Lecture

Cerebral Blood Flow and Brain Function in Hypertension

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In mild hypertensive patients, regional cerebral blood flow, measured by positron emission tomography, was reduced in the frontal cortex and basal ganglia compared with normotensive patients. In moderate to severe hypertensive patients, cerebral oxygen metabolism was diminished, although the patients were neurologically intact. In elderly hypertensives, white matter vascular lesions on brain imaging were more frequent and cognitive function was impaired, compared with age-matched normotensives. In non-treated spontaneously hypertensive rats (SHR), local cerebral blood flow was decreased in the cortex and thalamus, compared with normotensive rats (NTR). Spatial memory and learning in maze tests were more impaired in aged SHR than in old NTR or young SHR. This impairment was related to decreased cerebral glucose utilization in the medial septal nucleus, hippocampus, and other regions of the brain. Reduced cerebral blood flow, increased media thickness of the cerebral arteries and impaired cognitive function in SHR were improved by long-term antihypertensive treatment. In humans as well as animals, long-standing hypertension per se leads to reductions in cerebral blood flow, metabolism, and cognitive function, each of which possibly may be improved by controlling hypertension with long-term antihypertensive treatment. (Hypertens Res 1995; 18: 111-117)

Key Words: cerebral blood flow, brain metabolism, cognitive function, brain morphology, antihypertensive treatment

Hypertension is recognized as one of the major risk factors for cerebrovascular diseases, which are more common in Japanese or Orientals than in Caucasians (1, 2, 3). Cerebral hemodynamics, metabolism and function in hypertension before the development of cerebrovascular disease, however, are not fully understood in humans or in animals. In this communication, we contrast cerebral blood flow (CBF) and oxygen metabolism, measured by positron emission tomography in hypertensive patients, with those in normotensives. We also report on cognitive function tested by neuropsychological examinations and brain morphology studied by brain imaging in elderly hypertensives and normotensives. In addition, cerebral circulation and metabolism, and memory function were examined in young and old spontaneously hypertensive rats (SHR) and compared with normotensive rats. Finally, we discuss the effects of long-term antihypertensive treatment on the brain circulation, vascular morphology and cognitive function in SHR.

Cerebral Blood Flow and Metabolism in Hypertension

1. Mild Hypertension

Regional CBF and oxygen metabolism were measured using positron emission tomography (PET) in seven normotensive and eight mild hypertensive patients with mean arterial pressure (MAP) ranging from 81-130 mmHg (4). There were significant negative correlations between MAP and CBF in the cortex and the thalamus, indicating that CBF decreases with a rise in blood pressure (Fig. 1). These findings are inconsistent with previous evidence that hypertension per se did not change the CBF and metabolism of the whole brain measured by nitrous oxide technique (5).

Regional differences in CBF between normotensive and mild hypertensive groups were significant in several areas of the brain. Mean values for blood flow were significantly lower in hypertensives than normotensives in the supratentorial regions, such as the cortex, striatum and thalamus. The latter two, deep grey matter regions are sites where hypertensive vascular changes are more common, and where either hemorrhagic or ischemic cerebrovascular dis-
ease occurs most frequently. In contrast, blood flow to the infratentorial structures, such as the cerebellum and brain stem, was not different between the two groups. These results indicate that CBF reduction in hypertension differed among the brain regions, suggesting that persistent high blood pressure primarily affects the small arteries or so-called perforating arteries rather than large arteries in the supratentorial structures.

2. Severe Hypertension
Cerebral metabolic rate for oxygen (CMRO₂) in the frontal cortex was significantly lower (2.2 ± 0.1 ml/100 cc/min) in the hypertensive group, including patients with mild to severe hypertension (n = 15), than in the normotensive one (Fig. 2). A similar significant reduction in CMRO₂ was observed in the thalamus (6). The reduction in brain metabolism in hypertensives suggests that neuronal function or neurotransmitter activity is reduced in these patients, although they may be clinically asymptomatic and neurologically intact. Whether hypertension-induced CBF reduction leads to lowered CMRO₂ is not fully understood.

Cognitive Function and Brain Imaging in Hypertension

1. Neuropsychology
Cognitive functions were examined by using the revised Wechsler adult intelligence scale (WAIS-R) in 10 normotensive and 11 hypertensive elderly patients (≥ 65 years), whose age, sex, and educational level were matched and who had no history of stroke (16). Although full scaled scores of WAIS-R did not differ significantly between the two groups of patients, the backward digit span scale among the verbal scaled scores was significantly lower in hypertensives than normotensives, with a significant negative correlation to systolic blood pressure level (r = −0.47, p < 0.05). These results indicate that long-standing hypertension may lead to disturbed

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Fig. 1. Relationships between mean arterial blood pressure (MABP) and regional cerebral blood flow (rCBF), oxygen extraction fraction (rOEF) and metabolic rate for oxygen (rCMRO₂) in the cerebral cortex and thalamus in normotensive and mild hypertensive patients (4).
short-term memory in elderly hypertensives.

