Abstract
Subarachnoid hemorrhage (SAH) is a dominant cause of death and disability worldwide. A sharp increase in intracranial pressure after SAH leads to a reduction in cerebral perfusion and insufficient blood supply for neurons, which subsequently promotes a series of pathophysiological responses, leading to neuronal death. Many previous experimental studies have reported that excitotoxicity, mitochondrial death pathways, the release of free radicals, protein misfolding, apoptosis, necrosis, autophagy, and inflammation are involved solely or in combination in this disorder. Among them, irreversible neuronal apoptosis plays a key role in both short- and long-term prognoses after SAH. Neuronal apoptosis occurs through multiple pathways including extrinsic, mitochondrial, endoplasmic reticulum, p53 and oxidative stress. Meanwhile, a large number of blood contents enter the subarachnoid space after SAH, and the secondary metabolites, including oxygenated hemoglobin and heme, further aggravate the destruction of the blood-brain barrier and vasogenic and cytotoxic brain edema, causing early brain injury and delayed cerebral ischemia, and ultimately increasing neuronal apoptosis. Even there is no clear and effective therapeutic strategy for SAH thus far, but by understanding apoptosis, we might excavate new ideas and approaches, as targeting the upstream and downstream molecules of apoptosis-related pathways shows promise in the treatment of SAH. In this review, we summarize the existing evidence on molecules and related drugs or molecules involved in the apoptotic pathway after SAH, which provides a possible target or new strategy for the treatment of SAH.

Key Words: blood-brain barrier; mechanism; mediators; neuronal apoptosis; pathways; subarachnoid hemorrhage; targets; treatment

Introduction
Subarachnoid hemorrhage (SAH) is a type of hemorrhagic stroke that comprises 3% of all stroke types, 85% of which are caused by the rupture of intracranial aneurysms (IAs) (Go et al., 2014; Macdonald and Schweizer, 2017). SAH caused by ruptured IAs remarkably increases the chance of mortality and morbidity by 50% (32–67%) despite advances in management (Huang and van Gelder, 2002; van Gijn et al., 2007). Stroke has many genetic and environmental risk factors. A study of single-gene diseases has shown that common variations in approximately 35 loci are strongly associated with the risk of hemorrhagic stroke (Dichgans et al., 2019). In addition, various health-related and environmental factors, such as high blood pressure, diabetes, high cholesterol, high body mass index, smoking, and a history of hemorrhagic stroke, all increase the risk of hemorrhagic stroke (Donnan et al., 2008). The main causes of death are associated with the sharp increase in intracranial pressure due to initial hemorrhage and cerebral edema, which eventually lead to cerebral hernia. Several studies have shown that 20% of the fatality caused by SAH occurs because no medical attention is given, 30% of it occurs within 24 hours of onset, and 40–60% of the patients with early brain injury (EBI) caused by initial bleeding and delayed cerebral ischemia (DCI) resulting from cerebral vasospasm constitute the cause of subsequent mortality within a month, although emergency surgery and medication with drugs such as mannitol, Nimotop, and neurothin were performed after SAH (Hasegawa et al., 2011; Korja and Kaprio, 2016; Grasso et al., 2017). For survivors, long-term care is required in one-third of patients, and some recovered patients still suffer from neurologic and/or cognitive deficits (van Dijk et al., 2016). Although there are marked improvements in microsurgical clipping and endovascular coiling treatments, the mortality of SAH is not greatly reduced because the residual blood in the subarachnoid space continues to stimulate and damage the brain cells. Therefore, the pathophysiological mechanism of SAH has been the focus of research in recent years. Previous experimental studies have discovered a series of pathological mechanisms following SAH, such as inflammation, apoptosis of nerve cells and vascular endothelial cells, and oxidative stress (OS) (Luce-Wold et al., 2016; Mo et al., 2019). Many post-SAH responses, such as OS and inflammation, eventually lead to the death of neurons, vascular endothelial cells, and gial cells (Sekerga et al., 2018). Recent experimental studies have shown that apoptosis is closely associated with cerebral injury after experimental SAH (Wu et al., 2020b). Apoptosis refers to the orderly death of cells under the autonomous control of genes. It is controlled by multiple genes, such as the bcl-2 family, Caspase family, and oncogenes, such as C-myc and tumor suppressor gene p53 (Fleisher, 1997). Several molecules and/or pathways, such as the phosphatidylinositol-3-kinase/AKT signaling pathway (Endo et al., 2006), Mas/PKA/CREB/UCP-2 pathway (Mo et al., 2019) and p53 (Ling et al., 2019), are activated after SAH, which may cause blood-brain barrier (BBB) dysfunction and neuronal apoptosis. Some anti-apoptotic proteins or drugs, such as Mas, AVE 0991, melatonin, and heat shock protein 22, can greatly improve neurological function after SAH (Bader et al., 2014; Shi et al., 2018; Mo et al., 2019; Fan et al., 2021). In this review, we aimed to understand the mechanism and relevant mediators related to neuronal apoptosis and potential therapeutic targets after SAH.

