Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease

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Girouard, Helene, and Costantino Iadecola. Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. J Appl Physiol 100: 328–335, 2006; doi: 10.1152/japplphysiol.00966.2005.—The brain is critically dependent on a continuous supply of blood to function. Therefore, the cerebral vasculature is endowed with neurovascular control mechanisms that assure that the blood supply of the brain is commensurate to the energy needs of its cellular constituents. The regulation of cerebral blood flow (CBF) during brain activity involves the coordinated interaction of neurons, glia, and vascular cells. Thus, whereas neurons and glia generate the signals initiating the vasodilation, endothelial cells, pericytes, and smooth muscle cells act in concert to transduce these signals into carefully orchestrated vascular changes that lead to CBF increases focused to the activated area and temporally linked to the period of activation. Neurovascular coupling is disrupted in pathological conditions, such as hypertension, Alzheimer disease, and ischemic stroke. Consequently, CBF is no longer matched to the metabolic requirements of the tissue. This cerebrovascular dysregulation is mediated in large part by the deleterious action of reactive oxygen species on cerebral blood vessels. A major source of cerebral vascular radicals in models of hypertension and Alzheimer disease is the enzyme NADPH oxidase. These findings, collectively, highlight the importance of neurovascular coupling to the health of the normal brain and suggest a therapeutic target for improving brain function in pathologies associated with cerebrovascular dysfunction.

cerebral blood flow; astrocytes; NADPH oxidase; free radicals

A large body of evidence indicates that neural activity is closely related to cerebral blood flow (CBF). The close spatial and temporal relationship between neural activity and CBF, termed neurovascular coupling, is at the basis of modern neuroimaging techniques that utilize the cerebrovascular changes induced by activation to map regional changes in function in the behaving human brain. However, in several brain pathologies, the interaction between neural activity and cerebral blood vessels is disrupted, and the resulting homeostatic unbalance may contribute to brain dysfunction. This review provides a brief summary of neurovascular coupling in the normal state and in diseases including hypertension, ischemic stroke, and Alzheimer disease (AD).

NEUROVASCULAR COUPLING IN THE NORMAL STATE

Cerebral blood vessels have many unique structural and functional characteristics that differentiate them from vessels in other organs. Perhaps the most distinctive feature of cerebral blood vessels is their close interaction with neurons and glia. A growing body of evidence indicates that neurons, glia (astrocytes, microglia, oligodendrocytes), and vascular cells (endothelium, smooth muscle cells or pericytes, adventitial cells) are closely related developmentally, structurally, and functionally. The term “neurovascular unit” was introduced to highlight the intimate functional relationships between these cells and their coordinated pattern of reaction to injury (see Ref. 31 for references). The increase in CBF produced by brain activity, or functional hyperemia, is an example of the close interaction between neurons, glia, and vascular cells. In the next sections, we will describe the anatomical and functional bases of neurovascular coupling in the normal brain.

Cerebral Blood Vessels

Large cerebral arteries arising from the circle of Willis branch out into smaller pial arteries and arterioles that travel on the surface of the brain across the subarachnoid space. Pial arteries give rise to penetrating arteries and arterioles that enter into the substance of the brain. These arteries consist of an endothelial cell layer, a smooth muscle cell layer, and an outer layer, termed adventitia, containing collagen, fibroblasts, and perivascular nerves (68) (Fig. 1). Penetrating vessels are separated from the brain by the Virchow-Robin space, which contains cerebrospinal fluid. On the outer side of the Virchow-Robin space, astrocytes give rise to the glia limitans membrane. As the arterioles penetrate deeper into the brain, the Virchow-Robin space disappears and the vascular basement
membrane enters into direct contact with the astrocytic end feet. Arterioles become progressively smaller, lose the smooth muscle cell layer, and become cerebral capillaries. The density of brain capillaries within the brain is regionally heterogeneous and varies according to regional blood flow and regional metabolic demands (81). Capillaries consist of endothelial cells, pericytes, and the capillary basal lamina on which astrocytic feet are attached (68) (Fig. 1). Brain endothelial cells are unique in that they are not fenestrated and are sealed by tight junctions, features that underlie the blood-brain barrier. Endothelial cells play an important role in the regulation of vascular tone by releasing potent vasoactive factors, such as nitric oxide (NO), free radicals, prostacyclin, endothelium-derived hyperpolarizing factor, and endothelin (19). Pericytes have contractile properties and may modulate capillary diameter (31). Perivascular astrocytes surround most of the capillary abluminal surface with their end feet. There is close association between cerebral arteries, arterioles, and capillaries with nerves originating from central and peripheral sources (Fig. 1). These relationships are addressed elsewhere in this series (see Ref. 25a).

