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Cerebral vascular dysregulation in the ischemic brain

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The brain has limited fuel reserves and is highly dependent on a constant supply of oxygen and energy substrates delivered through blood flow (Hossmann, 1994). Interruption of cerebral blood flow (CBF) leads to brain dysfunction and, if the interruption is prolonged, brain death. Cerebral blood vessels are endowed with powerful regulatory mechanisms that assure that the brain is perfused at all times. However, during cerebral ischemia these mechanisms become dysfunctional and fail to compensate for the reduction in CBF. Thus cerebral ischemia produces profound alterations of the major control mechanisms governing the cerebral circulation. Such dysregulation, termed vasomotor paralysis (Langfitt et al., 1964; Hoedt-Rasmussen et al., 1967; Paulson, 1971), occurs in the setting of both focal cerebral ischemia, in which CBF is reduced in a restricted brain region, and global cerebral ischemia, in which CBF is globally reduced throughout the brain. The cerebrovascular dysregulation undermines the ability of the brain to maintain CBF, aggravates the intensity of the ischemic insult, and amplifies the tissue damage. Therapies aimed at restoring cerebrovascular regulation after ischemia offer the opportunity to improve cerebral perfusion and limit ischemic injury. In this chapter, we will briefly review the effects of cerebral ischemia on the regulation of CBF, focusing on the potential mechanisms involved in the cerebrovascular dysfunction and on the implications for ischemic brain injury.

14.1. Effects of cerebral ischemia and reperfusion on cerebral blood flow

14.1.1. Cerebral blood flow after arterial occlusion

The introduction of techniques for measuring regional CBF provided new insights into the alterations of CBF distribution following focal or global cerebral ischemia. Occlusion of a major cerebral artery produces a severe reduction in CBF to the area of the brain supplied by that particular artery. Thus, the CBF reduction is greatest in the center of the ischemic territory. Surrounding this ‘core’ area of cerebral ischemia there is an area in which a less severe CBF reduction is found. This peripheral region of the ischemic territory is termed ischemic penumbra. Whereas brain tissue in the ischemic core is irreversibly damaged, the penumbra represents potentially salvageable brain tissue, in which neuronal activity is suppressed but the tissue is potentially viable (Astrup et al., 1981). The fate of the penumbra depends on the residual CBF and the duration of the flow reduction (Astrup et al., 1981; Heiss and Rosner, 1983). Numerous clinical studies have attempted to define the CBF values corresponding to the ischemic penumbra. Using different imaging techniques the range of CBF in the penumbra has been estimated to be between 12 and 22 ml/100 g per minute (Heiss et al., 2001). If CBF drops below this critical threshold for a sufficient period of time the tissue will be damaged.

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14.1.2. Cerebral blood flow at reperfusion

In human ischemic stroke, the arterial occlusion can be either permanent or transient. It has been shown that an early re-establishment of the CBF in ischemic areas (reperfusion) can be associated with a favorable functional outcome (Minematsu et al., 1992; Ringelstein et al., 1992). On the other hand, reperfusion can also exacerbate brain injury through the development of space-occupying hemorrhagic transformations or cerebral edema (Nakagawa et al., 1990; Wang and Lo, 2003). Therefore, CBF changes at reperfusion have important pathophysiological implications. Focal cerebral ischemia induced by an acute occlusion of a cerebral artery leads to a pronounced decrease in CBF in the dependent brain area. After reopening the vessel occlusion, reperfusion in the ischemic core typically shows a biphasic pattern: a transient increase in CBF (post-ischemic hyperperfusion) followed by a more sustained reduction in CBF (hypoperfusion; Fig. 14.1). Post-ischemic hyperperfusion, also known as ‘luxury perfusion’, has long been demonstrated in animal stroke models and human stroke as well (Lassen, 1966; Sundt and Waltz, 1971; Pulsinelli et al., 1982; Traupe et al., 1982; Todd et al., 1986; Heiss et al., 1997; Marchal et al., 1999). Because of a lack of pre-ischemic CBF values, post-ischemic hyperperfusion is usually termed ‘post-ischemic hyperemia’ (Hoedt-Rasmussen et al., 1967; Olsen et al., 1981; Baron et al., 1989). The length of post-ischemic hyperperfusion is directly proportional to the duration of the ischemic phase (Gourley and Heistad, 1984). The hyperemic phase is not mediated by an increase in oxygen or glucose utilization (Gourley and Heistad, 1984) and can be attributed to abnormal vasodilation in the ischemic territory (Marchal et al., 1996, 1999). Such abnormal vasodilation has multiple causes, including lactic acidosis secondary to ischemia-induced anaerobic glycolysis (Rehncrona et al., 1981) and/or release of vasoactive mediators from the ischemic brain, including ions, metabolites, and reactive oxygen species (Berne et al., 1974; Traystman et al., 1991; Nelson et al., 1992; Silver and Erecinska, 1992; Wei et al., 1996).

The mechanisms leading to post-ischemic hypoperfusion are still unclear. Measurements of intravascular pressure and segmental vascular resistance in cats following global cerebral ischemia have shown that ischemia–reperfusion is followed by an increase in cerebrovascular resistance involving both extra- and intracranial arteries (Schmidt-Kastner et al., 1987). This increase in vascular resistance could be, in part, due to microvascular compression and vasospasm, as suggested by a scanning electron microscopy study of corrosion casts in rats following transient focal ischemia (Ohtake et al., 2004). In this study, microvessels appeared constricted, compressed, and narrowed, effects attributed to edema, hemorrhage, and vasospasm presumably induced by vasoconstrictors released from the ischemic brain (Ohtake et al., 2004). Additional causes of post-ischemic hypoperfusion may include reduced metabolic demand, reduced synthesis of parenchymal and endothelial vasoactive agents, and intravascular plugging by platelets and leukocytes (Hossmann, 1983; del Zoppo and Mabuchi, 2003). A deficit of the potent vasodilator nitric oxide (NO) does not seem to be involved because inhibition of NO synthesis reduces CBF further, suggesting that NO production helps to counteract the post-ischemic increase in vascular resistance (Clavier et al., 1994). Furthermore, administration of prostacyclin does not normalize post-ischemic flow, suggesting that the hypoperfusion is not due to a lack of endothelial-derived prostacyclin (van den Kerckhoff et al., 1983).

14.2. Cerebrovascular autoregulation

Cerebral blood flow is relatively independent of changes in mean arterial pressure with a certain range. The lower and upper limits of CBF autoregulation correspond to mean arterial pressures of approximately 50–60 and 150–160 mmHg respectively (Chillon and Baumbach, 2002; see Lassen, 1959; Heistad and Kontos, 1983; Paulson et al., 1990 for review) (Fig. 14.2). This property of the cerebral circulation, termed auto-regulation, is also a

characteristic of the circulation of other organs (Paulson et al., 1990). The vascular adjustments underlying autoregulation consist of a constriction of cerebral resistance vessels when cerebral perfusion pressure (arterial pressure minus intracranial pressure) increases and a vasodilation of these vessels when perfusion pressure decreases (Kontos et al., 1978). Thus, the changes in cerebral perfusion pressure induced by changes in arterial pressure are counteracted by changes in cerebrovascular resistance, which tend to keep CBF constant. However, if the change in arterial pressure exceeds the capacity of the vessels to compensate, autoregulation is lost. Thus, increases in arterial pressure above the upper limit of autoregulation lead to increases in CBF, while decreases below the lower limit lead to reductions in CBF (Chillon and Baumbach, 2002). Furthermore, rapid variations in arterial pressure are not compensated for by autoregulation and produce changes in CBF (Aaslid et al., 1989; Florence and Seylaz, 1992). This is because the vascular adjustments initiated by arterial pressure are not instantaneous and take several seconds to take effect. The cellular basis of cerebrovascular autoregulation resides in the intrinsic property of vascular smooth muscles to react to changes in transmural pressure (myogenic tone; Bayliss, 1902; Harder et al., 1995; Wellman et al., 2002). Neural activity, hypoxia, hypo- and hypercapnia, or stimulation of cerebrovascular nerves can modulate the intrinsic vascular myogenic response and may influence the rapidity of the vascular adjustments, the slope of the pressure–flow relationship, and the range of pressures over which CBF is autoregulated (Heistad and Kontos, 1983; Busija and Heistad, 1984; Paulson et al., 1990).

14.2.1. Effect of cerebral ischemia on autoregulation: animal studies

It is well established that cerebral ischemia impairs autoregulation. Whereas most experimental studies have investigated the effect of either hypertension or hypotension on CBF, a few studies have tested the full range of pressures over which CBF is autoregulated (Table 14.1). Experimental studies in different species have investigated cerebrovascular autoregulation during reperfusion following transient cerebral ischemia. One such study investigated CBF autoregulation before, during, and after transient bilateral carotid artery ligation in rats (Shiokawa et al., 1986). Resting CBF was markedly reduced 30 min after ligation and autoregulation during hypotension was severely impaired, resulting in almost zero flow. Such autoregulatory dysfunction persisted, even though less pronounced, in the acute phase after restoration of CBF to the ischemic lesion (Shiokawa et al., 1986). In the phase of hypoperfusion following transient global cerebral ischemia in dogs, autoregulation was present but attenuated (Christopherson et al., 1993). In that study, the CBF response to CO_2 was also markedly attenuated. This finding is at variance with other investigations that demonstrated restored autoregulation during the phase of post-ischemic hypoperfusion while the CO_2 response is still reduced (Hossmann et al., 1973; Nemoto et al., 1975). Perhaps, this discrepancy can be attributed to the different methods used for the induction of cerebral ischemia.

