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New insights into the causes and therapy of cerebral vasospasm following subarachnoid hemorrhage

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Cerebral vasospasm lingers as the leading preventable cause of death and disability in patients who experience aneurysmal subarachnoid hemorrhage. Despite the potentially devastating consequences of cerebral vasospasm, the mechanisms behind it are incompletely understood. Nitric oxide, endothelin-1, bilirubin oxidation products and inflammation appear to figure prominently in its pathogenesis. Therapies directed at many of these mechanisms are currently under investigation and hold significant promise for an ultimate solution to this substantial problem.

Introduction

It is estimated that between 7 and 20 per 100,000 people experience the rupture of an intracranial aneurysm annually [1–3]. Subarachnoid hemorrhage (SAH) accounts for between 3 and 8% of all strokes [4,5], however, because it affects a relatively young population, it is responsible for close to 25% of all years lost because of stroke [6]. Although advances have been made in the diagnosis and treatment of SAH, the overall prognosis of patients harboring ruptured intracranial aneurysms remains poor. Fifty percent of patients will eventually die from SAH, while 15% will be rendered severely disabled. Only 20–35% of patients who experience a ruptured intracranial aneurysm go on to have a moderate or good recovery [7,8].

Cerebral vasospasm following SAH is a potentially devastating condition in which the intracranial arteries constrict, diminishing blood flow to the regions of the brain supplied by the affected arteries. Cerebral vasospasm is a significant predictor of adverse outcome, and is the leading potentially treatable cause of death and disability in patients who experience aneurysmal rupture [9,10]. The presence of cerebral vasospasm does not, however, necessarily lead to clinical consequences, as radiographic vasospasm can be seen in up to 70% of patients, while clinically apparent vasospasm is seen in 20–30% of patients [9,11]. Of those patients who develop symptomatic vasospasm, approximately 50% will progress to infarction and 15–20% will develop a disabling stroke or die of ischemia [12,13]. Despite its clinical significance and the extensive research efforts placed into elucidating its pathogenesis and therapy, vasospasm lingers as an incompletely understood and important clinical problem.

Several promising theories have arisen from intense research efforts (Table 1), however, as of yet, no individual theory is able to completely elucidate the pathogenesis of cerebral vasospasm following SAH. The pathogenesis of cerebral vasospasm is, indeed, complex and probably multifactorial (Fig. 1). Cerebral vasospasm arises from the presence of clot (and specifically red blood cells (RBCs)) [14] within the subarachnoid space and there is a volume-dependent relationship between clot burden and subsequent risk of vasospasm [15–18]. How the specific agent, or agents, associated with the blood clot incite cerebral vasospasm has not, however, been clearly established. Compounds that may potentially cause cerebral vasospasm have been described as being in one of two classes: compounds or the metabolites of compounds found in the blood in SAH (such as hemoglobin (Hb) and bilirubin oxidation products (BOXes)); or, compounds that are induced or otherwise affected by the blood surrounding blood vessels (such as endothelin-1 (ET-1) or nitric oxide (NO)) [19]. The potential inciting substances and mechanisms that appear to play prominent roles in the pathogenesis of cerebral vasospasm following SAH are summarized below.

Causes and mechanisms of cerebral vasospasm

As mentioned, the pathogenesis of cerebral vasospasm is incompletely understood. Each of the causes and mechanisms of cerebral vasospasm discussed below have been shown to be potentially

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2007.11.010

TABLE 1

Contributors to vasospasm development and related therapies

Strategic approach to target	Expected outcome of intervention at target	Who is working on the target	Therapies in trial	Refs
Nitric oxide (NO) depletion	Increased vasodilation	Surgical Neurology Branch, NINDS[a]	Sodium nitrite	[21–28,57]
Endothelin-1 (ET-1)	Decreased vasoconstriction	Actelion	Clazosentan	[29–35,58]
BOXes[b]	Decreased vasoconstriction or decreased potentiation of vasospasm		None	[19,36]
Inflammation	Decreased vasospasm via lack of inflammation of vessel walls, increase in NO levels, decrease in free radicals		None	[30,31,37–48]

[a] National Institute of Neurological Disorders and Stroke.
[b] Bilirubin oxidation products.

important in its pathogenesis. It is unlikely, however, that each operates in isolation. For example, decreased production or activity of a vasodilator, such as NO, in the setting of normal or increased levels and/or activity of vasoconstrictors, such as ET-1, can potently shift the vasculature towards vasoconstriction. Additionally, inflammation can be associated with increased production of endothelin-1, generation of free radicals and decreased availability of NO.

