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Mechanisms Involved in the Cerebrovascular Dilator Effects of Cortical Spreading Depression

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Abstract

Cortical spreading depression (CSD) leads to dramatic changes in cerebral hemodynamics. However, mechanisms involved in promoting and counteracting cerebral vasodilator responses are unclear. Here we review the development and current status of this important field of research especially with respect to the role of perivascular nerves and nitric oxide (NO). It appears that neurotransmitters released from the sensory and the parasympathetic nerves associated with cerebral arteries, and NO released from perivascular nerves and/or parenchyma, promote cerebral hyperemia during CSD. However, the relative contributions of each of these factors vary according to species studied. Related to CSD, axonal and reflex responses involving trigeminal afferents on the pial surface lead to increased blood flow and inflammation of the overlying dura mater. Counteracting the cerebral vascular dilation is the production and release of constrictor prostaglandins, at least in some species, and other possibly yet unknown agents from the vascular wall. The cerebral blood flow response in healthy human cortex has not been determined, and thus it is unclear whether the cerebral oligemia associated with migraines represents the normal physiological response to a CSD-like event or represents a pathological response. In addition to promoting cerebral hyperemia, NO produced during CSD appears to initiate signaling events which lead to protection of the brain against subsequent ischemic insults. In summary, the cerebrovascular response to CSD involves multiple dilator and constrictor factors produced and released by diverse cells within the neurovascular unit, with the contribution of each of these factors varying according to the species examined.

Keywords

cerebral circulation; cerebral arteries; nitric oxide; calcitonin-gene related peptide; prostaglandins; neurons; ischemia; NMDA receptors; rats; rabbits; piglets; cats; migraine

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1. Introduction

As first described by Leão (1944), cortical spreading depression (CSD) represents a wave of neuronal depolarization followed by repolarization, which once initiated by a variety of chemical, electrical, and mechanical stimuli (Ayata and Moskowitz, 2006; Grafstein, 1956; Shibata *et al*., 1990; Somjen, 2001; Van Harreveld, 1959; Verhaegen *et al*., 1992; Verhaegen *et al*., 1992) progresses outward across the surface of the cerebral cortex of both lissencephalic and gyrencephalic brains at a speed of approximately 2-5 mm/minutes (Leão, 1944; Van Harreveld *et al*., 1956; Goadsby, 1996; Grafstein, 1956; Lauritzen, 1987; Shimizu *et al*., 2000a; Shibata *et al*., 1990; Smith *et al*., 2006; Wahl *et al*., 1996). Although leading to a transient depression of cortical activity, repeated CSDs in the healthy brain do not lead to pronounced neural damage (Nedergaard and Hansen, 1988) and may even be beneficial by promoting the development of protection against ischemic stress (Horiguchi *et al*., 2005b; Kawahara *et al*., 1995; Kiss *et al*., 2004; Kobayashi *et al*., 1995; Matsushima *et al*., 1996; Otori *et al*., 2003). However, CSD in physiologically impaired neural tissue can be detrimental (Somjen, 2006) and the induction of inflammatory genes even in healthy brain has unknown consequences (Thompson and Hakim, 2005). Spreading depression-like events occur in other brain locations such as cerebellum (Case *et al*., 2002) and hippocampus (Herreras and Somjen, 1993; Kunkler and Kraig, 1998), and can also be induced in retina (de Oliveira Castro and Martins-Ferreira, 1970; Martins-Ferreira and de Oliveira Castro, 1966; 1971; Farkas *et al*., 2008). Cortical spreading depression has been shown to occur in mature brains of all mammalian species studied including man (Van Harreveld *et al*., 1956; Somjen, 2001; Lauritzen, 1987a; Goadsby, 1996; Yokota *et al*., 2002; Shibata *et al*., 1990; Fabricius *et al*., 2006; Lauritzen, 1987 & 2001; Goadsby, 2005; Dalkara *et al*., 2006), and is associated with major changes in extracellular levels of ions (Hansen and Zeuthen, 1981; Hansen *et al*., 1980), neurotransmitters (Davies *et al*., 1995), metabolic rate (Mayevsky and Weiss, 1991), and cerebral blood flow (CBF) (Table 1). For example, CSD is associated with a dramatic but short-lived rise in K^+ concentration from 3 to more than 50 mM (Hansen and Zeuthen, 1981). Similarly, glutamate levels in extracellular fluid also increases transiently during CSD (Fabricius *et al*., 1993; Iijima *et al*., 1998; Scheller *et al*., 2000). In contrast, it appears that neonatal brains of many, but not all, species are relatively resistant to initiation of CSD (Domoki *et al*., 1999a; Richter *et al*., 1998; Somjen, 2001) although the underlying basis is not clear.

Cortical spreading depression has been induced experimentally in animals to study diverse topics such as memory (Case *et al*., 2002), learning (Koroleva and Bures, 1993), preconditioning (Shen and Gundlach, 1999; Horiguchi *et al*. 2005a; 2006), and CBF regulation (Table 1). In the presence of a constant initiating presence, such as a surgical sponge saturated with KCl on the intact surface of the dura mater, there is an innate frequency of spontaneous CSDs which is affected by level and/or type of anesthetic (Figure 1) (Horiguchi *et al*., 2005a) or other pathophysiological conditions (Back *et al*., 1994). In addition, CSD is thought to be closely associated with some types of migraines in people (Lauritzen, 1987 & 2001; Goadsby, 2005; Dalkara *et al*., 2006). It also occurs following head trauma and strokes, and exacerbates brain injury in experimental animals and people (Back *et al*., 1994; Mayevsky *et al*., 1996; Fabricius *et al*. 2006; Dreier *et al*., 2006). The documentation of CSD-like episodes in man has been possible only recently because of the current availability of sensitive imaging technologies and the combined efforts of clinical investigators at multiple centers (Dreier *et al*., 2006; Fabricius *et al*., 2006; Hadjikhani *et al*., 2001; Strong *et al*., 2007).

Of particular interest to many investigators are the dramatic changes in CBF which occur during and following CSD. However, we are unaware of a recent, comprehensive review of the studies which has examined the mechanisms underlying hemodynamic responses caused by CSD. Therefore, the purpose of this review is to critically examine the literature concerning the regulation of cerebral hemodynamics during CSD. The focus of this review will be on the

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hyperemia that occurs during CSD since this is the most characteristic and reproducible aspect of the cerebral arterial response. In particular, we will address three relevant issues. First, we will interpret the complex, underlying mechanisms of cerebral vascular responses during CSD in light of new information concerning the participation and interactions of diverse cell types composing the neurovascular unit (Xu and Pelligrino, 2007; Iadecola and Nedergaard, 2007; Jackovcevic and Harder, 2007). Second, we will evaluate whether information acquired in experimental animals concerning cerebrovascular control mechanisms during CSD can be extrapolated to humans during normal and pathological conditions such as migraines (Lauritzen, 1987 & 2001; Goadsby, 2005; Dalkara *et al*., 2006). Third, we will explore the enigmatic role and possible importance of nitric oxide (NO) production during CSD, where this substance is produced by the neurovascular unit (Horiguchi *et al*., 2005b; Read *et al*., 1997; Obrenovitch *et al*., 2002) but apparently does not mediate vasodilation at least in rodents (Shimizu *et al*., 2002).

2. Defining the “Playing Field” for integrated blood flow responses to CSD

To fully understand the mechanisms involved in regulation of the cerebral circulation during CSD, we must consider the cerebral blood vessels, astroglia, neurons, and perivascular nerves as functionally inter-related components of the neurovascular unit (Hawkins and Davis, 2005). The tight coupling of brain metabolism and blood flow is a well established concept (Roy and Sherrington, 1890; Busija and Leffler, 1987; Busija, *et al*., 1988) and provides the functional basis for the neurovascular unit. However, the precise inter-relationships among the components of the neurovascular unit are only now being defined for various stimuli such as CSD. While primary cortical neurons can exert a direct effect on cerebral vascular tone, a prominent role of astroglia (Fellin *et al*., 2004; Filosa *et al*., 2004; 2006; Mulligan and MacVicar, 2004; Zonta, *et al*., 2003; Koehler *et al*., 2006; Lalo *et al*., 2006) and local circuit neurons (interneurons) (Cauli *et al.*, 2004; Vaucher *et al.*, 2000) in conveying signals between primary neurons and blood vessels has been described recently with the use of several novel imaging approaches. Neurotransmitter released from perivascular nerves can also directly affect cerebral resistance vessels. Neuronal- and astroglial-derived factors act directly on vascular smooth muscle (Domoki *et al*., 2002; Filosa *et al*., 2006) or secondarily following production and release of endothelium-dependent dilator or constrictor agents (Murphy *et al*., 1994).

Neurons affect cerebral vascular tone either directly or indirectly following activation of interneurons and/or astroglia. For example, we and others have shown that application of N-methyl-D-aspartate (NMDA) is able to activate receptors on cortical neurons and produce NO, which apparently diffuses to vascular smooth muscle and dilates cerebral arteries and arterioles without substantial involvement of endothelium or astroglia (reviewed by Busija *et al*., 2007). In addition, increased neuronal activity leads to production of other metabolites, such as adenosine, which following release into the cerebrospinal fluid (CSF), are able to directly dilate resistance vessels in the cerebral circulation (Phillis, 2004). Synaptically connected interneurons can also adapt local blood flow responses to corresponding metabolic demand following increases in afferent signals from subcortical pathways (Hamel, 2006).

