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Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought

Ryszard M. Pluta, **Jacob Hansen-Schwartz**, **Jens Dreier**, **Peter Vajkoczy**, **R. Loch Macdonald**, **Shigeru Nishizawa**, **Hideotoshi Kasuya**, **George Wellman**, **Emanuela Keller**, **Alois Zauner**, **Nicholas Dorsch**, **Joseph Clark**, **Shigeki Ono**, **Talat Kiris**, **Peter LeRoux**, and **John H. Zhang**

Abstract

Objective—Delayed cerebral vasospasm has long been recognized as an important cause of poor outcome after an otherwise successful treatment of a ruptured intracranial aneurysm, but it remains a pathophysiological enigma despite intensive research for more than half a century.

Method—Summarized in this review are highlights of research from North America, Europe and Asia reflecting recent advances in the understanding of delayed ischemic deficit.

Result—It will focus on current accepted mechanisms and on new frontiers in vasospasm research.

Conclusion—A key issue is the recognition of events other than arterial narrowing such as early brain injury and cortical spreading depression and of their contribution to overall mortality and morbidity.

Keywords

Early brain injury; subarachnoid hemorrhage; vasospasm

INTRODUCTION

> When persons in good health are suddenly seized with pains in the head, and straightway are laid down speechless, and breathe with stertor, they die in seven days.
>
> Hippocrates 460–370 BC, *Aphorisms on Apoplexy*[1]

Hippocrates' 2400-year-old description of delayed death probably caused by a ruptured intracranial aneurysm with subsequent vasospasm is still valid today. Aneurysmal subarachnoid hemorrhage (SAH) affects about 10 out of 100,000 adults annually, and up to half of those affected die soon after[2]; most of the rest are successfully treated surgically and/or endovascularly. Despite obliterating the offending aneurysm and removing the risk of rebleeding, up to half of the treated patients develop a syndrome of focal and/or cognitive deficits due to cerebral vasospasm (delayed ischemic neurological deficit, symptomatic vasospasm) between the fourth and ninth day after the SAH[3]. As a result, many die or suffer permanent morbidity[2], and it has been described as the single most important cause of morbidity and mortality in patients whose ruptured aneurysm is successfully treated[4].

Patients require vigilant monitoring and treatment for up to 2 weeks, including invasive monitoring of blood pressure, cerebral blood flow and metabolism and often complex treatment

Correspondence and reprint requests to: J. H. Zhang, Department of Neurosurgery, Loma Linda University Medical Center, Room 2562B, 11234 Anderson Street, Loma Linda, CA 92354, USA. [E-mail: johnzhang3910@yahoo.com].

with calcium antagonists, hypertensive drugs, hemodilution and hypervolemia (triple H therapy), plus risky and often only temporarily effective intra-arterial administration of vasodilator drugs or balloon angioplasty[5]. These treatments have been documented in nine international conferences on cerebral vasospasm (Table 1).

Since the demonstration of arterial narrowing in the syndrome of cerebral vasospasm in 1951[6] and the further emphasis in 1978 by Weir *et al.*[3], it has been proven that SAH gives rise to arterial narrowing and in turn ischemia, causing infarction and poor outcome. Most research into delayed deterioration after SAH has been conducted in concordance with this axiom, with the goal of interrupting this perceived chain of events. There have been many clinical trials, but until the arrival of clazosentan, a selective endothelin 1A receptor antagonist, it has not been possible to reproducibly break this chain. Clazosentan did, however, effectively prevent and reverse arterial narrowing in one work[7], providing what was thought may at last be an effective treatment. However, the subsequent multi-center CONSCIOUS trial, despite significant reductions in angiographic vasospasm, failed to show any effect on long-term outcome.

The axiom has thus been challenged in such a fashion that it amounts to a paradigm shift.

Accumulated evidence suggests that (1) arterial narrowing is not the only cause of delayed clinical deterioration, (2) arterial narrowing is not necessarily multifactorial but (3) may actually be an effect of a single factor and finally (4) the entire picture of delayed clinical deterioration may be multifactorial. These facts should lead to a search for a more comprehensive and adequate theory that not only can explain observed discrepancies but also will lead to development of a specific and effective treatment strategy.

In recent years, two major concepts in pre-vasospasm research have developed: early brain injury and cortical spreading depression. Basic animal works and some clinical observations have long pointed to the importance of the pre-vasospasm period, with recognition of the importance of transitory ischemia at the onset of SAH [8], the opening of the blood–brain barrier[9,10], the existence of early arterial narrowing in clinical settings[11] and the detection of cortical spreading ischemia after SAH[12]. One or more of these events may replace arterial narrowing as important causes of poor outcomes after SAH[13].

PATHOPHYSIOLOGY OF ARTERIAL NARROWING: NEW DEVELOPMENTS

The idea of arterial narrowing has previously been central to understanding the syndrome of cerebral vasospasm, but as outlined above, a paradigm shift is underway. Even so, the association of arterial narrowing with delayed ischemic deficits and the fact that reversal of narrowing by angioplasty can reverse deficits make consideration of pathophysiological events in cerebral arteries still very relevant, as shown in several reviews. Highlights of recent developments are presented below.

Hemoglobin

Ferrous hemoglobin released from subarachnoid clot undoubtedly leads to delayed arterial narrowing by mechanisms, which are multiple and poorly understood. Possibilities include neuronal apoptosis[14], scavenging or decreased production of nitric oxide (NO)[15], increased endothelin 1 levels[16], direct oxidative stress on smooth muscle cells[13], free radical production and lipid peroxidation of cell membranes[17], modification of potassium and calcium channels[18] and differential up-regulation of genes[19,20].