The upper limit of autoregulation was impaired within the first hour after permanent middle cerebral artery occlusion in cats (Shima et al., 1983). However, 2 h after ischemia, autoregulation was partially restored (Shima et al., 1983). Measurement of pial artery pressure revealed that autoregulation in non-occluded collateral arteries supplying the ischemic territory is preserved (Shima et al., 1983). Therefore, collateral pathways could partially compensate for the CBF reduction following middle cerebral artery occlusion (Shima et al., 1983). Other studies found that autoregulation remains markedly impaired for several years after cerebral ischemia. For example, Symon and colleagues (1975) investigated autoregulation during hypotension in baboons 3 years after focal cerebral ischemia. They found that autoregulation was abolished in the infarct itself but it was present, albeit significantly impaired, in brain areas surrounding the infarcted tissue.

The degree of impairment of autoregulation is related to the magnitude of the CBF reduction. Dirnagl and Pulsinelli (1990) tested autoregulation during hypertension and hypotension in rats following permanent combined middle cerebral artery and common carotid artery occlusion. Autoregulation was attenuated in areas in which CBF fell to levels between 30% and 60% of preocclusion values and was lost in areas where CBF was below 30%. Similarly, in a study using intra-arterial injection of silicone for the occlusion of intracranial arteries, autoregulation was more or less impaired depending on the proximity of the region to the ischemic core, where the CBF reduction is most pronounced (Lauer et al., 1998). Another important finding that emerged from experimental studies is that in the ischemic brain autoregulation is also impaired in remote non-ischemic areas. For example, moderate hypotension 24 hours after transient focal cerebral ischemia in rats demonstrated that autoregulation is impaired in the normally perfused peri-infarct cortex and subcortical white matter, as well as in the subcortical white matter of the contralateral hemisphere (MacGregor et al., 2000). In another study, the lower limit of autoregulation was reduced in the rat cerebellum after transient bilateral carotid occlusion (Shiokawa et al., 1986). These remote effects are likely to be mechanistically related to the concept of diaschisis (see section 14.4.1).

14.2.2. Human studies

Alterations of cerebrovascular autoregulation following ischemic brain injury have also been investigated in humans (Table 14.2). The use of positron emission tomography (PET) provided valuable insights into the compensatory mechanisms that maintain cerebral perfusion in the initial stages of CBF reduction before brain injury occurs. Powers (1991) categorized these cerebrovascular adjustments into three stages: stage 0, when cerebral perfusion pressure is normal; stage 1, when cerebral perfusion pressure is reduced and autoregulation dilates cerebral vessels to maintain CBF; and stage 2, when the compensatory capacity for cerebral vasodilation is exceeded, CBF begins to decrease, and oxygen extraction fraction increases to maintain the cerebral metabolic rate of O_2 ($CMRO_2$) (Powers, 1991). In stage 2 cerebrovascular autoregulation is disrupted.

In patients with acute stroke, all studies found an impaired autoregulation in the affected vascular territory, even though different techniques were used for CBF measurement and estimation of autoregulation (Olsen et al., 1981; Heiss et al., 1992; Eames et al., 2002; Immink et al., 2005). Immink et al. demonstrated, using measurement of dynamic cerebral autoregulation, that patients with acute unilateral lacunar strokes have bilaterally impaired autoregulation, whereas, in patients with an acute middle cerebral artery territory stroke, autoregulation is affected only in the ischemic hemisphere (Immink et al., 2005). These results are consistent with the assumption that patients with acute lacunar strokes suffer from bilateral small vessel disease and are therefore at increased risk of further ischemic events. In addition, autoregulation was transiently impaired in patients who had recently suffered a transient ischemic attack, and the autoregulatory impairment outlasted the clinical symptoms (Skinhoj et al., 1970). Moreover, Olsen et al. (1983) found an impairment of autoregulation in collateral arteries supplying the penumbra in patients less than 72 h after middle cerebral artery occlusion. Remote disturbances of autoregulation in the contralateral hemisphere of two patients with subacute (< 6 days) cerebral ischemia have also been described (Paulson et al., 1972). However, these patients had space-occupying lesions and the possibility that the remote effect was due to an increase of intracranial pressure could not be ruled out.

Autoregulation is also impaired by stenosis or occlusion of cerebral arteries. Two investigations using transcranial Doppler sonography found that cerebral autoregulation is impaired in patients with critical internal carotid artery stenoses or occlusions (Gooskens et al., 2003; Reinhard et al., 2003). Using two different paradigms to assess autoregulation, both groups found a correlation between degree of stenosis and loss of autoregulation.

Furthermore, both studies concluded that the impairment in autoregulation is more severe in cases with bilateral internal carotid artery stenoses or occlusions, and that the alteration also depends on the collateral supply through the circle of Willis. Furthermore, Haubrich et al. (2007) demonstrated in a cohort of elderly patients that impaired cerebral auto-regulation may recover after carotid angioplasty. Gong et al. (2006) measured autoregulation in patients with middle cerebral artery stenosis and found impaired dynamic autoregulation, which correlated with the degree of stenosis, insufficient collateralization, and the severity of ischemic stroke. Furthermore, autoregulation improved after middle cerebral artery stentingangioplasty (Gong et al., 2006). Additional evidence of autoregulatory compromise in patients with internal carotid artery or middle cerebral artery occlusion was provided by Ouchi et al. (2001) using PET to measure CBF. A change in posture from supine to sitting was used as the autoregulatory challenge. Assuming that the sitting position was associated with a reduction in CBF and an increase in oxygen extraction fraction in regions ipsilateral to the stenotic vessels provided evidence for impaired autoregulation in post-stenotic resistance vessels. Similar results were described in a patient with recurrent transient ischemic attacks who had a critical ipsilateral internal carotid artery stenosis and a contralateral internal carotid artery occlusion and in whom CBF was measured during hypotension using xenon-133 inhalation (Tatemichi et al., 1990).

In summary, cerebral ischemia in animals, as in humans, impairs cerebrovascular autoregulation. The degree of impairment depends on the magnitude of the local CBF reduction but autoregulation is also impaired in remote non-ischemic regions. Although the temporal profile of the autoregulatory impairment following ischemic stroke suggests a trend towards improvement over time, severe disturbances in auto-regulation have also been observed in chronic stroke. In addition to acute cerebral ischemia, critical stenosis of cerebral arteries is also capable of compromising cerebrovascular autoregulation. Preliminary evidence suggests that stenting or angioplasty of diseased cerebral vessels may ameliorate the autoregulatory deficit.

14.3. Cerebrovascular reactivity to hypercapnia

Arterial partial pressure of carbon dioxide (P_{CO_2}) is a potent vasoactive stimulus for the cerebral circulation. Hypercapnia produces vasodilation whereas hypocapnia produces vasoconstriction. The cerebrovascular effects of hypercapnia are thought to be mediated by the changes in perivascular pH that accompany increases in P_{CO_2} (Kontos et al., 1977). The mechanisms of the pH effect are multifactorial and involve direct effects on smooth muscle cells via adenosine triphosphate (ATP)-sensitive K^+ channels (Faraci et al., 1994), prostanoids derived from cyclooxygenase-1 (Niwa et al., 2001), and NO (Iadecola, 1992; Faraci et al., 1994; Sandor et al., 1994; Thompson et al., 1996).

14.3.1. Effect of cerebral ischemia on cerebrovascular reactivity: animal studies

The cerebrovascular reactivity to changes in P_{CO_2} is impaired following focal or global cerebral ischemia (Table 14.3). Most studies have tested CBF reactivity to hypercapnia, while a few also examined the effects of hypocapnia (Nemoto et al., 1975; Jones et al., 1989; Christopherson et al., 1993). With permanent ischemia several studies found that CO_2 reactivity is abolished in the ischemic core but is still present but reduced in the brain tissue surrounding the core area (Symon et al., 1975; Jones et al., 1989; Dettmers et al., 1993; Harris et al., 2001). However, in transient ischemia, improvements in CO_2 reactivity have been reported during reperfusion (Koch et al., 1984; Schmidt-Kastner et al., 1986; Ono et al., 1997; Olah et al., 2000). With reperfusion, CO_2 reactivity recovered faster in penumbral regions whereas the ischemic core showed a lack of recovery (Olah et al., 2000). However, in the penumbra CO_2 reactivity, while improved, remained below normal values (Olah et al., 2000). The impairment of CBF reactivity to CO_2 is present despite full recovery of energy

metabolism (Olah et al., 2000). During post-ischemic hypoperfusion, most investigators found an attenuated or even abolished response to CO_2 (Nemoto et al., 1975; van den Kerckhoff et al., 1983; Schmidt-Kastner et al., 1987; Leffler et al., 1989; Christopherson et al., 1993). Most investigations suggest an association between persistently impaired CO_2 reactivity and irreversible brain damage (Seki et al., 1984; Schmidt-Kastner et al., 1986).

