· Review ·

Recent progress of the neural injury mechanism after aneurysmal subarachnoid hemorrhage

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[**Abstract**] Aneurysmal subarachnoid hemorrhage (aSAH) is one of the most devastating form of stroke. Many physiopathology mechanisms ensue after cerebral aneurysm rupture with blood silting up in the subarachnoid space, including hydrocephalus, cell apoptosis, blood-brain barrier dysfunction, macrovascular vasospasm, microthrombosis and cortical spreading depolarization which interact with each other and work throughout the damage process. Recently, clinical trials gradually pay more attention to two phases of injury after aSAH: the early phase known as early brain injury (EBI) and the delayed phase, delayed cerebral ischemia (DCI). These two phases are main processes accounting for neural injury and are thought to be closely linked with the outcomes of the patients. This review makes a brief summary on the mechanism of cerebral injury after aSAH, mostly on EBI and DCI.

[**Key words**] Aneurysmal subarachnoid hemorrhage; Early brain injury; Delayed cerebral ischemia; Neuroinflammation; Cerebral vasospasm

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动脉瘤性蛛网膜下腔出血后神经元损伤机制的研究进展

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[**摘要**] 动脉瘤性蛛网膜下腔出血(aSAH)是脑卒中最严重的表现形式之一。颅内动脉瘤破裂后血液瘀滞在脑蛛网膜下腔,引起多种病理生理改变,包括脑积水、细胞凋亡、血脑屏障功能障碍、血管痉挛、微血栓形成和皮层扩散性抑制,这些机制相互作用并贯穿于整个脑损伤过程。近年来,临床试验逐渐关注 aSAH 发生后的两个阶段:早期脑损伤(EBI)和延迟性脑缺血(DCI)。这两个时期是导致神经元损伤的主要阶段,并与患者的预后密切相关。我们就近年来蛛网膜下腔出血后脑损伤的机制作一简要总结,主要讨论 EBI 和 DCI 在神经损伤中的作用。

[**关键词**] 动脉瘤性蛛网膜下腔出血;早期脑损伤;延迟性脑缺血;神经炎症;脑血管痉挛

Aneurysmal subarachnoid hemorrhage (aSAH) is characterized by rupture of an intracranial aneurysm that injects blood under arterial pressure into the subarachnoid space. 85% of all cases of spontaneous subarachnoid hemorrhage are due to cerebral aneurysm rupture. The mortality is nearly half of SAH patients, including the pre-hospital death. 30% survivors develop the delayed neurological disability, which severely affect the patients' quality of life[1-3].

Usually, aneurysms mostly occur in the anterior circulation of circle of Willis, but the posterior circulation aneurysms located at the basilar tip and the posterior cerebral artery are more likely to rupture. In an aneurysm, the internal elastic lamina is absent or fragmented. The smooth muscle layers of the arterial wall are primarily responsible for resisting the pulse pressure but now it's up to the remaining connective tissue. With the dilation of aneurysm, the tension in

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the remaining wall increases so the wall is continually degraded and weakened, it is unable to withstand the tension generated under normal physiological intraluminal pressure, in particular the hypertensive conditions associated with aneurysm development or the acute pressure increases caused by behaviors such as smoking or cocaine. aSAH occurs when the wall of the vessel becomes too fragile to resist the forces created by arterial hydrostatic pulse pressure and then blood leaks into the subarachnoid connective tissue [4].

After the aneurysms rupture, the hallmark symptom of aneurysmal subarachnoid hemorrhage is a thunderclap headache. Associated symptoms or signs include nausea, vomiting, neck stiffness and a brief loss of consciousness. More severely affected patients present with altered mental status, from mild lethargy to profound coma; the degree of encephalopathy at presentation is the major determinant of the prognosis[5].

