Hypertension (HTN) is a major risk factor for all stroke subtypes, infarction as well as hemorrhage. Evidence from clinical trials shows that control of blood pressure (BP) leads to a substantially lower risk of stroke. HTN exerts detrimental actions on the cerebral circulation that play a critical role in its ability to promote cerebrovascular diseases. Angiotensin II (Ang II) is a key mediator by which HTN exerts its deleterious vascular effects. Recent findings raise the possibility that some of the detrimental actions of Ang II are independent of the associated elevation in BP. Here we will discuss the effect of HTN on stroke in light of recent advances indicating that the renin angiotensin system (RAS) may play a role greater than previously believed in the deleterious cerebrovascular actions of HTN and, as such, is a promising target for stroke prevention.

Hypertension Is a Major Risk Factor for Stroke

HTN is the most prevalent and powerful modifiable risk factor for stroke, irrespective of geographic region and ethnic group. Persons with HTN are about 3 or 4 times more likely to have a stroke. Whereas diastolic BP was once thought to be the most important predictor of stroke, the relationship between stroke and HTN may be stronger for systolic than for diastolic BP. The association between BP and stroke risk seems to occur on a continuum rather than as a threshold effect. The majority of strokes have been reported among persons with only “borderline” or “mild” HTN, and both persons classified as “hypertensive” as well as “normotensive” may benefit from BP lowering. Therefore, although the highest BP levels predict the highest relative risk of stroke, irrespective of geographic region and ethnic group, HTN exerts powerful effects on the cerebral circulation. In cerebral blood vessels, HTN produces hypertrophy and remodeling, defined as a reduction in the external diameter of the vessels. These proliferative changes increase vascular compliance and promote atherosclerosis. In addition, HTN alters the ability of endothelial cells to release vasoactive factors and increases the constrictor tone of systemic and cerebral arteries. HTN also alters cerebrovascular autoregulation, a property of cerebral arterioles that maintains cerebral blood flow (CBF) relatively constant despite variations in perfusion pressure within a certain range, usually 70 to 150 mm Hg. Chronic HTN shifts the autoregulated range toward higher pressures, rendering the brain more vulnerable to reductions in perfusion pressure. These structural and functional alterations increase the susceptibility of the brain to ischemic injury. For example, due to the shift in autoregulation and increased vascular compliance, the drop in perfusion pressure occurring distal to an occluded artery is likely to produce a greater reduction in CBF. Furthermore, the failure of endothelium-dependent relaxation impairs the ability of cerebral arterioles to dilate and supply collateral flow to the ischemic area.

Ang II Is a Major Causative Factor in the Cerebrovascular Effects of Hypertension

Ang II is a key mediator in the mechanisms of HTN. Ang II exerts its effects through specific G-protein–coupled receptors, 2 of which, AT1 and AT2, have been well characterized. AT1 receptors mediate vasoconstriction, vascular proliferation, and inflammation, while AT2 receptors mediate vasodilatation, promote apoptosis, and inhibit proliferation. Thus, AT1 receptors are thought to mediate the deleterious vascular effects of Ang II, while the AT2 receptors are potentially protective. Ang II mimics some of the effect of HTN on cerebral blood vessels. Structurally, Ang II induces both cerebrovascular hypertrophy and remodeling. Functionally, Ang II alters autoregulation, inhibits endothelium-dependent relaxation, and disrupts the blood-brain barrier. Ang II also impairs the increase in CBF produced by neural activity. This phenomenon, termed functional hyperemia, is a critical adaptive mechanism by which the brain matches increased energy demands with increased delivery of substrates and removal of metabolic waste. The Ang II–induced impairment of functional hyperemia renders the brain more vulnerable to reductions in blood supply and more susceptible to cerebral ischemia. Some of the cerebrovascular effects of Ang II are independent of the elevation in BP. For example, remodeling of cerebral arteries occurs in hypertensive mice overexpressing human renin and angiotensinogen but not in BHP-2 mice, in which HTN is independent of RAS, while...
vascular hypertrophy is observed in both strains. In addition, the alterations in endothelium-dependent relaxation and functional hyperemia are observed even if Ang II is applied directly on the cerebral cortex, bypassing systemic effects and functional hyperemia are observed even if Ang II is applied. Thus, although Ang II is an important factor in the deleterious cerebrovascular effects of HTN, it is not the only factor.14 The alterations in endothelium-dependent relaxation and functional hyperemia produced by Ang II in cerebral arterial pial vessels are independent of the elevation in BP.

