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Early Brain Injury, an Evolving Frontier in Subarachnoid Hemorrhage Research

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Summary

Subarachnoid hemorrhage (SAH), predominantly caused by a ruptured aneurysm, is a devastating neurological disease that has a morbidity and mortality rate higher than 50%. Most of the traditional *in vivo* research has focused on the pathophysiological or morphological changes of large-arteries after intracisternal blood injection. This was due to a widely held assumption that delayed vasospasm following SAH was the major cause of delayed cerebral ischemia and poor outcome. However, the results of the CONSCIOUS-1 trial implicated some other pathophysiological factors, independent of angiographic vasospasm, in contributing to the poor clinical outcome. The term early brain injury (EBI) has been coined and describes the immediate injury to the brain after SAH, before onset of delayed vasospasm. During the EBI period, a ruptured aneurysm brings on many physiological derangements such as increasing intracranial pressure (ICP), decreased cerebral blood flow (CBF), and global cerebral ischemia. These events initiate secondary injuries such as blood-brain barrier disruption, inflammation, and oxidative cascades that all ultimately lead to cell death. Given the fact that the reversal of vasospasm does not appear to improve patient outcome, it could be argued that the treatment of EBI may successfully attenuate some of the devastating secondary injuries and improve the outcome of patients with SAH. In this review, we provide an overview of the major advances in EBI after SAH research.

Keywords

Subarachnoid hemorrhage; Early brain injury; Cerebral vasospasm; Animal model

Introduction

Subarachnoid hemorrhage (SAH) is a common and frequently devastating condition, accounting for 5% of all stroke types [118]. Each year, approximately 1 in 10,000 North Americans suffer from an aneurysmal SAH, and this carries with it a greater than 50% combined morbidity and mortality rate [60]. Despite advances in diagnosis and surgical treatment of SAH, effective therapeutic interventions are still limited and clinical outcomes remain disappointing. Traditionally, delayed cerebral vasospasm (CVS) has been considered the single and most important cause of delayed cerebral ischemia and poor outcomes [57]. Although animal studies have found many agents which inactivate spasmogenic substances

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Conflict of interest statement
We declare that we have no conflicts of interest.

or block arterial smooth muscle contraction, no agent has brought tremendous improvement in the human patient outcome after SAH. Early brain injury (EBI) was reported as a primary cause of mortality in SAH patients [12], and many important pathological mechanisms have been recognized to be initiated within minutes after aneurysmal SAH [81]. Recently, intensive research efforts have aimed to reveal the mechanisms of EBI. In this review, we provide an overview of the major advances in EBI after SAH research.

The SAH Experiments before Early Brain Injury

Experimental Focus on Delayed Cerebral Vasospasm after SAH

Since the first demonstration of CVS, about 60 years ago [29], many experimental and clinical studies have tried to disclose mechanisms responsible for this persistent vasoconstriction and to find proper treatment for its prevention and/or reversal. In humans, CVS usually occurs on day 3 after SAH, peaks at day 6-8, and lasts for 2-3 weeks [125]. Delayed cerebral ischemia has been considered to be induced by CVS because several studies found a strong association between radiologically confirmed vasospasm and clinical signs of delayed cerebral ischemia [35, 37, 92]. Therefore, there was a widely held assumption that CVS was the major cause of the high mortality and poor outcome after an otherwise successful treatment of a ruptured intracranial aneurysm [25]. Thus the majority of research performed worldwide has focused on strategies to limit arterial narrowing and delayed cerebral ischemia following SAH [57]. Restoration of narrowed large-arteries, using pharmacological agents, was believed to improve vasospasm as a whole. This conclusion was arrived at by using, the most common model of SAH and vasospasm, the canine “two-hemorrhage” model, in which two injections of blood, into the dog’s basal cistern, are performed 48 hours apart in order to observe the large artery pathophysiological or morphological changes [76].

Translational Trials for Cerebral Vasospasm: from Animals to Humans

Many pathophysiological mediators have been demonstrated in CVS such as i) the dysfunction of nitric oxide (NO) - nitric oxide synthase (NOS) pathway, ii) endothelin-1, iii) ferrous hemoglobin released from the subarachnoid clot and subsequent oxidative stress, iv) inflammatory pathways, v) blood-brain barrier (BBB) breakdown by endothelial apoptosis or thrombin, vi) excitotoxicity and membrane pathology of Ca^{2+} channels [90, 137]. Numerous interventions are currently being investigated for CVS treatment [61]. Several promising pharmacological treatments, previously demonstrated in pre-clinical animal experiments, have translated to human randomized and blinded clinical trials such as: calcium channel antagonists (nimodipine and nicardipine) [48, 79, 87, 88], endothelin antagonists [73, 119, 121], erythropoietin [107], fasudil [102], magnesium sulfate [126], statins [23, 117], tirilazad [47, 56], and tissue plasminogen activator (tPA) [36]. However, most of them failed in clinical trials for prevention and treatment of CVS [85], except fasudil which is used clinically in Japan and China [69]. Nimodipine had a beneficial effect on the reduction of in morbidity and improvement in functional outcome but not CVS [9].

Therefore, even now patients suffering from CVS receive complex treatments with calcium antagonists (oral nimodipine treatment), hypertensive drugs, hemodilution and hypervolemia (triple H therapy), risky and often only temporarily effective intra-arterial administration of vasodilator drugs, or balloon angioplasty [26].

