Published in final edited form as:

Neuropharmacology. 2008 September ; 55(3): 281–288. doi:10.1016/j.neuropharm.2008.04.017.

Regulation of cerebral vasculature in normal and ischemic brain

Tobias Kulik, MD, Yoshikazu Kusano, MD, Shimon Aronhime, Adam L. Sandler, and H. Richard Winn, MD

From the Departments of Neurosurgery and Neuroscience Mount Sinai School of Medicine, New York, New York

In the present review, we focus on the regulation of cerebral blood flow (CBF) and cerebral vasculature in the normal and ischemic brain, with a special emphasis on the arterial microcirculation of the brain: the pial and penetrating vessels.

I. Background

The cerebral circulation can be divided into categories based on a number of criteria. For example, vessel size can be utilized to divide the brain circulation into the macro-circulation and the microcirculation. On the arterial side, the former begins in the neck and extends to pial arteries. The microcirculation consists of the pial and penetrating arterioles, the capillaries and the venules. Within the arterial circulation, the major function of the macro-circulation is conductance of blood whereas the principal activity of the arterial component of the microcirculation is regulation of flow. Although the capillaries and venules are a significant contributor to cerebrovascular resistance, their role in *regulation* of flow is minimal under physiologic conditions.

In addition to size, vessel location can be used to characterize the brain circulation. Thus, the brain vasculature can be divided in relation to the parenchyma into an extrinsic and an intrinsic component. The former encompasses the large conductance vessels (i.e., the macrocirculation) plus the pial circulation, whereas the latter consists of the intracerebral circulation composed of small arterioles, capillaries and venules. Penetrating arterioles represent the transition from the extrinsic to the intrinsic system. Clearly these two systems differ in regard to a number of features, such as proximity to the parenchyma, influence of neuronal and astrocytic activity, and presence and origin of innervation. However, despite these differences, both the extrinsic and intrinsic components of the cerebral circulation have an integrated response to cerebral challenges: co-dependency is the norm under physiologic and most pathologic conditions.

II. Microcirculation: Normal Anatomy & Special Features

A. Overview

As noted previously, the arterial cerebral circulation is composed of small pial arteries, arterioles and penetrating arterioles. The pial vessels exist either free in the subarachnoid space, surrounded by cerebrospinal fluid (CSF), or on the surface of the brain, in contact with and / or partially invested by the piaarachnoid and the glia-limitans (Jones, 1970; Kontos et al., 1977). The latter structure is the outer most layer of the cortex and is composed of astrocytic extensions. The complexity of the pial vascular organization is species dependent with spatial regulation increasing with higher phylogeny (McHedlishvili and Kuridze, 1984).

Mailing address and correspondence: H. Richard Winn, M.D. Professor of Neurosurgery and Neuroscience Mount Sinai School of Medicine One Gustave L. Levy Place, Box 1136 New York, New York 10029 Office phone: (212) 241-9128 Cell phone: (917) 520-1255 richard.winn@mountsinai.org.

After the pial vasculature, the next order of arterial circulation of the brain is the penetrating arteriole. These vessels are located in the Virchow-Robin space, and are located intracerebrally to a certain extent (Jones, 1970; Roggendorf and Cervos-Navarro, 1977). The Virchow-Robin space is a continuation of the subarachnoid space, but its degree of persistence and depth may vary by species (Jones, 1970). At some point, astrocytic footplates make incomplete and then complete contact with the basement membrane of the penetrating arterioles, and the arterioles become wholly intracerebral (Jones, 1970; Roggendorf and Cervos-Navarro, 1977). The large conductance arteries, the pial arteries and arterioles, and penetrating arterioles all have a blood brain barrier (Roggendorf and Cervos-Navarro, 1977).

Capillaries consist of a single layer of very special endothelial cells, but unlike arteries and arterioles, do not contain vascular smooth muscle (VSM). The density of brain capillaries varies significantly (Klein et al., 1986; Kuschinsky and Paulson, 1992), with higher density in gray, and lower density in white matter, and with variation even within the gray matter dependent on energy use and needs (Klein et al., 1986). In the non-pathologic state, all capillaries remain perfused with blood (Gobel et al., 1990). The regulation of flow in the capillary system is thus dependent on the regulation of flow in the arterioles (Heistad and Kontos, 1983; Kontos et al., 1978). However, some investigators have speculated, that pericytes, which cover less than 50% of the capillary diameter (Torack, 1961), are capable of regulating flow in the capillaries by acting as capillary sphincters (Reina-De La Torre et al., 1998; Peppiatt et al, 2006). Pericytes are flat, undifferentiated, contractile connective tissue cells that develop around capillary walls. They express non-muscle actins and also contain α - smooth muscle actin which is characteristic of the VSM (Lai and Kuo, 2005).

B. Unique Features

There are a number of features of the cerebral circulation which are unique and relevant for an understanding of the pathophysiology of brain ischemia: the arterial histology, species differences, collateral flow, the venous drainage, the blood brain barrier, and the influence of astrocytes and neurovascular nerves.

1. Histology of Cerebral Arteries and Arterioles—In humans and many other species, the cerebral arteries, unlike their counterparts elsewhere in the body, are lacking in vasa vasorum (Stehbens, 1960). Therefore cerebral arteries derive their nutrition from the cerebrospinal fluid (CSF), perhaps making them more resistant to the effects of hypotension and ischemia. With advancing age, vasa vasorum have been observed in the larger conductance arteries (Stehbens, 1960; Takaba et al., 1998). In addition, cerebral arteries have only a single elastic lamina which may influence their response to alteration in luminal pressure as compared to arteries elsewhere in the body (Stehbens, 1972).

2. Species differences—Across a wide range of species, two carotid and two vertebral arteries supply blood flow to the brain. However, the relative contribution of these large conductance vessels is highly variable (Purves, 1972). In primates, carotid arteries provide the majority of CBF, whereas in many other species the vertebral-basilar system predominates. The internal carotid artery is the main source of blood flow to the brain in primates, rabbits, pigs (Purves, 1972) and gerbil (Chandler MJ, 1985), whereas in dogs and cats the external carotid artery is more important. Occlusion of the carotid artery in rodents inconsistently results in brain ischemia unless combined with systemic hypotension (Nordstrom and Siesjo, 1978) or previous bilateral vertebral artery obliteration (Pulsinelli and Brierley, 1979). It is important to understand these differences between species when designing experimental protocols and extrapolating data obtained in animal models to the human. Possibly, some of these differences may explain the failure to translate laboratory advances to bedside successes.

3. Collateral Flow—Unlike other organs and to a certain degree irrespective of species, the CNS has a redundancy of arterial supply which can protect the brain in the event of focally restricted flow in a conductance vessel. Thus, an occlusion of the internal carotid artery in humans may be asymptomatic due to contralateral or ipsilateral collateral flow. In the laboratory setting, even within purebred lines, focal arterial occlusion of conductance arteries results in variable cerebral infarction.

4. Venous Drainage—The pial venous system has a unique architecture (Roggendorf et al., 1978): unlike the paired arterial-venous arrangement found in many organs in the body, the pial veins do not travel with pial arteries. Moreover, pial veins do not significantly change in diameter with physiologic changes in blood flow (Ngai et al., 1988). Although the venous endothelium is part of the blood brain barrier, the venous component of the blood brain barrier appears to be the most frequent site of breakdown (Mayhan and Heistad, 1985, 1986) in response to a variety of conditions, including acute hypertension (Hansson et al., 1975) and infection (Muller, 2003).

