Cerebral Circulation: Humoral Regulation and Effects of Chronic Hypertension

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ABSTRACT

New concepts have emerged in recent years concerning regulation of cerebral circulation. The purpose of this review is to summarize briefly several of these concepts. First, humoral mechanisms may have important effects on cerebral blood vessels and blood flow to choroid plexus. Recent evidence suggests that several vasoactive peptides may have major effects on fluid and ion balance in the brain by altering blood flow to the choroid plexus and possibly the production of cerebrospinal fluid. Second, chronic hypertension produces structural remodeling and hypertrophy of cerebral blood vessels and a shift in the relationship of cerebral blood flow to systemic blood pressure. Third, endothelium-dependent responses of cerebral arterioles to receptor and nonreceptor mediated agonists are impaired during chronic hypertension. Alterations in endothelium-dependent responses of cerebral arterioles to receptor and nonreceptor mediated agonists are impaired during chronic hypertension. Alterations in endothelium-dependent responses of cerebral arterioles during chronic hypertension appears to be due to release of an endothelium-derived contracting factor.

Key Words: choroid plexus, autoregulation, endothelium-dependent responses, structural remodeling, vascular mechanics

A major concept in cerebral vascular physiology has been that circulating humoral stimuli have little effect on the cerebral circulation. The blood-brain barrier limits the access of many circulating substances to vascular smooth muscle, so that a variety of blood-borne vasoactive stimuli do not alter cerebral blood flow. The blood-brain barrier is a structural barrier, with tight junctions between endothelial cells, and an enzymatic barrier, as endothelial cells contain relatively high levels of monoamine oxidases.

The concept that humoral stimuli are not important in the cerebral circulation should be revised. Blood-borne stimuli such as vasopressin and angiotensin may have major effects on specialized regions of the brain, such as the circumventricular organs and the choroid plexus, which lack tight junctions between endothelial cells. The choroid plexus has fenestrated capillaries, so that the blood-barrier is absent, but there are tight junctions between epithelial cells, which compose a blood-cerebrospinal fluid barrier.

The choroid plexus is the major site of formation of cerebrospinal fluid, and blood flow to the choroid plexus may be an important determinant of production of cerebrospinal fluid. Perfusion is substantially higher in the choroid plexus than in the cerebrum. High levels of blood flow support the filtration and transport functions of the choroid plexus, and they are similar to those of the kidney. Production of cerebrospinal fluid appears to require filtration of plasma out of the fenestrated capillaries and into the interstitial space of the choroid plexus and active transport of ions across the epithelial cells and into the cerebral ventricles.

Vasopressin, angiotensin II, and endothelin have a variety of vascular and epithelial effects in the kidney. Our studies suggest that these peptides also have important effects on the choroid plexus. Blood vessels of the choroid plexus are particularly sensitive to circulating vasopressin. Increases in plasma concentrations of vasopressin to levels observed under physiological and pathophysiological conditions reduce blood flow to the choroid plexus by more than 50% and decrease production of cerebrospinal fluid by approximately one third. Vasopressin levels in the blood can reach very high levels during hypoxia and intracranial hypertension. We have suggested that increases in circulating vasopressin may decrease blood flow the choroid plexus and formation of cerebrospinal fluid under
Metabolic Filtration/Transport

Blood Flow, ml-min⁻¹·100g⁻¹

0 300 600

Heart Brain Muscle

Choroid Plexus Kidney

Figure 1. Blood flow to several organs under resting conditions. Blood flow to choroid plexus and kidney, in which filtration and transport are major functions, is relatively high. In contrast, blood flow to the brain, heart, and muscle is much lower under basal conditions. Blood flow to these tissues is regulated to a major extent through mechanisms coupled with tissue metabolism. These data were obtained in conscious dogs (46).