Neuronal interactions with astroglia also participate in CBF regulation. Virtually the entire parenchymal segment of the cerebral vasculature is surrounded by astroglial endfeet, and this anatomical arrangement, with neurons also in contact with the astroglia, is thought to be an important means for adjusting CBF to local metabolic activity (Xu and Pelligrino, 2007; Iadecola and Nedergaard, 2007; Jackovcevic and Harder, 2007). In particular, astroglial swelling has been described as an early event in the progression of CSD, at least in mice, and this event may be involved in the subsequent cerebral vascular responses in this species (Takano *et al*., 2007; Tomita *et al*., 2005). While the surface of pial cerebral arteries and arterioles are

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not usually thought to be invested with astroglia (Mercier and Hatton, 2002), they are positioned over the *glia limitans* (Niermann *et al*., 2001) and thus can be influenced by glial-derived factors released into the CSF which is in contact with the blood vessels. Flushing of the cortical surface with appropriately gassed artificial CSF (aCSF) does not normally affect basal pial arteriolar tone, thus suggesting a minimal contribution of vasoactive influences from CSF under quiescent conditions in anesthetized animals. On the other hand, the ubiquitous positioning of the astroglia among cerebral blood vessels and neurons and the well known interactions involving these cells appear optimal for rapid and integrated control of local vascular tone in order to meet metabolic demands. Bulk CSF could also act as a "sink" and thus dilute the local vasodilator effects of metabolites released from the cortical surface during CSD.

Cortically-derived astroglial cells are avid producers of prostanoids (prostaglandins and thromboxane) (Nam *et al*., 1996; Thore *et al*., 1994; 1996) and cerebral arteries normally located close to cortical astroglia are responsive to even small concentrations of dilator and constrictor prostanoids which are present in CSF (Busija and Leffler, 2002; Leffler and Busija, 1985; Wagerle and Busija, 1990). In particular, the profile of prostanoids produced by cerebral arteries varies considerably from that produced by cortical astrogia of the same species (Busija, 1997; 2002) and thus the CSF bathing the cerebral arteries contains substantial amounts of vasoactive prostanoids arising from the brain parenchyma. Other studies have shown that similar to neurons, astroglia can produce and release a wide range of vasodilator substances such as NO, carbon monoxide (CO), adenosine, hydrogen ion, potassium ion, lipoxygenase products, and P-450 monooxygenase products (Bhardwaj *et al*., 2002; Zonta *et al*., 2003; Filosa *et al*., 2006; Koehler *et al*., 2006; Leffler *et al*., 2005).

Further complicating the situation is the presence of many types of perivascular innervation which may mediate or modulate cortical influences on cerebral resistance vessels. The cerebral arteries are richly innervated by sympathetic (Busija, 1996), parasympathetic (Goadsby and Hoskin, 1994; Dauphin and MacKenzie, 1995; El-Assouad and Tayebati, 2002) and sensory (Edvinsson *et al*., 1987; 1998; 2001) nerve fibers which release a large array of different neurotransmitters which can affect cerebrovascular tone via direct actions on smooth muscle (Edvinsson *et al*., 1987; 1998) or indirectly via endothelium (Rosenblum *et al*., 1993). In general, activation of sympathetic nerves causes cerebrovascular constriction while activation of parasympathetic and sensory nerves promotes dilator responses (Busija, 1996). Perivascular nerves can be activated centrally in a traditional manner involving pre-ganglionic pathways (Goadsby and Hoskin, 1994; Edvinsson *et al*., 1998), or via direct activation of post-ganglionic fibers by local factors such as potassium ions (Reuter *et al*., 1998). The presence of functional perivascular innervation provides the underlying basis of dramatic deviation from the concept of tight coupling of blood flow and metabolism, such that changes in cerebrovascular resistance can take place prior to and/or be independent of changes in metabolic demand. It is also possible that sustained activation of perivascular nerves could affect the slope of the blood flow/metabolism relationship.

3. Studies of cerebral hemodynamics during CSD

3.1. Responses during normal conditions

Leão (1944) was the first investigator to demonstrate that spreading depression is associated with dramatic changes in the tone of the cortical resistance vasculature. In anesthetized rabbits, he was able to show pronounced but transient dilation of pial arterioles to CSD. The veracity of these early observations by Leão (1944) on pial arteries and arterioles is such that they are very similar to more recent findings made in the same species over 40 years later (Shibata *et al*., 1990). The pioneering research of Leão (1944) was soon followed by cerebral vascular studies in the rabbit and cat by Van Harreveld and Stamm (1952) and Van Harreveld and Ochs

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(1956), respectively. During this period, the characteristics and mechanisms of CSD were examined in detail (Grafstein, 1956; Van Harreveld, 1959).

Following the development of new approaches to characterize cerebral vascular responses, Hansen *et al*. (1980) and Mies and Paschen (1981) were able to show using radioactively labeled iodoantipyrine that CSD is associated with major increases in CBF in anesthetized rats. Over the next two decades, other investigators using a variety of methods were able to confirm in many species, including rats (Lauritzen, 1984; Wahl *et al*., 1987), rabbits (Shibata *et al*., 1990; 1992), monkeys (Yokota *et al*., 2002), and cats (Wahl *et al*., 1987), that CSD is associated with transient dilation of cerebral arteries and arterioles and increased CBF (Table 1). Increased CBF occurs during CSD in awake as well as anesthetized animals, although variable CBF responses have been reported in non-anesthetized rats (Duckrow, 1991; Shimazawa and Hara, 1996; Sonn and Mayevsky, 2006). Depending upon the experimental conditions and species studied, a mild, very transient reduction in CBF has been reported to precede cerebral hyperemia in rodents (Duckrow, 1991; Fabricius *et al*., 1995; Ayata *et al*., 2004), and a sustained suppression of CBF or oligemia can be present afterwards in some species (Table 1). The mouse is perhaps unique in that it does not show a frank increase in CBF over baseline values during CSD, but rather demonstrates a cerebral hypoperfusion initially with a gradual return to baseline (Ayata *et al*., 2004). The authors of this report have suggested that enhanced sensitivity to elevated K^+, which is elevated greatly during CSD in brain extracellular fluid, may be a unique contributing factor, since preconstriction with KCl of isolated arteries reduced dilation to acetylcholine in mouse but not in rat cerebral arteries. An additional finding that may support the concept that cerebrovascular control mechanisms are different in mice than in most other common laboratory animals is the report that calcitonin gene related peptide (CGRP) is an endothelium-dependent rather than a direct smooth muscle-acting dilator agent in mouse cerebral arteries (Rosenblum *et al*., 1993). A biphasic cerebral vascular response has also been reported in the mouse cortex during CSD, where an initial dilation is followed first by an arterial constriction and then subsequently by a secondary dilation (Brennan *et al*., 2007). In contrast to these two previous reports, Takano *et al*. (2007) reported that in mouse CSD elicited an initial dilation of pial and parenchymal arterioles followed by a sustained constriction. The reasons for the variations in findings for mice are unclear at this time, but may reflect experimental differences and technical difficulties associated with the study of these very small animals. Recently, Takano et al. (2007) have reported that severe hypoxia and neuronal swelling accompany CSD in mouse cortex, and it is possible that these features are unique to mouse and contribute to the combination of cerebral vasoconstriction and slow progression of spreading depression across the cortical surface often described in this species. In contrast, Wolf *et al*. (1996) failed to show development of cortical anoxia during CSD in rats. It seems unlikely that localized tissue anoxia or hypoxia is present in most species demonstrating a robust increase in CBF during CSD. Similar to studies in mice, Chuquet *et al*. (2007) in P15 rats were able to show pial and parenchymal arteriolar constriction, and reduction in CBF, at the onset of CSD. The cerebral vascular constriction in neontatal rats was followed by dilation of pial arterioles while parenchymal arterioles returned only to baseline diameters. We are unaware of studies of hemodynamic changes in healthy cortex of man with CSD, but a paradoxical spreading oligemia usually without a preceding hyperemia has been described with the onset of migraines with accompanying aura (Woods *et al*., 1994; Hadjikhani *et al*., 2001). While a CSD-like component as suggested by the presence of aura occurs in approximately 30% of patients experiencing migraines (Rasmussen *et al*., 1991), it cannot be ruled out that other acute and chronic neurological events modify the overall cerebrovascular responses to this clinical condition. Thus, all laboratory species that have been studied except the mouse show the typical pronounced cerebral hyperemia or vasodilation during CSD. However, both mice and rats have been reported to sometimes show the initial, short-lived hypoperfusion. The prolonged oligemia following CSD has been reported to regularly occur

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in rats and mice (Brennan *et al*., 2007; Tokano *et al*., 2007) and in some, but not all, rabbits studied (Shibata *et al*., 1992).

The increase in CBF with CSD shows a typical response when there is a rapid rise with little or no plateau before a rapid restoration of baseline blood flow, with the entire hyperemic phase at any given location lasting approximately 90 seconds (Figure 1) (Shibata *et al*., 1990). The onset of the increase in pial arteriolar diameter and rise in CBF is spatially associated with the location of the CSD, defined with DC electrodes in the rabbit (Shibata *et al*., 1990;1992), but independent responses of pial arterioles and parenchymal blood flow during CSD has been described recently with confocal imaging methods in the P15 rat (Chuquet *et al*., 2007). Fabricius *et al*. (1997) showed a heterogeneous blood flow response based upon depth of the cortex in rats with CSD. Brennan *et al*. (2007) have suggested that the pial arteriolar dilation advances faster than the parenchymal depolarization across the cortical surface. It is possible that factors such as greater cellular density of the cortex, method of inducing CSD, enhanced metabolic rate, and/or larger baseline cortical blood flow in the rodent compared to the rabbit lead to these observed differences. Similar to our previous report in the rabbit (Shibata *et al*., 1990), Brennan *et al*. (2007) have shown in rats that CSDs repeated in quick succession can lead to elimination of pial arteriolar dilation during one or more CSDs in a series. Another feature of CSDs is that the hyperemia on the cortex ipsilateral to the spreading depression is spatially and temporally related to a modest pial arteriolar constriction on the contralateral cerebral cortex (Shibata *et al*., 1990). CSD apparently does not jump to adjacent gyri across a sulcus even in lissencephalic species such as the rabbit despite major increases in extracellular levels of ions and neurotransmitters in the CSD affected gyrus, and similar cerebral vascular dilations can be evoked with CSDs progressing from rostral to ventral cortex and *vice versa* (Shibata *et al*., 1990). In contrast to our findings (Shibata *et al*., 1990), Brennan *et al*. (2007) reported that pial arteriolar dilation occurs in cortical locations unaffected by CSD in mouse. The dilator responses in pial arterioles are size dependent, with smaller arterioles showing a slightly greater dilation than larger arterioles (Shibata *et al*., 1990;Chuquet *et al*., 2007). Small veins also dilate during CSD while larger ones do not, and venous responses appear to be secondary to diameter changes in resistance blood vessels (Van Harreveld and Ochs, 1957;Shibata *et al*., 1990;Tokano *et al*., 2007 Chuquet *et al*. 2007).