The Next Targets for SAH Research after the CONSCIOUS-1 Trial

Clazosentan, a selective endothelin receptor type A antagonist, has been proven effective to decrease CVS after experimental SAH [93]. The patients after SAH treated with clazosentan demonstrated a 65% relative risk reduction in angiographic vasospasm. However, mortality

or clinical outcome was not improved in the CONSCIOUS-1 trail (clazosentan to overcome neurological ischemia and infarction occurring after SAH) [73]. These observations indicate that the pathophysiology underlying delayed cerebral ischemia is multifactorial and that other pathophysiological factors, which are independent of angiographic vasospasm, can contribute to the outcome [74]. Additionally, it may be that the pathological mechanisms, activating within minutes after SAH and leading to EBI, play an important role in the pathogenesis of delayed ischemic injury and poor outcome [14].

Experiments on Early Brain Injury after SAH

Experimental transition from Cerebral Vasospasm to Early Brian Injury

The term EBI has been coined as the period which spans from the moment of initial bleeding to the onset of CVS. It describes the immediate injury to the brain after aneurysmal SAH as a whole, reported by Kusaka *et al* in 2004 [62]. It can be suggested that the EBI precipitates the occurrence of CVS in many ways, including vascular injury from acute ischemia, inflammation, and blood products, which may result in damage of NO-releasing neurons [89].

Since the main pathophysiological stage has changed from the large-arteries to the brain parenchyma, the experimental modeling of EBI began to simulate the intracranial artery rupture, and the common experimental model changed to the rodent “endovascular puncture” model. This model was independently described by Bederson *et al* and Veelken *et al* [10, 120], and the surgical procedure aims to perforate the internal carotid bifurcation, without craniotomy, by means of a sharp ended suture inserted through the external carotid artery (Figure 1).

Vascular injury highly correlates with brain edema generally evaluated by brain water content in rat experimental SAH, showing increased intracranial pressure (ICP), and decreased microvascular flow, as well as injury to neuronal tissues [28, 59, 80]. Since 48 hours after SAH is the time point at which maximal cerebral vasospasm is observed in rats, the 24-hour time point seems to be correct for the analysis of EBI after SAH [130]. Furthermore, understanding EBI has become more and more important than that of CVS itself. Many recent studies using interventions such as: pharmacological agents, transgenic and knockout animals, or hyperbaric oxygen have been used to elucidate the numerous intracellular second messenger cascades and to find a promising treatment for EBI (Table 1).

The Mechanisms of Early Brain Injury after SAH

Perhaps the most immediate event following the rupture of an intracranial aneurysm is an arrest in intracranial circulation, caused by a peak of ICP (rising as high as mean arterial blood pressure within 1 minute of ictus). The ICP then falls over several minutes to reach a much lower baseline, but remains higher than normal [43]. The temporary intracranial circulatory arrest promotes hemostasis and contributes to severe global ischemic injury, all leading to loss of autoregulation, the reduction in cerebral perfusion pressure (CPP), secondary raised ICP and decreased cerebral blood flow (CBF) [14, 81]. This hypoxic state also culminates in energy failure in neurons and glia, and initiates the cascade of events leading to cytotoxic edema [81]. Ischemia also results in apoptosis of cells that constitute the BBB [58]. Death of endothelial cells and perivascular astrocytes cause increased diffusion of serum from the vascular lumen into cerebral tissues (vasogenic edema). SAH also impacts brain parenchyma by activating astrocytes and microglia, and triggering up-regulation of the pro-inflammatory cytokines [78, 91].

Therefore, factors stemming from the initial bleeding in SAH include: raised ICP, decreases in CBF and CPP, BBB disruption, brain swelling, brain edema, acute vasospasm and

dysfunction of autoregulation, all of which constitute pathophysiological variables occurring during the EBI period (within the first 72 hours after SAH) [81]. Acute global ischemia, altered ionic homeostasis, degradation of vascular integrity, excitotoxicity, thrombin activation, oxidative stress, inflammation, elevated matrix metalloproteinase (MMP) 9, and activation of the NO-NOS pathway are all clinically relevant through their involvement in cell death and ultimate dysfunction that follows SAH (Figure 2) [7, 22, 98].

Cell Death and Anti-Apoptotic Therapy in Early Brain Injury after SAH

Even a brief ischemic insult to the brain may trigger complex cellular events which lead to progressive apoptotic and necrotic cell death [132]. In general, apoptosis can be regarded as an energy-dependent process whereas necrosis is not. In SAH, if the initial bleed were severe enough to prevent blood flow to the brain as in a global stroke, it is unlikely that the brain tissue would survive. As a result, necrosis is not a major factor in SAH [14], and apoptosis may play an important role in EBI after SAH. Akt (protein kinase B), a serine/threonine kinase, is one of the key antiapoptotic signaling molecules downstream of phosphoinositide 3-kinase (PI3K) in EBI after SAH [20, 27, 30]. Mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38, have all been studied in EBI. JNK and p38 are activated in response to inflammatory cytokines and cellular stress, up-regulating apoptotic cascades [52]. The tumor suppressor gene, p53, also regulates apoptosis. In EBI after SAH, anti-apoptotic therapies have reported to ameliorate outcomes by targeting the MAPK pathway [62, 106, 114, 131], activating p53 [13, 16, 68, 76], and hypoxia inducible factor-1 (HIF-1) target genes by hyperbaric oxygen [84].