Retrieval Strategy
Literature review was electronically performed using PubMed database. The following combinations of key words were used to initially select the articles to be evaluated: apoptosis and subarachnoid hemorrhage, neuronal apoptosis and subarachnoid hemorrhage, cell death and subarachnoid hemorrhage, apoptosis and stroke, neuronal apoptosis and stroke, cell death and stroke, treatment and subarachnoid hemorrhage, targets and subarachnoid hemorrhage, stem cells and subarachnoid hemorrhage, stem cells and stroke. Most of the selected studies (80% of all references) were published from 2011 to 2021.

Apoptosis Pathways
Apoptosis can occur through three different pathways, namely, the extrinsic pathway, intrinsic pathway, and endoplasmic reticulum (ER) stress-induced pathway, depending on the site of apoptosis. In addition, other molecular mechanisms such as p53 and oxidative stress pathways are also associated with apoptosis after SAH (Hasegawa et al., 2011).
Extrinsic mechanism

The external apoptosis pathway plays an important role in promoting the regulation of cell apoptosis by death receptors on the cell surface without passing through the mitochondrial and stress ER-induced pathways. Death receptors, such as tumor necrosis factor (TNF) receptor, P2X7R, death receptor 4/5, and Fas, mediate the apoptotic pathway in hemorrhagic stroke by activating caspase-8 or -10 (Martin-Villalba et al., 1999; Rosenbaum et al., 2000). Once activated, caspase-8 can activate the downstream effects of caspases to produce tBid through direct proteolytic cleavage or indirectly through the cleavage of the BH3-only protein Bid, which is translocated to mitochondria and induces Bax activation and mitochondrial outer membrane permeability (Zhao et al., 2018a). TNF-α and Fas ligands can induce partial neuronal apoptosis during the inflammatory process. The apoptotic pathway of motor neurons is Fas-dependent, involving p38 and NO, resulting in classic caspase-dependent apoptosis (Hiaase et al., 2008). For example, the stimulation of P2X7R can activate caspase-1, which promotes the maturation and release of IL-1β and increases IL-1β concentrations, thus triggering the induction of TNF, which also has pro-apoptotic effects causing the expansion of cell apoptosis (Lee et al., 2016). Some evidence suggests that extrinsic apoptosis may play a causal role in neuronal death after stroke (Li et al., 2006b), but these models lack clear evidence that caspase-8 leads to death because caspase-8 deficiency (and FADD) is fatal to embryonic mice. However, Krajeswka et al. (2011) solved this problem by using mice that specifically lacked caspase-8 expression in neuronal cell types and showed that neuron-specific caspase-8 loss makes neurons resistant to in vitro TNF-receptor connection-induced apoptosis and leads to increased neuronal survival. Many previous experimental studies have shown that TNF-α and IL-1β expression is upregulated, and neuronal damage and apoptosis occur to varying degrees after SAH (Sekerdag et al., 2018; Guo et al., 2019; Lai and Du, 2019). Therefore, the extracellular apoptotic pathway plays an important role in neuronal apoptosis after SAH (Figure 1).

**Figure 1 | Extrinsic apoptosis pathway after SAH.**

Death receptors on the cell membrane, such as P2X7R, TNFR, DR4/DR5 and FASR, can be stimulated by apoptotic signals to activate FADD, and then cause caspase-dependent apoptosis cascade reaction. AIF: Apoptosis inducing factor; DR4/DR5: death receptor 4/5 death receptor 5; FADD: Fas-associated protein with a novel death domain; SAH: subarachnoid hemorrhage; TNF: tumor necrosis factor.