The shape and magnitude of the cerebral arteriolar or CBF responses can be consistent with repeated CSDs or vary with time. For example, Fabricius *et al*. (1995) have shown in the rat that each CBF response has a varying waveform, while others have shown similar CBF responses with repeated CSDs in the rat (Bari *et al*., 2000; Reuter *et al*., 1998) or rabbit (Shibata *et al*., 1990). Often the first CBF response in rats can be unique but the subsequent ones are very similar to each other (Bari *et al*., 2000; Reuter *et al*., 1998; Shimizu *et al*., 2002). The reasons for these different cerebral vascular responses are unknown, but the physiological status of the animals as well as the mode of initiation of CSD is probably a relevant factor. Read *et al*. (1997) reported that NO production was much greater with the initial CSD, and then fell to a lower, but constant level during the next several CSDs, and this finding is consistent with changes in cerebrovascular responses with multiple CSDs. Fabricius *et al*. (1995) reported variable CBF responses in halothane anesthetized rats with repeated needle stabs to the cortex. Repeated needle punctures of the cortex with or without KCl injections may damage the surrounding tissues, and thereby alter CSD characteristics. In addition, repeated CSDs may continually alter the status of the neurovascular unit because of the increased metabolic load or because of depletion of substrates or neurotransmitters. However, we found that repeated KCl injections by needle insertion leads to reproducible blood flow responses to multiple CSDs in the urethane-anesthetized rabbit (Shibata *et al*., 1990), possibly due to factors such as a larger brain size and lower brain metabolic rate in this species compared to the rat. In addition, we have found that application of a surgical sponge saturated with KCl over the intact dura initiates a series of CSDs which show very similar CBF waveforms over

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at least an hour's duration despite differences in the numbers of CSDs due to the alterations of the depth of halothane anesthesia in rats (Figure 1) (Horiguchi *et al*., 2005a). Under these circumstances, there is an innate frequency of spontaneous CSDs which is dependent upon the experimental conditions. Richter and Lehmenkühler (1993) compared KCl application and needle prick and found that each approach had differential effects on the amount of cortex affected as well as the CSD characteristics. On the other hand, Brennan *et al*. (2007) reported that frequent, repetitive CSD induced by placing KCl crystals on the cortical surface in rats initially leads to vasodilation followed by constriction, but eventually the arterioles became persistently dilated with reduced vascular responsiveness.

Associated with the delayed oligemia in rats is a reduction in cerebrovascular dilator responsiveness to stimuli such as arterial hypercapnia, which can be demonstrated both *in vivo* (Lauritzen, 1987; Lacombe *et al*., 1992; Florence *et al*., 1994; Fabricius) and in isolated middle cerebral arteries removed after CSD (Seitz *et al*., 2004). The altered cerebrovascular responses to stimuli such as arterial hypercapnia occur in spite of continued CBF responsiveness to multiple CSDs that occur during this period (Horiguchi *et al*., 2005a). In people also, a reduced cerebrovascular response to arterial hypercapnia has been described during or immediately following migraine attacks (Lauritzen *et al*., 1983). The reduced responsiveness following CSD can be reversed in rats by stimulators of the cyclic GMP system or by administration of L-arginine (Fabricius *et al*., 1995; Zhang *et al*., 2002; Scheckenbach *et al*., 2006), thereby implying that impairment of the NO synthase (NOS) system is responsible for a reduction in dilator responses. This speculation is consistent with the reduced cerebral vascular responsiveness to arterial hypercapnia in rats, in which NO plays a prominent role (Fabricius and Laurizten, 1994). In the rabbit, in which some but not all animals show post-CSD cerebral vasoconstriction (Shibata *et al*., 1992), cerebral vascular responsiveness is intact following CSD (Busija and Meng, 1993). Additionally, in the piglet brain, which is resistant to CSD, transient depolarization by superfusion with topical KCl under the entire cranial window, followed by recovery, does not prevent normal dilator responses to several stimuli (Domoki *et al*., 1999a).

3.2. Comparison of CBF responses between people and animals

Findings, based upon available information, showed that responses of the human cerebral circulation to stimuli such as arterial blood hypercapnia, changes in arterial blood pressure, and changes in metabolism are similar in direction and magnitude to those determined in a variety of commonly used experimental animals (Katona *et al*., 2006; Meadows *et al*., 2005; Zhang *et al*., 2004; Drake and Iadecola, 2007). More specific to this discussion, the previously identified dilator agents released by other species during CSD, including CGRP, NO, and acetylcholine, apparently have similar dilator effects on human cerebral arteries (Edvinsson *et al*., 1987; Jansen-Olesen *et al*., 1996; Hansen *et al*., 2007; Sams *et al*., 2000; Zvan *et al*., 2002). On the other hand, the usual dramatic rise in CBF during CSD, which occurs in diverse species such as the monkey, cat, rabbit, and rat (Table 1), has been difficult to be detected consistently in the human cortex during CSD-like events (Bartonlini *et al*., 2005). The principal reason for this deficiency is the lack of studies due to the ethical and practical limitations of examining CBF responses during experimentally induced CSD in normal, human cerebral cortex. Initiating spreading depression in human cortex may lead to localized tissue damage, transient changes in cortical function, and alterations in gene expression (Caggiano et al., 1996a; 1996b; Shen and Gundlach, 1999; Horiguchi *et al*. 2005a; 2006). While spreading depression has been shown to occur in human neocortical slices (Gorji *et al*., 2001), responses of arteries and arterioles apparently have not been evaluated in this preparation.

A variety of electrophysiological, visual and psychological events have indicated that CSD-like events occur during the initiation of migraines (Bartolini et al., 2005; Lauritzen *et al*., 1983;

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Lauritzen, 2001; Dalkara *et al*., 2006; Mayevsky *et al*., 1996), and usually, but not always, a cerebral oligemia is the only cerebral vascular response consistently detected in these circumstances (Lauritzen *et al*., 1983; Olesen *et al*., 1981; Woods *et al*., 1994). From this perspective, it is possible that the human cortex displays CBF responsiveness more similar to that seen in the mouse during CSD than that observed in other species. Underlying reasons for an atypical cerebral vascular response may be due to pathological changes in the cortical thickness reported in patients with chronic migraines (DaSilva *et al*., 2007) and the relatively sparse presence of CGRP in perivascular nerves in cerebral arteries of people (Edvinsson *et al*., 1994).

Although CSDs may be initiated following strokes in people (Strong *et al*., 2007), the hemodynamic responses in compromised neural tissue may not reflect the normal condition as we have shown in rats (Shimizu *et al*., 2000b) and Strong *et al*. (2007) have shown in cats following transient brain ischemia. Prior CSDs are able to cause prolonged suppression of certain vascular responses in some situations in rats and rabbits, and also influence cortical levels of vaso-relevant proteins such as cyclooxygenase (COX)-2 (Caggiano *et al*., 1996a; 1996b; Horiguchi *et al*., 2006) and NO synthase (Shen and Gundlach, 1999), and so it would not be surprising to find altered cerebrovascular responsiveness to migraines in people. Another important consideration that has not been previously addressed is the effect of basal CBF and other factors on the hemodynamic response to CSD. A number of factors, such as level and type of anesthesia, resting CBF, and the presence of various pharmacological agents, are able to affect the observed changes in CBF with CSD in experimental animals as well as in people (Duckrow, 1991; Lauritzen, 1987; Sonn and Mayevsky, 2001; 2006; Shimazawa and Hara, 1996). For example, Piper and Lambert (1996) have shown anesthetic-type dependent effects on CSD initiation, and suggested the use of halothane in people following cerebral insults may interfere with detection of CSDs. Thus, in the absence of any direct experimental data, it may be misleading to overly interpret data from limited human studies in which neuronal injury has occurred due to strokes or concussive brain injury, or when the cortex has experienced previous migraines over the course of months or years. Also unstudied are the effects of gender on cerebral hemodynamic during CSD. Gender has many effects which are able to affect CBF responses to a variety of stimuli (Chrissobolis and Sobey, 2004; Li *et al*., 2004). Therefore, the cerebral hemodynamic consequences of CSD in normal human brain remain largely unknown.

3.3. Altered hemodynamic responses during pathological conditions

Since the cerebral hemodynamic changes during CSD are influenced by physiological factors such as basal CBF (Sonn and Mayevsky, 2001; Lauritzen, 1987), the method of inducing CSD (Fabricius *et al*., 1995; Shibata *et al*., 1990; Horiguchi *et al*., 2005a), and the level and type of anesthetic used (Horiguchi *et al*., 2005a), it is not surprising that pathological conditions also influence the response of the cerebral circulation to CSD. In one of the first such studies, Shimizu *et al*. (2000b) showed that the presence of cortical infarcts following transient, middle cerebral artery occlusion (MCAO) reduced or eliminated CBF increases during CSD. In these animals, the MCA was occluded for 75 minutes and blood flow responses were determined 24 hours later. Despite the presence of subcortical or cortical infarcts, normal DC deflections could be evoked suggesting energy metabolism had recovered sufficiently 1 day after MCAO to sustain multiple CSDs. However, an increase in CBF did not occur at the center of the infarct, although a reduced hyperemia occurred in the penumbral area. At both penumbral and infarcted sites the baseline CBF was greatly elevated over non-infarcted levels, and this situation may have lead to a reduced or eliminated cerebral hyperemia as the maximal CBF level was reached. Strong *et al*. (2007) has reported similar findings with spontaneous spreading depolarization in infarcted cortex in the cat. A recent study by Sukhotinsky *et al*. (2008) supports the concept that prior vasodilation adversely affects cerebral hyperemia during CSD. In addition, this group

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has shown that CBF in the penumbral region can be supported during cortical depolarization with mild hypertension (Shin *et al*., 2008). It is also possible that ischemia leads to depletion of substrates or neurotransmitters necessary for the full expression of the dilator response (Bari and Paprika, 2000). When only subcortical infarcts were present, baseline CBF was normal and cortical hemodynamic responses to CSD were intact. Similar findings were reported following occlusion of cerebral veins as a means to induce cortical infarction (Osuka *et al*., 2000). Kocher (1990) also found that the typical CBF responses to CSD continued to take place for the 3-6 hour reperfusion period following 30 minutes of global ischemia. In contrast to ischemic strokes, which cause the initiation of CSD into penumbral and normal tissue, with variable CBF responses (Shimizu *et al*., 2000b), the presence of hemoglobin, which would occur with hemorrhagic stroke, causes a spreading ischemia with cerebral vasoconstriction during pathological models of CSD, at least in rats (Petzold *et al*., 2003; Drierer *et al*., 2006).

