8-3-2021

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Journal of the American Heart Association

CONTEMPORARY REVIEW

Pathophysiology of Delayed Cerebral Ischemia After Subarachnoid Hemorrhage: A Review

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ABSTRACT: Delayed cerebral ischemia is a major predictor of poor outcomes in patients who suffer subarachnoid hemorrhage. Treatment options are limited and often ineffective despite many years of investigation and clinical trials. Modern advances in basic science have produced a much more complex, multifactorial framework in which delayed cerebral ischemia is better understood and novel treatments can be developed. Leveraging this knowledge to improve outcomes, however, depends on a holistic understanding of the disease process. We conducted a review of the literature to analyze the current state of investigation into delayed cerebral ischemia with emphasis on the major themes that have emerged over the past decades. Specifically, we discuss microcirculatory dysfunction, glymphatic impairment, inflammation, and neuroelectric disruption as pathological factors in addition to the canonical focus on cerebral vasospasm. This review intends to give clinicians and researchers a summary of the foundations of delayed cerebral ischemia pathophysiology while also underscoring the interactions and interdependencies between pathological factors. Through this overview, we also highlight the advances in translational studies and potential future therapeutic opportunities.

Key Words: delayed cerebral ischemia ■ intracranial aneurysm ■ stroke ■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (aSAH) is a particularly devastating event; the case-fatality rate is ≈40% to 50% and many survivors remain dependent on others for activities of daily living.[1–4] The disproportionate impact on people younger than 65 years old relative to ischemic stroke also imposes a burden on the healthcare system and society through increased costs and loss of productive life-years.[5] The prognosis for patients with SAH is heavily influenced by the development of delayed cerebral ischemia (DCI),[1,6] but adequate treatments to prevent DCI remain elusive.[7] Advances in critical care management and refinement of surgical techniques have helped the overall morbidity and mortality from aSAH decline slightly over the past few decades[8]; however, translationally focused scientific inquiry in this field remains vital to paradigm-shifting discoveries.

The conceptual framework of DCI after SAH has undergone vast transformations over the last century. Ischemic cerebral lesions were documented after aneurysmal SAH as far back as the 1940s,[9] around the same time that researchers noted relationships between hemorrhage, delayed infarctions, and cerebral vasospasm.[10,11] The associations between these phenomena, especially the time course of onset, led to the belief that vasospasm was the singular cause of DCI (also referred to as delayed ischemic neurological deficits).[3,12–14] Widespread use of the terms “clinical vasospasm” and “symptomatic vasospasm” reflect the conceptualization of cerebral ischemia after SAH as consequent function of “angiographic vasospasm” rather than a distinct, multifactorial entity. This paradigm began to shift in the early 21st century as it became increasingly apparent that the

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This manuscript was sent to Sean Savitz, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 11.

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ischemic areas did not necessarily correlate with the distribution of spastic arteries and DCI/hypoperfusion could occur without the presence of vasospasm.[15–18] The CONSCIOUS (Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage) trials[19–21] were foundational in transforming the understanding of DCI pathology by demonstrating that prevention of vasospasm does not necessarily reduce all-cause mortality or DCI. The renewed interest in clinical investigation also prompted a unified definition of DCI[22]:

> *The occurrence of focal neurological impairment … or a decrease of at least 2 points on the Glasgow Coma Scale … This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies.*

This definition is now widely used in clinical studies, facilitating efficient investigation and reliable meta-analysis. The SAHIT (Subarachnoid Hemorrhage International Trialists) Repository has also aided the development of well-designed, harmonized clinical trials by identifying critical data points.[23] Since then, further study into the underlying pathophysiology has revealed previously elusive effects on the microvasculature and inflammatory milieu associated with DCI that can inform future clinical trials and drug development.[24,25]

DCI is currently understood as a multifactorial process that evolves over time. The first 24 to 48 hours after ictus are referred to as the early brain injury phase, largely characterized by the sequelae of increased intracranial pressure and transient global ischemia during ictus. Cerebral edema, blood-brain barrier (BBB) disruption, sympathetic nervous system activation, autoregulatory failure, microthrombosis, spreading depolarizations (SDs), and inflammation have all been observed during this period.[26] Over time, the extravasated blood begins to aggravate and modulate the same core factors, culminating in the clinical manifestation of delayed cerebral ischemia around 4 to 10 days post-SAH.[12,27]

The purpose of this review is to both examine the current state of investigation into DCI as well as analyze the underlying mechanisms of the disease. In addition, we review novel therapeutic strategies as they relate to the novel insights into DCI pathophysiology. The pathological components of DCI are intimately interconnected, but for the purposes of this review we discuss 3 overarching areas: vascular dysfunction, inflammation, and cortical spreading depolarizations. For each topic we review the foundational studies demonstrating a role in DCI, the most recent advances within the field, and therapeutic strategies gleaned from those developments.

VASCULAR DYSFUNCTION

Inability of cerebral perfusion to match metabolic demand is the ultimate cause of DCI; thus any pathological event that decreases perfusion or increases metabolic demand can contribute to DCI. In this section, we focus on the former, specifically the mechanisms of inadequate vascular response that increase susceptibility to DCI.

Because of the lasting influence of the vasospasm-centered approach to DCI research, many vasodilatory or otherwise vasoactive agents have been tested in patients with SAH (Table). Triple H therapy (hypertension, hypervolemia, and hemodilution) or permissive hypertension alone are intended to mechanically vasodilate by intravascular volume expansion but are prone to cardiopulmonary and renal complications.[28,29] A meta-analysis of Triple H therapy found that, in addition to methodological issues in standardizing treatments, there was no effect on DCI.[30] As mentioned previously, the CONSCIOUS trials demonstrated that inhibition of the vasoconstrictive endothelin-1 pathway decreases vasospasm but has no effect functional outcomes.[19–21] Another phase 3 clinical trial with clazosentan, a selective endothelin-1 receptor anatagonist, has been announced since the end of CONSCIOUS-3, the REACT trial.[31] Unlike the CONSCIOUS trials that used a composite primary endpoint (all-cause mortality, DCI, or need for vasospasm rescue therapy), REACT will focus on the development of DCI. Additionally, the REACT trial will use the higher of the 2 clazosentan doses administered in CONSCIOUS-3 because of more support for possible efficacy. The MASH-2 (Magnesium for Aneurysmal Subarachnoid Haemorrhage-2) trial showed intravenous magnesium sulfate, putatively acting through inhibition of voltage-gated calcium channels,[32] is also not effective for improving outcomes.[33] Oral administration of the dihydropyridine-type calcium channel blocker nimodipine is the only treatment with consistent, high-quality evidence for decreasing DCI[34] and is now standard of care in patients with aSAH, although these results are principally driven by 1 large trial.[35] Importantly, those early studies showed oral nimodipine reduces DCI and improves outcomes without affecting vasospasm,[36,37] suggesting nimodipine may have important vessel-independent effects. A recent trial (NEWTON [Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage]) of intraventricular nimodipine administration found no improvements over standard oral administration.[38] These clinical trials clearly demonstrate that

