Current Neuropharmacology, 2022, *20*, 1278-1296

REVIEW ARTICLE

New Mechanisms and Targets of Subarachnoid Hemorrhage: A Focus on Mitochondria

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Abstract: Spontaneous subarachnoid hemorrhage (SAH) accounts for 5-10% of all strokes and is a subtype of hemorrhagic stroke that places a heavy burden on health care. Despite great progress in surgical clipping and endovascular treatment for ruptured aneurysms, cerebral vasospasm (CVS) and delayed cerebral ischemia (DCI) threaten the long-term outcomes of patients with SAH. Moreover, there are limited drugs available to reduce the risk of DCI and adverse outcomes in SAH patients. New insight suggests that early brain injury (EBI), which occurs within 72 h after the onset of SAH, may lay the foundation for further DCI development and poor outcomes. The mechanisms of EBI mainly include excitotoxicity, oxidative stress, neuroinflammation, blood-brain barrier (BBB) destruction, and cellular death. Mitochondria are a double-membrane organelle, and they play an important role in energy production, cell growth, differentiation, apoptosis, and survival. Mitochondrial dysfunction, which can lead to mitochondrial membrane potential ($\Delta\Psi m$) collapse, overproduction of reactive oxygen species (ROS), release of apoptogenic proteins, disorders of mitochondrial dynamics, and activation of mitochondria-related inflammation, is considered a novel mechanism of EBI related to DCI as well as post-SAH outcomes. In addition, mitophagy is activated after SAH. In this review, we discuss the latest perspectives on the role of mitochondria in EBI and DCI after SAH. We emphasize the potential of mitochondria as therapeutic targets and summarize the promising therapeutic strategies targeting mitochondria for SAH.

ARTICLE HISTORY

Received: August 06, 2021
Revised: October 06, 2021
Accepted: October 28, 2021

DOI:
10.2174/1570159X19666211101103646

Keywords: Subarachnoid hemorrhage, mitochondria, early brain injury, delayed cerebral ischemia, oxidative stress, apoptosis, mitophagy.

1. INTRODUCTION

Spontaneous subarachnoid hemorrhage (SAH) is a subtype of hemorrhagic stroke that accounts for 5-10% of all strokes [1]. More than 80% of cases are caused by the rupture of intracranial aneurysms [2]. SAH is a devastating disease with high mortality and morbidity, affecting approximately nine in 100,000 individuals each year in developed countries [3]. Compared to other types of stroke, SAH tends to affect younger patients (average 55 years old), which places a heavy burden on health care [2, 4].

Although great progress has been made in surgical clipping and endovascular obliteration for ruptured aneurysms, the long-term outcomes of SAH patients remain unfavorable. Approximately one-third of patients develop delayed cerebral ischemia (DCI) 3-14 days after SAH, which is an important factor for the poor outcomes of SAH patients [2]. Traditionally, cerebral vasospasm (CVS) was regarded as the sole cause of DCI after SAH. However, randomized controlled trials showed that CVS amelioration *via* endothelin-1 receptor antagonism did not improve the functional outcomes in patients with SAH [5, 6]. Currently, only nimodipine has shown effectiveness in reducing the risk of DCI and adverse outcomes in SAH patients [4]. Therefore, it is important to develop new therapeutic targets to address long-term neurological deficits after SAH. Current research emphasizes the importance of early brain injury (EBI), which occurs within the first 72 h following SAH onset [7]. New insight suggests that EBI after SAH may lay the foundation for further DCI development and poor prognosis. Current areas of study regarding the mechanisms of EBI primarily include excitotoxicity, oxidative stress, neuroinflammation, blood-brain barrier (BBB) destruction, and cellular death [7, 8].

Mitochondria are double-membrane organelles and are the main source of energy production in eukaryotic cells [9-11]. Mitochondria play a vital role in cell growth, differentiation, function, signaling, cell cycle regulation, apoptosis, and

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1875-6190/22 $65.00+.00

survival [9, 12]. Mitochondrial dysfunction may have harmful consequences, including mitochondrial membrane potential (ΔΨm) collapse, overproduction of reactive oxygen species (ROS), release of apoptogenic proteins, disorders of mitochondrial dynamics, and activation of mitochondria-related inflammation [13, 14]. Mitochondrial dysfunction has been found to be associated with multiple diseases, including neurodegenerative diseases, airway diseases, diabetic kidney disease, and cancer [15-20]. In 1990, Marzatico *et al.* reported that mitochondrial dysfunction existed in different brain areas after experimental SAH in rats [21]. A growing number of studies are focusing on mitochondrial changes after SAH and their relationship with SAH-induced brain injury. Some drugs, such as SB203580 and tea polyphenols, may reduce mitochondrial impairment-induced neuronal apoptosis by preventing mitochondrial depolarization and cytochrome c release, thereby alleviating EBI and exerting neuroprotective functions [22, 23]. In addition, mitophagy is activated after SAH and may play a neuroprotective effect [22]. Therefore, by focusing on the role of mitochondria in SAH, it is expected that new therapeutic targets for SAH may be found.

This article reviews the latest perspectives on the role of mitochondria in EBI and DCI after SAH, as well as potential therapeutic strategies targeting mitochondria in SAH.

2. PATHOPHYSIOLOGICAL MECHANISMS OF SAH

2.1. Early Brain Injury

Following the rupture of the intracranial aneurysm, blood entering the subarachnoid space causes a sharp increase in intracranial pressure, leading to a decrease in cerebral perfusion pressure and cerebral blood flow [24, 25]. Next, the resulting global cerebral ischemia and blood products will trigger a series of pathophysiological mechanisms (Fig. **1**).

Ischemia and hypoxia lead to excessive glutamate release, which causes excitotoxicity by activating the N-methyl-d-aspartate receptor (NMDAR). The activation of NMDAR can cause calcium overload, apoptotic cascade, as well as neuronal nitric oxide synthase activation to promote EBI [26]. In addition, calcium influx caused by excitotoxicity may lead to mitochondrial calcium overload, ΔΨm collapse, and mitochondrial permeability transition pore (mPTP) open, which promote oxidative stress and apoptosis [27, 28]. In experimental SAH, Annexin A7 aggravates EBI by promoting the release of glutamate, whereas NMDAR inhibition with ifenprodil significantly alleviates neuronal death [29, 30]. Multiple pathways, including mitochondrial respiration disruption, hemoglobin oxidation, and enzymatic reactions, can cause excessive ROS generation and oxidative stress after SAH [31]. Oxidative stress can damage proteins, phospholipids, nucleic acids, and other macromolecules, thereby leading to cellular death, vascular endothelial injury, and BBB disruption. ROS can initiate apoptosis by promoting the release of cytochrome c, increasing p53, and by activating caspase-9 and caspase-3 [32, 33]. The Kelch-like ECH-associating protein 1 (Keap1)-nuclear factor erythroid 2 related factor 2 (Nrf2)-antioxidant response element (ARE) pathway has been found to be one of the most important defense mechanisms against oxidative stress and is associated with many diseases such as neurodegenerative disease and cancer [34]. Animal experiments have proven that some antioxidants, including astaxanthin, dimethyl fumarate, and tert-butylhydroquinone, can alleviate EBI after SAH by activating this pathway [35-37]. Although no clinical trials have yet proven the effectiveness of these drugs in SAH patients, some of them have been tested in populations with other oxidative stress-related diseases. For example, one randomised phase III clinical trial showed that dimethyl fumarate ameliorated relapsing-remitting multiple sclerosis [38]. In addition, there is evidence to suggest that excessive ROS generated under pathological conditions can attack mitochondria, affecting their vital functions, such as maintenance of ΔΨm and oxidative phosphorylation [31, 39]. Impaired mitochondria can further release ROS and aggravate oxidative stress [40]. Neuroinflammation is also an important mechanism of EBI. After SAH, heme produced by blood degradation can activate microglia *via* toll-like receptor 4, thereby inducing a proinflammatory cascade [41-43]. Within 24 h of aneurysm rupture, microglia show activated morphological changes [44]. In the mouse model of SAH, apolipoprotein E can reduce the activation of microglia by inhibiting the Janus kinase 2 (JAK2)/signal transducers and activators of transcription 3 (STAT3) signaling pathway, thereby exerting neuroprotective effects [45]. Peripheral immune inflammatory cells are also involved in the post-SAH cerebral inflammatory response. Animal experiments show that 10 min after SAH, neutrophils accumulate in the central nervous system (CNS), particularly in the microvasculature [46]. Neutrophils may mediate oxidative stress and cerebral cortical hypoperfusion after SAH [47]. Additionally, inflammatory mediators play a role in EBI. For example, tumor necrosis factor-alpha causes a cerebral injury after SAH by inducing neuronal apoptosis [48]. It is worth noting that some mitochondrial components, such as mitochondrial deoxyribonucleic acid (mtDNA), cardiolipin, and formyl-peptides, can act as damage-associated molecular patterns (DAMPs) to cause inflammation [49]. Following SAH, blood product toxicity, ischemic injury, neuroinflammation, and mitochondrial dysfunction can lead to BBB destruction, which causes direct contact of the CNS with immune cells and blood components, further aggravating EBI [50-54].