Nitric oxide

Nitric oxide has been determined to play a primary role in the development of cerebral vasospasm, with decreased levels of NO being implicated in the formation of SAH-induced vasospasm. Nitric oxide is a potent vasodilator and depletion of NO and its vasodilatory effects have been observed to cause vasoconstriction [20]. The principal effect of NO on cerebral vessels is the relaxation of vascular smooth muscle cells. Nitric oxide activates soluble guanylyl cyclase, which subsequently activates cGMP-dependent protein kinases. Ultimately, this results in the dephosphorylation of myosin light chains, activation of potassium channels, as well as the closure of voltage-dependent calcium channels producing smooth muscle relaxation [21]. The depletion of NO has been theorized to occur via several mechanisms in the setting of SAH. Nitric oxide has been shown to have a high affinity for Hb, and thus, Hb released during the breakdown of subarachnoid blood decreases NO levels by acting as a scavenger [22,23]. It is also possible that the production of NO is decreased in SAH. This has been hypothesized to be a result of the downregulation or inhibition of two of the various forms of NO synthase (NOS), endothelial NOS (eNOS) and neuronal NOS (nNOS) [21]. This is supported by studies that revealed the downregulation/dysfunction of eNOS, and loss of nNOS in spastic arteries after SAH [24,25], as well as the finding that levels of ADMA, an endogenous inhibitor of eNOS, are elevated in the setting of cerebral vasospasm [26]. Complicating our understanding of the role of NO in vasospasm is the hypothesis that inducible NOS (iNOS) may, in fact, be excessively active in vasospasm, with a resultant increase in free radical production and oxidative stress that can damage smooth muscle cells, leading to vasoconstriction [27]. Although complex, decreased production of NO via eNOS and nNOS isoforms with possible unregulated and