Table 1. Summary of Major Clinical Trials and Meta-Analyses

Candidate	Mechanism	No. Patients Included in Trial or Meta-Analysis	Summary of Findings
Clazosentan[19–21] (IV)	Endothelin-1 receptor antagonist.	CONSCIOUS-2: 1147 total (764 treatment/383 placebo) CONSCIOUS-3: 571 total (188 high-dose/194 standard dose/189 placebo)	Clazosentan treatment (5 or 15 mg/h) does not improve outcomes after aSAH. Possible increase in pulmonary complications, anemia, and hypotension
Magnesium sulfate[33] (IV)	Inhibition of voltage-gated calcium channels, N-methyl-D-aspartate receptors, & glutamate release	Magnesium for Aneurysmal Subarachnoid Haemorrhage-2: 1201 total (604 treatment/597 placebo)	Intravenous magnesium sulfate therapy does not improve outcomes after aSAH
Simvastatin[39,40] (oral)	β-Hydroxy β-methylglutaryl-CoA reductase inhibition, but has important pleiotropic effects including improved endothelial function and decreased platelet activation	Simvastatin in Aneurysmal Subarachnoid Haemorrhage: 809 total (391 treatment/412 placebo) High-Dose Simvastatin for Aneurysmal Subarachnoid Hemorrhage: 255 total (124 high dose/131 standard dose)	Simvastatin (40 or 80 mg/d) does not improve short- or long-term outcomes after aSAH
Tirilazad[41] (IV)	Free radical scavenging and cell membrane stabilization	Meta-Analysis: 3821 total across 5 double-blind, placebo-controlled trials	Tirilazad does not reduce mortality or improve outcomes after aSAH
Cilostazol[42] (oral)	Phosphodiesterase enzyme$_3$ inhibition, leading to increased PKA activity. PKA relaxes vascular smooth muscle and inhibits platelet activation through multiple pathways	Meta-Analysis: 543 total across 5 studies	Cilostazol reduced "symptomatic vasospasm" and improved outcomes after aSAH; however, the component studies included in the meta-analysis were small and mostly not placebo controlled. A larger randomized controlled trial is needed
Calcium-channel blockers[34,35] (including oral nimodipine)	Inhibition of L-type calcium channels	Meta-Analysis: 3361 total across 16 trials; 6 trials specifically for oral nimodipine (969 patients total)	Oral nimodipine reduces incidence of poor outcomes and delayed cerebral ischemia. Importantly, the results are driven primarily by a large single-center study

aSAH indicates aneurysmal subarachnoid hemorrhage; CONSCIOUS, Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage; and PKA, protein kinase A.

targeting vascular dysfunction through vasodilation alone is not sufficient to reduce DCI.

In this article we highlight the clinical and animal studies that elucidated the fundamental processes of vascular dysfunction after SAH and those that expanded the understanding to include microvessels, arterioles, paravascular spaces, and lymphatic vessels. We also discuss the recently discovered mechanisms of vascular dysfunction that can be leveraged in the development of novel therapies.

Inciting Factors of Vascular Dysfunction

The first physiologic insult after SAH is a transient global ischemia as intracranial pressure approaches mean arterial pressure.[43,44] This ischemic episode can trigger vascular dysfunction even before the toxic effects of hemoglobin are realized (Figure 1). First, the process is initiated through an induction of the sympathetic nervous system,[45] often referred to as the "sympathetic surge" or "catecholamine surge." Initial activation involves both ischemic injury to the hypothalamus[46] as well as compression of the brain stem.[47] Plasma catecholamines remain elevated for several days post-SAH[45] and high concentrations predict poor outcomes,[48,49] perhaps involving injury to extracerebral organs.[50] A recent study by Takemoto et al demonstrated that attenuation of the sympathetic response via bilateral renal denervation decreases vasospasm and cerebral edema in rats.[51] Behavioral and neurological responses were not affected by this intervention, indicating that reducing sympathetic nervous system activation alone is not sufficient to prevent neurological deficits. Separate from sympathetic nervous system activation, transient global ischemia causes endothelial injury and BBB disruption as well. Endothelial injury and even apoptotic cell death have been reported to occur within the first 24 hours post-SAH,[52,53] which disrupts the BBB and promotes coagulation by exposing subendothelial collagen.[54] BBB disruption can be measured indirectly in humans, via abnormal tissue enhancement on contrast computed tomography or isotope scintigraphy studies.[55] Endothelial injury, BBB disruption, and the resulting vasogenic edema are all important avenues for future investigation, as all are predictive of patient outcome.[55,56] Yet another consequence of acute global ischemia is stimulation of the endothelin-1 pathway. Using a primate model, Pluta et al found that hypoxia, not oxyhemoglobin, was