Recent research has focused on oxidative stress as causing or contributing to vasospasm, possibly via direct activation of calcium channels in smooth muscle cells as well as on

vasoactive proteins[21] or through covalent modification by reactive oxygen species producing vasoactive molecules. For example, reactive oxygen species may act on arachidonic acid to produce vasoactive lipids, which in turn may contribute to vessel contraction. The lack of success of antioxidants such as tirilazad makes non-specific oxidation unlikely[22]. Other possible vasoactive compounds are bilirubin oxidation products (Figure 1), synthesized by the oxidation associated with oxidative stress. However, the location of the oxidations leading to the production of bilirubin oxidation products is unclear. It could be speculated that lysed blood cells are phagocytosed by lymphocytes, with resultant heme or bilirubin release after lysosomatic breakdown. In such a scenario, antioxidants that primarily target membranes would have relative little effect[22].

Oxidative stress in the subarachnoid space has also been reported to activate protein kinase C and Rho kinase, leading to smooth muscle cell constriction. Rho kinase initiates vascular contraction through protein kinase Cδ activity (Figure 2), which also induces proliferation and growth of vascular smooth muscle cells, a possible mechanism for the phenotypic change and remodeling of vascular smooth muscle seen in vasospasm[23]. Further support for a reorganization hypothesis comes from observations of increased β-actin messenger RNA (mRNA), of structural change in the 3′ untranslated region of β-actin mRNA and of induction of the embryonal isoform of myosin heavy chain accompanied by a decrease in the expression of smooth muscle myosin heavy chain in arteries in spasm[23]. Histological morphometric analysis also showed an increase in the area of the arterial wall without changes in the number of nuclei of smooth muscle cells[24]. Therapy for cerebral vasospasm may thus also need to address cerebral vascular remodeling.

Endothelin 1

The potent vasoconstricting peptide endothelin 1 was isolated from pig endothelial cells in 1988[25], and elevated endothelin 1 levels in the cerebrospinal fluid of patients and animals with vasospasm were soon reported[16,26,27]. This basic observation was supported by a number of experimental results. Oxyhemoglobin causes an increase in endothelin 1 synthesis from endothelial cells[28], astrocytes may synthesize endothelin 1 in response to ischemia[26] and leucocytes that have infiltrated the subarachnoid space after SAH may produce endothelin 1[29]. Furthermore, cerebral arteries may become more sensitive to endothelin 1, leading to increased cerebrovascular tone even in the absence of an increase in endothelin 1[30]. These findings provided the impetus for trials of endothelin receptor antagonists[7]. A phase II study of the endothelin receptor antagonist clazosentan in aneurysmal SAH randomized 413 patients, well balanced for prognostic factors. Moderate to severe angiographic vasospasm was significantly reduced in a dose-dependent manner from 66% in the placebo group to 36% in the high-dose clazosentan group. Despite this reduction, there was no significant effect on outcome based on the modified Rankin scale at 3 months[31]. Why this efficacy against angiographic vasospasm did not translate into improved outcome is a key question and a fundamental reason for the paradigm shift necessary to produce a more complete understanding of cerebral vasospasm and delayed deterioration.

Nitric oxide

Inhibition of relaxation can also cause or contribute to arterial narrowing because of the basic myogenic tone of cerebral arteries. Hence, the fate of NO (a powerful endogenous vasodilator) has attracted interest. The disappearance of neuronal NO synthase immunoreactivity from arteries in spasm, endothelial NO synthase dysfunction in cerebral vessels after SAH and the affinity for NO of the heme moiety in hemoglobin (‘NO sink effect’) suggest a role for NO depletion in the pathophysiology of arterial narrowing (Figure 3)[15]. New strategies for NO-based therapy against vasospasm include gene therapy[32,33] preclinical and early clinical trials

of NO donors administered intra-arterially[34], intrathecally[35], locally[36,37] or intravenously[38].

In terms of genetic predisposition in the NO synthase system, Khurana *et al.*[39] reported that the endothelial NO synthase T-786C single-nucleotide polymorphism, associated with a significant reduction in endothelial NO synthase gene promoter activity, was significantly more common in patients with cerebral vasospasm. Another development in relation to NO synthase is the statins, which improve endothelial function by up-regulating endothelial NO synthase expression[40]. A threefold increase in endothelial NO synthase mRNA, protein and enzymatic activity has been demonstrated following statin treatment, resulting in an increase in cerebral blood flow[41,42]. Statin treatment has attenuated cerebral vasospasm and prevented delayed ischemic deficits in a murine SAH model[40]. In a retrospective series, patients who received statin therapy for at least 1 month before SAH demonstrated an 11-fold decrease in the risk of developing symptomatic vasospasm after SAH[43]. In recent prospective, double-blind, randomized placebo-controlled clinical trials of statins given for 14 days after SAH, the incidence of symptomatic cerebral vasospasm was significantly reduced in treated patients[44,45].

Membrane pathology

Small diameter cerebral arteries (<200 μm) play important roles in the autoregulation of cerebral blood flow, matching local blood supply in the brain to neuronal activity (Figure 4)[46]. Although angiography, which can assess arteries >1 mm in diameter, has long been the standard to diagnose vasospasm[47], constriction of small cerebral arteries may also contribute to ischemia after SAH[21,48–51].