Multiple post-SAH mechanisms of pathology eventually lead to cellular death in the CNS, including apoptosis, autophagy, necrosis, pyroptosis, and ferroptosis. Cellular death leads to structural damage and functional impairment of nerves, vessels, and brain tissues, playing a critical role in EBI after SAH [55, 56].

2.2. Delayed Cerebral Ischemia

DCI commonly occurs 3-14 days after SAH onset and is the most important complication affecting long-term outcomes of patients with SAH [57]. To date, however, no drugs other than nimodipine have been shown to be effective in reducing the risk of DCI in patients with SAH [4].

CVS was once considered to be the cause of DCI in SAH patients (Fig. **1**). Approximately 70% of patients with aneurysmal SAH develop CVS [31]. Moreover, oxidative stress plays a role in the occurrence of CVS. Animal and human studies have shown that the post-SAH increase in superoxide anion levels in the cerebrospinal fluid (CSF) is associated with the development of CVS [58, 59]. In experimental

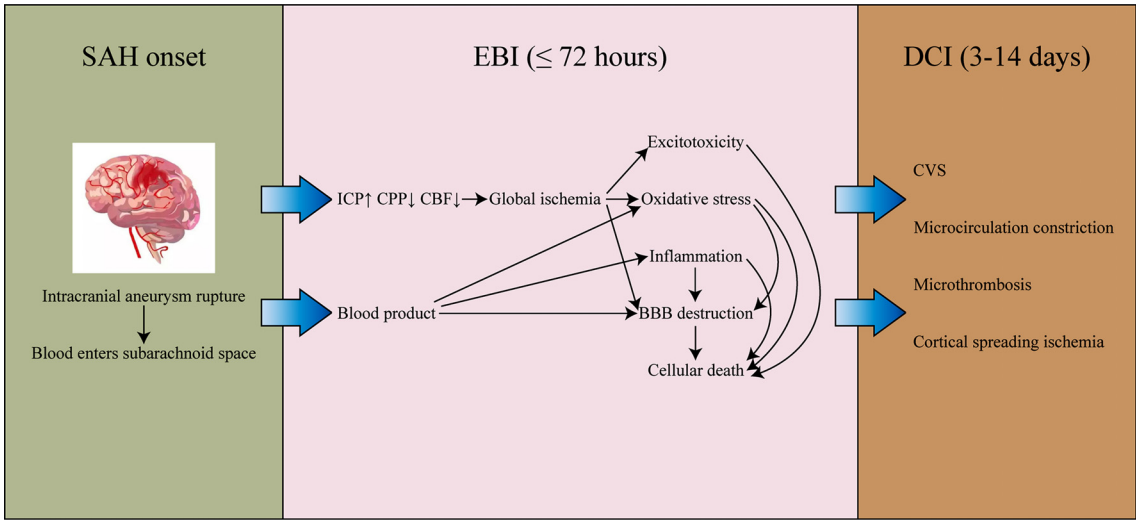

Fig. (1). Pathophysiological mechanisms of brain injury following SAH. After intracranial aneurysm rupture, blood enters the subarachnoid space to cause an increase in ICP, a decrease in CPP and CBF, which leads to global cerebral ischemia. Global ischemia and blood products entering the subarachnoid space cause EBI within 72 h, including excitotoxicity, oxidative stress, inflammation, BBB destruction, and cellular death. 3-14 days after SAH, multiple pathophysiological factors, including CVS, microcirculation constriction, microthrombosis, and cortical spreading ischemia, work together, leading to DCI. **Abbreviations:** SAH: subarachnoid hemorrhage; EBI: early brain injury; DCI: delayed cerebral ischemia; ICP: intracranial pressure; CPP: cerebral perfusion pressure; CBF: cerebral blood flow; BBB: blood-brain barrier; CVS: cerebral vasospasm. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

SAH, tetramethylpyrazine nitrone is found to alleviate CVS by reducing oxidative stress *via* up-regulation of Nrf2/heme oxygenase-1 (HO-1) [60]. However, it is currently believed that DCI is not only caused by CVS but that multiple pathophysiological mechanisms coexist, including microcirculation constriction, microthrombosis, and cortical spreading ischemia [61]. In addition, various damaging mechanisms of EBI, including oxidative stress and neuroinflammation, may contribute to subsequent DCI [61]. Due to the limited treatment options and their importance to the prognosis in patients with SAH, more mechanisms warrant exploration to explain the occurrence of DCI.

3. MITOCHONDRIA AND EBI AFTER SAH

Mitochondria control nearly every aspect of cellular function, including cellular growth, differentiation, signaling, and calcium homeostasis [9, 12]. The energy supplied by the mitochondria is vital to the excitability and survival of neurons. Mitochondria are the regulators of apoptosis and serve as the main source of ROS. Moreover, mitochondrial dynamics and mitophagy are critical for maintaining cellular function and homeostasis [62, 63]. Abundance of evidence has revealed the occurrence of mitochondrial dysfunction after SAH, which was found to be associated with EBI and neurological outcome [64-68]. The relationship between mitochondria and EBI after SAH needs to be further established. Herein, we systematically reviewed the role of mitochondrial-related oxidative stress, apoptosis, inflammation, and mitochondrial dynamics and mitophagy in EBI after SAH (Fig. **2**).

3.1. Mitochondria and Oxidative Stress

The mitochondrial respiratory chain is the core of biological energy production and adenosine triphosphate synthesis [69]. However, under normal metabolic conditions, the respiratory chain is also the main source of intracellular ROS. Complex I [nicotinamide adenine dinucleotide (NADH): ubiquinone oxidoreductase] and complex III (ubiquinol: cytochrome c oxidoreductase), two points in the electron transport chain, are the predominant sources of ROS in mitochondria [70]. Approximately 1-2% of molecular oxygen can be converted into superoxide radicals during normal cell respiration, which triggers the production of a series of ROS [71, 72]. To avoid oxidative stress caused by mitochondria, an intricate antioxidant defense system balances the physiological ROS generation to mitigate this stress [31, 70]. For example, superoxide dismutase could convert superoxide radicals into hydrogen peroxide, which is then further detoxified by catalase [70]. However, when various stimuli, such as hypoxia and ischemia, promote the sudden generation of large amounts of ROS and exceed the scavenging ability of the antioxidant defense system, the body will be in a state of oxidative stress [62].

Mitochondria are the main source of ROS production in the CNS after SAH. Hypoxia and calcium overload caused by SAH-induced global cerebral ischemia can affect the electron transport chain and promote the release of excess ROS from mitochondria, which act as signaling agents that trigger diverse functional responses [73]. Due to the accumulation of mitochondria and consumption of high oxygen in the CNS, nerve tissues appear to be vulnerable to oxidative stress [74-76]. Excessive ROS could convert nitrogen oxide to peroxynitrite anion, leading to the formation of cytotoxic hydroxyl radicals and destruction of the structure of lipids, proteins, and deoxyribonucleic acid (DNA) [77]. Excess cellular levels of ROS activate the signaling pathways of apoptosis through multiple mechanisms [78]. Animal experiments showed that the antioxidants, hydrogen sulfide and melatonin, reduce neuronal apoptosis after SAH *via* the ROS-mammalian STE20-like kinase 1 (MST1) pathway