Future Directions of SAH Research

Now, EBI is considered to have a great potential for the implementation of treatment modalities in patients with SAH, attenuating some of the devastating secondary injuries that can be seen in the long term [14]. Mortality should be examined, and neurological functioning ought to be thoroughly evaluated because this information is very important in terms of translation from animals to humans. The mismatch between treatment of angiographical CVS and poor clinical outcome could result from mechanisms other than vasospasm, such as EBI, but also from the use of inadequate animal models of vasospasm. Since both EBI and CVS may contribute to the pathogenesis of delayed neurological deficits, experimental CVS should also be made by mimicking human SAH, in terms of having an injured artery and direct hemorrhagic brain lesion under arterial blood pressure [90]. The endovascular perforation model seems suitable to employ in acute SAH research, as it can produce more severe pathophysiological changes and a comparable insult to a ruptured aneurysm, as opposed to the double blood injection model [65].

Research regarding EBI after SAH is limited, and further studies are needed to clarify the exact mechanisms involved. Furthermore, it is postulated that cell death mechanisms such as apoptosis, autophagy, necroptosis and endoplasmic reticulum stress, as well as microcirculatory dysfunction, cortical spreading ischemia, and delayed neuronal injury may also be contributing to the outcomes.

Conclusion

Given the fact that the reversal of CVS does not appear to improve the outcome, it could be argued that the treatment of EBI may successfully attenuate some of the devastating secondary injuries following SAH. Further studies targeting EBI may lead to the development of new therapies and the improvement of outcomes for patients suffering from SAH.

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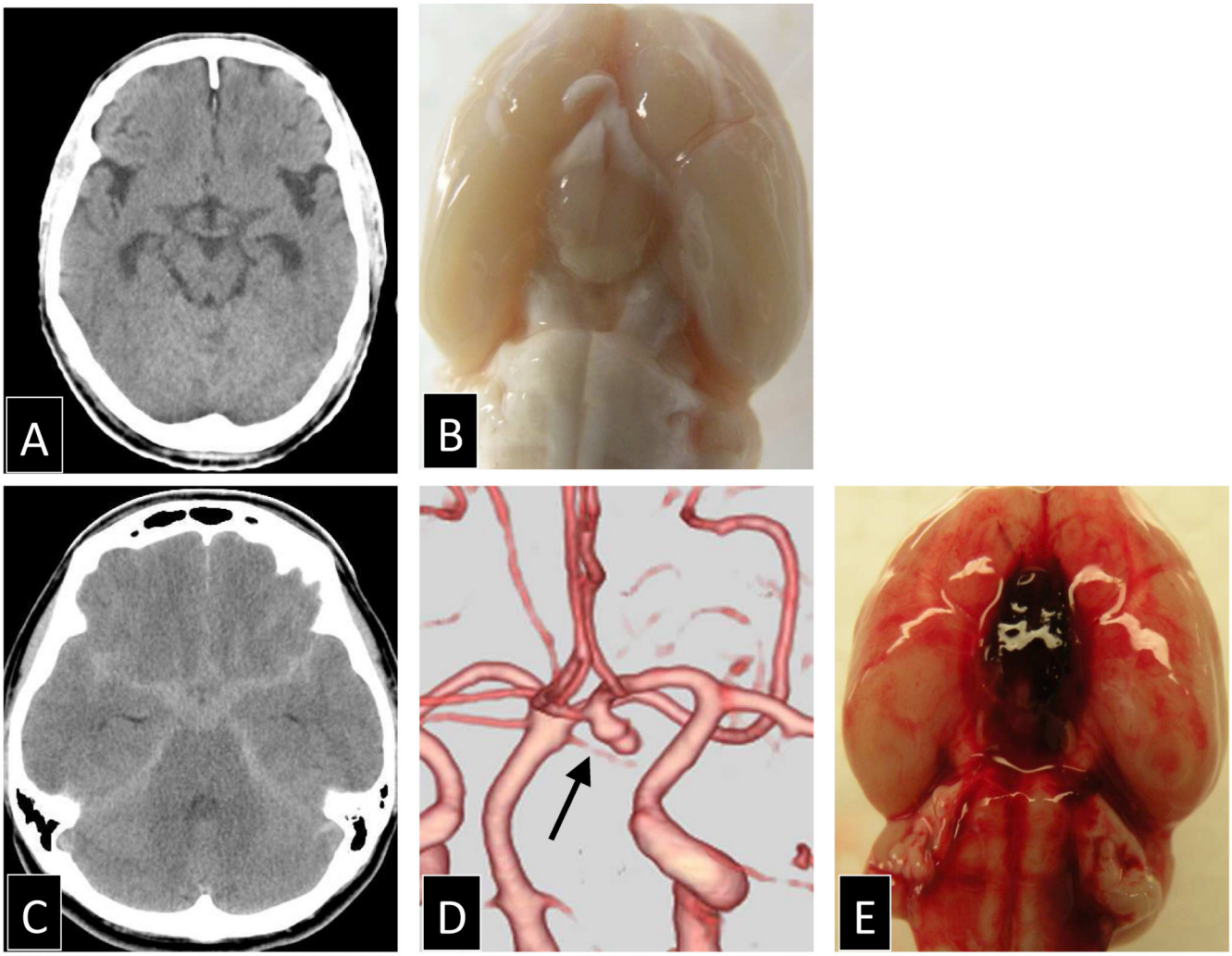

Figure 1.
Comparison of subarachnoid hemorrhage in human and experimental endovascular perforation model of rat: (A) normal brain computed tomography (CT) scan in human around the circle of Willis, (B) a photograph of a sham-operated rat after cardiac perfusion, (C) high density area in the basal cistern on the CT scan after subarachnoid hemorrhage in human, (D) the cause of subarachnoid hemorrhage was an ruptured aneurysm in human (arrow), and (E) subarachnoid hemorrhage at the ventral surface induced by the endovascular perforation of the internal carotid artery in rat.