People used to think that the outcomes are closely linked with angiographic vasospasm. But despite all efforts, there seems no significant improvement for the outcome which suggests that we do need to redefine our understanding for this disease, especially the pathophysiological mechanism. During recent years, clinical trials gradually pay more attention to the events of all aspects after aSAH. Two phases of injury after aSAH are recognized: the early phase, which begins at aneurysmal rupture and extends through the first 3 days, and typically results in the earliest consequences of aSAH EBI; the delayed phase, which appears 3-14 days later and usually accompanies with delayed cerebral ischemia (DCI).

The main determinants for poor outcome after SAH are the degree of early brain injury (EBI) and the incidence of DCI. It has been suggested that the etiology of DCI and EBI is linked. Biochemical processes involved in DCI have commonalities with those hypothesized to mediate EBI, and include further endothelial damage, blood-brain barrier (BBB) disruption, microthrombi, ischemia from vasospasm, oxidative stress, and inflammation. DCI complicates a third of cases of aSAH [6]. However, not everyone will develop both EBI and DCI, that's to say, DCI can develop in absence of EBI and DCI may not always occur. Causality between the two processes has not yet been established.

The following sections will briefly expound the complex brain injury mechanisms following aneurysmal SAH.

1. Events occurring in early brain injury exacerbate outcomes

The term EBI is a concept to explain acute pathophysiological events that occur in brain before the onset of cerebral vasospasm (CVS) within the first 72 hours of subarachnoid hemorrhage (SAH). Mostly, it is used to describe some pathophysiological mechanism responsible for any type of brain insult other than iatrogenic brain injury during the first 72 hours post-SAH, some of which may be a precursor for cerebral vasospasm and (or) vasospasm-unrelated DCI and others of which may contribute to increased tissue vulnerability to secondary insults [7].

After SAH, the decrease of cerebral perfusion pressure and rise in the intracranial pressure can lead to a long-term injury which results in hydrocephalus, brain edema, BBB dysfunction and inflammation and so on. Meanwhile, early autoregulation dysfunction significantly correlates with unfavorable clinical outcome and severity of angiographic vasospasm [8].

1.1 Hydrocephalus related to global cerebral ischemia: Hydrocephalus may develop soon after subarachnoid hemorrhage. Estimates of the incidence of hydrocephalus range from 15% to 85%; most cases are not clinically significant. Chronic symptomatic hydrocephalus occurs in up to one third of patients in whom acute hydrocephalus develops and is treated with a ventriculoperitoneal shunt for permanent diversion of cerebrospinal fluid[5]. As blood rushes into the subarachnoid space under high arterial pressure, there is a rise in intracranial pressure (ICP) [9, 10]. Blood and its breakdown products can also further contribute to this rise in ICP from obstruction of flow of cerebrospinal fluid (CSF), resulting in hydrocephalus. Also, hydrocephalus is usually related to the damage to arachnoid granulations as well as to brain tissue. Inflammatory reaction and the ensuing fibrosis process impede fluent CSF flow outward to sinus [11]. And it is likely that degradation of the basal lamina may be involved in the formation of post-hemorrhagic hydrocephalus [10]. The sharp rise in ICP results in a significant reduction in both cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) that can lead to both loss of consciousness and global cerebral ischemia. Additionally, there are many other

pathophysiological responses important to consider at this stage, including neuroinflammation, activation of platelets and clotting factors, endothelial injury, and excitotoxic effects of blood and its breakdown products on neurons [11].