Cerebrovascular responses during CSD have been studied in only a few other diseases. However, CSD-induced cerebrovascular dilation is unaffected by metabolic disease states, such as hyperglycemia (Wolf *et al*., 1997) or mild, nutritionally induced-insulin resistance (Shimizu *et al*., 2002), even though these diseases normally alter vascular responsiveness to dilator agents associated with CSD (Erdős *et al*., 2004; 2006). Cerebrovascular responses to CSD apparently are also resistant to alcohol administration in rats (Sonn and Mayevsky, 2001).

4. Mechanisms of cerebral hyperemia during CSD

4.1. Dilator Mechanisms

Given our current knowledge about the regulation of CBF in experimental animals, there are a number of dilator stimuli arising from cerebral arteries and parenchyma, including neurotransmitters from sensory and parasympathetic nerves, NO, adenosine, reactive oxygen radicals (ROS), potassium ion, glutamate, and prostanoids, which could cause or modify cerebral arterial dilation and hyperemia during CSD.

4.1.1. Nitric oxide—A role for NO was shown first by Goadsby *et al*. (1992) in the cat, in which a NOS inhibitor completely abolished the increase in CBF seen with this species during CSD. Additional studies in cats (Wahl *et al*., 1994; Read *et al*., 1997) and rabbits (Colonna *et al*., 1994b) supported these initial reports and demonstrated that NOS inhibition reduced cerebral arterial dilation during CSD by approximately 50%. However, the reason for the discrepancy between complete and partial suppression of cerebral vasodilation during CSD by NOS inhibition for the cat reported by Goadsby *et al*. (1992) and others (Wahl *et al*., 1994; Read *et al*,. 1997), respectively, is not clear. While it could be argued that the underlying basis for the difference was due to the measurement of CBF in one study and pial arterial diameter in the others, parallel studies evaluating the relative importance of NO involvement in cerebrovascular changes during CSD with the cranial window and microsphere methods in rabbits in the same laboratory have led to consistent conclusions (Colonna et al., 1994b; 1997). Nonetheless, the source of the NO appears to be neuronal or glial in origin, since selective inhibition of neuronal NOS had similar effects to general inhibition of NOS (Colonna *et al*., 1997). However, it has not been determined whether the source of the NO is from cortical neurons or astroglia, or from perivascular nerves since NOS is associated with several types of innervation of cerebral arteries (Edvinsson *et al*., 1998; 2001; Goadsby *et al*., 1996; Nozaki *et al*., 1993). While NOS is co-localized with CGRP in sensory nerve endings, activation of trigeminal pathways apparently releases little or no vasoactive NO despite major cerebral vasodilation (Edvinsson *et al*., 1998). On the other hand, astroglia may be involved in mediating the NO-dependent component of cerebrovascular dilation to arterial hypercapnia in the rat (Xu *et al*., 2004). The relative contribution of NO is dependent upon the physiological status of the brain, since inhibition of prostaglandin synthesis with indomethacin prevented detection

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of a NO component in the cerebral vascular dilator response to CSD in rabbits (Meng *et al*., 1995).

Despite early, preliminary indications in rats, numerous subsequent studies have failed to support an important contribution of NO to cerebral hyperemia in rats. Thus, while NO appears to be produced in significant amounts by cortex during CSD in this species (Obrenovitch *et al*., 2002; Horiguchi *et al*., 2005; Read *et al*., 1997), there apparently is no substantial contribution which would counter-act the initial, brief hypoperfusion (Duckrow, 1993; Fabricius *et al*., 1995) or promote the subsequent hyperemia (Table 1). Nonetheless, despite the lack of a significant NO contribution to CSD-induced cerebral hyperemia, administration of exogenous NO or cGMP activators are able to restore a major part of the post-CSD dilation to hypercapnia or other vasodilators (Fabricius *et al*., 1995; Zhang *et al*., 2002; Scheckenbach *et al*., 2006). Additionally, pharmacological blockade of NOS or degradation of NO with hemoglobin leads to a spreading ischemia rather than hyperemia following induction of a CSD-like event (Windmüller *et al*., 2005). Thus, the role of NO in vascular responses to CSD is complex in rats, and does not involve direct vasodilator actions that would lead to increased CBF, but rather would promote other, potentially beneficial effects in brain (see below).

4.1.1.1. Paradoxical roles of NO during CSD in rats: The lack of a significant impact of NO on cerebral hyperemia during CSD in the rat is surprising because of its potency in promoting cerebral vascular dilation and because NO is a mediator of CBF increases in this species during a variety of experimental conditions involving activation of the cerebral cortex (Dreier *et al*., 1995; Busija *et al*., 2007). Iadecola *et al*. (1993) and others (Estada *et al*., 1993) have shown that cerebral arterioles including those in the parenchyma are innervated by NOS containing nerves from the sphenopalatine ganglia. It is possible, but unexplored, that NO effects on cerebral arteries are blocked by another substance produced during CSD or because of the activation of a signaling cascade which interferes with functioning of vascular smooth muscle guanylate cyclase. For example, CO from heme oxygenase-2 in cerebral arteries has been shown to reduce vascular effects of NO (Ishikawa *et al*., 2005). Additionally, serotonin, which apparently is released near cerebral arteries during CSD (Gold *et al*., 1998), is able to suppress release of NO in rats (Read *et al*., 1999). Nonetheless, NO is produced in substantial quantities by brain during CSD and have other non-vascular effects on the cortex such as restoration of the physiological status of the brain (Obrenovitch *et al*., 2002) and the promotion of preconditioning against ischemic stress (Matsushima *et al*., 1996; Horiguchi *et al*., 2005b). Petzold *et al*. (2008) recently have reported NO derived from endothelial NOS maintains the threshold for initiating CSD in rodent and human brains. Additionally, NO produced by the cortex or cerebral vasculature may affect CGRP release in the dura mater (Strecker *et al*., 2002) and thus modulate the degree of pain associated with migraines.

In recent studies we have shown that repetitive CSDs induced in rat cortex results in NO-induced preconditioning against neural damage caused by MCAO (Horiguchi et al., 2005b; 2006). Thus, pretreatment with N(G)-nitro-l-arginine methyl ester (L – NAME) abolishes preconditioning by CSD, probably by reducing the delayed enhancement of cortical cyclooxygenase-2 (COX-2) expression. Other investigators have shown that levels of COX-2 increase after CSD in the rat (Cui *et al*., 2007) and in other species such as primates (Yokota *et al*., 2003). Rather than being a final mediator of preconditioning , enhanced COX-2 expression and production of prostaglandins of the J-series appear to be final steps in preparing the cortex to withstand potentially lethal ischemia in experimental strokes (Horiguchi *et al*., 2005b). Whether similar events take place in human cerebral cortex following CSD-like events such as migraines or following localized depolarizations associated with transient ischemic events is currently unknown. Also unclear is whether altered gene expression following CSD alters subsequent cortical or vascular responses to CSD. Finally, it appears that while NO does not mediate the increase in CBF during CSD in rats, the presence of NO is able to prevent

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cerebral vascular vasoconstriction and spreading ischemia in the rat cortex under some CSD-like conditions (Windmüller *et al*., 2005).

4.1.2. Perivascular nerves—The involvement of a more universally accepted dilator agent was shown simultaneously by Colonna *et al*. (1994a) and Wahl *et al*. (1994), who were able to demonstrate that pharmacological blockade of the CGRP receptors attenuated cerebral hyperemia by approximately 40-50% in rabbits and cats, respectively. Similar results were obtained in the rat from studies involving pharmacological blockade of CGRP receptors (Reuter et al., 1998), destruction of sensory nerves with capsaicin (Bari and Paprika, 2000; Bari *et al*., 2000), and chronic interruption of neural pathways supplying sensory nerves containing CGRP to cerebral arteries (Reuter *et al*., 1998). Thus, chronic sensory denervation achieved by the sectioning of the trigeminal nerves supplying cerebral arteries reduces CBF increases with CSD (Reuter *et al*., 1998), thereby providing strong evidence that the predominant source of dilator stimuli is from perivascular nerves. Chemical destruction of the capsaicin-sensitive trigeminal nerve endings resulted in time-dependent effects on CBF during CSD, such that reduced cerebral vasodilation soon after treatment was followed by development of vascular supersensitivity to CSD (Bari and Paprika, 2000; Bari *et al*., 2000). Trigeminal pathways are also important in mediating dilator responses in the cerebral circulation under other physiological and pathological conditions (Wei *et al*., 1992; Macfarlane *et al*., 1991). Thus, in all species studied, approximately one-half each of the dilation to CSD comes from CGRP (Bari *et al*., 2000; Colonna *et al*., 1994a; Reuter *et al*., 1998; Wahl *et al*., 1994), with a similar portion coming from NO (Colonna *et al*., 1994b; Wahl *et al*., 1994) in the rabbit and cat and with a similar percentage coming from perivascular parasympathetic nerves in the rat (Reuter *et al*., 1998). It is not surprising that dilator responses following activation of trigeminal fibers in the rat involve primarily the actions of CGRP. While NOS is present in trigeminal nerve endings, its distribution is limited and the dilator responses to trigeminal nerve stimulation appear to involve smooth muscle actions primarily of CGRP and not NO (Edvinsson *et al*., 1998). The involvement of additional dilator factors originating from the parasympathetic innervation in the cat and rabbit hasn't been examined. An unusual finding is that while parasympathetic denervation and blockade of muscarinic receptors with atropine reduce cerebral hyperemia with CSD in the rat (Reuter *et al*., 1998) these effects did not involve production and effects of endothelial-derived NO (Shimizu *et al*., 2002) as seen during direct activation of parasympathetic nerves supplying cerebral arteries (Goadsby *et al*., 1996b). Parasympathetic activation or acetylcholine application also typically dilates arteries from peripheral circulations via production of NO from endothelial NOS (Toda and Okamura, 2003).