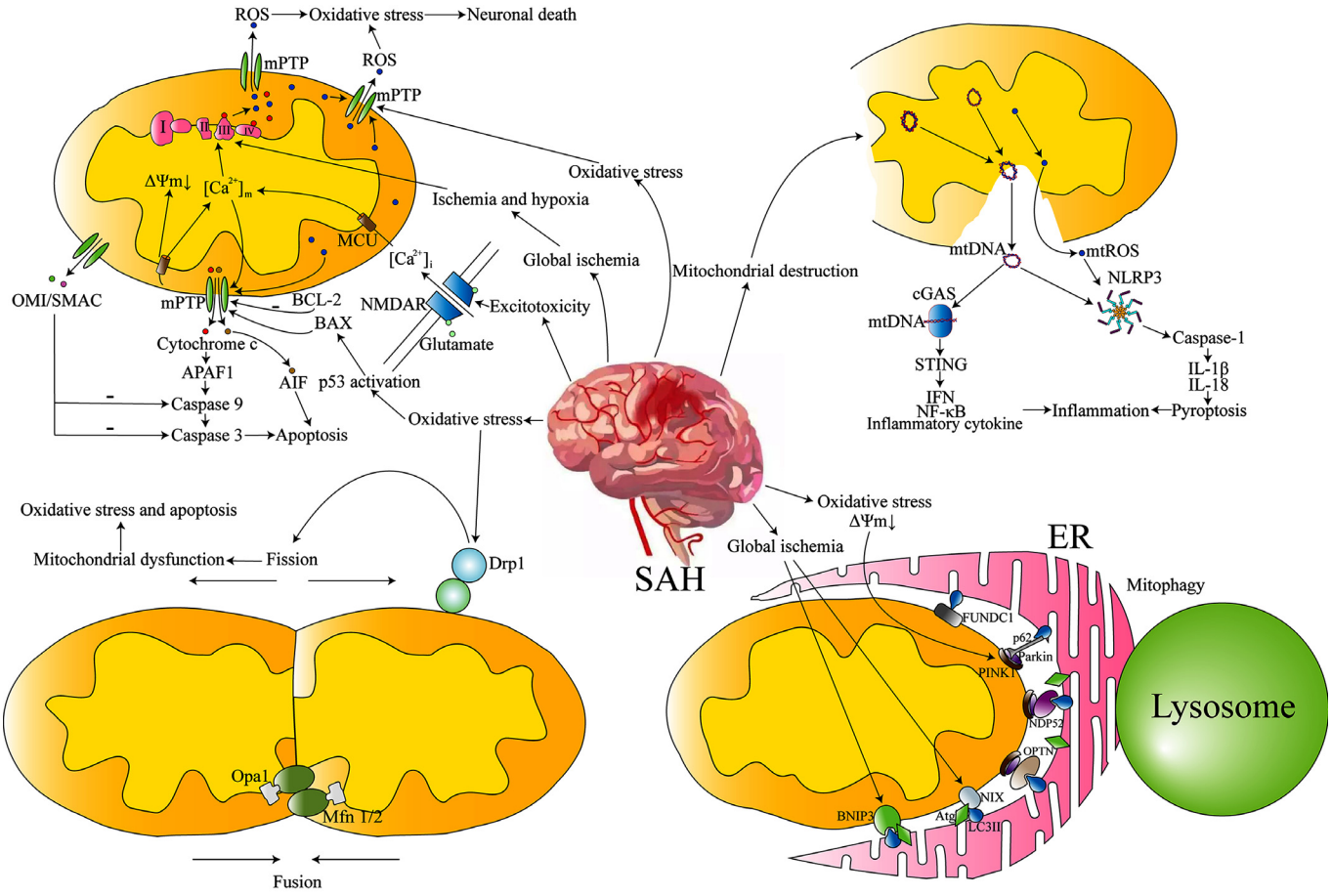

Fig. (2). The role of mitochondria in EBI after SAH. After SAH, a series of mitochondria-related events play a role in EBI, including mitochondria-induced oxidative stress, mitochondria-dependent apoptosis, mitochondria-related inflammation, mitochondrial dynamics disorder, and mitophagy activation. **Abbreviations:** EBI: early brain injury; SAH: subarachnoid hemorrhage; ROS: reactive oxygen species; mPTP: mitochondrial permeability transition pore; ΔΨm: mitochondrial membrane potential; MCU: mitochondrial calcium uniporter; SMAC: second mitochondria-derived activator of caspase; BCL-2: B cell lymphoma 2; APAF1: apoptotic peptidase activating factor 1; AIF: apoptosis-inducing factor; NMDAR: N-methyl-d-aspartate receptor; mtDNA: mitochondrial deoxyribonucleic acid; mtROS: mitochondrial reactive oxygen species; cGAS: cyclic guanosine monophosphate-adenosine monophosphate synthase; STING: stimulator of interferon gene; NLRP3: NACHT, LRR, and PYD domains-containing protein 3; IFN: interferon; NF-κB: nuclear factor kappa beta; IL: interleukin; Drp1: dynamin-related protein 1; Opa1: optic atrophy protein 1; Mfn: mitofusin; ER: endoplasmic reticulum; FUNDC1: FUN14-domaincontaining protein 1; PINK1: phosphatase-and-tensin-homolog-induced putative kinase 1; NDP52: nuclear dot protein 52 kDa; OPTN: optineurin; NIX: NIP3-like protein X; LC3II: light chain 3 II; BNIP3: BCL2/adenovirus E1B 19 kDa protein-interacting protein 3. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

[79, 80]. In addition, increased ROS and calcium overload could mediate the sustained opening of mPTP, which results in the release of cytochrome c and apoptosis-inducing factor (AIF) from mitochondria to the cytoplasm [27]. At a higher ROS level, a longer mPTP opening may release a ROS burst, known as ROS-induced ROS release, leading to the destruction of the mitochondria and the cells [40]. Cyclosporin A, which could inhibit mitochondrial mPTP opening, significantly decreases the expression of cytochrome c and AIF and ameliorates elements of EBI, including brain edema, cortical apoptosis, and neurobehavioral deficits in rat models of SAH [28].

3.2. Mitochondria-dependent Apoptosis

Apoptosis, a form of programmed cell death, is an important mechanism of EBI after SAH. Numerous animal experiments demonstrate that apoptosis can be noted in most regions of the brain, including the hippocampus and basal cortex, following the global ischemia seen with SAH [81]. There are two pathways, the intrinsic and extrinsic, that ultimately execute apoptosis by activating caspase 3. The mitochondrial pathway of apoptosis, an important aspect of the intrinsic apoptotic pathway, promotes the release of soluble proteins from the mitochondria *via* transition in mitochondrial permeability, leading to cell death [82]. The B cell lymphoma (BCL) 2 protein family can be divided into three subsets: the anti-apoptotic members [BCL-2, BCL-W, and myeloid cell leukemia-1 (MCL1)], pro-apoptotic members [BCL-2-antagonist/killer (BAK), BCL-2-associated protein x (BAX) and BCL-2-related ovarian killer (BOK)], and pro-apoptotic BH3-only members (BID, BIM, and BAD). Moreover, the BCL-2 protein family regulates the mitochondrial permeability transition, and therefore plays a role in the regulation of apoptosis [83]. Mitochondrial permeability

transition involves the mPTP, a transmembrane channel between the outer and inner mitochondrial membrane [84]. In the early stage of apoptosis, the pro-apoptotic proteins, BAX and BAK, translocate to the outer mitochondrial membrane (OMM), driving mitochondrial outer membrane permeabilization and mPTP opening. Under normal conditions, anti-apoptotic proteins, such as BCL-2, prevent mitochondrial outer membrane permeabilization and mPTP opening by binding activated pro-apoptotic proteins and BH3-only proteins [82-84]. Therefore, it is believed that the ratio of BCL-2 and BAX is correlated with the extent of cellular apoptosis [85]. It has been widely reported that there is a reduction of BCL-2/BAX in the brain tissue in setting experimental SAH, reflecting the activation of the mitochondrial pathway of apoptosis [86, 87]. The upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins after SAH may be related to the activation of the p53 gene [82, 88].

The mitochondrial permeability transition causes the release of pro-apoptotic proteins, such as cytochrome c and AIF, from the mitochondrial intermembrane space [82, 83]. Cytochrome c can bind to apoptotic peptidase activating factor 1, forming a heptameric complex known as the apoptosome. The apoptosome then recruits and activates caspase 9, which subsequently cleaves and activates caspase 3 to execute apoptosis. In addition, the mitochondrial permeability transition leads to the release of OMI and second mitochondria-derived activator of caspase, which could block X-linked inhibitor-of-apoptosis protein, a caspase inhibitor, to facilitate cellular apoptosis [83]. A previous study has shown that cytochrome c is present in subarachnoid blood products and is associated with subsequent neuronal death [89]. AIF is a caspase-independent mediator of cellular apoptosis, which can inhibit poly (adenosine diphosphate-ribose) polymerase and accelerate the apoptotic process [90, 91]. A recent animal experiment showed that AIF was upregulated and was mainly expressed in the nucleus after SAH. Additionally, the decreased AIF expression was related to the decrease of neuronal apoptosis and attenuation of EBI [92].

