Cerebral artery remodeling in stroke-prone spontaneously hypertensive rats

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Stroke is a major cause of disability and presents a serious and growing threat to public health [1]. Epidemiological studies have shown that stroke is the second leading cause of death in the world [2]. Among the risk factors for stroke, hypertension is the most powerful modifiable factor and the second most powerful risk factor after age [3–5]. Hypertension eventually results in target organ damage such as myocardial hypertrophy and artery remodeling [6]. Over 70% of stroke cases can be attributed to hypertension

[7]. Arterial baroreflex (ABR) is one of the most important physiological mechanisms controlling blood pressure (BP) regulation. Its function, manifested as baroreflex sensitivity (BRS), correlates to the degree of end-organ damage in spontaneously hypertensive rats (SHR), a genetic model for hypertension [8]. Stroke-prone SHR (SHR-SP) is a substrain of SHR that exhibits much higher incidence of stroke compared with age-matched SHR. The mechanisms underlying such a difference remain to be fully understood.

Figure 1 Comparison of incidence of stroke, neuroethology assessment, BP and BRS between SHR and SHR-SP. 28-week-old SHR ($n = 25$, male 13, female 12) and SHR-SP ($n = 26$, male 13, female 13) were used. **(A)** Positive symptoms occurred in 9 of 26 SHR-SP, with a stroke incidence of 34.62%, and no animal with positive symptom was found in SHR. **(B)** Zea-Longa score of SHR-SP was significantly higher than that of SHR. **(C)** BP of SHR-SP was significant higher than that of SHR. **(D)** BRS of SHR-SP was significantly lower than that of SHR. ** $P < 0.01$, *** $P < 0.001$ versus SHR.

Table 1 Morphological parameters of cerebral arteries in 28-week-old SHR and SHR-SP

Strain	Gender	n	W ($\times 10^{-1}$ mm)	L ($\times 10^{-1}$ mm)	W:L	WCSA ($\times 10^{-2}$ mm ²)
<i>external diameter 0.07–0.09 mm arteries</i>						
SHR	Male	13	0.119 $\pm$ 0.033	0.572 $\pm$ 0.064	0.217 $\pm$ 0.052	0.264 $\pm$ 0.053
SHR-SP	Male	13	0.118 $\pm$ 0.044	0.577 $\pm$ 0.094	0.205 $\pm$ 0.097	0.254 $\pm$ 0.063
SHR	Female	12	0.121 $\pm$ 0.082	0.573 $\pm$ 0.044	0.211 $\pm$ 0.105	0.256 $\pm$ 0.047
SHR-SP	Female	13	0.121 $\pm$ 0.032	0.581 $\pm$ 0.125	0.208 $\pm$ 0.084	0.262 $\pm$ 0.085
SHR	Total	25	0.120 $\pm$ 0.024	0.572 $\pm$ 0.056	0.215 $\pm$ 0.059	0.260 $\pm$ 0.050
SHR-SP	Total	26	0.120 $\pm$ 0.036	0.579 $\pm$ 0.092	0.218 $\pm$ 0.087	0.258 $\pm$ 0.071
<i>external diameter 0.7–0.9 mm arteries</i>						
SHR	Male	13	0.647 $\pm$ 0.144	6.481 $\pm$ 0.435	0.100 $\pm$ 0.033	14.563 $\pm$ 3.145
SHR-SP	Male	13	0.823 $\pm$ 0.214***	6.216 $\pm$ 0.537*	0.132 $\pm$ 0.033***	18.102 $\pm$ 4.853***
SHR	Female	12	0.619 $\pm$ 0.153	6.477 $\pm$ 0.503	0.096 $\pm$ 0.040	14.214 $\pm$ 3.267
SHR-SP	Female	13	0.804 $\pm$ 0.188***	6.217 $\pm$ 0.586*	0.129 $\pm$ 0.041***	17.872 $\pm$ 4.824***
SHR	Total	25	0.638 $\pm$ 0.136	6.479 $\pm$ 0.462	0.099 $\pm$ 0.024	14.248 $\pm$ 3.124
SHR-SP	Total	26	0.814 $\pm$ 0.190***	6.217 $\pm$ 0.563*	0.133 $\pm$ 0.036***	17.964 $\pm$ 4.504***

W, wall thickness; L, lumen diameter; W:L, wall-to-lumen ratio; WCSA, wall cross sectional area.

* $P < 0.05$.

*** $P < 0.001$ versus SHR.

Signs of stroke, including movement of limbs, respiration, diet, fur and consciousness, were observed in 25 SHR (male 13, female 12) and 26 SHR-SP (male 13, female 13) at the age of 28 weeks. The neuroethology assessment was performed by using the Zea-Longa score (maximum score: 5, higher score indicates more severe neurological impairment). Systolic blood pressure (SBP), diastolic blood pressure (DBP) and BRS were determined in conscious rats as previously described [9]. Serial transverse paraffin sections (5 μ m thick separated by 100 μ m) were prepared using routine techniques. Ten slides were stained with hematoxylin-eosin and observed under light microscope. Structure of cerebral arteries with external diameter of 0.07–0.09 mm and 0.7–0.9 mm were evaluated with a SDK-2000 system for image analysis. Data are expressed as mean $\pm$ SD. Differences between the two groups were evaluated by unpaired *t*-test. Stroke incidence was analyzed with chi-square test. The relationships of SBP and BRS with wall thickness of cerebral arteries were assessed by univariate regression analysis. $P < 0.05$ was considered statistically significant.

The behavior of each rat was observed separately. Positive signs occurred in 9 of the 26 SHR-SP (incidence: 34.62%), and none out of the 25 SHR (Figure 1A). The Zea-Longa score was significantly higher in SHR-SP (Figure 1B, $P < 0.001$ vs. SHR). SBP and DBP were significantly higher in SHR-SP (Figure 1C, $P < 0.01$ vs. SHR).

BRS was significantly lower in SHR-SP (Figure 1D, $P < 0.01$ vs. SHR).

There was no significant difference in wall thickness, lumen diameter, wall-to-lumen ratio and wall cross sectional area between SHR-SP and SHR in the cerebral arteries with external diameter of 0.07–0.09 mm (Table 1). For cerebral arteries with external diameter of 0.7–0.9 mm, wall thickness, wall-to-lumen ratio and wall cross sectional area were significantly larger ($P < 0.001$), and the lumen diameter was significantly smaller ($P < 0.05$) in SHR-SP compared with that in SHR. In SHR-SP, the wall thickness was positively correlated with SBP ($r = 0.366$, $P < 0.05$), and negatively correlated with BRS ($r = 0.596$, $P < 0.01$).

ABR dysfunction has been repeatedly reported to be present in acute stroke [10]. A recent study from this laboratory in hypertensive rats indicated that BRS is an independent predictor for stroke [9]. Results from the current study showed that hypertension and ABR dysfunction were more severe in SHR-SP than in SHR. Consistent with the relatively high BP and low BRS in SHR-SP, cerebral artery remodeling, e.g., increased vascular wall thickness and decreased lumen diameter, was also more pronounced in SHR-SP.

In conclusion, cerebral artery remodeling may represent a key pathological feature that makes SHR-SP much more vulnerable to stroke than SHR.

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