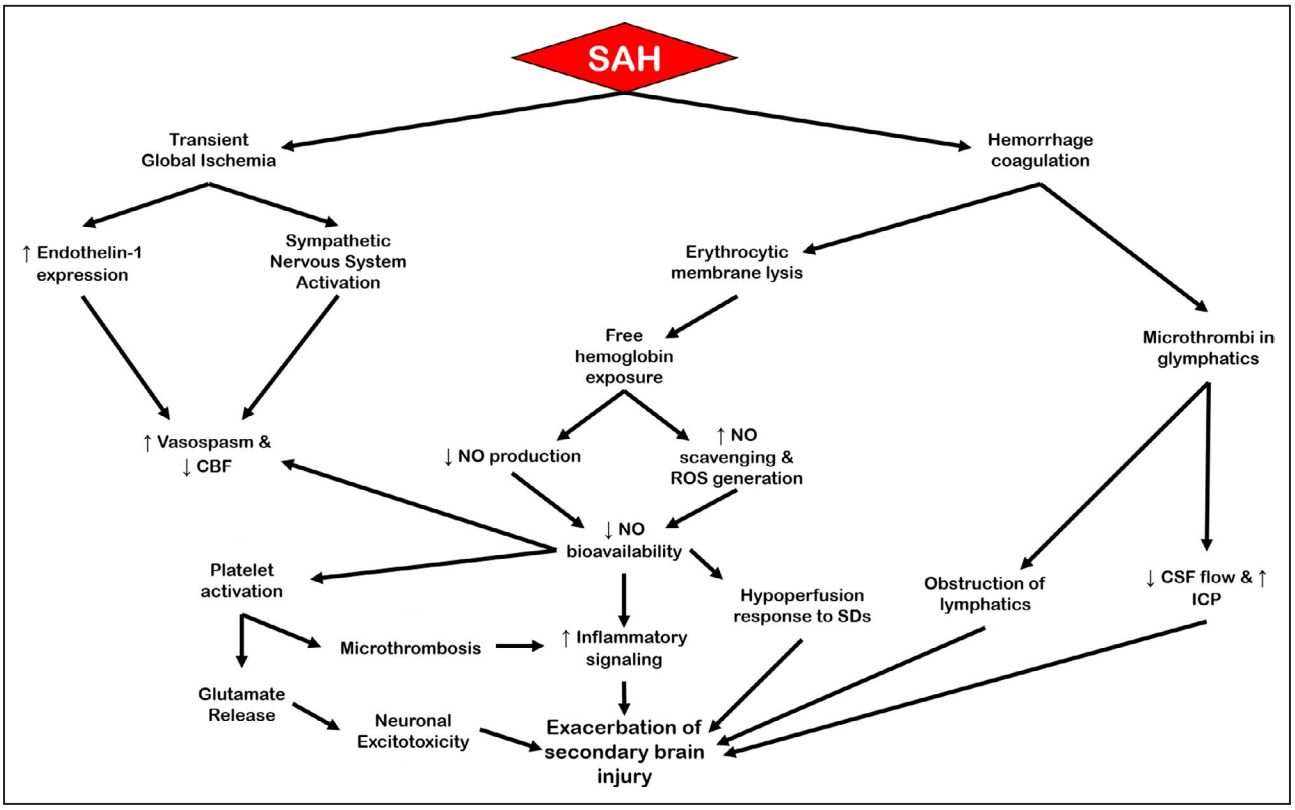

Figure 1. Vascular dysfunction after subarachnoid hemorrhage.
Transient global ischemia and free hemoglobin toxicity are the ultimate sources of vascular dysfunction leading to microthrombosis and vasospasm. Perturbation of the NO pathway is a pivotal mechanism connecting vascular dysfunction to inflammation and cortical spreading ischemia. The glymphatic system and meningeal lymphatic vessels are also emerging as a possible mediator of delayed cerebral ischemia. CBF indicates cerebral blood flow; CSF, cerebrospinal fluid; ICP, intracranial pressure; ROS, reactive oxygen species; SAH, subarachnoid hemorrhage; and SDs, spreading depolarizations.

responsible for the SAH-induced increase in endothelin-1 expression.[57] Some early clinical studies into this pathway found that plasma endothelin-1 concentrations correlated with DCI[58] and endothelin-1 inhibition reversed SAH-associated reductions in cerebral blood flow.[59] So, although endothelin-1 antagonism alone does not prevent DCI, it is still important to consider the acute phase sequelae of increased intracranial pressure that occur independently of hemoglobin-mediated vascular dysfunction.

Management of elevated intracranial pressure and hydrocephalus is also significant to outcomes after SAH. Aggressive clearance of cerebrospinal fluid (CSF) through continuous external ventricular drainage is a conceptually tempting approach to lower intracranial pressure and accelerate clearance of spasmogenic blood products; however, this strategy does not lead to decreased DCI.[60] Further, intermittent CSF drainage and rapid external ventricular drainage weans are associated with fewer complications and shorter intensive care unit length of stay.[60–62] Lumbar drainage has emerged as an alternative to external ventricular drainage that has the potential to provide the benefits of CSF drainage, including reduced vasospasm, with a lower rate of complications.[63,64] There is an ongoing trial assessing neurapheresis using a lumbar drainage filtration system as an intervention to reduce DCI.[65] These approaches demonstrate the ability of refined techniques to not only prevent complications but actively suppress DCI pathology as well.

Hemoglobin and other blood products remain sequestered until the erythrocytic membranes become unstable and lyse, releasing oxyhemoglobin and other vasoactive blood products. Oxyhemoglobin and deoxyhemoglobin concentrations in the CSF peak around day 7 post-SAH in primates,[66] roughly corresponding to the onset of secondary brain injury. Even before the precise mechanisms were clarified, the hypothesis that hemoglobin must be the primary spasmogen was supported by reports that hematoma evacuation prevents vasospasm in primates.[67,68] A few years later, purified oxyhemoglobin alone was shown to induce a contractile response in canine cerebral arteries[69] and later studies demonstrated this occurred through the Rho/ROCK (Rho/Rho-associated protein kinase) and PKC (protein kinase C) pathways.[70]

Fasudil, an inhibitor of the Rho/ROCK pathway, has been shown to reduce smooth muscle cell contraction, reduce vasospasm, and improve clinical outcomes after aSAH,[71–73] but it is not approved for use by the Food and Drug Administration or European Medicines Agency. Cilostazol, a phosphodiesterase enzyme$_3$ inhibitor that relaxes vascular smooth muscle and inhibits platelet activation,[74] has also been shown to reduce vasospasm and improve clinical outcomes in several trials.[42,75] Oxyhemoglobin is also a potent scavenger of NO and reduces the availability of NO in the surrounding cerebral vasculature.[76,77] Production of NO is unable to compensate for this loss owing to a rise in asymmetric dimethylarginine,[78,79] an endogenous nitric oxide synthase (NOS) inhibitor, and decreased expression of endothelial- and neuronal-specific NOS isoforms.[80,81] The remaining NOS enzymes are also damaged through oxidation of essential enzymatic cofactors by reactive oxygen species from hemoglobin metabolism and local inflammation. This results in the "NOS uncoupling" phenomenon whereby consumption of substrates L-arginine and O_2 is "uncoupled" from NO production and instead results in superoxide ($O_2^{\cdot-}$) generation.[82] The presence of superoxide further reduces NO bioavailability by reacting with the remaining NO to form peroxynitrite, a potent oxidizing agent.[82] This perfect storm of vasoconstrictive, NO-depleting, and reactive oxygen species-generating events after SAH is central to the resulting vascular dysfunction (Figure 1). This has been demonstrated experimentally by administration of NO-donors, which improved cerebral hemodynamics in humans and non-humans primates after SAH[83,84]; however, NO donors have little translational potential owing to their adverse effects.[83] Nonspecific antioxidant therapies are also ineffective after SAH, demonstrated most clearly by the failure of tirilazad to improve outcomes in a meta-analysis of 3821 patients.[41] Interestingly, the clinical importance and relative pathological contribution of the "NOS uncoupling" phenomenon is still not completely resolved, as some studies report genetic knockout of endothelial NOS in mice reduces vascular dysfunction after SAH whereas others show phenotypes similar to wild-type mice.[85,86] In any case, future therapeutic application must account for the complexities of the NOS pathway and the context-dependent relationship between NOS activation and NO bioavailability.

