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Controversies and Evolving New Mechanisms in Subarachnoid Hemorrhage

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Abstract

Despite decades of study, subarachnoid hemorrhage (SAH) continues to be a serious and significant health problem in the United States and worldwide. The mechanisms contributing to brain injury after SAH remain unclear. Traditionally, most *in vivo* research has heavily emphasized the basic mechanisms of SAH over the pathophysiological or morphological changes of delayed cerebral vasospasm after SAH. Unfortunately, the results of clinical trials based on this premise have mostly been disappointing, implicating some other pathophysiological factors, independent of vasospasm, as contributors to poor clinical outcomes. Delayed cerebral vasospasm is no longer the only culprit. In this review, we summarize recent data from both experimental and clinical studies of SAH and discuss the vast array of physiological dysfunctions following SAH that ultimately lead to cell death. Based on the progress in neurobiological understanding of SAH, the terms "early brain injury" and "delayed brain injury" are used according to the temporal progression of SAH-induced brain injury. Additionally, a new concept of the vasculo-neuronal-glia triad model for SAH study is highlighted and presents the challenges and opportunities of this model for future SAH applications.

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1.Introduction: It is Time to Reawaken Interest in the Mechanisms of Subarachnoid Hemorrhage Pathophysiology

Subarachnoid hemorrhage (SAH) is a devastating cerebrovascular disease with complex mechanisms that threaten brain perfusion and function. The definition of a SAH has recently been updated to mean *bleeding into the subarachnoid space*, i.e., the area between the arachnoid membrane and the pia mater of the brain or spinal cord (Sacco et al., 2013). Despite recent improvements our knowledge of SAH pathophysiology and the management of ruptured aneurysms, which can include surgical clipping or endovascular treatment, SAH remains a serious and significant health problem in the United States and throughout the world (Sehba et al., 2012). Although it accounts for only 5% of all strokes, its burden to society is significant, given the young age at which it occurs, its high rates of mortality and disability, and poor clinical outcomes (Venti, 2012). Approximately one in six patients die during the sudden onset of bleeding. The mean age at which SAH occurs is 50 years old, and the onset of SAH in this younger population renders members of an otherwise productive age group unable to return to work. Additionally, it necessitates long-term care. Those who survive initially may succumb to early rebleeding or a delayed ischemic neurological deficit (DIND) that occurs with or without cerebral vasospasm.

Hippocrates demonstrated the presentation of spontaneous SAH followed by subsequent delayed neurological deficient nearly 2,400 years ago. Delayed cerebral vasospasm, a syndrome first reported in 1951 (Ecker and Riemenschneider, 1951) was regarded as the single most crucial and treatable cause of mortality and morbidity after SAH in subsequent decades. The Fisher Grade was applied in predicting the onset of vasospasms (Fisher et al., 1980). Arterial vasospasm after SAH can be visualized and evaluated by digital subtraction angiography or magnetic resonance angiography in clinical research and by India ink angiography, synchrotron radiation angiography or H&E staining in basic research (Bederson et al., 1998; Cai et al., 2012; Suzuki et al., 2010a).

Historically, considerable efforts have been made to investigate vasospasm as the primary mechanism underlying SAH injury that leads to tissue ischemia, and ultimately to infarctions and poor neurological outcome. However, in recent years, that theory is being questioned increasingly. First, the peak incidence of angiographic vasospasm during the second week post-SAH is approximately 70% (Dorsch and King, 1994), but the incidence of clinically delayed cerebral ischemia (DCI) is only around 30% (Dorsch, 2011). Secondly, the relationship between vessel constriction and cerebral infarction is somewhat poor (Minhas et al., 2003). It is unlikely that all cases of cerebral infarction are due to a SAH-induced vasospasm, because in some instances infarction can occur immediately after a SAH, and a vasospasm in the territorial artery is not always detected by angiography (Naidech et al., 2006). Furthermore, the presence of angiographic or Transcranial Doppler (TCD) vasospasm had only 67% positive predictive value, but 72% negative predictive value for the occurrence of cerebral infarction, respectively (Rabinstein et al., 2005). Cerebral infarction can develop even in an unaffected vascular distribution without vasoconstriction after SAH (Brown et al., 2013; Naidech et al., 2006). Cerebral infarction contributed to poor outcome by both vasospasm-dependent and -independent effects in the majority of 194 patients with moderate to severe vasospasm (Naidech et al., 2006). Therefore, poor outcome seems to be directly dependent on infarction, but independent of

vasospasm (Vergouwen et al., 2011). Thirdly, a wide range of cerebral perfusion disturbances has been observed among patients who developed delayed neurological deficits after SAH (Minhas et al., 2003). Cerebral blood flow (CBF) measured via CT perfusion in areas supplied by vessels with vasospasm ranged from 26.4 to 41.5 ml/100 g/min (Dankbaar et al., 2009; Sviri et al., 2006; Wintermark et al., 2006), which is higher than the assumed threshold for ischemic injury (25 ml/100 g/min) (Murphy et al., 2006). This raises a critical question for future studies: Are the effects of vasospasm on CBF sufficient to cause cerebral ischemia and brain infarct?

The treatment of SAH has not improved despite nearly four decades experimental studies targeting vasospasms. Additionally, the calcium channel antagonist nimodipine, which is the only proven drug treatment to improve outcomes after SAH, seems to provide beneficial effects without angiographic evidence of cerebral vasodilation (Petruk et al., 1988). Finally, treating vasospasm does not always lead to improvement in functional outcomes (Macdonald et al., 2008; Polin et al., 2000). Disappointing results were observed in the two randomized, double-blind, placebo-controlled, phase III trials using endothelin A receptor antagonist, clazosentan (CONSCIOUS-2 and CONSCIOUS-3) (Macdonald et al., 2011; Macdonald et al., 2012). Clazosentan reduced vasospasm in patients after SAH, but failed to reduce mortality and to ameliorate neurological deficits. In recent years, increasing evidence has revealed that some new mechanisms, such as early brain injury (EBI), cortical spreading depolarization (CSD) and impaired microcirculatory function, may closely dictate patients' prognosis following SAH. Hence, a new review is necessary to appraise those research advances of SAH.

SAH, as an untreatable CNS disease, promotes collaborative efforts from neurosciences, neurosurgery, neurology, neuro-ICU and other interrelated fields. Recent advances in SAH research suggest that we need to look beyond vasospasm after SAH and target other coexisting factors that might be involved in the pathogenesis of delayed cerebral ischemia, which should improve outcomes in patients after SAH (Vergouwen et al., 2011). This review aims to summarize the evolving new pathophysiological mechanisms that are implicated in brain injury after SAH and to improve our understanding of these mechanisms in order to explore potential novel therapeutic options for patients with SAH.

2. SAH Background

"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,"(Clarke, 1963). His description is similar to the classic and dramatic presentation of patients with SAH, such as a middle-aged person who collapses at restroom, reports a sudden onset of the "worst headache of my life," subsequently projectile vomits, briefly loses consciousness, and presents with subhyaloid ocular hemorrhages and a stiff-neck. A brief history of SAH is summarized in Figure 1.

2.1 Etiology of spontaneous SAH

A SAH can be caused by trauma; however, only spontaneous, nontraumatic SAH is included under the definition of stroke (Sacco et al., 2013). Approximately 85% of cases of spontaneous SAH are due to the rupture of an intracranial aneurysm and bleeds into the subarachnoid space. Cerebral aneurysms may be present in 2–3% of the population with the annual risk of rupture being relatively low, about 0.7–4% (Rinkel et al., 1998). Spontaneous SAH also can occur in the absence of an aneurysmal rupture. Indeed, perimesencephalic non-aneurysmal conditions account for 10% of SAH (Inagawa, 2010). The normal angiographic findings in these instances are consistent with a venous origin of the bleeding, which can occur due to the rupture of a prepontine or interpeduncular vein (Hashimoto et al.,

2000). Approximately 5% of SAH are associated with other medical conditions such as arteriovenous malformation, intracranial artery dissections, mycotic aneurysms, bleeding disorders, reversible cerebral vasoconstriction syndrome, vasculitis, moyamoya disease, cerebral amyloid angiopathy, or drug abuse (Cabral et al., 2013; Cuvinciuc et al., 2010; Rinkel et al., 1993; Santos Carvalho et al., 2013; Venti, 2012; Viswanathan et al., 2012). This review focuses only on current neurobiological knowledge of aneurysmal SAH.

2.2 Epidemiology: incidence, mortality and racial differences

A large multinational World Health Organization epidemiological investigation reported that the annual incidence of aneurysmal SAH ranges from 2.0 cases in China to 22.5 cases in Finland per 100,000 in age-adjusted adults (Ingall et al., 2000). In the United States, the annual prevalence of aneurysmal SAH is approximately 30,000 persons (Bederson et al., 2009; Loftspring, 2010). The incidence of SAH has been reported to be age-related with a higher incidence among individuals aged 40 to 60 years, peaking at age 55. It also appears to be gender-dependent, with women having an incidence rate that is approximately 1.6 times higher than that of men (Rinkel et al., 1998). Previous studies suggest the risk of SAH further varies based on a female's hormonal status. Premenopausal women (Longstreth et al., 1994), women of older age at the birth of their first child, and those of older age at the onset of menarche have lower risk for SAH (Okamoto et al., 2001).

Most studies report mortality rates ranging from 25% to 35% in high-income countries and up to 48% in low-income countries (Feigin et al., 2009). The median mortality rate of SAH in the United States alone is as high as 32% (Connolly et al., 2012). However, because these data do not include pre-hospital deaths, the actual rate of mortality for SAH is likely to be much higher than that that reported (Inagawa, 1997). Indeed, approximately 12% of patients die before receiving medical attention or are misdiagnosed (Fridriksson et al., 2001; Huang and van Gelder, 2002). Nevertheless, the rates of morbidity and mortality due to SAH have slowly decreased, with nearly a 1% reduction in the mortality rate per year since 1974 (Johnston et al., 1998).

There also appear to be racial differences in the risk of SAH (Brinjikji et al., 2012). Black Americans are at higher risk than are white Americans (Broderick et al., 1992). Mortality rates for SAH also seem to vary by race. White Americans have a lower mortality rate than do African Americans, Hispanics, American Indians/Alaskan Natives, and Asian/Pacific Islanders residing in the United States (Connolly et al., 2012).

2.3 Perspectives on the Current Status of SAH Animal Models

There is a clear need for rigorous translational research using animal models so that we can make further progress in the management of patients with SAH (Figure 2). Indeed, although the human cerebral artery may be considered an ideal tool for studying the pathogenesis and treatment options of SAH, using live human brain vessels *in vivo* is not a viable option. Moreover, postmortem evaluation of arteries taken from humans who died from SAH provide only minimal information (Crompton, 1964).

Various animal species, including mice, rats, rabbits, dogs, primates, cats, pigs, and goats have been used to produce SAH models to closely mimic the physiological situation in humans (Marbacher et al., 2010a). Non-human primates are very similar in their genome, anatomy, and physiology to humans, and thus the models of non-human primates' SAH are believed to be the best candidates for replicating clinical SAH. The puncture monkey model through a small anterior craniotomy was first reported in 1968 (Simeone et al., 1968). Non-human primates are usually time-consuming and demand complex surgical manipulation, such as anesthesia, angiography, craniotomy, etc, and are also not cost effective. Therefore,

the puncture technique was also adapted to small animals with the advancement of microsurgical technology. For example, the rat is an excellent species, because it is relatively lower cost and that easy to manipulate in a laboratory setting. The endovascular puncture SAH model has also been produced in the mouse, though it is technically more challenging (Kamii et al., 1999). Recently, the therapeutic effect of potential drug candidates against EBI has been examined on the mouse endovascular puncture model (Altay et al., 2012a). The advantage of a mouse SAH model would be the option to use transgenic mice, which is becoming the preferred research tool for gene-specific silencing *in vivo*. Using transgenic mice with spontaneous aneurysmal SAH would better mimic the natural history seen in patients with SAH.

Because there are no spontaneously occurring animal models of SAH, a number of animal models of SAH have been developed in various species to simulate SAH. SAH researchers can choose from a number of SAH animal models to suit their research objectives. The SAH models that mainly utilize two techniques: 1) endovascular punctures, in which puncture of an intracranial artery allows blood to quickly spread in the subarachnoid space, and 2) blood injection into the subarachnoid space after blood is obtained by the surgical exposure of a distant artery or vein.

Each animal model has its own advantages and disadvantages. It is generally accepted that the endovascular perforation model of SAH better mimics EBI, whereas the blood injection model better mimics the vasospasm that can occur after SAH (Lee et al., 2009b). In recent years, as the concept of EBI gains more popularity over delayed vasospasm, the blood injection model has been less favored as compared to the monofilament puncture model, since researchers are beginning to explore changes not only in the large cerebral arteries but also in the brain parenchyma (Bederson et al., 1995; Titova et al., 2009).

The endovascular puncture model was independently described in 1995 by Bederson et al. and Veelken et al. (Bederson et al., 1995; Veelken et al., 1995). The surgical procedure involves perforation of the internal carotid bifurcation by a sharpened suture, which is inserted through the external carotid artery without craniotomy. Because this method does not entail craniotomy, it best represents a clinical scenario, as it mimics the acute pathophysiological changes of an aneurysmal rupture in humans (Schwartz et al., 2000a; Schwartz et al., 2000b). It results in with considerably high rate of mortality, which ranges from 30% to 50% within 24 hr after SAH (Prunell et al., 2004). However, the brief period of ischemia caused by temporal clip, the lack of control over the volume of the hemorrhage, and the high rate of morbidity and mortality significantly impacts its use for studies exploring possible therapeutic options. Furthermore, the CBF on the side with the perforation tends to be lower than that of the non-perforated side, thus suggesting that this model results in some degree of laterality to the hemorrhagic event.

The blood injection model, in which blood is directly injected into the subarachnoid space either once or twice, is another widely used technique for inducing experimental SAH. This technique elicits early and delayed vasospasm in a variety of species, although its presence depends on the site of injection. More recently, Marbacher et al. reported vasospasm in a number of SAH models: The most frequently injected volume of blood amount (ml), the peak onset of the vasospasm (day), and amount by which the blood vessel narrowed (%): mice endovascular puncture (a range, day 3, 20–62%); rat single injection (0.3 ml, day 2, 19–29%); rat double injection (0.3 ml, two times, day 7, 28–47%); rabbit single injection (3 ml, day 3, 19–55%); rabbit double injection (not established, day 5, not established); dog double injection (4–5 ml, two times, day 7, 45–66%); primate clot placement (5 ml, day 7, 32–52%) (Marbacher et al., 2010a). Recently, a novel technique of inducing SAH by extra-intracranial blood shunt has been established to trigger delayed cerebral vasospasm under a

controlled intracranial pressure (ICP) (Marbacher et al., 2010b). In the future, experimental models of cerebral vasospasm should be improved so as to better mimic human SAH, in terms of having a direct hemorrhagic brain lesion under systolic pressure (Pluta et al., 2009).

