Significance of Cerebral Blood Flow in the Mechanism of Stroke in Stroke-prone Spontaneously Hypertensive Rats (SHRSP)

Evidence Obtained by Acute Ischemic Hypoxia

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Emphasis has been placed on the cerebral circulation for the clarification of the initiation mechanism of stroke (Yamori et al: Stroke 8: 456, 1977). That is, when stroke-prone SHR (SHRSP) develop severe hypertension over 200 mmHg around the age of 2 months, regional cerebral blood flow (rCBF) begins to decrease abruptly. Long-lasting reduction in rCBF causes arterionecrosis due to increased vascular permeability following chronic ischemic hypoxia. These experimental facts have given us a clue to clarify the reason why severe hypertension plays a prime role in developing stroke (cerebral hemorrhage and/or softening) in SHRSP as previously reported (Okamoto, Yamori, and Nagaoka: Circulat Res 34–35 (Suppl 1): 143, 1974), and also the reason of a dramatical prophylactic effect of moderate control of blood pressure on stroke (Yamori and Horie: Jap Circulat J 39: 616, 1975).

Thus, the establishment of SHRSP confirmed the clinical data concerning the importance of hypertension as a cause of stroke, and further it is noteworthy that these experimental progresses using SHRSP which develop stroke " spontaneously " first substantiated the results obtained by prospective study on stroke in relation to cerebral circulation in human cases (Terashi and Atarashi :" Cerebral Stroke 3 ", 69, 1976).

In the present study, the pathogenic importance of rCBF reduction in stroke was reconfirmed by acute experiments using SHRSP, stroke-resistant SHR (SHR-SR), and Wistar-Kyoto rats (WK). In addition, relationship between results from acute and chronic experiments was clarified by other parameters, i.e., serial records of electroencephalograph (EEG), detection of metabolic intermediate levels and fluorescence microscopic study.

Materials and Methods:

(1) Bilateral carotid artery ligations were performed under ether anesthesia in 3-month-old male SHRSP, SHRSR, and WK, around 15–20 in each group, and rCBF in the frontal cortices of them were measured by the hydrogen clearance method 30 min and 2 hours after the operation. (2) Cortical EEG was also recorded together with rCBF measurements. (3) Metabolic intermediate levels (ATP, phosphocreatine (PCr), lactate, pyruvate, and glucose) were assayed by the enzymic method in 3-month-old male SHRSP, SHRSR, and WK, 5 in each group,

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	ATP	PCr	Glucose	Lactate	Pyruvate
SHRSP	0.74±0.36*	0.61±0.29«	1.27±0.43	29.86±5.3*	0.027±0.015*
SHRSR	2.78±0.02	2.75±0.07	2.14±0.16	4.95±0.84	0.118±0.011
WK	2.66±0.08	2.44±0.15	2.10±0.19	9.16±1.69	0.152±0.014

* Significant difference from SHRSR and WK ($p<0.01$)

2 hours after the operation. (4) As to predilection sites of stroke, fluorescence study was performed to observe central noradrenaline and dopamine by Falck-Hillarp method in 3-month-old SHRSP and WK 2–3 hours after the operation under light or deep pentobarbital anesthesia (30 mg/Kg or 60 mg/Kg, i.p.).

Results:

(1) rCBF in the frontal cortex of SHRSP was markedly decreased 30 min after bilateral carotid artery ligation (less than 10 ml/100 Gm/min in absolute values or more than 90% in percentage decrease) and hardly detected 2 hours after the operation. The reduction was irreversible in all. In contrast, those of WK and SHRSR showed a milder reduction, i.e., 30–40 ml/100 Gm/min in absolute values or 60–50% in percentage decrease, 30 min after the operation and 10–20 ml/100 Gm/min or 30–40%, 2 hours after the operation. In addition, rCBF reductions in SHRSR were rather severer than those in WK and almost irreversible in contrast to reversible rCBF reduction in WK. (2) Marked differences were recognized in serial EEG records between SHRSP and WK. In the cortical EEG of SHRSP, high voltage slow waves (θ-δ) with or without spiky components were frequently or almost sequentially appeared 30 min after the operation and no activities were recorded in 2 hours. WK showed slight alterations (slowing of background activity and appearance of high voltage θ and δ waves) and they were reversible. (3) Metabolic intermediates (ATP, phosphocreatine (PCr), glucose, lactate and pyruvate) 2 hours after the bilateral carotid artery ligation revealed marked differences in levels between SHRSP and SHRSR or WK as shown in the following table. (4) Dopamine and noradrenaline fluorescence in the nucleus candatus putamen and frontal cortex was clearly depleted in SHRSP, which developed such signs and symptoms as hyperirritability, aggressiveness, and convulsive seizure etc, 2–3 hours after bilateral carotid artery ligation under light anesthesia. These changes, however, were less or not detectable in normotensive WK and in deeply anesthetized SHRSP which were asymptomatic 2–3 hours after the operation.

Summary and Discussion:

After bilateral carotid artery ligation abrupt severe reduction of rCBF was observed and lasted until death in SHRSP (mortality: 100%), as compared with mild reduction followed by a prompt recovery in WK (motality: 0%). EEG alterations ran parallel to rCBF reduction. rCBF reduction was accompanied with cerebral metabolic changes. Central amines were depleted at the predilection sites of stroke. And these young SHRSP developed neurological signs and symptoms of cerebrovascular accident after the operation.

As previously reported, the predilection sites of stroke in young SHRSP with bilateral carotid arteries ligated were just the same as those in SHRSP which died

" spontaneously " (Yamori et al : Jap Heart J 17 : 387, 1976). Further, similar findings obtained in the present study were observed in male SHRSP at the age of 9 months around the time when they developed stroke " spontaneously ". When SHRSP developed severe hypertension in young age, abrupt decrease in rCBF was observed, but rCBF decrease was not so severe (around 50% of normal range) as caused cerebral metabolic disorders accompanied with marked EEG changes due to an acute ischemic hypoxia after bilateral carotid ligation. At the advanced age, such marked alterations as observed by acute experiments occurred in SHRSP with typical symptomatological abnormalities.

In SHRSP, long-lasting moderate reduction of rCBF due to severe hypertension results in increased cerebrovascular permeability due to ischemic chronic hypoxia, followed by cerebrovascular organic change (detected by decreased chemical cerebrovascular reactivity to CO_2 inhalation), and if finally causes arterionecrosis as peviously reported (Yamori and Horie : In " Vascular Reactivity " 124, 1977). The release of central amines in the predilection sites of stroke is presumed to accelerate such a process (Yamori et al :Hypertension and Brain Mechanism, Progress in Brain Research 47 : 219, 1977). Present study reconfirmed the importance of cerebral blood flow in the initiation mechanism of stroke, and further indicated the relationship between rCBF and cerebrovascular organic change because similar findings to those obtained from acute experiments were observed " spontaneously " in SHRSP with reduced cerebrovascular reactivity.

This study was supported by the Science and Technology Agency of Japanese Government, Ministry of Education, National Institutes of Health, USA (grant HL 17754), Japan Medical Research Foundation, Mitsubishi Foundation for Scientific Research, Foundation for Research on Metabolic Diseases, Japan Tabacco and Salt Public Corporation, and Foundation for Research on Adult Diseases.