Mitochondrial (intrinsic) pathway

The mitochondrial pathway (also known as the intrinsic pathway) is mainly regulated by B-cell lymphoma-2 (Bcl-2) family proteins, which contain proapoptotic (e.g., Bax, Bak, Bad, Bid, Bim, and Noxa) and antiapoptotic (e.g., Bcl-2 and Bcl-xL) proteins (D’Orsi et al., 2017). Under normal circumstances, Bcl-2 and Bcl-xL protect the mitochondrial outer membrane, whereas they are oligomerized and mediate mitochondrial outer membrane permeabilization, leading to the release of pro-apoptotic factors, such as cytochrome C (Lovell et al., 2008). In addition, Bax and BH3 proteins increase in expression and then combine with Bcl-2 and Bcl-xL to release Bax/Bak. Free Bax and Bak form oligomers and are embedded in the outer membrane of mitochondria (Dlugosz et al., 2006; Youle and Strasser, 2008). Once the outer mitochondrial membrane permeability increases, mitochondrial proteins, such as cytochrome c, are released into the cytoplasm. Cytochrome c can interact with apoptotic protease activating factor-1 (Apaf1) to form apoptosomes and cause caspase-9 activation. Caspase-9, as an initiator of the cytochrome-dependent cascade, activates caspase-3 and causes DNA damage (Hasegawa et al., 2011). In addition, proteins such as AIF, Smac, and Endo G are also associated with mitochondrial apoptosis. During apoptosis, these proteins are also released from the mitochondrial membrane space into the cytosol. Smac OMI can bind to inhibitor of apoptosis proteins (IAPs) and resist the inhibition of IAPs on caspase 3 and caspase 9, which is a caspase-dependent protein. AIF and EndoG can translocate to the nucleus to cause chromatin condensation and large-scale DNA fragmentation, which are non-caspase-dependent events (Xiong et al., 2014; Figure 2). Cleaved caspase-3 levels have been reported to be upregulated in the hippocampus and cortex after SAH (Zhang et al., 2019b). Mitochondrial dysfunction is a common cause of neuronal apoptosis in SAH (Wang et al., 2018), and it is considered to be a crucial therapeutic target for EBI after SAH (Mo et al., 2019). The activation of mitochondrial aldehyde dehydrogenase 2 (ALDH2) has been reported to markedly preserve mitochondrial function via PKCe phosphorylation, which has been shown to provide marked protection against apoptosis in the setting of cardiac and cerebral ischemia/reperfusion injury (Aldi et al., 2014; Wang et al., 2017b). TGR5 combines with INT-777 to attenuate neuronal apoptosis via the CAMP/ PKCα/ALDH2 pathway after SAH (Zuo et al., 2019). The c-Jun N-terminal kinase signaling pathway may be independent of the p38 and NF-κB signaling pathways and is upregulated to promote apoptosis in the SAH model (Ling et al., 2019). Docosahexaenoic acid alleviates apoptosis following SAH by improving mitochondrial dynamics in EBI (Zhang et al., 2018).

