Pathogenetic Similarity of Strokes in Stroke-Prone Spontaneously Hypertensive Rats and Humans

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SUMMARY The predilection sites of cerebrovascular lesions (cerebral hemorrhage and/or softening) were studied in 1,278 stroke-prone spontaneously hypertensive rats (SHRSP). The precise supply to the main cerebral arteries was determined by trypan blue injections and microangiography. The three major territories were the anteromedial cortex, the occipital cortex, and the basal ganglia. A common angioarchitectural characteristic of these three areas was the blood supply through "recurrent branching" from the main stream. In the basal ganglia, where there is a preponderance of lesions, the arteries responsible for these lesions belonged to the lateral group of lenticulostriate arteries. The primary pre-stroke arterial lesions were further studied microangiographically in SHRSP killed at the time the initial symptoms of stroke were detected. These points were located at the "boundary zone" of the main cerebral arteries. Our findings indicated the importance of these two angioarchitectural minor loci as the basis for functional or organic circulatory disturbances that may cause stroke. Since these local factors of stroke are common in the cortex and basal ganglia of rats and basal ganglia of humans, these SHRSP are regarded as good pathogenetic models for studies on stroke in humans.

Introduction

STUDIES on the pathogenesis of cerebrovascular lesions had been limited by the lack of appropriate animal models. Recently, Okamoto et al.¹ reported the establishment of stroke-prone spontaneously hypertensive rats (SHRSP) in which stroke (cerebral hemorrhage and/or softening) developed spontaneously, with a high incidence (more than 80%) in males. The establishment of this strain showed the importance of heredity in the pathogenesis of some forms of stroke.² Our studies on this strain reveal that the systemic factor responsible for stroke is the rapidly developing systemic hypertension,¹³ and that prophyactic control of the blood pressure under the critical level decreased the incidence of stroke.⁴ Since our preliminary study⁵ indicated that the predilection sites for stroke in SHRSP seemed related to certain angioarchitectural characteristics, local factors for stroke were analyzed by re-examining more than 1,000 autopsies of SHRSP, examining precisely the appropriate feeding areas of the main cerebral arteries and the primary pre-stroke arterial lesion in SHRSP killed when they showed the initial symptoms of stroke. These local factors for stroke were compared with those in humans and the qualification of an SHRSP as a model for stroke in man was ascertained in this study.

Methods

SHRSP¹ used or examined in this study were the F₂₀-₂₄ generation of SHR maintained at the Department of Pathology, Faculty of Medicine, Kyoto University (Kyoto, Japan). Stroke (cerebral hemorrhage and/or infarction) developed in these rats spontaneously, as shown in figure 1. The incidence of stroke in these SHRSP, which died a natural death, was 84% in males and 80% in females. Controls were stroke-resistant SHR (SHRSR) (the incidence of stroke about 7%), and normotensive control rats of Wistar-Kyoto (WK), from which the SHR had been derived. The developmental course of hypertension at the F₂₀-₂₃ generations of SHRSP and SHRSR is shown in figure 2.

In order to determine the areas supplied by the main cerebral arteries in SHRSP, SHRSR and WK rats, physiological saline with 0.5% trypan blue was injected into the aortic catheter in the rat under Nembutal anesthesia (30 mg per kilogram). Those rats perfused with the contrast medium were immediately frozen in a refrigerator for one hour and later fixed in cold 10% formalin. The brains were sectioned coronally or sagittally for x-ray photography using a Softex Type CMB (Softex Co, Ltd, Tokyo, Japan). The brain slices were dehydrated for the preparation of histological sections or made more transparent with tetraethyltetrachloro-1-hydroxynaphthalene for three-dimensional study of the course of arteries.

The frequency distribution of branching angles in the main cerebral arteries of rats and humans was statistically analyzed using microangiographical or angiographical pictures. As the main stream of the anterior cerebral artery in both rats and humans follows the path of the corpus callosum in the cerebral longitudinal fissure, and that of the middle cerebral artery of rat extends around over the surface of the cerebral hemisphere, their branching angle measurements in the lateral projection could be accepted as a grossly adequate method, though such measurements of the middle cerebral artery in humans and the posterior...
cerebral artery in both rats and humans could have no significance. Branching angles were determined by two lines: the interorifice line of branching vessels and the line between the two points which were the midpoint of the interorifice line and the midpoint of the line connecting two points which locate at the same distance as the radius of the parent vessel from the orifice of the branching vessel (see diagram in fig. 8).