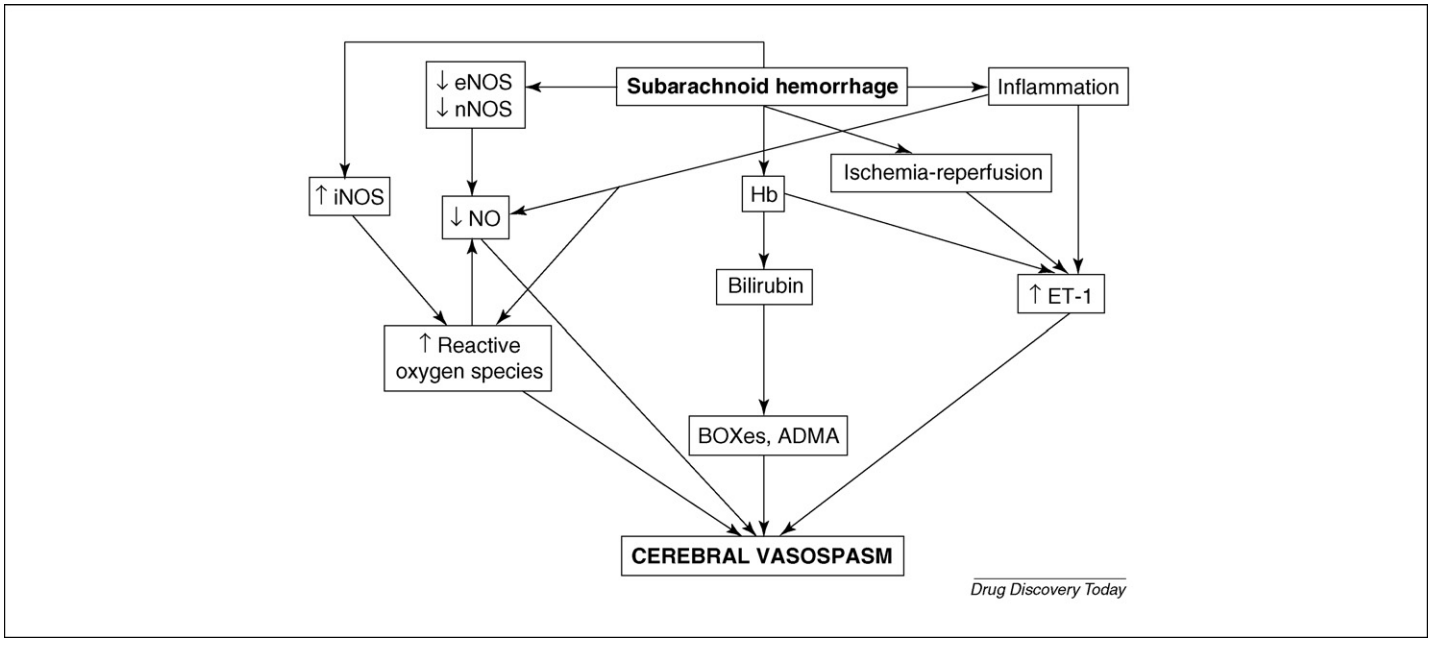

FIGURE 1

Potential contributors to the development of cerebral vasospasm in the setting of subarachnoid hemorrhage.

excessive production of NO through iNOS isoforms (and generation of oxidative stress) contributes to the development and maintenance of cerebral vasospasm following SAH. Furthermore, NO may reverse the effects of the potent vasoconstrictor ET-1 and, through negative feedback, reduce levels of ET-1 [21,28]. In the setting of decreased NO bioavailability, increased or inappropriately normal ET-1 levels can potentiate cerebral vasospasm.

Endothelin-1

Endothelin-1 is another potential contributor to SAH-induced vasospasm. Endothelin-1 is a potent vasoconstrictor that is synthesized as a 212-amino-acid precursor peptide that is ultimately cleaved by an endothelin-converting enzyme (ECE) to its active form [29]. The effects of ET-1 are mediated by two receptor subtypes, ET_A and ET_B, that activate a G protein and second messenger system. ET_A receptors are located predominantly on smooth muscle cells and mediate vasoconstriction and proliferation. The vasoconstriction is mediated by extracellular calcium influx [29]. ET_B receptors are located on endothelial cells where they mediate the release of relaxing factors [30–32], and on venous smooth muscle cells, where they help mediate vasoconstriction [33]. ET_A receptors appear to be crucial in cerebral vasospasm. Endothelin-1 is primarily produced by endothelial cells in response to ischemia, though it can also be produced by neurons, astrocytes and activated leukocytes [29,34,35]. Levels of ET-1 have been shown to be elevated in the plasma and CSF of SAH patients, with the presence of elevated levels of ET-1 correlating with the persistence of cerebral vasospasm [21,36,37]. Additionally, ET-1 levels have been observed to decline in the absence of cerebral vasospasm [36]. Moreover, there is accumulating evidence to suggest that sensitivity to ET-1 is increased in cerebral blood vessels in the setting of SAH [38]. Conversely, the administration of ET-1 antagonists or ECE inhibitors prevents vasospasm [39]. As mentioned, there is interplay between the NO and ET-1 systems, such that increased ET-1 levels may result in decreased NO availability thereby predisposing to vasoconstriction [21,28].

Bilirubin oxidation products

Another mechanism postulated to be involved in the induction of cerebral vasospasm is through free radical oxidation of bilirubin, biliverdin and possibly heme, to produce BOXes. Bilirubin oxidation products act on vascular smooth muscle cells, producing vasoconstriction and vasculopathy by inciting smooth muscle cell injury. As heme is metabolized into bilirubin, peak concentrations occur three to four days after SAH [19]. Once bilirubin is formed, it is subsequently oxidized into BOXes, reaching maximum concentrations during the peak vasospasm period of 4–11 days. Data have accrued implicating BOXes in the pathogenesis of cerebral vasospasm pursuant to SAH [19]. Bilirubin oxidation products can be found in the CSF of patients with vasospasm following SAH. Furthermore, BOXes are vasoactive *in vitro* and closely mimic the biochemical actions of CSF from patients with vasospasm. They are also active *in vivo*, evoking constriction in animal cerebral blood vessels. Finally, CSF concentrations of BOXes correlate with the clinical occurrence of vasospasm in patients with SAH [19,40]. Recent data suggest that BOXes are thought to be potentiators of cerebral vasospasm once it has already been initiated, rather than primary initiators of vasospasm [19].