5. The Blood Brain Barrier—Another unique feature of the cerebral circulation is the blood brain barrier. The blood brain barrier regulates ion balance, facilitates transport of micro- and macronutrients, and shields the parenchyma from potentially toxic substances found in the blood stream. The anatomical substrate of the blood brain barrier is the cerebral endothelium. Morphological correlates are tight junctions (Rubin and Staddon, 1999) between endothelial cells and limited transport by pinocytotic vesicles (Johansson, 1990). Tight junctions limit the paracellular flux of hydrophilic molecules across the blood brain barrier, whereas small lipophilic molecules diffuse freely across plasma membranes along their concentration gradient. Tight junctions are composed of transmembrane (junctional-adhesion molecule-1, occludin, and claudins) and cytoplasmic proteins (zonula occludens-1 and -2, cingulin, AF-6, and 7H6) linked to the actin cytoskeleton (Abbott, 2002). In comparison to the endothelium found in other organs, the cerebral microvasculature lacks fenestration, possesses only a small number of pinocytotic vesicles (Abbott, 2002) and has five to six times more mitochondria (Oldendorf et al., 1977). The endothelial cells, as well as pericytes, are ensheathed by the basal lamina, a membrane 30–40 nm thick composed of collagen type IV, heparin sulfate proteoglycans, laminin, fibronectin and other extracellular matrix proteins (Ballabh et al., 2004; Hawkins and Davis, 2005; Persidsky et al., 2006). This lamina is contiguous with the plasma membrane of astrocytic endfeet, which ensheath cerebral capillaries (Ballabh et al., 2004; Hawkins and Davis, 2005; Persidsky et al., 2006). Bordering the 3rd and 4th ventricles are unique midline structures deficient in a BBB. These areas, known as circumventricular organs (CVOs) are recognized as important sites for communicating with the CSF and between the brain and peripheral organs via blood-borne products. CVOs include the pineal gland, median eminence, subfornical organ, area postrema, subcommissural organ, and organum vasculosum of the lamina terminalis. The intermediate and neural lobes of the pituitary are sometimes included as well.

In addition to this physical barrier, there is also a metabolic barrier in place at the cerebral endothelium, which is capable of metabolizing drugs and nutrients. Following a polar distribution on the surfaces of the membrane, γ -glutamyl transpeptidase (γ -GTP) and alkaline phosphatase (AP) are found at the luminal endothelium (Abbott, 2002). In contrast, Na^+/K^+ ATPase and the Na-dependent neutral amino acid transporter are present on the abluminal surface (Abbott, 2002; Oldendorf et al., 1977). Moreover, studies in humans suggest an asymmetric distribution of the brain glucose transporter (GLUT-1), with 3–4 times more GLUT-1 transporters present on the luminal than the abluminal membranes (Cornford et al., 1998). The opposite has been shown in rodent brain (Farrell and Pardridge, 1991).

6. Astrocytic Influence on Cerebral Vessels—Astrocytes are the most abundant glial population in the brain and spinal cord. The number of astrocytes per neuron increases dramatically with brain complexity and size: neurons outnumber glia by 6:1 in the nematode *C. elegans*, whereas there are 1.4 astrocytes per neuron in the human cortex. The latter also exhibits a nearly 30-fold greater astrocytic volume than in rodents and a single human astrocyte may contact almost 30-times more neuronal synapses than a single rodent astrocyte (Oberheim et al., 2006).

Astrocytes can be divided in protoplasmic and fibrous. The former are found within the gray matter, the latter within the white matter. Protoplasmic astrocytes extend two types of processes from their cell body: fine perisynaptic processes, covering most synapses, and larger processes, whose terminations end on significant portions of the intracerebral circulation (Nedergaard et al., 2003). These terminal processes are also known as “endfeet”, and cover 99% of the abluminal vascular surface of capillaries, intracerebral arterioles, and venules (Simard et al., 2003). The extent of contact between endfeet and penetrating and pial arterioles remains unclear. Pial arterioles and arteries lying free in the subarachnoid space are not covered (Jones, 1970). Nevertheless, much of the pial circulation is in contact with the glia-limitans, a de-facto extension of astrocytic processes (Kontos et al., 1971; Xu et al., 2004).

Astrocytes are arranged in non-overlapping spatial domains (Bushong et al., 2002; Halassa et al., 2007), but coupled to each other in a syncytial network (Haydon and Carmignoto, 2006). Since one astrocyte maintains contacts with approximately 160,000 synapses (Bushong et al., 2002), this cell population is well positioned to integrate neuronal activity and link neuronal activity to the vascular network (Ransom et al., 2003).

Astrocytes are critical in the development and/or maintenance of blood brain barrier characteristics. Interactions of astrocytes with endothelial cells greatly enhanced tight junctions and reduced gap junctional area and this interaction increased the number of astrocytic membrane particle assemblies and astrocyte density (Tao-Cheng and Brightman, 1988).

It has long been known that astrocytes play an important role in cerebral ion homeostasis (Kuffler and Potter, 1964), transmitter regulation (Nedergaard et al., 2002; Newman, 2003), contribute to the maintenance of the blood brain barrier (Ballabh et al., 2004), and structural, as well as metabolic, support of neuronal cells, e.g. in the form of a glucose-lactate shuttle (Magistretti, 2006; Pellerin, 2003). Recently, astrocytes have been proposed as being the key linking element of the neuronal-(astrocyte)-vascular unit (Volterra and Meldolesi, 2005). For example, working with neocortical slices, Zonta et al. (Zonta et al., 2003) demonstrated, that electrical stimulation of neuronal processes raises intracellular Ca^{2+} levels in astrocytic endfeet and leads to a slowly developing dilatation of local intracerebral arterioles. Additionally, electrical stimulation of individual astrocytes had the same effect. Since this initial report, several investigators observed a vascular response in conjunction with an elevation of intracellular Ca^{2+} levels in astrocytic endfeet. However, these studies reported inconsistent vascular responses ranging from vasorelaxation to vasodilatation or the combination of both (Gordon et al., 2007; Iadecola and Nedergaard, 2007). Mediators implicated in this mechanism are vasoactive metabolites of the cyclooxygenase or cytochrome P450 ω -hydroxylase pathways. All of these studies were performed in brain slices in which the vessels are lacking in intraluminal pressure. This might account for disparate results. *In vivo* analysis with two-photon laser scanning microscopy revealed that increases of astrocytic Ca^{2+} by photolysis of caged Ca^{2+} evoked a vasodilatation of cortical arterioles (Takano et al., 2006). This interaction between the vessel and the endfeet appeared to be mediated by metabolites of the COX-1 pathway, because inhibitors of nitric oxide synthetase (NOS), COX-2, p450 epoxygenases, and adenosine receptor antagonists had no effect. These and other studies strongly implicate a

role for astrocytes in CBF regulation during neuronal activation (Haydon and Carmignoto, 2006).

Astrocytes are less sensitive to oxygen and glucose deprivation than neurons (Rossi et al., 2007). This increase in resistance may be related to a number of factors including the presence of high intracellular glycogen stores which may allow the astrocyte to preserve ATP concentrations, Na⁺-K⁺ ATPase activity and trans-membrane ion gradients. In addition, astrocytes have a lower density of ion channels and lesser energy requirements for maintaining concentration gradients; these characteristics would also render astrocytes more resistant to ischemia (Rossi et al., 2007; see Hertz, this issue).