Microthrombosis and Thromboinflammation

The NO-cyclic guanosine monophosphate pathway is central to preserving vascular homeostasis through inhibition of platelet aggregation, leukocyte adhesion, and smooth muscle cell proliferation in addition to maintaining vasodilatory tone.[87–90] The procoagulant effects of platelet aggregation and spasm within intraparenchymal arterioles, known as microthrombosis, has been an emerging area of intense research because the incidence of microclots was shown to correlate with DCI and clinical outcome.[15,91–94] The endothelial protease ADAMTS13 normally represses platelet adhesion and thrombosis-induced inflammatory change through downregulation of von Willebrand factor and P-selectin,[95] making microvascular endothelial injury and ADAMTS13 dysregulation a potential link between microthrombosis and pathological inflammation. Interestingly, decreased ADAMTS13 activity and increased von Willebrand factor and P-selectin levels all predict the development of DCI in patients with SAH,[96–99] indicating thromboinflammation could be a clinically relevant therapeutic target. Preclinical animal models have demonstrated increased P-selectin expression in the microvascular endothelium after SAH corresponding to areas of microthrombosis and neuronal cell death.[100] Moreover, treatment with a monoclonal anti-P-selectin antibody can reduce platelet-endothelial and leukocyte-endothelial interations,[101] suggesting P-selectin may be a particularly suitable translational candidate to target thromboinflammatory pathways. In addition to inciting inflammation, activated platelets release glutamate,[102] high concentrations of which can be neurotoxic.[103] In rats, glutamate levels in the CSF increase after SAH[104] and there is an association between the location of microthrombi and regional markers of excitotoxicity,[105] indicating that the platelets within microthrombi could be the source of toxic glutamate. Moreover, glutamate and glutamate receptor activity are important regulators of the incidence and propagation of spreading depolarizations (see "Spreading Depolarizations"). A small, exploratory study in humans found extracellular glutamate concentrations rise after SAH, vary from region to region, and may predict clinical outcome.[106] Although more study is needed to confirm and expand upon these findings, regional variation in glutamate levels could be explained by the presence of microthrombi in areas that progress to delayed ischemia. Taken together, the available evidence strongly suggests microcirculatory dysfunction is central to DCI pathology and an important area for more intense investigation.

There have been several trials aiming to reduce DCI through inhibiting coagulation or platelet aggregation. An important point to consider in the interpretation of these studies is that the effects of anticoagulative therapies on primary hematoma dissolution and prevention of secondary microthrombi cannot be readily discerned from one another. The design of these protocols has to be done carefully as rebleeding of a previously secured aneurysm and other hemorrhagic complications are of primary concern with these treatment modalities. Systemic anticoagulation with

enoxaparin was shown to reduce DCI when given to Hunt-Hess grade I–III patients,[107] but this effect was lost when the patient population was expanded to include more severe hemorrhage.[108] Three retrospective studies have also found that treatment with low-dose intravenous heparin reduces DCI and improves functional outcomes.[109–111] A rat model suggests that heparin may work through reducing the neuroinflammatory response to SAH.[112] Antiplatelet therapy has also been tested through trials of aspirin, ozagrel hydrochloride, dipyridamole, and ticlopidine. A meta-analysis (1385 patients total) of trials with these agents to date showed a modest trend for better outcomes but also a possible increase in hemorrhagic complications.[113] A recent retrospective study found dual therapy of aspirin and clopidogrel was associated with reduced incidence of DCI and no increased risk of hemorrhagic complications,[114] suggesting antiplatelet therapy could be useful with refined protocols. We are currently evaluating the glycoprotein IIb/IIIa inhibitor tirofiban as one such therapeutic. Compared with aspirin and clopidogrel, tirofiban has a narrow therapeutic window, making it an ideal antiplatelet agent for aSAH that may require further neurosurgical interventions.[115] After carefully establishing safety and efficacy profiles in patients with aSAH,[116,117] a small trial showed promising reductions in DCI without increase hemorrhagic complications.[118] Larger clinical trials will be instrumental in definitive evaluation of tirofiban and other antiplatelet therapies as a treatment to prevent DCI.

Glymphatic and Meningeal Lymphatic System

Lack of a lymphatic system was long believed to be a unique characteristic of the central nervous system until Louveau et al discovered lymphatic vessels within the lining of the dural sinuses that interface with the deep cervical lymph nodes.[119] This discovery led to the hypothesis that alterations in this novel meningeal lymphatic system and the central nervous system (CNS) paravascular glymphatics contribute to the development of DCI. Even before the discovery of meningeal lymphatics, it was demonstrated that cervical lymph node blockage intensified oxidative stress after SAH.[120] More recently, the meningeal lymphatic system was found to be important for clearing the extravasated erythrocytes from SAH and disruption of the lymphatic vessels exacerbated the neuroinflammatory response, especially microglial activation.[121]

Upstream from the meningeal lymphatics, paravascular glymphatic pathways lie next to penetrating arteries and constitute the direct interface between CSF and parenchymal interstitial fluid.[122] This pathway provides a route for blood products from SAH to quickly penetrate brain parenchyma and stimulate neuroinflammation.[123] Liu et al demonstrated that knockout of AQP4 (aquaporin 4), which is expressed in astrocytes at the interface of the paravascular pathways,[124] worsens outcome after SAH in rats.[125] Their study indicates that AQP4 may be involved in the impaired glymphatic flow observed after SAH. Further, microthrombi formed in the paravascular spaces after SAH can obstruct CSF flow through the glymphatic system and contribute to increased intracranial pressure.[126] Administration of tissue plasminogen activator can clear the thrombi from the paravascular space, increase cerebral blood flow in the early brain injury phase, and improve neurological function in the delayed phase.[123,126]

Investigation into the paravascular space and meningeal lymphatics as a therapeutic target for DCI is still in its infancy; however, the foundational studies demonstrate an exciting avenue for future research. The exposure of brain parenchyma to the toxic effects of hemoglobin, hemoglobin metabolites, and other blood products is clearly regulated by the paravascular pathways. Strategies to limit the dissemination of toxic metabolites into healthy tissue while permitting their clearance through the lymphatic system may prove valuable. Earlier research on fibrinolytic therapies presumed the therapeutic mechanism was clearing the primary hematoma or microthrombi within penetrating arterioles and capillaries. Reinterpretation of these studies with respect to the influence of paravascular microthrombi could prove worthwhile.