In addition to apoptosis, recent studies reported that mitochondria were also involved in other programmed cell deaths, including pyroptosis and ferroptosis [83]. NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome is a multiprotein platform activated by cellular infection or stress. Activated NLRP3 can induce caspase-1 to cleave pro-interleukin (IL)-1β and pro-IL-18, thereby causing pyroptosis [93]. Some mitochondria-derived molecules, such as mitochondrial ROS (mtROS), mtDNA, and cardiolipin, were found to play a role in the activation of NLRP3 [94]. In an animal model of SAH, mitochondria-induced NLRP3 activation promoted pyroptosis and aggravated EBI [95]. Additionally, multiple mitochondria-related events were involved in the regulation of ferroptosis, including mitochondrial energetic metabolism, mitochondrial iron metabolism, and mitochondria-lipid metabolism axis [96]. Recently, several experimental studies revealed the detrimental role of ferroptosis in EBI after SAH [97-99].

3.3. Mitochondrial Dynamics Disorder

Mitochondria are dynamic organelles that continuously change shape through fission, fusion, and movement along cytoskeletal tracks. These dynamic processes control the shape, size, and intracellular distribution of mitochondria, enabling the cell to respond to changing physiological conditions [100]. In general, large mitochondrial networks generated by fusion are adapted to metabolically active cells, whereas small spherical or short rod-shaped mitochondria generated by fission often appear in quiescent cells [101]. In recent years, the study of mitochondrial dynamics (fusion and fission) has received extensive attention, as they play critical roles in many biological processes, such as apoptosis, aging, and mitophagy [100, 101].

Dynamin-related protein 1 (Drp1), a soluble protein containing a C-terminal guanosine triphosphate enzyme (GTPase) effector domain, a middle domain, and an N-terminal GTPase, is the main regulator of mitochondrial fission in mammals [101]. It is generally believed that phosphorylation at Ser616 (S616) accelerates the recruitment of Drp1 to the mitochondrial membrane, while phosphorylation at S637 inhibits this process [102, 103]. Under normal conditions, mitochondrial fission is beneficial to the removal of damaged mitochondria, thereby maintaining mitochondrial stability [104]. However, excessive fission can interrupt the mitochondrial respiratory chain, increase mitochondrial-derived ROS, and activate the apoptotic pathway [105, 106]. In vitro studies showed that in dominant-negative Drp1 mutant cell lines, mitochondrial fragmentation and apoptosis were significantly reduced in a variety of insults [107, 108]. In turn, mitochondrial oxidative stress can also up-regulate the expression of Drp1 to promote fission, causing mitochondrial dysfunction and apoptosis [109]. In vitro and in vivo experiments have reported excessive mitochondrial fission, as well as increased expression and phosphorylation at S616 of Drp1 after SAH [110, 111]. The selective inhibition of Drp1 was found to play an effective role in attenuating elements of EBI, such as oxidative stress, cellular apoptosis, and BBB disruption, after experimental SAH [111, 112].

Mitochondrial fusion requires three large guanosine triphosphate (GTP)-hydrolyzing enzymes, including mitofusins (Mfn) 1 and 2, which mediate outer membrane fusion, as well as optic atrophy protein 1 (Opa1), which mediates inner membrane fusion [113]. Under normal conditions, mitochondrial fusion maintains mitochondrial integrity through diffusion and sharing components between organelles [114]. Fusion has neuroprotective effects in neurodegenerative diseases. Moreover, defects in the fusion process may cause neurodegeneration [115, 116]. An animal experiment showed that the expression of Mfn 1/2 in the CNS decreased significantly 24 hours after SAH [117]. In another study, the expression of Opa1 had begun to decline at 3 hours after SAH and continued to decline until 72 hours after SAH [54]. Increasing the expression of Mfn 1/2 and Opa1 was found to be beneficial in alleviating EBI after SAH [54, 117]. The potential beneficial effect of mitochondrial fusion in SAH remains to be elucidated.

3.4. Mitophagy

Autophagy is a process of self-deg radation of cellular components involved in organelle turnover and protein quality control, playing a role in removing misfolded, aggregated, or overabundant proteins, clearing damaged organelles, and

eliminating intracellular pathogens [118]. Mitophagy is a type of selective autophagy, which eliminates impaired mitochondria to support mitochondrial homeostasis. The accumulation of impaired mitochondria can cause increased oxygen consumption and excessive ROS generation, ultimately leading to cellular degeneration and activation of cell death pathways [119]. Therefore, as an important mechanism of mitochondrial quality control, mitophagy is pivotal for cell survival and health.

Phosphatase-and-tensin-homolog-induced putative kinase 1 (PINK1)/parkin-dependent pathway is the most characteristic pathway for mitophagy regulation [120]. Under normal conditions, parkin remains in an inactive state in the cytosol as a means of suppressing mitophagy in normally respiring cells [121]. When mitochondria are impaired, the reduction in ΔΨm will activate the PINK1 on the OMM through dimerization and phosphorylation. Activated PINK1 recruits and phosphorylates cytosolic parkin, thereby initiating the PINK1/parkin-dependent mitophagy [121]. Parkin is an E3 ubiquitin ligase that can ubiquitylate OMM substrates and adaptor proteins, including sequestosome 1/p62, optineurin, and nuclear dot protein 52 kDa [122]. Through the binding of ubiquitylated adaptor proteins and microtubule-associated protein light chain 3 II (LC3II), the impaired mitochondria and endoplasmic reticulum (ER) membrane combine to form the autophagosome. Finally, the autophagosome and lysosome fuse to form the autophagolysosome to complete mitophagy [121]. In parkin-independent mitophagy, mitochondria and ER can be combined through BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), NIP3-like protein X (NIX), or FUN14-domain-containing protein 1 [123].

Some studies have focused on the role of mitophagy in EBI after SAH. Cerebral ischemia and hypoxia can reportedly enhance the expression of BNIP3 and NIX and ultimately induce mitophagy [124]. The surge in ROS levels can disrupt the ΔΨm and cause the translocation of parkin from the cytosol to the impaired mitochondria, which also facilitates mitophagy [62]. Moreover, several animal experiments confirmed the increase of mitophagy after SAH. In a mouse model, autophagic markers, including Beclin-1 and LC3II, were found to increase significantly at 24 hours after the onset of SAH [125]. Another study showed that the expression of mitophagy markers, including PINK1 and parkin, increased at 24 hours after SAH [95]. In addition, these two studies also indicated that the administration of melatonin further promoted mitophagy after SAH and was related to the reduction of ROS, the inhibition of neuroinflammation, the decrease of neuronal apoptosis, and the improvement of neurological scores [95, 125]. Conversely, 3-methyladenine (3-MA), an autophagy inhibitor, reversed the promotion of mitophagy by melatonin and the beneficial effects on SAH [95]. Moreover, mitoquinone could induce mitophagy through the Nrf2/Keap1/prohibitin 2 (PHB2) pathway to reduce EBI after SAH [126]. These findings suggest that mitophagy may exert a neuroprotective effect after SAH. However, excessive mitophagy may cause unwarranted degradation of functional mitochondria, eventually leading to cell dysfunction and cell death [127]. The role of mitophagy in SAH remains incompletely understood. Further research is necessary to determine if mitophagy is beneficial for SAH resolution.

3.5. Mitochondria-related Inflammation

The endosymbiotic hypothesis regarding mitochondrial origin proposes that mitochondria evolved from α-proteobacteria in eukaryotic organisms two billion years ago. Over time, mitochondria have become an endosymbiotic organelle of eukaryotic cells, playing an important role in metabolism, calcium homeostasis, and cell death [49]. Thus, mitochondria retain the features of their bacterial ancestry that could trigger inflammatory responses through the innate and adaptive immune pathways. In addition, overproduction of mtROS and mitochondrial damage may lead to sustained inflammation [128].