7. Direct Neural Influence on CBF—In a variety of organs, there is substantial evidence for direct neural control of blood flow (Feigl, 1998). In the cerebral circulation, the hypothesis that the vasculature is innervated, and that CBF is regulated, by neurovascular nerves is a long standing concept. In the past, the data in support of this idea has been mixed, but recent studies have added growing evidence for direct neural influence on CBF (Sandor, 1999). Nerve fibers associated with cerebral vessels have been identified within both the macro-circulation and the microcirculation (Hamel, 2006).

There are two proposed origins of these nerves: extrinsic and intrinsic to the brain. The first category arises extra-cerebrally and consists of sympathetic and parasympathetic autonomic fibers which are found to terminate in the vicinity of large and small conductance vessels with innervation sparse in the pial arterioles (< 50 μ m) and absent in penetrating arterioles (Cohen et al., 1997). Studies employing stimulation or ablation of these nerves and their ganglia have demonstrated a varied effect on the CBF of the physiologic state (D'Alecy and Feigl, 1972; Ibayashi et al., 1991; Toda et al., 2000). During ischemia caused by permanent middle cerebral artery occlusion in rat, Henninger and Fisher reported that unilateral stimulation of post-synaptic parasympathetic fibers reduced the infarct size (Henninger and Fisher, 2007). In addition, during hypertension, Heistad et al. found that sympathectomized animals had a higher frequency of intracerebral hemorrhage. These authors hypothesized that sympathetic induced vasoconstriction protected the brain from intracerebral bleeding during hypertension (Busija et al., 1980; Faraci and Heistad, 1990; Heistad et al., 1978; Raper et al., 1972).

The intrinsic neural system proposed for cortical blood flow regulation is further divided into a distal, and a local component. Immunohistochemical, pharmacological and electrophysiological data indicate that the distal system originates in the brain stem (locus coeruleus and raphe nuclei) (Reis et al., 1997), cerebellum (fastigial nucleus) (Reis et al., 1997), and basal forebrain (nucleus basalis magnocellularis) (Rancillac et al., 2006). In ischemia caused by middle artery occlusion, stimulation of the subthalamic vasodilator area and fastigial nucleus independently protected against focal ischemia (Glickstein et al., 2001). In a subsequent study, electrical stimulation of dorsal periaqueductal gray decreased the brain volume independent of the accompanying hypertension and cerebrovascular dilatation (Glickstein et al., 2003).

The local component of the intrinsic neural system is thought to arise in the cortex and involve interneurons projecting to nearby arterioles (Rancillac et al., 2006). A variety of factors have been suggested to play a role in this intrinsic system, such as nitric oxide (NO), acetylcholine (ACh), vasoactive intestinal peptide (VIP), gamma-aminobutyric acid (GABA), and prostaglandin E₂ (PGE₂) (Hamel, 2006). In ischemia, demonstration of a causal role for the intrinsic neuronal system is lacking, in part, due to the nature of studies documenting these local neurons in non-perfused slices.

III. Physiology of the Pial and Penetrating Arterial Circulation

The microcirculation of the brain shares many anatomic, physiologic and pharmacologic features with the microcirculation elsewhere in the body, but also has unique aspects (see below, III). The general principles of fluid dynamics apply: CBF (F) is directly related to pressure (P) and inversely affected by resistance (R):

$$F=P/R.$$

Resistance is theoretically and experimentally inversely related to the 4th power of the diameter (Kobari et al., 1984). Thus, small increases in the diameter of the arterioles result in significant decreases in resistance, and, assuming that there is sufficient perfusion pressure, flow will increase dramatically.

Flow is also affected by rheology and varies with hematocrit, erythrocyte flexibility, platelet aggregation and plasma viscosity (Kee and Wood, 1984). In vessels smaller than 200 to 300 μ m diameter, red blood cells move into the central, rapid moving part of the flowstream, while white blood cells and other constituents of the plasma move more slowly next to the vessel wall (Chien et al., 1984). At asymmetrical branch points cells are distributed in an uneven fashion, the greater proportion goes to the branches deviating the least from the original direction and to those with higher flow. Tributaries close to a right angle may receive only plasma, platelets and a few white cells. Thus, hematocrit in the microvasculature is lower than in the average large blood vessel (Chien et al., 1984). White blood cells, on the contrary, are represented in a higher proportion in the microcirculation (Chien et al., 1984).

Furthermore, two distinct physiologic entities exert a dominant influence on CBF in the microvasculature: the Fahraeus effect (Fahraeus and Lindqvist, 1931) and the inversion phenomenon (Dintenfass, 1967). The Fahraeus effect describes an apparent decrease in the viscosity of blood flowing through tubes of progressive smaller diameter, whereas the inversion phenomenon explains that this reduction in blood viscosity ceases when the vessel diameter approaches 5–7 μ m and reverses with further vessel diameter reductions.

Under physiologic conditions, a significant proportion of the arterial cerebrovascular resistance (CVR) is located in the pial and penetrating circulations (Heistad and Kontos, 1983). In order to increase flow to the intrinsic circulatory bed, the extrinsic pial vessels must dilate, otherwise a vascular steal would occur. Therefore, a coordinated response between extra- and intraparenchymal components of the vascular circulation is necessary to fulfill the flow demands of the cerebral tissue. The mechanisms responsible for coordinating the pial and penetrating arteriolar response are unclear and may be stimulus specific. Thus, with cortical activation and increased metabolic demand (and in the absence of hypoxia or hypotension), the initiation of pial arteriolar dilatation may involve a signal conducted from the activated parenchymal compartment to the pial vessels. The pathway of this conducted signal may involve astrocytes and their extensions into the glia limitans (Xu et al., 2008). Alternatively, the conducted signal for vasodilatation may travel in the arterial wall, as occurs in the non-cerebral circulation (Segal et al., 1989). Conduction in the arteriole wall by the endothelium and the vascular smooth muscle has been shown in penetrating arterioles (Horiuchi et al., 2002) and to be increased after ischemia (Ngai et al., 2007). In contrast to cortical activation, hypoxia and hypotension (and ischemia) may have direct effects on the wall of the extra-parenchymal arteries, obviating a need for a conducted signal from the cortex and the parenchymal circulation.

The arterial vasculature has characteristics intrinsic to the vessels (i.e., present in the absence of brain parenchyma). For example, isolated penetrating arterioles are capable of reacting to

changes in pH and to a number of chemicals, compounds and peptides [e.g., NO (Furchgott and Zawadzki, 1980), adenosine (Meno et al., 1993), ATP (Dietrich et al., 1996; Janigro et al., 1993), K^+ (Horiuchi et al., 2002; Kuffler and Potter, 1964), VIP (Heistad et al., 1980)]. Some of these substances exert their effects selectively with luminal or abluminal application. For example, ATP evokes a more significant vasodilation when applied intraluminally (Janigro et al., 1997), whereas H^+ and adenosine are more potent applied abluminally (Ngai and Winn, 1993). Moreover, the response to some of these agents is size dependent (Kontos et al., 1978; Morii et al., 1986).