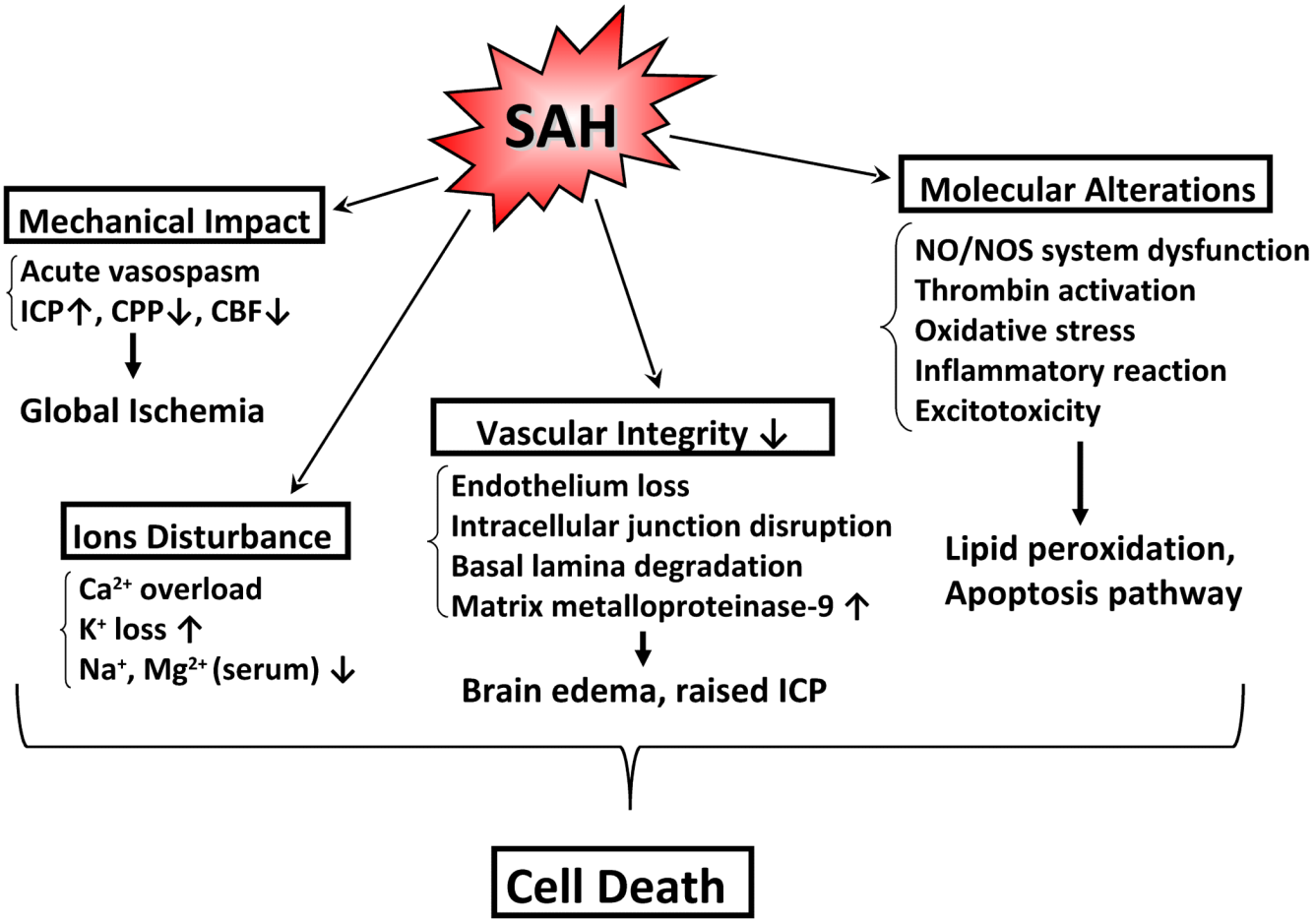

Figure 2.
Mechanism of early brain injury after SAH: SAH causes acute global ischemia, altered ionic homeostasis, degradation of vascular integrity, and molecular alterations, all leading to cell death.

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Table 1

Experimental *in vivo* studies of pathomechanisms in EBI after SAH, using any drugs and interventions