For comparative studies between human and rat brains, carotid angiographical pictures of 41 men without cerebral lesions were taken at random at the Department of Neurosurgery, Faculty of Medicine, Kyoto University. The frequency distribution of branching angles was obtained by measuring the angles of 137 branches from the anterior cerebral arteries taken at random.

The primary pre-stroke arterial lesions (fig. 3) were detected by the application of the aforementioned microangiographical technique to about 50 SHRSP which were suspected to be in the initial stage of stroke after a long-term daily observation with the closest attention on their behavior, characteristic appearance, symptoms of stroke, and loss of body weight.

All numerical data were statistically analyzed by the Student small sample t-test.

Results

SHRSP, SHRSR and WK rats showed no differences in the basic angioarchitectural pattern for cerebral blood supply, which was clarified as follows. The feeding areas of the main cerebral arteries in the rat brain were demonstrated
by coloring the brain with trypan blue injected into the anterior, middle and posterior cerebral arteries, respectively. Figure 4 shows the brain preparations in the horizontal and coronal sections. The cortical blood supply demonstrated by this study is illustrated in figure 5.

The internal carotid artery took a horizontal path forward (comparatively longer than in man) after giving off the posterior cerebral artery, and terminated in two main branches (the anterior and middle cerebral arteries) which formed a "carotid fork" (more sharply than in man). The anterior cerebral arteries formed an "azygos" vessel which supplied the cortex and medullary substance of the anterior two-thirds of the cerebral hemisphere in the sagittal section. The middle cerebral arteries extend upward over the lateral and dorsal surface of the hemisphere, dividing into multiple branches. The posterior cerebral arteries originate from the "internal carotid" artery, curve and extend upward to supply the tentorial surface of the hemisphere including the occipital cortex and medullary substance (5 mm-wide zone

**Figure 2** Blood pressure in stroke-prone and stroke-resistant SHR of the F26-33 generations.

**Figure 3** Localization of primary pre-stroke arterial lesions in the boundary zone of the main cerebral blood supply.
along the rear edge of the occipital lobe in adult rats.

The blood supply to the basal ganglia in the rat was investigated further by the microangiographical technique with the tetralin transparency method or by serial sectioning, and the detailed feeding area of each branch was determined. The anterior part of the caudate-putamen nucleus (corresponding to the head of the caudate nucleus in man) was supplied medially by Heubner's arteries from the anterior cerebral arteries and laterally by the lateral group of lenticulostriate arteries, while the posterior part was supplied by the medial group of lenticulostriate arteries.

The statistical analysis of the predilection sites of stroke, consisting of 1,740 lesions in 1,278 autopsy cases of SHRSP, is summarized in table 1.

In SHRSP the predilection site with the highest incidence was the cortical region (69.8%). Cortical lesions were classified into three types according to the areas supplied by the main cerebral arteries: (1) anteromedial lesion (33.7%), supplied by the anterior cerebral artery, (2) lateral lesion (6%), supplied by the middle cerebral artery, and (3) occipital lesion (30.1%), supplied by the posterior cerebral artery. The frequency of anteromedial and occipital lesions was significantly higher than that of lateral lesions. The site of second greatest frequency in rats was the basal ganglia (24.5%), especially the anterior part of the basal ganglia (88.8%). This area was supplied by the lateral group of lenticulostriate arteries and Heubner's arteries (table 2). The most frequent site of infarction was in the left hemisphere; the occipital cortex and basal ganglia were involved but not the anteromedial cortex which was supplied by the "azygos" anterior cerebral artery.

Angioarchitectural characteristics common to these sites of predilection were examined. The anterior and posterior cerebral arteries (fig. 5) were supplying the anteromedial and

![Figures 4A and B](http://stoke.ahajournals.org/) Feeding areas of anterior (A) and middle (B) cerebral arteries in horizontal (top) and coronal sections (bottom), demonstrated by the selective infusion of trypan blue through an ultramicro glass tube into the anterior or middle cerebral arteries.
FIGURE 5  Cerebral blood supply in rats.