Inflammation

Inflammation, following subarachnoid hemorrhage, has also been postulated to play a crucial role in the pathogenesis of cerebral vasospasm [34,41]. First, circumstantial evidence indicates that antecedent inflammation of the subarachnoid space evokes arterial constriction. Cerebral vasospasm has been shown to complicate bacterial meningitis and nonspecific inflammation of the subarachnoid space via injection of substances such as talcum and latex beads produces marked vascular constriction and vessel morphological changes mimicking those occurring after SAH [34]. Inflammation and leukocyte infiltration is prominent in the blood vessel walls following exposure to blood in the subarachnoid space [42,43]. Furthermore, leukocyte concentrations are elevated in the CSF of patients who develop SAH-related ischemia [44]. Leukocyte recruitment is promoted by expression of adhesion molecules that facilitate leukocyte adherence to the endothelium. Indeed, adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin, have been found to be elevated in the CSF of patients with SAH and in blood vessel walls exposed to clot, in a pattern that correlates temporally with the natural course of cerebral vasospasm [34,45]. Leukocytes can contribute to vasospasm in several potential ways. Leukocytes can promote free radical formation that may evoke endothelial dysfunction and calcium influx [46,47]. They also produce a variety of substances that can have powerful vascular effects, including leukotrienes and ET-1 [35]. Another significant mechanism by which leukocytes potentially contribute to vasospasm is through the consumption of nitric oxide. The effect that such consumption of NO has on vasospasm is twofold. First and foremost is the decreased availability of NO and its vasodilatory effects. Secondly, is the formation of injurious reactive nitrogen species accompanying the consumption of NO [41]. Cytokines are proteins that are powerful mediators and regulators of immune responses and have been examined in the pathogenesis of cerebral vasospasm following SAH. Cytokine expression is profoundly altered following SAH correlating with the time course of vasospasm. Several cytokines have been found to be upregulated in cerebral vasospasm, including TNF-α, IL-1, IL-6 and IL-8 [48–50] and therapies targeting cytokines have demonstrated therapeutic efficacy [51,52].

Therapy

Despite extensive research effort directed toward SAH-induced cerebral vasospasm, the pathogenic mechanisms underlying cerebral vasospasm remain incompletely understood. This incomplete mechanistic understanding of cerebral vasospasm has, at least in part, hindered the development of rational, targeted therapy. As such, there is no presently universally efficacious therapy available, though several promising therapies are presently being investigated in clinical trials based on robust preclinical and early clinical data.

Prevention of rebleeding

A ruptured intracranial aneurysm should be secured as soon as possible after the initial rupture, often considered to be within the first 24–48 hours after rupture [1]. Although cerebral vasospasm is typically not seen any earlier than three to five days after the onset of subarachnoid hemorrhage, the primary reason for early treatment of the ruptured aneurysm is the prevention of rebleeding

[1,53]. It does, however, have the added benefit of allowing the neurosurgical team to treat cerebral vasospasm aggressively if vasospasm should arise (e.g. by raising blood pressure as discussed below). Other general measures to prevent cerebral vasospasm and its consequences (namely cerebral ischemia) include avoidance of hypovolemia and hypotension and treatment of potential contributors to secondary injury such as raised intracranial pressure, fever and severe anemia. Specific therapy of cerebral vasospasm can be divided into prophylactic treatments and treatments for established vasospasm.

Intracisternal thrombolysis

Clot burden is unequivocally linked to risk of development of cerebral vasospasm. Treatments to prevent vasospasm by reducing clot burden (either at the time of surgery with direct clot removal or peri-operatively with intracisternal thrombolysis with the administration of thrombolytics such as tPA delivered into the subarachnoid cisterns via a catheter) have been reported [54–57]. In 1995, Findlay *et al.* performed the only randomized trial studying the effects of intraoperative injections of rt-PA into the basal subarachnoid cisterns following aneurysm clipping. Although they found many patient groups trended toward lesser degrees of vasospasm when rt-PA was administered, the only statistically significant improvement was seen in patients with thick subarachnoid clots [57]. Amin-Hanjani later performed a meta-analysis looking at a total of 652 patients who were treated with intracisternal thrombolytics [54]. They concluded that thrombolytic therapy had a statistically significant beneficial effect; however, they acknowledged the lack of large, randomized prospective trials. Interestingly, they found no difference between patients who received intraoperative injections, versus patients who received postoperative treatments. Ultimately, although it remains theoretically appealing, there is a paucity of well-designed prospective, randomized studies, and thus there is no consistent data supporting this routine practice.