The concentration of free intracellular Ca^{2+} ($[Ca^{2+}]_i$), and thus the contractile state of smooth muscle cells in cerebral resistance arteries, is determined primarily by Ca^{2+} influx through voltage-dependent Ca^{2+} channels[52], the open-state probability of which is dictated by the membrane potential of the smooth muscle cells[53]. Following SAH, changes have been reported in the electrical properties of smooth muscle cells of small diameter cerebral arteries leading to enhanced Ca^{2+} influx, with vasoconstriction and decreased cerebral blood flow[54]. Cerebral arteries from healthy animals express only L-type voltage-dependent Ca^{2+} channels encoded by the gene Ca_V 1.2. Expression of an additional type of voltage-dependent Ca^{2+} channels (R-type, Ca_V 2.3) occurs after SAH, leading to increased Ca^{2+} channel density, increased Ca^{2+} influx and vasoconstriction[55].

After SAH, calcium entry is further enhanced by membrane depolarization[54,56]. Oxyhemoglobin causes suppression of the voltage-dependent K^+ channel (K_V) current in cerebral artery smooth muscle cells through a mechanism involving tyrosine kinase-mediated channel endocytosis[55]. Decreased activity of large conductance calcium-activated K^+ channels may also contribute to membrane depolarization via potential mechanisms, such as a decrease in Ca^{2+} spark frequency[57] and increased production of the cytochrome P450 metabolite 20-hydroxyarachidonic acid[58]. This combination of increased voltage-dependent Ca^{2+} channel density and membrane depolarization will increase $[Ca^{2+}]_i$ and lead to vasoconstriction. At the same time, decreased sensitivity of voltage-dependent Ca^{2+} channels s to L-type Ca^{2+} channel antagonists[55] may limit the utility of agents, such as nimodipine, in the treatment of arterial narrowing. Targeting voltage-dependent Ca^{2+} channels and K^+ channels in small diameter cerebral arteries may lead to safer and more effective treatments for SAH.

NEW FRONTIERS OF CEREBRAL VASOSPASM RESEARCH

Acute and early changes after aneurysmal SAH

One of the most important advances in recent years is the recognition of early brain injury after SAH, from the impact of the initial bleed and its detrimental effect on patient outcome. The term early brain injury has only recently been coined and refers to the injury to the brain as a whole within the first 72 hours after the ictus[59], i.e. before the development of vasospasm. This early brain injury includes an elevation of intracranial pressure, a global reduction of cerebral blood flow, blood–brain barrier disruption, brain edema and neuronal cell death.

Decreased perfusion pressure after SAH was reported in patients by Nornes[8], but its influence on outcome has only recently been recognized. The initial event of intracranial aneurysm rupture is the stop flow phenomenon[14], with an acute transient global cerebral ischemia, which may itself be lethal[2]. When the patient survives, there may be a secondary ischemic insult due to blood–brain barrier disruption[60] progressing to global cerebral edema[61] or to delayed neuronal apoptosis[14]. Brain edema contributes to a further rise in intracranial pressure[13] and thus a further reduction of cerebral blood flow. The mechanism of blood–brain abrrier disruption is unclear, but apoptosis affecting the brain and arteries may be involved[13,60].

Cortical spreading depression

In experimental works by Dreier *et al.*[62], fluid with a composition similar to the cerebrospinal fluid after SAH was applied in the subarachnoid space. This induced spreading depolarization waves over the cortex, which in turn triggered spreading microvascular spasm and spreading ischemia[62], leading to widespread cortical necrosis[12]. This pathomorphological finding corresponds with autopsy works of non-operated SAH patients, in which 80% of fatal cases showed widely scattered triangular, round or laminar ischemic cortical lesions, 13 times more common than infarcts in the territories of large arteries[63,64]. In a clinical work of 18 patients undergoing craniotomy for hematoma evacuation or aneurysm treatment following aneurysmal SAH[65], 13 showed waves of spreading depolarization. In several patients, clusters of spreading depolarizations occurred at the onset of neurological deterioration, and in some, prolonged periods of depressed electrocorticographic activity were followed by radiographic evidence of ischemia. There is thus clinical evidence for the first part of the ‘spreading ischemia theory’ of cortical infarcts after SAH, i.e. association with a cluster of spreading depolarizations (Figure 5). The decisive second part of the hypothesis, that a marked *propagating* decrease of cortical blood flow occurs in conjunction with spreading depolarizations and leads to delayed infarcts, remains open.

It is assumed that breakdown products of erythrocytes in the subarachnoid space induce delayed neurological deficits after SAH, based on observations that the risk of developing delayed neurological deficits correlates with the amount of blood in the initial computed axial tomography scan and that its onset coincides with the time of peak subarachnoid hemolysis in the primate model of SAH. According to the double hit model (Figure 5), breakdown products of erythrocytes have four major synergistic pathological effects: They induce chronic vasospasm of (1) proximal cerebral arteries and (2) the microcirculation; (3) they promote spreading depolarizations via chronic vasospasm/energy depletion, increase of the baseline extracellular K^+ concentration and endothelin 1 and a decrease of NO; (4) they invert the coupling between spreading depolarization of the cortex and cerebral blood flow by direct effects ($K^+ \uparrow$, NO↓) and indirectly via chronic vasospasm/energy depletion. Consistently with the double hit model, it was recently shown using subdural electrodes that delayed ischemic infarcts in SAH patients are preceded and accompanied by clusters of spreading depolarizations with prolonged depression periods[65]. There is still no direct evidence of spreading ischemia in the human brain. Spreading depolarization is an energy-demanding perturbation of brain

cortical ion homeostasis and energy metabolism; in response to this demand, cerebral blood flow rises during spreading depolarization under physiological conditions. However, in the presence of breakdown products of erythrocytes in rats[12,62], as well as in the ischemic penumbra after middle cerebral artery occlusion in mice[66], spreading depolarization induces severe acute microarterial spasm and spreading ischemia, rather than microarterial dilation and spreading hyperemia. This process is called 'inverse coupling'[12,62]. Spreading ischemia is associated with virtual disappearance of the pial circulation for periods of minutes or hours and leads to widespread cortical infarcts in these rat experiments[12].