**Mechanisms of the Cerebrovascular Effect of Ang II**

Activation of AT1 receptors by Ang II initiates a complex signaling cascade (Figure). Some but not all of the downstream effects of Ang II are mediated by reactive oxygen species (ROS) produced by the enzyme NADPH oxidase, a recently identified source of ROS in blood vessels. NADPH-derived ROS are responsible for the proliferative and pro-inflammatory effects of Ang II in the systemic circulation. Preliminary studies suggest that ROS, probably derived from NADPH oxidase, contribute also to the cerebrovascular effects of Ang II. The attenuation in functional hyperemia produced by Ang II is associated with free radical production and is rescued by free radical scavengers. Furthermore, DPI, a flavoprotein inhibitor that blocks NADPH oxidase, prevents the attenuation of endothelium-dependent relaxation produced by Ang II in cerebral arteries. Thus, NADPH-derived radicals may be an important pathogenic factor in the deleterious cerebrovascular effects of Ang II.

**Beneficial Effects of RAS Inhibition Independent of BP Lowering**

Although there is substantial epidemiological evidence that lowering of BP is associated with the reduction of stroke risk, inhibition of RAS may have beneficial effects independent of BP. Recent clinical trials—Heart Outcomes Prevention Evaluation (HOPE), Perindopril Protection Against Recurrent Stroke Study (PROGRESS), Losartan Intervention for Endpoint Reduction in Hypertension study (LIFE), and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)—provide new insights about possible non–BP lowering effects of RAS inhibition. In HOPE, which featured the angiotensin-converting enzyme inhibitor (ACE-I) ramipril, there was modest BP lowering (3 mm Hg systolic and 2 mm Hg diastolic) compared with the placebo group, yet there was a 32% reduction in stroke.22 In PROGRESS, a trial designed as a BP lowering–type study,23 there was a 28% reduction in recurrent stroke with the combination of the ACE-I perindopril and the thiazide-like diuretic indapamide. Although the reduction in stroke was generally greater as BP lowering increased, the higher-than-expected reduction of some cardiovascular disease outcomes, eg, nonfatal myocardial infarction, suggested beneficial non–BP lowering effects of the ACE-I.2 In LIFE, there was greater reduction of stroke with the AT1 receptor blocker (AT1RB) losartan than with the beta-blocker atenolol, despite almost identical BP-lowering effects.21 The results of ALLHAT are more difficult to interpret because the findings were confounded by differences in BP lowering between the ACE-I (lisinopril), calcium channel blocker (amlodipine), and diuretic (chlorothalidone) treatment groups, with less BP lowering in the lisinopril group.24,25 The results of these trials suggest that non–BP lowering effects of ACE-I and AT1RB may contribute to the reduction of stroke risk. Thus, BP-independent effects on cerebrovascular regulation and compliance, and, in the case of AT1RB, activation of potentially protective AT2 receptors, could play a role.
Conclusions

These basic and clinical findings indicate that BP, due to its profound effects on the cerebral circulation, is the most critical determinant of the risk of stroke. Therefore, it is unquestionable that reduction in BP should be the centerpiece of any strategy for stroke prevention. Any of the commonly used antihypertensive agents (ACE-I, AT1RBs, calcium channel blockers, beta-blockers, diuretics) reduce the risk of stroke, with larger reductions in BP resulting in larger reduction in risk. On the other hand, there is highly suggestive evidence from clinical trials that pharmacological strategies to inhibit the RAS reduce the risk of stroke beyond the degree expected from the reduction in BP. These clinical findings are supported by experimental evidence indicating that Ang II has powerful cerebrovascular effects unrelated to its ability to elevate BP. Therefore ACE-I and AT1RBs may possess unique properties that influence reduction of stroke beyond BP lowering. More focused therapies targeting the mechanisms by which the RAS may increase the risk for stroke, such as inhibition of vascular NADPH oxidase, could more selectively counter the deleterious effects of Ang II, sparing the purported beneficial actions of AT2 receptor activation. However, in the clinical arena, the evidence for BP-related and unrelated stroke risk is not sufficiently strong to justify favoring the exclusive use of agents targeting the RAS system or its signaling pathways. Nonetheless, these new findings expand our views by emphasizing that agents involved in the mechanisms of cardiovascular diseases may exert their detrimental actions independently of their ability to elevate BP. This line of thinking may lead to new and more powerful treatments to limit the devastating cerebrovascular effects of HTN and its mediators.

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