ± 11, WKY 105 ± 18, *p < .001) (fig. 2).

**Discussion**

In this study, the capacity for sympathetic outflow of SP was similar to that of WKY and much less than SHR. One must consider the possibility that the lack of capacity for elevated sympathetic nerve activity in SP may be a contributing factor to the accelerated stroke found in these animals compared to SHR.

It has been shown that the sympathetic nerves play an important role in cerebral vascular protection during acute hypertension when the autoregulatory capacity of the cerebrovascular bed has been exceeded.4 5 This protective influence of the sympathetic nerves outside

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>WKY (n = 6)</th>
<th>SHR (n = 8)</th>
<th>SP (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>107 ± 6</td>
<td>191 ± 11*</td>
<td>181 ± 6*</td>
</tr>
<tr>
<td>Resting SNA</td>
<td>10 ± 2</td>
<td>21 ± 3†</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>Maximal SNA</td>
<td>114 ± 18</td>
<td>250 ± 11†</td>
<td>114 ± 12</td>
</tr>
<tr>
<td>ΔSNA</td>
<td>105 ± 18</td>
<td>228 ± 10†</td>
<td>101 ± 11</td>
</tr>
</tbody>
</table>

ΔSNA = changes in sympathetic nerve activity; MAP = mean arterial pressure; WKY = Wistar-Kyoto; SHR = spontaneously hypertensive rat, not stroke prone; SP = stroke prone spontaneously hypertensive rat.

* p < 0.001 compared to WKY.
† p < 0.02 compared to WKY and SP.
‡ p < 0.001 compared to WKY and SP.
SYMPATHETIC NERVE ACTIVITY: A LINK TO STROKE?/Mueller and Black

of the autoregulatory range would be expected to be attenuated in SP. Thus, although the SP rats are hypertensive like SHR, they did not appear to have the same protection of their cerebral vasculature by sympathetic nerves as SHR.

In addition to the acute protective effect of an elevation in sympathetic nerve activity on the cerebral vasculature,9 a chronic influence of sympathetic nerves on the vasculature has been reported that appears to be protective during profound cerebral vasodilation and blood-brain barrier disruption.10 It has been suggested that this long term effect is due to a "trophic" influence on smooth muscle proliferation in the vessel wall.11,12 Denervation of the sympathetic supply of several vascular beds has been shown to decrease smooth muscle mass and alter the structural integrity of the vessel.12,13 This long term "trophic" influence of sympathetic nerves on the SP vasculature might also be altered compared to SHR.

In summary, the present experiment directly demonstrated that the SP had an attenuated capacity for superior cervical sympathetic nerve activity when compared to SHR. An elevated sympathetic nerve activity to the cerebral vessels in SHR may be protective against stroke both acutely8,9 and chronically.10,11 One can conjecture that alterations in superior cervical sympathetic nerve activity, possibly genetic in origin, may contribute to stroke in selected hypertensive individuals.

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