Autoregulatory Failure

Cerebrovascular autoregulation is the process by which cerebral blood flow is held constant over a spectrum of perfusion pressures and blood gas partial pressures.[127,128] There are myogenic, neurogenic, metabolic, and endothelial factors contributing to cerebral autoregulation[129,130]; thus, autoregulatory failure after SAH is best conceptualized as a summative process rather than an independent pathological mechanism. Yundt et al found that patients with SAH, regardless of the presence of vasospasm, have decreased cerebral blood volume compared to age-matched healthy volunteers, whereas healthy volunteers subjected to carotid compression display an increase in cerebral blood volume.[131] This study was important in that it showed not just a diminished autoregulatory capacity but a complete inversion of normal function. Another similar study found diminished autoregulatory capacity, as measured by the transient hyperemic response, predicted the development of DCI.[132] This phenomenon has been replicated in recent years in a variety of settings and using different imaging[133,134] and vascular reactivity stimuli,[135] reaffirming the association between diminished autoregulatory capacity and development of DCI after SAH.

The nature of autoregulation as an integrative process makes its relationship with DCI difficult to delineate through interventional studies. A phase II trial found that pravastatin treatment reduced the duration of impaired autoregulation and improved outcomes compared to placebo.[136] Overall, the current literature supports autoregulation as a useful biomarker in clinical studies, but more research is required to determine if autoregulatory disturbance is required for the development of DCI.

INFLAMMATION

Systemic Inflammation After SAH

Inflammation is an extremely broad category of physiological and pathophysiological host responses to infection and tissue injury.[137] The severity of the inflammatory response after SAH predicts DCI and poor outcomes. Retrospective studies find that lactate concentration, CRP (C-reactive protein) levels, erythrocyte sedimentation rate, leukocyte count, negative nitrogen balance, neutrophil-lymphocyte ratio, and systemic inflammatory response syndrome burden, all nonspecific markers of inflammation, predict outcome following SAH.[138–145] Accordingly, systemic immunosuppression with corticosteroids was one of the first experimental treatments to prevent DCI.[146,147] These and more recent studies[148] analyzing steroid treatment have shown no effect on DCI and only a modest benefit toward functional outcome. The mixed effects of these small trials are not sufficient to prove benefit or overcome the multitude of adverse side effects; thus, glucocorticoids are not currently indicated in patients with SAH. Additional clinical trials are also unlikely after a large randomized controlled trial showed corticosteroid treatment increased mortality in the pathophysiologically related setting of traumatic brain injury.[149] Cyclosporine (discussed further in the next section) and nonsteroidal anti-inflammatory drugs have also been used as general anti-inflammatories after SAH. A prospective observational study of 138 patients found that cumulative nonsteroidal anti-inflammatory drug usage correlated with better outcome (Glasgow Outcome Scale score >3) and fewer cerebral infarctions.[150] Another study of 178 patients found nonsteroidal anti-inflammatory drug use led to lower mortality and shorter intensive care unit stay, but the effects on DCI and functional outcome were nonsignificant.[151] Aspirin alone has shown no benefit to DCI or outcome.[152,153] Overall, nonspecific anti-inflammatory therapies have proven disappointing for prevention of DCI and poor outcomes.

Clear delineation of the complex inflammatory cascades induced after SAH is necessary in order to develop targeted anti-inflammatory therapies. Clinical studies have demonstrated that CSF concentrations of the classical pro-inflammatory cytokines interleukin-6, interleukin-8, interleukin-1β, tumor necrosis factor-alpha, and MCP-1 (monocyte chemoattractant protein-1) correlate with DCI and poor outcomes.[154–157] Unfortunately, many early mechanistic studies in animal models have focused primarily on vasospasm instead of neuronal cell death or behavioral outcome, obscuring their relevance to translational application. Within the last 15 years, this paradigm has begun to shift, and the cellular and molecular mechanisms of SAH-induced inflammation are emerging from animal studies. We present these advances in the context of the inflammatory cells, resident microglia, and peripheral leukocytes, which mediate host response to SAH and react to inflammatory change within the CNS.

Cellular Mediators—Glia

Glial involvement in SAH pathology had been suspected since the establishment of free heme as a toll-like receptor 4 (TLR4) activator.[158] TLR4, a pattern recognition receptor central to innate immune function, is expressed in all myeloid-origin cells[159]; however, the function of microglia as resident TLR4-expressing cells makes them well positioned to respond first to TLR4-heme interactions in the CNS. TLR4 expression was shown to increase after SAH,[160] but the evidence for microglial participation in SAH pathology remained speculative until a landmark paper from Hanafy demonstrated microglia-depleted mice have reduced vasospasm and neuronal apoptosis.[161] The same study showed neuronal apoptosis and vasospasm are diminished in TLR4 knockout mice early after SAH but evolve to be driven by TLR4-independent mechanisms in the delayed phase. The contribution of microglia to neuronal cell death after SAH was reaffirmed by Schneider et al through selective depletion of microglia using a ganciclovir-sensitive "suicide gene."[162] This study left peripheral macrophages intact to differentiate between resident and peripheral myeloid cell involvement. They found that microglia-depleted mice had decreased neuronal cell death as far out as 9 days post-SAH. Together, these studies clearly establish microglia as critical mediators of neuroinflammation and neuronal injury after SAH (Figure 2).

The precise molecular mechanisms of microglia action in the DCI phase remain elusive; the Hanafy study demonstrated neuronal cell death is TLR4-dependent only in the early brain injury phase. There are several other proposed pathways that contribute to microglia-mediated neuroinflammation after hemorrhagic stroke. In cultured microglia cells, the inflammatory reaction to thrombin exposure (ie, interleukin-6, tumor necrosis factor-alpha, CCL2/MCP1 [chemokine ligand 2/monocyte chemoattractant protein 1] production) is muted by TGFβ1 (transforming growth factor beta 1)