Studies on the predilection sites of stroke in numerous autopsy cases of SHRSP suggested that the primary pre-stroke arterial lesions were localized in the "boundary zone" of the main cerebral arteries. As indicated by the examples shown in figure 3, minute lesions in the anteromedial cortex,

occupital areas and had a high incidence of "recurrent branchings" from the main stream. However, the middle cerebral arteries, which did not supply areas commonly infarcted, had few recurrent branchings (figs. 6a and b). These recurrent branchings from the anterior and posterior cerebral arteries were commonly observed in the brains of SHRSP, SHRSR and WK rats; such typical recurrent branchings were rare in the human brain (fig. 6c). Heubner's arteries and lenticulostriate arteries also had recurrent branchings (fig. 7). These recurrent branchings were commonly observed in SHRSP, SHRSR and WK rats.

Statistical comparisons in the frequency distribution of branching angles in the main cerebral arteries of rats and humans are summarized in figure 8. The main branches of the anterior cerebral arteries had a high frequency of branching angles less than 90° both in SHRSP (89.3 ± 1.6°, mean ± SE) and in WK rats (88.9 ± 1.9°). There was a significant difference in the frequency distribution between rats and humans. The mean of the branching angles of main branches from the anterior cerebral artery was 114.6 ± 1.9° in humans. Therefore, it was concluded that the areas supplied by the anterior and posterior cerebral arteries were mainly through recurrent branchings in rats but not in humans. However, such recurrent branchings were not noted in the main branches of the middle cerebral arteries in SHRSP (137.2 ± 1.4°) and WK rats (128.9 ± 1.9°).

TABLE 2  Analysis of Lesions in the Basal Ganglia of Rat Brain

<table>
<thead>
<tr>
<th></th>
<th>Anteromedial</th>
<th>Antrolateral</th>
<th>Posterior</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Lesions</td>
<td>219</td>
<td>160</td>
<td>48</td>
<td>427</td>
</tr>
<tr>
<td>%</td>
<td>61.3</td>
<td>37.5</td>
<td>11.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Heubner's artery.
Lateral lenticulostriate artery.
Medial lenticulostriate artery.
FIGURE 6 Microangiographical manifestation of recurrent branchings from the anterior and posterior cerebral arteries in rat brain compared to human brain. A: Medial part of the brain in a sagittal section. B: Lateral part of the brain in a sagittal section. C: Branchings from the anterior cerebral artery in the human brain. (A modified reproduction of a microangiographical picture from reference 7.)

between the anterior and middle cerebral arteries, were found medially in the area supplied by the anterior cerebral arteries, while starting points in the occipital cortex between posterior and middle cerebral arteries were localized posterolaterally in the area covered by the posterior cerebral arteries. These findings indicated that both anterior and posterior cerebral arteries were responsible for the development of cerebral lesions.

Discussion

The successful establishment of SHRSP by Okamoto and colleagues\(^1\) suggested the existence of genetic factors for stroke\(^2\) and made it possible to confirm the great importance of hypertension in the development of cerebral stroke.\(^1,9\)

Further evidence of SHRSP as models for human stroke was obtained in the present studies by analyzing local factors of stroke in SHRSP and comparing them with the same factors in humans.

SHRSP and WK rats showed no differences in their cerebral blood supply patterns; there were no specific angiarchitectural characteristics in SHRSP that could explain their stroke-proneness.

In SHRSP the most preponderant site for stroke was the cortical region (69.8%), in contrast to the relatively low incidence of stroke in the human cortex (13.1% according to the mean of the clinical statistics by Stehbens\(^6\) and others). Massive cortical lesions in SHRSP were seen as compared to small asymptomatic cortical lesions in man. Further statistical analysis of the three types of cortical lesions revealed that anteromedial and occipital lesions showed significantly higher incidences than lateral lesions in SHRSP.

On the other hand, the common site of stroke in rats and...
Development of Cerebral Arteries in Human Embryo

Recurrence of Current Blood Stream

Developmental Convolution of Human Brain

FIGURE 9 Persistence of recurrent branching from anterior and posterior cerebral arteries in rats, in phylogenetic comparison with human brain. (Diagrams of ontogenic arterial development of human brain were referred to Padget.)