Given the availability of various types of SAH models, it is imperative that the model chosen is appropriate for the objective of the study and that the model is replicable. In addition, genome-wide association studies are helpful to identify novel genetic factors that contribute to intracranial aneurysm susceptibility. Consequently, it is possible to produce an aneurysm on cerebral vessels experimentally using genetic technology (Suda et al., 2013). Furthermore, ensuring reproducibility of results, the efficacy of a treatment option should be confirmed in multiple species and in multiple laboratories before beginning translation to a clinical study (Tajiri et al., 2013).

2.4 Failure in Current SAH Studies

Despite the promising results seen in animal models, clinical studies have failed to translate the outcomes seen in animal models to human subjects (Feuerstein et al., 2008; Savitz, 2007). The failure to translate animal studies could be due to methodological flaws during animal experiments including the following: First, studies do not always indicate if the animals used in the experiments were randomized or how the randomization was performed. Yet, studies may not be translatable the animals used in the experiments were not randomly allocated. Furthermore, control groups are often inadequate, and some studies do not even include a control group. In addition, evaluations performed during experiments are not always blinded, which is essential for a non-biased meaningful study. Second, most studies utilize young, non-diseased male animals, which, therefore, does not simulate the age, physical condition, or gender-specific risks seen in patients with SAH, who are more likely to be (45–55 years old, have hypertension, and be female) (Kassell et al., 1996; Kongable et al., 1996; Lanzino and Kassell, 1999). Furthermore, young rats are more resistant to the effect of the products of bilirubin oxidation compared to aged rats post-SAH (Clark et al., 2011). Third, sample size is not always adequate for statistical analysis, which can lead to incorrect conclusions about the results of an experiment. Accurate power and statistical analyses are crucial for drawing valid conclusions from a study.

Further, in depth evaluation of outcomes in preclinical models is crucial to measure an agent's efficacy for the successful clinical translation of novel therapies (Knight et al., 2013). Given the high mortality rates in patients with SAH, mortality should be examined in experimental studies. Neurological function also should be thoroughly evaluated, because this information is crucial for translation of animal studies. Clinical evaluations of patients after SAH commonly reveal cognitive deficits, and this information is critical to providing for proper care (Wong et al., 2013). However, cognitive function, fatigue, and emotional disturbances are seldom evaluated in preclinical experiments (Boyko et al., 2013; Tso and Loch Macdonald, 2013). Additionally, for many patients with SAH and their relatives, the activities of daily living is as important as, or even more important than, the life prolonged. Therefore, efficacy of therapies should be evaluated using tests to examine not only sensory motor function but also cognitive function, speech, and memory. Experimental studies need to incorporate an assessment of neurobehavioral outcomes in the acute phase as well as a more detailed evaluation of long-term neurological function.

It also is important to examine potential side effects of compounds being tested in animal studies in order to eliminate drugs that may be too toxic for clinical use. Indeed, recent failures in the CONSCIOUS trials may have occurred due to adverse effects, such as hypotension and pulmonary complications, that are common after taking endothelin receptor antagonists (Macdonald, 2012). For example, complications such as hypotension, pulmonary complications, and anemia were encountered more often in patients who were treated with

clazosentan than in those who received placebos (Macdonald et al., 2012). Similarly, use of several of the synthetic N-methyl D-aspartate (NMDA) antagonists have been abandoned because of concerns regarding drug toxicity, particularly in strokes (Muir, 2006). Using two or three gradual dosages is helpful to show dose dependent and potential toxic effects in experimental studies. The successful clinical translation of future studies requires the careful design of experiments, adequate controls, and rigorous testing in experimental SAH models. It may be prudent to develop a set of guidelines for SAH translational studies (Lapchak et al., 2013).

2.5 Major Complications after SAH

2.5.1 Acute and Chronic Hydrocephalus—SAH often can lead to hydrocephalus, an outcome with a frequency that varies from 9% to 67% in some patients (Milhorat et al., 1970; Woernle et al., 2013; Yasargil et al., 1973). Traditionally, it has been believed that patients with SAH suffer from hydrocephalus that is due to two major problems: 1) blockage of cerebrospinal fluid (CSF) pathways in the ventricular system, and 2) compromised reuptake of CSF within the subarachnoid granulations. The obstruction of CSF pathways in the acute setting, largely due to the mass effect of blood clots, has been established as the cause of acute hydrocephalus. Several studies have shown correlations between the amount of cisternal and ventricular blood and the likelihood of developing acute hydrocephalus after SAH (Graff-Radford et al., 1989). Recently, CSF overproduction by stimulation of the irritant receptor glossopharyngeal and vagal nerve endings has been suggested to the etiology of early hydrocephalus after SAH (Kanat et al., 2012), which, although plausible, has yet to be confirmed with substantial scientific evidence (Shah and Komotar, 2013). In contrast, the latter usually occurs in the chronic setting secondary to fibrosis of the arachnoid villi as a result of inflammatory reaction or blood clotting products, which prevents the reabsorption of CSF (Massicotte and Del Bigio, 1999; Suzuki et al., 2008).

Previous analyses also indicate multifactorial causes in the development of chronic hydrocephalus after SAH. These include poor neurological condition upon the admission of a patient, the presence of intraventricular hemorrhage, ruptured vertebral artery aneurysm, surgical clipping and endovascular coiling, meningitis, hyperglycemia, gender, increased sympathetic activity, and a prolonged period of external ventricular drainage (de Oliveira et al., 2007; Dorai et al., 2003; Graff-Radford et al., 1989; Lai and Morgan, 2013; Lambert et al., 2002; Yang et al., 2013). In experimental SAH, rats seem to develop hydrocephalus as measured by magnetic resonance imaging if the SAH grade is high or if there is intracerebroventricular bleeding, and if the cerebroventricular wall is damaged (Okubo et al., 2013). The hepatocyte growth factor and vascular endothelial growth factor may participate in the periventricular white matter injury in rats with chronic hydrocephalus after SAH (Chu et al., 2011). The cascade of transforming growth factor β1-Smad3 induced by thrombin might be a mechanism of communicating hydrocephalus after SAH in rats (Li et al., 2013). To clarify and strengthen these observations, future studies should differentiate in detail suitable SAH models that target this complication. More studies of the neurobiological mechanisms of hydrocephalus, including prospective, double-blinded, randomized trials are needed.

2.5.2 Seizures—Seizures are a well-recognized complication of SAH, although the administration of prophylactic antiepileptic medication following an aneurysmal SAH is still controversial (Ibrahim et al., 2013). Seizures occur in 5–35% of survivors of SAH, most commonly onset time in the first 24 hr (Baker et al., 1995; Connolly et al., 2012; Ohman, 1990). They are associated with higher Hunt-Hess grade and Fisher scores, lower admission Glasgow Coma Scale scores, hypertension, infarction, and rebleeding (Cabral et al., 2009; Hasan et al., 1993). However, reports about the association between seizures and functional

outcomes are heterogeneous (Butzkueven et al., 2000; Choi et al., 2009; Rhoney et al., 2000). Therefore, further neurobiological investigation is warranted to understand the mechanism of epilepsy and seizure disorders after SAH. To clarify and strengthen these observations, a suitable model of SAH should be developed to target this complication. Then, the efficacy and timing of prophylactic antiepileptic medication should be tested carefully in that model before a multiple-center, double-blinded, randomized prospective evaluation.

3. 3. Neurobiological Response after SAH

In cases when SAH is not immediately fatal, secondary complications can occur after the initial bleeding (Figure 3). Recently, we have begun to see that SAH clearly has a complex, multisystem, and multifaceted pathogenesis that involves several ongoing processes other than vasospasm of the major cerebral vessels (Cahill et al., 2006; Hansen-Schwartz et al., 2007; Macdonald et al., 2007). In this review, the term “EBI” and “delayed brain injury” (DBI) are used according to the temporal progression of SAH-induced brain injury. In fact, the term “EBI” was first coined in 2004 to explain the acute pathophysiological event that occurs within the first 72 hr of the SAH (Kusaka et al., 2004). With advances in understanding the pathophysiology of SAH, in the present review the term “DBI” is used to demonstrate a host of critical, interrelated pathological pathways that arise in the late phase of SAH as a consequence of EBI. Many of the pathogenic triggers of DBI are interrelated, and furthermore, the mechanisms leading to delayed vasospasm and DBI are not mutually exclusive. We believe that delayed vasospasm is a clinical manifestation and not a separate entity of the many mechanisms of DBI after SAH.

3.1 Early Brain Injury

More than 300 articles in a PubMed/MEDLINE search provide an extensive coverage of advances in the research on EBI over the last ten years; however, most of that information comes from animal studies. The term “EBI” refers to global brain injury that starts immediately after aneurysms rupture (Sabri et al., 2013b). A number of animal studies and some data from human autopsies provide evidence that EBI begins within minutes after the initial bleeding (Bederson et al., 1998; Nau et al., 2002). This correlates well with the clinical scenario in which clinical deterioration is commonly observed within the first 2 hr (Miyazaki et al., 2006; Ohkuma et al., 2001), and SAH fatalities occur within 48 hr of the ictus (Ingall et al., 2000).

The major causes of death within 72 hr after the initial bleed are the effects of the initial hemorrhage and aneurysms’ rebleeding (Broderick et al., 1994). Indeed, survivors with SAH can succumb to injury at a later period or present with severe deficits, due to secondary insult. Brain injury following SAH is not only limited to the distribution of the ruptured vessel, but also extends to brain regions distant to the site of hemorrhage. In recent years, increasing study efforts have been directed at elucidating the mechanisms of EBI after SAH, which challenges the already tenuous link between vasospasm and DIND. The cascade of events that occur with EBI is responsible for the initial signs and symptoms of patients with SAH, which is believed to be a precursor for both delayed vasospasm and DIND. In addition, a range of physiological derangements that occurs early on can trigger a number of devastating cascades that lead to blood brain barrier (BBB) dysfunction, inflammation, necrosis, apoptosis and oxidative stress (Ayer and Zhang, 2010). The physiological changes that occur with EBI and the mechanisms responsible for EBI are discussed below.

3.1.1 Initial Physiological Changes: A Culprit of EBI

3.1.1.1 Intracranial Pressure (ICP): Once an aneurysm ruptures, blood extravasates from a ruptured defect and spreads into the subarachnoid space. The size of the ruptured defect in vessel correlates with the amount of the blood clot. At the time of the SAH occurrence, ICP sharply elevates, and the rate of increase is indicative of the severity of the initial bleed. The rapid increase in ICP accounts for the “thunderclap” headache, which is the classical presentation seen in patients at the clinics. ICP is normally less than 13mmHg. There are two types of ICP increase. First, ICP rapidly increases to a value approximating the arterial pressure (~120 mmHg), then decreases to a level slightly above baseline (Bederson et al., 1995). Within 1–2 min after SAH induction, ICP rapidly rises to peak values in a new blood shunt model, and it decreases to a plateau that is higher than the baseline values within 5–10 min (Marbacher et al., 2012). This initial increase in the ICP is thought to be a protective mechanism, which arrests the initial aneurysmal bleed and preventing rebleeding, the so-called “brain tamponade” (Nornes, 1973). This pattern is usually accompanied by a small volume hematoma.

The other pattern of ICP increase is characterized by a sustained increase in ICP, which may be due to an enlarging hematoma volume, vasoparalysis, distal cerebral arteriolar vasodilation or the development of acute hydrocephalus (Asano and Sano, 1977; Brinker et al., 1990; Grote and Hassler, 1988; Nornes and Magnaes, 1972). This pattern is less common. The peak ICP elevation is a response to both the amount of blood released into the subarachnoid space and the volume of hemorrhage (Bederson et al., 1998; Schwartz et al., 2000a). High ICP predicts poor outcome after SAH (Czosnyka et al., 2005; Soehle et al., 2007), as it disrupts cerebral perfusion pressure (CPP), the pressure driving cerebral blood flow, and may lead to a critical loss of cerebrovascular autoregulation (Czosnyka et al., 2005). The time course assessment of ICP suggests that it may contribute to a high rate of early clinical deterioration in patients (Ohkuma et al., 2001). The results of the study conducted by Westermaier et al. describe that a sharp increase of ICP does not correlate with the development of edema (Westermaier et al., 2012). Unfortunately, early ICP monitoring of patients is generally not feasible, so that the accurate impact of early ICP remains unclear.

3.1.1.2 Cerebral Perfusion Pressure (CPP): CPP is the net pressure gradient of blood flow to the brain. Normal CPP, which is equal to mean arterial blood pressure minus ICP, approximates 80 mm Hg (Huang et al., 2006). The relationship between ICP and CPP is imprecisely understood, although it is predicted to be related to the “Monroe-Kelly” doctrine (Ayer and Zhang, 2010; Schoffer et al., 2002). A profound fall in CPP to almost zero has been observed immediately after SAH in animals and humans (Marbacher et al., 2012; Nornes, 1973; Voldby and Enevoldsen, 1982). After a few minutes, CPP gradually recovers with the decline of ICP. This pattern looks like global cerebral ischemia with gradual reperfusion. Interestingly, some experimental studies suggest that decrease in CPP was negatively associated with ICP (Kuyama et al., 1984). While CPP recovers, the reduction of CBF persists, which indicates acute vasoconstriction within 6 hr (Westermaier et al., 2009). However, reduction in CPP does not always correlate with a poor clinical outcome (Heuer et al., 2004).

3.1.1.3 Cerebral Blood Flow (CBF): The rise in ICP and subsequent fall in the CPP results in a significant decrease in the CBF, which can drop to zero after the initial impact of SAH in experimental studies (Bederson et al., 1995). Once there is a transitory fall of CBF, the consequences are significant, both short and long term. In some instances, severe global hypoperfusion can exhibit as syncope or unconsciousness in patients with SAH (Jakobsen, 1992). Also, mortality rate increases with severe reduction in the CBF. In an experimental study, Bederson et al. observed that CBF reduction to less than 40% of baseline in the first

hour after SAH predicted 100% mortality and was defined as “lethal” SAH, while a lesser degree of CBF reduction resulted in 19% mortality (Bederson et al., 1998). Furthermore, the study showed that the mortality rate was independent of ICP and CPP in the first hour after SAH. It appears that marked acute cerebral vasoconstriction can occur at this critical time independent of changes in CPP and ICP, which likely contribute to the cerebral ischemia (Bederson et al., 1998; Friedrich et al., 2012a).

Cerebral perfusion is essential for life, since the brain has high metabolic demands and is very sensitive to hypoxia-ischemia. Early CBF reduction was accompanied by a lessened cerebral metabolic rate of oxygen investigated by positron emission tomography analysis (Frykholm et al., 2004). Positron emission tomography has the potential to increase our knowledge of the role of cellular hypoxia in SAH, which described that hypoxia (increased (18) F-FMISO uptake) was present in symptomatic patients with SAH (Sarrafzadeh et al., 2010).