**Mechanisms of Neurovascular Coupling: The Quest for the Mediators**

The mechanisms underlying neurovascular coupling have been the subject of enquiry for more than a century (31), and numerous vasoactive factors have been implicated in neurovascular coupling (Table 1). These include ions, metabolic by-products, vasoactive neurotransmitters, and vasoactive factors released in response to neurotransmitters.

**Vasoactive ions.** $K^+$ and $H^+$ are generated by the extracellular ionic currents induced by action potentials and synaptic transmission. Elevations in extracellular $K^+$ up to 8–10 mM cause dilation of arterioles both in vitro and in vivo (45, 54). This effect is mediated by the opening of $K^+$ channels, mainly of the inward rectifier type, on the membrane of arterial smooth muscle cells (20, 54), leading to their hyperpolarization and subsequent relaxation. During sustained activation, ATP depletion could lead to opening of ATP-sensitive $K^+$ channels ($K_{ATP}$) on vessels. Therefore, $K_{ATP}$ channels have been implicated in the mechanisms of neurovascular coupling (54). Furthermore, $K_{ATP}$ could also participate in neurovascular coupling by mediating the vasodilation produced by agents that increase cAMP, such as adenosine or prostacyclin (20). The vasodilatory effect of increased concentrations of $H^+$ is also mediated, at least in part, by the opening of $K^+$ channels (20). It has also been suggested that activity-induced reductions in extracellular $Ca^{2+}$ may produce vasodilation (28).

**Vasoactive factors related to energy metabolism.** The brain has little energy reserve and requires a continuous supply of glucose and $O_2$ through CBF. A sudden increase in the demand

<table>
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<td>P450 products</td>
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<td>CO</td>
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NO, nitric oxide; COX-2, cyclooxygenase-2; CO, carbon monoxide.

![Fig. 1. Relationship of cerebrovascular cells with neurons, glia, and perivascular nerves. Pial arteries and arterioles are innervated by nerve fibers arising from cranial autonomic ganglia. Smaller cerebral arterioles (<100 μm) come in contact with nerve terminals arising from local interneurons and from central pathways originating from distant sites in the brain stem or basal forebrain. These neurovascular associations often terminate on astrocytic end feet lining the abluminal vascular surface. Pericytes, contractile cells embedded in the capillary wall, are closely associated with astrocytic end feet and endothelial cells. The term “neurovascular unit” has been coined to define the close structural and functional relationships between brain cells and vascular cells. In diseases states, such as ischemic stroke, Alzheimer disease, and hypertension, the function of the neurovascular unit is profoundly disrupted resulting in alterations in cerebrovascular reactivity that compromise brain function.](http://jap.physiology.org/)

Invited Review

**NEUROVASCULAR COUPLING**

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for energy during synaptic activity could result in a relative lack of \( \text{O}_2 \) and glucose, which may be a factor in triggering the hemodynamic response (3). However, the reduction in brain \( \text{O}_2 \) concentration at the site of activation is small and transient and cannot account for sustained increases in flow (2). Furthermore, the CBF response to activation is not altered by hypoglycemia or hypoxia, suggesting that lack of glucose or \( \text{O}_2 \) is not the primary factor triggering vasodilation (3). On the other hand, adenosine, a potent vasodilator produced during ATP catabolism, is involved in neurovascular coupling in cerebellum (47) and cerebral cortex (41). Lactate produced during brain activation could also be an important mediator of functional hyperemia by increasing \( \text{H}^+ \) concentration and producing vasodilation (3). Pellerin and colleagues (66) hypothesized that astrocytes metabolize glucose through glycolysis, leading to lactate production. Lactate, in turn, is taken up by neurons and used as fuel for ATP synthesis. Recent data in hippocampal slices support this theory. Using two-photon confocal microscopy of NADH fluorescence, Kasischke et al. (38) have investigated the spatial and temporal characteristics of energy metabolism in neurons and astrocytes during activation. They provided evidence of an early NADH decrease in neurons, reflecting oxidative metabolism, followed by a NADH increase in astrocytes, reflecting glycolytic metabolism (38). These observations are consistent with the hypothesis that neuronal oxidative metabolism precedes glial glycolysis and fit well with the reduction in tissue \( \text{O}_2 \) (“dip”) observed at the onset of activation with optical imaging, functional MRI, and \( \text{O}_2 \) electrodes (2). However, the data of Kasischke et al. do not shed light on the role of lactate in the vasodilation produced by neural activation. Rather, the lactate rise is small and transient, and it cannot account in full for the increase in flow produced by neural activity (3).