Endoplasmic reticulum pathway

The endoplasmic reticulum (ER) is the site in which secreted proteins and membrane proteins are synthesized and folded. Properly folded and modified proteins can be transported to the Golgi apparatus for further processing. In addition, the ER also stores Ca²⁺ and regulates Ca²⁺ metabolism. The imbalance of Ca²⁺ ions in the endoplasmic reticulum and the increase in misfolded or unfolded proteins will cause endoplasmic reticulum stress (ERS) (Zeeshan et al., 2016). A moderate ERS response can reduce protein synthesis, ensure that proteins are folded correctly, and maintain intracellular Ca²⁺ homeostasis, but an excessive stress response can trigger apoptosis signals and promote apoptosis. The unfolded protein response (UPR) is an important self-protection mechanism of cells against ERS (Sun et al., 2017). There are three ER transmembrane proteins (Irel, ATF6, and PERK) in mammalian cells, all of which play a role in the aggregation of the UPR in the cavity (Ghemrawi and Khair, 2020). They regulate the quality and quantity of basic leucine zippers and produce different responses to different UPRs through interaction. If this response does not sufficiently reduce ERS, apoptosis may occur (Oslowski and Uran, 2013). The UPR response is a cellular protective response. However, whether this response can restore ER homeostasis depends on the intensity and duration of the stimulus. If the stimulation is too strong or lasts too long and these responses are not enough to restore and maintain ER homeostasis, programmed death will be initiated, leading to apoptosis...
p53
p53, as a tumor suppressor gene, is also the most important factor in generating the apoptosis process in response to DNA damage, hypoxia, and severe DNA damage (Calimisi and Mattson, 2005; Chai et al., 2022). Under normal conditions, p53 levels are low and even undetectable. However, stress signals such as DNA damage and hypoxia can stabilize the p53 protein and induce cellular p53 levels to increase by post-translational modifications such as phosphorylation, ubiquitination, and acetylation (Zhou et al., 2005). Activation of p53 can cause a variety of responses, including cell cycle arrest or apoptosis (Wang et al., 2015b). p53 is one of the crucial factors that lead to neuronal cell death after SAH. Our experimental studies have confirmed that the expression levels of p53 increased by 24–48 hours and 72 hours after SAH, and an inhibitor of p53 decreased brain injury and neuronal cell death (Gao et al., 2009). The Bcl-2 family is well known to participate in cell apoptosis and is mediated by p53 on the mitochondrial, leading to apoptosis. Moreover, the expression of p53 was markedly increased in basilar artery endothelial cells of rats post-SAH, and apoptosis was detected (Li et al., 2016b). In addition, it was also reported that pifithrin-a, a p53 inhibitor, suppresses p53 protein expression, decreases microRNA-22 expression and inhibits Bax protein expression in a SAH mouse model (Yu et al., 2018a). p53 mediates apoptosis mainly by activating mitochondrial and death receptor-induced apoptotic pathways, which induce caspase signaling and apoptosis (Yu and Zhang, 2005).

Apoptosis in Delayed Cerebral Ischemia and Cerebral Vasospasm
Once past the EBI stage of SAH, prognosis often depends on the occurrence of DCI, which is detected in approximately 40% of patients by cerebral perfusion imaging (El Amki et al., 2018). Finally, the prognosis of patients with SAH is