1.2 BBB dysfunction: BBB permeability is known to increase in certain conditions such as ischemia, malignancy, infection, and autoimmune disease. SAH also disrupts the integrity of the BBB, which can further compromise cerebral perfusion and facilitate neuroinflammation. An experiment on rats model observed that the blood brain barrier permeability increased in the early stage (0-3 hours) of SAH, reaching the first peak value at 3 hours. Afterwards, BBB permeability recovered to the baseline level at 24 hours and reached to the second peak at 72 hours, followed by reduction at 1 week [12]. But how the BBB permeability change has confused us for a long time. On the molecular level, the BBB mainly composes of microvascular endothelial cells with tight junctions and astrocyte plays a fundamental role in brain homeostasis since it regulates the entry of intravascular molecules from blood into brain. The endothelial cell contraction and disassembly of tight junctions result in increased vascular permeability which is related to BBB damage and formation of brain edema caused by SAH [12]. The down-regulated zo-1 and occludin, as well as protein kinase B (Akt)/forkhead box O (FOXO) signaling pathway were found that it was possible to be involved in the regulation of tight junction opening and the BBB permeability in the early stage after SAH. Besides, many other mechanisms are speculated as followed. Matrix metalloproteinases (MMP) are believed to be crucial and versatile participants in breaking down BBB, and the tissue inhibitors of MMP have been verified to share the homologous protective effects in vasospasm after SAH for BBB integrity in apoplectic patients [12]. It is also suggested that neutrophils may constitute the major source of MMP-9 acting on the BBB [13]. Basal lamina protein degradation is correlated with BBB dysfunction. Vascular endothelial growth factor protein levels rise and restrict the growth of abnormal blood vessels. Subsequently, the hypersecretion of CSF triggers or exacerbates its circulatory disorder and eventually leads to hydrocephalus [10, 11]. Hopefully, results of current studies may be beneficial for the selection of treatment time after SAH and therapy target. Now that enhanced BBB permeability plays a role in subsequent brain injury caused by the entry of pathologic molecules and inflammatory cytokines into the brain parenchyma after SAH. Therefore, attenuating EBI by preserving the BBB may be a sensible strategy for improving post-SAH neurologic outcomes. However, the mechanisms of BBB permeability after SAH are still not fully understood and need to be further studied.

1.3 Cell apoptosis: Apoptosis varies in severity. According to our acknowledge, there are a number of pathways involved in apoptosis, such as the death receptor pathway, Caspase-dependent and independent pathways, as well as the mitochondrial pathway. But there isn't a specific mechanism that how can the SAH initiate cellular apoptosis. Apoptotic cell death may be seen in both cortical, subcortical or hippocampal neurons and endothelium following SAH. It has been shown that there is a link between c-Jun N-terminal kinases (JNK), MMP-9 and Caspase-3 activation following SAH. As mentioned, MMP-9, a member of endopeptidase family, can mediate apoptosis through cleaving main components of the extracellular matrix. Laminins are heterotrimeric molecules that are critical components of the extracellular matrix (ECM) and are known to play an important role in the nervous system. It was found that after various insults, MMP-9 was upregulated and led to anoikis of neurons and endothelial cells because of laminin degradation [12]. P53 has also been shown to be an orchestrating protein in the apoptotic pathways following a SAH [14]. P53 activates the mitochondrial apoptotic pathway through the B-cell lymphoma-2 (Bcl-2) family of proteins as stress response. Then the Bcl-2 family can stimulate cytochrome C release from mitochondria dependent pathway. P53 acting independently can also initiate the caspase cascades through its action on pro-Caspase-8, which is cleaved to form Caspase-8 which in turn cleaves Bid to form truncated Bid (tBid). tBid then permits the release of cytochrome C from mitochondria which is further regulated by Bcl-2 and Bcl-xL. Once released, cytochrome C combines with apoptotic protease activating factor-1 (Apaf-1) to form the apoptosome, which in turn recruits and cleaves pro-Caspase-9, thereby activating the Caspase cascade. In addition, a novel Caspase-12-mediated apoptotic pathway has been reported to be induced by excess

endoplasmic reticulum (ER) stress. Significant upregulation of Caspase-12 expression after experimental SAH also offer important implications for further investigations of the therapeutic potential of Caspase-12 associated apoptosis in SAH [15].