It appears that other dilator substances which may derive from perivascular nerves in rats, such as serotonin (Gold *et al*., 1998), make modest contributions to the overall cerebrovascular response to CSD. However, it is untested whether perivascular sympathetic nerves provide counteracting constrictor influences on cerebral arteries during CSD.

In addition to directly mediating much of the cerebral vasodilation by local release of CGRP, stimulation of trigeminal afferents during CSD leads to vasodilation and neurogenic inflammation in the meninges via axon-reflex activation of collateral trigeminal branches and central-reflex activation of parasympathetic nerves, respectively (Bolay *et al*., 2002; Dalkara *et al*., 2006; Edvinsson, 2007). Intravenous CGRP administration can also trigger headaches or migraines in migraine patients (Iversen, 2001; Lassen *et al*., 2002; 2008). It is thought that meningeal effects lead to the head pain associated with migraines with aura, and that the optical distortions represent CSD over the visual cortex. However, experimental induction of CSDs in awake rats apparently does not lead to aversive behaviors (Koroleva and Bures, 1993) and thus whether it causes headaches in this species is not known. An earlier report by Lambert and Michalicek (1994) in the cat indicated that CSD was associated with decreased meningeal

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blood flow, and it is unclear whether species differences or other aspects of the experiments affected the results. Although increased vascular permeability of meningeal blood vessels during migraines has been suggested to occur in some patients (reviewed by Dalkara *et al*., 2006), we are unaware of direct evidence that migraine-associated vasodilation in the meninges occurs in people. Antagonists against CGRP receptors have been reported to be effective against migraines in people (Olesen *et al*., 2004; Goadsby, 2005; Ho *et al*., 2008). Furthermore, other anti-migraine medicines such as dihydroergotamine and sumatriptan may provide beneficial effects by inhibiting activation or actions of the trigeminal nerves (Buzzi *et al*., 1991). Lastly, NO donors have been reported to induce headaches in people (Christiansen *et al*., 1999; Iversen *et al*., 2001) perhaps through the release of CGRP near cerebral arteries (Wei *et al*., 1992) with resultant effects on meningeal blood vessels. Nitric oxide produced by the cortex or cerebral vasculature also may directly affect CGRP release in the overlying dura mater (Strecker *et al*., 2002). Although usually not directly examined, it appears that removal of the dura mater in cranial window preparations, which would eliminate potential axonal and reflexive interactions between pial and dura mater nerves, has little detectable effect on cerebral hemodynamics during CSD (Shibata *et al*., 1990).

4.1.3. Potassium ions and glutamate—Potassium ions and glutamate are released into cortical interstitial fluid during CSD and both have been implicated in the propagation of spreading depression (Grafstein, 1956; Van Harreveld, 1959). Potassium ions exert potent vasoactive effects on cerebral arteries (Schuh-Hofer *et al*., 2001), but their direct participation in cerebral vascular responses during CSD is unclear since the predominant mediator of dilator effects appear to be the activation of perivascular nerves rather than the direct influence of potassium ions diffusing to vascular smooth muscle. However, potassium ions could affect CBF responses during CSD in two other ways. First, elevated potassium ion levels during CSD could activate perivascular nerves and thus indirectly induce cerebral vascular responses (see below and Figure 1). Second, elevated potassium ion levels during CSD may reduce vascular responses to dilator agents such as acetylcholine released from parasympathetic nerves (Ayata *et al*., 2004), at least in mice.

Glutamate and specific glutamate receptor agonists such as NMDA are potent dilator agents when applied to intact brain (Busija and Leffler, 1989; Busija *et al*., 2007), but there is no evidence that glutamate can exert direct vascular effects on the cerebral arteries of animal species used in CSD studies. The available information indicates that cerebral vascular dilator effects of glutamate and NMDA involve NO production from cortical neurons and/or astroglia (Busija *et al*., 2007) or other events not involving NO production subsequent to the activation of perivascular astroglia (Filosa *et al*., 2006; Straub and Nelson, 2007). The direct production of NO from cortical neurons and/or astroglia probably is not a major factor in rats because of the lack of inhibition of the CBF response by L-NAME in this species. However, glutamate-induced NO production in cortical cells may be an important vasodilator mechanism in cats and rabbits, although it is not possible to rule out perivascular nerves as the source of NO. Alternatively, Nelson and colleagues (Filosa *et al*., 2006; Straub and Nelson, 2007) have suggested that increased extracellular levels of glutamate will activate metabotropic glutamate receptors on astrocytes, which in turn initiates the spread of increased calcium levels from the cytosole through processes to the astrocytic endfeet. At the astrocytic endfeet, which are in close proximity to the pial and parenchymal resistance vessels, it is suggested that the increased cytosolic calcium level will: 1) Activate PLA_2 with subsequent release and metabolism of arachidonic acid to prostanoids and epoxyeicosatrienoic acids (EETs), and/or 2) Promote the release of potassium from endfeet via stimulation of large conductance calcium-activated potassium (BK) channels. However, at least in the rat, the involvement of such mechanisms in promoting dilator responses is unlikely. In this species, administration of indomethacin (Shimizu *et al*., 2000a) as a blocker of cyclooxygenase-induced production of prostanoids, miconazole (Shimizu *et al*., 2002) as a blocker of epoxygenase-induced production of 11,12

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and 14, 15 EETs (Alkayed et al., 1996), glibenclamide (Horiguchi *et al*., 2005; Shimizu *et al*., 2000a) as a blocker of ATP-sensitive potassium channels which may mediate dilator prostanoid effects, and charybdotoxin (Shimizu *et al*., 2000a) as a blocker of BK channels fails to reduce cerebrovascular dilation during CSD. Even in the rabbit, indomethacin potentiates rather than decreases CBF responses (Shibata *et al*., 1992). Finally, Iijima *et al*. (1998) have reported that increases in brain extracellular glutamate levels during CSD were not well correlated with cerebral hyperemia.

4.1.4. Reactive oxygen species—Only a few studies have examined the roles of ROS and adenosine in mediating cerebral hyperemia during CSD and the results are negative. ROS scavengers fail to alter CSD-induced hemodynamics in rat and rabbits (Duckrow and Beard, 1992; Meng and Busija, 1996). This lack of a significant role of ROS in mediating changes in cerebral vascular tone or CBF during CSD is surprising because it would be expected that the cellular disruption under these circumstances should activate ROS-generating pathways. While modest elevations in ROS levels may occur during CSD and are insufficient in magnitude to affect cerebral vascular tone, we cannot rule out the activation of ROS-dependent signaling pathways which could promote the development of neuronal preconditioning (Nagy *et al*., 2004).

4.2. Counteracting constrictor influences

Lauritzen (1987) was the first to examine the possible involvement of prostanoids on the cerebral arterial dilation to CSD by administering a blocker of cyclooxygenase. For example, he found that inhibition of the cyclooxygenase pathway with indomethacin enhanced dilation in rats. Furthermore, CSD in rats is associated with increased amounts of free arachidonic acid in cortex, and the availability of arachidonic acid is the rate limiting step in the production of prostanoids (Lauritzen *et al*., 1990). However, it is unclear whether prostanoids modulate CBF responses in rats. First, it seems likely that reduced CBF, which is a characteristic of indomethacin in rats, leads to the appearance of an enhanced response since it occurred also during arterial hypocapnia and other CBF reducing strategies (Lauritzen, 1987; Sonn and Myevsky, 2006). Second, many subsequent investigators have failed to show a significant increase in the cerebral hyperemia during CSD following indomethacin administration in rats (Table 1).

In contrast, the evidence is stronger for an important cyclooxygenase-dependent component in the rabbit capable of opposing cerebral vasodilation (Shibata *et al*., 1991b). In this species, indomethacin application enhances arteriolar dilation and augments CBF increases (Shibata *et al*., 1991b), and eliminates the post-CSD vasoconstriction (Shibata *et al*., 1992). In contrast to the situation in rats, baseline arteriolar diameter or CBF failed to show a significant reduction following indomethacin administration in rabbits. Furthermore, measurements of cyclooxygenase metabolites in the CSF bathing the pial surface show that levels of constrictor prostanoids, particularly $PGF_{2\alpha}$, increase with CSD, and this increase is eliminated with indomethacin administration (Shibata *et al*., 1991b). Thus, constrictor prostanoids appear to restrict increases in CBF during CSD and impair restoration of basal CBF in the post-CSD period in at least one species. The constrictor prostanoids appear to have access to the cerebral arteries from within the vessel wall and via the surrounding CSF, and the relative contribution from each source is time dependent. The dilator component of the pial arteriolar response to CSD is unaffected by aCSF superfusion (Shibata et al., 1991), perhaps because the prostanoids arise from within the vessel wall. The putative vascular origin of constrictor prostanoids during the immediate CSD period is supported by the virtually simultaneous effects of dilator and constrictor agents on cerebral arteries and arterioles. However, it is unclear whether the prostanoids exert a direct, counteracting constrictor influence, or whether they restrict release and/or actions of vasodilator agents. Since superfusion of the cortical surface with aCSF has

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similar effects as indomethacin administration on the sustained, post-CSD oligemia, it seems likely that parenchyma-derived prostanoids are able to exert a direct, constrictor effect on pial arteries under these conditions (Shibata *et al*., 1991b). Although it has been suggested that cytochrome P-450 monooxygenase products are produced by astroglia and affect cerebral hemodynamics, especially in the rat, we were unable to show any effect of miconazole on the increase in CBF during CSD in this species (Shimizu *et al*., 2002). Furthermore, endothelin does not appear to mediate the oligemia which occurs following CSD (Goadsby *et al*., 1996a).