After SAH, pattern recognition receptors on immune cells activate the innate and adaptive immune response by recognizing DAMPs, causing the activation and infiltration of immune cells at the site of injury [129]. When cells undergo damage or stress, mitochondrial components, such as mtDNA, cardiolipin, and formyl-peptides, can be released into the cytoplasm or into the extracellular milieu, where they act as DAMPs [49]. One clinical study found that high CSF mtDNA levels were significantly associated with poor outcomes in patients with aneurysmal SAH (aSAH) [130]. In another study, serum mtDNA levels were found to be related to the occurrence of post-aSAH complications, including pneumonia, hydrocephalus, and epilepsy [131]. MtDNA can trigger various pro-inflammatory signal pathways by cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS)-stimulator of interferon gene (STING) or inflammasomes [132]. CGAS is a cytosolic DNA sensor, which can activate STING to trigger the downstream cascade when ligated to mtDNA [49]. STING is an ER protein associated with mitochondrial antiviral signaling protein. Once activated, STING transfers from the ER to the perinuclear endosomes and activates nuclear factor kappa beta, interferons, and inflammatory cytokines [49]. An animal experiment showed that the level of STING in the CNS was significantly increased at 12 hours after SAH and peaked at 24 hours. In addition, the administration of the STING agonist, CMA, significantly aggravated the EBI after SAH, whereas the STING antagonist, C-176, reversed this effect [133]. MtDNA can also cause the activation of the NLRP3 inflammasome, which induces caspase-1 to cleave pro- IL-1β and pro-IL-18, eventually leading to pyroptosis [93]. An animal experiment showed that NLRP3 inflammasome-mediated pyroptosis aggravated the inflammatory response and EBI after SAH [134]. Moreover, mtROS can promote the inflammatory cascade by enhancing the effect of mtDNA on NLRP3 activation [93]. In a rat model of SAH, upregulating the mitophagy to promote the clearance of impaired mitochondria and reduce the production of mtROS could inhibit the activation of NLRP3 inflammasomes, as well as the downstream inflammation cascade, exerting a neuroprotective effect in EBI [95].

4. MITOCHONDRIA AND DCI AFTER SAH

Several studies have explored the relationship between the mitochondria and DCI after SAH. One study found more CSF mitochondrial particles in DCI patients than in non-DCI patients [135]. DCI patients had lower ΔΨm at the fifth day after SAH onset, especially in endothelial cell-derived mito-

chondria. CVS, the most important mechanism of DCI after SAH, involves a series of pathological events, including endothelial cell dysfunction, smooth muscle contraction, and changes in vascular responsiveness [136]. SAH is usually caused by the rupture of an aneurysm; therefore, endothelial cell dysfunction might play a pivotal role in the ictus and subsequent process after SAH. Endothelial cell dysfunction can promote CVS by inducing endothelial nitric oxide synthase dysfunction, increased expression of endothelin-1, and remodeling of vascular wall structure [137-139]. Thus, mitochondrial dysfunction in CSF may reflect endothelial damage and dysfunction in DCI pathogenesis. Moreover, the decrease of ΔΨm in the CSF after SAH was also associated with a worse prognosis [65]. An additional study found that mitochondrial dysfunction was a common cause of disturbed cerebral energy metabolism in SAH patients, which increased the tissue sensitivity to DCI [64]. Some studies showed that the occurrence of DCI was not always associated with vasospasm and ischemia. Despite adequate brain tissue oxygenation, some patients with SAH still suffer from a cerebral metabolic crisis [140]. Wagner and colleagues reported that mitochondrial dysfunction might reflect global metabolic changes after SAH, independent from visible perfusion deficits. This also helps explain the correlation between mitochondrial dysfunction and DCI [141]. Additionally, a clinical trial investigated the systemic levels of mtDNA after SAH and determined the association between mtDNA and post-SAH complications. It was found that cytochrome b, a gene fragment of mtDNA, was positively correlated with the occurrence of DCI [131].

Since current opinions agree that EBI after SAH is an important cause of subsequent DCI, EBI caused by mitochondrial dysfunction may be the mechanism of DCI. The role of mitochondria in EBI has been described above. In a rat model of SAH, the administration of astaxanthin was found to attenuate SAH-induced EBI and CVS by stabilizing the ΔΨm and inhibiting the mitochondria-dependent apoptosis [142]. Further research is needed to clarify the relationship between mitochondria and DCI after SAH and the underlying mechanism.

5. TRANSLATIONAL STRATEGIES OF MITOCHONDRIA-TARGETED THERAPY FOR SAH

Although surgical clipping and endovascular obliteration have reduced the acute mortality after SAH, drugs to improve the long-term outcome of SAH patients are still limited [2]. It is imperative to develop new therapeutic targets to address long-term neurological deficits after SAH. Based on the role of mitochondria in EBI and DCI after SAH, we believe that mitochondria present a promising therapeutic target for SAH. We summarized mitochondria-related treatment strategies according to recent research, which may provide a novel direction for SAH treatment. In addition, some novel materials for mitochondria-targeted drug delivery were reviewed. The studies exploring mitochondria-targeted therapy for SAH are listed in Table **1**.

5.1. Antioxidant Therapy

Since the excessive production of ROS induced by mitochondrial dysfunction can aggravate EBI after SAH, antioxidant therapy may be a promising treatment for SAH. Edaravone, a non-selective antioxidant, has been found to be effective in animal studies. In a rat SAH model, the administration of edaravone effectively decreased the ROS levels in CNS, diminished neuronal apoptosis, and attenuated the functional impairment of the brain [143]. In a randomized controlled trial including 91 patients, edaravone decreased the incidence of neurological deficits and poor outcomes caused by CVS after aSAH [144]. However, the sample size of this study is small, and large-scale clinical trials are needed to confirm this finding.

Recent studies have reported that selective mtROS scavengers, such as mitoquinone and SS31, were superior to non-selective ROS scavengers in the treatment of many diseases involving mitochondrial dysfunction-induced oxidative stress [145, 146]. Mitoquinone is a potent mitochondria-targeted antioxidant whose antioxidant properties are hundreds of times better than that of untargeted antioxidants. One experimental study showed that mitoquinone activated mitophagy through the Keap1/Nrf2/PHB2 pathway to inhibit oxidative stress-related neuronal death after SAH [126]. Another study found that mitoquinone attenuated BBB disruption through the Nrf2/PHB2/Opa1 pathway following experimental SAH [54]. Although the mitochondria-targeted antioxidant effect of mitoquinone has not been tested in SAH patients, it was found to decrease oxidative stress-caused liver damage in a phase II study of hepatitis C patients [147]. In an animal study, SS31, a novel mitochondria-targeted antioxidant peptide, was found to alleviate EBI after SAH due to its antioxidant properties and ability to inhibit neuronal apoptosis [148].

Some drugs exert antioxidant and neuroprotective effects after SAH by regulating the function of mitochondria. MitoNEET is a newly discovered protein located in the mitochondrial membrane, and it plays an important role in the regulation of mitochondrial function [149]. In an experimental study based on a rat model, TT01001 reduced oxidative stress damage following SAH by activating mitoNEET to improve mitochondrial dysfunction, thereby alleviating EBI [67]. In addition, docosahexaenoic acid can prevent oxidative stress-based apoptosis after SAH by ameliorating mitochondrial dysfunction through the regulation of mitochondrial dynamics-related signaling pathways [150]. One clinical study found that administration of docosahexaenoic acid after aSAH reduced the incidence of CVS and improved clinical outcomes [151].

5.2. Anti-Apoptosis Therapy

Mitochondria-dependent apoptosis is one of the main mechanisms of neuronal death after SAH, playing an important role in EBI. Inhibition of this process is expected to become a treatment strategy for SAH. Some animal experiments have indicated that inhibiting the mitochondria-dependent apoptosis pathway can improve neurological outcomes after SAH. One study based on a rat SAH model showed that mangiferin attenuated SAH-induced EBI by influencing mitochondrial apoptotic proteins. The administration of mangiferin significantly reduced the expression of BCL-2 protein in the brain tissue while upregulating the expression of BAX. Cytochrome c and cleaved caspase-3 were found to be significantly decreased. After the treatment with mangiferin, the neurological outcomes of rats with SAH

Table 1. Related studies exploring mitochondria-targeted therapy for SAH.