Experimental paradigm	Intervention	Pathogenic factor	Contributing pathway and/or mechanism	Key effect	Outcome after treatment	Reference
EVP, rat	MK-801 (NMDA receptor antagonist)	Activation of c-fos and c-jun	Glutamate pathway	Spreading depression, cell death	Not tested	[49]
EVP, rat	NOS inhibitor	Blood components released during SAH	Scavenging NO by blood, impaired NO vasodilation	Acute vasoconstriction and ischemia	Not tested	[99]
SHI, mice	Mutant mice deficient in Mn-superoxide dismutase	Subarachnoid hemolysate	Superoxide production and cytochrome c release	DNA fragmentation and cell death	Not tested	[75]
SIN, rat	Isamoltane hemifumarate(5-HT1B receptor antagonist) or HET0016 (an inhibitor of the synthesis of 20-HETE)	Activation of 5-HT1B receptors	Synthesis of 20-HETE and rise in intracellular Ca^{2+}	Acute fall in rCBF	Not tested	[15]
SIN, rat	Recombinant adenovirus encoding human Cu/Zn SOD-1	Superoxide anion mesured as a vascular NADPH oxidase activation	Sounperoxide production	Impairment of autoregulatory CBF and oxydative stress	Not tested	[103]
EVP, rat	z-VAD-FMK (a pan-caspase inhibitor)	Acute ischemia	Caspase-3 activity	Apoptosis, BBB disruption, and vasogenic brain edema	NS↑, MT↓	[86]
EVP, rat	Hypertonic fluid (NaCl 7.5% plus 6% dextran 70)	Global ischemia	Osmotic mobilization of parenchymal water and improvement of microcirculation	Increasing ICP and decreased CBF	NS↑	[133]
EVP, rat	PP1 (an Src-family kinase inhibitor)	VEGF	Src tyrosine kinase and ERK1/2, p38, and JNK pathways	BBB disruption, brain edema, and incresed ICP	MT↓	[62]
EVP, rat	Hyperbaric oxygen	Acute ischemia	HIF-1alpha dependent Bcl-2/ adenovirus E1B 19kDa-interacting protein 3 (BNIP3) activation	Decreasing CBF and CPP, increasing ICP, brain edema, and neuronal damage	NS↑, MT↓	[80]
EVP, rat	Hypertonic fluid (NaCl 7.5% plus 6% dextran 70)	Global ischemia	Small volume resuscitation	Increasing ICP and neuronal damage	MT↓	[11]
EVP, mice	ApoE-mimetic peptide	Inflammation	APOE4 genotype expression	Increasing brain edema	NS↑, MT↓	[40]
SHI, rat	ZnPPIX (zinc protoporphyrin IX ; heme oxygenase(HO))	Inhibited the production of endogenous carbon monoxide (CO)	Heme oxygenase/CO pathway	Brain damage (LDH activitivation in serum)	Not tested	[109]
EVP, rat	Hyperbaric oxygen	Expression and activation of NADPH oxidase	Superoxide anion production, increased neuronal immunoreactivity of gp91phox and regulation of gp91phox mRNA	Neuronal injury	NS↑, MT→	[83]
EVP, rat	Hyperbaric oxygen	Up-regulated NADPH oxidase	Superoxide anion production and enhancing gp91 (phox)	Decrease CBF and production of lipid peroxidation	NA	[82]

Experimental paradigm	Intervention	Pathogenic factor	Contributing pathway and/or mechanism	Key effect	Outcome after treatment	Reference
EVP, rat	LY294002 (Phosphoinositide 3-kinase(PI3K) inhibitor	Neuronal injury by ischemia	PI3K/Akt/Glycogen synthase kinase-3beta (GSK3β) pathway	Apoptotic cell death	Not tested	[30]
EVP, rat	p-toluenesulfonate (iNOS inhibitor)	Transient global ischemia	Not formating BBB disruption and brain edema by iNOS	Increasing iNOS expression and NO metabolites concentration	Non improvement in NS or MT	[130]
EVP, rat	Cu/Zn SOD-1 transgenic (Tg) rats	Oxidative stress	Decrease of SOD-Akt-Glycogen synthase kinase-3beta activation	Apoptotic cell death	MT↓	[31]
EVP, rat	Pifithrin-alpha (a selective inhibitor of p53-mediated transcription)	Up-regulation of p53	Activation of the caspase -dependent and -independent pathways and the mitochondrial cascades	Increasing neuronal apoptosis and brain edema	NS↑, MT↓	[13]
EVP, rat	SP600125 (JNK inhibitor)	Phosphorylation of JNK	c-Jun phosphorylation, aquaporin-1 expression, MMP-9 activity, increased VEGF tissue level, and cleaved caspase-3 expression	BBB disruption, brain swelling, and apoptosis	NS↑, MT→	[131]
EVP, rat	S-nitrosoglutathione (NO donor)	depletion of NO	Collagen IV decrease, and collagenase activity increase	BBB disruption in the microvessels	Not tested	[97]
SIN, rat	Felbamate (a NMDA receptor antagonist)	Ischemia induced glutamate and aspartate	Stimulation of NMDA receptor	BBB disruption and brain edema	NS↑	[42]
EVP,mice	gp91phox knockout mice	NADPH oxidase	Superoxide production	Not reducing the intensity of the oxidative stress	MT→	[70]
EVP, rat	Melatonin	Oxidative stress	Melatonin may reduce down regulation of VEGF and astrocytic aquaporin 4 protein expression.	Brain edema	MT↓	[6]
EVP, rat	3% Hypertonic saline	Ischemic brain injury	Osmotic and rheologic properties	Not decrease brain edema	NS→	[66]
DIN, rat	Magnesium	Vasoconstriction effect through Ca^{2+} influx	Anti-vasodilation effect	CBF reduction	Not tested	[77]
EVP, rat	Melatonin	Oxidative stress	No effect on the lipid peroxidation	Increasing brain edema	NS→, MT↓	[5]
EVP, rat	Tetramethylpyrazine (an oxygen free radical scavenger)	Oxidative stress	Increasing cleaved caspase-3, no expression change of bax or bcl-2	BBB disruption, brain edema, and apoptotic cell death	NS↑, MT→	[39]
EVP, rat	Pifithrin-alpha (a selective inhibitor of p53-mediated transcription)	p53 gene	NF-kappaB/MMP-9 expression pathway activation and decreasing occludin and collagen IV	BBB disruption and brain edema	Not tested	[128]
SIN, rat	Clazosentan (an endothelin A receptor antagonist)	Immediate increase in ICP	Acute decrease in CPP and loss of autoregulation	CPP-dependent and -independent hypoperfusion in first hours	Not tested	[95]