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Figure 3 | ER apoptotic pathway in neuronal apoptosis after subarachnoid hemorrhage.
ER stress induced by subarachnoid hemorrhage activates three transmembrane proteins on the ER, which induces apoptosis through PERK/eIF2α/CHOP/iRE1α and ATF6-CHOP, respectively. Meanwhile, Ca2+ imbalance and homeostasis of the ER is unbalanced, and a large amount of Ca2+ enters the cells and mitochondria. It affects the activity of mitochondria and Bcl-2 family proteins, leading to apoptosis. It also activates the caspase cascade and affects apoptosis (Burton et al., 2017; Marchi et al., 2018, Figure 3). In recent years, increasing numbers of experimental studies have supported the view that ERS plays an important role in neuronal apoptosis after SAH (Li et al., 2016a; Zhao et al., 2017). SAH activates ERS in a variety of ways to induce apoptosis. Upregulated expression of caspase-12, a proteolytic enzyme specific to the ER, was observed in the ER after experimental SAH, and its activation can be considered a marker of neuronal apoptosis mediated by ERS (Datta et al., 2018). The downstream molecule of ASK1, JNK, is a member of the signal transduction protein family, which regulates the expression of ant-apoptotic genes by activating MAPKS, JNKs, and p38MAPKS, thereby inducing apoptosis (Li et al., 2006a). CHOP can mediate apoptosis by up-regulating the sensitivity of OS cells and downstreaming the secretion of the anti-apoptotic B-cell lymphoma-2 (Bcl-2) protein (Hetz, 2013; Qi et al., 2018). ERS can lead to calcium disorder in the ER, and inhibition of ER stress can restore the homeostasis of the ER (Han et al., 2019). ER-mediated apoptosis can exist in neurons and endothelial cells, resulting in the destruction of the BBB and irreversible apoptosis of neurons. A recent study has reported that the morphology of the coarser ER changed within 6 hours after SAH, the swelling of cortical neurons was the most severe at 24 hours and subsequently subsided within 24–48 hours (Tian et al., 2020). There was no marked difference between the SAH and normal groups at 72 hours, which was consistent with the expression of stress-related apoptotic protein cleavage of ER, caspase-12 ASK1, p-JNK in a rat model (Tian et al., 2020). PERK/eIF2α/ATF6/CHOP signaling is activated after SAH and promotes apoptosis by activating the ER stress-related apoptotic signaling pathway, reducing ER stress-induced apoptosis and SAH-associated cerebrovascular dysfunction (Chen et al., 2020b). The persistence of the UPR indicated that ERS was not relieved, and homeostasis was not restored. The severity and duration of ERS are related to the survival of ER neurons (Hetz and Saxena, 2017). Tauroursodeoxycholic acid inhibits the PERK/eIF2α/ATF4/CHOP signaling pathway and reduces ERS-mediated apoptosis, thereby improving SAH-associated cerebrovascular dysfunction (Deng et al., 2021). Oxidative stress OS refers to a state of imbalance between oxidation and antioxidation in the body. The balance tilts toward oxidation, resulting in increased secretion of protease and the production of a large number of oxidative intermediates (Deng et al., 2021). OS is a type of negative effect produced by free radicals in the body that can induce cell apoptosis and has an extensive association with apoptosis (Mo et al., 2019). It has been shown that hemoglobin (Hb) activates the caspase pathway and induces the apoptosis of cultured cortical neurons and microvascular endothelial cells (Katsu et al., 2010). After SAH, the central nervous system is exposed to high levels of Hb and Hb degradation products released in the subarachnoid space. The pathological process involves excessive ROS and RNS and promotes cerebral vasospasm, cerebral stenosis, and DCI (Vergouwen et al., 2010). In addition, a number of harmful events occur in SAH survivors, including altered ion homeostasis, excitotoxicity, disrupted mitochondrial integrity, inflammation, apoptosis, autophagy, and the activation of NOS pathways (Fan et al., 2017; Han et al., 2017a; Shi et al., 2017c; Zhang et al., 2017).
usually unfavorable, with mortality estimated in clinical investigation ranging from 20% to 60% (Bogason et al., 2014) and neuropsychological disorders observed in 50–60% of patients who survived (Mayer et al., 2002). Recent clinical studies have confirmed that cerebral vasospasm is one of the factors contributing to DCS (Francouer et al., 2022; Labak et al., 2022). It may occur 3–14 days after SAH and is visible by computed tomography angiography in up to 70% of patients (Yuksel et al., 2012). In SAH animal experiments, by reducing basilar artery apertures by 72% by western blotting (Cahill et al., 2006). In addition, microcirculation, spasm, microthrombogenesis, extensive cortical depolarization, and brain dysfunction are also considered to be important reasons for the development of DCS (Geraghty and Testai, 2017). Many pathological processes have been suggested as possible mechanisms for delayed cerebral vasospasm after SAH, including endothelial injury, smooth muscle contraction, vascular reactivity changes, and inflammation and/or immune responses to vascular wall. Apoptosis exists in vascular tissues with different degrees of necrosis after SAH, which is involved in the proliferation of spasmic arterial smooth muscle cells (Tsai et al., 2020). The cascade of apoptosis may be the cause of vasospasm (El Amki et al., 2018). Large vessel vasospasm leads to cerebral ischemia after SAH. Blood cell contents are released into the subarachnoid space, inducing the production of a large number of inflammatory factors, leading to neuroinflammation and loss of BBB function and causing apoptosis of neurons and endothelial cells. Persistent and irreversible damage ultimately leads to DCS and a poor prognosis. Apoptosis is considered to be one of the most critical factors that may be connected with delayed neurological deterioration and poor long-term prognosis (Chen et al., 2014).

Blood-Brain Barrier Dysfunction and Cerebral Edema Facilitate Apoptosis

The BBB is made up of endothelial cells, pericytes, basement membranes, and astrocyte end feet. The properties of the BBB are largely manifested with blood cells, but are induced and maintained by critical interactions with mural cells, immune cells, glial cells, and neural cells, which interact in the neurovascular unit (Daneman and Prat, 2015). The BBB, with low vascular permeability, limits the entry of potentially neurotoxic plasma components, blood cells, and pathogens into the central nervous system (Wegiel et al., 2011). Many factors are unique to VCECs forming the BBB, including endothelial tight junctions and adherens junction proteins, bulk-flow transcytosis, pinocytosis, nonselective fenestrae, and the suppression of leukocyte adhesion molecules (Obermeier et al., 2013). Many diseases, such as hemorrhagic shock, ischemic stroke, cause BBB dysfunction. It has been reported that BBB disruption occurs as early as 10 minutes after ictus and can persist up to 7 days (Tsai and Macdonald, 2014). In addition, a great amount of blood flowing into the subarachnoid space leads to acute intracranial hypertension, and subsequent release of blood content promotes apoptosis of brain cells (neurons, microglia, astrocytes, endothelial cells, and pericytes; Figure 4).