Studied Drugs	Mechanisms	Related Study Results	Studied Species	References
Edaravone	A non-selective free radical scavenger	Edaravone decreased ROS levels in CNS, reduced neuronal apoptosis, and attenuated neurological impairment after SAH.	SD rats	Gao *et al.*, 2009 [143]
		Edaravone decreased neurological deficits and poor outcome caused by CVS in patients with aSAH.	Human	Munakata *et al.*, 2009 [144]
Mitoquinone	A selective mtROS scavenger; Inducing mitophagy; Promoting mitochondrial fusion	Mitoquinone inhibited oxidative stress-related neuronal death after SAH through activating mitophagy *via* Keap1/Nrf2/PHB2 pathway.	SD rats	Zhang *et al.*, 2019 [126]
		Mitoquinone promoted mitochondrial fusion and attenuated BBB disruption after SAH through Nrf2/PHB2/Opa1 pathway.	SD rats	Zhang *et al.*, 2019 [54]
SS31	A mitochondria-targeted antioxidant peptide	SS31 exerted antioxidant property and inhibited neuronal apoptosis after SAH.	SD rats	Shen *et al.*, 2020 [148]
TT01001	Activating mitoNEET to improve mitochondrial dysfunction	TT01001 reduced oxidative stress damage caused by mitochondrial dysfunction following SAH.	SD rats	Shi *et al.*, 2020 [67]
Docosahexaenoic acid	Regulating mitochondrial dynamics; Promoting mitochondrial fusion	Docosahexaenoic acid reduced oxidative stress and neuronal apoptosis after SAH through regulating mitochondrial dynamics-related signaling pathways and up-regulating the expression of Opa1.	Wistar rats	Zhang *et al.*, 2018 [150]
		Docosahexaenoic acid reduced CVS incidence and improved clinical outcomes after aSAH.	Human	Nakagawa *et al.*, 2017 [151]
Mangiferin	Influencing expression of mitochondrial apoptotic proteins	Mangiferin reduced BCL-2 expression, upregulated BAX expression, and improved neurological outcomes after SAH.	SD rats	Wang *et al.*, 2017 [152]
Neuroglobin	Inhibiting activation of mitochondrial apoptotic pathway	Neuroglobin decreased pro-apoptotic factors including BAX, caspase-9, and caspase-3 as well as improved neurological outcomes after SAH.	Rabbits	Chen *et al.*, 2018 [155]
JNK	Inhibiting p53 phosphorylation to reduce mitochondria-dependent apoptosis	JNK decreased mitochondria-dependent apoptosis and alleviated EBI after SAH through reducing the level of p53 phosphorylation.	SD rats	Ling *et al.*, 2019 [156]
Cyclosporin A	Inhibiting mitochondrial mPTP opening to reduce mitochondria-dependent apoptosis	Cyclosporin A decreased the expression of cytochrome c, AIF, and cleaved caspase-3, inhibited mitochondria-dependent apoptosis, and alleviated EBI after SAH.	SD rats	Xie *et al.*, 2012 [28]
		Cyclosporine A reduced neurological deterioration of patients with aSAH.	Human	Ryba *et al.*, 1991 [157]
z-VAD-FMK	A pan-caspase inhibitor	Z-VAD-FMK suppressed endothelial cell apoptosis, reduced BBB permeability, alleviated cerebral edema, and improved neurological outcomes after SAH.	SD rats	Park *et al.*, 2004 [158]
Ac-DEVD-CHO	A specific caspase-3 inhibitor	Ac-DEVD-CHO reduced endothelial cell apoptosis and CVS following SAH.	Dogs	Zhou *et al.*, 2004 [159]
Mdivi-1	Inhibiting mitochondrial fission	Mdivi-1 decreased the expression of Drp1 and phosphorylated Drp1(S616), inhibited excessive mitochondrial fission, reduced the ROS levels, and suppressed the mitochondria-dependent apoptosis after SAH.	Wistar rats; SD rats	Fan *et al.*, 2017 [112]; Wu *et al.*, 2017 [111]
Rapamycin	Inhibiting mitochondrial fission; Inducing mitophagy	Rapamycin ameliorated excessive mitochondrial fission, restored mitochondrial function, and reduced EBI after SAH by inhibiting the activity of mTOR.	Wistar rats	Li *et al.*, 2020 [110]
		Rapamycin increased the expression of autophagy-related proteins including ATG5, Beclin 1, and LC3II, as well as reduced mitochondria-dependent neuronal apoptosis, cerebral edema, and neurological deficits after SAH.	SD rats	Jing *et al.*, 2012 [164]
Honokiol	Activating SIRT3 to promote mitochondrial fusion	Honokiol up-regulated the expression of mitochondrial fusion protein Mfn 1/2, promoted mitochondrial fusion, maintained mitochondrial morphology and function, and reduced EBI after SAH.	C57BL/6 mice	Wu *et al.*, 2020 [117]

(Table 1) contd….

Studied Drugs	Mechanisms	Related Study Results	Studied Species	References
Melatonin	An ROS scavenger; Inducing mitophagy	Melatonin reduced neuronal apoptosis after SAH *via* the ROS-MST1 pathway.	SD rats	Shi *et al.*, 2018 [80]
		Melatonin protected against EBI after SAH through mediating mitophagy.	C57BL/6 mice	Sun *et al.*, 2018 [125]
		Melatonin-enhanced mitophagy protected against the mitochondrial pathway of apoptosis after SAH.	SD rats	Chen *et al.*, 2014 [161]
		Melatonin-mediated mitophagy alleviated SAH-induced EBI through inhibition of NLRP3 inflammasome activation.	SD rats	Cao *et al.*, 2017 [95]
		Melatonin decreased fatigue after aSAH.	Human	Gilard *et al.*, 2016 [163]
VDAC	Promoting mitophagy	VDAC protected neurons from death in EBI after SAH by promoting mitophagy.	SD rats	Li *et al.*, 2014 [166]
Ruthenium red	Blocking MCU to prevent ΔΨm depolarization and mitochondrial dysfunction	Ruthenium red prevented ΔΨm depolarization, reduced oxidative stress, and inhibited neuronal apoptosis after SAH.	SD rats	Yan *et al.*, 2015 [27]
EGCG	Blocking VGCC to weaken accumulation of intracellular calcium and prevent ΔΨm depolarization	EGCG diminished SAH-induced ΔΨm depolarization, mPTP opening, and release of ROS and cytochrome c.	Kunming mice	Chen *et al.*, 2018 [66]; Chen *et al.*, 2017 [168]
SB203580	Inhibiting p38 to prevent ΔΨm depolarization and mitochondrial dysfunction	SB203580 inhibited ΔΨm decrease, reduced neuronal death, and improved neurological outcomes after SAH.	Kunming mice	Huang *et al.*, 2013 [22]
		SB203580 reduced ΔΨm depolarization and ROS release after SAH through induction of DJ-1 mitochondrial translocation.	SD rats	Huang *et al.*, 2018 [170]
Tetramethylpyrazine	Preventing ΔΨm depolarization and mitochondrial calcium overload	Tetramethylpyrazine exerted an anti-apoptotic property to attenuate EBI in SAH by alleviating ΔΨm decrease and ameliorating mitochondrial calcium overload.	Wistar rats	Li *et al.*, 2017 [171]
BMS-470539	Activating melanocortin 1 receptor to promote mitochondrial biogenesis and control mitochondrial metabolism	BMS-470539 attenuated EBI following SAH by promoting mitochondrial biogenesis and controlling mitochondrial metabolism through the AMPK/SIRT1/PGC-1α pathway.	SD rats	Xu *et al.*, 2021 [175]
Resveratrol	Promoting mitochondrial biogenesis	Resveratrol reduced mitochondrial dysfunction-induced oxidative stress and mitochondria-dependent apoptosis after SAH by improving mitochondrial biogenesis through the PGC-1α pathway.	SD rats	Zhou *et al.*, 2021 [176]
heat shock protein 22	Promoting mitochondrial biogenesis; Inhibiting mitochondrial fission	Heat shock protein 22 alleviated post-SAH EBI by promoting mitochondrial biogenesis through the AMPK-PGC-1α signaling pathway and by inhibiting mitochondrial fission *via* Drp1 modulation.	SD rats	Fan *et al.*, 2021 [179]
Irisin	Improving mitochondrial biogenesis	Irisin exerted neuroprotective effects against SAH by improving mitochondrial biogenesis through UCP2-related targets.	C57BL/6 mice	Tu *et al.*, 2021 [182]

Abbreviations: ROS: reactive oxygen species; CNS: central nervous system; SAH: subarachnoid hemorrhage; mtROS: mitochondrial reactive oxygen species; Keap1: Kelch-like ECH-associating protein 1; Nrf2: nuclear factor erythroid 2 related factor 2; PHB2: prohibitin 2; BBB: blood-brain barrier; Opa1: optic atrophy protein 1; BCL-2: B cell lymphoma 2; BAX: BCL-2-associated protein x; JNK: c-Jun N-terminal kinase; CVS: cerebral vasospasm; Drp1: dynamin-related protein 1; S616: Ser616; EBI: early brain injury; mTOR: mammalian target of rapamycin; ATG: autophagy-related gene; LC3II: light chain 3 II; Mfn: mitofusin; MST1: mammalian STE20-like kinase 1; NLRP3: NACHT, LRR, and PYD domains-containing protein 3; VDAC: voltage-dependent anion channel; MCU: mitochondrial calcium uniporter; EGCG: (-)-Epigallocatechin-3-gallate; VGCC: voltage-gated calcium channel; ΔΨm: mitochondrial membrane potential; mPTP: mitochondrial permeability transition pore; AMPK: AMP-activated protein kinase; SIRT: sirtuin; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; UCP2: uncoupling protein 2.