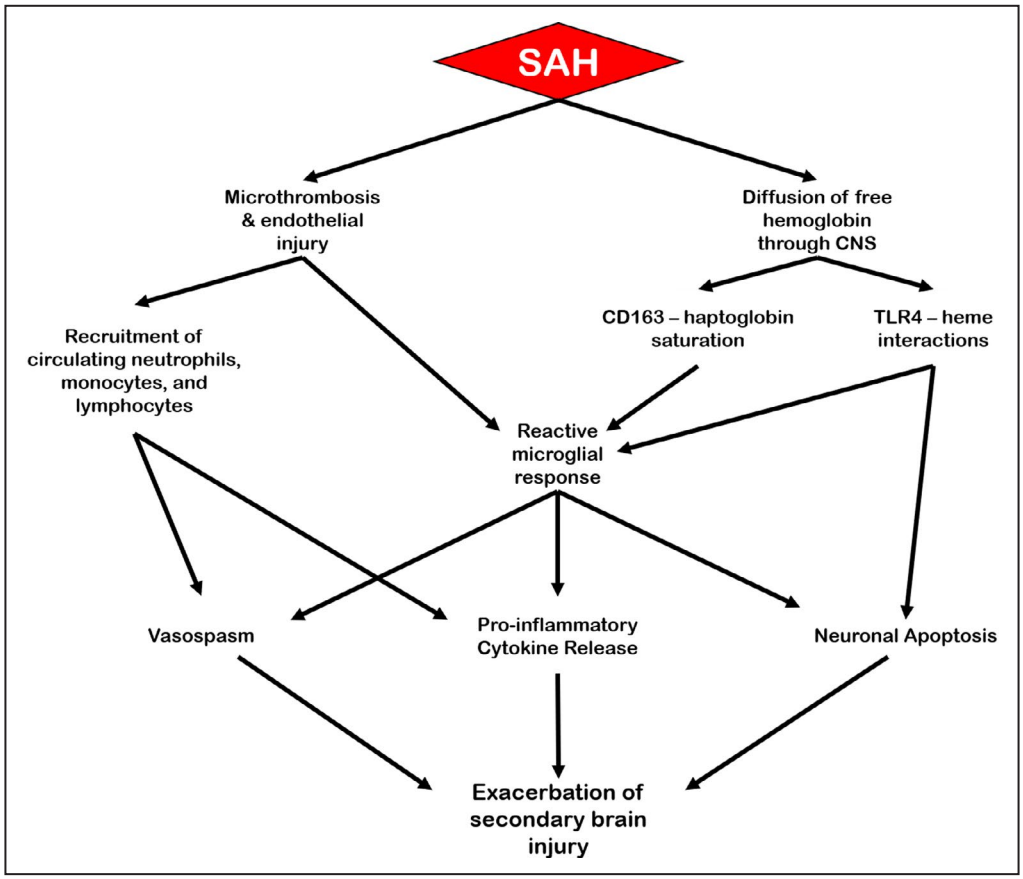

Figure 2. Mechanisms of inflammatory response after subarachnoid hemorrhage.
Subarachnoid hemorrhage elicits an inflammatory response from resident CNS glia directly through TLR4 and CD163 receptor signaling. Reactive microglia then contribute to inflammatory cytokine production, vasospasm, and neuronal apoptosis. The endothelium of the cerebrovasculature also contributes to inflammation by recruiting circulating leukocytes. Neutrophils, monocytes, and lymphocytes all enter the CNS after SAH and promote vasospasm and inflammatory cytokine release. CD163 indicates cluster of differentiation 163; CNS, central nervous system; SAH, subarachnoid hemorrhage; and TLR4, toll-like receptor 4.

treatment.[163] Further, the same study showed reactive microglia express lower levels of TGFβ1, and human patients with increased TGFβ1 after intracerebral hemorrhage had better outcomes at 90 days; These findings have yet to be replicated in humans after SAH, but simvastatin therapy was found to induce lymphocytic TGFβ1 expression in a rat model,[164] suggesting there could be similarities in TGFβ1's actions. HMGB1 (high mobility group box 1 protein is a nuclear protein that regulates chromatin remodeling and gene transcription; however, it is also secreted as an inflammatory cytokine by myeloid lineage cells, including microglia.[165] Neutralization of HMGB1 with a monoclonal antibody attenuates microglial reactivity and improves neurological function after SAH.[166] In humans, higher HMGB1 CSF concentrations are correlated with unfavorable outcomes.[156] Unfortunately, these studies are unable to differentiate between microglia-derived and macrophage/monocyte-derived HMGB1, complicating their interpretation. Future investigation should evaluate the mechanisms of microglial involvement in the delayed phase after SAH.

Cellular Mediators—Peripheral Leukocytes

An association between peripheral immune response and outcome after SAH has been observed for many years,[167] including recently when outcome measures were updated to match the current consensus definition of DCI.[143] Markers of both myeloid and lymphoid lineage cells have also been directly observed in the CSF and tissue near the subarachnoid space, implying these cells could be directly involved with SAH pathology.[154,168,169] Other correlational studies support this notion by showing the degree of peripheral immune reaction predicts outcome.[140,141,170] One hypothesis to explain this phenomenon is that peripheral immune cells respond when the resident CNS macrophages

(microglia) are overwhelmed by massive hemolysis following SAH. The baseline capacity of the CNS CD163 (cluster of differentiation 163)-haptoglobin scavenger system is much lower than in the periphery and is easily saturated after SAH.[171] Administration of haptoglobin into the subarachnoid space has been shown to reduce vasospasm.[172] Haptoglobin genotype also affects hemoglobin affinity and outcome after SAH indicating that the response after CD163-haptoglobin saturation could be responsible for some of the detrimental effects.[173,174] Cyclosporine A, an immunosuppressant that acts primarily through T cells but also inhibits myeloid cell function,[175] was used to target this immune reaction but has resulted in mixed effects in underpowered trials and animal studies.[176–179] Animals studies have shown generally positive results from peripheral myeloid cell depletion. Monoclonal antibody-mediated neutralization of CD11b/CD18-positive cells resulted in decreased vasospasm in rabbits and nonhuman primates.[180,181] The limitation of these studies is the emphasis on vasospasm as an outcome measure rather than DCI. The expression of CD11b/CD18 on multiple cell types also limits their interpretation. A similar study from Provencio et al improved on previous studies by demonstrating improved functional outcome in addition to decreased vasospasm in mice after treatment with anti-lymphocyte antigen 6 complex antibody.[182] Lymphocyte antigen 6 complex is primarily expressed on neutrophils but certain monocyte, macrophages, and lymphocyte subpopulations also express this marker.[183] Taken together, these data show a strong scientific premise for peripheral myeloid and lymphoid cell involvement in the SAH pathology (Figure 2). More studies with emphasis on DCI and functional outcome are needed before translational therapies can be trialed in human patients.