1.4 Neuroinflammation: Inflammation plays multiple roles after SAH, mediating vasospasm as tissue damage as well as leading to regeneration or recovery. There is experimental evidence from animal studies showing that blocking inflammatory pathways can improve both BBB breakdown and neuronal survival after SAH [16]. As the blood deposits within the subarachnoid space, red blood cells breakdown and degradation over time lead to the deposition of hemoglobin. Methemoglobin, heme, and hemin resulting from red blood cell breakdown can lead to activation of toll like receptor 4 (TLR4), which can lead to downstream activation of nuclear factor κB (NF-κB). Immunomodulatory cells within the central nervous system (CNS), such as microglia, are activated trigger the upregulation of numerous cell adhesion molecules within endothelial cells, which subsequently allow a multitude of inflammatory cells to bind and enter the subarachnoid space [17]. Then the macrophages and neutrophils rapped within the subarachnoid space undergo degranulation, which releases a multitude of inflammatory factors. The inflammatory course can be divided into two phases. The proinflammatory phase characterized by the participation of enzymes (matrix metalloproteinases 2 and 9), cytokines [tumor necrosis factor α (TNFα), interferon γ, interleukin (IL)-1β, IL-2, and IL-6], chemokines (monocyte chemoattractant protein-1 and stromal cell-derived factor-1 α), and cells (microglia and certain lymphocytes). Proinflammatory cytokines can potentiate brain damage and thus are associated with worse outcomes[17, 18]. TNFα has been implicated in plasminogen activator inhibitor-1 upregulation and in cell death pathways. Brain-derived IL-6 is elevated in the extracellular fluid in poor-grade SAH patients. The proinflammatory phase is followed by an anti-inflammatory phase. In cerebral ischemic injury, the activity of IL-10 and regulatory T lymphocytes predominates. However, the anti-inflammatory phase contributes to the onset of infection. IL-6 has been reported to both improve and worsen cerebral ischemic injury. The effects of TNFα seem to depend on the type of receptor that is activated. Effects of microglia and chemokines dependent on the phase. In the proinflammatory phase, microglia and chemokines attract leukocytes and prevent newly formed neurons (neuroblasts) from surviving. However, in the anti-inflammatory phase, they contribute to the survival, migration, maturation, and integration of migrating neuroblasts[18]. In contrast, anti-inflammatory mediators, such as IL-10 and various fatty acid-derived lipid mediators, may promote resolution of inflammation[19, 20]. There are plenty of inflammatory factors participating in the reaction and they usually form a complex network that nearly comes down to every part of the post-syndrome. Not only is inflammation closely correlated with the EBI, it can also last for more than 72 hours and thus aggravate DCI in some way. Though anti-inflammatory treatments will likely improve the lives of patients with SAH, it must be remembered that neuroinflammation has beneficial effects as well and could also play a role in recovery after SAH.

2. Cerebral injury originated from delayed cerebral ischemia

One of the most commonly studied mechanisms of delayed injury involves DCI, a major cause of morbidity and mortality for those who survive EBI. DCI is thought to be a result of interaction of multiple processes, including EBI, angiographic vasospasm, cortical spreading ischemia, micro-thromboembolism, delayed neuronal apoptosis, and autoregulatory dysfunction [21].

2.1 Cerebral vasospasm: After aneurysmal rupture, a transient, self-limited narrowing of the intracranial arteries occurs in the days. This phenomenon, termed CVS is associated with the clinical deterioration caused by DCI and can affect up to 30%-40% of patients, leading to DCI in 20%-30% of cases. Vasospasm may occur from 3 to 5 days after SAH and typically affect the medium-and large-sized intracranial arteries and occurs within day 3 and day 14 after SAH. The incidence is higher between post hemorrhage day 5 and day 14, progressively lower in the following 2 weeks, and practically absent in later periods [18, 22]. CVS occurring in the main artery feeding the aneurysm is known as a parent artery vasospasm (PAV) and is the leading cause of morbidity after aneurysmal SAH. PAV tends to present clinically and/or radiographically 3-15 days and peaks at 7 day after an ictal event[2, 16, 22, 23].