In some cases, hypercapnia produced a paradoxical reduction in CBF (Shima et al., 1983; Ono et al., 1997; Olah et al., 2000). Such reversal of hypercapnic vasodilation to vasoconstriction has been attributed to a 'steal' of blood flow into neighboring areas where CO_2 reactivity is retained (Symon et al., 1974). Although this phenomenon has been confirmed in some animal studies (Waltz, 1970; Paulson, 1971; Symon et al., 1971; Ott et al., 1975; Olah et al., 2000), other studies could not find evidence for an intracerebral steal in hypercapnia (Olsen et al., 1983; Jones et al., 1989) or during administration of cerebrovasodilators (Date and Hossmann, 1984; Gogolak et al., 1985). Therefore, the existence of an intracerebral steal phenomenon during hypercapnia or vasodilator administration remains controversial. Like cerebrovascular autoregulation, CBF reactivity to CO_2 is also altered in regions remote from the ischemic lesion. For example, in baboons it has been shown that the CO_2 reactivity 6 h after permanent middle cerebral artery occlusion is also attenuated in non-infarcted, non-penumbral tissue supplied by the affected middle cerebral artery (Dettmers et al., 1993).

14.3.2. Human studies

Consistent with findings obtained in animal studies, investigations in patients with ischemic stroke have demonstrated alterations in the cerebrovascular reactivity to changes in P_{CO_2} (Table 14.4). Olsen et al. (1981) examined cerebrovascular reactivity to hyper- and hypocapnia in hyperemic areas of nine patients with acute ischemic stroke and found an impaired CO_2 response in four of these patients. Other studies have shown a more consistent attenuation in CO_2 reactivity. For example, Novak and colleagues (2003) used transcranial Doppler sonography for the analysis of CO_2 reactivity in 20 patients with minor stroke and found an impaired response in the ipsilateral hemisphere.

Simultaneous measurements of cerebrovascular autoregulation and CO_2 reactivity revealed that CO_2 reactivity is better preserved than autoregulation in hemodynamically compromised brain areas (Paulson et al., 1972). Thus in this study, a state of dissociated vasoparalysis with impaired autoregulation and preserved CO_2 reactivity was described. The authors stated that dissociated vasoparalysis might represent a stage in a gradual change between normal vasomotor function and complete vasoparalysis (Paulson et al., 1972).

As in animal studies, remote alterations in cerebrovascular CO_2 reactivity have also been found in humans. In some cases, these remote alterations could be related to the phenomenon of diaschisis (see section 14.4.1). For example, in patients with capsular infarcts the CBF response to hypocapnia was reduced and the response to hypercapnia was enhanced in a restricted ipsilateral cortical area with reduced basal CBF, presumably because of diaschisis (Takano et al., 1988). More diffuse changes in CBF reactivity to CO_2 have also been reported in patients with cerebrovascular diseases. Maeda and colleagues (1993) compared CO_2 reactivity in patients with cortical or lacunar infarction with those of normal subjects. Patients with cortical infarctions exhibited reduced CO_2 reactivity in the ischemic hemisphere compared to normal control subjects. In contrast, patients with subcortical infarctions exhibited a diffuse attenuation in CO_2 responses in both hemispheres. These findings have been confirmed more recently (de Leeuw et al., 2003). Based on the finding of a reduced CO_2 response in the non-ischemic hemisphere also, it was concluded that this impaired CO_2 reactivity is a marker of generalized small-vessel disease. Another example of generalized impaired CO_2 reactivity was provided by Yamamoto and colleagues

(1980). In this study, the hemispheric response to hypercapnia was significantly reduced in patients with hemispheric infarction as well as in patients with vertebrobasilar ischemia. Similarly, Levine et al. (1988) demonstrated reduced CO_2 reactivity in the ischemic hemisphere of patients with transient ischemic attack or minor ischemic stroke, as well as in the nonischemic hemisphere of stroke patients. The influence of generalized pathological alterations in the cerebral vasculature on the CBF reactivity to CO_2 has also been demonstrated in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in whom a profound attenuation was reported (Pfefferkorn et al., 2001). These findings underline the importance of the functional state of cerebral blood vessels in the mechanisms of the vascular reactivity to CO_2.

As noted for cerebrovascular autoregulation, CBF reactivity to CO_2 is reduced in patients with stenosis or occlusion of one or more large cerebral arteries (Clifton et al., 1988; Keyeux et al., 1988; Tatemichi et al., 1990; Miller et al., 1992; Bakker et al., 2003). Several studies found a correlation between the degree of internal carotid artery stenosis, the number of affected arteries, and the impairment in CO_2 reactivity (Brown et al., 1986; Levine et al., 1991; Gooskens et al., 2003; Reinhard et al., 2003). Furthermore, some studies considered the degree of collateral circulation to be an important factor for the preservation of CO_2 reactivity. Accordingly, it was found that the CO_2 reactivity is more impaired in patients with poor collateral blood supply (Norrving et al., 1982; Bullock et al., 1985; Ringelstein et al., 1988, 1994). Two PET studies correlated CO_2 reactivity with CBF, cerebral blood volume (CBV) and oxygen extraction fraction in patients with occlusive carotid artery disease. In one study, a positive correlation between the CBF/CBV ratio and CO_2 reactivity was found, while oxygen extraction fraction was negatively correlated with CO_2 reactivity in most patients (Herold et al., 1988). In the other study, a negative correlation between oxygen extraction fraction and hypercapnic response was observed, a finding suggesting a relationship between reduced vasodilatory capacity of cerebral arteries and increase in oxygen extraction fraction. Using this correlation, Kanno et al. (1988) defined the oxygen extraction fraction value that corresponds to exhausted vasodilatatory capacity in cerebral arteries. Interestingly, this value coincided with the upper limit of the oxygen extraction fraction measured in normal tissue. The robust correlation between CBF response to CO_2 and oxygen extraction fraction indicates that CO_2 reactivity is a suitable method for assessing the cerebrovascular and metabolic reserves of the hemodynamically compromised brain (Herold et al., 1988; Kanno et al., 1988).

An alternative approach to assess cerebrovascular reactivity in humans is the intravenous injection of acetazolamide, a carbonic anhydrase inhibitor. Administration of acetazolamide produces a gradual decline in brain pH (Heuser et al., 1975). Acidosis is a potent stimulus for cerebral arteries to dilate. Considering that the cerebrovascular effects of arterial P_{CO_2} are mediated by the changes in perivascular pH (Kontos et al., 1977), the acetazolamide test simulates the cerebrovascular vasodilation induced by hypercapnia. Unlike CO_2, assessing cerebrovascular reactivity with acetazolamide does not require the assistance of the patient, which is an advantage in acutely ill stroke patients who might be unable to cooperate. In general, CO_2 and acetazolamide responses show similar results in patients with cerebrovascular diseases (Ringelstein et al., 1992). The CBF reactivity to acetazolamide is impaired in patients with transient ischemic attack (Chollet et al., 1989), occlusive internal carotid artery disease (Schreiber et al., 1998), and acute and chronic cerebral ischemic disease (Vorstrup et al., 1986; Nariai et al., 1995). Nemoto et al. (2007) published a PET study in which the relationship between the cerebrovascular acetazolamide reserve and the oxygen extraction fraction reactivity to acetazolamide was analyzed in patients with symptomatic internal carotid artery occlusion. The authors found a close correlation between hemispheric cerebrovascular reserve and oxygen extraction fraction reactivity. They suggest that the oxygen extraction fraction reactivity to acetazolamide may be a valuable measure of

hemodynamic compromise (Nemoto et al., 2007). However, by comparing acetazolamide and hypercapnic challenges, some studies found differences in the cerebrovascular reactivity to acetazolamide and hypercapnia in patients with cerebrovascular occlusive diseases (Kazumata et al., 1996). Therefore, the CBF reactivity to CO_2 and acetazolamide cannot always be considered to be identical.

In summary, cerebral ischemia impairs the reactivity of CBF to CO_2, and the degree of impairment is related to the magnitude of the local CBF reduction. CO_2 reactivity recovers after reperfusion in areas that are not damaged. Following focal cerebral ischemia, CO_2 reactivity is reduced in non-ischemic areas, suggesting a remote effect leading to impairment even in the normally perfused brain. Moreover, CO_2 reactivity is globally impaired in patients with diffuse microvascular disease. Because of its close correlation with indices of brain oxygen metabolism, cerebrovascular CO_2 reactivity may be a valuable tool to assess the vascular and metabolic reserves of the hemodynamically compromised brain.