Another inherent property of the arterial vasculature is the ability to react to changes in intraluminal flow and pressure. Bayliss in 1902 (Bayliss, 1902) reported direct contraction and relaxation of canine hind limb arteries in response to an increase or decrease of intravascular pressure respectively, a reaction attributed to intrinsic properties of VSM. As demonstrated in Fig 1, isolated rat and mouse cerebral penetrating arterioles have the ability to constrict with increasing pressure, and to dilate with decreasing pressure (Ngai and Winn, 1995), (Coyne et al., 2002). The latter response is also observed with increasing flow and this flow-mediated vasodilatation can be altered by blocking NO production (see Fig. 2). Harder et al. suggest that VSM metabolizes arachidonic acid via a P4504A dependent pathway to 20-hydroxyeicosatetraenoic acid (20-HETE) (Harder et al., 1997). This compound is known as a potent vasoconstrictor and acts in part by blocking the open-state probability of Ca^{2+} activated K^+ channels, thereby depolarizing VSM and causing vasoconstriction (Rubanyi et al., 1990). With a decrease in intraluminal pressure and possibly flow, the endothelium presumably acts as a mechanoreceptor, transducing variations in transmural pressure and shear stress into altered vascular tone.

Extrapolation of conclusions based on isolated vessel preparations may be questionable since these arterial segments are largely devoid of astrocytic endfeet, either because of their *in vivo* anatomy or because of loss of endfeet during harvesting. *In vivo*, astrocytes may directly influence or add a permissive element to the function of wholly intracerebral arterioles which not to be observed or attenuated in the *in vitro* setting. On the other hand, the penetrating arterioles, and to a significant extent, the pial arterioles and arteries, have variable contact with the astrocytic endfeet.

During hypotension *in vivo*, pial arteries and arterioles vasodilate, thereby decreasing cerebrovascular resistance (Kontos et al., 1978). This vasodilatation is prompt (5–20 s), with the smaller pial arteries and arterioles responding to a greater degree than the macrocirculation (Fig. 2). In a similar fashion, increases in MABP result in vasoconstriction (Kontos et al., 1978). Beyond either extreme, CBF becomes passive and varies directly with hypotension and hypertension.

IV. Changes in the Cerebral Vascular Response and Microcirculation during Ischemia

Hypotension and ischemia are in a continuum. In hypotension, the changes in the brain and the cerebral vasculature are, in general, physiologic and recoverable. The dominant response may be in the vascular compartment as demonstrated in isolated arterioles subjected to decreased intraluminal pressure and perfusion. In contrast, ischemia elicits pathophysiologic responses with the parenchyma being more sensitive to ischemia than the vasculature. Within the parenchyma, astrocytes are more resistant to ischemia than neurons, relating to differences in their intrinsic metabolism and signaling characteristics (Rossi et al., 2007; see Hertz, this issue).

Ischemia itself can be further divided by the degree (complete vs. incomplete), the volume (focal vs. global), the duration (transient or permanent) and the location within the brain, with certain areas being more vulnerable to ischemia.

The vascular response in ischemia will depend on the interplay of the factors noted above, as will the success of reperfusion. With ischemia, alteration in the endothelial cell wall results in leukocyte adherence and platelet rupture (del Zoppo and Hallenbeck, 2000) leading to potentially non-reversible intravascular injury within hours (Tagaya et al., 2001; Wagner et al., 1997). The breakdown of the blood brain barrier, occurring first in the venules, allows entry of multiple restricted substances into the brain. Larger arterial vessels are also affected by ischemia as demonstrated by the alteration of the biomechanics of the middle cerebral artery which occurs within 30 minutes of ischemic onset (Cipolla et al., 2001). Reperfusion after ischemia can trigger a series of events that are highly destructive and can add further injury to both the vasculature and the brain parenchyma. During minimal perfusion or reperfusion, activated leukocytes interact with the damaged abluminal endothelial wall, leading to plugging of the microvasculature and the development of a “no-reflow” phenomenon (Ames et al., 1968), although the existence of a leukocyte related no-flow phenomenon has been questioned (Aspey et al., 1989; Dirnagl et al., 1994). Reperfusion also has an independent effect on the parenchyma with the development of destructive processes, such as the release of inflammatory factors, cytokines and free radicals (Chan, 2001; Kuroda and Siesjo, 1997).

From a hemodynamic perspective and as noted previously, the capillaries and venules are a significant contributor to cerebrovascular resistance, but their role in regulation of flow is minimal under physiologic conditions. With ischemia, the resistance arterioles and arteries maximally dilate and become less responsive. The capillaries and the venules thus account for a greater component of the CVR, but are then directly exposed to unbuffered arterial blood pressure. As a consequence and in concert with cellular and molecular events related to alteration in the blood brain barrier, cytotoxic edema results with increase in tissue pressure and closure of capillaries (Hossmann, 2006). This phenomenon replicates the “choked flow” or “hemodynamic waterfall” predicted from the theoretical collapsible tube further complicating tissue perfusion (Hoffman and Spaan, 1990).

The alterations in the brain parenchyma during ischemia are multiple and complex whether the insult be local or global, transient or permanent, neuronal or astrocytic. The changes can be divided into early or late phases. The former is measured in seconds, whereas the latter extends from minutes to hours. Since this review focuses on factors affecting and potentially regulating the arterial micro-vasculature during ischemia, we restrict our assessment to the acute period. The major event during the initial period of complete ischemia is energy failure due to the lack of glucose and oxygen. With these deficits, synthesis of ATP attenuates or ceases, ATP concentrations fall, Na^+ - K^+ ATPase activity decreases and trans-membrane ion gradients are disrupted (Rossi et al., 2007). Within 5 s of the onset of complete ischemia (Fig. 3), a time span during which pial arterioles dilate (Kontos et al., 1978), the concentration of phosphocreatine (PCr) and adenosine (ADO) are significantly altered (PCr down, ADO up), as demonstrated in freeze blown rat tissue (Winn et al., 1979). Adenosine is a potent vasodilator. Consequently, the rapid increase in adenosine concentrations may account for the changes in cerebral arteriolar diameter and the decrease in CVR during the acute period of ischemia. By 60 s, ATP begins to fall and other adenine nucleotides are altered (Winn et al., 1979). K^+ concentration then rises in two stages: an initial (60–120 s) moderate increase followed by a more profound elevation, and is associated with a decrease in Na and pH (Rossi et al., 2007). Dependent on the species, spreading depression and anoxic depolarization occurs (Nedergaard and Hansen, 1993) with subsequent release of extracellular glutamate (Obrenovitch and Urenjak, 1997), stimulation of the N-methyl-D-aspartate receptors (Choi and Rothman, 1990) and increase in intracellular calcium (Choi and Rothman, 1990), leading to eventual cell

death by either necrotic or apoptotic mechanisms (Zhao et al., 2007; Doyle et al., this issue). As previously noted, astrocytes are less sensitive to oxygen and glucose deprivation, therefore it would be reasonable to conclude that metabolic changes during the acute period of ischemia outlined above are reflective of neuronal rather than astrocytic alterations.

Almost all ischemic insults to the brain can be divided into a central core of dead or destined to die tissue and a surrounding region, the penumbra, which has marginal flow and cells with the potential to survive (Hossmann, 2006). All the changes reviewed above also apply to a variable extent to these two zones, but with some unique events in the penumbra such as reduction in protein synthesis (Castellanos et al., 2006; Rebel et al., 2005). A complex interplay of these factors with reperfusion determines the ultimate outcome of the parenchyma in the penumbra zone (Hossmann, 2006).