TREATMENT OF VASOSPASM

The importance of the therapeutic approach of multimodality treatment is stressed

Delayed neurological deficits after aneurysmal SAH are not caused by one single factor and therefore cannot be expected to be prevented or reversed by a single treatment such as clazosentan. Clinical trials have shown promising results for the cisternal placement of controlled-release nicardipine or papaverine pellets, for intravenous magnesium sulfate, for oral pravastatin or simvastatin, for lumbar cerebrospinal fluid drainage and for lamina terminalis fenestration[67–69]. There have been reports on variations of the head shaking technique with cisternal lavage, enoxaparin, cervical sympathetic block, aortic balloon counterpulsation or partial blockage and nitroglycerine patches[5]. Many of these works showed significantly reduced delayed neurological deficits and/or lower mortality.

Systemic: fasudil and multimodal therapy

Intra-arterial fasudil hydrochloride (a Rho-kinase inhibitor) is part of the multimodal therapy after SAH in Japan[70], along with cisternal urokinase injection[71], drainage of subarachnoid clots[69] and strict maintenance of general conditions. The result of multimodal treatment with fasudil when compared with patients without multimodal therapy was a decrease in incidence of vasospasm from 57 to 37% with subsequent reduced mortality and improved outcome.

Topical: nicardipine

Clinical trials have tested the efficacy against vasospasm of local prolonged-release nicardipine-loaded polymers[72,73] implanted at the time of aneurysm clipping into the basal cisterns close to the proximal arteries, with the drug being released over 14 days. In the first work, arterial narrowing was completely prevented in arteries surrounded by thick clot. The second work confirmed reductions in vasospasm (73% control versus 7% nicardipine-loaded polymers) and delayed ischemic lesions (47% control versus 14% nicardipine), and the outcome was significantly better. This polymer-based drug-delivery system offers a new and promising treatment approach. However, the lack of drug penetration to areas covered by blood clot is a potential limitation, needing further elucidation for the routine clinical setting.

Intra-arterial: nicardipine/verapamil

Safer endovascular treatments for severe refractory arterial narrowing are now available[74]. In one series of 350 SAH patients, 47 developed severe clinical vasospasm requiring endovascular therapy, including 175 intra-arterial injections of nicardipine (average dose, 6.0 mg; maximum, 22 mg per patient) or verapamil (8.0 mg per vessel, maximum 16 mg per patient) and 49 balloon angioplasties. There was significant improvement after the intra-arterial drug treatment, lasting for 24–48 hours, while balloon angioplasty, mostly (49%) for middle cerebral arteries, was more effective for proximal artery spasm. There were no complications from the angioplasty itself (A Zauner, unpublished data).

CONCLUSION

While our understanding of the pathophysiology of delayed vasospasm has progressed significantly, this knowledge has not been translated into clinically effective treatment. Possible sources of this mismatch include the multifactorial nature of the disease, the use of inadequate animal SAH models (e.g. models that create SAH but do not alter intracranial pressure), the lack of randomization or blinded assessment in many preclinical and some clinical works, underpowered experimental and clinical works, the lack of *a priori* identified inclusion/exclusion criteria and bias toward publication of positive but not negative findings[75]. The results of the phase II international clazosentan study support the concept that linking outcome solely to delayed vasospasm is an oversimplification, focusing attention on vasospasm rather than on patients' well-being (RL Macdonald, unpublished data). This work opens up the question of why the prevention of vasospasm did not translate into improved outcome. It seems clear now that research must focus more on the acute subacute, delayed and late events after aneurysmal SAH and their influence on outcome.

These new developments in the understanding of the pathophysiology of SAH and vasospasm and advances in the treatment, as well as controversies around both pathophysiology and treatment, make it mandatory to 'spread the word' among researchers and clinicians that a widening of interest from delayed arterial narrowing to other SAH-evoked events is now essential. Research on the relationship between all post-hemorrhage events and their contribution to outcome should hasten the development of effective treatment for vasospasm and other events. A crucial element will be the use of improved animal models to help elucidate the contributions of the various mechanisms discussed above, as well as others not specifically addressed in this work such as thromboembolism[76] platelet activation or inflammation, to delayed vasospasm or deterioration after aneurysmal SAH.