By responding to inflammatory change on endothelial surfaces, circulating immune cells serve as the link between vascular dysfunction, vascular inflammation, and systemic immune response. Cell adhesion molecules (CAMs) are a family of proteins that facilitate immune cell—endothelium interaction after vascular injury.[184] Increased CAM expression after SAH is well-established, having been demonstrated in the serum and CSF of humans as well as directly in the vascular and cerebral tissues of animal studies.[185–187] A study by Polin et al showed several CAMs (intercellular adhesion module-1 [ICAM-1], VCAM-1, and E-selectin) are upregulated in CSF after SAH and E-selectin levels correlate with poor outcomes.[188] Another study similarly showed P-selectin but not ICAM-1, vascular CAM-1, or platelet endothelial CAM was increased in patients with low-grade SAH and DCI.[98] These studies suggest that the selectin subtype of CAMs may be more important in the development of DCI than the immunoglobulin superfamily subtype (ICAM-1, vascular CAM-1, etc); however, no interventional studies have proven a direct role. One study has shown E-selectin inhibition decreases vasospasm in rodents.[189] Treatments neutralizing ICAM-1 via antibody treatment have shown decreased leukocyte infiltration, demonstrating the putative mechanism of CAMs in DCI pathology.[190–192] One of these studies coadministered an anti-CD18 (ICAM-1 ligand) antibody and found that vasospasm was decreased more than with anti-ICAM-1 treatment alone, suggesting that inflammatory cells contribute to vasospasm in a partially CAM-independent fashion.[192] The use of vasospasm as outcome rather than neurobehavioral function is a major limitation of these studies; nonetheless, the entirety of the current literature supports the hypothesis that peripheral immune cells respond to inflammatory changes in the endothelium after SAH. More investigation into these pathways with a focus on functional outcome is necessary to determine their utility as therapeutic targets.

Statins have been tested extensively owing to their anti-inflammatory effects independent of hepatic β-Hydroxy β-methylglutaryl-CoA reductase inhibition.[193] Some early single-center randomized controlled trials with simvastatin[194] and pravastatin[136] showed reductions in vasospasm and DCI, encouraging more investigation into statin therapy. The largest trials to date (STASH [Simvastatin in Aneurysmal Subarachnoid Haemorrhage] and HDS-SAH [High-Dose Simvastatin for Aneurysmal Subarachnoid Hemorrhage]), however, demonstrated simvastatin does not improve outcomes or reduce DCI.[39,40]

SPREADING DEPOLARIZATIONS

Physiology of Spreading Depolarizations

Spreading depolarizations, as the term implies, are slowly propagating waves of almost complete membrane depolarizations in both neuronal and glial cells. Usage of the terms “spreading depolarization” and “spreading depression” often varies between authors and disciplines; for the purposes of this review, we consider “spreading depolarization” to best describe the underlying biophysical phenomenon, “spreading depression” to be its manifestation as decreased neuroelectric activity, and use the initialism “SD” to refer in general to both spreading depolarizations and depressions. Spreading depressions were first discovered by Leão in 1944 while studying epilepsy and he noted its hyperemic effect on pial vasculature soon after.[195,196] In healthy brain tissue, SDs can be elicited by increasing extracellular K^+ concentrations to a point where passive ion channels open and overload the capacity for ATP-dependent Na^+, K^+, and Ca^{2+} pumps to maintain ion homeostasis.[197] SDs are initiated by similar mechanisms in metabolically compromised brain tissue but

can be more severe and longer lasting.[198] Mechanisms of SD propagation are still under intense investigation, but it is generally accepted that passive diffusion of extracellular K^+ and glutamate provoke depolarization in surrounding grey matter.[198,199] A positive feedback loop mediated by N-methyl-D-aspartate receptor- and Ca^{2+} channel-dependent glutamate release and other voltage-gated channels also seems crucial to the self-sustaining nature of SDs.[198] Because of their uniqueness and powerful suppression of normal brain activity, SDs have been studied extensively in the context of many neurological disorders and diseases including stroke.[199]

Spreading Depolarizations After SAH

SDs evoke a hyperemic response in healthy tissues as a result of the increased metabolic demand during disrupted ion homeostasis.[200] Injured or otherwise compromised brain tissues are more prone to neurovascular uncoupling and often show hypoperfusion after SDs (Figure 3).[200] These depolarizations are also sometimes referred to as "peri-ischemic depolarizations" or "cortical spreading ischemia," although they are functionally indistinguishable from SDs when they spread into healthy tissue.[201,202] Early investigation into neuroelectric sequelae of cerebrovascular disease revealed that ischemic stroke induces multiple occurrences of SDs through the cortex.[203] Just a few years later, Dreier et al demonstrated that topical application of K^+ and hemoglobin could induce SDs/cortical spreading ischemia in rats.[204] K^+ cations and free hemoglobin in the subarachnoid space are characteristic of hemolyzed red blood cells after SAH, leading to the hypothesis that SDs induced in this manner might play a pathologic role in the poor outcomes are SAH. Consistent with this notion, Dreier et al again showed that "products of hemolysis" (K^+ and hemoglobin added to artificial CSF) cause SDs and cortical spreading ischemia in the cortex as well as massive neuronal cell death and reactive gliosis (Figure 3).[205] A landmark paper from the same group found that SDs occur after SAH in humans and predict the development of DCI.[206] Later studies also revealed that clusters of SDs magnify the duration of tissue hypoxia and that clustered SDs may be more important to DCI pathology than isolated depolarizations.[207,208] Further, the correlation between SDs and DCI remains even after the successful treatment of angiographic vasospasm.[209] The totality of these studies, driven in large part by the COSBID (Co-Operative Studies on Brain Injury Depolarizations) Study Group, have revolutionized the conceptualization of DCI pathology. SDs and related factors are now rightly at the forefront of investigation into improving SAH outcomes.