3.1.2 Disturbance in Cerebral Autoregulation—Cerebral autoregulation is a process in mammals that plays an important role in maintaining adequate and stable cerebral blood flow (Paulson et al., 1990). Cerebral autoregulation is able to deliver sufficient blood containing oxygen and nutrients to the brain tissue for metabolic needs, and removes CO_2 and other waste products (Muller et al., 2002). Under normal circumstances, CBF is regulated through adjustment in the arteriolar size, which, in turn, drives the changes in vascular resistance according to Hagen–Poiseuille’s Law (Kontos et al., 1978). Three different mechanisms contribute to the process of cerebral autoregulation, including metabolic, myogenic and neurogenic (Aries et al., 2010; Paulson et al., 1990).

Haemodynamic communication between neurons and the vasculature is necessary to efficiently regulate CBF by neuronal activation (Attwell et al., 2010). In humans, CBF autoregulation typically operates between mean arterial pressures of the order of 60 and 150 mmHg. The initial aneurysmal rupture seems to lead to acute impairment of cerebral autoregulation (Lang et al., 2001; Ratsep and Asser, 2001). CBF, therefore, is dependent on changes in CPP, blood viscosity, and systemic arterial pressure. Additionally, a degree of cerebral dysautoregulation is also observed to occur throughout the subacute stage following SAH as well during the delayed stage at the time of delayed vasospasm (Budohoski et al., 2013).

Currently, TCD remains the most commonly used noninvasive tool to assess early alterations in vascular diameter. Clinical studies have described primary autoregulation failure measured by TCD as a direct result of SAH and, therefore, it is proportional to severity of the ictus (Budohoski et al., 2012). In addition, experimental analysis has revealed numerous activated molecular pathways that could lead to the observed dysfunction of cerebral autoregulation in the acute phase after SAH (Cho et al., 2003; Shin et al., 2002). In consideration of the existing reports on cerebral autoregulation following SAH, it is imperative to determine the exact time course of autoregulatory impairment following SAH and to determine the most appropriate methodology to detect the impairment, which might be beneficial in patients especially who present with mild neurological deterioration.

3.1.3 Excitotoxicity, Spreading Depolization and Ionic Imbalance: A Path to Neuroprotection—After the onset of SAH, there is a derangement in neurotransmitter release and inhibition of the reuptake (Jung et al., 2012; Kahn et al., 2012) occurrence of CSD (Hartings et al., 2013; Winkler et al., 2012) and loss of energy stores, which causes ionic imbalance (Aihara et al., 2004; Hubschmann and Nathanson, 1985). Excitotoxicity, CSD, and ionic imbalance are inextricably linked and contribute to SAH-induced cell death

(Ohta et al., 2001; Petzold et al., 2005b; Sakowitz et al., 2013), and have been implicated in poor outcomes in comatose patients after SAH.

3.1.3.1 Excitotoxicity: Excitotoxicity is defined as toxicity resulting from the excessive activation of ionotropic and metabotropic glutamate receptors (Puyal et al., 2013). Excessive glutamate causes neurotoxicity effects. Mounting evidence describes that glutamate, a major excitatory transmitter, is elevated in the CSF after SAH, suggesting that it may play a significant role in the pathophysiology of the ictus (Jung et al., 2013a). Glutamate is not synthesized in neurons nor acquired from circulation (Hertz et al., 2007), but rather synthesized and released by activated astrocytes and microglia through the hemichannels of gap junctions (Takeuchi et al., 2006). Maintaining a minimal level of glutamate is critical for normal neuronal function after brain injury (Zlotnik et al., 2012).

Glutamate concentration was significantly high in double-hemorrhage SAH rats from day 1 to day 7 after SAH, especially at day 1, which has an important role in neuronal death (Wu et al., 2011). In the double-injection SAH rat model, an excessive and prolonged increase level of glutamate in the CSF and a reduced level of glutamate transporters GTs, including glutamate/aspartate transporter, glutamate transporter-1, and excitatory amino acid carrier 1 were observed on day 7, which was accompanied by wall thickness of the basilar artery and neuronal degeneration in hippocampus (Wu et al., 2011). Moreover, the toxicity effect mediated by glutamate includes excessive activation of the NMDA receptor leading to massive Ca^{2+} influx and subsequent apoptotic cell death and necrosis (Owens et al., 1997). Ionotropic glutamate receptors promoted an excessive influx of sodium with concomitant cell swelling and edema. It has been reported that the NMDA receptor antagonist, felbamate, improved neurological performance and limited the BBB disruption in a single-injection rat model of SAH (Germano et al., 2007).

Currently, various strategies have been explored to target glutamate that include inhibiting its synthesis, blocking its release from the presynaptic terminals, antagonizing its receptors on the postsynaptic terminal, and accelerating its reuptake from the synaptic cleft. Blood glutamate scavengers, oxaloacetate and pyruvate, have been shown to effectively reduce blood glutamate concentrations, ameliorate BBB disruption, and improve neurological outcome after SAH in rats (Boyko et al., 2012). Therefore, preventing glutamate-induced neurotoxicity can potentially improve neurological outcomes after SAH. However, it should be noted that clinical trials using NMDA receptor antagonists after ischemic stroke have not lived up to the expectations from the experimental data in animals, because the blockade of NMDA receptor-mediated synaptic transmission hinders neuronal survival (Ikonomidou and Turski, 2002).

3.1.3.2 Cortical Spreading Depolarization (CSD): The term “cortical spreading depolarization” has been characterized by Aristides Leão as a wave in the cortex of the CNS (Leao, 1947). It is a self-propagating wave of neuronal and glial depolarization, which travels at a characteristic 2 to 5 mm/min and can be induced by a variety of noxious stimuli (Somjen, 2001). However, it does not spontaneously originate in normal brain tissue. CSD near-completely results in a breakdown of ion gradients and a sustained depolarization in individual metabolic impact observed as a result of cytotoxic edema after SAH (Canals et al., 2005; Dijkhuizen et al., 1999; Dreier et al., 1998; Takano et al., 2007). The magnitude of CSD-induced the disturbances of electrical, ionic, and metabolic is even larger than those of epileptic seizure activity (Dreier, 2011). CSD results in massive ion translocation between the intra- and extracellular space, redistribution of neurotransmitters, neurons swelling, distortion of dendritic spines, slowing of electrical potential, and silencing of electrical activity (Dreier, 2011; Somjen, 2001). Furthermore, CSD is associated with severe vasoconstriction (Dreier et al., 1998). Under conditions similar to those of SAH, in the

presence of extravascular hemoglobin and elevated extra-cellular K^+ or low glucose, CSD causes a vascular response ranging from hyperemia to hypoperfusion. The combination of decreased CBF and increased energy requirements imposed by CSD may further worsen neuronal injury (Strong et al., 2007). Thus, CSD represents an electrical circle between intra- and extra-cellular space, and represents a biochemical and morphological alteration after SAH.

Unequivocal electrophysiological evidence indicates that CSD frequently occurs in a clinical setting after SAH (Sanchez-Porras et al., 2013): During the past few years, several studies using subdural electrode strips have confirmed the presence of CSD in the cortex of patients with SAH (Dreier et al., 2006; Schlenk et al., 2008). Neocortical application of a solution containing hemoglobin with high K^+ or a low level of glucose triggered CSD (Dreier et al., 2000). Thus, CSD can be ignited by intense neural activity resulting in increases of extracellular K^+ and excitatory neurotransmitters.

In vivo, the noncompetitive NMDA receptor antagonist MK-801 inhibited CSD propagation under physiological conditions, but an elevated baseline $[K^+]o$ reduced the efficacy of MK-801 on depolarization (Petzold et al., 2005b). Furthermore, antagonists of NMDA channels or voltage-gated Na^+ channels or certain types of Ca^{2+} channels can postpone or mitigate CSD (Addae et al., 2011). The recent demonstration that SAH is associated with waves of CSD has revealed yet another potential mechanism for DCI after SAH (Sanchez-Porras et al., 2013).

In view of experimental and their clinical evidence, Dreier et al. proposed that clustered CSD with prolonged periods of depression is an early indicator of the start of delayed neurological deterioration after SAH (Dreier et al., 1998; Dreier et al., 2006). However, at the present an important issue is whether CSD is a possible new culprit for DCI, which would require a more comprehensive understanding of CSD after SAH. If CSD is an early manifestation of reversible neuronal dysfunction after SAH, then therapies that suppress CSD may lead to decreased DCI and eventually improved clinical outcomes. However, if CSD is manifested only as a terminal metabolic failure, then treatments targeting CSD may not revive brain tissue already fated to die.

3.1.3.3 Ion and Ion Channels Change: Approximately 20% of the body's resting metabolism is consumed by the brain to establish ionic gradients (Mies and Paschen, 1984). Several different ion channels are expressed in cerebrovascular myocytes, including those for potassium, sodium, calcium, and often ignored anions, specifically, chloride. The myocytes control cerebral autoregulation. More specifically, they regulate resting membrane potential, vascular diameter, and vascular tone. Ionic distribution in the intra- and extra-cellular space and ion channel expression in the brain is rapidly and severely impaired after SAH, which thereby promotes a disturbance in electrical activity (Kamp et al., 2012).

3.1.3.3.1 Potassium (K^+) and Its Channels: A high level of serum K^+ has been detected after SAH and this varies by gender (Fukui et al., 2004). K^+ can be released into the CSF from the blood clot in the subarachnoid space due to a decrease in sodium pump activity. Microthrombosis, endogenous digitalis-like compounds, as well as activation of neuronal K^+ channels play a key role in the rise of basal K^+ after SAH (Dreier et al., 2000). Subarachnoid hemoglobin combined with a high concentration of K^+ causes widespread constriction of cerebral arteries and a decrease in CBF, eventually leading to cell necrosis in the cortex. Several authors have emphasized the role of loss of functional voltage-gated K^+ channel (Kv) in arterial constriction in dog double-injection SAH models (Jahromi et al., 2008; Weyer et al., 2006). For instance, Kv1.5, Kv2.1 and Kv2.2 transcripts and protein levels were reduced in basilar arteries of dogs in response to SAH, suggesting that Kv dysfunction

contributes to the pathogenesis of delayed cerebral vasospasm after SAH (Aihara et al., 2004; Jahromi et al., 2008). Furthermore, Ishiguro et al. demonstrated downregulation of Kv1.5 protein in rabbit cerebral arteries after oxyhemoglobin exposure (Ishiguro et al., 2006). The study also showed that oxyhemoglobin-induced suppression of Kv1.5 channels was mediated by increased tyrosine phosphorylation-dependent trafficking of the channels from the cell surface (Ishiguro et al., 2006). Therapeutic manipulation of the K^+ channels has been attempted to reduce vasospasm after SAH. The K_{ATP} channel activator, levcromakalim, or endogenous activator, calcitonin gene-related peptide, displayed vasorelaxation after SAH in dogs, rabbits and monkeys (Ahmad et al., 1996; Sugai et al., 1999; Zuccarello et al., 1996). However, it failed to significantly attenuate vasospasm to a greater degree than that provided by standard care in a randomized multicenter single-blind clinical trial.

3.1.3.3.2 Sodium (Na^+) and Related Syndromes: Hyponatraemia, which can occur in 10–30% of patients with SAH, is strongly linked to adverse outcomes and should be avoided in all victims of SAH (Naval et al., 2006). It is an early biochemical change seen in patients with SAH that is difficult to remedy (Berendes et al., 1997). Patients with hyponatraemia are at higher risk of developing cerebral ischemia and infarction, and mortality (Hasan et al., 1990; Wijdicks et al., 1985). The cerebral salt-wasting syndrome (CSWS) and inappropriate secretion of anti-diuretic hormones (SIADH) are suggested as the mechanisms underlying SAH-induced hyponatremia (Bruder et al., 2009), though still debated (Benvenga, 2006). CSWS is probably related to the outcome of the patients with severe SAH, and can occur due to high sympathetic tone, hyperreninemic hypoaldosteronism syndrome, and enhanced natriuretic peptides release (Audibert et al., 2009). Atrial natriuretic peptide (ANP) has been suggested as a causal natriuretic factor in CSWS. By the time a patient is admitted, both plasma ANP and brain natriuretic peptide (BNP) have been found to be increased, whereas levels in CSF were unaffected (Espiner et al., 2002).

Kleindienst et al. concluded that ICP generates the delayed CSWS, and ADH release does not mediate natriuresis in a rat model of SAH (Kleindienst et al., 2012). SIADH, the most common etiology of hyponatremia (Sherlock et al., 2006), is a condition in which the body produces excessive antidiuretic hormones and clinically manifests with hypertonic urine, hypo-osmolar serum, and apparent euvolemia without renal, adrenal, or thyroid disorders (Kao et al., 2009). In a retrospective case-note study consisting of 316 patients with SAH, Sherlock et al. found that 56.6% of patients developed hyponatremia, which was related to SIADH (Sherlock et al., 2006).

For clinicians it is important to distinguish between the two conditions that may account for hyponatremia after SAH, because the treatment strategy is opposite for the two conditions: They should restrict fluids and sodium in cases of CSWS but order increase sodium intake for SIADH. Many biochemical parameters are similar between CSWS and SIADH, and a compensatory hypersecretion of ADH to correct fluid depletion can occur with CSWS. The status of blood volume is helpful to differentiate between these two situations; patients with CSWS are hypovolemic, but SIADH patients are either normovolemic or hypervolemic (Audibert et al., 2009).

3.1.3.3.3 Calcium (Ca^{2+}) Channels and Magnesium (Mg^{2+}): Ca^{2+} is a cofactor in multiple intracellular processes. Disruption of intracellular Ca^{2+} regulation and Ca^{2+} overloading have been hypothesized to play an important role in the process of cell injury, which results in vasoconstriction and sometimes cell death following exposure to oxyhemoglobin. In cultured cerebrovascular smooth muscle cells from primates, a significant increase in free intracellular Ca^{2+} was observed as early as 2 min after application of oxyhemoglobin and remained continuously elevated for 7 d (Takanashi et al., 1992). *In vivo* studies suggest that

intracellular Ca^{2+} starts to increase at a very early stage – as soon as 15 min after SAH (Ishiguro et al., 2008; Kohno et al., 1991; Meguro et al., 2001). Endothelin and oxyhemoglobin, but not bilirubin, induced acute dose-dependent increases in intracellular Ca^{2+} concentration in cultured vascular smooth muscle cells (Takenaka et al., 1991a; Takenaka et al., 1991b). It has been shown that hemolysate released Ca^{2+} from endoplasmic reticulum and promoted Ca^{2+} influx from voltage-independent Ca^{2+} channels in endothelial cells of cerebral arteries (Zhang et al., 1996). Moreover, non-L-type Ca^{2+} channels play an important role in the oxyhemoglobin-induced rise in intracellular Ca^{2+} to produce acute vasoconstriction after exposure of the vessel to blood (Takenaka et al., 1991a). Long-term oxyhemoglobin exposure enhanced the expression of voltage-gated calcium channels (VGCC), pointing toward important roles for VGCC in delayed vasoconstriction after SAH (Ishiguro et al., 2008).