Additional influences on the extent and severity of parenchymal injury caused by ischemia are the temperature of the brain and the level of the blood glucose. Thus, even mild increases or decreases in brain temperature can significantly alter the metabolic rate and the lethality of the same degree of ischemia (Busto et al., 1987). Zhao, Steinberg and Sapolsky, in a recent review, comprehensively summarize the suggested mechanism involved in hypothermia in ischemic brain, but question its effectiveness in attenuating ischemic insults (Zhao et al., 2007).

High blood glucose levels result in worse outcomes in experimental settings and in humans following stroke and head injury (Lam et al., 1991; Pulsinelli et al., 1982). Hyperglycemia has been demonstrated by Cipolla et al. to dilate cerebral arteries and to diminish myogenic tone (Cipolla et al., 1997). This direct effect of hyperglycemia on the arteries could be abolished with the removal of the endothelium (Cipolla et al., 1997). The mechanisms responsible for the more extensive and pronounced parenchymal injury seen with hyperglycemia are unclear, but studies suggest a variety of possible causes, such as an increase in lactic acid and decrease in pH (Folbergrova et al., 1997), although MR spectroscopy failed to show a difference in intracellular pH with hyperglycemic or normoglycemic ischemia (Hsu et al., 1994), a release of glucocorticoids (Schurr, 2002), or a decrease in cerebral adenosine production (Higashi et al., 2002; Hsu et al., 1991; Meno et al., 2003; Zhou et al., 1994).

V. Conclusion

Ischemia has multi-factorial and complex effects on the cerebral vasculature and the brain parenchyma. During ischemia, the pathophysiologic responses in the vasculature and the brain compartments are interconnected. Further understanding of the physiology and pathophysiology of ischemia will allow the rational development of pharmacological therapies for human stroke and brain injury.

Acknowledgments

This work was supported by grants from the NIH: NS 21078 (25) to HRW, American Heart Association to ALS and the NY Academy of Medicine (Glorney Raisbeck) and the American Association of Neurological Surgeons to SA.

This work was supported by grants from the NIH: NS 21078 (25) to HRW, American Heart Association to ALS and the NY Academy of Medicine (Glorney Raisbeck) and the American Association of Neurological Surgeons to SA.

Bibliography

- Abbott NJ. Astrocyte-endothelial interactions and blood-brain barrier permeability. *J Anat* 2002;200:629–638. [PubMed: 12162730]
- Ames A 3rd, Wright RL, Kowada M, Thurston JM, Majno G. Cerebral ischemia. II. The no-reflow phenomenon. *Am J Pathol* 1968;52:437–453. [PubMed: 5635861]

- Aspey BS, Jessimer C, Pereira S, Harrison MJ. Do leukocytes have a role in the cerebral no-reflow phenomenon? *J Neurol Neurosurg Psychiatry* 1989;52:526–528. [PubMed: 2486297]
- Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview: structure, regulation, and clinical implications. *Neurobiol Dis* 2004;16:1–13. [PubMed: 15207256]
- Bayliss N. On the local reactions of the arterial wall to changes of internal pressure. *Journal of Physiology* 1902;28:220–231. [PubMed: 16992618]
- Bushong EA, Martone ME, Jones YZ, Ellisman MH. Protoplasmic astrocytes in CA1 stratum radiatum occupy separate anatomical domains. *Journal of Neuroscience* 2002;22:183–192. [PubMed: 11756501]
- Busija DW, Heistad DD, Marcus ML. Effects of sympathetic nerves on cerebral vessels during acute, moderate increases in arterial pressure in dogs and cats. *Circ Res* 1980;46:696–702. [PubMed: 7363418]
- Busto R, Dietrich WD, Globus MY, Valdes I, Scheinberg P, Ginsberg MD. Small differences in intraschemic brain temperature critically determine the extent of ischemic neuronal injury. *J Cereb Blood Flow Metab* 1987;7:729–738. [PubMed: 3693428]
- Castellanos M, Sobrino T, Castillo J. Evolving paradigms for neuroprotection: molecular identification of ischemic penumbra. *Cerebrovasc Dis* 2006;2(21 Suppl):71–79. [PubMed: 16651817]
- Chan PH. Reactive oxygen radicals in signaling and damage in the ischemic brain. *J Cereb Blood Flow Metab* 2001;21:2–14. [PubMed: 11149664]
- Chandler MJ, et al. An unethetized-gerbil model of cerebral ischemia-induced behavioral changes. *J Pharmacol Meth* 1985;14:137–146.
- Chien S, Usami S, Skalak R. Blood flow in small tubes. *Handbk. Physiol* 1984:217–250.
- Choi DW, Rothman SM. The role of glutamate neurotoxicity in hypoxic-ischemic neuronal death. *Annu Rev Neurosci* 1990;13:171–182. [PubMed: 1970230]
- Cipolla MJ, Lessov N, Hammer ES, Curry AB. Threshold duration of ischemia for myogenic tone in middle cerebral arteries: effect on vascular smooth muscle actin. *Stroke* 2001;32:1658–1664. [PubMed: 11441216]
- Cipolla MJ, Porter JM, Osol G. High glucose concentrations dilate cerebral arteries and diminish myogenic tone through an endothelial mechanism. *Stroke* 1997;28:405–410. discussion 410–401. [PubMed: 9040698]
- Cohen Z, Molinatti G, Hamel E. Astroglial and vascular interactions of noradrenaline terminals in the rat cerebral cortex. *J Cereb Blood Flow Metab* 1997;17:894–904. [PubMed: 9290587]
- Cornford EM, Hymann S, Swartz BE. The human brain GLUT1 glucose transporter: an ultrastructural localization to the blood-brain barrier endothelia. *J. Cereb. Blood Flow Metab* 1994;14:106–112. [PubMed: 8263045]
- Coyne EF, Ngai AC, Meno JR, Winn HR. Methods for isolation and characterization of intracerebral arterioles in the C57/BL6 wild-type mouse. *J Neurosci Methods* 2002;120:145–153. [PubMed: 12385764]
- D'Alecy LG, Feigl EO. Sympathetic control of cerebral blood flow in dogs. *Circ Res* 1972;31:267–283. [PubMed: 5049742]
- del Zoppo GJ, Hallenbeck JM. Advances in the vascular pathophysiology of ischemic stroke. *Thromb Res* 2000;98:73–81. [PubMed: 10812160]
- Dietrich HH, Kajita Y, Dacey RG Jr. Local and conducted vasomotor responses in isolated rat cerebral arterioles. *Am J Physiol* 1996;271:H1109–1116. [PubMed: 8853348]
- Dintenfass L. Inversion of the Fahraeus-Lindqvist phenomenon in blood flow through capillaries of diminishing radius. *Nature* 1967;215:1099–1100. [PubMed: 6070339]
- Dimagl U, Niwa K, Sixt G, Villringer A. Cortical hypoperfusion after global forebrain ischemia in rats is not caused by microvascular leukocyte plugging. *Stroke* 1994;25:1028–1038. [PubMed: 8165674]
- Fahraeus R, Lindqvist T. The viscosity of blood in narrow capillary tubes. *Amer J Physiol* 1931;96:562–568.
- Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure. *Circ Res* 1990;66:8–17. [PubMed: 2403863]