Figure 2. Schematic of epithelium and a fenestrated capillary in the choroid plexus. Secretion of cerebrospinal fluid is dependent on 1) plasma filtration through choroidal capillaries, which is regulated in part by the level of blood flow, and 2) active ion transport, which establishes and maintains an ionic gradient for the movement of water into the ventricles. Arterioles of the choroid plexus are very responsive to vasopressin, angiotensin II, and endothelin. It is not known whether epithelial cells of the choroid plexus are also sensitive to these peptides.

EFFECTS OF CHRONIC HYPERTENSION

Autoregulation of Cerebral Blood Flow

A well-established concept regarding effects of chronic hypertension on the cerebral circulation is that the autoregulatory "plateau" of cerebral blood flow shifts to a higher range of arterial pressure. Thus, cerebral blood flow is normal in patients with chronic hypertension (19) and in experimental models of chronic hypertension (20–23), despite levels of arterial pressure that would be expected to produce passive vasodilatation and "breakthrough" of autoregulation in normotensive individuals. Furthermore, reductions in cerebral blood flow during acute hypotension occur at higher levels of arterial pressure in hypertensive than in normotensive ba-boons (21) and rats (20). During chronic hypertension, therefore, cerebral vasoconstriction is enhanced during acute increases in arterial pressure, and cerebral vasodilatation is impaired during acute reductions in pressure.

Alterations in autoregulation presumably are related in large part to structural changes of the vessel wall during hypertension. Cerebral vessels in spontaneously hypertensive rats (SHR) (20,24) and stroke-prone spontaneously hypertensive rats (SHRSP) (25,26) undergo hypertrophy, which encroaches on the vascular lumen and augments responses to constrictor stimuli (27,28). Hypertrophy of large cerebral arteries is associated with a reduction in distensibility (24,29,30). It is likely, therefore, that alterations of autoregulatory responses are related to hypertrophy of cerebral vessels and to a reduction in distensibility of large cerebral arteries.

In addition to enhancing autoregulatory responses to acute hypertension, structural changes during chronic hypertension probably play a role in impairing autoregulatory responses to acute hypotension. Encroachment on the lumen by vascular hypertrophy and reduced distensibility of the vessel wall would be expected to impair dilatation during reductions in pressure. Thus, one might postulate that the contribution of structural changes to alterations in autoregulation of cerebral blood flow might be similar at both ends of the autoregulatory curve. If this hypothesis were correct, the degree of impairment at the lower end of the autoregulatory curve would be
arterioles may tend to counteract encroachment on the lumen during vasocostriction. Thus, vasoconstriction is preserved in the hypertrophied vessel despite the increase in arteriolar distensibility.

**Minimal Resistance**

Another well-established concept is that chronic hypertension results in a reduction in maximal dilator capacity of cerebral blood vessels. We (33) and others (34) have found that increases in cerebral blood flow during seizure (Figure 3, right panel) or hypercapnia are less than SHR than in normotensive Wistar Kyoto rats (WKY).

The primary mechanism that has been proposed to account for impairment of dilatation by chronic hypertension is hypertrophy of the vessel wall with reduction of internal diameter by encroachment on the vascular lumen (34,35). If reductions in internal diameter resulted solely from encroachment by hypertrophy, external diameter of cerebral arterioles would be expected to be similar in hypertensive and normotensive animals. We recently measured external diameter of pial arterioles during maximal dilatation in WKY and SHRSP (36). External, as well as internal, diameter was significantly reduced in SHRSP (Figure 4). Therefore, another mechanism, in addition to inward growth of the vessel wall on the vascular lumen, must be invoked to account for impairment of maximal dilatation of cerebral arterioles in chronic hypertension.

![Figure 4. Comparison of external diameter in maximally dilated pial arterioles of WKY and SHRSP. Internal diameter of pial arterioles was measured at a pial arteriolar pressure of 70 mm Hg. External diameter was calculated from measurements of internal diameter and cross-sectional area of the arteriolar wall. External, as well as internal, diameter was significantly smaller in SHRSP than in WKY. Reduction in external diameter suggests that reduction of internal diameter in SHRSP results from remodeling of the arteriolar wall as well as from encroachment of the wall on the vascular lumen. Drawn to a scale of 375:1.](image-url)

Extension of the autoregulatory range during chronic hypertension may be related to differential changes in distensibility of large and small cerebral blood vessels. In a recent study, we found that, in contrast to large cerebral arteries, which become less distensible during chronic hypertension (24,29,30), distensibility of cerebral arterioles is increased in stroke-prone spontaneously hypertensive rats, despite significant hypertrophy of the vessel wall (26). We speculate that the increase in distensibility of arterioles may tend to counteract encroachment on the lumen by hypertrophy of the wall, thus attenuating impairment of vasodilatation during acute hypotension and other vasoconstrictor stimuli. Increases in arteriolar distensibility during chronic hypertension, therefore, may contribute to a relative preservation of autoregulatory dilatation, which in turn may help to protect the cerebral circulation during severe reductions in arterial pressure. Furthermore, because distensibility of blood vessels is altered by activation of smooth muscle (31,32), it is likely that the protective effect of encroachment on the lumen during vasocostriction is preserved in the hypertrophied vessel despite the increase in arteriolar distensibility.
We have proposed that, during chronic hypertension, cerebral arterioles may undergo structural remodeling (36). The possibility of vascular remodeling in hypertension is supported by the observation that wall-to-lumen ratio of intestinal arterioles is increased in humans with chronic hypertension, even without evidence of hypertrophy of the arteriolar wall (37). The findings suggest that chronic hypertension may produce remodeling of the wall of cerebral arterioles, which reduces external diameter without reducing vascular distensibility. Based on this concept, maximal dilatation of cerebral arterioles is impaired by reductions in external diameter, as well as by hypertrophy of the wall, with encroachment on the vascular lumen.

**Endothelium-dependent Responses**

Endothelium modulates vascular tone through the production and release of endothelium-derived relaxing and contracting factors, as well as prostacyclin (38,39). During chronic hypertension, relaxation to endothelium-dependent agonists is impaired in the thoracic aorta and carotid artery of SHR in vitro (40,41). We have examined responses of cerebral arterioles to endothelium-dependent agonists in vivo. In SHRSP, vasodilator responses to acetylcholine, adenosine 5’-diphosphate (ADP), and bradykinin are impaired compared with responses of normotensive WKY (42-44). Dilator responses to the calcium ionophore A23187, which releases endothelium-derived relaxing factor by a non-receptor mediated mechanism, are also impaired in SHRSP (45). Altered responses of cerebral arterioles appear to be selective for agonists that act through the endothelium because dilatation to adenosine, nitric oxide, and nitroglycerin, which act directly on vascular muscle, is not impaired in SHRSP (42-44).

Responses of the aorta to endothelium-dependent agonists are impaired in SHR in part because, in addition to releasing a relaxing factor, endothelium also releases a contracting factor (41). This contracting factor appears to be a cyclooxygenase product, or perhaps an oxygen-derived radical that is generated by the cyclooxygenase pathway.

Indomethacin potentiates dilatation of cerebral arterioles to ADP and converts responses to serotonin from moderate constriction to moderate dilatation in SHRSP (43). Indomethacin has no effect on responses of cerebral arterioles in WKY. These findings suggest that cerebral arterioles of SHRSP release a contracting factor in response to ADP and serotonin. This contracting factor contributes to decreased endothelium-dependent dilator responses of cerebral vessels during chronic hypertension.

Intuitively, it seems reasonable that hypertension predisposes to cerebral hemorrhage, but it is some what paradoxical that hypertension predisposes to cerebral ischemia and infarction. Impairment of endothelium-dependent responses may contribute to this predisposition. We have speculated that, when platelets aggregate and release their vasoactive products (serotonin, ADP, and thromboxane), an endothelium-derived contracting factor is released from cerebral arterioles (43). Thus, platelets may initiate a cerebral vasoconstrictor response in the presence of chronic hypertension, in contrast to cerebral vasodilation during normotension, and thereby produce cerebral ischemia and perhaps stroke.

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**REFERENCES**