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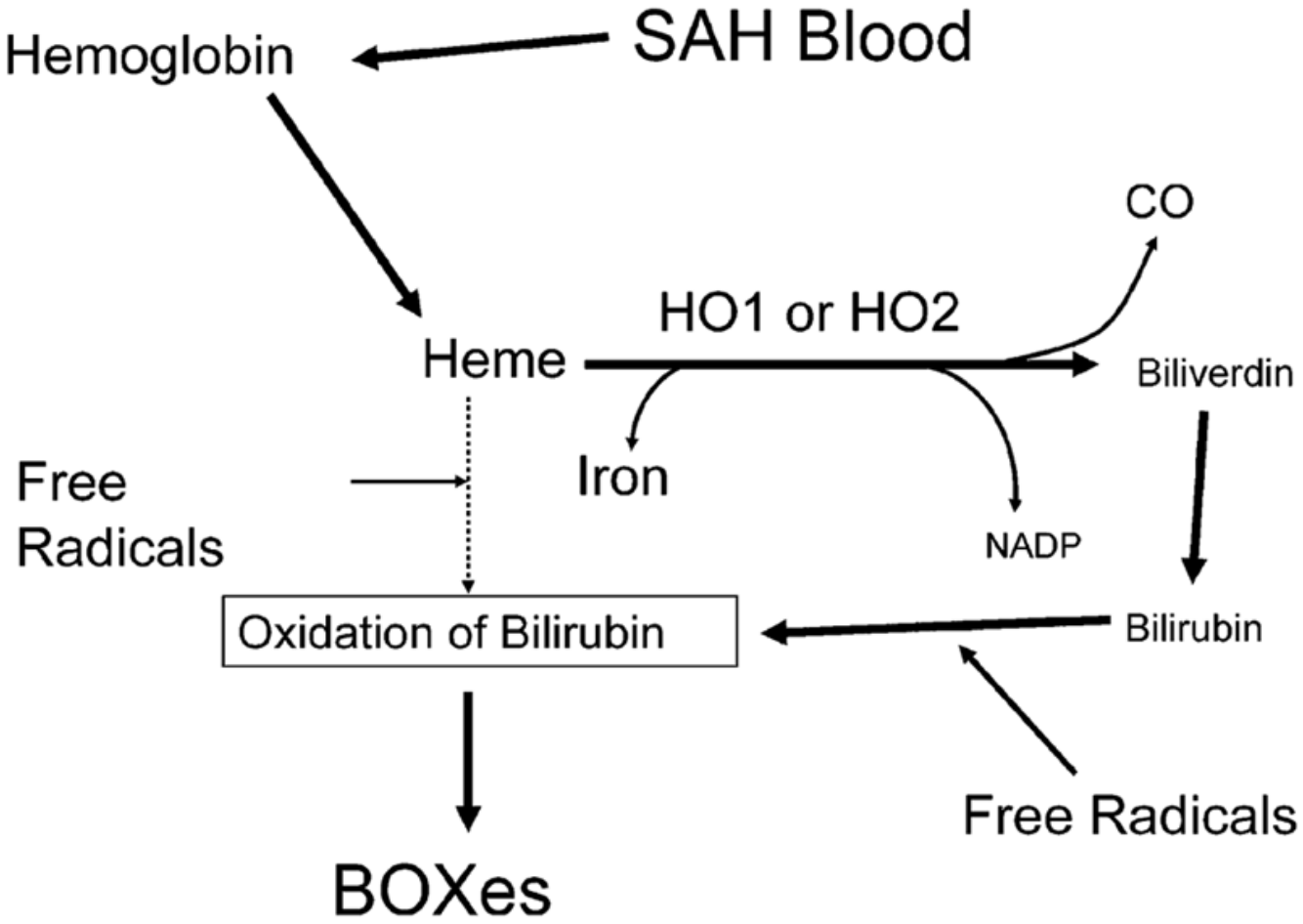

Figure 1.
A putative pathway for the production of bilirubin-oxidized fragments (BOXes) from blood present post-SAH. Key steps are the liberation of heme from blood and oxidation from free radicals. The dotted line between the heme and oxidation of bilirubin is a pathway for the production of BOXes that has not yet been demonstrated