4.3. Integration of multicellular contributions to cerebral hemodynamics

The final cerebrovascular responses to CSD involve additive and competing vasoactive factors derived from diverse cell types within the neurovascular unit (Figure 2). Of these, undoubtedly the perivascular nerves are the most important in promoting cerebral artery dilation. Thus, in all species studied, it appears that trigeminal fibers promote much of the cerebral artery dilation (Table 1) In addition, at least in the rat, parasympathetic nerves also contribute substantially to cerebral vascular dilation during CSD (Reuter *et al*., 1998). While NO is also an important component of dilation in several, but not all species, during CSD, the most that we can say at this time is that the source is neuronal rather than from the endothelium (Colonna *et al*., 1997;Shimizu *et al*., 2002), and therefore could include perivascular nerves, astrocytes, or cortical neurons. On the other hand, constrictor prostanoids are able to suppress dilation during CSD and promote post-CSD vasoconstriction in species such as rabbit. Based upon the results from the aCSF perfusion experiments and timing of vascular effects with respect to the location of the CSD, our findings show that the source of vasoactive agents during the hyperemic period appears to be from the vessel wall. Thus, we have shown that in CSD-induced cerebrovascular dilation in rabbits, neurally-derived NO, perivascular nerve-derived calcitonin gene-related peptide, and prostaglandins from parenchyma and/or blood vessels all contribute to the final, integrated blood flow response (Colonna *et al*., 1994a;1994b,1997) (Figure 1). Furthermore, as previously described the relative contribution of any of these vasoactive stimuli would be modified by physiological or pathological status.

The key unresolved issue is the nature of the functional coupling between events occurring among neurons and astroglia during CSD and the subsequent transfer of this information to the pial and parenchymal arteries and arterioles. Since acute denervation of sensory and parasympathetic neural pathways, which leaves the peripheral nerve endings intact, does not substantially reduce cerebral hyperemia during CSD, cerebrovascular responses are dependent upon stimuli that arise from the cortex and do not involve centrally integrative reflexes. At least for the pial circulation, the involvement of vasoactive substances arising from large areas of the cortex during CSD appears unlikely. Superfusion of the cortical surface with aCSF does not reduce hyperemia during CSD (Shibata *et al*., 1992), and spreading depression on one gyrus in rabbit does not dilate pial arterioles on an adjacent gyrus. In addition, the close temporal relationship of the actions of diverse dilating and competing constricting agents with each other and with the location of the spreading depression, as well as the rapid return of blood flow to baseline values, supports the tight coupling between cortical and vascular events during CSD. Given the inclusive nature of spreading depression, in which virtually all cortical cells would be affected, actions involving astroglia and interneurons near parenchymal arterioles will contribute to CBF changes. Increases in cortical extracellular fluid levels of substances such as K^+ and/or other ions and neurotransmitters may directly depolarize perivascular nerves on pial and parenchymal arteries and arterioles. These factors alternatively may indirectly activate perivascular nerves via axonal responses involving local, non-vascular projections of trigeminal fibers on the pial surface (Hildebrand *et al*., 1997; Risling *et al*., 1994). In addition, increased levels of ions or other substances can selectively activate perivascular nerves associated with parenchymal arterioles (Benagiano *et al*., 2000; Iadecola *et al*., 1993) present

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within the Robins-Virchow space, and result in upstream conduction of neural or vascular activation. The report that upstream propagation of arterial dilation occurs during CSD in mice (Brennan *et al*., 2007) supports the concept that activation of perivascular fibers on parenchymal arterioles, or other components of the vascular wall, initiates a propagated dilator response that projects to the pial arterioles. However, other evidence makes it unlikely that flow dependent dilation in the "classical" sense is involved in some animal models, since the normal delay in dilation seen in surface arterioles following parenchymal blood flow increases with a carotid occlusion model (Fujii *et al*., 1991) is not seen during CSD (Shibata *et al*., 1991b).

In support of a local, tight coupling between cortical events and dilator responses of cerebral arteries and arterioles, rather than vascular responses that are mediated by the generalized diffusion of substances from the cortex, superfusion of the cortical surface with aCSF was able to effectively suppress not only pial arteriolar dilation to arterial hypercapnia (Shibata *et al*., 1991a), but also the delayed and prolonged post-CSD vasoconstriction which is due to constrictor prostanoids diffusing from the parenchyma. Nonetheless, several factors, including a close anatomical association of pial arteries and arterioles to the *glia limitans*, the relative isolation of the parenchymal arterioles within the Virchow-Robins space, and unknown flow dynamics within the cranial window, can reduce effectiveness of superfusion with aCSF against the dramatic, but transient cerebral vascular dilation during CSD.

Glial-derived substances are able to directly interact with the cerebral arteries and arterioles on the pial surface and in the protected Virchow-Robins space. A tight, functional coupling between the *glial limitans* and pial arterioles, which are in close anatomical proximity to each other, has been described recently for dilator responses associated with neuronal activation (Xu et al., 2004; Xu and Pelligrino, 2007; Iadecola and Nedergaard, 2007; Jackovcevic and Harder, 2007). Cortical astroglia have been reported to swell during CSD in rodents (Anderová *et al*., 2001), and astroglia are activated during the processing of various ions and neurotransmitters released into extracellular fluid during CSD (Llian and Stringer, 2004). Thus, it would not be surprising that events leading to CSD would lead to astroglial activation with subsequent effects on cerebral arteries including activation of perivascular nerves. For example, neuronal activation leads to events which result in astrocyte stimulation with the release of potassium ion and/or ATP into the perivascular space to cause dilation of parenchymal arterioles (Filosa *et al*., 2006; Xu *et al*., 2007). However, the involvement of astroglia in mediating cerebrovascular responses during CSD has never been directly assessed.

While the potential role of interneurons in mediating changes of cerebral vascular tone, especially in parenchymal arterioles, has received attention recently (Hamel, 2006), their contribution to hemodynamic changes during CSD remains unclear. Cortical neurons are stimulated and depolarized during CSD, and release various vasoactive substances. In addition, similar to astroglia, neurons have been shown to swell during CSD in rodents (Takano *et al*., 2007). However, the majority of the changes in CBF during CSD appear to involve release of dilator neurotransmitters from perivascular nerves, although the source of NO during CSD in rabbits and cats can be from cortical neurons and/or astrocytes as well as from perivascular nerves. On the other hand, the observation that parenchymal blood flow increases are sustained even following the elimination of pial arteriolar dilation either through repeated CSDs or via chemical means may indicate that interneuron influences are present but normally masked (Chuquet et al., 2007).

5. Summary and Perspectives

Cortical spreading depression is a useful model for studying brain function and control mechanisms of the cerebral circulation. The combined contributions of many investigators

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especially over the last two decades have lead to a basic understanding of the factors controlling cerebrovascular responses during CSD as well as the relevance of CSD to clinical situations such as migraines and brain injury. However, more research is needed not only to verify previous, key findings, but also to clarify additional topics of interest in this field. These include investigating the:

1. functional linkage between events in the cortex and the subsequent cerebral vascular responses;
2. underlying basis for major species differences in cerebrovascular responsiveness during CSD;
3. reasons for lack of a prominent role of NO in mediating increased CBF especially in rodents during CSD;
4. possibility of gender differences in CBF responses during CSD;
5. normal cerebral hemodynamic responses in people during CSD; And
6. mechanisms of cerebral oligemia associated with CSD-like events during migraines.

We also suggest that genetically altered rats and mice, whose advantages have been shown in many studies in the cerebral circulation (Faraci, 2003) including several recent ones involving CSD (Petzold *et al*., 2008; Shin *et al*., 2007; Sukhotinsky *et al*. 2008), can be useful in the elucidation and validation of mechanisms of cerebral vascular control during CSD.