Vasogenic and cytotoxic edema lead to cerebral edema

Early cytotoxicity and vasogenic edema occurred within 72 hours after SAH (Weimer et al., 2017). To confirm the presence of edema after SAH injury, magnetic resonance imaging (MRI), particularly T2WI imaging (T2WI), was used to provide visual information on BBB rupture and tissue edema (Jadhav et al., 2008). Generally, the T2 relaxation time in T2WI sequences is considered to be a valuable parameter reflecting hydrodynamics and is sensitive to water binding, and the T2 time is longer in the SAH group than in the normal group, suggesting the presence of vasogenic edema. Further Evans blue tests and IgG staining also confirmed the destruction of BBB integrity. Therefore, we can conclude that the development of vasogenic edema increases BBB destruction and the subsequent accumulation of cerebral edema. Cytotoxic edema is another type of brain edema addition to vasogenic edema. Diffusion weighted imaging and apparent diffusion coefficient imaging are more sensitive and noninvasive tools for detecting intracerebral cytotoxic edema (Jadhav et al., 2008). The pathogenesis of cytotoxic edema is mainly related to the decline in sodium pump function. After SAH, acute hypoxia and anoxia may reduce the production of ATP, resulting in decreased activity of the sodium pump, which depends on ATP to provide energy, so Na+ cannot be transported actively to the outside of the neuron. This causes the cell to restore the balance, resulting in excessive Na+ and water accumulation in brain cells (Bano et al., 2005). In addition, the imbalance of Ca2+ homeostasis is also an important reason for brain edema. Under normal conditions, the extracellular concentration of Ca2+ is much lower than the intracellular Ca2+ concentration, and such a large concentration difference is completely maintained by the Ca2+ pump. Cerebral edema after SAH causes ischemia and hypoxia, the Ca2+ pump is imbalanced, and Ca2+ enters the cells, further aggravating cerebral edema (Azad et al., 2016; Boyaci et al., 2019).

Treatment

Novel molecular and cellular treatment strategies

SAH in 85% cases is caused by ruptured intracranial aneurysms (Macdonald and Mayer, 2017). The treatment of SAH should first identify the cause of hemorrhage. If SAH is caused by ruptured IAs, the ruptured IAs should be treated first. Cerebral edema and cerebral vasospasm caused by SAH should be alleviated at the same time. If multiple causes exist in the long term, different approaches seek to minimize damage to neurons while maximizing the repair potential of the lost neurons (Yuksel et al., 2012). Because damaged neurons are difficult to regenerate, treatment is often insufficient to restore physiological functions and inhibit the development of late-stage complications. In recent years, therapies targeting potential receptors, signaling pathways, and miRNAs have received increasing scientific attention. The AKT signaling pathway has been widely reported to be involved in the pathophysiological mechanisms of SAH, and early evaluation of AKT contributes to the reduction of EBI and neuronal apoptosis after SAH (Hasegawa et al., 2011). For example, KPS4 can reduce neuronal apoptosis and oxidative stress after SAH and improve neurobehavioral deficits in rats.
Figure 1  Potential targets for drug therapy after SAH.