In addition to R-type VGCCs, the components of low-voltage-activated (T-type) channels Cav3.1 and Cav3.3 have been shown to be significantly increased in the dog basilar artery after SAH (Nikitina et al., 2010); however the functional significance of this kind of channel in SAH is a matter of debate (Cook et al., 2012). Intracellular Ca^{2+} can activate endonucleases responsible for the cleavage of double stranded DNA (Moss et al., 1997). Furthermore, increased intracellular Ca^{2+} can trigger apoptosis of endothelial and smooth muscle cells, which is one of the factors attributed to BBB disruption and vasospasm (Macdonald et al., 1995; Zhang et al., 2013b; Zhang et al., 2001). In addition, a defect in the ionic mechanisms regulating Ca^{2+} permeability in the membrane of smooth muscle after SAH impairs smooth muscle relaxation (Aihara et al., 2004).

Treatments that target Ca^{2+} dysregulation have been explored in clinical and preclinical studies. In a model of SAH, glibenclamide, a selective antagonist of the Sur1-NCCa-ATP channel, attenuated several pathologic effects associated with the inflammatory response in response to extravasated blood (Simard et al., 2009; Simard et al., 2012b). Nimodipine, an L-type Ca^{2+} channel antagonist, is currently the only pharmacologic agent that has been shown to consistently improve neurological outcomes. However, it has not been found to be effective in clinical trials of cerebral vasospasm in patients with SAH (Dorhout Mees et al., 2007).

Mg^{2+} is a physiological antagonist of Ca^{2+}, which plays a crucial role in maintaining the intracellular concentration of Ca^{2+}. Moreover, it is neuroprotective and has a well documented clinical profile (McLean, 1994). The total level of Mg^{2+} in serum normally remained unchanged, but the level of biologically active free ionized Mg^{2+} decreased after traumatic brain injury (Memon et al., 1995). The various mechanisms of action of Mg^{2+} include reduction of excitatory amino acid release, blockage of the NMDA-glutamate receptor and voltage-dependent calcium channels, inhibition of platelet aggregation, inhibition of endothelin-1 synthesis, vasodilation through the release of endothelial nitric oxide (NO), and increased synthesis of prostacyclins (Berthon et al., 2003; Nadler et al., 1987; van den Bergh et al., 2004; Yang et al., 2000). Both animal studies and pilot clinical trials using magnesium sulfate have reported trends toward improved outcomes (Mori et al., 2011, 2012). In the Field Administration of Stroke Therapy–Magnesium (FAST-MAG) pilot trial, prehospital administration of magnesium is feasible and safe in acute ischemia stroke patients (Saver et al., 2004). Therefore, the results from FAST-MAG phase III are worthy of exception. However, intravenous magnesium sulfate administered after SAH did not improve the clinical outcome for patients in a phase 3 randomized, double-blind, placebo controlled, multicenter study (MASH-2 and IMASH) (Dorhout Mees et al., 2012; Wong et al., 2010). Likewise, intravenous magnesium sulfate did not benefit patients with ischemic stroke and intracerebral hemorrhage in the Intravenous MAGnesium Efficacy in acute Strokes (IMAGES) trial (Muir et al., 2004). There are some possible reasons for the

unsatisfactory results from the IMAGES trial. First, magnesium solutions were administered at the median time of 7 hr after stroke, which might be somewhat longer than the short-time window. In fact, only 3% of participants received the treatment within 3 hr of stroke onset. Second, unfortunately, the IMAGES trial did not measure the initial stroke severity, which is the most important predictor for outcomes. Finally, the detrimental effects from magnesium treatment in some patients may obscure the beneficial effects in others.

3.1.3.3.4 Chloride (Cl^-), a Neglected, but Important, Ion: Injury to the CNS by SAH results in a loss of ionic homeostasis that can lead to neuronal death. An increase in intracellular cations has been well established, but there are no studies of changes in intracellular anions after SAH (Galeffi et al., 2004). A rise in intracellular Cl^- has been observed in other CNS diseases except SAH, such as ischemia, seizure, neurodevelopmental disorders, and pain (Ben-Ari et al., 2012; Galeffi et al., 2004; Yeo et al., 2013; Zhang et al., 2013c). One of the major consequences of a rise in intracellular Cl^- is that $GABA_A$ becomes depolarizing, whereas it is normally hyperpolarizing. A loss of $GABA_A$-mediated inhibition may contribute to neuronal hyperexcitability observed after stroke, leading to neuronal damage (Gao et al., 1999; Urban et al., 1989; Zhang et al., 2013c). The Na-K-Cl cotransporter and the K-Cl cotransporter play a particularly important role in controlling the intracellular concentration of Cl^- (Ben-Ari et al., 2012). Thus, these two ion channels are considered novel targets for brain edema (Walcott et al., 2012).

Cl^- is a major anion in the brain (Terry, 1994), but to the best of our knowledge, there are no studies addressing changes in chloride and the expression of its cotransporter in pathophysiological events of SAH. As previously mentioned, a balance in intracellular Cl^- is necessary for the hyperpolarizing effects of $GABA_A$ in the adult brain. It is possible that attenuation of neuronal concentration of Cl^- post-SAH prevents the depolarizing effects of $GABA_A$, thereby influencing secondary brain injury. Future studies are needed to explore changes in intracellular Cl^- and its functional roles in SAH-induced neuronal death, which may provide a novel therapeutic target for SAH treatment.

3.1.3.3.5 Promising Ion Channels: The hyperpolarization-activated/cyclic nucleotide (HCN) channels are important regulators of neuronal excitability and network activity in a variety of nervous system diseases, such as neuropathic pain, epilepsy, and SAH (Jung et al., 2007; Tibbs et al., 2013). Li et al. found that oxyhemoglobin-induced neuronal hyperexcitability was mediated by HCN channels (Li et al., 2012). An important observation made in the study was that whole-cell recordings in rat brain slices indicated that perfusion of bloody CSF promoted neuronal hyperexcitability and blocked HCN currents in CA1 pyramidal neurons by scavenging NO (Li et al., 2012). Given the evidence of a potential role in SAH, these channels may emerge as an attractive therapeutic target to attenuate neurovascular dysfunction after SAH; however, this necessitates more research.

Another promising ion channel that warrants further investigation in regard to SAH is the purinergic receptor. Cytotoxic events following SAH, such as extracellular accumulation of ATP, may activate the purinergic receptor to stimulate the innate immune response and apoptotic/pyroptotic cell death as seen in ischemic stroke and CNS trauma (Burnstock et al., 2011; Dahl and Keane, 2012). Bloody CSF elicits a steep, transient rise in Ca^{2+} by activating ATP-sensitive P2 receptors in human astrocytes culture (Kasseckert et al., 2013). Depending on the activation scheme, *in vivo* purinergic receptors are non-selective cation channels (Locovei et al., 2006; Sperlagh et al., 2006). These receptors result exclusively in the formation of non-selective large ion pores, termed pannexin (Locovei et al., 2007). Based on the properties of these receptors, purinergic signaling may be a potential therapeutic target for limiting ion distribution after SAH.

3.1.4 Oxidative Stress: An Opportunity for Intervention—Reactive oxygen radicals are a key mediator of SAH pathology. Mounting data supports the early generation of reactive oxygen species (ROS) and oxidative stress after a SAH. The ROS produced include superoxide anion (O_2•), hydroxyl radical (OH•), hydrogen peroxide (H_2O_2), NO, and peroxynitrate(ONOO•) (Asano and Matsui, 1999; Ayer and Zhang, 2008; Gaetani et al., 1994; Lin et al., 2006; Marzatico et al., 1993; Petzold et al., 2005a; Schulz et al., 2000). The major origin of ROS following SAH is the leakage of O_2• from disrupted mitochondria due to a disturbance in the electron transport chain, and from the auto-oxidation of hemoglobin upon the lysis of erythrocytes into the subarachnoid space (Asano, 1999; Marzatico et al., 1993; Piantadosi and Zhang, 1996; Sercombe et al., 2002). Other sources of ROS include increased nitric oxide synthase (NOS) activity (Ayer and Zhang, 2008; Sehba et al., 2004a), hypoxic conversion of endothelial xanthine dehydrogenase to xanthine oxidase (Sermet et al., 2000), lipid peroxidation (Schulz et al., 2000), and an upregulation of NADPH oxidase post-SAH (Liu et al., 2007). Additionally, high levels of Ca^{2+}, Na^{+}, and ADP in the damaged cells stimulate excessive production of ROS by mitochondria (Martin et al., 2011; Viola and Hool, 2013).

There are several enzymatic antioxidant systems that are activated to combat free radical production during the typical cellular damage that occurs after SAH. Superoxide dismutase (SOD), glutathione peroxidases, and catalase are the major enzymatic scavengers in brain tissue (Lewen et al., 2000). However, levels of those endogenous antioxidant enzymes normally are not adequate to eradicate excess free radical formation. In both experimental models and clinical studies, there is an imbalance between the intrinsic antioxidant system and the production of ROS in the brain after SAH (Gaetani et al., 1998a; Kaynar et al., 2005; Marzatico et al., 1993; Marzatico et al., 1998). Thus, oxidative stress has been speculated to be one of the factors involved in the short- and long-term pathogenesis of SAH (Asaeda et al., 2005; Liu et al., 2007; Pyne-Geithman et al., 2009).

A large number of studies have provided evidence that oxidative stress plays a significant role in EBI (Zhuang et al., 2012). Experimental studies in rats indicate that the activities of enzymatic and non-enzymatic antioxidant systems (Cu-Zn and Mn SOD) decreased 1 hr after SAH and remained so until 48 hr later (Marzatico et al., 1993). The metabolic products of lipid peroxidation increased from 1 to 6 hr after SAH (Gaetani et al., 1990). Similarly, in humans, a decrease in antioxidant capacity and an increase in lipid peroxidation products were found within 72 hr after ictus and correlated well with poor clinical status and eventual outcome (Gaetani et al., 1997; Gaetani et al., 1998a; Hsieh et al., 2009; Kamezaki et al., 2002). The nuclear factor E2-related factor 2/antioxidant-response element (Nrf2/ARE) pathway, an important antioxidant defense (Zhang et al., 2013a), was activated in the brain after SAH, playing a beneficial role in EBI (Chen et al., 2011b; Zhao and Aronowski, 2013).

ROS can damage elements of the neurovascular unit by promoting lipid peroxidation, protein breakdown, and DNA damage (Ostrowski et al., 2006a). Some of the consequences of oxidative stress after SAH include neuroinflammation, disruption of the BBB, and production of spasmogens (Gaetani et al., 1990; Yun et al., 2013). Intracellular ROS activate NF-κB to upregulate NOS 2 (Chen et al., 2012). In addition, ROS can activate apoptotic signals, including p53, caspase-3 and caspase-9 to promote apoptotic cell death (Lu et al., 2013). Overexpressing CuZn-SOD in transgenic mice prevented apoptotic cell death (Matz et al., 2000), and reduced mortality via activation of Akt/GSK3 beta survival signaling after SAH (Endo et al., 2007).

Therapeutic avenues to reduce EBI and vasospasm after SAH by targeting oxidative stress have been explored. Treatment with hydrogen, a medical gas used in novel experimental studies of SAH, alleviated EBI and vasospasm by decreasing the oxidative stress-induced

injury (Hong et al., 2012; Zhan et al., 2012). Hyperbaric oxygen suppressed NADPH oxidase and the level of oxidative stress in cerebral tissues at 24 hr after SAH (Ostrowski et al., 2006b). Although systemic antioxidants showed substantial success in preventing oxidative stress and decreasing vasospasm in experimental SAH, there has been minimal success in translating this approach into clinical trials (Germano et al., 1998; Zhang et al., 2010). Also, oxidative stress seems to occur soon after SAH; thus, an effective therapeutic window is the biggest challenge for clinical translation. It is possible that the injury caused by free radicals may occur even before a patient can receive effective treatment (Haley et al., 1997; Kassell et al., 1996; Lanzino and Kassell, 1999; Lanzino et al., 1999), which is a possible explanation as to why clinical trials of free radical scavengers have failed.

3.1.5 Inflammation: A Promising Area of Research for New Treatments—A burgeoning body of researches suggests that many components of the inflammatory response contribute to the progression of an injury after an aneurysm ruptures. Microglias are the resident immunocompetent and phagocytic cells in the CNS, which play a crucial role in neuroinflammation (Kim et al., 2013; Xiao et al., 2013). Similar to microglias, astrocytes are capable of synthetizing and secreting inflammatory factors, such as cytokines and chemokines (Hutchison et al., 2013). The existing literature provides evidence that a variety of factors that are linked to the development of inflammatory lesions. It emphasizes brain injury mediated by inflammatory cells, which proliferate in response to the secretion of cytokines from leukocytes and glia cells, which itself is in response to the free radical-inducing properties of extravascular hemoglobin in the subarachnoid space.

3.1.5.1 Cytokines: A variety of inflammatory cytokines, including interleukin (IL)-1α, IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α, have been shown to be strongly associated with brain injury in both patients and animals after SAH (Gaetani et al., 1998b; Greenhalgh et al., 2012; Larysz-Brysz et al., 2012). High-mobility group box 1, a potent proinflammatory mediator, was increased after SAH and has been proposed to be a useful, complementary tool for predicting functional outcome and mortality after SAH (Zhu et al., 2012). In addition, convincing data implicate cytokines in the development and maintenance of neurovascular injury. IL-1β, IL-6, and matrix metalloproteinase (MMP)-9 expressions were elevated over time. They showed an early increase at around 6 hr, and a late peak between 48–72 hr, post-SAH in the cerebral arteries. This occurred via early activation of the mitogen activated protein kinase kinase (MEK)- extracellular signal-regulated kinase 1/2 (ERK1/2) pathway (Maddahi et al., 2012). A significant difference was observed in the mRNA expression of IL-1α, IL-6, and IL-8 in the canine basilar artery over the course of days after SAH, with maximal expression during the peak of vasospasm (Aihara et al., 2001).

Additionally, the role of NF-κB, a key transcriptional regulator of inflammatory genes, has been elaborately studied after SAH. You et al. recently demonstrated that the activated NF-κB in neurons plays an important role in regulating the expression of inflammatory genes in the brain and ultimately contributes to delayed brain injury after SAH (You et al., 2013).

A number of anti-inflammatory strategies have been utilized to reduce inflammation after SAH. Pyrrolidine dithiocarbamate, an NF-κB inhibitor, reduced the levels of TNF-α and IL-1β mRNA 5 d after SAH in a rabbit model and thereby suppressed the post-SAH inflammatory response (You et al., 2013). Neutralization of IL-1β by an anti-rat antibody resulted in a significant decrease of both endothelin-1 and TNF-α, but not of IL-6, in the peripheral blood (Larysz-Brysz et al., 2012). Furthermore, inhibition of IL-1β by its pharmacological antagonist attenuated EBI via the inhibition of c-Jun N-terminal kinase (JNK)-mediated induction of MMP-9 and consequent preservation of tight junction protein zonula occludens-1 after SAH (Sozen et al., 2009). Thus, a novel, safe, and effective anti-

inflammatory drug might be a promising strategy to improve the outcome of patients with SAH (Sercombe et al., 2002).