Emotional state was also examined in our series of elderly normotensives (n = 12) and hypertensives (n = 14) using the Zung depression rating scale, in which a score of ≥ 50 points was defined as depression. There was a significant relationship between the Zung scale and the systolic blood pressure level (Fig. 3), indicating a more depressive state in hypertensives. The potential of antihypertensive drugs to cause depression should be considered, but the hypertensive patients mostly received drugs that do not induce depression, such as calcium antagonists, angiotensin converting enzyme (ACE) inhibitors, or both. Therefore, hypertension per se appears to be responsible for the increased depression rating.

A review by Waldstein et al. (7) describing the neuropsychological correlates of hypertension stated that hypertensives performed more poorly on tests of memory, attention and abstract reasoning than did normotensives. In contrast, general intelligence and verbal skill were essentially the same in hypertensives and normotensives. Therefore, there was no evidence of impaired performance of daily activities in hypertensives.

2. Brain Morphology
Using magnetic resonance imaging (MRI), brain morphology was studied in elderly normotensives and hypertensives who had not had a stroke (6). Asymptomatic or silent cerebrovascular lesions were equally found in both groups (67% vs. 64%), while moderate to marked brain atrophy was observed more often in hypertensives (82%) than normotensives (56%), but the difference was not significant. The number of white matter lesions on either T1 or T2 weighted MRI, however, was significantly greater in hypertensives (18 ± 8, p < 0.05) than in normotensives (9 ± 6).

Van Swieten et al. (8) examined the frequency of lesions in the brain by MRI in elderly hypertensives and age, sex-matched normotensive controls. They found white matter confluent lesions in 10 of the 42 hypertensives but only one of the 42 controls (p = 0.01), and thus concluded that long-standing hypertension causes hypertensive vascular changes of the white matter structure. Likewise, Salerno et al. (9) quantitatively measured brain volumes and cerebrospinal fluid space by MRI in 18 hypertensive patients (69 ± 8 years) and 17 age-matched healthy normotensive controls. They observed a significantly greater enlargement of the right and left lateral ventricles, and a significantly smaller hemispheric brain volume in hypertensives, indicating brain atrophy that was not related to age or the duration of hypertension. Smaller brain volume and weight were also evident in 6–7-month-old hypertensive rats compared with age-matched normotensive rats (10).

These neuropsychological and morphological findings suggest that long-standing hypertension per se is commonly associated with white matter lesions, which correspond to demyelination and arteriosclerosis in the brain and seem to be responsible for a
Cognitive Function and Brain Metabolism in Hypertensive Rats

1. Memory
To determine whether aging or duration of hypertension affects cognitive function in hypertension, memory tests were performed using an eight-arm radial maze in SHR and normotensive Wistar Kyoto rats (WKY) (11). A food pellet was placed at the distal end of each arm, and when the rat entered an arm for the first time and successfully obtained the food, a correct choice was recorded. When the rat re-entered an arm that was previously visited in a trial, an error choice was recorded. The criterion for maze learning acquisition was at least eight correct responses among the first nine choices for three consecutive days. A radial-maze task was performed every day for a total of 36 times.

The time course of error choice was different among the groups of young (aged 3-4 months) and old SHR (16-17 months), and age-matched young and old normotensive WKY. Young SHR had a higher error choice score than did young WKY, but the difference was not significant. Among the four groups of rats (Fig. 4), old SHR showed the highest error score or the lowest acquisition of learning, indicating that memory is impaired in old SHR.

2. Brain Glucose Metabolism
Brain glucose uptake was regionally measured by using [14C]-2-deoxy glucose radioautography in hypertensive and normotensive rats. The glucose uptake was reduced in old SHR (11). There was a negative correlation between brain glucose metabolism and behavioral scores, defined as the mean error choice scores of the last 10 trials on the maze task described above. The best correlation was obtained between the score and the local glucose uptake in the medial septal nucleus (Fig. 5), which projects cholinergic fibers to the hippocampus, one of the important centers for memory. Such negative correlations were also found in the hippocampus CA1, basal nucleus of Meynert, frontal cortex, and other regions. Marked impairments of learning and spatial memory in old SHR may reflect profound metabolic decline in the areas related to memory function. Wei et al. (12) also found that cerebral glucose utilization was lower in adult SHR than WKY in 14 of the 28 gray matter areas of the brain studied, but they did not test memory function in these rats.

Effects of Antihypertensive Treatment on Cerebral Blood Flow, Vascular Morphology and Cognitive Function

Effects of long-term antihypertensive treatment on CBF and cerebral vascular morphology were studied in treated SHR and non-treated SHR.

1. Cerebral Blood Flow
The relationship between CBF and MAP was examined in three different groups of hypertensive rats: SHR given antihypertensive treatment for 16 weeks, SHR given antihypertensive treatment for 8 weeks, and non-treated SHR (13). CBF in the cortex and the thalamus measured by hydrogen clear-
ance technique was inversely correlated with MAP level \((r = -0.58, p < 0.01)\) (Fig. 6), indicating that long-standing hypertension reduces regional blood flow, while long-term treatment of hypertension with drugs restores the reduced CBF to the level of normotensive rats.