Patients with CVS appeared to be at high risk for developing delayed neurological deficits. We used to think that large-vessel vasospasm is a late contributor to an ongoing injury pattern that starts much earlier. But therapies exclusively targeting large caliber arterial vasospasm have fallen short, and thus it is asked that whether micro-vasospasm contributes to DCI after subarachnoid hemorrhage. With the deepening of the research on vasospasm, it has been recognized that the occurrence of CVS after SAH is the result of a combination of factors. At present, the pathogenesis mainly involves the following aspects. The vasoactive substances such as oxyhemoglobin, nitric oxide (NO), endothelin-1 (ET-1) and protein kinase C (PKC) play a critical role in CVS. NO is produced by the endothelial nitric oxide synthase (eNOS) in the cerebrovascular endothelium. It diffuses to adjacent smooth muscle cells and stimulates soluble guanylyl cyclase (sGC), leading to generation of cyclic guanosine monophosphate (cGMP). cGMP activates intracellular calcium channels, transporting free Ca^{2+} into intracellular compartment and relaxing smooth muscle cells. Both NO concentration and eNOS activity drop acutely with the onset of hemorrhage, and the level of cGMP, the downstream mediator of NO-induced vasodilatation, is reduced. Another widely studied molecules in SAH is ET-1, a vasoconstrictor produced by endothelial cells. ET-1 has been implicated in the development of vasospasm after SAH[16]. Hypoxia inducible factor 1 (HIF-1) is a transcription factor involved in various processes including energy metabolism, angiogenesis, erythropoiesis, cell survival and apoptosis. Activation of HIF-1 at an early stage after SAH may be detrimental whereas HIF-1 stimulation at a later stage could be neuroprotective. As therapeutic intervention, 17b-estradiol benzoate (E2) was reported to attenuate vasospasm and preserve the eNOS expression by activating HIF-1 estrogen laboratory biological receptor subtype a (ERa). Furthermore, the same demonstrated that E2 mediated vasoprotection through inhibiting SAH-induced increase in expression levels of inducible nitric oxide synthase (iNOS) via NF-κB signaling pathway [16, 24]. Inflammation likely mediates the development of macrovascular vasospasm. The nadir of the inflammatory cytokines (IL-1b, IL-6, TNF-a) in the CSF and serum after aSAH occurs on SAH day 7, which also correlates with the peak severity of vasospasm. The CSF levels of cytokines are much higher than control levels. Leukocytes are recruited into the CSF by E-selectin, among other adhesion molecules, and this adhesion molecule has been found in much higher concentrations in the CSF of aSAH patients [2, 17, 24, 25]. The inhibition of E-selectin with a monoclonal antibody demonstrated reduced macrovascular vasospasm in an animal aSAH model. Moreover, SAH induces an increase in the NF-κB DNA-binding activity and the mRNA levels of TNFα, IL-1β, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 on day 5 after SAH in a double-hemorrhage model [24]. Also, vasospasm has been attributed to hemoglobin degradation products. The iron, heme, and biliverdin that are released during degradation contribute to the formation of free radicals. More recently, other mechanisms for vasospasm have been described, with endothelin appearing to play a role in increasing cerebral vascular tone [18]. According to the American Heart Association, the Neurocritical Care Society, and the European guidelines, nimodipine is the only medication proven to improve outcomes after SAH and to reduce the rate of angiographic vasospasm [26]. But recently milrinone, an inhibitor of phosphodiesterase Ⅲ, with positive inotropic and vasodilatory effects, was reported to undergo an effective use in CVS [27]. Thus, understanding its mechanisms may help us choose more better solutions.