Central pathways, interneurons, and vasoactive neurotransmitters. It has long been proposed that vasoactive neurotransmitters released during neural activity contribute to the vasodilation (Table 1). These neurotransmitters could be released from neurovascular projections that terminate close to blood vessels originating from local interneurons or from distant nuclei and modulate CBF (Fig. 1). However, the contribution of the vascular innervation to functional hyperemia has not been firmly established. The role of interneurons has recently been addressed by Cauli et al. (8), who, using forebrain slices, have been able to show that activation of interneurons with neurovascular contacts produces vasodilation. Furthermore, in cerebellum the CBF response evoked by somatosensory activation is decreased in cyclin D2-null mice, which lack stellate interneurons in the cerebellar molecular layer (84). These data implicate specific classes of interneurons in the regulation of the cerebral microcirculation during neural activity (see also Ref. 25a).

Other vasoactive factors released by neural activity. Vasoactive factors can also be generated by the intracellular signaling induced by activation of neurotransmitter receptors. For example, activation of glutamate receptors produces vasodilation and increases blood flow. In neocortex and hippocampus, exogenous glutamate or \( N \)-methyl-\( \text{d} \)-aspartate (NMDA) dilates pial arterioles and/or cerebral microvessels (18, 49). Functional hyperemia in cerebral and cerebellar cortex is inhibited by DL-\( \alpha \)-amino-3-hydroxy-5-methylisoxazole-propionic acid (CAMPA) and/or NMDA receptor blockers (1, 33, 62). Because glutamate is not vasoactive in isolated cerebral arteries (18), the vasodilation is mediated by vasoactive factors whose synthesis is triggered by the changes in intracellular \( \text{Ca}^{2+} \) associated with glutamate receptor activation. The increase in \( \text{Ca}^{2+} \) activates \( \text{Ca}^{2+} \)-dependent enzymes that produce potent vasodilators. One such enzyme is the neuronal isoform of NO synthase (nNOS), which produces the vasodilator NO. The vasodilation produced by topical application of NMDA or glutamate is reduced by nNOS inhibitors (18, 85). There is ample evidence that NO contributes to the increase in CBF produced by functional activity. Thus the increase in CBF in the somatosensory cortex induced by sensory stimulation is associated with NO release and is attenuated by nNOS inhibitors (5, 48, 61). However, in cerebral cortex, the effect of NO synthase inhibition on functional hyperemia can be reversed by application of exogenous NO. This finding suggests that the presence of NO is required for the vasodilation, but that NO is not the ultimate mediator of smooth muscle relaxation (48). NO is also involved in the increase in CBF induced by activation of the cerebellar cortex (1, 33). However, at variance with the cerebral cortex, in cerebellum the attenuation of the CBF response cannot be reversed by NO donors and is observed also in nNOS null mice (86, 87). These findings suggest that, in cerebellum, NO plays an obligatory role in the mechanisms of the vasodilation.