14.4. Neurovascular coupling

There is substantial evidence that neural activity is a major factor controlling CBF. In the resting brain, there is a general correspondence between the flow of a given brain region and its rate of cerebral glucose utilization, a variable reflecting neural activity (Reivich, 1974; Sokoloff et al., 1977; Kuschinsky, 1987; Iadecola, 1993). Thus, regions with low glucose utilization, such as the white matter, have low flow, whereas regions with high glucose use, such as the auditory cortex, have high flow (Kuschinsky, 1987). In addition, when the activity of the brain is enhanced, either focally or globally, local blood flow increases in proportion to the intensity of the activation (Raichle et al., 1975; Greenberg et al., 1979; Tsubokawa et al., 1980; Iadecola et al., 1983; Fox and Raichle, 1984; Frostig et al., 1990). Conversely, if brain activity is decreased CBF decreases proportionally (Nilsson et al., 1978; Ueki et al., 1988). The close correspondence between CBF and neural activity reflects a homeostatic mechanism by which the delivery of substrates through blood flow, as well as the removal of metabolites produced by brain activity, are coupled to the energy demands of neurons and glia. Neuronal, glial, and vascular factors, acting in concert, mediate the increase in CBF produced by neural activity (Zonta et al., 2003; Cauli et al., 2004; Mulligan and MacVicar, 2004; Takano et al., 2006; Iadecola and Nedergaard, 2007). Neurons and astrocytes release vasoactive agents, such as ions (K^+, H^+), neurotransmitters (acetylcholine, vasoactive intestinal polypeptide, etc.), and neuromodulators (adenosine, nitric oxide, prostanoids, p450 metabolites) that act on local vessels to initiate the response (Iadecola, 1993; Iadecola and Nedergaard, 2007). Vascular cells, including endothelial cells, pericytes, and smooth muscle cells, transduce these neuronal and glial signals into changes in vascular resistance that ultimately mediate the increases in CBF (Iadecola and Nedergaard, 2007).

14.4.1. Effect of ischemia on neurovascular coupling: animal studies

Cerebral ischemia attenuates the CBF increase produced by functional activation (Table 14.5). Some studies have focused on the effect of focal or global ischemia on the coupling between CBF and cerebral glucose utilization in the resting state, while other studies have focused on the increase in CBF induced by brain activity. For example, Ginsberg et al. (1989) found reduced resting CBF and cerebral glucose utilization in the left barrel-field cortex and other left cortical regions in rats with a left frontal photothrombotic ischemia. Moreover, following contralateral vibrissa stimulation a marked suppression of the increase in CBF and cerebral glucose utilization produced by activation was observed throughout the barrel-field cortex (Ginsberg et al., 1989). In support of these findings, Kunz et al. (2007b) showed that the increase in CBF produced by whisker stimulation is markedly attenuated 1 h after transient focal cerebral ischemia in mice. Similarly, permanent middle cerebral artery occlusion attenuated the increase in CBF and estimated $CMRO_2$ produced by somatosensory

activation in rats, in which CBF was measured by magnetic resonance imaging (MRI) with arterial spin labeling (Shen et al., 2005). However, the increases in CBF and $CMRO_2$ produced by somatosensory activation were not attenuated 30 min after middle cerebral artery occlusion lasting 15 min, an ischemic challenge that did not lead to brain injury (Shen et al., 2005). Therefore, the alterations in neurovascular coupling are graded according to the intensity of the ischemic insult.

Duckrow et al. (1981) examined the effect of transient global ischemia on the activation-induced changes in the redox state of cytochrome a,a_3 in the rat cerebral cortex. Before ischemia, focal electrical stimulation of the cerebral cortex increased the oxidation of cytochrome a,a_3, and increased local blood volume, a parameter reflecting stimulus-induced hyperemia. After ischemia, the amplitude of the oxidative response and of the blood volume increase was reduced up to 30 min after ischemia. Also, the length of time required for the oxidative response to return to baseline was increased, despite full recovery of the mitochondrial baseline redox state. These observations provide evidence that increasing the work of the post-ischemic cortex unveils metabolic abnormalities that cannot be appreciated in the resting state. Another study investigated the correlation between hemodynamic parameters and field potentials evoked by somatosensory activation after transient global ischemia in the rat (Ueki et al., 1988). In the normal state, somatosensory stimulation increased CBF, cerebral glucose utilization, and local brain lactate concentration. By 3 h after global ischemia, the increases in CBF were suppressed while somatosensory evoked potentials had already reappeared (Ueki et al., 1988). No local changes in brain pH, lactate, glucose, and ATP were observed. Therefore, after global ischemia, both CBF and metabolic responses are depressed, despite recovery of somatosensory evoked potentials. The data suggest that, after ischemia, the metabolic workload of the cortex during functional activation is reduced and does not require increased delivery of substrates via an increase in CBF. The findings also indicate that ischemia disrupts the coupling between synaptic activity and CBF/cerebral glucose utilization, which may have long-term consequences for brain function.

Dietrich et al. (1986) investigated the time course of the ischemia-induced attenuation of the cerebral glucose utilization increase evoked by stimulation of the facial whiskers in the rat. They found that, 1 day after transient global ischemia, metabolic responses are severely depressed in the neocortex and thalamus but not in the trigeminal complex. Resting cerebral glucose utilization in the cortical barrel field and in the ventrobasal thalamus were also decreased. However, the activation-induced increase in cerebral glucose utilization returned to baseline 5 days after the ischemic insult. At this time, the spatial pattern of activation within the cortical barrel field was different from that of normal rats, suggesting that different local pathways were used. These observations support the idea that ischemia induces reorganization of cortical circuits in an attempt to compensate for the neuronal dysfunction and loss (Nudo, 2003). Alterations in regional blood flow and metabolism have also been described in brain areas remote from the ischemic lesion. These alterations are probably related to the concept of diaschisis (von Monakow, 1914), a term indicating brain dysfunction in areas remote from the ischemic regions, crossed cerebellar diaschisis being a typical example (Feeney and Baron, 1986). Gold and Lauritzen (2002) examined the neurophysiological basis of crossed cerebellar diaschisis in rat. Inactivation of the cerebral cortex by focal ischemia, spreading depression, or topical application of the Na^+ channel blocker tetrodotoxin reduced contralateral Purkinje cells' spiking activity and cerebellar blood flow (Gold and Lauritzen, 2002). These cerebellar alterations, which represent the neurophysiological basis of crossed cerebellar diaschisis, were not related to reductions in the excitability of Purkinje cells or cerebellar vascular reactivity. Thus, crossed cerebellar diaschisis is mediated by deactivation of the cerebellar cortex resulting from interruption of neocortical excitatory inputs (Gold and Lauritzen, 2002). Therefore, the remote changes in

brain function produced by cerebral ischemia are likely to result from deafferentation rather than intrinsic changes in the neural circuitry or blood vessels of the remote region.

14.4.2. Human studies

Although several investigations have addressed the effects of ischemic stroke on neurovascular coupling, most of these studies have been performed in patients with chronic stroke (Table 14.6). Inao et al. (1998) used PET to examine patients with minor strokes and critical ipsilateral internal carotid–middle cerebral artery stenosis or occlusion. Despite an impaired ipsi-lateral acetazolamide response, the authors found a nearly normal CBF response to neural activation. Based on these results, it can be hypothesized that CBF response to neural activity is more robust than CBF reactivity to CO_2. Unfortunately, the authors only tested the acetazolamide response and not the CO_2 response or cerebrovascular autoregulation. Yamauchi et al. (2005) examined CBF responses in the primary visual cortex during visual stimulation in patients with internal carotid artery stenoses or occlusions using PET. Visual stimulation increased CBF in the primary visual cortex ipsilateral to the internal carotid artery lesion. However, the CBF increase in the surrounding regions was significantly reduced compared to the non-affected hemisphere. This finding raises the possibility that the local hemodynamic response evoked by visual stimulation might occur at the expense of perfusion of the surrounding region in brain areas with an already compromised vascular reactivity (Yamauchi et al., 2005).