- Farrell CL, Pardridge WM. Blood-brain barrier glucose transporter is asymmetrically distributed on brain capillary luminal and abluminal membranes: an electron microscopic immunogold study. *Proc. Natl. Acad. Sci. USA* 1991;88:5779–5783. [PubMed: 2062858]
- Feigl EO. Neural control of coronary blood flow. *J Vasc Res* 1998;35:85–92. [PubMed: 9588871]
- Folbergrova J, Li PA, Uchino H, Smith ML, Siesjo BK. Changes in the bioenergetic state of rat hippocampus during 2.5 min of ischemia, and prevention of cell damage by cyclosporin A in hyperglycemic subjects. *Exp Brain Res* 1997;114:44–50. [PubMed: 9125450]
- Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980;288:373–376. [PubMed: 6253831]
- Glickstein SB, Ilch CP, Golanov EV. Electrical stimulation of the dorsal periaqueductal gray decreases volume of the brain infarction independently of accompanying hypertension and cerebrovasodilation. *Brain Res* 2003;994:135–145. [PubMed: 14642639]
- Glickstein SB, Ilch CP, Reis DJ, Golanov EV. Stimulation of the subthalamic vasodilator area and fastigial nucleus independently protects the brain against focal ischemia. *Brain Res* 2001;912:47–59. [PubMed: 11520492]
- Gobel U, Theilen H, Kuschinsky W. Congruence of total and perfused capillary network in rat brains. *Circ Res* 1990;66:271–281. [PubMed: 1688741]
- Gordon GR, Mulligan SJ, MacVicar BA. Astrocyte control of the cerebrovasculature. *Glia* 2007;55:1214–1221. [PubMed: 17659528]
- Halassa MM, Fellin T, Takano H, Dong JH, Haydon PG. Synaptic islands defined by the territory of a single astrocyte. *Journal of Neuroscience* 2007;27:6473–6477. [PubMed: 17567808]
- Hamel E. Perivascular nerves and the regulation of cerebrovascular tone. *J Appl Physiol* 2006;100:1059–1064. [PubMed: 16467392]
- Hansson HA, Johansson B, Blomstrand C. Ultrastructural studies on cerebrovascular permeability in acute hypertension. *Acta Neuropathol* 1975;32:187–198. [PubMed: 1180001]
- Harder DR, Lange AR, Gebremedhin D, Birks EK, Roman RJ. Cytochrome P450 metabolites of arachidonic acid as intracellular signaling molecules in vascular tissue. *J Vasc Res* 1997;34:237–243. [PubMed: 9226306]
- Hawkins BT, Davis TP. The blood-brain barrier/neurovascular unit in health and disease. *Pharmacol Rev* 2005;57:173–185. [PubMed: 15914466]
- Haydon PG, Carmignoto G. Astrocyte control of synaptic transmission and neurovascular coupling. *Physiol Rev* 2006;86:1009–1031. [PubMed: 16816144]
- Heistad DD, Kontos HA. Peripheral circulation and organ blood flow. American Physiological Society; Bethesda, Md: 1983.
- Heistad DD, Marcus ML, Gross PM. Effects of sympathetic nerves on cerebral vessels in dog, cat, and monkey. *Am J Physiol* 1978;235:H544–552. [PubMed: 103441]
- Heistad DD, Marcus ML, Said SI, Gross PM. Effect of acetylcholine and vasoactive intestinal peptide on cerebral blood flow. *Am J Physiol* 1980;239:H73–80. [PubMed: 7396021]
- Henninger N, Fisher M. Stimulating circle of Willis nerve fibers preserves the diffusion-perfusion mismatch in experimental stroke. *Stroke* 2007;38:2779–2786. [PubMed: 17761922]
- Higashi H, Meno JR, Marwaha AS, Winn HR. Hippocampal injury and neurobehavioral deficits following hyperglycemic cerebral ischemia: effect of theophylline and ZM 241385. *J Neurosurg* 2002;96:117–126. [PubMed: 11794592]
- Hoffman JJ, Spaan JA. Pressure-flow relations in coronary circulation. *Physiol Rev* 1990;70:331–390. [PubMed: 2181499]
- Horiuchi T, Dietrich HH, Hongo K, Dacey RG Jr. Mechanism of extracellular K⁺-induced local and conducted responses in cerebral penetrating arterioles. *Stroke* 2002;33:2692–2699. [PubMed: 12411663]
- Hossmann KA. Pathophysiology and therapy of experimental stroke. *Cell. Mol. Neurobiol* 2006;26:1057–1083. [PubMed: 16710759]
- Hsu SS, Meno JR, Gronka R, Kushmerick M, Winn HR. Moderate hyperglycemia affects ischemic brain ATP levels but not intracellular pH. *Am J Physiol* 1994;266:H258–262. [PubMed: 8304507]

- Hsu SS, Meno JR, Zhou JG, Gordon EL, Winn HR. Influence of hyperglycemia on cerebral adenosine production during ischemia and reperfusion. *Am J Physiol* 1991;261:H398–403. [PubMed: 1877666]
- Iadecola C, Nedergaard M. Glial regulation of the cerebral microvasculature. *Nat Neurosci* 2007;10:1369–1376. [PubMed: 17965657]
- Ibayashi S, Ngai AC, Howard MA 3rd, Meno JR, Mayberg MR, Winn HR. Lack of sympathetic and cholinergic influences on cerebral vasodilation caused by sciatic nerve stimulation in the rat. *J Cereb Blood Flow Metab* 1991;11:678–683. [PubMed: 2050756]
- Janigro D, Nguyen TS, Meno J, West GA, Winn HR. Endothelium-dependent regulation of cerebrovascular tone by extracellular and intracellular ATP. *Am J Physiol* 1997;273:H878–885. [PubMed: 9277506]
- Janigro D, West GA, Gordon EL, Winn HR. ATP-sensitive K⁺ channels in rat aorta and brain microvascular endothelial cells. *Am J Physiol* 1993;265:C812–821. [PubMed: 8214038]
- Johansson BB. The physiology of the blood-brain barrier. *Adv Exp Med Biol* 1990;274:25–39. [PubMed: 2239426]
- Jones EG. On the mode of entry of blood vessels into the cerebral cortex. *J Anat* 1970;106:507–520. [PubMed: 5423942]
- Kee DB Jr, Wood JH. Rheology of the cerebral circulation. *Neurosurgery* 1984;15:125–131. [PubMed: 6206438]
- Klein B, Kuschinsky W, Schrock H, Vetterlein F. Interdependency of local capillary density, blood flow, and metabolism in rat brains. *Am J Physiol* 1986;251:H1333–1340. [PubMed: 3098116]
- Kobari M, Gotoh F, Fukuuchi Y, Tanaka K, Suzuki N, Uematsu D. Blood flow velocity in the pial arteries of cats, with particular reference to the vessel diameter. *J Cereb Blood Flow Metab* 1984;4:110–114. [PubMed: 6693510]
- Kontos HA, Raper AJ, Patterson JL. Analysis of vasoactivity of local pH, PCO₂ and bicarbonate on pial vessels. *Stroke* 1977;8:358–360. [PubMed: 16363]
- Kontos HA, Raper AJ, Patterson JL Jr. Mechanisms of action of CO₂ on pial precapillary vessels. *Eur Neurol* 1971;6:114–118. [PubMed: 5153412]
- Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL Jr. Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *Am J Physiol* 1978;234:H371–383. [PubMed: 645875]
- Kuffler SW, Potter DD. Glia in the Leech Central Nervous System: Physiological Properties and Neuron-Glia Relationship. *J Neurophysiol* 1964;27:290–320. [PubMed: 14129773]
- Kuroda S, Siesjö BK. Reperfusion damage following focal ischemia: pathophysiology and therapeutic windows. *Clin Neurosci* 1997;4:199–212. [PubMed: 9186042]
- Kuschinsky W, Paulson OB. Capillary circulation in the brain. *Cerebrovasc Brain Metab Rev* 1992;4:261–286. [PubMed: 1389958]
- Lam AM, Winn HR, Cullen BF, Sundling N. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg* 1991;75:545–551. [PubMed: 1885972]
- Magistretti PJ. Neuron-glia metabolic coupling and plasticity. *Journal of Experimental Biology* 2006;209:2304–2311. [PubMed: 16731806]
- Mayhan WG, Heistad DD. Permeability of blood-brain barrier to various sized molecules. *Am J Physiol* 1985;248:H712–718. [PubMed: 2581459]
- Mayhan WG, Heistad DD. Role of veins and cerebral venous pressure in disruption of the blood-brain barrier. *Circ Res* 1986;59:216–220. [PubMed: 3742745]
- McHedlishvili G, Kuridze N. The modular organization of the pial arterial system in phylogeny. *J Cereb Blood Flow Metab* 1984;4:391–396. [PubMed: 6332116]
- Meno JR, Higashi H, Cambray AJ, Zhou J, D'Ambrosio R, Winn HR. Hippocampal injury and neurobehavioral deficits are improved by PD 81,723 following hyperglycemic cerebral ischemia. *Exp Neurol* 2003;183:188–196. [PubMed: 12957503]
- Meno JR, Ngai AC, Winn HR. Changes in pial arteriolar diameter and CSF adenosine concentrations during hypoxia. *Journal of Cerebral Blood Flow & Metabolism* 1993;13:214–220. [PubMed: 8436613]