Angioarchitectural characteristics common to these predilection sites in both rats and humans were confirmed by our studies to be recurrent branchings. Anterior and posterior cerebral arteries, which seemed to be responsible for anteromedial and occipital lesions in SHRSP, have recurrent branchings and the lenticulostriate arteries (responsible for stroke in basal ganglia in both SHRSP and humans) branch off recurrently from the middle cerebral arteries. However, four main arteries (seemingly not so responsible for cortical lesions), i.e., the middle cerebral artery in rats, and three main cerebral arteries in humans, had few recurrent branchings. Statistical comparison of the frequency distribution of branching angles in the main cerebral arteries confirmed the importance of "recurrence" in the predilection sites of stroke in both SHRSP and humans. It is generally recognized that few cortical branchings of the middle and posterior cerebral arteries in man show such a recurrence.

The persistence of such "recurrent branching" of the anterior and posterior cerebral arteries in rats is understandable when phylogenetic difference in the degree of developmental convolution of the brain between rats and humans is considered, referring to the arterial development following the ontogenic developmental convolution of human brain described by Padget (fig. 9).

Analysis of lesions in the rat basal ganglia revealed that the anterior part of the basal ganglia, supplied by the lateral
group of lenticulostriate arteries and Heubner’s arteries, showed a high incidence of stroke in the SHRSP (88.8%) in contrast to the highest incidence of putamen with the body of caudate nuclei in man. The head of the caudate nucleus in man proved to be supplied by Heubner’s arteries and the body of the caudate nucleus with putamen is supplied by the lateral group of lenticulostriate arteries. This fact indicates the significance of the lateral group of lenticulostriate arteries (and Heubner’s arteries which are markedly developed in the rat brain) for the development of stroke in both rats and humans.

Figure 10 illustrates the microangiographical manifestation of lenticulostriate arteries (and Heubner’s arteries) in the basal ganglia common to rat and human brains. Heubner’s arteries and lenticulostriate arteries in rats and humans also have “recurrent branchings” from their main streams, that is, anterior and middle cerebral arteries, respectively. Double feeding of the anterior part of the striatum by Heubner’s and lateral lenticulostriate arteries in rats also may be explained by a phylogenetic difference in the degree of developmental convolution of the brain between rats and humans.

These comparative studies between rat and human brains confirmed the significance of “recurrent branchings” as one of the local factors of stroke in the cortical region in rats and in the basal ganglia of both rat and human brains. In fact, the areas supplied by recurrent arteries show an increase in vascular permeability before the development of stroke, and later cerebral softening and/or hemorrhage in a high incidence as proved by our present studies.

Statistically significant differences in the incidence of stroke between the right and left hemispheres and between right and left basal ganglia also might be caused by right and left differences in the main cerebral blood supply. The left common carotid artery shows “recurrent branching” from the aortic arch in contrast to “current branching” of the right brachiocephalic artery from the aorta in rats. On the other hand, no laterality was observed in the incidence of stroke in the hemispheres supplied by the anterior cerebral arteries which form an “azygos” artery.

There is some experimental evidence that “recurrent branching” causes a decrease in flow in the distal portion of branching when flow pressure is controlled at a constant level, and that laminar flow causes a decrease in particles contained in the distal portion of “recurrent branchings.” These phenomena might result in circulatory disturbances (hypoxia) such as a decrease in blood flow and anemic blood flow in the distal portion of “recurrent branching.” In particular, circulatory disturbances (hypoxia) might be intensified in the regions supplied by the anterior cerebral artery, which is the “azygos” artery, and by the posterior cerebral arteries, which also “recurrently” branch off from the internal carotid arteries in rats.

Shellshear (1921) was the first to find the existence of “recurrent branching” in the lateral group of lenticulostriate arteries. Matsuoka was the first to suggest the significance of “recurrent branchings” of the lenticulostriate arteries for the pathogenesis of stroke. Katsuki, stressed its importance in stroke by examining the brain by a plastic injection method. Finally, the establishment of SHRSP made it possible to clarify the responsibility of “recurrent branching” for the pathogenesis of stroke.

The present study indicates not only “recurrent branching” but also a “boundary zone” as the local factors of stroke. The importance of a “boundary zone” in the pathogenesis of stroke in humans was suggested by Van Den Bergh, but was confirmed by our study on the primary pre-stroke arterial lesions in SHRSP killed at the initial stage of stroke.

The difference of predilection sites of stroke between rat and human brains is very important for clarifying the local factors of stroke such as “recurrent branching” and “boundary zone.” Now that cortical lesions characteristic in SHRSP are supposed to be caused by the same mechanism as the most frequent lesions of the basal ganglia in man, SHRSP can be regarded as good pathogenetic models for studies on stroke in humans.

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