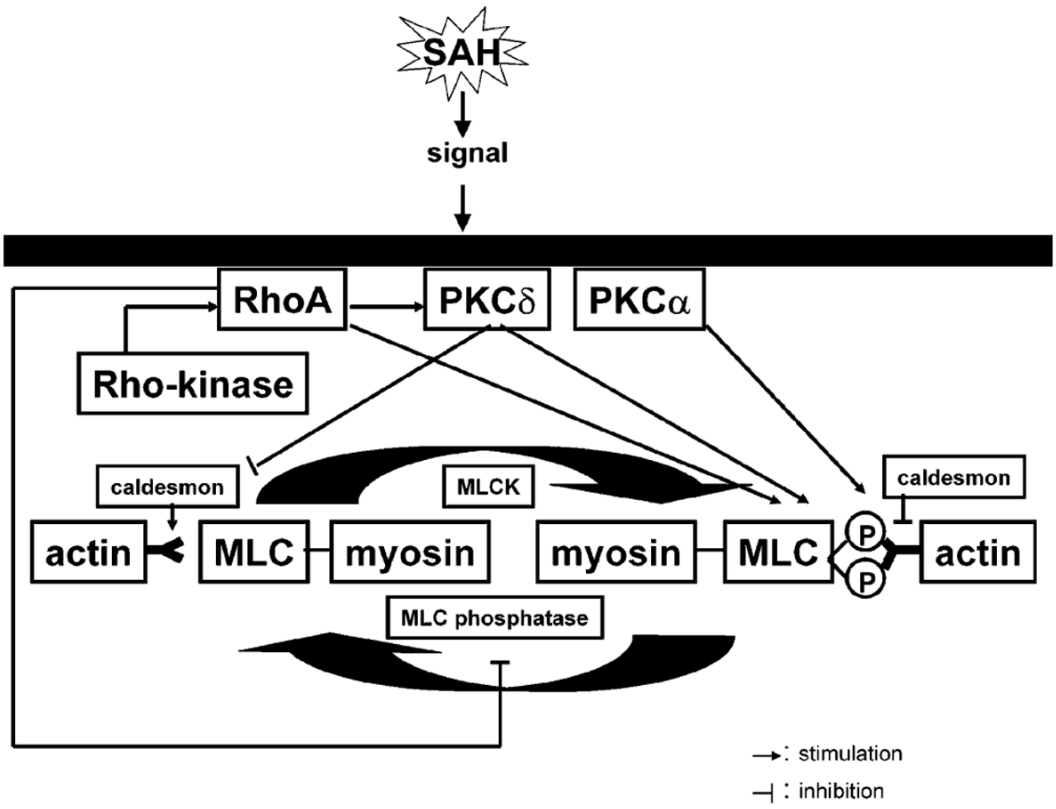

Figure 2.

Relations among Rho kinase, Rho A, PKCI′ and PKCI± for the regulation of myosin and actin in the contraction and relaxation of vascular smooth muscle cells. Rho kinase and Rho A activate myosin light chain (MLC) phosphorylation directly. Rho kinase and Rho A inhibit MLC phosphatase, resulting in long lasting MLC phosphorylation. They also activate PKCI′, which enhances the contraction of vascular smooth muscle cells. PKCI± independently activates the contraction of vascular smooth muscle cells. Caldesmon is an actin-side regulatory protein acting on the detaching between actin and MLC and relaxation of the vascular smooth muscle cells. PKCI′ inhibits the activity of caldesmon through phosphorylates of caldesmon, which causes long lasting interaction between actin and MLC. MLC, myosin light chain; MLCK, myosin light chain kinase; P, phosphorylation; PKC, protein kinase C

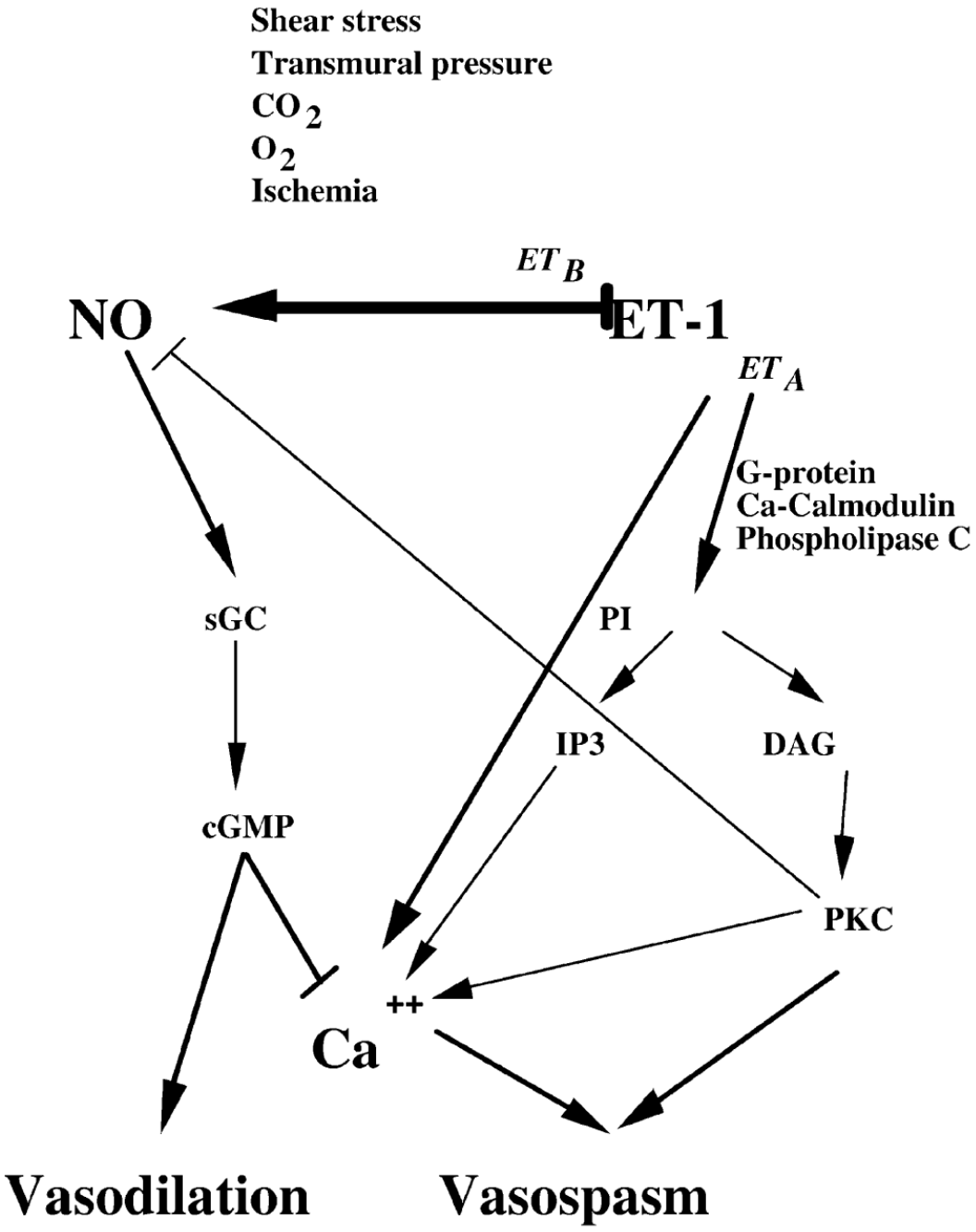

Figure 3.