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Glossary

Ach
: acetylcholine

aCSF
: artificial cerebral spinal fluid

BBB
: blood brain barrier

CBF
: Cerebral blood flow

CGRP
: calcitonin gene-related peptide

CO
: carbon monoxide

COX
: cyclooxygenase

CSD
: cortical spreading depression

CSF
: cerebrospinal fluid

EC
: endothelial cell

EET
: epoxyeicosatrienoic acid

fNIRS
: near-infrared spectroscopy

K^+
: potassium ion

KCl
: potassium chloride

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L-NAME
N(G)-nitro-l-arginine methyl ester

LPDI
laser-Doppler perfusion imaging

MCAO
middle cerebral artery occlusion

MMP-9
metalloproteinase-9

7-NI
7-nitroindazole

NMDA
N-methyl-D-aspartate

NMDAR
NMDA receptor

NO
nitric oxide

NOS
nitric oxide synthase

Parasymp. N
Parasympathetic nerve

ROS
reactive oxygen species

Trig. A
Trigeminal afferent

VSM
vascular smooth muscle cell

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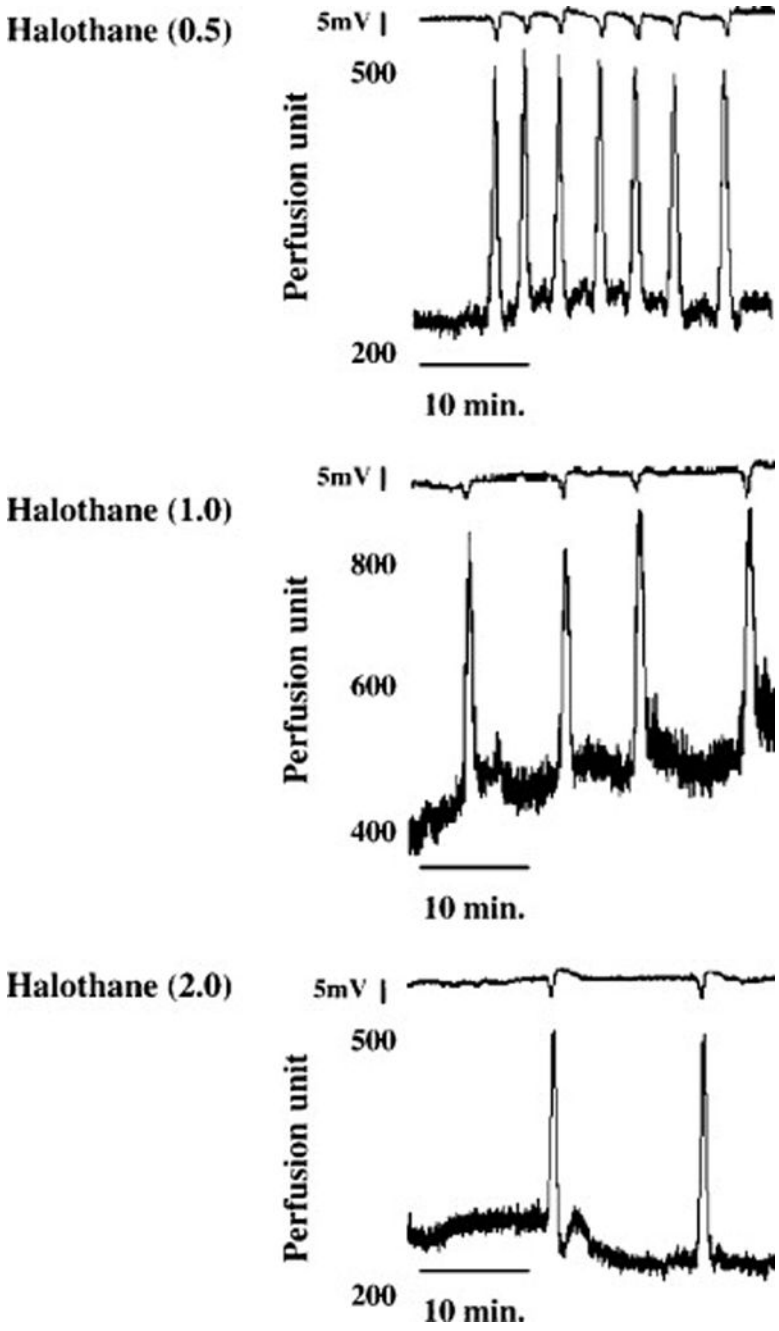

Figure 1.

Representative tracings of direct current deflections in mV (smaller tracings) and cerebral blood flow changes (CBF; larger tracings) associated with repeated, spontaneous CSDs. CSDs were elicited by the presence of a surgical sponge soaked with a KCl solution on the dura mater in rats exposed to 0.5% (0.5; top panel), 1.0% (1.0; middle panel), or 2.0% (2.0; bottom panel) halothane. While numbers of CSDs varied from 27 ± 3, 12 ± 2, and 6 ± 1 per minute with 0.5%, 1.0% and 2.0 % halothane exposure, respectively, the duration and amplitude of the DC deflections and the peak changes in CBF were not different among groups (n=8 for each group). From Horiguchi *et al*. (2005a), with permission.

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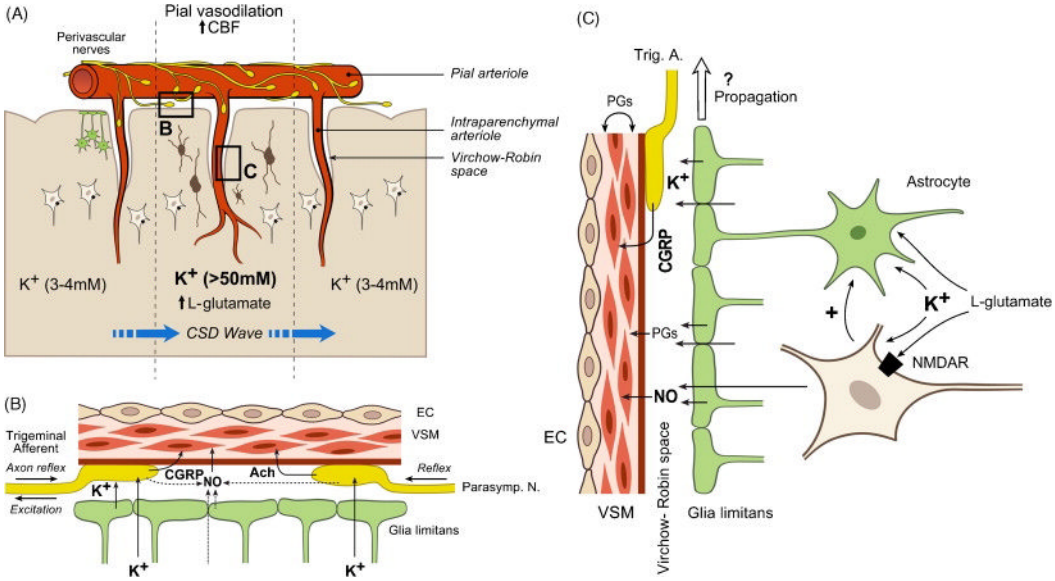

Figure 2. Schematic demonstrating possible mechanisms involved in integrated cerebral vascular dilator responses to CSD

A. Overview of neurovascular unit showing perivascular innervation, astroglia projecting end feet to the pial surface, NMDA receptor neurons (lower cells), and interneurons (dark cells). NMDA receptor containing neurons may also contain neuronal NOS (nNOS) or alternatively activate nNOS containing interneurons. **B.** The major dilator influences on pial arteries and arterioles. The major dilator agents are calcitonin gene-related peptide (CGRP) release by trigeminal afferents and acetylcholine (Ach) released from perivascular nerves and nitric oxide (NO) derived from neural sources (perivascular nerves or parenchyma). In each species studied the relative importance of each type of vasoactive influence appears to vary. In addition, the pathophysiological and pharmacological status of the animal would affect the relative importance of each component. **C.** The major vasoactive influences on parenchymal arterioles. In addition to neurotransmitters such as CGRP from trigeminal afferents and neuronally-derived NO promoting dilation, vascular and perivascular prostaglandins will reduce constriction in parenchymal as well as pial resistance vessels (not shown) during CSD. In addition, parenchymal-derived prostaglandins will promote vasoconstriction during the post CSD period. Upstream propagation of arterial dilation may involve perivascular nerves or other vascular components as well as well as substances released from glial end feet, although flow dependent dilation in the “classical” case probably does not occur for reasons stated in the text. Abbreviations: EC, endothelial cell; VSM, vascular smooth muscle cell; NMDAR, NMDA receptor; Trig. A.,Trigeminal afferent; Parasymp. N., Parasympathetic nerve.

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Table 1

Vasoactive stimuli and cerebral vascular tone during CSD

Year	Investigators	Preparation	Species	Observation
A. Basic Characteristics				
1944	Leão	Cranial Window	Rabbit	Dilation Only
1952	Van Harreveld & Stamm	Cortical photocell	Rabbit	Vasoconstriction
1956	Van Harreveld & Ochs	Frozen cortical sections	Rabbit, Cat	Vasoconstriction followed by dilation in rabbit, dilation only in cat
1980	Hansen *et al*.	^{14}C iodoantipyrine	Rat	Hyperemia following increased extracellular potassium
1981	Mies *et al*.	^{131}I iodoantipyrine ^{14}C deoxyglucose	Rat	Coupled CBF and metabolism
1981	Olesen *et al.*	^{133}Xenon	Human	Hyperemia followed by oligemia with migraine
1982	Lauritzen *et al.*	^{14}C iodoantipyrine	Rat	Hyperemia followed by oligemia
1983a	Lauritzen *et al.*	^{133}Xenon	Human	Reduced CBF responsiveness to hypercapnia during induced migraines
1983b	Lauritzen *et al.*	^{133}Xenon	Human	Oligemia following migraine
1984	Mies and Paschen	^{14}C iodoantipyrine	Rat	Dilation with reduced ATP levels
1984	Lauritzen	^{14}C iodoantipyrine	Rat	Oligemia with reduced CO_2 responsiveness but preserved autoregulation
1986	Lauritzen & Diemer	^{14}C iodoantipyrine	Rat	Reduced CBF with intact metabolic rate (^{14}C-deoxyglucose)
1987a	Lauritzen	^{14}C iodoantipyrine	Rat	Increased CBF which is resting CBF dependent
1987	Wahl *et al*.	Cranial window	Rat, Cat	Post CSD vasoconstriction in rat but not cat, reduced responsiveness to constrictor and dilator stimuli
1990	Shibata *et al*.	Cranial Window	Rabbit	Dilation of pial arteries and arterioles
1991	Piper *et al*.	Laser Doppler	Cat	Hyperemia followed by oligemia, reduced CO_2 responsiveness
1991	Mayevsky & Weiss	^{14}C Iodoantipyrine	Rat	Hyperemia, oxygen delivery matched to metabolic need
1991	Duckrow	^{14}C Iodoantipyrine	Rat	Different rCBF patterns in awake or anesthetized animals
1992	Shibata *et al*.	Cranial Window	Rabbit	Hyperemia, oligemia in some but not all animals
1992	Lacombe *et al.*	Mass spectrometry	Rat	Hyperemia, oligemia, and reduction in post-CSD CO_2 responsiveness
1992	Mraovitch *et al*	^{14}C iodoantipyrine ^{14}C deoxyglucose	Rat	Long lasting cerebrovascular and metabolic changes in brainstem
1993	Fabricius & Lauritzen	^{14}C iodoantipyrine	Rat	Post-CSD oligemia
1993	Busija & Meng	Cranial window	Rabbit	Post-CSD responsiveness intact
1994	Florence et al.	Laser Doppler	Rabbit	Post-CSD response to hypotension and hypercapnia reduced
1994	Lambert & Michalicek	Laser Doppler	Cat	Reduced meningeal blood flow
1995	Fabricius *et al.*	Laser Doppler	Rat	Brief hypoperfusion, hyperemia, and prolonged oligemia L-arginine restored normal response to hypercapnia
1995	Lauritzen & Fabricius	LDPI	Rat	Increased blood flow is segment-dependent
1996	Shimazawa & Hara	Laser Doppler	Rat	Vasoactive responses are similar in awake animals
1997	Wolf *et al*.	Laser Doppler	Rat	Dilation unaffected by hyperglycemia
2000b	Shimizu	Laser Doppler	Rat	CBF increases restricted by cortical but not subcortical infarcts
2001	Dunn *et al.*	Laser Speckle	Rat	2-3 mm area of increased CBF