Experimental paradigm	Intervention	Pathogenic factor	Contributing pathway and/or mechanism	Key effect	Outcome after treatment	Reference
SIN, rabbit	Dexmedetomidine (an α2-adrenoceptor agonist)	Catecholamine release and excessive free radicals production	Activated lipid peroxidation and Xanthine oxidase, and decreasing of antioxidant mechanisms	Neuronal degenerative change	Not tested	[24]
EVP, rat	Glibenclamide (selective sulfonylurea receptor 1 (SUR1) inhibitor)	Inflammation	TNFα/NF-kappaB/*Abcc8* mRNA/SUR1 receptor upregulation and disruption of ZO-1 expression	BBB disruption and caspase-3 activation	Not tested	[104]
EVP, rat	Atorvastatin (HMG-CoA reductase inhibitor)	Global ischemia	Caspase-dependent apoptosis without p53 expression pathway	BBB disruption, brain edema, apoptotic cell death, and mRNA expression of caspase-3 and caspase-8	NS↑, MT↓	[21]
SIN, rat	Melatonin (antioxidant)	Oxidative stress	Increasing myeloperoxidase and malondialdehyde levels, and decreasing glutathione levels and Na+-K+-ATPase activity	BBB disruption and brain edema	NS↑, MT→	[33]
EVP, rat	Argatroban (a direct thrombin inhibitor)	Thrombin	decreasing ZO-1 level, and increasing IL-1β level	BBB disruption, brain edema, apoptotic cell death, and inflammatory response	NS↑, MT→	[108]
SIN, rat	N-acetylcysteine (a sulfhydryl-containing antioxidant)	Oxidative stress	Decreasing Cu/Zn SOD and glutathione peroxidase activity, and increasing lipid peroxidation product	Brain edema	NS↑	[71]
EVP, mice	Ac-YVAD-CMK (a selective inhibitor of IL-1beta converting enzyme)	IL-1β	JNK and MMP-9 activation, and ZO-1 degradation	BBB disruption and brain edema	NS↑, MT↓	[106]
SIN, rat	Extract of Ginkgo biloba (including flavonol glycosides and other common compound	Oyhemoglobin from extravasated blood	Enhanced VEGF mRNA and VEGF protein but not enough	VEGF mRNA and VEGF protein expression	Not tested	[110]
EVP, rat	Anatibant (a bradykinin B2 receptor antagonist)	Impairment of cerebral autoregulation	Increasing expression of bradykinin B2 receptors and kininogen (Kng1) mRNA	Brain edema	NS↑, MT→	[116]
EVP, rat	Edaravone (=MCI-186, a potent free radical scavenger)	Oxidative stress	Increasing malondialdehyde	Reduced SOD, and apoptotic neuronal cell death	NS↑, MT↓	[41]
PCI, rat	SB-3CT (a selective MMP-9 inhibitor)	Inflammation	MMP-9 activation and laminin degradation	Apoptotic neuronal cell death	NS↑	[44]
SIN, rat	Alpha lipoic acid (a dithiol antioxidant)	Free radical generation and neutrophil accumulation	Increasing ROS formation, DNA fragmentation ratio, malondialdehyde, and myeloperoxidase activity ; and decreasing glutathione content and Na^+-K^+-ATPase activity	BBB disruption and brain edema	NS↑	[32]

Experimental paradigm	Intervention	Pathogenic factor	Contributing pathway and/or mechanism	Key effect	Outcome after treatment	Reference
EVP, rat	Osteopontin (an extracellular matrix glycoprotein)	Inflammation	Activation of NF-kappaB improving the balance between up-regulated MMP-9 and down-regulated TIMP-1 expression, and degradation of substrates of MMP-9 (laminin and ZO-1) pathway	BBB disruption and brain edema	NS↑, MT→	[111]
EVP, mice	Adenosine A(2A) receptor knockout mice	increased ICP and decreased CPP	Increasing collagen type IV by early Adenosine A(2A) receptor response	CBF reduction by decreasing of internal diameter of major cerebral vessels	Not tested	[96]
SIN, rabbit	Simvastatin	Global ischemia	PI3K/Akt/Glycogen synthase kinase-3beta (GSK3β) pathway	BBB disruption, brain edema and apoptotic cell death	NS→, MT→	[20]
EVP, rat	Octonal and carbenoxolone (gap junction inhibitors)	Global ischemia	Connexin 43 phosphorylation	Not reducing apoptotic cell death	NS→, MT→(octanol), MT↑ (carbenoxolone)	[3]
PCI, rat	U46619 and GR3219b (a thromboxane A2 receptor agonist and antagonist)	Cerebral ischemia	Up-regulation of Thromboxane A2 receptors and their mRNA levels	Global and rCBF redution	Not tested	[2]
SIN, mice	Aquaporin-4 null mice	Impairment of glial water channel protein	Reduction in glia limitans osmotic permeability and increasing ICP	BBB disruption and brain edema	NS↑, MT→	[115]
SIN, rat	Neutalized IL-1β by anti-rat IL-1beta antibodies	Extravasated blood and inflammation	IL-1β inducing S-100β protein production	Brain injury and BBB disruption	Not tested	[54]
SIN, rat	Ghrelin (an endogenous ligand for growth hormone secretagogue receptor)	Oxidative stress	Increasing plasma levels of TNF-α and IL-1β, ROS generation, lipid peroxidation, and accumulation of neutrophils, reducing antioxidant status and Na^+-K^+-ATPase activity	BBB disruption, brain edema, and cell death	NS↑	[34]
DIN, rat	Ginsenoside Rb1 (an active component of Chinese medicine Panax Ginseng)	Global ischemia	P53 and Bax dependent proapoptosis pathway	BBB disruption, brain edema, and apoptotic cell death	NS↑, MT↓	[68]
EVP, rat	Osteopontin (OPN) siRNA	Inflammation	Reduction of angiopoietin-1 and MAPK phosphatase-1,and activation of MAPKs and its both upstream and downstream VEGF-A	BBB disruption	NS↓, MT→	[114]
EVP, rat	Deferoxamine (an iron chelator)	Blood breakdown products and oxidative stress	increasing nonheme iron levels, heme-oxygenase-1 (HO-1) expression, and iron-handling proteins (transferrin and its receptor)	Apoptotic cell death and oxidative DNA damage with ferritin	MT↓	[63]