were significantly improved [152]. As a plant extract, the safety of mangiferin in the human body has been confirmed, and it was found to improve serum lipid profiles [153, 154]. A study evaluated the neuroprotective effects of neuroglobin in a rabbit model of SAH. It was found that neuroglobin inhibited the SAH-induced activation of the mitochondrial apoptotic pathway, and it improved the neuronal viabilities and neurological outcomes after SAH. Pro-apoptotic factors, including BAX, caspase-9, and caspase-3, were significantly decreased after neuroglobin treatment [155]. The mitochondrial pathway of apoptosis may reportedly function as a signaling pathway downstream of p53 phosphorylation activation, which is likely a cross-signaling molecule in SAH-induced apoptosis [82, 88]. In a rat experiment, c-Jun N-terminal kinase inhibited SAH-induced apoptosis of the mitochondrial pathway by reducing the level of p53 phosphorylation, thereby reducing EBI [156]. In addition, cyclosporin A could inhibit mitochondrial mPTP opening from

preventing the release of cytochrome c and AIF from mitochondria after SAH, thereby inhibiting mitochondria-dependent apoptosis [28]. An early clinical trial found that the administration of cyclosporine A could prevent neurological deterioration in patients with aSAH [157].

Several experimental studies tested the effects of caspase inhibitors in SAH. Park *et al.* found that z-VAD-FMK, a pan-caspase inhibitor, could suppress endothelial cell apoptosis, reduce BBB permeability, alleviate cerebral edema, prevent CVS, and improve neurological outcome after experimental SAH in rats [158]. In addition, a specific caspase-3 inhibitor, Ac-DEVD-CHO, was also found to prevent endothelial cell apoptosis and CVS in a dog model of experimental SAH [159]. Although there has been no clinical trial of caspase inhibitors for SAH, their potential in SAH treatment is expected to promote further preclinical and clinical research.

5.3. Modulation of Mitochondrial Dynamics

The abnormal regulation of mitochondrial dynamics after SAH turns the balance of fusion and fission into fission, which can cause an increase in mtROS production and activation of apoptotic pathways. Modulation of mitochondrial dynamics may reduce oxidative stress and neuronal apoptosis to alleviate EBI after SAH. Mdivi-1 is a selective inhibitor of the mitochondrial fission protein Drp1, which can penetrate the BBB to enter the CNS. Two animal experiments have explored the role of Mdivi-1 in EBI after SAH, and both found that Mdivi-1 significantly decreased the expression of Drp1 and phosphorylated Drp1 (S616), inhibited excessive mitochondrial fission, restored the ultra-structure of mitochondria, reduced the ROS levels in CNS, and suppressed the mitochondria-dependent apoptosis [111, 112]. In addition, Li *et al.* found that rapamycin ameliorated excessive mitochondrial fission, restored mitochondrial function, and reduced EBI after SAH by inhibiting the activity of the mammalian target of rapamycin (mTOR). Conversely, 3-MA, which can increase the activity of mTOR, aggravated excessive mitochondrial fission and dysfunction, as well as worsened the neurological deficits after SAH [110]. Although there are currently no clinical trials of rapamycin for SAH patients, it is an approved drug with known pharmacokinetics and is expected to be available in clinical research for SAH treatment in the future [160].

Mitochondrial fusion helps maintain the structure and function of mitochondria [114]. Some studies have found that fusion may exert a neuroprotective effect in SAH. Mitoquinone was found to promote mitochondrial fusion, improve mitochondrial morphology, and attenuate BBB disruption after SAH through the Nrf2/PHB2/Opa1 pathway [54]. Docosahexaenoic acid can up-regulate the expression of the mitochondrial fusion protein, Opa1, to promote mitochondrial fusion, as well as reduce oxidative stress and neuronal apoptosis after SAH [150]. Sirtuin (SIRT)3 is a deacetylase mainly located in mitochondria, and it was indicated that dysfunction of this deacetylase contributes to many diseases of the CNS. In a mouse model of SAH, SIRT3 agonist, Honokiol, significantly reduced EBI through up-regulating the expression of mitochondrial fusion protein Mfn 1/2, promoting mitochondrial fusion, and maintaining mitochondrial morphology and function [117].

5.4. Mitophagy Modulation

Mitophagy can eliminate impaired mitochondria to support mitochondrial homeostasis, which is critical for cell survival and health. Studies have shown that mitophagy was activated after SAH and that it exerted neuroprotective effects. It was found that the reduction of EBI after SAH by melatonin may be related to the activation of mitophagy [125]. A rat experiment suggested that melatonin-enhanced mitophagy can protect against the mitochondrial pathway of apoptosis in EBI after SAH [161]. In addition, melatonin-mediated mitophagy can alleviate SAH-induced EBI through inhibition of NLRP3 inflammasome activation [95]. In animal and human studies, short-term use of melatonin was found to be safe, even in extreme doses [162]. A clinical study found that melatonin could decrease fatigue after aSAH [163]. Although the relationship between melatonin administration and long-term outcome of SAH patients is not clear, it is a potential drug for clinical trials of SAH treatment. In a rat model of subarachnoid hemorrhage, autophagy inducer, rapamycin, significantly increased the expression of autophagy-related proteins, autophagy-related gene (ATG) 5, Beclin 1, and LC3II, as well as reduced neuronal apoptosis, cerebral edema, and neurological deficits. Moreover, rapamycin administration also reduced the translocation of BAX to mitochondria, as well as the release of cytochrome c from the mitochondria to the cytoplasm [164]. Conversely, an autophagy inhibitor, 3-MA, reversed these changes and exacerbated EBI [164]. Voltage-dependent anion channels (VDACs) were found to serve as mitochondrial docking sites to promote mitophagy [165]. Li and colleagues reported that VDACs protected neurons from death in EBI by promoting mitophagy [166]. Additionally, another study found that mitoquinone inhibits oxidative stress-related neuronal death by activating mitophagy through the Keap1/Nrf2/PHB2 pathway after SAH [126].

5.5. ΔΨm Depolarization Inhibition

Under pathological conditions, excessive ΔΨm depolarization can lead to mitochondrial dysfunction, mitochondrial calcium overload, continuous opening of mPTP, and escape of cytochrome c and ROS from mitochondria [27, 40]. Some animal experiments demonstrated that inhibition of ΔΨm depolarization might alleviate mitochondrial-induced EBI after SAH. Mitochondrial Ca^{2+} ($[Ca^{2+}]_m$) uptake is undertaken by the mitochondrial calcium uniporter (MCU) located in the inner mitochondrial membrane, which can cause ΔΨm depolarization and mitochondrial calcium overload under pathological conditions [167]. One study found that blockage of MCU by ruthenium red prevented ΔΨm depolarization and $[Ca^{2+}]_m$ accumulation, reduced oxidative stress, and inhibited neuronal apoptosis after experimental SAH [27]. Moreover, (-)-Epigallocatechin-3-gallate (EGCG) can inhibit cytosolic Ca^{2+} ($[Ca^{2+}]_i$) accumulation by blocking voltage-gated calcium channels, which also weakens the accumulation of $[Ca^{2+}]_m$. Two studies have found that the administration of EGCG significantly diminished SAH-induced mitochondrial dysfunction, including ΔΨm depolarization, mPTP opening, and release of ROS and cytochrome c [66, 168]. Recently, p38 mitogen-activated protein kinase was found to be a potential target to directly or indirectly inhibit mitochondrial dysfunction [169]. In a mouse model of SAH, p38

specific inhibitor, SB203580, inhibited ΔΨm decrease, reduced neuronal death, and improved neurological outcomes after SAH [22]. Another study showed that p38 inhibitor, SB203580, reduced ΔΨm depolarization and ROS release after SAH through induction of DJ-1 mitochondrial translocation [170]. In addition, it was found that tetramethylpyrazine could exert an anti-apoptotic property to attenuate EBI in SAH by alleviating ΔΨm decrease and ameliorating calcium overload in the mitochondria and cytoplasm [171].