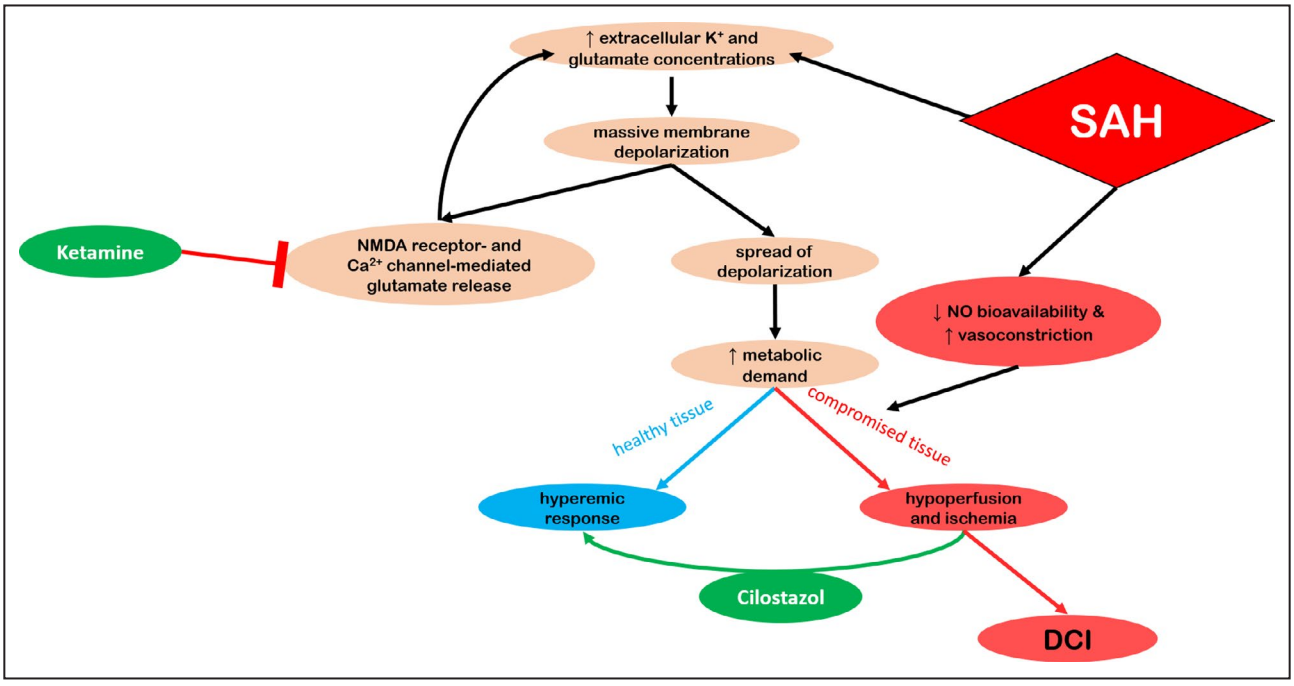

Figure 3. Spreading depolarizations after subarachnoid hemorrhage and potential therapeutic targets.
Spreading depolarizations cause cerebral ischemia by increasing metabolic demand in injured tissue unable to compensate with increased perfusion. SAH itself also promotes the development of spreading depolarizations by the release of K^+ and glutamate from extravasated erythrocytes and platelets. A couple of promising therapeutic agents to prevent spreading depolarizations/cortical spreading ischemia are ketamine and cilostazol. Ketamine works through inhibiting NMDA receptors and the propagation of spreading depolarizations. Cilostazol reduces ischemia by improving neurovascular response to depolarization. DCI indicates delayed cerebral ischemia; NMDA, N-methyl-D-aspartate; and SAH, subarachnoid hemorrhage.

Spreading Depolarizations as a Therapeutic Target

Inquiry into treatments that target SDs/peri-ischemic depolarizations to prevent DCI is still in its early stages; nonetheless, several promising avenues of investigation have been identified. Vasoactive drugs can modulate the neurovascular response to SD and prevent pathological hypoperfusion. The earliest work was based on the finding from Dreier et al that inhibition of NOS produced similar SD effects as topical hemoglobin application, implying that NO scavenging and vasoconstriction by hemoglobin could be critical to transforming the hyperemic SD response into a cortical spreading ischemia response.[204] Treatment with NO-donors and NO-independent vasodilators reduced the ischemia/hypoperfusion after K^+-induced SDs.[210] The same group of researchers also showed nimodipine treatment reduces SD-induced ischemia in rats.[211] Years later, the phosphodiesterase enzyme$_3$ inhibitor cilostazol was shown to reduce spreading ischemia after mimicked SAH-induced SDs (Figure 3).[212] The same study tested cilostazol in a relatively small number of human patients with aSAH and observed a nonsignificant trend for decreased DCI, indicating a larger clinical trial may be worthwhile. These studies exemplify the interdependency between pathological factors after SAH. Given the discrepancy in perfusion response between healthy and injured tissues, SDs/peri-ischemic depolarizations reveal vulnerabilities in the cerebrovasculature that might not have otherwise progressed far enough to cause DCI. The second area of investigation into therapeutics is direct inhibition of SD propagation. N-methyl-D-aspartate receptors have long been known to play a pivotal role in SD propagation in otherwise healthy tissue[213–215]; thus, N-methyl-D-aspartate receptor antagonism was a logical place to explore post-SAH therapies. A 2012 study analyzing various classes of sedatives and analgesics found that the N-methyl-D-aspartate receptor antagonist ketamine decreased the incidence of SDs in patients with traumatic brain injury and SAH, whereas midazolam increased SDs and propofol, fentanyl, and morphine had no effect.[216] More recent studies have found that ketamine reduces SDs in a dose-dependent fashion and can inhibit SD incidence when started in patients with SAH who have already had multiple SDs (Figure 3).[217,218] Larger clinical trials are needed to fully evaluate the efficacy of ketamine in this context. The anticonvulsant valproate has also been investigated based on its SD-inhibiting properties in healthy tissue.[219,220] Valproate treatment was found to reduce cerebral lesion growth after SAH with and without added SD induction (topical potassium chloride application).[221] To our knowledge, these findings have yet to be replicated in human patients with SAH but still contribute to the mounting evidence that blocking SD propagation could yield favorable outcomes. Additionally, older treatments need to be reassessed with respect to their effects of SDs. As previously discussed, nimodipine reduces SD-induced ischemia and it is tempting to assume this occurs through inhibition of L-type calcium channels in the smooth muscle of the cerebrovasculature; however, nimodipine can work in a vessel-independent fashion to directly alter the ion flux/electrical response to stress in neurons.[222] This finding could help explain why nimodipine reduces secondary ischemia after SAH without reducing vasospasm.[34,36,37] The scientific rationale for targeting SDs to reduce DCI is strong; now the objective of the field is to conduct powerful clinical trials in order to demonstrate a clear benefit in patients.

CONCLUSIONS

Rigorous investigation into the pathophysiology of delayed cerebral ischemia is imperative to improve outcomes following SAH. The efficacy of current standard of care is suboptimal and large trials of new therapeutics have failed to demonstrate benefit. We believe a deeper understanding of DCI will lead to novel therapeutic strategies and improve the lives of those who suffer from this devastating disease. The goal of this review was to assist in this endeavor by providing an up-to-date examination of the literature in regard to 3 main areas of DCI pathology: vascular dysfunction, inflammation, and spreading depolarizations. Moreover, we pay special attention to the relationships between these areas in order to gain an integrative perspective of DCI and properly interpret study results. This analysis also serves to accentuate the recent discoveries that are the most promising candidates for clinical investigation.

ARTICLE INFORMATION

Received March 29, 2021; accepted June 9, 2021.

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Sources of Funding

This work was supported by the National Institutes of Health (R01NS110710), the Brain Aneurysm Foundation, the James and Brigette Marino Family Professorship Endowment, the Eblen Research Endowment, and the Christine Desmond Fund.

Disclosures

None.

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