Experimental paradigm	Intervention	Pathogenic factor	Contributing pathway and/or mechanism	Key effect	Outcome after treatment	Reference
PCI, rat	Recombinant human erythropoietin	Oxidative stress	Erythroid 2-related factor 2 and antioxidant responsive element (Nrf2-ARE) pathway	BBB disruption, brain edema, and cortical apoptosis	Not tested	[135]
EVP, rat	CL-IB-MECA (a selective Adenosine A3 receptor agonist)	Inflammation	Increasing TNF-α and IL-1β, and microglial activation	Brain edema	NS↑, MT↓	[72]
EVP, rat	Sodium orthovanadate(a tyrosine phosphatase inhibitor)	Global ischemia	Tyrosine phosphatase activation	Brain edema and apoptosis cell death	NS↑, MT→	[51]
PCI, rat	Minocycline	Global ischemia	MMP-9 expression	Clinical assessments	NS↑	[45]
EVP, rat	Osteopontin (OPN) siRNA	Inflammation	Activation of NF-kappaB, inhibition of MMP-9 induction and TIMP-1 reduction, and the consequent preservation of laminin and ZO-1 pathway	BBB disruption and brain edema	NS↓	[112]
PCI, rat	SB-3CT (a selective MMP-9 inhibitor)	Global ischemia	MMP-9 expression and laminin decrease	Apoptotic cell death	NA	[46]
DIN, rat	Ginsenoside Rb1 (an active component of Chinese medicine Panax Ginseng)	Ischemic brain injury	Vasculature thickening	Brain edema	NS↑	[67]
EVP, rat	Sodium orthovanadate(a tyrosine phosphatase inhibitor)	Global ischemia	Mature brain-derived neurotrophic factor/ phosphorylated TrkB/Akt pathway	Brain edema and apoptotic cell death	NS↑, MT→	[50]
EVP, mice	S-nitrosylated hemoglobin enhanced by ethyl nitrite inhalation	Arteriopathy due to disruption of NO bioactivity	Decreasing of cortical tissue PO_2 and parenchymal RBC flow velocity without blood pressure change	Brain edema and cerebral vessel diameters	NS↑, MT→	[100]
PCI, rat	Sulforaphane (a specific Nrf2 activator)	Oxidative stress	Erythroid 2-related factor 2 and antioxidant responsive element (Nrf2-ARE) pathway	BBB disruption, brain edema, and cortical apoptosis	NS↑	[18]
PCI or EVP, rat	NAT (n-acetyl-l-tryptophan, a neuropeptide substance P blocker)	Global ischemia	Albumin immunoreactivity and secondary ICP elevation	No change of brain edema and ICP elevation	NS→	[8]
DIN, rat	Z-ligustilide (a primary lipophilic component of the radix Angelica sinensis)	Global ischemia	Increasing expression of p53 and cleaved caspase-3, and decreasing Bcl-2 expression on day7	BBB disruption and brain edema	NS↑, MT→	[16]
PCI, rat	Progesterone	Inflammation	Increasing toll-like receptor 4/ NF-κB pathway, and up-regulation of pro-inflammatory cytokines, MCP-1, and ICAM-1	BBB disruption and brain edema	NS↑	[122]
PCI, mice	Clazosentan (an endothelin A receptor antagonist)	Oxidative stress	Clazosentan treatment did not affect superoxide anion radical,	Decreasing CBF and NO levels, and increasing	MT→	[94]