3.1.5.2 Chemokines: Chemokines are a class of small cytokines or signaling proteins that induce the migration of nearby blood borne inflammatory cells toward the source (Lakhan et al., 2009; Li and Ransohoff, 2008; Reaux-Le Goazigo et al., 2013). Consequently, these molecules play an important role in cell recruitment in the damaging inflammatory processes after stroke. They also are involved in cell to cell communication (Hughes et al., 2002; Kim et al., 1995).

Expression of chemokines, such as monocyte chemotactic protein-1 (MCP-1) (Wang et al., 2011), chemokine (C-C motif) ligand 5 (CCL5) (Smithason et al., 2012), and chemokine (C-X-C motif) ligand 1 (CXCL1), are strongly upregulated in the cortex following SAH. The elevation of chemokines CCL5 and CXCL1 were suppressed in mice with myeloid cell depletion after SAH (Smithason et al., 2012). The level of MCP-1 was increased in a time course parallel to the development of cerebral vasospasm in a prospective clinical study (Kim et al., 2008). These findings suggest that the administration of specific MCP-1 antagonists might prevent cerebral vasospasm and improve the poor outcome caused by SAH (Lu et al., 2009). It also implies that serum MCP-1 could be a possible biomarker for SAH.

Another report that evaluated the human cerebral response of the neurotrophins fibroblast growth factor-2 (FGF2) following SAH shows that FGF2 peaked 2 d after SAH. This study also identified the potential threshold values for the chemokine to serve as a monitoring indicator in the neurosurgical intensive care unit (Mellergard et al., 2010). In conclusion, chemokines are a fascinating family of peptide mediators that contribute to neuron-neuron, glia-glia, or neuron-glia communications relevant to SAH and are possible targets for developing new therapeutic approaches for SAH.

3.1.5.3 Cellular Adhesion Molecules: Mounting evidence shows that the leukocyte-endothelial interaction exerts a crucial effect in the pathogenesis of SAH. Elevated leukocyte count has been reported to increase the risk of experiencing symptoms of vasospasm, and it was closely associated with a 90% rate of poor outcomes. Adhesion molecules are important mediators of inflammation after stroke, and essentially help cells stick to each other or to their surroundings. They are proteins located on the surface of cells including the immunoglobulin superfamily, integrins, cadherins, and selectins, all of which have been detected in patients with SAH. These adhesion molecules are well known to mediate endothelial capture, adhesion, extravasation of leukocytes, and recruitment to the site of injury (Chaichana et al., 2010; Polin et al., 1998; Yang et al., 2012).

Studies have demonstrated that the levels of soluble forms of E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) were significantly elevated in the CSF and serum of patients after SAH as compared to normal controls (Kubo et al., 2008). ICAM-1 is heavily glycosylated and possesses binding sites for a number of immune-associated ligands. ICAM-1 binds to LFA-1 (Lymphocyte Function-Associated Antigen-1), a glycoprotein receptor found on the surface of leukocytes (Marlin and Springer, 1987). When activated, leukocytes bind to endothelial cells via ICAM-1/LFA-1 and then transmigrate into brain tissue through the vascular endothelium (Yang et al., 2006).

In a rat model of SAH, the expression of ICAM-1 was enhanced in the endothelial layer of the basilar artery (Handa et al., 1995). The level of ICAM-1 mRNA increased early soon after SAH, and peaked around day 7 in parallel with the persistent contraction of the basilar

artery (Aihara et al., 2001). The anti-ICAM-1 antibody reduced vasospasm by 22% following SAH (Bavbek et al., 1998). 6-mercaptopurine was effective in preventing and reversing arterial narrowing by inhibiting ICAM-1 and E-selectin in a rodent model of SAH (Chang et al., 2010).

E-selectin and P-selectin may also play an important role in mediating SAH-induced inflammation. A marked increase in the concentration of E-selectin was observed in both the CSF and serum from patients with SAH as compared to control (Tanriverdi et al., 2005). It was especially high in patients who later developed moderate to severe vasospasm (Polin et al., 1998). Furthermore, it has been reported that the monoclonal antibody against E-selectin has a therapeutic effect similar to that of the anti-ICAM-1 antibody in terms of attenuating vascular injury after SAH (Lin et al., 2005). A higher serum level of neutrophil P-selectin glycoprotein ligand-1 at time of admission suggests an impending DCI in patients with aneurysmal SAH (Yang et al., 2012).

Additionally, a new target for SAH is the adhesion molecule vascular adhesion protein-1 (VAP-1), a novel type of adhesion molecule with semicarbazide-sensitive monoamine oxidases activity. Mounting evidence suggests that VAP-1 is an inflammation-inducible endothelial glycoprotein. The expression and role of VAP-1 has been explored in both patients and animal models of stroke (Airas et al., 2008; Ma et al., 2011). However, there are no studies exploring the role of VAP-1 in SAH, which has the potential to be a target of pharmaceutical interest.

3.1.5.4 Inflammasomes: An Emerging Inflammatory Mediator: The nucleotide-binding domain, leucine-rich repeat containing (NLR) recently received attention because of its role in innate immune regulation and genetic linkage to human inherited autoinflammatory syndromes (Jha and Ting, 2009). Inflammasome complexes that are assembled in response to danger signals lead to the autoactivation of pro-caspase-1, which in turn activates pro-IL-1β/IL-18 (Deroide et al., 2013; Lippai et al., 2013). Since there are more than 20 NLR members, the next step would be to identify which of the inflammasomes are involved in the SAH pathology. Understanding inflammasome pathways may provide insight into the development of neuroinflammation after SAH.

3.1.6 Apoptosis: A Target for Future Therapeutic Intervention—Apoptosis is a potentially reversible process that is characterized by energy-dependent programmed cell death to dispose of redundant cells (Taylor et al., 2008). Apoptosis after SAH may be caused by elevated ICP, the neurotoxicity of blood breakdown components, ischemia, and reperfusion, as well as by acute vasospasm (Bederson et al., 1998; Matz et al., 2001). Even a brief brain insult is sufficient to trigger complex cellular events that subsequently can lead to progressive apoptotic cell death.

Apoptosis was first identified in a patient who died of SAH-induced cerebral vasospasm (Zubkov et al., 2000). A number of studies have since revealed apoptotic pathways and cascades within the cortical, subcortical or hippocampal neurons, endothelium, and vascular cells following the onset of SAH (Ostrowski et al., 2006a). A number of intrinsic and extrinsic apoptotic pathways are activated after SAH, including the death receptor pathway, the caspase-dependent and -independent pathways, as well as the mitochondrial pathway (Cahill et al., 2006; Cheng et al., 2009; Endo et al., 2007; Hasegawa et al., 2011b).

3.1.6.1 Apoptosis in Neuronal Cells: If the initial bleed following SAH is severe enough to block blood flow into the brain, as in the case of a global stroke, it is unlikely that the cerebral tissue will survive. Apoptosis might play an important role in SAH pathology, and neuronal apoptosis can occur after SAH (Cahill et al., 2006). Matz et al. injected hemolysate

into the subarachnoid space and then observed apoptotic cells in the neocortex closest to the injection site (Matz et al., 2001). In an endovascular perforation rat model of SAH, pathological changes of apoptosis were noted in most brain regions, especially in the basal cerebral cortex and hippocampus (Park et al., 2004). Caspase-3 and apoptotic cells were present not only in the basal cerebral cortex, which was exposed to bloody CSF, but were also evident in the hippocampal dentate gyrus and CA1 region, which is the region most vulnerable to damage. Further, apoptosis related proteins, including apoptosis-inducing factor, cytochrome C, P53, and caspases, have been shown to be activated after SAH (Simard et al., 2012a; Yuksel et al., 2012). Endoplasmic reticulum stress has also been implicated in orchestrating neuronal apoptosis via C/EBP homologous protein (CHOP) in response to SAH (He et al., 2012a).

The role of mitogen-activated protein kinases (MAPKs), including ERK1/2, JNK, and p38, in EBI induced apoptosis has been studied. JNK and p38 were activated in response to apoptotic cascades (Hasegawa et al., 2011b), while ERK1/2 was significantly decreased in the dentate gyrus but, not in the cortex or hippocampus (Lin et al., 2009). Yatsushige et al. demonstrated the neuronal programmed death was mediated through the activation of JNK/c-Jun pathway (Yatsushige et al., 2007). MAPKs alter both a variety of proapoptotic proteins, including c-Jun, p53, bim, and bax, and anti-apoptotic proteins, such as Bcl-2 and Bcl-xl following SAH. Furthermore, the “tropomyosin-related kinase” receptor family is usually associated with cell survival, differentiation and apoptosis (Boulle et al., 2012). Preservation of tropomyosin-related kinase B signaling by sodium orthovanadate attenuates neuronal apoptosis after SAH (Hasegawa et al., 2011a).

Akt, a serine/threonine kinase, is one of the key anti-apoptotic signaling molecules downstream of phosphoinositide 3-kinase, which mediates a protective effect against neuronal apoptosis and vasospasm after SAH (Duris et al., 2011; Endo et al., 2006; Sugawara et al., 2008; Zhuang et al., 2011). An elevated expression of phospho-Akt and phospho-GSK3βwas described in the cerebral tissue after SAH, but it was not sufficient to protect the brain. Administration of pharmacological agents, such as the α7 nicotinic acetylcholine receptor agonist and simvastatin, enhanced p-Akt and p-GSK3β and attenuated neuronal apoptosis (Cheng et al., 2010; Duris et al., 2011). Recently studies have shown that anti-apoptotic drugs ameliorate negative outcomes after SAH in animal models (Zhou et al., 2004; Zubkov et al., 2002). Current anti-apoptotic therapies for SAH focus on the MAPK pathway (Cahill et al., 2007; Suzuki et al., 2010b), the tumor suppressor p53 (Chen et al., 2011a; Li et al., 2010), and hypoxia inducible factor-1 (HIF-1) target genes. Additionally, intravenous mesenchymal stem cell administration *in vivo* provided neuroprotective effects by ameliorating neural cell apoptosis in SAH animal models (Khalili et al., 2012).

3.1.6.2 Apoptosis in Endothelial Cells and Blood Brain Barrier (BBB) Disruption:
Under normal physiological conditions, the BBB permits only water, ions, small lipophilic molecules, and a limited number of nutrients transported via receptor-mediated transcytosis (i.e., glucose, some amino acids, heparin, and transferrin) to enter the brain (Broadwell et al., 1996). Plasma-borne macromolecules and most cellular elements are prevented from crossing the BBB because of continuous-type endothelial cells and the junction complexes that maintain the integrity of the BBB. A remarkable increase in capillary permeability occurs at a very acute stage after experimental SAH (Peterson et al., 1990). Increased extravasation of Evans blue dye in the ipsilateral hemisphere occurred as early as 3 hr after SAH in rats, with a maximal extravasation at 48 hr (Doczi et al., 1986a; Doczi et al., 1986b). A difference in barrier disruption of the intraparenchymal vessels located from proximal to distal to cisternal clots was detected following SAH in rabbits (Johshita et al., 1990). Early impairment of the BBB contributes to vasogenic edema, which results in brain volume expansion and prolongs ICP elevation after SAH.

Endothelial cells are an important component of the BBB and essential for maintaining the integrity of the BBB. Apoptotic death of endothelial cells can lead to destruction of the BBB and directly exposes smooth muscle cells to harmful blood components that can ultimately worsen the consequences of SAH. Zubkov et al. introduced the concept of apoptosis of cerebral endothelial cells in relation to a delayed cerebral vasospasm in a patient with SAH (Zubkov et al., 2000). Early apoptosis of endothelial cells may trigger, aggravate, and maintain delayed cerebral vasospasm (Chen et al., 2008; Zubkov et al., 2001). The mechanism of apoptosis in endothelial cells involves the TNF-α receptor-1 and the caspase-8 and caspase-3 pathways. Caspase-3 activation and DNA fragmentation in the endothelial cells starts within 10 min of SAH (Friedrich et al., 2012b). Additionally, upregulated p53 modulation of apoptosis induced apoptosis of microvascular endothelial cells in the hippocampus may play a significant role in the disruption of the BBB that occurs after SAH (Yan et al., 2011).

A variety of anti-apoptotic strategies have shown favorable results in treating endothelial apoptosis after SAH. Beneficial effects have been reported upon inhibition of caspase activity in endothelial cells after SAH (Gules et al., 2003), and caspase inhibitors may also have a potential role in the treatment of cerebral vasospasm (Zhou et al., 2004). For example, CHOP siRNA reduced apoptosis signaling effectors, bim and caspase-3, to ameliorate EBI. Furthermore, inhibition of CHOP effectively combats apoptotic mechanisms of cerebral vasospasm set in the basilar artery endothelia (He et al., 2012b). The beneficial effect of recombinant human erythropoietin on vasospasm after SAH may be related to its anti-apoptotic effects of the endothelial cells in the basilar arteries, mediated in part by the JAK2/signal transducer and activator of the transcription signaling pathway (Chen et al., 2009). Treatment with antioxidants such as alpha lipoic acid attenuated the severity of endothelial apoptosis (Erdi et al., 2011).

3.1.7 Autophagy: A New Player in EBI—Autophagy is a cellular process that causes degradation of long-lived proteins and organelles and recycling of cellular constituent to ensure cell survival. It plays a role in regulating the turnover of cellular constituents, which plays a role in mediating in cell homeostasis. Autophagy has recently been recognized as a form of cell death that occurs after SAH, as do apoptosis and necrosis. Indeed, Lee et al. identified the autophagic death of neurons as the third mode of cell death after SAH (Lee et al., 2009a).

To date, autophagy has been studied extensively in stroke, but only to a limited degree in SAH. In experimental SAH, autophagy was found to be activated in neurons as early as 6 hr after experimental SAH (Zhao et al., 2013). Moreover, the conversion of light chain-3 I to light chain-3 II and expression of beclin-1 increased significantly, thus suggesting that autophagy is activated during EBI (Lee et al., 2009a; Zhao et al., 2013). However, it remains an open issue as to whether activation of autophagy is an inducer of death as a part of harmful response or a stopper of death as a part of an endogenous neuroprotective response (Carloni et al., 2008; Wen et al., 2008).

After an interaction between apoptosis and autophagy was demonstrated, rapamycin and simvastatin were tested and shown to inhibit apoptosis by activating post-SAH autophagy (Zhao et al., 2013). Conversely, ischemic insult triggered autophagy, and thus an autophagic mechanism may contribute to neuronal injury after cerebral ischemia (Wen et al., 2008). When autophagy was inhibited by 3-methyladenine and wortmann in SAH rats, neuronal apoptosis were increased and neurological function deteriorated. Brain edema and disruption of the BBB were further aggravated, suggesting that autophagy may have a beneficial effect (Jing et al., 2012; Wang et al., 2012). However, the precise role of autophagy in the pathogenesis following SAH is requires further investigation, as in other CNS diseases.