Signaling for smooth muscle contraction

The calcium channel blocker, nimodipine, has been shown in clinical trials to improve outcome in patients with SAH when used for a period of 21 days after aneurysmal rupture [58,59]. Although it was initially thought that nimodipine would prevent vasospasm, its predominant effect does not seem to involve a decrease in the incidence of angiographic vasospasm. However, it is thought that the beneficial effects of nimodipine can be ascribed to effects on the microcirculation or through neuroprotection.

Another calcium channel blocker, nicardipine, has been shown to decrease the incidence of both symptomatic and angiographic cerebral vasospasm [60,61]. It did not, however, improve outcome, a finding that may be explained, in part, by failure to account for use of rescue therapy. In addition, both intraventricular and intra-arterial nicardipine shows early therapeutic promise, but requires further investigation [62,63].

Studies looking at the role of magnesium in the setting of SAH have also had mixed results. Macdonald *et al.* looked at magnesium in primates, and found that it did not prevent vasospasm [64]. Similarly, Veyna *et al.* saw no improvement in vasospasm rates with magnesium therapy, though they did see trends toward improved outcome [65]. No adverse events were seen associated with magnesium therapy. In their randomized, prospective trial, van den Bergh *et al.* observed a 34% reduction in delayed cerebral ischemia when patients were treated with intravenous magnesium sulfate, as well as a reduction of poor outcome at three months by 23% [66]. Certainly the use of magnesium has potential benefits in the setting of SAH, with minimal risk of adverse effects. As such, some advocate maintaining high levels of magnesium in patients with aneurysmal rupture; however, to this point, there is not definitive evidence that it is useful in SAH patients.

Other drugs to inhibit vascular smooth muscle contraction, such as Rho-kinase inhibitors, have been studied in the setting of cerebral vasospasm. Studies suggest that Fasudil, a Rho-kinase inhibitor, may decrease angiographic vasospasm and CT hypodensities, and decrease symptomatic vasospasm and poor outcome [67,68]. This drug has been approved for use in Japan but has not been extensively investigated or implemented in the United States.

Enhancing NO bioavailability

Other interventions with considerable potential in the prevention of cerebral vasospasm following SAH include drugs that increase nitric oxide levels. Primate studies have demonstrated that the infusion of the NO donor sodium nitrite, and its subsequent release of NO, prevented cerebral vasospasm without causing systemic hypotension [69]. A Phase I clinical trial examining sodium nitrite is nearing completion and subsequent clinical trials are presently being planned. Erythropoietin (EPO) has also been examined in the setting of cerebral vasospasm. In addition to being potentially neuroprotective [70,71], EPO may play a role in preventing vasospasm by increasing the phosphorylation of eNOS [72], a potentially important mechanism for increasing NO production.

Endothelin-1 antagonism

Perhaps the most promising drug that has been studied for the prevention or reversal of cerebral vasospasm is clazosentan, one of several endothelin receptor (ET_A specific) antagonists to be studied in the setting of cerebral vasospasm [29]. Clazosentan has been the subject of a Phase IIb clinical trial, the Clazosentan to Overcome Neurological iSChemia and Infarct OccUrring after Subarachnoid hemorrhage (CONSCIOUS-1) study. CONSCIOUS-1 was a double-blind, randomized clinical trial that examined the effects of the clazosentan on cerebral vasospasm. Clazosentan decreased the incidence of severe vasospasm, delayed ischemic neurological deficits and new infarcts seen on CT scans in a dose-dependent fashion. However, it did not show a reduction in patient mortality, though the study was underpowered for this endpoint [73]. A Phase III clinical trial, CONSCIOUS-2, is scheduled to begin enrolling patients later this year.

Targeting BOXes

Potential therapy aimed at attenuating the effects of BOXes include the prevention of bilirubin formation, inactivating bilirubin or BOXes or removing clots before vasospasm occurs. Heme oxygenase inhibitors could, potentially, decrease bilirubin formation and the formation of BOXes, though this has not been carefully examined [19]. Although free radical scavengers, such as Tirilazad, have failed to produce benefit in the setting of SAH

[74,75], specific, new antioxidant therapies could potentially attenuate the impact of BOXes in the development of cerebral vasospasm. Decreasing the substrate that evokes vasospasm by decreasing clot burden has been discussed above.