2.2 Microthrombosis: Another novel mechanism under investigation in DCI is the development of microscopic thrombi after SAH. Increased microthrombi can have detrimental effects on the neurological function by creating quite a few areas of microinfarction throughout the brain. Microthrombi is more possible to form in situ within micro-vessels following arteriolar vasoconstriction related to changes in NO, P-selectin, and shifts in other coagulation and fibrinolytic factors[2, 21]. Coagulation begins with the formation of a weak platelet plug. During the fibrinolytic cascades, activators such as tissue plasminogen activator (tPA) and inhibitors such as plasminogen activator inhibitor-1 (PAI-1) are altered after SAH so that the balance is shifted towards reduced fibrinolysis. Microthrombosis formed at sites where spasms reduced CBF to levels low enough to cause spontaneous aggregation of platelets

and activation of the coagulation cascade. Platelet aggregation can also be caused or further promoted by decreased levels of cerebrovascular NO and NOS inhibition, as NO can inhibit platelet aggregation under physiological conditions and vascular NO is reduced after SAH [28]. DCI is associated with a high number of microthrombosis. An induced hypercoagulable state will worsen microthrombosis and gives more evidence for microthrombosis playing a significant role in DCI. Platelet aggregation has also been suggested and may therefore disrupt the BBB.

2.3 Cerebral ischemia: DCI is not always secondary to vasospasm, and may develop in the absence of vasospasm and likely is driven by other factors [29]. Some hypothesized that vasospasm initiates structural changes within the vessel wall, possibly aggravating ischemia and leading to resistance to vasodilator treatment [30]. And it is also demonstrated that SAH causes a profound decrease in capillary blood flow leading to brain ischemia and hypoxia [31]. Assessment of cerebral blood flow derangement may be critical for identification of patients at high risk and for targeting treatment strategies most effectively to reduce neurologic morbidity. Thus, minimizing cerebral infraction appears to the most important targets for future studies. Prevention or treatment of capillary dysfunction after SAH may reduce the incidence or severity of subarachnoid hemorrhage induced DCI [32].

2.4 Cortical spreading depression: spreading depolarizations (SDs) is defined as waves of abrupt, near-complete breakdown of neuronal transmembrane ion gradients. And cortical spreading depressions (CSDs) are a depolarization wave in the gray matter that propagates across the brain at 2 to 5 mm/min and depress the spontaneous and evoked EEG activity[33]. They constitute a major pathophysiologic disruption of viable cerebral gray matter and is a crucial mechanism of DCI. CSDs are related to multiple alterations which come down to the arteriolar vasoconstriction, inverse neurovascular coupling and neurotransmitters release[21, 34-37]. Besides, the presence of hemoglobin and ET-1 may precipitate cortical spreading depolarizations[36]. Patients with aSAH can have a high incidence of CSD events which peak firstly during the early injury period and again during the delayed period, so there is a closely correlation between CSD occurrence and development of delayed ischemic neurological deficits[34, 36]. After SAH, focal ischemia can develop via a number of mechanisms including microvascular plugging due to in situ thrombosis or microembolization. SAH-induced vascular dysfunction diminishes collateral flow and expands the volume of ischemic tissue. Focal ischemia in turn triggers peri-infarct SDs, facilitated by SAH in a delayed fashion possibly via blood breakdown products or vascular dysfunction. Peri-infarct SDs add some additional metabolic burden, exacerbate vascular dysfunction, and then expand the perfusion defect, particularly when they occur with high frequency and in clusters. Such a vicious cycle may give an explanation to the occurrence and timing of delayed ischemic neurological deficits and infarction[38]. SDs and microvascular dysfunction after SAH lead to DCI. SAH alone is not sufficient to directly trigger SDs (dashed line). Indeed, small cortical infarcts are more common than large territorial infarcts corresponding to major cerebral arteries after aSAH, which indicates that SD events might contribute to delayed ischemia[39] (Fig.1).