The increase in intracellular \( \text{Ca}^{2+} \) evoked by glutamate also activates phospholipase A2, leading to production of arachidonic acid. Arachidonic acid is then metabolized by the cyclooxygenase (COX) pathway, producing vasodilatory prostaglandins (25). Although there are several isoforms of COX (COX-1, -2, and -3) (25), COX-2 is the main isoform involved in functional hyperemia. COX-2 is present in axon terminals and dendritic processes separated from penetrating arterioles and capillaries by glial processes (80). Functionally, the CBF increase evoked by somatosensory stimulation is attenuated by COX-2 inhibitors or in COX-2 null mice, whereas COX-1 does not participate in the response (55, 57). The COX-2 metabolites responsible for the vasodilation are likely to involve vasodilatory prostaglandins. Other arachidonic acid products that are involved in functional hyperemia include metabolites of the p450 pathway, such as epoxyeicosatrienoic acids (67). Furthermore, carbon monoxide has also been proposed to contribute to functional hyperemia (51). Epoxyeicosatrienoic acids and carbon monoxide are addressed elsewhere in this series (see Leffler CW, Parfenova H, Jaggar JH, and Wang R, unpublished review and Koehler RC, Gebremedhin D, and Harder DH, unpublished review).

Neurovascular Coupling: Role of Astrocytes

Astrocytes are uniquely positioned to contribute to the increase in CBF produced by activation (see Koehler RC, Gebremedhin D, and Harder DH, unpublished review). Paulson and Newman (65) provided theoretical evidence that astrocytes could participate in functional hyperemia by shunting \( K^+ \) ions, which are vasoactive, from the synapses to the astrocytic end feet surrounding blood vessels. However, this theory remains to be proven experimentally. More direct evidence for a role of astrocytes has been provided by Zonta et al. (90) in brain slices. These investigators showed that glutamate released by neural activity activates metabotropic glutamate receptors in cortical
Astrocytes, leading to increases in intracellular Ca\(^{2+}\), COX activation, and local vasodilatation (90). A critical role for Ca\(^{2+}\) fluxes from neurons to astrocytes and arterioles is also supported by another study in brain slices (23). Arterioles at rest exhibit periodic contractions and relaxations, called vasomotion, a phenomenon resulting from Ca\(^{2+}\) oscillations in smooth muscle cells (23). It was found that electrical stimulation of brain slices induces Ca\(^{2+}\) waves in astrocytes, which then propagate to arterioles and inhibit vasomotion (23). The inhibition of vasomotion would allow the arteriole to be more relaxed and, presumably, increase flow. In contrast, Mulligan and MacVicar (52) demonstrated that release of caged Ca\(^{2+}\) in hippocampal astrocytes produces vasoconstriction, a response mediated by the cytochrome p450 metabolites 20-HETEs. The discrepancy between the studies of Zonta et al. and Mulligan and MacVicar is perhaps due to differences in the experimental conditions. For example, Zonta et al. preconstricted the vessels with a NO synthase inhibitor. A major limitation of studies in brain slices is the lack of cerebral perfusion. Changes in vessel diameter under these conditions are difficult to assess because the vessels lack the intrinsic smooth muscle tone provided by intravascular pressure (myogenic tone) and are not subjected to shear stress, which has profound effects on endothelial cell function (44). Nevertheless, these studies are noteworthy because they provide evidence that activity-induced Ca\(^{2+}\) transients in astrocytes are linked to changes in cerebrovascular tone.

**Neurovascular Coupling: Local vs. Remote Vasodilation**

In brain, flow is controlled by pial arteries, which are the major site of vascular resistance (27). Consequently, to optimize perfusion, the dilation of intracerebral vessels at the site of activation must be associated with dilation of upstream pial arteries (32). Additional vascular adjustments are needed to increase flow in the activated area, but not in inactive regions vascularized by other branches of the same pial artery. The mechanisms responsible for this complex and coordinated chain of events have not been completely elucidated, but several factors have emerged. The dilation initiated by active neurons may be propagated retrogradely to pial arterioles through an intrinsic mechanism such as the retrograde vasodilation of Duling and Berne (75). Indeed, retrograde vasodilation in response to ATP has been observed in isolated rat cerebral arterioles (12), whereas upstream vasodilation has been demonstrated in cerebellar cortex arterioles during activation of the parallel fibers (34). In systemic vessels, the cellular mechanisms by which the vasodilation is transmitted upstream involves intercellular conduction of signals between endothelial cells and/or vascular smooth muscle cells via gap junctions (75). The increase in shear stress on the endothelium of the feeding vessels could contribute to propagate the response further upstream (flow-mediated vasodilation) (32), but there is limited evidence supporting this possibility in the neocortical microcirculation. Less clear are the mechanisms by which the vasodilation is restricted only to the arterial branches supplying the activated areas. One possibility is that the upstream dilatation leads to increased transmural pressure in nondilated downstream branches supplying nonactivated areas inducing a myogenic response that constricts the vessels and maintains CBF constant. It is unlikely that release of vasodilator substances from the glia limits adjacent to upstream pial arteries plays a role in remote vasodilation because flushing the brain surface with artificial cerebrospinal fluid does not attenuate the pial vasodilation induced by activation (53). Irrespective of the cellular mechanisms of the retrograde propagation of the vasodilatory signals, vascular cells play a key role in the expression of functional hyperemia by coordinating a complex hemodynamic response that, in the end, results in focused and timely increase in CBF to the activated area.