Blood-oxygen-level-dependent (BOLD) functional MRI (fMRI) is a powerful tool for studying functional activation in humans. BOLD-fMRI is based on the paramagnetic property of deoxyhemoglobin. During functional activation, a local decrease in the concentration of deoxyhemoglobin is observed (Ogawa et al., 1990). This decrease in deoxyhemoglobin gives rise to the BOLD signal, which reflects the interplay between changes in CBF, CBV, and $CMRO_2$ during functional activation (Dirnagl et al., 2002). A few studies have examined functional activation using BOLD-fMRI in ischemic stroke patients. Krainik et al. (2005) investigated BOLD signal changes induced by manual tasks in patients who had fully recovered from stroke in the frontal lobe. The authors found that the BOLD signal changes in the sensorimotor cortex and supplementary motor area of the lesioned hemisphere was decreased despite the fact that these regions were anatomically intact. Interestingly, an impaired BOLD response to hypocapnia was a predictor of impaired BOLD response to functional activation as well. Based on these findings, the authors could provide a relationship between a reduced CO_2 reactivity in brain areas surrounding the ischemic infarct and an impaired neurovascular coupling. Similar findings were described in a population of patients with a lacunar stroke (Pineiro et al., 2002). These patients exhibited a lower BOLD signal increase and a lower rate of rise of the BOLD signal during a sequential finger-tapping task performed contralaterally to the ischemic lesion. These changes were also found in the non-lesioned hemisphere for the same task performed with the corresponding hand. Unfortunately, CBF reactivity to CO_2 was not investigated in these patients. Since CO_2 reactivity is globally impaired in patients with lacunar stroke (Maeda et al., 1993; de Leeuw et al., 2003), it can be assumed that cerebral small-vessel disease is a major factor responsible for the impairment of both CO_2 reactivity and neurovascular coupling. Also, Sakatani et al. (2003) described only limited activation areas with BOLD-fMRI in the sensorimotor cortex on the lesion side in ischemic stroke patients performing a motor task. In addition to BOLD-fMRI measurements, the authors performed near-infrared spectroscopy (NIRS) during the motor tasks, and they were able to measure the local changes in deoxyhemoglobin, oxyhemoglobin, and total hemoglobin. During the hand grasping task, increases in the focal concentrations of oxyand total hemoglobin were observed in the sensorimotor cortex, reflecting local increases in CBF. Also, a sustained increase in the concentration of deoxyhemoglobin was observed throughout the task in

stroke patients, whereas a decrease was observed in control subjects. The increased deoxyhemoglobin signal measured by NIRS in stroke patients was accompanied by reduced BOLD signal activation in sensorimotor cortex (Sakatani et al., 2003; Murata et al., 2006). Similar changes in NIRS signals were also found in the left prefrontal cortex of aphasic stroke patients (Sakatani et al., 1998). The mechanism of the increase in deoxyhemoglobin in stroke patients remains unclear, although the possibility of a more pronounced increase in oxygen consumption by neuronal activity in patients with ischemic stroke has been considered (Sakatani et al., 2003).

The relationship between BOLD-fMRI and neural activity after stroke was examined more directly by Rossini et al. (2004). These investigators studied neural activity detected by magnetoencephalography (MEG) and BOLD-fMRI in patients with a history of stroke or transient ischemic attack, using median nerve stimulation to activate the somatosensory cortex. While MEG signals were detected in the affected and the unaffected hemispheres, the corresponding BOLD signal was not observed. Such uncoupling between neuro-physiological responses and BOLD signal was related to a reduced vasomotor reactivity as assessed by transcranial Doppler sonography during CO_2 inhalation. Therefore, even though CO_2 reactivity and functional hyperemia are impaired in stroke patients, the neural response evoked by the activation is still preserved (Rossini et al., 2004). Similar findings were described in a patient with bilateral internal carotid artery occlusions and unilateral vertebral artery occlusion (Rother et al., 2002).

In general, the results with BOLD-fMRI in patients with stroke differ from those with PET in that a reduction in the BOLD response to activation was usually found. Changes in regional CBF evoked by neural activation measured by PET are likely to reflect more precisely the hemodynamic changes. This is not surprising considering that the BOLD response is an indirect measure of CBF and also reflects CBV and $CMRO_2$ (Dirnagl et al., 2002; Ugurbil et al., 2003). This is especially true after stroke, where the normal relationship between CBF, CBV, and $CMRO_2$ may be altered by the disease process (Sakatani et al., 2003). Therefore, observations with fMRI need to be interpreted with caution because the BOLD signal may not reliably reflect CBF in the injured brain (Sakatani et al., 2003).

A few studies investigated BOLD responses in patients with stenosis or occlusion of major cerebral arteries. Bilecen et al. (2002) performed fMRI of the auditory cortex during auditory stimulation (1000 Hz, sine-tone) in acute stroke patients with unilateral internal carotid artery stenosis or occlusion and found a reduced BOLD response only in patients with ischemic lesions in the watershed areas between the anterior and middle or posterior and middle cerebral arteries. Patients without cerebral lesions or internal carotid artery disease had symmetric responses. The authors concluded that the presence of borderzone lesions in patients with reduced BOLD responses suggests that internal carotid artery stenosis is hemodynamically significant and contributes to the reduced BOLD response (Bilecen et al., 2002). Reduced or negative BOLD effects in patients with occlusive diseases of major cerebral arteries and without ischemic stroke were also described (Carusone et al., 2002; Hamzei et al., 2003). The negative BOLD effect is difficult to interpret and could reflect a more pronounced increase in $CMRO_2$ compared to CBF, as suggested by the observation that deoxyhemoglobin is increased in patients with stroke during activation (Sakatani et al., 2003).

In summary, acute cerebral ischemia in animals results in an attenuation of the CBF and metabolic responses induced by neural activation. Most studies in humans have been performed in patients with chronic stroke. While in PET and NIRS studies the increases in local CBF and metabolism evoked by activation were found to not be impaired, in studies using BOLD-fMRI an impaired cerebrovascular response to neural activation was found,

often coupled to a reduction in CO_2 reactivity. In addition, alterations in neurovascular coupling are also present in patients with generalized impairment of cerebrovascular reactivity due to cerebral small-vessel disease or occlusive disease of major cerebral arteries. Although BOLD-fMRI seems to be more sensitive to the neurovascular disturbance induced by stroke, the basic mechanisms of the BOLD response in the ischemic brain have not been completely elucidated and BOLD-fMRI findings need to be interpreted with caution.

14.5. Role of reactive oxygen species in the cerebrovascular dysregulation following cerebral ischemia

There is accumulating evidence that reactive oxygen species are a major contributor to the disturbances in the regulation of the cerebral vasculature following ischemic brain injury. Reactive oxygen species are molecules that often have an unpaired electron in the outer orbital ring. Cerebral ischemia results in an overproduction of reactive oxygen species, which overwhelms endogenous antioxidant enzymes (Traystman et al., 1991; Chan, 2001). The production of reactive oxygen species following cerebral ischemia has been demonstrated in several animal studies (Armstead et al., 1988; Cao et al., 1988; Kontos et al., 1992; Zhang and Piantadosi, 1994; Globus et al., 1995; Kil et al., 1996; Piantadosi and Zhang, 1996; Chan et al., 1998; Murakami et al., 1998; Kawase et al., 1999; Kim et al., 2000, 2001, 2002; Kunz et al., 2007a). A peak in reactive oxygen species production occurs in the early reperfusion period after global ischemia in cats (Nelson et al., 1992), raising the possibility that reperfusion provides the oxygen needed for the formation of reactive oxygen species. Similarly, in transient focal cerebral ischemia in mice, reactive oxygen species production exhibits a peak at 2 h after reperfusion and at 72 h as well (Kunz et al., 2007a). The late post-ischemic increase in reactive oxygen species formation may reflect a radical produced by inflammatory cells infiltrating the ischemic brain through the enzyme NADPH oxidase (Kunz et al., 2007a). However, reactive oxygen species production has also been reported to occur before reperfusion (Liu et al., 2003), indicating that reestablishment of CBF is not needed to provide the oxygen for the formation of reactive oxygen species.

14.5.1. Reactive oxygen species and ischemic cerebrovascular dysregulation

Reactive oxygen species, including superoxide, hydrogen peroxide, and peroxynitrite, are potent dilators of cerebral arterioles and may play a role in normal cerebrovascular regulation (Kontos, 2001; Niwa et al., 2001). However, higher concentrations produce vasoconstriction and disrupt cerebrovascular regulation (Traystman et al., 1991; Kontos, 2001; Iadecola, 2004; Faraci, 2005). There is growing evidence that the cerebrovascular dysregulation associated with several brain diseases is mediated by reactive oxygen species (Iadecola, 2004; Faraci, 2005; Girouard and Iadecola, 2006). For example, the cerebrovascular dys-regulation that occurs in Alzheimer's disease, diabetes, hyperhomocystinemia, and angiotensin-II-induced hypertension is mediated by reactive oxygen species (Mayhan and Sharpe, 1998; Zhang et al., 1998; Iadecola et al., 1999; Didion and Faraci, 2003; Kazama et al., 2004; Park et al., 2004, 2005; Girouard et al., 2006).