Several apoptosis pathways are activated after SAH, including extrinsic, mitochondrial, ER, p53 and ROS pathways. SAH can be treated with a variety of apoptosis inhibitors including death-receptor inhibitors, Fas ligand-related apoptosis pathway inhibitors, caspase-3 inhibitors, ROS inhibitors, p53 inhibitors, and Ca2+ antagonists. ER/KER: Endoplasmic reticulum/endoplasmic reticulum stress; ROS: reactive oxygen species; SAH: subarachnoid hemorrhage.

by activating the AKT signaling pathway (Huang et al., 2021). S-Lipoxygenase inhibitors attenuate neuronal apoptosis and inflammation through the AKT signaling pathway after SAH (Liu et al., 2021). C-Abl tyrosine kinase mediates neuronal apoptosis after SAH by activating the AKT/GSK-3β pathway (Yan et al., 2021). AKT activation (phosphorylation) can be activated by recombiant OX40. Silencing of tenasinc-C, FGF-2, and apelin-13 can markedly reduce neuronal apoptosis and neuroinflammation induced by SAH (Liu et al., 2019; Okada et al., 2019; Tong et al., 2020; Wu et al., 2020b). Caspase 3 inhibitors, such as liraglutide (Tu et al., 2021), calpeptin (Zhou and Cai, 2019), and methazolamide (Li et al., 2016c), can inhibit the expression of caspase-3, thereby reducing the cascade of apoptosis induced by caspase 3 and ultimately reducing neuronal apoptosis. Table 1 lists several potential targets for SAH recovery. Next to targeting apoptosis inhibitors, focus can be led on the antioxidant drugs. Nanomaterials loaded with antioxidant drugs are emerging in recent years. Astaxanthin, for example, is an antioxidant that has been hampered by its easy degradation and low bioavailability as a therapeutic agent for clinical advancement. The stability and solubility of astaxanthin are greatly increased by nanomaterial encapsulation. In vitro and in vivo studies have confirmed that it can inhibit neuronal apoptosis after SAH through an antioxidant effect (You et al., 2019; Cai et al., 2021). NLRP3 inflammasomes are involved in neuroinflammation and apoptosis after SAH (Wu et al., 2021). Regulation of NLRP3 inflammasome activation at the molecular level may contribute to development of potential new therapeutic approaches (Bai et al., 2021). The inflammasome inhibitor has revealed a neuroprotective effect. In addition, miRNAs, as endogenous noncoding short single-stranded RNAs that regulate gene expression at the post-transcriptional level, are also gradually becoming new molecular targets after SAH. While therapies targeting individual genes have not been successful due to complex overlapping pathways, miRNAs are particularly useful for their ability to simultaneously regulate multiple target genes. Mice overexpressing mir-132 were less likely to develop nervous system defects (Sekerdag et al., 2018). Lentiviral overexpression of mir-126 has a protective effect against ICH and exerts an antiapoptotic effect by downregulating caspase-3 levels (Kong et al., 2017). Moreover, mir-103-3p was significantly upregulated in experimental models of SAH. Mir-103-3p plays a neuroprotective role in reducing neuronal death by reducing cavelolin-1 (Xu et al., 2018b). Experimental models of SAH showed that overexpression of miR-126 can provide some protection against neuronal death, but apoptosis still occurred (Yuksei et al., 2012). This may be due to a series of complex reactions after SAH, including apoptosis, inflammation, oxidative stress, autophagy, and cognitive death (Castro et al., 2018; Sekerdag et al., 2018; Wu et al., 2021). The efficacy of a single inhibitor is limited, and research efforts are still needed. Moreover, most of the current researches are limited to preclinical studies, and the safety and reliability of stem cell therapy are not clear, especially the risk of tumor formation. Finally, detailed treatment strategies including the optimal timing window for treatment, stem cell types and numbers, delivery sites and pathways, need to be further explored.

Conclusion

In recent years, many pathological mechanisms have been proposed for brain injury after SAH. Apoptosis is a very important link, including damage to neural stem cells, which leads to destruction of the BBB and the occurrence of cerebral edema. The stimulation of blood contents and secondary cerebral ischemia increase the apoptosis of brain cells and aggravate the neurological deficit of patients with SAH. Fortunately, a number of anti-apoptosis drugs and stem cell therapies are being developed and have been shown to be effective in vivo and in vitro. However, many aspects need to be perfected before these approaches can be translated into clinical research. In this study, the pathological mechanism and treatment methods related to apoptosis after SAH are discussed, which will provide direction for clinical treatment and development of targeted drugs in the future.

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Conflicts of interest: The authors declare that they have no competing interests.