**Mechanisms of Neurovascular Coupling: an Integrated View**

For many decades, investigators believed that functional hyperemia was the result of the action of a single vasoactive agent reaching local blood vessels by simple diffusion and producing the vasodilation (32). However, as discussed in the previous section, this view is no longer tenable. Active neurons and glia release a multitude of vasoactive factors that act in concert to increase CBF (31). Cerebral endothelial cells, pericytes, and smooth muscle cells are the target of these signals and transduce them into coordinated vascular adjustments that ultimately lead to an increase in CBF. Therefore, the increase in flow evoked by brain activity is mediated by the concerted action of multiple mediators that originate from different cells and act at different levels of the cerebral vasculature.

**NEUROVASCULAR COUPLING IN DISEASE**

The relationship between neural activity and CBF is altered in several pathologies. These alterations perturb the delivery of substrates to active brain cells and impair the removal of potentially deleterious by-products of cerebral metabolism. The ensuing disruption of the cerebral microenvironment is likely to contribute to brain dysfunction. In this section, we will focus on the cerebrovascular dysfunction that occurs in hypertension, AD, and ischemic stroke (Table 2).

**Hypertension**

Hypertension exerts deleterious actions on the brain and its circulation. Hypertension alters the structure of cerebral blood vessels by producing vascular hypertrophy and remodeling and by promoting atherosclerosis in large cerebral arteries and lipohyalinosis in penetrating arterioles (11, 17). These structural alterations facilitate vascular occlusions and compromise cerebral perfusion. In addition, hypertension impairs the function of cerebral blood vessels (17, 27). Hypertension impairs endothelium-dependent relaxation (19) and alters cerebrovascular autoregulation (27), defined as the ability of the cerebral circulation to maintain relatively constant CBF in the face of changes in arterial pressure within a certain range. Recent evidence suggests that hypertension also alters neurovascular coupling. Administration of ANG II to mice increases arterial pressure (20–30 mmHg) and attenuates the increase in somatosensory cortex CBF produced by whisker stimulation (~65%), without reducing resting CBF (40). The effects of ANG II on neurovascular coupling are blocked by losartan, indicating that they are mediated by AT1 receptors (40). The attenuation in functional hyperemia is observed even if the increase in arterial pressure is prevented by removal of a small amount of arterial blood, or if the pressor effect of ANG II is avoided by applying the peptide directly to the cerebral cortex (40). Furthermore, elevation of arterial pressure by phenylephrine administration
Table 2. Alterations in functional hyperemia in Alzheimer disease, cerebrovascular diseases, and hypertension: selected human studies

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CBF: cerebral blood flow; PET, positron emission tomography; NIRS: near-infrared spectroscopy; fMRI, functional magnetic resonance imaging; ↓, attenuation of the CBF increase.

Alzheimer Disease

Alzheimer disease (AD) is the most common form of dementia and is characterized by deposition of amyloid β-peptide (Aβ) in the neuropil (neuritic plaques) and blood vessels (amyloid angiopathy), and by accumulation of hyperphosphorylated neurofilament in neurons (neurofibrillary tangles) (76). Cerebrovascular structure is profoundly altered in AD (21). Cerebrovascular diseases are flattened, and smooth muscle cells undergo degeneration (21). Cerebrovascular function is also altered in AD (31). Resting CBF is reduced and the increase in CBF produced by activation is attenuated (Table 2). The cerebrovascular dysfunction often precedes the onset of cognitive impairment, suggesting a role in the mechanisms of the dementia (31).