Experimental paradigm	Intervention	Pathogenic factor	Contributing pathway and/or mechanism	Key effect	Outcome after treatment	Reference
			peroxynitrite, microthromboemboli in the brain, or reduction of endothelial NOS uncoupling and neuronal injury after SAH	uncoupled and phosphorylated eNOS and superoxide level		
PCI, rat	Clazosentan (an endothelin A receptor antagonist)	Secondary complication other than large-artery vasospasm	Clazosentan treatment did not affect microthromboemboli, neuronal degeneration, apoptosis, or loss of long-term potensiation after SAH	Increasing microthromboemboli, neuronal degeneration, and apoptotic cell death, and decreasing long-term potentiation	MT→	[19]
EVP, rat	PUMA (p53 upregulated modulator of apoptosis) siRNA	Global ischemia	PUMA, BAX, BAK, GRP78, and DRP1 expression	BBB disruption, brain edema, and apoptotic endothelial cell death	NS↑, MT↓	[129]
EVP, rat	Osteopontin (OPN) siRNA	Inflammation	Activation of NF-kappaB and JNK pathways, activation of MMP-9 induction, and VEGF expresison	BBB disruption and brain edema	NS→, MT→	[113]
EVP, mice	NS398 (a specific COX-2 inhibitor)	Inflammation	Increasing BBB disruption	Neurological funtion	NS↑, MT→	[4]
EVP, rat	Deferoxamine (an iron chelator)	Blood breakdown products and oxidative stress	Increasing non-heme iron and ferritin levels, and heme-oxygenase-1 (HO-1) up-regulation	Apoptotic cell death	NA	[64]
EVP, rat	PNU-282987 (an α7 nicotinic acetylcholine receptor agonist)	Global ischemia	PI3K/Akt/caspase-3 pathway	BBB disruption and apoptotic cell death	NS↑, MT→	[27]
EVP, rat	Minocycline	Inflammation	MMP activation	BBB disruption and neuronal loss	NS↑, MT→	[101]
EVP, rat	Hydroxyfasudil (Rho kinase inhibitor)	BBB disruption	Increasing occludin and ZO-1 disruption	BBB disruption and brain edema	NS↑, MT→	[38]
EVP, rat	small interfering RNAs for CHOP	Global ischemia	Bim-Caspase-3 pathway	BBB disruption and apoptotic cell death	NS↑, MT→	[53]
EVP, rat	Hydrogen gas inhalation	Oxidative stress	Oxidative injury of lipid, protein, and DNA	BBB disruption, brain edema, and apoptotic cell death	NS↑	[134]
NA, rabbit	Hydrogen-rich saline (a cytotoxic oxygen radical scavenger)	Oxidative stress	upregulated MDA, caspase-12/3, and brain edema	BBB disruption and apoptotic cell death	NA	[138]
EVP, mice	Isoflurane inhalation	Global ischemia	Sphingosine kinase 1/Akt/ caspase-3 pathway	BBB disruption, brain edema, and apoptotic cell death	NS↑	[1]
PCI, rat	Rapamycin (autophagy inducer) or 3-methyladenine (autophagy inhibitor)	Autophagy and apoptosis	Rapamycin ameliorated NS and brain edema via increasing MP1 LC3-II to LC3-I ratio and reducing caspase-3 activity	BBB disruption, brain edema, and apoptotic cell death	NS↑	[55]

Experimental paradigm	Intervention	Pathogenic factor	Contributing pathway and/or mechanism	Key effect	Outcome after treatment	Reference
SIN, rat	Heparin	Inflammation	Neutrophils invasion, activated phagocytic microglia, increasing NF-kappa B and IL-1β	Neuroinflammation, demyelination, and transsynaptic apoptosis	Not tested	[105]
NA, rat	SP600125 (JNK inhibitor)	Global ischemia	Increasing claudin-5 and ZO-1, up-regulated JNK1 and JNK3	BBB disruption, apoptotic cell death	NA	[17]
PCI, rat	Melatonin	Oxidative stress	Nrf2-ARE pathway	BBB disruption, brain edema, and apoptotic cell death	NS↑	[123]
PCI, rat	Anti-aquaporin-4 antibody, minocycline (an inhibitor of MMP-9) , or 2-methoxyestradiol (an inhibitor of HIF-1α)	BBB disruption	Inhibition of HIF-1α significantly suppressed the level of aquaporin-4 and MMP-9	BBB disruption	NA	[124]
PCI, rat	Cyclosporin A	Mitochondrial permeability transition pore opening	Increasing cytochrome C, apoptosis-inducing factor, and cleaved caspase-3	BBB disruption, brain edema, and apoptotic cell death	NS↑	[127]
EVP, rat	Rapamycin (autophagy inducer), simvastatin	Autophagy and apoptosis	Autophagy flux by microtubule-associated protein light chain-3 (LC3 II/I) and beclin-1 expression	Autophagy activation ameliorated BBB disruption and neuronal apoptosis	NS↑	[136]

BBB blood-brain barrier, *CBF* cerebral blood flow, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CL-IB-MECA* 2-chloro-N^6-(3-iodobenzyl)-adenosine-5′-N- methyluronamide, *CPP* cerebral perfusion pressure, *CSF* cerebrospinal fluid, *Cu/Zn SOD* copper/zinc superoxide dismutase, *DIN* Double blood injection model, *ERK* extracellular signal-related kinase protein, *EVP* Endovascular perforation model, *20-HETE* 20-hydroxyeiscosatetraenoic acid, *HIF-1* Hypoxia-inducible factor-1, *HMG-CoA* 3-hydroxyl-3-methyl-glutaryl-coenzyme A, *5-HT1B* 5-hydroxytryptamine1B, *ICAM-1* intercellular adhesion molecule-1, *ICP* intracranial pressure, *IL* interleukin, *iNOS* inducible nitric oxide synthase, *JNK* c-Jun N-terminal kinase, *LC3* light chain 3, *LDH* lactate dehydrogenase, *MAPKs* mitogen-activated protein kinases, *MCP-1* monocyte chemotactic protein-1, *MMP* matrix metalloproteinase, *MP1* microtubule-associated protein 1, *MT* mortality, *NA* not applicable, *NADPH* nicotinamide adenine dinucleotide phosphate, *NF-kappaB* nuclear factor kappa B, *NO* nitric oxide, *NOS* Nitric oxide synthase, *Nrf2-ARE* nuclear factor erythroid 2-related factor 2 and antioxidant responsive element, *NS* neurological score, *PCI* pre-chiamatic blood injection model, *RBC* red blood cell, *rCBF* regional cerebral blood flow, *ROS* reactive oxygen species, *SHI* Subarachnoid hemolysate injection model, *SIN* Single blood injection model, *siRNA* small interfering RNA, *SOD* superoxide dismutase, *TIMP* tissue inhibitor of MMP, *TNF* tumor necrosis factor, *VEGF* vascular endothelial growth factor, *ZO-1* zona occludens 1.