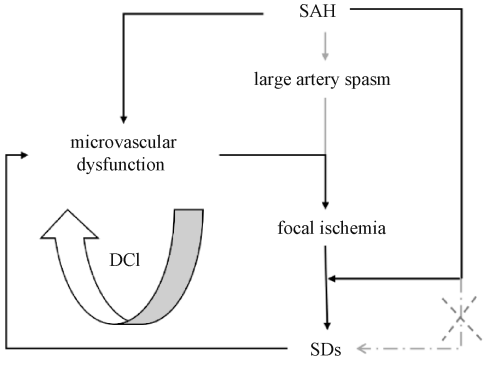

Fig.1 Vicious cycle involved with SDs, DCI and CVS
SAH-induced vascular dysfunction diminishes collateral flow and expands the volume of ischemic tissue; Focal ischemia in turn triggers peri-infarct SDs, facilitated by SAH in a delayed fashion possibly via blood breakdown products or vascular dysfunction; Peri-infarct SDs add some additional metabolic burden, exacerbate vascular dysfunction, and then expand the perfusion defect, particularly when they occur with high frequency and in clusters; SDs and microvascular dysfunction after SAH lead to DCI; SAH alone is not sufficient to directly trigger SDs (dashed line)

On the other hand, associated with massive transmembrane ion and water shifts, SDs impose severe metabolic mismatch by increasing the energy demand and reducing blood supply in already critically compromised brain tissue. As a result, SDs finally expand the injury volume and worsen neurological outcomes[38]. During an CSD, neuronal membrane potentials approach 0 due to opening of yet unidentified

large conductance, non-selective cation channels, leading to massive transmembrane ion fluxes, dramatic elevations of extracellular K^+ and intracellular Na^+ and Ca^{2+} concentrations, and cell swelling. The extracellular concentrations of virtually all neurotransmitters, metabolites and small signaling molecules show significant changes, including the excitatory amino acid glutamate. The extracellular K^+ increases, whereas Ca^{2+} decreases, Cl^- decreases, and Na^+ decreases[39]. Elevated extracellular K^+ diffuses into the adjacent brain tissue and trigger the same depolarization cycle with the help of glutamate, allowing CSD to propagate at a slow pace of 3 mm/min by way of chemical contiguity. Because high extracellular K^+ and glutamate are critical for wave spread, SDs are limited to gray matter with high neuronal and synaptic density, and don't propagate into white matter where the extracellular space fraction is larger, synapses are sparse, and myelin acts as a barrier[40]. Despite our accumulated knowledge, however, CSD is still among the most underappreciated pathophysiological process in the evolution of brain injury. More underlying mechanisms are still waited to be explored.

3. Summary

EBI and DCI interact with each other, and are closely related to the prognosis of patients. Events occurring in EBI may exacerbate outcomes to some extent. Immediately after the aneurysm rupture, blood deposition leads to ICP and then hydrocephalus, which is related to unconsciousness and global cerebral ischemia. Meanwhile, neuroinflammation and apoptosis ensued after blood brain barrier dysfunction accelerate neural injury. A series of responses induced EBI are to some extent necessary conditions and aggravating factors for DCI. After 72 hours, as vasospasm aggravates and hemodynamics change, there's going to be thrombus and ischemia diffusely. Specific for cerebra, cortical spreading depression, ischemia and vasospasm, the three can form a vicious circle throughout entire DCI process which finally explains what happens and what counts for the neural injury.

The mechanism of brain injury after subarachnoid hemorrhage has been studied for decades. The deepening of research will provide more useful clues for our clinical therapies. However, previous efforts to reduce brain damage by reducing vasospasm have not been particularly successful. Therefore, the treatment of SAH still needs to be explored. Respectively, future research direction should be started in the following aspects: the further analysis of mechanisms of EBI and DCI, attenuation of neuroinflammation, reduction of ischemia areas, and novel pharmaceutical targets strategies to limit or reverse the extent of EBI and DCI. All in all, our ultimate goal is to achieve the optimization and harmonization cure and care for SAH patients.

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