A significant inverse correlation between CBF and MAP has also been reported in hypertensive patients. For example, CBF measured by \(^{133}\)Xe inhalation technique was higher in hypertensive patients who were receiving antihypertensive agents than in those with newly diagnosed, non-treated hypertension \((14)\). The appropriate treatment of hypertension, the longer the better, may therefore possibly improve cerebral hypoperfusion in hypertensive patients.

2. Vascular Morphology
The effects of long-term antihypertensive treatment on the vascular morphology of the brain were studied in SHR \((15)\). Vascular medial thickness was morphometrically measured at the proximal, intermediate, and distal portions of the middle cerebral artery (Fig. 7). Ten-week antihypertensive treatment significantly reduced the wall thickness of large (240 \(\mu\)m in diameter) and medium-sized (170 \(\mu\)m) arteries \((p < 0.001)\). These changes indicate that the regression of hypertensive-induced hypertrophy of the cerebral arteries is evident following long-term antihypertensive treatment.

Hajdu et al. \((16)\) reported that the internal and external diameters of the cerebral arteries in stroke-prone SHR (SHRSP) were respectively 20% and 15% less than in normotensive rats. Thus, chronic hypertension is accompanied by not only hypertrophy but also by “vascular remodeling”, with a reduction in the external diameter of the vessel walls. Both vascular hypertrophy and remodeling result in encroachment on the vascular lumen. Their findings, however, suggest that vascular remodeling is primarily responsible for the reduction in luminal diameter in hypertension. Antihypertensive treatment with cilazapril (an ACE inhibitor) and hydralazine reduced the cross-sectional area of the vessel wall of SHRSP to the level obtained in normotensive rats, indicating prevention of vascular hypertrophy \((16)\). Furthermore, cilazapril, but not hydralazine, increased internal and external diameters of the vessel, thus preventing vascular remodeling with a reduction in external diameter. The findings suggest that ACE inhibitors have a direct, preventive effect on hypertensive vascular wall alterations in addition to reducing blood pressure.

3. Cognitive Function
As mentioned above, long-standing hypertension is associated with cognitive impairment and reduced cerebral glucose utilization in SHR. We studied whether long-term antihypertensive treatment can prevent or reduce impaired brain function and metabolism in hypertensive animals \((17)\). In aged SHR (20 months old) receiving 16–17 months treatment with either the calcium antagonist isradipine or the ACE inhibitor ceronapril, the mean systolic blood pressure was approximately 160 mmHg, which was significantly lower than the 230 mmHg in untreated SHR but still higher than the 140 mmHg in normotensive WKY. The treatment facilitated radial-maze learning and reduced the total error choices to the levels of young (3-4 months old) SHR and WKY. The treatment also fully normalized the local cerebral glucose utilization to the levels of young SHR and WKY in all 35 regions of the brain examined. These findings indicate that the early and long-term control of hypertension is important for preventing brain dysfunction in senescence.
Similar studies by Wyss et al. (18) also revealed that 12-month-old SHR had significant learning and memory deficits in an eight-arm radial-maze task compared with age-matched normotensive rats. The precise mechanism that disturbs learning and memory is still uncertain, but the dysfunction of the retrosplenial cortex may be involved because the cortex is known to importantly contribute to the transfer of information related to learning and memory. In addition, they found that antihypertensive therapy with captopril partially prevented age and hypertension-related cognitive dysfunction.

Antihypertensive Agents and Cerebral Circulation

Among antihypertensive agents (Table 1), calcium antagonists are known to have a direct vasodilatory effect on cerebral arteries and to increase CBF (19). However, care should be taken because some calcium antagonists might have a strong hypotensive effect, which may lower blood pressure beyond the lower limit of CBF autoregulation and decrease CBF. Particularly in elderly patients with long-standing hypertension and in hypertensive patients who have had a stroke, the lower limit of autoregulation is shifted to the right or upwards in a resting state (20, 21), and therefore even a small reduction in perfusion pressure leads to a decrease in CBF (Fig. 8). In contrast, ACE inhibitors do not alter the resting CBF but appear to change the lower limit of CBF autoregulation to the lower levels of blood pressure, which is beneficial because it protects the cerebral circulation during hypotension (22). At the same time, however, intravenous ACE inhibitors greatly shift the upper limit of autoregulation to lower levels in hypertensive animals, which may predispose the animals to the early development of CBF breakthrough phenomena in the event of acute and excessive rises in blood pressure (23).

References


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Table 1. Effect of Antihypertensive Agents on Cerebral Blood Flow (CBF) and CBF Autoregulation

<table>
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Fig. 8. Cerebral blood flow autoregulation in various pathophysiological states. Cerebral blood flow is reduced and the lower limit of autoregulation is shifted upwards in hypertensives.


17. Mori S, Fujishima M, Sadoshima S, Ibayashi S: Facilitation of maze learning and cerebral glucose utilization after long-term antihypertensive medication. (submitted to *Stroke*).