Next, the cross-talk between autophagy (self-eating) and apoptosis (self-killing) merit the imagination of stroke scientists.

3.1.8 Necrosis: An Unregulated Cell Death—SAH simultaneously activates both apoptotic and necrotic pathways. Apoptosis and necrosis can be differentiated according to the morphological and biochemical differences, especially in early membrane disruption. Conventional knowledge categorizes necrosis to be an accidental and uncontrolled mode of cell demise, characterized by swollen organelles, increased cell volume, early membrane integrity loss, and cellular collapse. Currently, necrosis is observed to contribute to a wide range of pathological forms of cell death following SAH. However, little research effort has been made to eliminate necrosis after SAH, possibly due to the widely held belief in its unregulated manner. A study using cultured cells showed a high oxyhemoglobin concentration induced necrosis in aortic smooth muscle cells, suggesting necrosis contributes to vascular wall changes after SAH (Ogihara et al., 2001). Oxyhemoglobin also exerts a necrotic effect on cultured astrocytes (Rollins et al., 2002). Considering the discrepancy between *in vitro* study and *in vivo* studies, animal SAH experiments must be performed. After continuous superfusion with artificial CSF containing hemoglobin, necrosis was induced in focal areas of the cortex (Dreier et al., 2000). Additionally, tumor necrosis factor levels are elevated after SAH, which can lead to necrosis (Lin et al., 2004). Neuronal necrosis began very early in SAH rat models (Friedrich et al., 2012b). Some mechanisms are responsible for SAH-induced necrosis. ATP depletion is an initial trigger in SAH-induced necrotic cell death. The other potential candidates are calcium and ROS. ROS stimulates oxidative stress that damages lipids, proteins, and DNA, subsequently leading to mitochondrial dysfunction, ion balance deregulation, rapid loss of membrane integrity, and finally necrosis. Elevated cytosolic calcium levels result in mitochondrial calcium overload and activation of calcium-dependent proteases and phospholipases, which trigger necrosis. Bloody CSF from hemorrhagic patients causes necrosis in cultured human astrocytes via increased calcium levels. An ATP-sensitive P2 receptor antagonist inhibited the bloody CSF-induced calcium peak and consequent necrosis (Kasseckert et al., 2013).

Recently, accumulating studies revealed necrosis could be a programmed process like apoptosis, which challenged the traditional view of necrosis. A new form of non-apoptotic caspase-independent cell demise, termed as necroptosis, has attracted attention in the CNS (Fricker et al., 2013). Our next step is to evaluate whether necroptosis is a novel death pathway after SAH.

3.1.9 Cerebral Edema: A Major Contributor to Poor Outcomes—Global cerebral edema is a common and important feature of both experimental and clinical SAH (Altay et al., 2012b; Westermaier et al., 2012). It is evident in 6–8% of patients at admission and develops in an additional 12% over the first 6 d, as assessed by CT scans (Claassen et al., 2002; Kassell et al., 1990). Four types of cerebral edema have been characterized: vasogenic, cytotoxic, osmotic, and interstitial. In SAH, cerebral edema that develops soon after the initial bleeding could be classified mainly as both a primary vasogenic and secondary cytotoxic component (Barry et al., 2012). Global cerebral edema after SAH reflects disruption of the BBB due to the apoptosis of endothelial cells, degradation of the basal-lamina by proteases, diffuse inflammatory reaction or neurotoxic effects of blood and its degradation products, ischemic injury due to transient ictal cerebral circulatory arrest, abnormal autoregulation due to microvascular damage, or dysfunction of vasomotor centers located in the brainstem (Claassen et al., 2002; Keep et al., 2005; Sehba et al., 2007).

In experimental studies, cerebral edema has historically been quantified as a change in the percentage of water content in brain (i.e., water content divided by wet weight) (Adachi and Feigin, 1966). However, that measurement can be influenced by the technical abilities of the

investigator and by other conditions, such as room temperature, humidity, and air flow. Therefore, if not measured carefully, the number can, be misleading as “small” changes in the percentage water content actually mirror much larger changes in brain swelling. Thus, constant temperature and humidity are needed when measuring brain edema using the dry/wet method. Furthermore, some investigators have even suggested that it would be valuable to find a new equation that might better reflect the impact of edema after SAH (Keep et al., 2012). Until then, it is recommended that researchers measure brain swelling by imaging techniques, such as computed tomography and magnetic resonance imaging, or by thermal conductivity (Keric et al., 2012; Ko et al., 2012).

3.2 Delayed Brain Injury (DBI)

DIND is the leading cause of morbidity and mortality in patients who survive the initial impact of SAH and have had their aneurysm effectively treated (Crowley et al., 2008; Fergusen and Macdonald, 2007). Recent studies have demonstrated a host of critical, interrelated pathologies arising in the subacute phase of SAH as a result of EBI, and this phenomenon is designated as DBI. With advances in understanding the pathophysiology of SAH, it has become clear that the mechanisms leading to EBI and DBI are not mutually exclusive. In fact, many of the pathogenic triggers are interrelated.

3.2.1 Delayed Cerebral Vasospasm: From Extravascular Blood to Vessel Lumen—

Historically, cerebral vasospasm after SAH was considered to be a prolonged contraction of the smooth muscle cells and abnormal endothelial hypertrophy, inflammatory changes, and gene expression in the cerebral arteries, finally leading to tissue ischemia (Rothoerl and Ringel, 2007). The central event in the contraction of vascular smooth muscles is an increase in the concentration of intracellular Ca^{2+}. Indeed, in the last century, there was a wide assumption that vasospasm was the main cause of poor outcomes for patients with SAH (Kassell et al., 1990). Several studies found a strong link between radiologically confirmed vasospasm and clinical symptoms of DCI (Fergusen and Macdonald, 2007; Rabinstein et al., 2004). As mentioned above, SAH-induced DCI is a clinical syndrome of focal neurological and cognitive disorder. Unpredictably, it occurs in 30% patients from 3–14 d after the initial bleeding (Dorsch and King, 1994).

In vasospasm, overflowed blood from a ruptured aneurysm triggers a chain reaction of cerebral artery vasoconstriction, brain tissue infarction, and clinical condition deterioration. The most powerful predictors of vasospasm is including the volume, density, and prolonged presence of subarachnoid blood surrounding the arteries (Fisher et al., 1980; Loch Macdonald, 2006; Reilly et al., 2004; Suzuki et al., 1980). Conversely, vasospasm was invariably absent in those patients with only a minimal subarachnoid blood load (Fisher et al., 1980). In the filament model of SAH, contraction of the large arteries in the Willis circle in rats after SAH is ascribed to the persisting subarachnoid blood clot. Vasospasm began on the third day after the onset of SAH, and was maximal at 6–8 d, eventually lasting 2–3 wk (Wilkins, 1990). In sum, it is reasonable to suppose that cerebral vasospasm commonly takes place during DBI. However, there is not adequate evidence to conclude that vasospasm, in and of itself, could be used as a surrogate marker to monitor SAH progression and the efficacy of interventions (Nolan and Macdonald, 2006).

The effects of vasoactive agents have long been studied in regard to the pathogenesis of vasospasm (Roman et al., 2006). These include neurogenic factors, biogenic amines (such as histamine and norepinephrine), 20-hydroxyeicosatetraenoic acid (Mulligan and MacVicar, 2004), eicosanoids (such as prostaglandins, thromboxans and leukotrienes), ion (Girouard et al., 2010), and free radicals (Nishizawa and Laher, 2005). Astrocytes and leukocytes release endothelin-1, a potent vasoconstrictor in response to SAH. In addition, endothelin receptors

are upregulated (Beg et al., 2006; Fassbender et al., 2000; Hansen-Schwartz et al., 2003b; Pluta et al., 1997).

SAH increased the expression of G-protein-coupled vasoconstrictor receptors in cerebral arteries, including ET_B, 5-HT_{1B}, AT_1, and TX_{A2} receptors (Hansen-Schwartz et al., 2003a; Povlsen et al., 2012). The Rho/Rho-kinase pathway is the main regulator of these actin-dependent cell functions in the pathogenesis of sustained smooth muscle cell contraction and vasospasm (Satoh et al., 2012; Takai et al., 1995). Therefore, the combination of treatment with an inhibitor of RhoA, pitavastatin, and an inhibitor of Rho-kinase, fasudil, could extensively prevent cerebral vasospasm after SAH (Naraoka et al., 2013). Furthermore, phosphorylations trigger SAH-induced vasculopathy in cerebral arteries, as determined by quantitative mass spectrometry, including focal adhesion complexes, ERK1/2, calcium calmodulin-dependent kinase II, STAT3, and c-Jun (Parker et al., 2013). Tenascin-C, a matricellular protein, induces cerebral vasospasm via TLR4 and activation of JNK and p38 (Fujimoto et al., 2013; Suzuki et al., 2013). Animal experiments have shown a benefit from inhibiting the PKC and MAPK pathways on cerebral vasoconstriction (Beg et al., 2007; Hansen-Schwartz et al., 2008) thus engendering enthusiasm that preconditioning stimuli may protect against SAH, as vasospasm-induced brain damage is anticipated after SAH (Wang et al., 2013b).

3.2.2 Microcirculatory Spasm and Dysfunction—Study of the changes in the microcirculation due to SAH started about 30 years ago (Herz et al., 1975; Wiernsperger et al., 1981). The concept of microvascular spasm is evolving, and recently, more attention has been paid to the functional and structural changes in microcirculation (Kozniewska et al., 2006). Under normal conditions, the cerebral microvasculature can accommodate, to a certain extent, decreased perfusion pressure through vasodilation, a process underlying pressure autoregulation (Paulson et al., 1990). SAH resulted in failure of the microcirculation, including a significant decrease in the mass density of capillaries, vasocontraction in small arteries, and changes of the vessel wall that might lead to laminar, triangular, or round cortical infarcts (Ohkuma et al., 2000; Weidauer et al., 2008). Herz et al., demonstrated that topical applications of homologous blood alone could result in a 33% vasoconstriction in guinea pigs, which was consistent with a subsequent cortical infarction (Herz et al., 1975). Progressive disturbances of the microcirculation result in, and/or contribute, to formation of microthrombi (Sabri et al., 2012). Disturbances in the microcirculation were found to be accompanied by disruption of the barriers of the intraparenchymal microvessels located distal or proximal to experimental clots in rats (Johshita et al., 1990). The thrombin receptor (protease-activated receptor-1) has been observed as playing a role in disruption of the endothelial barrier of hippocampus tissue (Yan et al., 2013). In addition, a spasm may occur in microcirculation in dissociation with the state of extraparenchymal vessels (Ohkuma and Suzuki, 1999).

Aside from measuring CBF, which is the more common method, a study utilizing orthogonal polarizing spectral imaging showed that mono- and multi-segmental cortical arterioles constrict after SAH with a reduction in diameter of up to 75% (Uhl et al., 2003). Ohkuma et al. noted that CBF was clearly associated with a prolonged circulation time in the cerebrum, even in patients without demonstrable spasms of large vessel, thus suggesting the impact of microcirculatory changes on constriction (Ohkuma et al., 2000). Although these data suggest that there are likely some microvascular perturbations after SAH, how these factors independently contribute to poor outcomes after SAH remains unknown.

3.2.3 Microthrombosis: An Additional Explanation for DCI—Microthrombosis has been attributed to the aggregation of platelets subsequent to the activation and amplification of the coagulation cascade after SAH. The presence of multiple microthrombi were, for the

first time, confirmed in the autopsy of an SAH patient in 1983 (Suzuki et al., 1983), and have since then been confirmed in larger studies. A number of markers of microthrombosis are significantly upregulated after SAH, including fibrinopeptide A, tissue factor, and thrombin-antithrombin complexes (Stein et al., 2006; Vergouwen et al., 2008). Endothelial NOS knockout and decreased P-selectin reduce the formation of microthrombi after SAH (Sabri et al., 2012; Sabri et al., 2013a). Furthermore, the concentrations of these thrombotic markers were significantly elevated within days of SAH in patients who eventually developed DCI (Dorsch, 2011).

A very recent study showed that approximately 30% of constricted arterioles were occluded by the microthrombi, suggesting that microthrombosis may be an etiology of the perfusion deficits and CPP-independent decrease in CBF after SAH (Friedrich et al., 2012a). Another line of investigation has suggested that microthrombi not only mechanically occlude the vessel, but also mediate vascular damage and constriction as the platelets aggregate and neutrophil infiltrates (Friedrich et al., 2011; Sehba et al., 2005). Intraluminal platelet aggregates can occur as soon as 10 min after SAH and are associated with injury to the vessel wall, including damage to the endothelium and the microvascular basal lamina (Friedrich et al., 2010). Further, platelet aggregates can be amplified and stabilized through thrombin activation as well. The intracellular contents of platelets include serotonin, thrombin and adenosine diphosphate and MMP-9, which are known to potentially mediate vasoconstriction, degrade collagen IV in the microcirculation, and thus lead to disruption of the BBB (Scholler et al., 2007; Sehba et al., 2004b).

3.2.4 Cortical Spreading Ischemia—Cortical spreading ischemia is a newly described phenomenon in which ischemia is the consequence of neuronal/glial depolarization in experimental SAH and in patients with SAH (Dreier et al., 1998; Dreier et al., 2009). Spreading ischemia in the cortex occurred when CBF reached 40%–70% compared to baseline, which was deemed to be 100%. Cortical spreading ischemia produced widespread cortical necrosis. In animal models, a number of pathologic conditions have been demonstrated to trigger CSD with spreading ischemia, such as hypoxia, hypotension, transient ischemia from microemboli, low glucose level, NO depletion, and free hemoglobin and high extracellular K^+ from erythrocytes (Dreier et al., 2000; Dreier et al., 1998; Nozari et al., 2010).

3.3 Are We Close to Solving the Mystery of SAH?

Recent data challenge the traditional concept of delayed vasospasm as the sole cause of DCI after SAH (Kusaka et al., 2004; Macdonald et al., 2007). Beyond vasospasm, an emerging body of evidence at present suggests that DIND is likely to have a multifactorial etiology. Recently, in the randomized, double-blind, placebo-controlled, phase III trial, clazosentan (15mg/h), an endothelin receptor antagonist, significantly decreased vasospasm-related morbidity, but did not significantly improve functional outcome in patients with aneurysmal SAH (Macdonald et al., 2012; Sabri et al., 2011). The mismatch between treatment of vasospasm and poor clinical outcome after SAH could have resulted from other underlying mechanisms of injury as opposed to vasospasm. To date, clinical trials have concentrated on vasospasm, which may be a wrong focus for SAH studies, since our increasing understanding of the SAH pathophysiology reveals EBI to be a major player in SAH-induced injury (Gomis et al., 2010).