Mouse models of AD, in which mutated amyloid precursor protein (APP) is overexpressed to increase Aβ levels, have a profound dysregulation of the cerebral circulation (31). Whereas endothelium-dependent responses are attenuated, responses to vasoconstrictors are exaggerated (35, 59). Hyperemia is impaired and cerebrovascular autoregulation is nearly abolished (58, 60). These cerebrovascular effects are present in the absence of plaques or vascular amyloid (58, 63). The cerebrovascular dysfunction observed in APP mice can be reproduced in normal mice by topical superfusion of Aβ1–40 on the neocortex (56, 63). Furthermore, alterations in vascular reactivity can also be observed in isolated vessels of normal mice exposed to Aβ1–40 (9, 59). In APP mice, the deleterious vascular effects of Aβ worsen cerebral ischemia and enhance the ensuing brain damage (88).

How do these cerebrovascular alterations contribute to the brain dysfunction? The reduced cerebral perfusion can promote ischemic lesions, which act synergistically with Aβ to exacerbate the dementia (31). Furthermore, insufficient CBF may alter Aβ trafficking across the blood-brain barrier (89). Therefore, reduced CBF may slow down Aβ clearance and promote its accumulation in the brain. In addition, the CBF reduction may attenuate cerebral protein synthesis, which is essential for normal cognition (31). Thus the structural and functional alterations of the microvasculature in AD could contribute to the mechanisms of the brain dysfunction underlying the dementia.

Ischemic Stroke

Focal or global cerebral ischemia exerts profound effects on the normal regulation of the cerebral circulation (30). In focal cerebral ischemia, the flow reduction resulting from the arterial occlusion is greatest in the center of the ischemic territory (ischemic core) and less pronounced at the periphery (ischemic penumbra) (30). In global ischemia, the perfusion of the entire brain is interrupted, usually because of cardiac arrest. In both focal and global ischemia, when perfusion is reestablished there is a transient increase in flow (postischemic hyperemia) followed by a period of reduced flow (postischemic hypoperfusion). After ischemia, the cerebral circulation is in a state of vasoparalysis (30). After ischemic stroke in patients, the reac-

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CBF: cerebral blood flow; PET, positron emission tomography; NIRS: near-infrared spectroscopy; fMRI, functional magnetic resonance imaging; ↓, attenuation of the CBF increase.

Alzheimer disease (AD) is the most common form of dementia and is characterized by deposition of amyloid β-peptide (Aβ) in the neuropil (neuritic plaques) and blood vessels (amyloid angiopathy), and by accumulation of hyperphosphorylated neurofilament in neurons (neurofibrillary tangles) (76). Cerebrovascular structure is profoundly altered in AD (21). Cerebrovascular diseases are flattened, and smooth muscle cells undergo degeneration (21). Cerebrovascular function is also altered in AD (31). Resting CBF is reduced and the increase in CBF produced by activation is attenuated (Table 2). The cerebrovascular dysfunction often precedes the onset of cognitive impairment, suggesting a role in the mechanisms of the dementia (31).

Mouse models of AD, in which mutated amyloid precursor protein (APP) is overexpressed to increase Aβ levels, have a profound dysregulation of the cerebral circulation (31). Whereas endothelium-dependent responses are attenuated, responses to vasoconstrictors are exaggerated (35, 59). Hyperemia is impaired and cerebrovascular autoregulation is nearly abolished (58, 60). These cerebrovascular effects are present in the absence of plaques or vascular amyloid (58, 63). The cerebrovascular dysfunction observed in APP mice can be reproduced in normal mice by topical superfusion of Aβ1–40 on the neocortex (56, 63). Furthermore, alterations in vascular reactivity can also be observed in isolated vessels of normal mice exposed to Aβ1–40 (9, 59). In APP mice, the deleterious vascular effects of Aβ worsen cerebral ischemia and enhance the ensuing brain damage (88).

How do these cerebrovascular alterations contribute to the brain dysfunction? The reduced cerebral perfusion can promote ischemic lesions, which act synergistically with Aβ to exacerbate the dementia (31). Furthermore, insufficient CBF may alter Aβ trafficking across the blood-brain barrier (89). Therefore, reduced CBF may slow down Aβ clearance and promote its accumulation in the brain. In addition, the CBF reduction may attenuate cerebral protein synthesis, which is essential for normal cognition (31). Thus the structural and functional alterations of the microvasculature in AD could contribute to the mechanisms of the brain dysfunction underlying the dementia.