The impaired cerebrovascular regulation observed after cerebral ischemia is also related to vascular oxidative stress. Cerebral ischemia induces markers of oxidative damage in cerebral blood vessels (Chan et al., 1998; Maneen et al., 2006). The cerebrovascular response to acetylcholine, which is mediated by endothelial NO, is abolished following transient global cerebral ischemia in cats (Nelson et al., 1992) and is prevented by the superoxide scavengers superoxide dismutase and catalase. Additionally, the alterations in CO_2 reactivity are prevented by the administration of deferoxamine, an iron scavenger, suggesting a role also for the hydroxyl radical in cerebrovascular dysregulation after transient ischemia (Nelson et al., 1992). Free radical scavengers prevent the attenuation in

the cerebrovascular response to NMDA induced by global ischemia in piglets (Bari et al., 1996). Furthermore, intravenous administration of polyethylene-glycol-conjugated superoxide dismutase improves post-ischemic hypercapnic CBF after global cerebral ischemia in piglets (Kirsch et al., 1993). In a global ischemia model in dogs, combined administration of superoxide dismutase and deferoxamine reduced post-ischemic hypoperfusion and enhanced recovery of evoked potentials (Cerchiari et al., 1987). In the isolated rat middle cerebral artery, studied after ischemia reperfusion, the attenuation in the smooth muscle relaxation produced by activation of Kir2.x, a barium-sensitive inward rectifier K^+ channel, is counteracted by a free radical scavenger (Petrault et al., 2004). Interestingly, in this model, the ischemia-induced attenuation in endothelium-dependent vasodilation to acetylcholine was not normalized by the free radical scavenger (Petrault et al., 2004), suggesting that factors other than reactive oxygen species may also be involved. Similar results were obtained in rodents with topical cortical application of acetylcholine in situ (Rosenblum and Wormley, 1995; Rosenblum, 1997). Subsequent experiments demonstrated that the endothelium-dependent dysfunction, but not the Kir2.x dysfunction, was ameliorated by inducing neutropenia prior to ischemia, implicating neutrophils in mechanisms of the vascular dysregulation, possibly through metalloprotease-induced disruption of microvessels (Petrault et al., 2004). Supporting a role of neutrophils, activation of intravascular neutrophils induces endothelial cell dysfunction in rabbits (Akopov et al., 1994). Therefore, although reactive oxygen species are important pathogenic effectors in the cerebrovascular dysregulation induced by ischemia, loss of microvascular integrity through metalloprotease activation, disruption of the extracellular matrix, and loss of integrins is also likely to play a role (del Zoppo and Mabuchi, 2003).

14.5.1.1. NADPH oxidase as a potential source of reactive oxygen species mediating cerebrovascular dysfunction—There are several cellular and enzymatic sources of reactive oxygen species in the ischemic brain (Traystman et al., 1991; Chan, 2001). However, because reactive oxygen species diffuse poorly and are highly reactive, they tend to act at the site of formation (Stamler, 1996; Halliwell and Whiteman, 2004). It is therefore likely that the reactive oxygen species responsible for the cerebrovascular dysfunction are produced in cerebrovascular cells. The enzyme NADPH oxidase has recently emerged as a major source of reactive oxygen species in cerebral blood vessels (Cai et al., 2003). NADPH oxidase is a multi-unit enzyme initially described in phagocytic cells and responsible for reactive oxygen species production in leukocytes and macrophages (Babior, 2004; Lambeth, 2004). NADPH oxidase is composed of membrane-bound subunits (Nox and $p22^{phox}$) and cytoplasmic subunits ($p40^{phox}$, $p47^{phox}$, $p67^{phox}$, Rac1 and Rac2) (Lambeth, 2004). Activation stimuli lead to phosphorylation of $p47^{phox}$, which results in the assembly of the enzyme and production of superoxide (Vignais, 2002). NADPH oxidase is involved in production of reactive oxygen species and cerebrovascular dysfunction in several brain conditions associated with vascular oxidative stress, including models of Alzheimer's disease (Park et al., 2005), and with the cerebrovascular complications of angiotensin II hypertension, diabetes, and hyperhomocystinemia (Cooper et al., 2002; Faraci and Lentz, 2004; Kazama et al., 2004; Girouard et al., 2006). Mice lacking the Nox2 subunit of NADPH oxidase have reduced ischemic brain injury (Walder et al., 1997) and reduced reactive oxygen species production 72 h after middle cerebral artery occlusion (Kunz et al., 2007a) but it has not been established whether vascular factors contribute to the protection. Therefore additional studies are needed to clarify the role of NADPH oxidase in the mechanisms of the cerebrovascular dysregulation associated with cerebral ischemia.

14.5.1.2. Mechanisms by which reactive oxygen species mediate cerebrovascular dysfunction—The mechanisms by which reactive oxygen species disrupt cerebrovascular regulation are diverse (Iadecola, 2004; Faraci, 2006). One

mechanism is based the interaction of superoxide with NO. NO reacts with superoxide highly efficiently, forming peroxynitrite (Beckman et al., 1990; Pacher et al., 2007). Recent studies implicate peroxynitrite in the cerebrovascular dys-function induced by ischemia. Transient ischemia with reperfusion reduces the ability of the middle cerebral artery to constrict in response to increased intramural pressure (myogenic tone) (Cipolla et al., 1997). Such reperfusion-induced reduction in myogenic tone can account for the profound disruption of autoregulation observed after focal cerebral ischemia (see section 14.2). The effect was more pronounced for longer duration of reperfusion and was related to depolymerization of the vascular smooth muscle protein F-actin (Maneen et al., 2006). The loss of myogenic tone was associated with an increase in the peroxynitrite marker nitrotyrosine and could be reproduced by exogenous peroxynitrite (Maneen et al., 2006). In addition to its actions on myogenic tone, peroxynitrite has other deleterious effects on cerebrovascular regulation. First, peroxynitrite formation reduces the bioavailability of NO, resulting in an impairment of NO-dependent vasodilation (Adachi et al., 2004; Faraci, 2005). Peroxynitrite inhibits the enzyme prostacyclin synthase and reduces the ability of cerebral arteries to dilate through impaired synthesis of the potent vasodilator prostacyclin (Zou et al., 1999). Peroxynitrite also inhibits the mitochondrial isoform of superoxide dismutase, enhancing ischemia-induced oxidative stress (Guo et al., 2003). Furthermore, peroxynitrite induces DNA strand breaks, which activate the DNA repair enzyme poly-ADP-ribose polymerase and lead to endothelial cell dysfunction through energy depletion (Soriano et al., 2001). Reactive oxygen species and peroxynitrite oxidize tetrahydrobiopterin, a cofactor for the enzymatic activity of nitric oxide synthase. Deficiency of tetrahydrobiopterin results in uncoupling of nitric oxide synthase, a process by which this enzyme produces superoxide instead of NO and increases oxidative stress (Katusic, 2001). However, peroxynitrite is not uniformly deleterious and can also be beneficial in certain settings. For example, low levels of peroxynitrite are required for the neuroprotection induced by preconditioning with the proinflammatory mediator lipopolysaccharide (Kunz et al., 2007b). However, relatively large amounts of peroxynitrite produced during ischemia–reperfusion are likely to be damaging to the brain and blood vessels.

In summary, reactive oxygen species can alter post-ischemic cerebrovascular regulation through numerous factors, including depletion of vasodilators (NO, prostacyclin), enhanced oxidative stress and energy deplede tion. However, reactive oxygen species are not the only factor responsible for the cerebrovascular dys-function and loss of microvascular integrity through disruption of extracellular matrix and integrins is also likely to play a role.

14.6. Conclusions

Cerebral ischemia results in a profound disruption of cerebrovascular regulatory mechanisms that assure that the brain is adequately perfused. Cerebral ischemia impairs cerebrovascular autoregulation, attenuates functional hyperemia, and alters hypercapnic vasodilation, critical mechanisms by which active brain cells maintain the homeostasis of their microenvironment through delivery of nutrients and removal of waste. These alterations are in large part mediated by a surge of free radicals, which leads to neurovascular oxidative stress and impairs the function of neurons, glia, and vascular cells. These alterations in vascular regulation render the brain more vulnerable to the changes in perfusion pressure and to the metabolic dysfunction induced by ischemia, thereby increasing the susceptibility of the tissue to injury. Therapeutic strategies targeting the cerebrovascular dysfunction induced by ischemia offer the opportunity to preserve post-ischemic vascular regulation and improve the outcome of cerebral ischemia. Such a vasoprotective approach, in combination with cytoprotective therapies, may open new avenues for the treatment of ischemic stroke.

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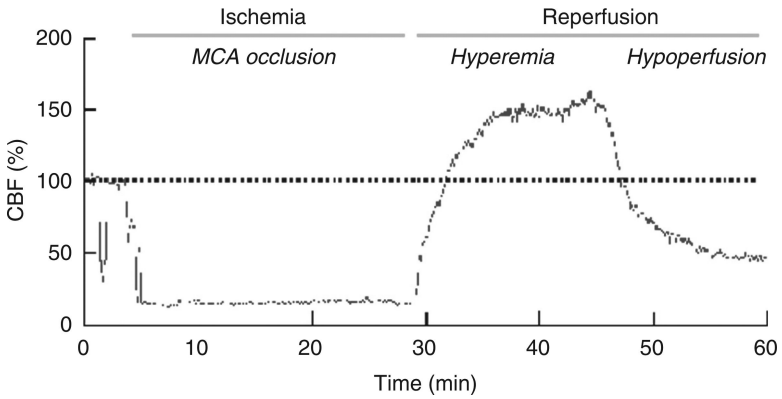

Fig. 14.1.