A severe increase of ICP during the initial bleeding event has been identified as triggering subsequent pathophysiological changes after SAH. In recent years, EBI has evolved as a potential target to implement treatment modalities in patients with SAH, which could ameliorate some of the devastating injuries in the long term (Cahill et al., 2006). It can be

suggested that vasospasm might be only a late manifestation of EBI (Povlsen et al., 2013), because they share many of the same pathogenic factors. Further, EBI may also contribute to the pathogenesis of delayed neurological deficits. Nevertheless, research on EBI after SAH has been relatively limited; further studies are needed to clarify the exact mechanisms involved in EBI, which may reveal new therapeutic avenues that can be exploited in combination with anti-vasospasm medications. A comprehensive assessment of patterns of biomarkers during the past three years for predicting the SAH outcome is provided in Table 1.

Spontaneous recovery can occur in other types of stroke. For instance, in rats, a small fraction of dead striatal neurons is replaced by new neurons after ischemic stroke (Arvidsson et al., 2002). Neurogenesis in the hippocampus may affect functional outcome 30 d after SAH (Mino et al., 2003). However, the involvement of neurogenesis in SAH has not yet been sufficiently examined. It will be important to clarify whether and how SAH induces the differentiation of new neurons. Furthermore, signaling molecules that attract neuronal migration to the damaged area should be identified. A novel therapeutic strategy could be explored if neuronal regeneration can be stimulated, and the developing neurons can sustain and remain functional at the injury site after SAH.

4. The Vasculo-Neuronal-Glia Triad Model in SAH—A Paradigm

In recent years, strategies targeting neurons have been uniformly unhelpful in clinical trials. Mechanistic investigations into brain function have shifted from a purely “neurocentric” focus into emphasizing a more integrative perspective that involves all cell types in the CNS diseases, including stroke and neurodegenerative diseases (Gorelick et al., 2011; Guo and Lo, 2009; Lecrux and Hamel, 2011; Zlokovic, 2011).

Traditionally, the neurovascular unit was though of as a structural arrangement, with microvessel components and neurons connect via common astrocytes. It is a conceptual framework that links microvesicular and neuronal functions and their responses to injury without including the large vessels (del Zoppo, 2012). Here, we propose an emerging concept of the vasculo-neuronal-glia triad model in SAH pathology, in order to emphasize the interactions among different types of cells, including neurons, astrocytes, capillary and noncapillary endothelial cells, pericytes, smooth muscle cells, perivascular nerves, fibroblasts, smooth muscle progenitor cells, and veins (Figure 4).

4.1 The Rationale of Vasculo-Neuronal-Glia Triad Model in SAH

The brain receives up to 20% of its blood from cardiac output. It does not possess any reserve of energy or oxygen. Thus, it relies on a constant perfusion to fulfill its energetic demands, particularly when neuronal activity is increased (Siesjo and Plum, 1971). The blood can adequately deliver supplies of oxygen, glucose, and other nutrients, while taking away metabolic products, such as lactic acid and carbon dioxide. When blood flow to the brain stops or is greatly reduced, the functions of the brain stop within seconds and damage to neurons may occur within minutes (Girouard and Iadecola, 2006). Thus, a normal neuronal-vascular link is critical for maintaining normal brain function, and it is estimated that nearly every neuron in the human brain is coupled with its own capillary (Zlokovic, 2005). Conversely, neuronal activity plays a major role in regulating vascular tone and controlling blood flow (Figure 5).

The concept of a “neurovascular unit” was first described by Cohen et al. in 1996 to describe the intimate interaction of a triad consisting of neurons, astrocytes, and blood vessels (Cohen et al., 1996). Nowadays, the neurovascular unit is an emerging issue in several CNS diseases, including ischemic stroke, SAH, and Alzheimer’s disease (Koide et al., 2013b;

Urra and Chamorro, 2013). The large arteries are critical in determining the delivery of blood to the parenchymal circulation in SAH. The large-vessels occurs contract after SAH (Rajajee et al., 2012). This raises an interesting question as to whether information from the traditional concept of neurovascular unit might be conveyed “upstream” to the arterioles of the pia-arachnoid.

In this review, we endorse the concept of “the vasculo-neuronal-glia triad model” in SAH over that of “the neurovascular unit”, which includes neurons, glial and vascular cells, especially large arteries. In sum, the rationale for this model in SAH involves the observations that (i) SAH is a vascular disorder with pathophysiological consequences affecting the large arteries to the brain parenchyma, (ii) neurological consequences are associated with all cell types in the CNS and large vessels, (iii) neuron–vascular communication is interdependent and its interaction, acute cell–cell anatomic and physiological relationships, and neurotransmission are fixed in the adult brain, (iv) SAH causes inversion of neuron-vascular communication on both the local and global levels.

4.2 Neurons in the Model

Neurons are the core components of the nervous system. According to a traditional neuron-centric view of SAH, neurons are the primary targets affected by the disease process. Neuronal death results in edema. Activity within a localized brain region elicits increased blood flow to that region, supplying oxygen and nutrients to the active neurons, termed as functional hyperemia (Koide et al., 2013b), thereby releasing vasodilatory substances (Attwell et al., 2010; Filosa et al., 2006; Gordon et al., 2007). However, under certain conditions, neuronal activation can also lead to parenchymal arteriolar constriction by triggering sufficient K^+ efflux from large-conductance Ca^{2+}-activated K^+ (BK) channels (Gordon et al., 2008; Metea and Newman, 2006). Localized neuronal activation can elevate astrocytic endfeet Ca^{2+} and produce vasoconstricting agents such as 20-hydroxyeicosatetraenoic acid (Newman, 2005; Schipke and Kettenmann, 2004), resulting in decreased CBF (Alkayed et al., 1996).

Neuron-stimulating vasoconstriction may represent a pathological status promoting a decrease. Although the mechanisms remain elusive, evidence suggests that elevated perivascular K^+ may underlie this inversion of neurovascular coupling with vasodilative effects at concentrations of extracellular K+ below 20 mM, and constrictive effects when the threshold of 20 mM is exceeded. This inversion of neurovascular coupling contributes to decreased CBF and development of neurological deficits following SAH (Koide et al., 2013a). Neuronal activity by electrical stimulation elevated astrocytic endfeet Ca^{2+} that caused vasodilation in brain slices from normal animals. However, in brain slices from SAH animals, neuronal activity by electrical stimulation induced a similar increase in astrocytic endfeet Ca^{2+} that caused arteriolar constriction rather than vasodilation (Koide et al., 2013a). Inversion of neurovascular coupling by SAH depends on large-conductance BK channels (Koide et al., 2012). Moreover, neuron-to-glia signaling-evoked vasoactivity was regulated by neuronal release of ATP and was interrupted by a purinergic antagonist (Metea and Newman, 2006; Newman, 2005). Conversion of the neurovascular response from vasodilation to vasoconstriction after SAH may act in concert with other reactions, such as direct constrictor effects on parenchymal arterioles, microthrombi formation, and cortical spreading depolarization, which compromises cortical blood flow.

4.3 Astrocytes in the Model

In neurovascular coupling, astrocytes are in close contacts with both neurons and capillary endothelial cells through their microdomains or “foot processes” (Anderson and Nedergaard, 2003). Additionally, their endfeet are completely encased parenchymal arterioles (Gordon et

al., 2007). Astrocytes tightly maintain local homeostasis, deliver glucose and provide metabolic substrates. This unique position of the astrocytes might contribute to their role in neurovascular coupling, which synchronizes neuronal activity and metabolic demands with local regulation of CBF (Zonta et al., 2003). If the availability of oxygen is lowered, the concentration of astrocytic Ca^{2+} is elevated, which maximizes astrocytic glycolysis and the release of lactate. Astrocytes also clear neuronal waste, including not only metabolic byproducts but also neurotransmitters released during synaptic transmission, which are sequestered through active uptake. In short, astrocytes are multifunctional cells that, by their housekeeping functions, allow neurons to progressively become the perivascular nerves and vascular endothelial cells that regulate blood flow. Several mediators of astrocyte-neuron signaling have been identified, including glutamate, ATP, adenosine, and gap-junction signaling. Astrocytes contribute to brain communication pathways by regulating synaptic transmission (Newman, 2003), neuronal firing thresholds, and plasticity (Nedergaard et al., 2003).

A vasodilating effect of astrocytes in the control of cerebral microcirculation mediated by P450 2C11-catalyzed conversion of arachidonic acid to epoxyeicosatrienoic acids was observed, which amplified K^+-evoked current in the vascular smooth muscle cells of large cerebral arteries (Alkayed et al., 1996). Neuronal stimulation up to ~300 nM by Ca^{2+} elevated astrocytic endfeet Ca^{2+} to ~400 nM and subsequently caused vasoconstriction in post-SAH brain slices; however it dilated parenchymal arterioles in control brain slices (Koide et al., 2012). It is possible that components of the blood such as oxyhemoglobin or their breakdown products act directly to alter Ca^{2+} signaling in astrocytic endfeet (Asano, 1999; Nishizawa and Laher, 2005). The cytosolic concentration of Ca^{2+} in human astrocytes was elevated by blood CSF via activation of ATP-sensitive P2 receptors and subsequent inositol 1,4,5-trisphosphate-dependent Ca^{2+} release from endoplasmic reticulum (Kasseckert et al., 2013). In cortical brain slices from rats, the responses of parenchymal arterioles to increases of astrocytic endfeet Ca^{2+} evoked by electrical field stimulation were of three distinct types: (I) 40% exhibited a sustained vasoconstriction, (II) 30% exhibited a transient vasoconstriction (diameter restored within 1 min after stimulation), and (III) 20% responded with a biphasic response (brief vasodilation followed by vasoconstriction) (Koide et al., 2013a). BK channels on astrocytic endfeet play an important role in transducing altered astrocytic Ca^{2+} signaling pathway into alternations in the diameter of arteries and blood flow within the brain, perhaps leading to the development of neurological deficits following SAH (Koide et al., 2012). The high-amplitude spontaneous events after SAH promote BK channel activity to elevate basal $[K^+]o$ in the perivascular space between astrocyte endfeet and arteriolar muscle cells. This inversion of neurovascular coupling may play a particularly important role in the development of DBI following SAH.

4.3 Vascular Cells in the Model

The brain cortex is at risk if blood flow through parenchymal arterioles is restricted. Matching the blood flow to regional brain function and metabolism involves the coordinated activity of neurons, astrocytes, and parenchymal arterioles (Filosa et al., 2004). A persistent interruption of blood flow results in subsequent swelling of perivascular astrocytes, neuronal cells, and capillary endothelium. However, perhaps owing to the contemporary idea that arterial cell types are only minor players in the pathophysiology of stroke, the physiological importance of vascular smooth muscle cells in the traditional neurovascular unit has not been emphasized (Zhang et al., 2012). Vascular smooth muscle cells were included in the original model of the neuron–astrocyte–vasculature triad in 1996, but were replaced by capillary endothelial cells in the revised definition published in 2002. Pathological circumstances after SAH modulate the magnitude and timing of the vasomotor components. Under such conditions the vascular response becomes predominantly vasoconstrictive, that

is, inverted (Sonn and Mayevsky, 2000; Sukhotinsky et al., 2010). The smooth muscle cells in blood vessels are highly dynamic, and their phenotype is influenced by multiple factors in the perivascular environment. Acute applications of the blood component oxyhemoglobin, suppress voltage-gated K^+ channels in parenchymal arteriolar myocytes through heparin-binding epidermal growth factor (EGF)-like growth factor-mediated activation of EGF receptors. Activation of the EGF/EGF receptor pathway contributes to the suppression of $K(_V)$ current and enhanced constriction of the parenchymal arterioles after SAH (Koide and Wellman, 2013). This acute oxyhemoglobin-induced $K(_V)$ channel suppression is mediated via a cell-signaling pathway involving activation of MMP-2 in SAH animals. SAH-induced depolarization of membrane potentials, which involves altered K^+ homeostasis, leads to enhanced activity of voltage-dependent Ca^{2+} channels, increased cytosolic Ca^{2+} in smooth muscles, and the constriction of parenchymal arterioles (Wellman and Koide, 2013). Perivascular nerve fibers can promote smooth muscle growth and differentiation (Hamel, 2006). SAH significantly reduced the nerve fibers, which resulted in deleterious changes in the function and phenotype of cerebrovascular smooth muscle cells (Alabadi et al., 1994). More importantly, in all arteries, vascular smooth muscle cells exhibit multiple coexisting functions and phenotypic characteristics, including migration, proliferation, secretion of extracellular matrix proteins, and contraction (Alexander and Owens, 2012).

In addition, endothelial cells release numerous factors that can influence the proliferation and differentiation of adjacent vascular smooth muscle cells. Endothelial cells can mediate both vasodilatation and vasoconstriction by releasing vasoactive substances including both vasodilator (acetylcholine, nitric oxide) and vasoconstrictor (endothelin) (Burnstock and Ralevic, 1994). Additionally, vascular function during cerebral injury can be modulated through active substances, including platelet-derived growth factors, vascular endothelial growth factors, brain-derived neurotrophic factors, nerve growth factors, angiopoietins, adenosine, and glutamate (Alexander and Owens, 2012).

5. Conclusions

Despite extensive research and vast efforts, patient outcomes following SAH remain poor. More recently, EBI has emerged as a new frontier and requires further investigation and consideration in devising therapeutic strategies for improving SAH outcomes. In addition, a better understanding of animal models, evaluation methods, and the guidelines for translational studies are essential for the successful translation of basic science research into human trials of SAH. The vasculo-neuronal-glia triad model should provide a critical platform in identifying potential therapies to ameliorate SAH injury. Success may come with the development of a monotherapy targeting the contents of the model.

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Abbreviations

SAH	subarachnoid hemorrhage
DIND	delayed ischemic neurological deficit
DCI	delayed cerebral ischemia
TCD	transcranial Doppler
EBI	early brain injury

DBI	delayed brain injury
ICP	intracranial pressure
CPP	cerebral perfusion pressure
CBF	cerebral blood flow
CSD	cortical spreading depolarization
BBB	blood-brain barrier
NMDA	N-methyl D-aspartate
ANP	atrial natriuretic peptide
BNP	brain natriuretic peptide
CSWS	cerebral salt-wasting syndrome
SIADH	syndrome of inappropriate secretion of anti-diuretic hormone
VGCC	voltage-gated calcium channel
VAP-1	vascular adhesion protein-1
MAPKs	Mitogen-activated protein kinases
ERK	extracellular signal-regulated kinase
JNK	c-Jun Nterminal kinase
STAT3	signal transducer and activator of transcription
Kv	voltage-gated K+ channel
NO	nitric oxide
NOS	nitric oxide synthase
MEK	mitogen activated protein kinase kinase
SOD	Superoxide dismutase
IL-1α	interleukin-1α
TNF-α	tumor necrosis factor-α
MCP-1	chemotactic protein-1
CCL5	chemokine (C-C motif) ligand 5
CXCL1	chemokine (C-X-C motif) ligand 1
CAMs	Cell adhesion molecules
ICAM-1	intercellular adhesion molecule-1
VCAM-1	vascular cell adhesion molecule-1
CHOP	C/EBP homologous protein
EGF	epidermal growth factor

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Highlights

1. A better understanding of the role of vasospasm after SAH.
2. Summary of recent data on the neurobiological role of EBI and DBI after SAH.
3. Description of the possible role of the vasculo-neuronal-glia triad model in SAH.