Ischemic Stroke

Focal or global cerebral ischemia exerts profound effects on the normal regulation of the cerebral circulation (30). In focal cerebral ischemia, the flow reduction resulting from the arterial occlusion is greatest in the center of the ischemic territory (ischemic core) and less pronounced at the periphery (ischemic penumbra) (30). In global ischemia, the perfusion of the entire brain is interrupted, usually because of cardiac arrest. In both focal and global ischemia, when perfusion is reestablished there is a transient increase in flow (postischemic hyperemia) followed by a period of reduced flow (postischemic hypoperfusion). After ischemia, the cerebral circulation is in a state of vasoparalysis (30). After ischemic stroke in patients, the reac-
ivity of the cerebral circulation to vasomotor stimuli is altered, autoregulation is impaired, and the increase in CBF produced by functional activation is decreased (30). Studies in which indexes of neural activity were measured have suggested that the reduction in the CBF response to activation is secondary to a reduction of the neural activity driving the hemodynamic response (6). Thus, in a rat global ischemia model, the reduction in the CBF response to cortical electrical stimulation is associated with a reduction in the amplitude of the oxidative response (oxidation of cytochrome \( a \)) evoked by activation (14). Similarly, the increase in cerebral glucose utilization evoked by stimulation of the rat whiskers after transient global ischemia is severely depressed 1 day after ischemia (13). Therefore, after focal and global ischemia, both CBF and metabolic responses are depressed even in intact regions.

Vascular Oxidative Stress: a Final Common Pathway to Cerebrovascular Dysfunction

There is accumulating evidence that vascular oxidative stress leads to profound alterations in cerebrovascular regulation (16). Hypertension, AD, and cerebral ischemia are associated with evidence of oxidative stress in cerebral blood vessels (10, 31, 78). Thus it is likely that vascular oxidative stress is responsible for the cerebrovascular alterations observed in these conditions. There is ample evidence that ANG II-induced experimental hypertension, as well as hypertension in humans, is associated with vascular oxidative stress (15). Furthermore, studies in APP mice have shown that there is free radical production in cerebral vessels at a time when there is no evidence of oxidative stress in the brain parenchyma (63). Antioxidants attenuate the cerebrovascular dysfunction in models of ANG II-induced hypertension and in APP mice, whereas transgenic mice overexpressing the free radical scavenging enzyme SOD are protected from the dysregulation (35, 63). Because an increase in reactive oxygen species (ROS) generation has been demonstrated in cerebral ischemia (78), it is conceivable that the mechanisms responsible for an impaired functional hyperemia after ischemia are similar to those observed in hypertension and AD. Indeed, ROS scavengers ameliorate the disturbance in CBF produced by ischemia-reperfusion (30, 78), but it is not known whether ROS scavengers improve the alteration in neurovascular coupling.

ROS are produced by several enzymatic systems (78), but recent findings have identified NADPH oxidase as a major source of ROS at the vascular level (7). Inhibition of NADPH oxidase attenuates the ROS production in models of hypertension and AD, whereas mice lacking the catalytic subunit of the enzyme (gp91phox) are protected from the deleterious cerebrovascular effects of hypertension or Aβ (39, 64). Mice lacking gp91phox have reduced brain damage after middle cerebral artery occlusion (79). Therefore, NADPH oxidase-derived ROS could also play a role in postischemic cerebrovascular dysregulation.

FUTURE DIRECTIONS

As discussed above, the mechanisms of the regulation of CBF during brain activity involve the coordinated interaction of neurons, glia, and vascular cells. However, the molecular nature of these highly complex processes has not been elucidated in sufficient detail. New and powerful tools are needed to probe into the functional relationship among these cells without disruption of their natural working environment. Recently introduced in vivo imaging technologies, such as two-photon confocal microscopy, may provide the opportunity to shed light on these complex relationships. In disease states, vascular dysregulation may act synergistically with other pathologies to aggravate the intensity of the insult. It would be important to gain insight into these synergistic interactions to determine the extent to which the deleterious effects of vascular dysregulation contribute to the overall brain dysfunction. Vascular dysregulation may prove to be a valuable therapeutic target in a wide variety of brain diseases.

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