Recording of cerebral blood flow (CBF) measured by laser Doppler flowmetry in the center of the ischemic territory (ischemic core) before, during, and after occlusion of the middle cerebral artery using an intravascular filament in mice. CBF is markedly reduced during the arterial occlusion. At reperfusion, CBF first increases (post-ischemic hyperemia) and then drops below pre-ischemic levels (post-ischemic hypoperfusion).

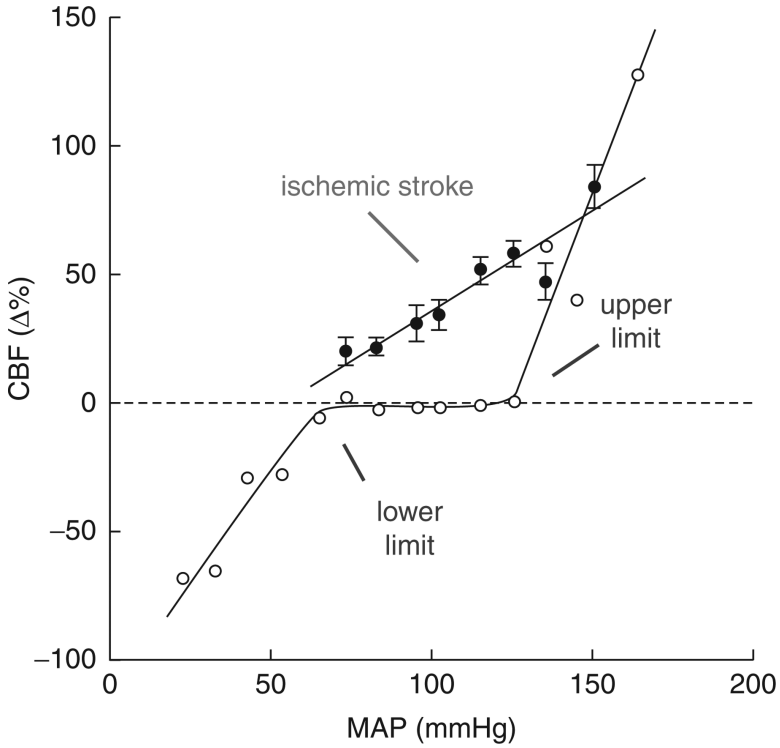

Fig. 14.2.

Relationship between cerebral blood flow (CBF) and mean arterial pressure (MAP) in physiological conditions (gray) and following cerebral ischemia (black). In the normal state, CBF is kept constant over a relatively wide range of MAPs, a phenomenon termed cerebrovascular auto-regulation. Thus, cerebral resistance vessels dilate when MAP decreases and constrict when MAP increases and, as a result, CBF remains relatively constant. When the change in MAP exceeds this compensatory ability of cerebral vessels, CBF increases when MAP rises (upper limit) and decreases when MAP is reduced (lower limit). Following cerebral ischemia, cerebral resistance arteries are in a state of vasoparalysis and lose their ability to constrict or dilate in response to changes in MAP. Thus, autoregulation is lost and CBF follows MAP passively. Such disruption of autoregulation can amplify the damage by aggravating cerebral ischemia if MAP falls and by inducing blood-barrier damage and cerebral edema when MAP rises.

Table 14.1

Cerebral ischemia and autoregulation—selected animal studies

Ischemia model (duration)	Species	CBF measurement	Effect on autoregulation (upper–lower limit)	Reference
Global ischemia (30 and 60 min)	Cat	^{133}Xe-injection	Preserved (LL)	Hossmann et al., 1973
3 years after pMCAO	Baboon	H_2 clearance	Abolished in infarct, impaired in peri-infarct area (LL)	Symon et al., 1975
Global ischemia (15 min)	Dog	^{133}Xe-injection	Partially preserved (UL, LL)	Nemoto et al., 1975
pMCAO	Cat	Heated thermocouple	Impaired (UL)	Shima et al., 1983
Global ischemia (60 min)	Rat	H_2 clearance	Abolished (LL)	Shiokawa et al., 1986
pMCAO	Rat (SHR)	LDF	Impaired if ischemic CBF >30%, abolished if ischemic CBF <30% (UL, LL)	Dirnagl and Pulsinelli, 1990
Global ischemia (12 and 18 min)	Dog	Sagittal sinus venous outflow	Impaired (UL, LL)	Christopherson et al., 1993
pMCAO	Rat	LDF	Impaired, dependent on proximity to core (UL, LL)	Lauer et al., 1998
tMCAO (endothelin-1 administration)	Rat	IAP, SPECT	Abolished in viable tissue with normal CBF (LL)	MacGregor et al., 2000

CBF, cerebral blood flow; IAP, C^{14}-iodoantipyrine; LDF, laser-Doppler flowmetry; LL, lower limit; pMCAO, permanent middle cerebral artery occlusion; SHR, spontaneously hypertensive rats; SPECT, single photon emission computed tomography; tMCAO, transient middle cerebral artery occlusion; UL, upper limit.

Table 14.2

Cerebral ischemia and autoregulation—selected human studies

Pathology	CBF measurement	Effect on autoregulation (upper–lower limit)	Reference
TIA (ICA territory)	^{133}Xe-injection	Impaired/abolished in 2 of 12 patients (UL, LL)	Skinhoj et al., 1970
Stroke (ICA territory)	^{133}Xe-injection	Abolished, restored by hypocapnia (UL)	Paulson et al., 1972
Stroke within 72 h (MCA territory)	^{133}Xe-injection	Impaired in 3 of 16 patients (UL)	Olsen et al., 1981
Subacute stroke (MCA territory)	^{133}Xe-injection	Impaired in collaterally perfused areas (UL)	Olsen et al., 1983
TIA (bilateral ICA stenosis/occlusion)	^{133}Xe-inhalation, TCD	Impaired (LL)	Tatemichi et al., 1990
Stroke (ICA, MCA territory)	PET	Impaired (LL)	Ouchi et al., 2001
Stroke within 72 h (ICA, VB territories)	TCD*	Impaired (spontaneous ABP fluctuations)	Eames et al., 2002
ICA stenosis/occlusion	TCD*	Impaired (spontaneous ABP fluctuations)	Gooskens et al., 2003
ICA stenosis/occlusion	TCD*	Impaired (spontaneous ABP fluctuations)	Reinhard et al., 2003
MCA stroke, lacunar stroke (within 72 h)	TCD*	Impaired (spontaneous ABP fluctuations)	Immink et al., 2005
MCA stenosis/occlusion	TCD*	Impaired, improvement after MCA stent angioplasty (thigh cuff)	Gong et al., 2006
ICA stenosis (before/after angioplasty)	TCD*	Impaired (spontaneous ABP fluctuations), improvement after angioplasty	Haubrich et al., 2007

ABP, arterial blood pressure; CBF, cerebral blood flow; ICA, internal carotid artery; LL, lower limit; MCA, middle cerebral artery; PET, positron emission tomography; TCD, transcranial Doppler; TIA, transient ischemic attack; UL, upper limit; VB, vertebrobasilar artery.

*'Dynamic autoregulation' was estimated based on spontaneous ABP fluctuations except for Gong et al. (2006), who used the thigh cuff technique.

Table 14.3

Cerebral ischemia and cerebral blood flow reactivity to carbon dioxide—selected animal studies

Ischemia model	Species	CBF measurement	Effect on CO_2 reactivity	Reference
Global ischemia (30 and 60 min)	Cat	^{133}Xe-injection	Abolished	Hossmann et al., 1973
Global ischemia (15 min)	Dog	^{133}Xe-injection	Abolished	Nemoto et al., 1975
pMCAO	Baboon	H_2 clearance	Impaired, steal phenomenon	Symon et al., 1974
3 years after pMCAO	Baboon	H_2 clearance	Impaired	Symon et al., 1975
pMCAO	Baboon	^{133}Xe-injection	Paradoxical CBF increase in ischemic area during hypocapnia	Ott et al., 1975
pMCAO	Cat	Heated thermocouple	Abolished or steal phenomenon	Shima et al., 1983
Global ischemia (60 min)	Cat	^{133}Xe-injection	Abolished during postischemic hypoperfusion	Van den Kerckhoff et al., 1983
Global ischemia (12 min)	Dog	Microspheres	Abolished at 3 h, restored at 24 h after ischemia	Koch et al., 1984
tMCAO (30 min, 1, 2, 6 h)	Dog	H_2 clearance	Impaired, dependent on duration and severity of stroke	Seki et al., 1984
Global ischemia (60 min)	Cat	^{133}Xe-injection	Prolonged impairment	Schmidt-Kastner et al., 1986
Global ischemia (60 min)	Cat	^{133}Xe-injection	Abolished during postischemic hypoperfusion	Schmidt-Kastner et al., 1987
pMCAO	Rat	IAP	Abolished in core	Jones et al., 1989
Global ischemia (20 min)	Piglet	Pial diameter	Abolished	Leffler et al., 1989
Global ischemia (12 and 18 min)	Dog	Sagittal venous outflow	Impaired	Christopherson et al., 1993
pMCAO	Baboon	Microspheres	Core: abolished or steal phenomenon Penumbra: impaired	Dettmers et al., 1993
p or tMCAO (30 and 90 min)	Rat	MRI (T2*, DWI)	Abolished, recovery of CO_2 reactivity in viable tissue	Ono et al., 1997
tMCAO (60 min)	Rat	Perfusion MRI	Prolonged impairment	Olah et al., 2000
pMCAO	Rat	BOLD imaging	Core: abolished/reduced Borderzone: normal	Harris et al., 2001

BOLD, blood-oxygen-level-dependent; CBF, cerebral blood flow; DWI, diffusion-weighted imaging; IAP, C^{14}-iodoantipyrine; MRI, magnetic resonance imaging; pMCAO, permanent middle cerebral artery occlusion; tMCAO, transient middle cerebral artery occlusion.