- Morii S, Ngai AC, Winn HR. Reactivity of rat pial arterioles and venules to adenosine and carbon dioxide: with detailed description of the closed cranial window technique in rats. *J Cereb Blood Flow Metab* 1986;6:34–41. [PubMed: 3080442]
- Muller WA. Leukocyte-endothelial-cell interactions in leukocyte transmigration and the inflammatory response. *Trends Immunol* 2003;24:327–334. [PubMed: 12810109]
- Nedergaard M, Hansen AJ. Characterization of cortical depolarizations evoked in focal cerebral ischemia. *J Cereb Blood Flow Metab* 1993;13:568–574. [PubMed: 8314912]
- Nedergaard M, Ransom B, Goldman SA. New roles for astrocytes: redefining the functional architecture of the brain. *Trends Neurosci* 2003;26:523–530. [PubMed: 14522144]
- Nedergaard M, Takano T, Hansen AJ. Beyond the role of glutamate as a neurotransmitter. *Nat Rev Neurosci* 2002;3:748–755. [PubMed: 12209123]
- Newman EA. New roles for astrocytes: regulation of synaptic transmission. *Trends Neurosci* 2003;26:536–542. [PubMed: 14522146]
- Ngai AC, Ko KR, Morii S, Winn HR. Effect of sciatic nerve stimulation on pial arterioles in rats. *Am J Physiol* 1988;254:H133–139. [PubMed: 3337250]
- Ngai AC, Nguyen TS, Meno JR, Britz GW. Postischemic augmentation of conducted dilation in cerebral arterioles. *Stroke* 2007;38:124–130. [PubMed: 17122418]
- Ngai AC, Winn HR. Effects of adenosine and its analogues on isolated intracerebral arterioles. Extraluminal and intraluminal application. *Circ Res* 1993;73:448–457. [PubMed: 8348689]
- Ngai AC, Winn HR. Modulation of cerebral arteriolar diameter by intraluminal flow and pressure. *Circ Res* 1995;77:832–840. [PubMed: 7554130]
- Nordstrom CH, Siesjo BK. Effects of phenobarbital in cerebral ischemia. Part I: cerebral energy metabolism during pronounced incomplete ischemia. *Stroke* 1978;9:327–335. [PubMed: 27884]
- Oberheim NA, Wang X, Goldman S, Nedergaard M. Astrocytic complexity distinguishes the human brain. *Trends Neurosci* 2006;29:547–553. [PubMed: 16938356]
- Obrenovitch TP, Urenjak J. Altered glutamatergic transmission in neurological disorders: from high extracellular glutamate to excessive synaptic efficacy. *Prog Neurobiol* 1997;51:39–87. [PubMed: 9044428]
- Oldendorf WH, Cornford ME, Brown WJ. The large apparent work capability of the blood-brain barrier: a study of the mitochondrial content of capillary endothelial cells in brain and other tissues of the rat. *Ann Neurol* 1977;1:409–417. [PubMed: 617259]
- Peppiatt CM, Howarth C, Mobbs P, Attwell D. Bidirectional control of CNS capillary diameter by pericytes. *Nature* 2006;443(7112):700–704. [PubMed: 17036005]
- Pellerin L. Lactate as a pivotal element in neuron-glia metabolic cooperation. *Neurochem Int* 2003;43:331–338. [PubMed: 12742077]
- Persidsky Y, Ramirez SH, Haorah J, Kanmogne GD. Blood-brain barrier: structural components and function under physiologic and pathologic conditions. *J Neuroimmune Pharmacol* 2006;1:223–236. [PubMed: 18040800]
- Pulsinelli WA, Brierley JB. A new model of bilateral hemispheric ischemia in the unanesthetized rat. *Stroke* 1979;10:267–272. [PubMed: 37614]
- Pulsinelli WA, Waldman S, Rawlinson D, Plum F. Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. *Neurology* 1982;32:1239–1246. [PubMed: 6890157]
- Purves, M. The physiology of the cerebral circulation. Cambridge University Press; Cambridge: 1972. Anatomy of cerebral blood vessels..
- Rancillac A, Rossier J, Guille M, Tong XK, Geoffroy H, Amatore C, Arbault S, Hamel E, Cauli B. Glutamatergic Control of Microvascular Tone by Distinct GABA Neurons in the Cerebellum. *J Neurosci* 2006;26:6997–7006. [PubMed: 16807329]
- Ransom B, Behar T, Nedergaard M. New roles for astrocytes (stars at last). *Trends Neurosci* 2003;26:520–522. [PubMed: 14522143]
- Raper AJ, Kontos HA, Wei EP, Patterson JL Jr. Unresponsiveness of pial precapillary vessels to catecholamines and sympathetic nerve stimulation. *Circ Res* 1972;31:257–266. [PubMed: 5049741]