Anti-inflammatory therapy

Several drugs aimed at limiting the inflammatory response associated with subarachnoid hemorrhage and, subsequently, cerebral vasospasm, have been used with varying levels of success, including nonsteroidal anti-inflammatory agents, cyclosporine A, FK-506, methylprednisolone and other anti-inflammatory drugs [34]. Currently, however, standard practice for SAH does not include anti-inflammatory therapy. Partial efficacy of anti-inflammatory therapies thus far may be explained, at least in part, by the fact that the inflammatory response accompanying SAH has not been defined. The critical components of the inflammation cascade in the pathogenesis of vasospasm may not be presently targeted. In the transplant literature, multidrug regimens are required in the acute period to target the multifaceted and robust immune response.

Statins – pleiotropic effects

Statins have been shown to possess cholesterol lowering-independent pleiotropic effects in different clinical settings. This includes decreasing the incidence of cerebral vasospasm, reducing the duration of severe vasospasm and decreasing mortality rate in the setting of SAH [76–78]. Statins are thought to be beneficial in the prevention of cerebral vasospasm by down-regulating inflammation and upregulating/preserving the expression of eNOS and therefore NO [76–78].

In their Phase II, randomized, placebo-controlled trial, Tseng *et al.* [76] observed improvement of cerebral vasospasm, and a decrease in delayed ischemic neurological deficits related to vasospasm, in patients treated with pravastatin in the setting of aneurysmal SAH. They also found statin administration to be the only independent predictor of improved outcome at the time of hospital discharge. Lynch *et al.* [77] looked at the effects of simvastatin on patients with aneurysmal SAH, and found that 80 mg given daily attenuated both radiographic vasospasm and delayed ischemic neurological deficit. Currently at our institution, all patients with spontaneous SAH are started on 80 mg of simvastatin upon hospital admission, with eventual discontinuation after completion of a 14-day treatment course, or after failure to demonstrate an aneurysm with two negative radiographic studies (CTA or DSA) performed several days apart.

Prophylactic angioplasty

Prophylactic angioplasty has been examined for the prevention of cerebral vasospasm. Although invasive and associated with significant risks, prophylactic angioplasty in patients at high risk for vasospasm prevented subsequent development of vasospasm [79]. This preventative strategy, however, has not been adopted routinely and awaits further investigation.

Therapy for established vasospasm

The therapy of established vasospasm involves several strategies including both medical and endovascular approaches. The current practice for the treatment of established cerebral vasospasm begins with standard triple-H therapy, which includes the induction of hypertension, hypervolemia and mild hemodilution [80]. The use of vasopressors in combination with volume expansion is still the most effective way to rapidly reverse the neurological deficits associated with cerebral vasospasm, with a reported response of up to 70% [81,82]. As interventional techniques have become more sophisticated, the use of endovascular methods for the treatment of cerebral vasospasm has become more widespread. This includes transluminal balloon angioplasty of spastic segments of large intracranial arteries [83,84], and the intra-arterial injection of vasoactive substances such as papaverine or verapamil. These therapies can be efficacious, though must be applied in a timely fashion to avoid permanent cerebral ischemic injury.

Conclusion

Cerebral vasospasm following SAH remains a common and formidable problem in patients harboring ruptured intracranial aneurysms. Burgeoning research efforts have facilitated the development of several important theories concerning its pathogenesis. Although cerebral vasospasm pursuant to SAH is complex and likely to have a mutlifactorial pathogenesis, central to its development is an imbalance between vasoconstrictory substances, such as ET-1, and vasodilatory substances, such as NO, with a resultant relative or absolute excess of the former and a relative or absolute deficiency of the latter. Inflammation and free radical formation also appear to figure prominently in the pathogenesis and all proposed mechanisms are likely to be inextricably linked. Targeted therapy aimed at increasing NO bioavailability through NO donors, such as sodium nitrite, or antagonizing the effects of ET-1, through ET receptor antagonism, appears to offer considerable potential in the therapy of cerebral vasospasm following SAH. Similarly, the role of inflammation in vasospasm is becoming increasingly elucidated, and as such anti-inflammatory agents appear to have significant promise. It is our opinion that the bulk of future successful pharmacotherapy aimed at cerebral vasospasm will probably involve these proposed mechanisms of ET-1, inflammation and NO. Ongoing and future clinical trials, based upon our current understanding, are poised to produce a final solution for this lingering but significant complication of patients with SAH.

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