Table 14.4

Cerebral ischemia and cerebral blood flow reactivity to carbon dioxide—selected human studies

Pathology	CBF measurement	Effect on CO_2 reactivity	Reference
Stroke (hemispheric, VB)	^{133}Xe-inhalation	Impaired	Yamamoto et al., 1980
Stroke within 72 h (MCA territory)	^{133}Xe-injection	Impaired	Olsen et al., 1981
TIA or stroke (MCA territory)	^{133}Xe-inhalation	Impaired	Norrving et al., 1982
TIA, stroke in patients with ICA stenosis/occlusion	^{133}Xe-inhalation	Impaired	Bullock et al., 1985
Uni-/bilateral ICA stenosis occlusion (TIA, stroke, no symptoms)	^{133}Xe-injection	Impaired	Brown et al., 1986
Hemispherical stroke/TIA (ICA occlusion), follow-up after EC/IC bypass	^{133}Xe-inhalation	Acetazolamide reactivity impaired in 9 of 18 patients, two patients with steal, improvement in two patients after EC/IC bypass	Vorstrup et al., 1986
Stroke/TIA, patients with unilateral ICA occlusion	^{133}Xe-inhalation	Impaired	Clifton et al., 1988
ICA stenosis occlusion (TIA, stroke, no symptoms)	PET, ^{133}Xe-injection	Impaired, correlates with CBF/CBV ratio	Herold et al., 1988
ICA/MCA stenosis occlusion, moyamoya disease	PET	Impaired, correlates with OEF	Kanno et al., 1988
TIA, stroke, ICA stenosis occlusion	^{133}Xe-inhalation	Impaired	Keyeux et al., 1988
TIA, minor stroke (ICA territory)	PET	Impaired	Levine et al., 1988
Uni-/bilateral ICA occlusion (stroke, TIA, no symptoms)	TCD	Impaired	Ringelstein et al., 1988
Chronic capsular stroke	^{133}Xe-injection	Vasoconstriction to hypocapnia attenuated in regions with diaschisis	Takano et al., 1988
TIA (ICA territory)	^{133}Xe-inhalation	Acetazolamide reactivity impaired in 14 of 15 patients	Chollet et al., 1989
TIA, severe ICA disease	^{133}Xe-inhalation, TCD	Impaired	Tatemichi et al., 1990
TIA (ICA territory), ICA stenosis occlusion	PET	Impaired	Levine et al., 1991
TIA, stroke, ICA stenosis occlusion	TCD	Impaired	Miller et al., 1992
ICA stenosis occlusion (TIA, stroke, no symptoms)	TCD	CO_2 and acetazolamide reactivity impaired	Ringelstein et al., 1992
Stroke (ICA territory)	TCD	Impaired	Maeda et al., 1993
Uni-/bilateral ICA occlusion (stroke, TIA, no symptoms)	TCD	Impaired	Ringelstein et al., 1994
TIA, stroke (ICA/MCA territory, moyamoya disease)	Stable Xe-CT, PET	Acetazolamide reactivity impaired	Nariai et al., 1995
TIA, stroke (MCA territory)	^{133}Xe-inhalation	Preserved reactivity; CO_2: 23/24pts, acetazolamide: 13/24pts	Kazumata et al., 1996
Stroke, TIA (ICA/MCA stenosis occlusion)	Dynamic MRI	Acetazolamide reactivity impaired in 5/8 patients	Schreiber et al., 1998
CADASIL	TCD	Impaired	Pfefferkorn et al., 2001
TIA (ICA territory)	TCD	Impaired	Bakker et al., 2003
Lacunar stroke (MCA territory, within 1 week)	TCD	Impaired	De Leeuw et al., 2003
ICA stenosis/occlusion	TCD	CO_2 reactivity correlates with degree of stenosis	Gooskens et al., 2003
Minor stroke (MCA territory)	TCD	Impaired	Novak et al., 2003

Pathology	CBF measurement	Effect on CO_2 reactivity	Reference
ICA stenosis/occlusion	TCD	Impaired	Reinhard et al., 2003
ICA occlusion	PET	Correlation between reduced acetazolamide reactivity and OEF increase to acetazolamide	Nemoto et al., 2007

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CBF, cerebral blood flow; CBV, cerebral blood volume; CT, computed tomography; EC/IC, extracranial/intracranial; ICA, internal carotid artery; MCA, middle cerebral artery; MRI, magnetic resonance imaging; OEF, oxygen extraction fraction; PET, positron emission tomography; TCD, transcranial Doppler; TIA, transient ischemic attack; Xe, Xenon; VB, vertebrobasilar.

Table 14.5

Cerebral ischemia and neurovascular coupling—selected animal studies

Ischemia model	Species	CBF measurement	Effect on CO_2 reactivity	Reference
Global ischemia (10 min)	Rat	Mitochondrial redox state	Transient mitochondrial dysfunction	Duckrow et al., 1981
Global ischemia (30 min)	Rat	2-DG	Transient reduction of CGU	Dietrich et al., 1986
Photothrombotic frontal lesion	Rat	IAP, 2-DG	5 days post-lesion: activation of rCBF in barrel cortex suppressed	Ginsberg et al., 1989
Global ischemia (30 min)	Rat	IAP, 2-DG	Impaired neurovascular coupling	Ueki et al., 1988
Focal ischemia (30 min)	Mouse	LDF	Impaired neurovascular coupling	Kunz et al., 2007b

2-DG, 2-deoxyglucose; CGU, cerebral glucose utilization; IAP, C^{14}-iodoantipyrine; LDF, laser-Doppler flowmetry; rCBF, regional cerebral blood flow.

Table 14.6

Cerebral ischemia and functional activation—selected human studies

Pathology	CBF measurement	Effect on functional activation	Reference
TIA, stroke (ICA territory)	PET	Motor activation: ipsilateral CBF increase Acetazolamide: no CBF increase	Inao et al., 1998
Stroke (MCA territory)	NIRS	Increased deoxyhemoglobin (five of ten patients)	Sakatani et al., 1998
ICA stenosis/occlusion	BOLD-fMRI	Reduced BOLD response in auditory cortex if ischemic borderzone lesions present	Bilecen et al., 2002
ICA/MCA stenosis/occlusion	BOLD-fMRI	Reduced BOLD response ipsilateral	Carusone et al., 2002
TIA, stroke (within 3–12 months)	BOLD-fMRI, NIRS	Reduced BOLD response ipsilaterally, increased deoxyhemoglobin	Murata et al., 2002
Lacunar stroke	BOLD-fMRI	Reduced BOLD response (ipsi-/ contralateral)	Pineiro et al., 2002
TIA (ICA territory), ICA occlusion	BOLD-fMRI	Negative BOLD response in a patient with impaired CO_2 reactivity	Rother et al., 2002
TIA (stenosis extra-/intracranial)	BOLD-fMRI	Reduced BOLD response in patients with impaired CO_2 reactivity	Hamzei et al., 2003
Stroke, TIA (ICA territory)	BOLD-fMRI, NIRS	BOLD: limited activation, NIRS: sustained increase in deoxyhemoglobin	Sakatani et al., 2003
TIA, stroke (ICA territory)	MEG, evoked field BOLD-fMRI	VMR preserved, BOLD absent	Rossini et al., 2004
Stroke (frontal lobe)	BOLD-fMRI	Reduced BOLD response on lesion side	Krainik et al., 2005
ICA stenosis/occlusion (stroke, TIA, no symptoms)	PET	Increased CBF in primary visual cortex, decreased CBF in surrounding areas	Yamauchi et al., 2005
TIA, stroke	BOLD-fMRI, NIRS	Reduced BOLD response and increased deoxyhemoglobin after severe ischemia	Murata et al., 2006

BOLD, blood-oxygen-level-dependent; CBF, cerebral blood flow; fMRI, functional magnetic resonance imaging; ICA, internal carotid artery; MCA, middle cerebral artery; MEG, magnetoencephalography; NIRS, near-infrared spectroscopy; PET, positron emission tomography; TIA, transitory ischemic attack; VMR, vasomotor reserve.