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Year	Investigators	Preparation	Species	Observation
2002	Shimizu *et al.*	Laser Dopppler	Rat	Cerebral hyperemia independent of intact endothelium
2002	Zhang *et al*.	Laser Doppler	Rat	Post-CSD vasoactivity is restored by NO donor
2002	Otsuka *et al.*	Laser Doppler	Rat	Reduced CBF response after venous occlusion, increased infact area
2002	Yokota *et al*	PET	Monkey	Hyperemia without preceding hypoperfusion or oligemia
2002	Dreier *et al*	Laser Doppler	Rat	CSD initiated by endothelin-1 receptor agonist
2003	Otori *et al*.	Laser Doppler/^{14}C Iodoantipyrine	Rat	CBF depression for 3 days, preserves CBF during subsequent MCAO
2004	Sietz *et al*.	Isolated MCA	Rat	Reduced *ex vivo* vasoactivity of MCA by previous CSD
2004	Gursoy-Ozdemir *et al.*	BBB	Rat	Increased MMP-9 activity increases BBB permeability
2004	Ayata *et al.*	Laser Speckle	Mouse	Initial pronounced hypoperfusion and return to baseline CBF
			Rat	Initial mild hypoperfusion followed by hyperemia
2005	Tomita *et al.*	Capillary Flow	Rat	CSD-induced astoglial swelling stops capillary flow and triggers increased flow
2006	Sonn and Mayevsky	Laser Doppler	Rat	CBF increases in awake and anesthetized animals
2006	Scheckenbach *et al.*	Laser Doppler	Rat	Restoration of post-CSD reactivity by exogenous NO or cGMP
2006	Akin & Bilensoy	fNIRS	Human	Reduced CBF to hypercapnia associated with migraines
2007	Shin *et al.*	Cranial Window	Mouse	CSD-hypoperfusion unaffected by cerebral amyloid deposition
2007	Brennan *et al.*	Cranial Window	Mouse	Dilation, constriction, followed by persistent dilation
			Rat	Dilation followed by persistent constriction
2007	Takano *et al*.	Two photon imaging	Mouse	Prolonged dilation of pial and parenchymal arterioles followed by oligemia, tissue hypoxia and neuronal swelling
2007	Chuquet *et al.*	Two photon imaging	P15 Rat	Constriction of pial and parenchymal arterioles followed by differential responses
2008	Sukhotinsky *et al*.	Laser Doppler	Rat	Hypoxia and hypotension convert hyperemia to reduction in CBF
2008	von Baumgarten *et al.*	Contusion volume	Mice	Unaffected by post trauma CSDs

B. Mediators of Vascular Responses

Year	Investigators	Preparation	Species	Approach	Effect
1987	Lauritzen	^{14}C iodoantipyrine	Rat	Indomethacin	Increased CBF from reduced baseline
1990	Shibata *et al*.	Cranial Window	Rabbit	Indomethacin	Enhanced dilation from same baseline
1991	Duckrow	^{14}C iodoantipyrine	Awake rat	Indomethacin	Increased CBF from reduced baseline
1991a	Shibata *et al*.	Cranial Window	Rabbit	Superfusion with aCSF	Fails to reduce arterial dilation
1991b	Shibata *et al*.	Cranial Window/Laser Doppler	Rabbit	Indomethacin	Enhanced dilation/increased CBF
1992	Shibata *et al*.	Cranial Window	Rabbit	Indomethacin	Enhanced dilation and prevention of post-CSD oligemia
				Superfusion with aCSF	Prevented post-CSD oligemia
1992	Goadsby *et al*.	Laser Doppler CBF	Cat	NOS inhibition	Complete blockade of CBF increase
1992	Goadsby	Laser Doppler	Cat	Tirilazad	Lack of ROS contribution
1992	Duckrow & Beard	^{14}C iodoantipyrine	Rat	Tirilazad	Lack of ROS contribution
1993	Duckrow	^{14}C iodoantipyrine	Awake Rat	NOS inhibition	Uncovered brief hypoperfusion

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Year	Investigators	Preparation	Species	Observation	
1993	Piper *et al*.	Exernal Jugular Vein	Cat	Sampling for CGRP	No detectable CGRP in venous blood
1994a	Colonna *et al.*	Cranial Window	Rabbit	CGRP receptor blockade	Decreased dilation by 39%
1994b	Colonna *et al.*	Cranial Window	Rabbit	NOS inhibition	Reduced dilation by 50%
1994	Wahl *et al*.	Cranial Window	Cat	CGRP Receptor blockade	Decreased dilation 50%
				NOS inhibition	Decreased dilation by 50%
				Combined inhibition/blockade	Decreased dilation by 75%
1994	Zhang *et al*.	CBF	Rat	NOS inhibition	No effect
1994	Fabricius *et al*	Laser Doppler	Rat	Topical/intravenous NOS inhibition	Enhanced hyperemia
1995	Meng *et al.*	Cranial Window	Rabbit	Indomethacin	Blocks effects of NOS inhibition
1995	Fabricius *et al.*	Laser Doppler	Rat	NOS inhibition	Potentiated hypoperfusion and oligemia but not hyperemia
				L-Arginine administration	Accentuated hypoperfusion but no effect on hyperperfusion; accelerated return of responsiveness
				Tetrodotoxin	Accentuated hypoperfusion but no effect on hyperperfusion
1996a	Goadsby *et al*.	Laser Doppler	Cat	Endothelin receptor antagonist	No effect on oligemia
1996	Meng & Busija	Cranial Window	Rabbit	ROS scavenger	No effect
1996	Wolf *et al*.	Laser Doppler	Rat	NOS inhibition	No effect
1997	Colonna *et al.*	Microspheres	Rabbit	Specific nNOS inhibition	Decreased CBF by 36%
1997	Reid et al	NO electrode	Cat	NOS inhibition	Reduced NO production
		Laser Doppler		NOS inhibition	Reduced hyperemia
1998	Reuter *et al*.	Laser Doppler	Rat	Acute nasociliary nerve section	No effect
				Chronic nasociliary nerve section	Reduced CBF by 23%
				Chronic nasociliary and parasympathetic nerve section	Reduced CBF by 55%
				Muscarinic receptor blockade	Reduced CBF by 41%
				CGRP receptor blockade	Reduced CBF by 49%
				Combined muscarinic and CGRP receptor blockade	Reduces CBF by 69%
1998	Read & Parsons	NO electrode	Rat	NOS inhibition	Increased NO blocked
		Laser Doppler		NOS inhibition	No reduction in CBF
1998	Gold *et al*.	Laser Doppler	Rat	Serotonin receptor blockers	Reduced cerebral hyperemia
1998	Dreier *et al*.	Laser Doppler	Rat	NOS inhibition	Reduction in CBF
1999	Kaube *et al*.	Laser Doppler	Cat	Amyl nitrite and isoproterenol application	No effect
2000	Bari *et al.*	Laser Doppler	Rat	Topical or intravenous capsaicin	Reduced CBF
2000a	Shimizu *et al.*	Laser Doppler	Rat	Glibenclamide	Enhanced increase in CBF
				Indomethacin	No effect
2000b	Shimizu *et al.*	Laser Doppler	Rat	NOS inhibition	No effect on CBF
2000	Read & Parsons	NO electrode	Rat/Cat	Sumatriptan	Reduced NO levels
		O_2 electrode	Rat/Cat	Sumatriptan	Low O_2 levels during CSD
2002	Shimizu *et al.*	Laser Doppler CBF	Rat	Indomethacin, miconazole,	No effect
				NOS inhibition	No effect
				Endothelial “stunning”	No effect
				Dietary insulin resistance	No effect
2002	Obrenovitch *et al*.	NO microdialysis	Rat	NOS inhibition	Prolonged NO production occurs during CSD
2004	Ayata *et al.*	Laser Speckle	Mouse	NOS inhibition	Reduced normalization of CBF
				Specific nNOS inhibition	No effect
2005	Horiguchi *et al*.	Laser Doppler	Rat	Adenosine-1 receptor blocker	Enhanced CBF increase
2007	Shin *et al.*	Cranial Window	Mouse	Cerebral amyloid deposition	CSD-hypoperfusion unaffected
2008	Petzold *et al*.	Brain slices	Mouse, Rat Human	NOS inhibition	CSD threshold maintained by endothelial NO

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Year	Investigators	Preparation	Species	Observation

CSD, cortical spreading depression; fNIRS, near-infrared spectroscopy; NO, nitric oxide; NOS, nitric oxide synthase; nNOS, neuronal nitric oxide synthase; ROS, reactive oxygen species; CGRP, calcitonin gene-related peptide; CBF, cerebral blood flow; MMP-9, metalloproteinase-9; MCAO, middle cerebral artery occlusion; BBB, blood brain barrier; LPDI, laser-Doppler perfusion imaging; aCSF, artificial cerebral spinal fluid.

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