Signal transduction for nitric oxide (NO) and endothelin 1 (ET-1). These are antagonistic regulators of cerebral blood flow, released from endothelial cells in response to changes in the shear stress, transmural pressure, concentration of CO_2 and O_2, ischemia or presence of hemoglobin. NO (vasodilator) and ET-1 (vasoconstrictor) regulate blood vessel tension via smooth muscle cells. NO, due to its high affinity to the heme moiety (1000 times higher than oxygen), stimulates guany(ly)l cyclase, leading to an increase of 3,5′ cyclic guanosine monophosphate and dephosphorylation of MLCs, smooth muscle cell hyperpolarization and closure of calcium channels resulting in vasodilation and an increase of blood flow. ET-1 is a product of several post-translational modifications of pre-pro-ET-1 and big ET-1. It acts on

smooth muscles via two types of receptors: ETA, present mostly on smooth muscle cells, whose stimulation leads to smooth muscle constriction (paracrine action), and ETB, present mostly on endothelial cells, stimulation of which leads to an increased NO release and to smooth muscle relaxation (endocrine action). ET-1 stimulation of the ETA receptor leads to the formation of diacylglycerol and inositol 1,4,5-triphosphate, which in turn increases the concentration of intracellular calcium directly or via protein kinase C, resulting in vasoconstriction and decrease of blood flow

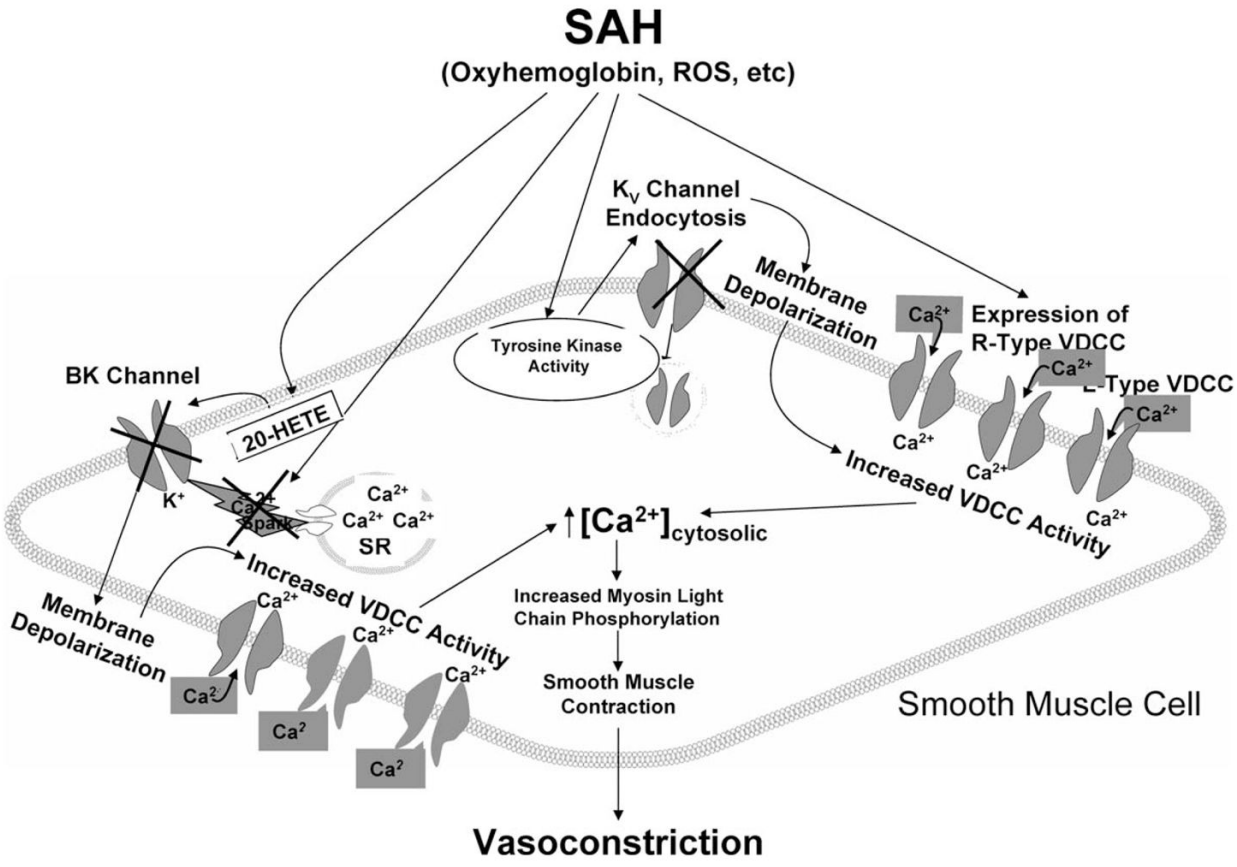

Figure 4.