- Rebel A, Koehler RC, Martin LJ. In situ immunoradiographic method for quantification of specific proteins in normal and ischemic brain regions. *J Neurosci Methods* 2005;143:227–235. [PubMed: 15814155]
- Reina-De La Torre F, Rodriguez-Baeza A, Sahuquillo-Barris J. Morphological characteristics and distribution pattern of the arterial vessels in human cerebral cortex: a scanning electron microscope study. *Anat Rec* 1998;251:87–96. [PubMed: 9605225]
- Reis DJ, Golanov EV, Galea E, Feinstein DL. Central neurogenic neuroprotection: central neural systems that protect the brain from hypoxia and ischemia. *Ann N Y Acad Sci* 1997;835:168–186. [PubMed: 9616772]
- Roggendorf W, Cervos-Navarro J. Ultrastructure of arterioles in the cat brain. *Cell Tissue Res* 1977;178:495–515. [PubMed: 870204]
- Roggendorf W, Cervos-Navarro J, Lazaro-Lacalle MD. Ultrastructure of venules in the cat brain. *Cell Tissue Res* 1978;192:461–474. [PubMed: 699028]
- Rossi DJ, Brady JD, Mohr C. Astrocyte metabolism and signaling during brain ischemia. *Nat Neurosci* 2007;10:1377–1386. [PubMed: 17965658]
- Rubanyi GM, Freay AD, Kauser K, Johns A, Harder DR. Mechanoreception by the endothelium: mediators and mechanisms of pressure- and flow-induced vascular responses. *Blood Vessels* 1990;27:246–257. [PubMed: 2242445]
- Rubin LL, Staddon JM. The cell biology of the blood-brain barrier. *Annu Rev Neurosci* 1999;22:11–28. [PubMed: 10202530]
- Sandor P. Nervous control of the cerebrovascular system: doubts and facts. *Neurochem Int* 1999;35:237–259. [PubMed: 10458655]
- Schurr A. Bench-to-bedside review: a possible resolution of the glucose paradox of cerebral ischemia. *Crit Care* 2002;6:330–334. [PubMed: 12225609]
- Segal SS, Damon DN, Duling BR. Propagation of vasomotor responses coordinates arteriolar resistances. *Am J Physiol* 1989;256:H832–837. [PubMed: 2923241]
- Simard M, Arcuino G, Takano T, Liu QS, Nedergaard M. Signaling at the gliovascular interface. *J Neurosci* 2003;23:9254–9262. [PubMed: 14534260]
- Stehbens WE. Focal intimal proliferation in the cerebral arteries. *Am J Pathol* 1960;36:289–301. [PubMed: 13834049]
- Stehbens, WE. *Pathology of the Cerebral Blood Vessels*. C. V. Mosby; St. Louis: 1972.
- Tagaya M, Haring HP, Stuver I, Wagner S, Abumiya T, Lucero J, Lee P, Copeland BR, Seiffert D, del Zoppo GJ. Rapid loss of microvascular integrin expression during focal brain ischemia reflects neuron injury. *J Cereb Blood Flow Metab* 2001;21:835–846. [PubMed: 11435796]
- Takaba M, Endo S, Kurimoto M, Kuwayama N, Nishijima M, Takaku A. Vasa vasorum of the intracranial arteries. *Acta Neurochir (Wien)* 1998;140:411–416. [PubMed: 9728239]
- Takano T, Tian GF, Peng W, Lou N, Libionka W, Han X, Nedergaard M. Astrocyte-mediated control of cerebral blood flow. *Nat Neurosci* 2006;9:260–267. [PubMed: 16388306]
- Tao-Cheng JH, Brightman MW. Development of membrane interactions between brain endothelial cells and astrocytes in vitro. *Int J Dev Neurosci* 1988;6:25–37. [PubMed: 3213567]
- Toda N, Tanaka T, Ayajiki K, Okamura T. Cerebral vasodilatation induced by stimulation of the pterygopalatine ganglion and greater petrosal nerve in anesthetized monkeys. *Neuroscience* 2000;96:393–398. [PubMed: 10683579]
- Torack RM. Ultrastructure of capillary reaction to brain tumors. *Arch Neurol* 1961;5:416–428. [PubMed: 13921919]
- Volterra A, Meldolesi J. Astrocytes, from brain glue to communication elements: the revolution continues. *Nature Reviews Neuroscience* 2005;6:626–640.
- Wagner S, Tagaya M, Koziol JA, Quaranta V, del Zoppo GJ. Rapid disruption of an astrocyte interaction with the extracellular matrix mediated by integrin alpha 6 beta 4 during focal cerebral ischemia/reperfusion. *Stroke* 1997;28:858–865. [PubMed: 9099208]
- Winn HR, Rubio R, Berne RM. Brain adenosine production in the rat during 60 seconds of ischemia. *Circ Res* 1979;45:486–492. [PubMed: 476871]

- Xu HL, Koenig HM, Ye S, Feinstein DL, Pelligrino DA. Influence of the glia limitans on pial arteriolar relaxation in the rat. *Am J Physiol Heart Circ Physiol* 2004;287:H331–339. [PubMed: 14962837]
- Xu HL, Mao L, Ye S, Paisansathan C, Vetri F, Pelligrino DA. Astrocytes are a key conduit for upstream signaling of vasodilation during cerebral cortical neuronal activation in vivo. *Am J Physiol Heart Circ Physiol* 2008;294:H622–632. [PubMed: 18055520]
- Zhao H, Steinberg GK, Sapolsky RM. General versus specific actions of mild-moderate hypothermia in attenuating cerebral ischemic damage. *J Cereb Blood Flow Metab* 2007;27:1879–1894. [PubMed: 17684517]
- Zhou JG, Meno JR, Hsu SS, Winn HR. Effects of theophylline and cyclohexyladenosine on brain injury following normo- and hyperglycemic ischemia: a histopathologic study in the rat. *J Cereb Blood Flow Metab* 1994;14:166–173. [PubMed: 8263053]
- Zonta M, Angulo MC, Gobbo S, Rosengarten B, Hossmann KA, Pozzan T, Carmignoto G. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nat Neurosci* 2003;6:43–50. [PubMed: 12469126]

Fig 1.

A. Intracerebral arterioles response to intraluminal pressure in the absence of flow (n=8).

B. The change in diameter of intracerebral arterioles as a function of intraluminal flow rate at constant intravascular pressure of 60 mm Hg (n=12). Values are mean $\pm$ SEM. * $P < .05$, # $P < .01$ vs diameter at pressure of 20 mm Hg (left) or at flow of 0 $\mu\text{L}/\text{min}$ (right), respectively (Ngai and Winn, 1995; used with permission)

Response of pial arteries and arterioles to hypotension

Fig 2. Steady-state responses of pial arteries and arterioles to induced hypotension. Note that smaller arterioles have the most vigorous response to hypotension. (Kontos et al., 1978; used with permission)

Fig. 3.

Changes in adenosine (**Ado**), phosphocreatine (**PCr**), lactate (**Lac**), Energy Charge (**E.C.**) and adenosine triphosphate (**ATP**) during 60 seconds of complete cerebral ischemia in rat. Note that measurable changes in adenosine and PCr occurred at 5 sec., lactate at 10 sec., energy charge at 30 sec. and ATP at 60 sec. after the onset of ischemia.

Cerebral tissue obtained by freeze-blow technique. Ischemia induced by transection of the retroperitoneal aorta with brain perfusion pressure decreasing to 0 mm Hg by ~ 0.1sec. $E.C. = (ATP + 0.05 ADP) / (ATP + ADP + AMP)$

* = The earliest time period when value differed ($p < 0.05$) from baseline (pre-ischemia). All subsequent values were significantly different from baseline. $n \geq 4$ at each time period. (Winn et al., 1979; used with permission)