5.6. Mitochondrial Biogenesis Activation

Mitochondrial biogenesis keeps mitochondrial homeostasis during the mitochondrial life cycle [172]. There is strong evidence to suggest that mitochondrial biogenesis may reverse mitochondrial dysfunction and reduce ROS production [173]. Therefore, exploring the role of mitochondrial biogenesis in EBI may contribute to the development of SAH treatment strategies. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a transcriptional coactivator, is a major regulator of mitochondrial biogenesis [174]. A previous study demonstrated that the activation of the melanocortin 1 receptor by BMS-470539 attenuated EBI following SAH by promoting mitochondrial biogenesis and controlling mitochondrial metabolism through the AMP-activated protein kinase (AMPK)/SIRT1/PGC-1α pathway [175]. Another study found that resveratrol reduced mitochondrial dysfunction-induced oxidative stress and mitochondria-dependent apoptosis following SAH by improving mitochondrial biogenesis through the PGC-1α pathway [176]. The safety and pharmacokinetics of resveratrol in human subjects have been documented in more than two hundred clinical trials [177]. Although the efficacy of resveratrol has not been demonstrated in patients with SAH, a study found that resveratrol could extend the clinical therapeutic window of recombinant tissue plasminogen activator in patients with ischemic stroke [178]. In addition, heat shock protein 22 alleviated EBI after SAH by promoting mitochondrial biogenesis through the AMPK-PGC-1α signaling pathway and by inhibiting mitochondrial fission *via* Drp1 modulation [179]. Mitochondrial uncoupling protein 2 (UCP2) is a crucial ROS-detoxifying protein, which could regulate mitochondrial ROS production to prevent neuronal damage and death [180]. UCP2 can act as a downstream of PGC-1α to regulate mitochondrial biogenesis and metabolism [181]. In an animal experiment, irisin was found to exert neuroprotective effects against SAH by improving mitochondrial biogenesis through UCP2-related targets [182]. In a clinical study, a low serum irisin level was associated with poor early functional outcomes in ischemic stroke patients [183]. Therefore, irisin may have neuroprotective effects in the human body as well.

5.7. Novel Materials for Mitochondria-targeted Drug Delivery

Although mitochondria-targeted therapy is promising for SAH treatment, mitochondria-targeted delivery of therapeutic agents is very important to ensure that they reach their full potential. First, targeting drugs to mitochondria can prevent off-target toxic side effects on normal tissues. Moreover, mitochondria-targeted drug delivery can increase the bioavailability of drugs to allow lower doses of drug administration [184].

Currently, biomaterials-based nanomedicine has been widely investigated for mitochondria-targeted drug delivery and has shown great potential in the treatment of some diseases [184]. Delocalized lipophilic cations, including triphenylphosphonium, dequalinium, and rhodamine 123, show high intrinsic affinity towards mitochondria, playing an important role in mitochondria-targeted therapy [185]. A recent experimental study showed that resveratrol loaded biomimetic nanoparticles localize to mitochondria efficiently with the aid of triphenylphosphonium and relieve mitochondria-induced oxidative stress after Alzheimer's disease [186]. Mitochondria-targeted peptide SS31 has the ability to permeate the plasma membrane and selectively accumulate in mitochondria. Zhang *et al.* used SS31 to prepare a mitochondria-targeted nanoparticle that could precisely deliver cyclosporin A into mitochondria of ischemic cardiomyocytes to treat myocardial ischemia reperfusion injury in rats and exhibit significant cardioprotective effects [187]. In one study, a mitochondria-targeted hybrid nanozyme was constructed to treat cardiac ischemia-reperfusion injury, which greatly reduced the oxidative stress damage of the myocardium [188]. In addition, Haddad *et al.* reported a design of a mitochondria-targeted metal-organic framework, which greatly enhanced mitochondria-targeted drug delivery and increased the efficacy of cancer drugs [189].

Although the novel materials for mitochondria-targeted drug delivery have not been tested in the treatment of SAH, it has shown great potential in mitochondria-targeted therapy. Future SAH research should actively focus on this aspect.

CONCLUSION

SAH is a devastating disease associated with high mortality and morbidity, but treatment options remain limited. Despite extensive research in EBI and DCI, the understanding of SAH mechanisms is still insufficient, hindering the development of targeted therapies for this devastating disease. Cumulative evidence has confirmed SAH-induced mitochondrial dysfunction and has revealed important roles of mitochondria-related events in EBI and DCI after SAH, including mitochondria-induced oxidative stress, mitochondria-dependent apoptosis, mitophagy activation, mitochondrial biogenesis, mitochondria-related inflammation, and changes in mitochondrial dynamics. Therapies targeting mitochondria in the setting of SAH have shown potential in animal experiments and provide a new direction for research into future SAH treatments. However, the efficacy and safety of this treatment strategy for SAH have not been verified in clinical trials. In addition, it must be recognized that mitochondrial dysfunction is only one component of the multifactorial brain injury mechanisms of SAH. Moreover, the exact role of mitochondria in SAH and their crosstalk with other organelles remains unclear. Further exploration is necessary to broaden our knowledge of the role that mitochondria play in the pathogenesis of SAH and to facilitate the development of novel therapeutic strategies for SAH. The near and future direction in this field would be very helpful for readers and researchers.

LIST OF ABBREVIATIONS

SAH = Subarachnoid hemorrhage

DCI	=	Delayed cerebral ischemia
CVS	=	Cerebral vasospasm
EBI	=	Early brain injury
BBB	=	Blood-brain barrier
ΔΨm	=	Mitochondrial membrane potential
ROS	=	Reactive oxygen species
NMDAR	=	N-methyl-d-aspartate receptor
mPTP	=	Mitochondrial permeability transition pore
Keap1	=	Kelch-like ECH-associating protein 1
Nrf2	=	Nuclear factor erythroid 2 related factor 2
ARE	=	Antioxidant response element
JAK2	=	Janus kinase 2
STAT3	=	Signal transducers and activators of transcription 3
CNS	=	Central nervous system
mtDNA	=	Mitochondrial deoxyribonucleic acid
DAMP	=	Damage-associated molecular pattern
CSF	=	Cerebrospinal fluid
HO-1	=	Heme oxygenase-1
NADH	=	Nicotinamide adenine dinucleotide
DNA	=	Deoxyribonucleic acid
MST1	=	Mammalian STE20-like kinase 1
AIF	=	Apoptosis-inducing factor
BCL	=	B cell lymphoma
MCL1	=	Myeloid cell leukemia-1
BAK	=	BCL-2-antagonist/killer
BAX	=	BCL-2-associated protein x
BOK	=	BCL-2-related ovarian killer
OMM	=	Outer mitochondrial membrane
NLRP3	=	NACHT, LRR, and PYD domains-containing protein 3
IL	=	Interleukin
mtROS	=	Mitochondrial reactive oxygen species
Drp1	=	Dynamin-related protein 1
GTPase	=	Guanosine triphosphate enzyme
GTP	=	Guanosine triphosphate
Mfn	=	Mitofusin
Opa1	=	Optic atrophy protein 1
PINK1	=	Phosphatase-and-tensin-homolog-induced putative kinase 1
LC3II	=	Light chain 3 II
ER	=	Endoplasmic reticulum
BNIP3	=	B cell lymphoma 2/adenovirus E1B 19 kDa protein-interacting protein 3
NIX	=	NIP3-like protein X
3-MA	=	3-methyladenine
PHB2	=	Prohibitin 2
aSAH	=	Aneurysmal subarachnoid hemorrhage
GMP	=	Guanosine monophosphate
AMP	=	Adenosine monophosphate
cGAS	=	Cyclic GMP-AMP synthase
STING	=	Stimulator of interferon gene
mTOR	=	Mammalian target of rapamycin
SIRT	=	Sirtuin
ATG	=	Autophagy-related gene
VDAC	=	Voltage-dependent anion channel
$[Ca^{2+}]_m$	=	Mitochondrial free calcium ion
MCU	=	Mitochondrial calcium uniporter
EGCG	=	(-)-Epigallocatechin-3-gallate
$[Ca^{2+}]_i$	=	Cytosolic free calcium ion
PGC-1α	=	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
AMPK	=	AMP-activated protein kinase
UCP2	=	Uncoupling protein 2

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This study was supported by the National Natural Science Foundation of China (81971107, to SC) and the Basic Public Welfare Research Project of Zhejiang Province (LGF19H090014, to XMH).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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