Potential mechanisms of increased vascular smooth muscle intracellular Ca^{2+} and enhanced contraction of cerebral artery myocytes following SAH. Enhanced Ca^{2+} influx through voltage-dependent Ca^{2+} channels (VDCCs) may result from a combination of increased VDCC expression (L- and R-type) and increased VDCC activity due to membrane depolarization. Mechanisms contributing to depolarization include oxyhemoglobin-induced internalization of voltage-dependent (K_V) K^+ channels and decreased activity of large-conductance Ca^{2+} -activated (BK) K^+ channels due to inhibition of Ca^{2+} sparks and/or increased levels of the cytochrome P450 metabolite 20-hydroxyeicosatetraenoic acid

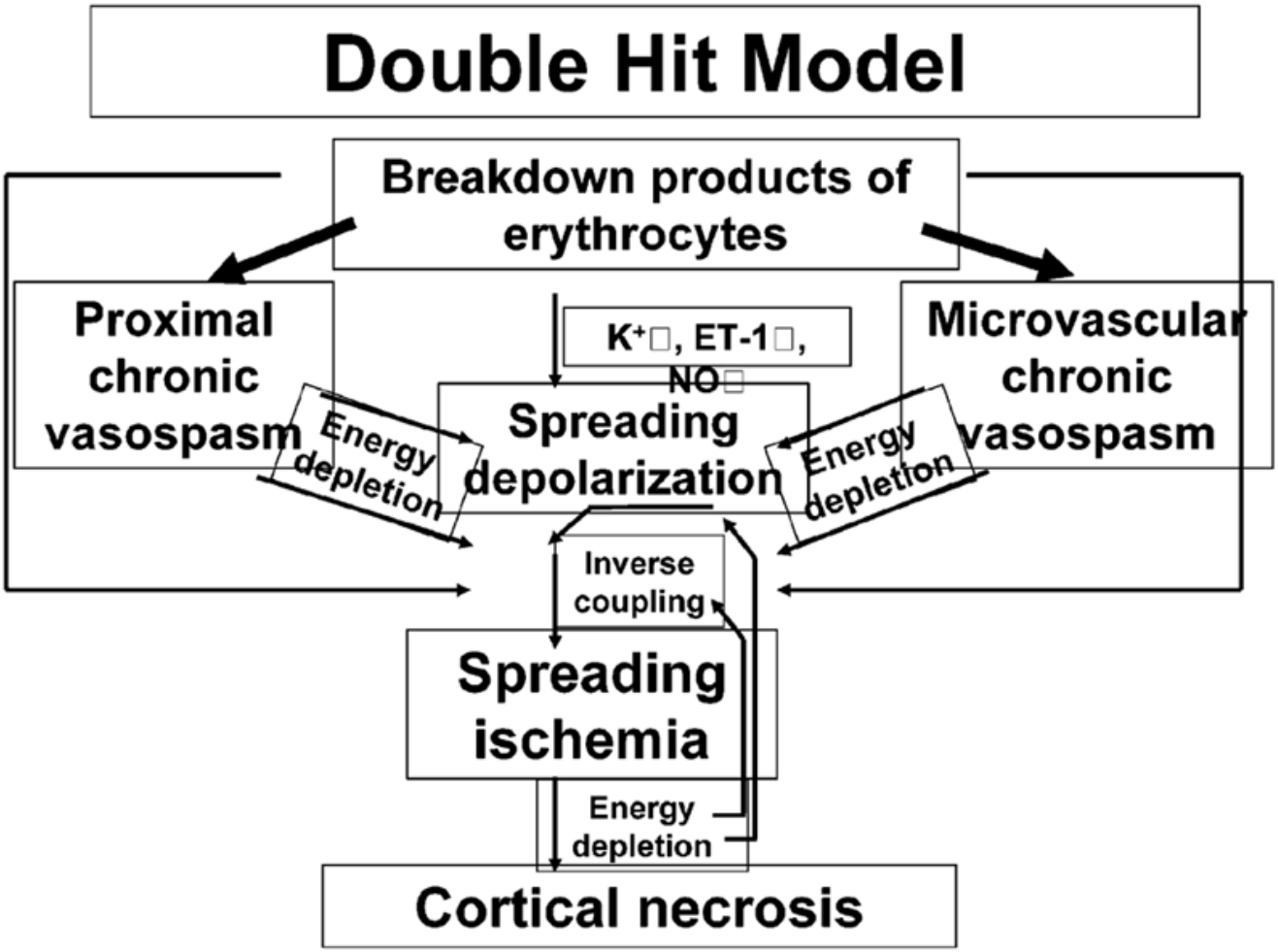

Figure 5.
Double-hit model of delayed ischemic neurological deficits after SAH based on Dreier *et al.* [12]. The two hits on the brain parenchyma consist of acutely triggered microvascular spasm in response to spreading depolarizations, superimposed on chronic vasospasm

Table 1

Summary of international conferences on cerebral vasospasm, 1972–2006

Year	Location	Chairman	Honored guest	Honorary president	Other officers
1972	Jackson, MI, USA	RR Smith, JT Robertson	FA Echlin		
1979	Amsterdam, The Netherlands	RH Wilkins	C Miller Fisher		AJM van der Werf, S Ishii, SJ Peerless, L Symon
1987	Charlottesville, VA, USA	NF Kassell	K Sano	CG Drake	D Vollmer
1990	Tokyo, Japan	K Sano	BK Weir	L Symon	K Takakura, NF Kassell, I Saito, T Sasaki
1993	Alberta, Canada	BK Weir	NF Kassell		JM Findlay
1996	Sydney, Australia	NWC Dorsch	RR Smith		
2000	Zurich, Switzerland	R Seiler	H Nornes		
2003	Chicago, IL, USA	RL Macdonald	T Ohta, S Suzuki		J Zhang
2006	Istanbul, Turkey	T Kiris	R Seiler	Young Investigator: T Ogawa	