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| Methods | Drug/hormone/protein | Cell category | Pathways | Activity or inhibition | Attenuate | Reference |
|---------|---------------------|---------------|----------|-----------------------|-----------|-----------|
| EP      | M617                | Neuron        | ERK, GSK3β/β | I                     | NA        | Shi et al., 2021 |
| EP      | Kisspeptin-54       | Neuron        | GPR54/ARHBB/AKT | I | OS, NA | Huang et al., 2021 |
| EP      | 5-Lipoxigenase inhibition | Neuron | AKT       | I                     | NI, NA   | Liu et al., 2021 |
| EP      | c-Abi Tyrosine kinase | Neuron | LRP-1-dependent AKT/GSK3β | A | NA | Yan et al., 2021 |
| EP      | Heat shock protein 22 | Neuron | AMPK-PGC1α | I                     | OS, MA   | Fan et al., 2021 |
| EP      | TRAF3               | Neuron        | TAK1-dependent MAPKs and NF-κB | I | NA | Zhou et al., 2021 |
| EP      | Tauroursodeoxycholic acid | Neuron | TGR5/SIRT3 | I | NA | Wu et al., 2020b |
| EP      | Tim-3               | Neuron        | NFκB2/MG63 | A | NI, NA | Guo et al., 2020 |
| EP      | Liraglutide         | Neuron        | Bcl-2/Bax and cleaved caspase-3 | I | NI, NA | Tu et al., 2021 |
| EP      | Melatonin           | Neuron        | Oligodendrocyte | Bim and Bcl-2 | OA | Liu et al., 2020 |
| EP      | TT01001             | Neuron        | Mitoneet   | I                     | OS, NA   | Shi et al., 2020 |
| EP      | HLY78               | Neuron        | LRP6/GSK3β/β-catenin | I | NA | Luo et al., 2020 |
| EP      | Paeoniflorin        | Neuron        | NFκB2/HD-1 | I | NA, OS | Wang et al., 2020 |
| EP      | OxyHb               | Neuron        | miR-502-5p and PPAR/NF-κB | I | NA, OS | Chen et al., 2020a |
| EP      | Recombinant DK40    | Neuron        | GAXD4/DAX4L/P3X/AKT | I | NA | Wu et al., 2020b |
| EP      | Intracellular wnt-3a | Neuron        | Frz-1/β/AdoC/PPARα | I | NA | Ruan et al., 2020 |
| BSI     | SS31                | Neuron        | Mitochondrial | I | OS, NA | Shen et al., 2020 |
| EP      | Tauroursodeoxycholic acid | BBB | PERK/eif2α/ATF4/CHOP | I | ERSA | Chen et al., 2020b |
| EP      | Inhibition of HDAC4  | Neuron        | JNK/c-Jun-dependent | I | NA | Wu et al., 2019 |
| EP      | Exogenous brain-derived neurotrophic factor | Neuron | TrkB | I | NA | Chen et al., 2019 |
| EP      | TGR5 with mI-777    | Neuron, astrocytes, microglia | cAMP/Pkcs6/ALDH2 | I | OS, NA | Zuo et al., 2019 |
| EP      | Osteopontin         | Neuron        | Autophagy   | I | AA | Sun et al., 2019 |
| EP      | GPR30 with G1       | Neuron        | src/EGFR/ata3 | I | NA | Peng et al., 2019 |
| EP      | FGF-2               | Neuron        | FGR3/P3X/Akt | I | NA | Okada et al., 2019 |
| EP      | Apelin-13           | Neuron        | GLP1R1/P3X/Akt | A | NA | Liu et al., 2019 |
| BSI     | Sodium,hydrogen exchanger 1 | Neuron | CHP1 | A | NA | Song et al., 2019 |
| EP      | Annexin A7          | Neuron        | Glutamate release | I | NA | Lin et al., 2019 |
| BSI     | c-Jun N-terminal kinase inhibition | Neuron | p53 phosphorylation | I | PAA | Ling et al., 2019 |
| BSI     | Peroxiredoxin 1/2   | Neuron        | H2O2/OASk | I | NA | Lu et al., 2019 |
| EP      | Tat-mGluR1          | Neuron        | MglUs3a truncation | I | NA | Wang et al., 2019 |
| EP      | Calpeptin           | Neuron        | caspase 3   | I | NA | Zhou and Cal, 2019 |
| EP      | AVE 0991            | Neuron        | Max/Pka/Creb/Ucp2 | I | OS, NA | