Regulation of Cerebral Blood Vessels by Humoral and Endothelium-Dependent Mechanisms

Update on Humoral Regulation of Vascular Tone

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Recent studies suggest that humoral and endothelium-dependent mechanisms may play an important role in the cerebral circulation. Angiotensin may acutely and chronically increase resistance of large cerebral arteries and reduce cerebral microvascular pressure without changing cerebral blood flow. We hypothesize that the brain may sense reductions in microvascular pressure and initiate compensatory neurohumoral responses to raise arterial pressure. Vasopressin appears to play an important role in regulation of production of cerebrospinal fluid and brain fluid volume. Vasopressin also may be protective when intracranial pressure is elevated. Endothelium-dependent mechanisms also may have important influences on tone of cerebral vessels. Synthesis of the endothelium-derived relaxing factor nitric oxide, or a nitric oxide-containing compound, appears to influence both basal tone and responses of large cerebral arteries to acetylcholine in vivo. Large cerebral arteries dilate in response to increased blood flow in vivo, and this response may be mediated in part by release of a humoral factor by endothelium. Endothelium-dependent responses of cerebral arterioles to receptor- and nonreceptor-mediated agonists are impaired during chronic hypertension. The mechanism of impairment of endothelium-dependent responses of cerebral arterioles appears to involve production of an endothelium-derived contracting factor. (Hypertension 1991;17:917–922)

Circulating catecholamines and vasoactive peptides play an important role in regulation of the peripheral circulation. These humoral stimuli generally are considered to have little effect on the cerebral circulation. The concept that circulating vasoactive stimuli have minimal effect on cerebral blood flow is based on the observation that cerebral endothelium (the blood–brain barrier) restricts access of many blood-borne substances to cerebral vascular smooth muscle.

In this review, we will propose, based on recent findings, revision of the concept that humoral stimuli are not important in the cerebral circulation. Blood-borne vasoactive substances may have important effects on large cerebral arteries, and thus on cerebral microvascular pressure, and on regions of the brain such as the choroid plexus, which lack a blood–brain barrier.

Thus, one role of cerebral endothelium is to modulate responses of cerebral blood vessels to humoral stimuli. In addition, endothelium releases endothelium-derived relaxing and contracting factors, which influence vascular tone.1,2 We will describe recent evidence that endothelium-dependent mechanisms have important effects on cerebral blood vessels under some conditions, and these mechanisms may be altered during chronic hypertension.

Regulation of Cerebral Blood Flow and Microvascular Pressure

Large arteries are important resistance vessels in the cerebral circulation. Blood pressure in pial arteries on the surface of the cerebrum is approximately 50–60% of aortic pressure,3 and resistance of large arteries appears to be greater in the brain than in other vascular beds.4 Thus, vasoactive stimuli that affect large cerebral arteries have the potential to
influence both cerebral microvascular pressure and blood flow.

Recent studies have demonstrated that several neurohumoral stimuli may selectively alter resistance of large cerebral arteries. For example, blood-borne angiotensin II and serotonin and stimulation of sympathetic nerves all increase resistance of large cerebral arteries and decrease microvascular pressure.\(^5\) Compensatory dilatation of smaller downstream vessels maintains cerebral blood flow at normal levels. Humoral stimuli also can produce dilatation of large arteries. For example, increases in plasma levels of vasopressin to pathophysiological levels decrease resistance of large arteries and increase microvascular pressure without altering cerebral blood flow.\(^5\) Large cerebral arteries are not responsive to some vasoactive stimuli, however. High levels of circulating angiotensin II may decrease cerebral microvascular pressure without altering cerebral blood flow (unpublished observations). Previous studies suggest that the effects of captopril on cerebral blood vessels are not mediated through central mechanisms or effects on sympathetic nerves.\(^12\) Captopril inhibits contraction of large cerebral arteries in response to angiotensin I in vitro, which provides evidence for a vascular renin-angiotensin system in cerebral arteries.\(^13\) Based on these findings, we suggest that the effect of captopril on cerebral microvascular pressure may involve modulation of a local vascular renin-angiotensin system that influences basal tone of large cerebral arteries. Activity of angiotensin converting enzyme is greater in some large cerebral arteries in spontaneously hypertensive rats (SHRs) than in normotensive controls.\(^14\) This finding suggests that a portion of the increased resistance of large cerebral arteries during chronic hypertension\(^15\) may be due to a greater influence of the vascular renin-angiotensin system. In patients with essential hypertension, acute administration of captopril significantly increased diameter of the carotid artery,\(^17\) which suggests that this mechanism may be important during chronic hypertension in humans.

Circumventricular Organs

**Choroid Plexus**

The choroid plexus is the major site of formation of cerebrospinal fluid.\(^18\) High levels of blood flow to the choroid plexus support the filtration and transport functions of this structure.\(^19,20\) Epithelial cells of the choroid plexus form a tight barrier, which is a major site of selective exchange of substances between blood and brain.\(^19,21\)

Because endothelial cells of blood vessels in the choroid plexus are fenestrated,\(^21,22\) blood-borne substances have the potential to reach smooth muscle and influence vascular tone. Recent studies suggest that several vasoactive peptides have important effects on the choroid plexus. Increases in plasma concentrations of vasopressin to levels observed under physiological and pathophysiological conditions produce marked reductions in blood flow to the choroid plexus and decrease production of cerebrospinal fluid by approximately one third.\(^23,24\) Vasopressin may decrease formation of cerebrospinal fluid both by reducing blood flow and by an inhibitory effect of the peptide on ion transport by choroidal epithelial cells.\(^25\)

We have suggested that endogenous release of vasopressin may reduce formation of cerebrospinal fluid during hypoxia or intracranial hypertension,\(^24\) two conditions in which large quantities of vasopressin are released into the circulation.\(^26,27\) Thus, a major extrarenal role of vasopressin may be to attenuate increases in intracranial pressure. Recent studies suggest that modest elevations in production of cerebrospinal fluid may produce significant increases in intracranial pressure.\(^28\) Because small increases in

**Figure 1. Schematic illustration of the hypothesis that circulating angiotensin II may decrease cerebral microvascular pressure without altering cerebral blood flow.**

A reduction in microvascular pressure may initiate neural or humoral compensatory mechanisms that contribute to the maintenance of elevated systemic pressure in chronic hypertension.
intracranial pressure may produce sustained increases in systemic pressure,29 mechanisms that participate in regulation of cerebrospinal fluid balance also may influence control of systemic blood pressure. Blood vessels of the choroid plexus are very responsive to angiotensin II and endothelin,8-30 as well as to vasopressin. These peptides produce at least as much response in blood vessels of the choroid plexus as in the kidney.8-30 Preliminary studies indicate that endothelin also reduces formation of cerebrospinal fluid.31 These studies suggest that several vasoactive peptides may play an important role in modulating cerebrospinal fluid and in regulating fluid and ion balance in the brain.

Area Postrema

The area postrema is one of the specialized circumventricular organs that lacks a blood-brain barrier.32-33 The area postrema appears to function as a sensing region for circulating peptides, such as angiotensin and vasopressin, and to play an important role in autonomic regulation of the circulation.34-35

We recently examined regulation of the microcirculation of the area postrema. The hypothesis was that, because the blood–brain barrier is absent, circulating humoral stimuli would have pronounced effects on arterioles of the area postrema.36 To our surprise, intravascular vasopressin did not have selective constrictor effects on arterioles that supply the area postrema.36 The explanation for these findings became apparent when we observed that the blood–brain barrier, which is absent in capillaries of the area postrema, appears to be present in arterioles to the area postrema.36 Based on these findings, we suggest that, in contrast to the choroid plexus, circulating stimuli such as vasopressin may not have selective effects on blood flow to the area postrema (Figure 2).

Median Eminence

The median eminence and neural lobe are circumventricular organs that lack a blood–brain barrier and play a major role in regulating anterior pituitary function and vasopressin release, respectively.33,37 Because of the unique portal system between the median eminence and adenohypophysis, the concentration of regulatory factors released by the median eminence as they reach the anterior pituitary depends on the rate of release and the rate of blood flow through the median eminence.37 Recent studies suggest that both catecholamines and opiate peptides play an important role in regulation of blood flow to the median eminence.37-39 Thus, humoral mechanisms that modulate blood flow to the median eminence may indirectly have major effects on the function of the adenohypophysis.

Endothelium-Dependent Responses

Role of Nitric Oxide

A diverse group of stimuli results in synthesis and release of a variety of endothelium-derived relaxing and contracting factors.2 Lee40 was the first to examine endothelium-dependent relaxation of cerebral blood vessels in vitro. Recent studies using a bioassay technique and selective damage to endothelium in vivo suggest strongly that dilatation of pial arterioles in response to bradykinin and acetylcholine occurs through endothelium-dependent mechanisms.41-44

Increasing evidence suggests that nitric oxide (NO), or a closely related compound derived from the amino acid L-arginine, is a major endothelium-derived relaxing factor in peripheral blood vessels.45,46 Evidence that production of NO influences vascular tone under basal conditions and in response to specific agonists has been obtained in vitro, in vivo, and in several species, including humans.47-50

We recently examined the hypotheses that formation of NO influences basal tone of large cerebral arteries in vivo and that dilatation of the basilar artery in response to acetylcholine is dependent on NO synthesis.51 Application of N\textsuperscript{ω}-monomethyl L-arginine (LNMMA), an analogue of L-arginine that inhibits enzymatic formation of NO,47,52 produced constriction of the basilar artery under basal conditions in vivo. Dilatation of the basilar artery in response to acetylcholine was selectively inhibited by
LNMMA. These effects of LNMMA were inhibited by L-arginine. These findings suggest that NO synthesis influences both basal tone and responses of large cerebral arteries to acetylcholine in vivo.

**Flow-Mediated Responses**

Endothelial cells appear to sense changes in shear stress or blood flow. Flow-mediated dilatation has been described in peripheral blood vessels in vitro and in vivo. In general, this response appears to be endothelium dependent and is not blocked by inhibitors of cyclooxygenase. It should be noted, however, that arteriolar dilatation in the cremaster microcirculation in vivo appears to be endothelium dependent, and it is inhibited by indomethacin and meclofenamate.

In cerebral blood vessels, Bevan and coworkers have demonstrated flow-induced relaxation in pial arteries in vitro that is partially independent of the endothelium. The response to increases in flow in cerebral arteries in vitro may be contraction or relaxation, depending on the level of basal tone.

We have obtained evidence that marked flow-mediated dilatation occurs in large cerebral arteries in vivo. Unilateral or bilateral occlusion of the common carotid arteries, with systemic pressure maintained at control levels, produces an increase in blood flow velocity through the basilar artery. After a delay of 10–15 seconds, there is a marked increase in diameter of the basilar artery (Figure 3). Mechanisms that produce flow-mediated dilatation of the basilar artery are not clear, but the response does not appear to require activation of cyclooxygenase or NO formation. Because resistance of large arteries is higher in the cerebral circulation than in other vascular beds, flow-mediated dilatation may be a particularly important mechanism in the brain.

**Effects of Chronic Hypertension**

Chronic hypertension alters the synthesis and release of endothelium-derived relaxing and contracting factors. Endothelium-dependent relaxation of peripheral arteries to acetylcholine in vitro is impaired in several models of hypertension. In hypertensive humans, dilatation of the forearm vasculature in response to acetylcholine in vivo is impaired.

We have examined responses of cerebral arterioles to several endothelium-dependent agonists in vivo in stroke-prone spontaneously hypertensive rats (SHRSPs) and normotensive Wistar-Kyoto (WKY) rats. Dilatation of pial arterioles to acetylcholine, bradykinin, the calcium ionophore A23187, and adenosine 5'-diphosphate (ADP) is impaired in SHRSPs compared with responses of WKY rats. Responses of these blood vessels to agonists that are not endothelium dependent, such as adenosine, nitroglycerin, and NO, are similar in SHRSPs and WKY rats, which suggests that impaired responses of pial arterioles in SHRSPs are specific for endothelium-dependent agonists.

In peripheral arteries from SHRs, endothelium-dependent relaxation in response to acetylcholine is impaired compared with responses in WKY rats. This impairment is in part due to simultaneous release of an endothelium-derived contracting factor in response to acetylcholine. In SHRSPs, treatment with indomethacin selectively potentiates dilatation of pial arterioles to ADP. Serotonin, which produces modest constriction in SHRSPs under control conditions, produces modest dilatation after indomethacin. Vascular responses of cerebral arterioles in normotensive WKY rats are not altered by indomethacin, suggesting that production of an endothelium-derived contracting factor that inhibits endothelium-dependent dilatation is specific for SHRSPs.

Findings of a recent study suggest there may be differences in the mechanism of impairment of endothelium-dependent dilatation between small pial arterioles and large cerebral arteries.

**Figure 3.** Line graphs showing effect of unilateral occlusion of one carotid artery in an anesthetized rat on blood flow velocity through the basilar artery, diameter of the basilar artery, and aortic pressure. Increases in aortic pressure during carotid occlusion were prevented by withdrawal of venous blood. Findings suggest that increases in blood flow produce marked dilatation of the basilar artery.
rioles and large cerebral arteries during chronic hypertension. In SHRs, dilatation of the basilar artery to acetylcholine and bradykinin in vivo are impaired compared with responses in WKY rats. Impaired dilatator responses of the basilar artery to endothelin-dependent agonists in SHRs were not altered by indomethacin. These findings suggest that in contrast to pial arterioles, large cerebral arteries do not produce an endothelium-derived contracting factor in response to acetylcholine and bradykinin during chronic hypertension. Impaired endothelin-dependent dilatation of the basilar artery in SHRs may be related to reduced production or release of endothelin-derived relaxing factor, or to both.

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