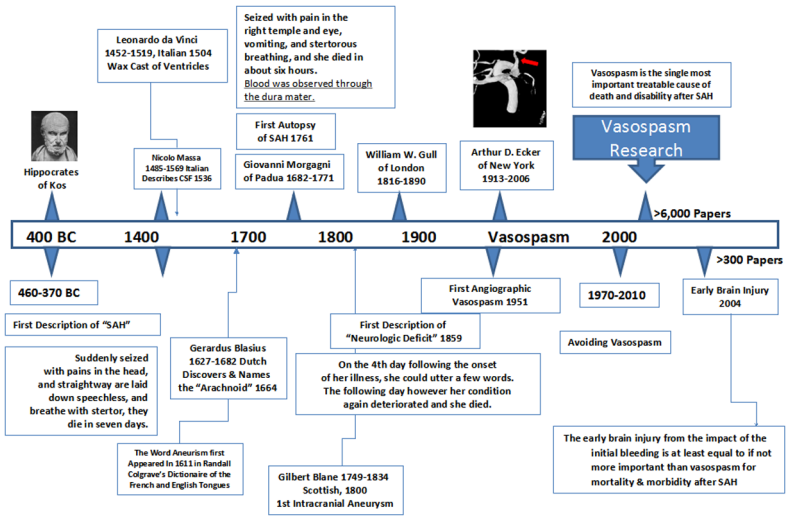
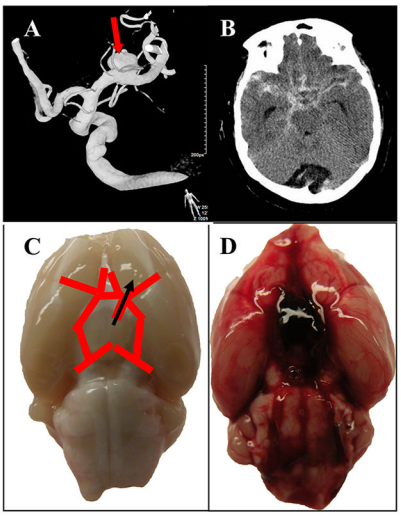


Figure 1. Schematic of a brief SAH history



E

The ideal animal model for SAH
1.Consistent blood deposition in the subarachnoid space
2.Uniform degree of hemorrhage and ICP increase
3. Mechanism of hemorrhage closely simulating aneurysmal rupture
4. Easily performed and reasonable cost

Figure 2. Comparison of subarachnoid hemorrhage (SAH) in human subjects and experimental endovascular perforation rat model

A, a ruptured aneurysm (red arrow) in a middle cerebral artery causes SAH in the human brain. B, a brain computed tomography (CT) scan showed a high density area in the cistern. C, SAH was produced by the endovascular filament (slim black arrow) of the internal carotid artery in a rat. D, an image of rat brain post-SAH showed a thick blood clot around the circle of Willis. E, a table summarizes the conditions of the ideal SAH model.

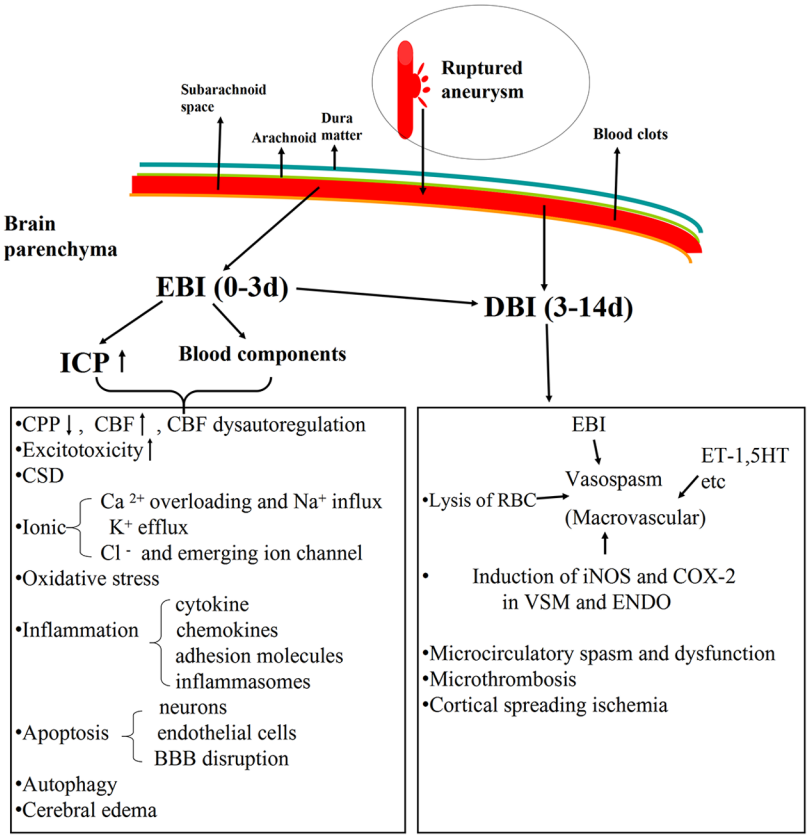


Figure 3. Mechanisms of early brain injury (EBI) and delayed brain injury (DBI) after SAH

The neurobiological responses contributing to all outcomes are listed. RBC, red blood cell; CPP, cerebral perfusion pressure; CBF, cerebral blood flow; CSD, cortical spreading depolarization; BBB, blood-brain barrier; ET-1, endothelin-1; 5-HT, 5-hydroxytryptamine; COX-2, cyclooxygenase-2; VSM, vascular smooth muscle; ENDO, endothelium.

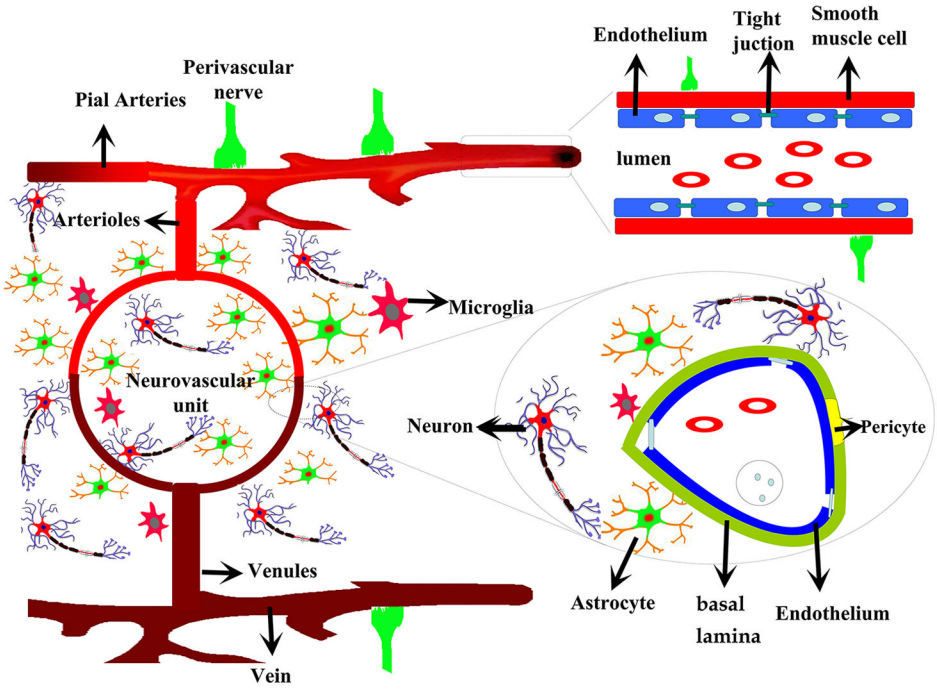


Figure 4. The components of the Vasculo-Neuronal-Glia Triad Model

A. Schematic representation showing the traditional neurovascular unit as a component of the Vasculo-Neuronal-Glia triad model, which includes neurons, astrocytes, capillary endothelial cells, pericytes, smooth muscle cells, noncapillary endothelial cells, perivascular nerves, smooth muscle progenitor cells, and veins. The Vasculo-Neuronal-Glia triad model is larger than the neurovascular unit, therefore comprising all cells and structures required to maintain cerebral blood flow under physiological and pathological conditions.

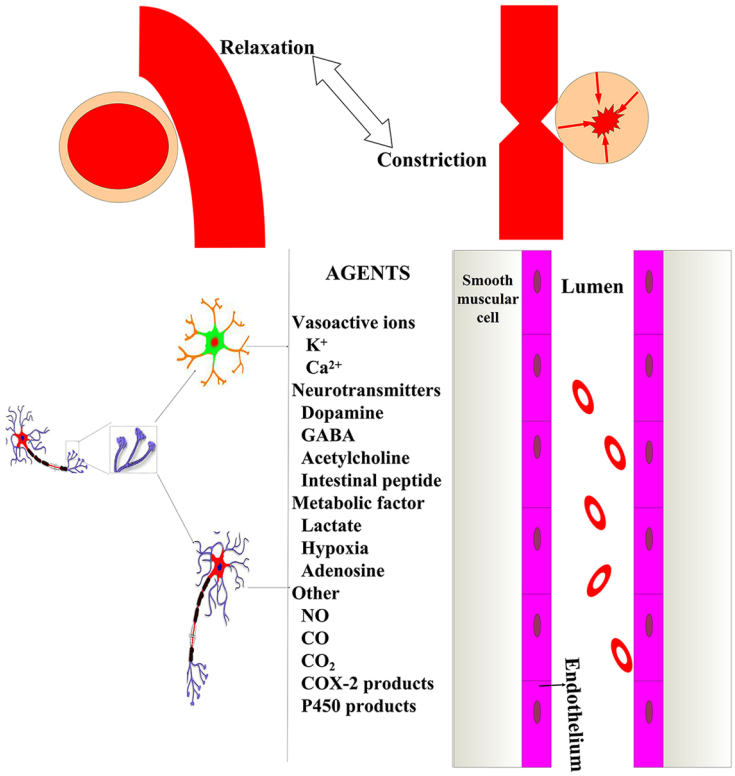


Figure 5. Agents implicated in the connection of neurons and vessels

Table 1

Agents listed were new biomarkers for predicting the outcome of SAH in the past three years

Agents	Sample	Main finding
Bradykinin (BK)	CSF	Elevated BK is correlation with brain edema (Kunz et al., 2013)
TNF-α	serum CSF	High level is associated with DCI, poor outcome and hydrocephalus, but not vasospasm (Beeftink et al., 2011; Chou et al., 2012)
Tau protein	CSF	Tau level is proportional to SAH severity (Zanier et al., 2008; Zanier et al., 2013)
TGF-β1	CSF	TGF-β1 was upregulated in SAH-induced hydrocephalus (Lee et al., 2012)
Mitochondrial DNA	CSF	Higher CSF DNA levels on presentation are associated with worse outcomes (Wang et al., 2013a)
Adrenomedullin (AM)	CSF	AM concentration 8 days after SAH is related to appetite loss and DIND (Kubo et al., 2013)
Ceramide	CSF	Ceramide is associated with the occurrence of symptomatic vasospasm and poor neurological outcome (Testai et al., 2012)
Catecholamine	CSF	Epinephrine serves as an useful index of outcome (Moussouttas et al., 2012)
20-hydroxyeicosat etraenoic acid (20-HETE)	CSF	20-HETE concentrations are associated with DCI and poor outcomes (Crago et al., 2011)
Heart-type fatty acid binding protein (H-FABP)	serum CSF	The Hunt and Hess and Fisher grading scales are correlated with an increase in H-FABP level on administration (Yilman et al., 2012; Zanier et al., 2008; Zanier et al., 2013)
Monomethylated L-arginine (L-NMMA)	CSF serum	L-NMMA is associated with the occurrence of cerebral ischemic events (Jung et al., 2013b)
Neuropeptide Y (NPY)	CSF serum	Higher levels of NPY were in patients with cerebral infarction caused by vasospasm (Schebesch et al., 2011)
Haptoglobin (Hp) phenotype	serum	The Hp phenotype is associated with angiographical vasospams and clinical deterioration by DCI but does not affect the cerebral infarction(Ohnishi et al., 2013)
Interleukin-6 (IL-6)	serum	Higher IL-6 levels are associated with worse clinical outcome and the occurrence of DIND (Muroi et al., 2013)
S100B	serum	S100B is a suitable marker for ischemia after SAH (Hassan et al., 2012; Jung et al., 2013a)
Kallikrein 6(KLK6)	serum	Decreased KLK6 is correlated with poor outcome after SAH (Martinez-Morillo et al., 2012)
High-mobility group box 1(HMGB1)	serum	HMGB1 on admission predicts poor outcome and mortality and vasospasm (Zhu et al., 2012)
Myeloperoxidase (MPO)	serum	Elevated MPO correlates with clinically vasospasm (Lim et al., 2012)
Free fatty acid (FFA)	serum	n-6:n-3 FFA ratio is associated with DCI (Badjatia et al., 2012)
Glucose	blood	Glucose levels at admission are predictive of an elevated 1-year mortality rate (Bian et al., 2012)
Copeptin	plasma	Copeptin indicates clinical severity of the initial bleeding and has prognostic value for outcome of patients with SAH (Fung et al., 2013; Zhu et al., 2011)
Angiopoietin-1 (Ang-1)	serum	Ang-1 is significantly altered in patients suffering from cerebral ischemia (Fischer et al., 2011)
C-reactive protein(CRP)	plasma	CRP levels correlate with outcome but do not seem to predict DCI or infarction (Juvela et al., 2012; Romero et al., 2012)
Asymmetric dimethyl arginine (ADMA)	plasma	ADMA ratios predict mortality after SAH (Staalso et al., 2013)
Taurine	plasma	Taurine concentrations on admission predict a poor outcome (Barges-Coll et al., 2013)
B-type natriuretic peptide (BNP)	plasma	BNP is useful in detecting patients at risk for adverse outcomes without large vessel vasospasm (Taub et al., 2011)

Agents	Sample	Main finding
Matrix metalloproteinase-9 (MMP-9)	Micro-dialysis sample, CSF Blood	MMP-9 was related to World Federation of Neurological Surgeons (WFNS) grade severity and SAH outcome (Sarrafzadeh et al., 2012)
Metabolic ratio		Metabolic ratio is a reliable marker for predicting the outcome of poor-grade patients with SAH (Barcelos et al., 2013)
Prolonged QT interval and tachycardia		Prolonged QT interval and tachycardia are independently associated with Angiographic vasospasm (Ibrahim and Macdonald, 2012)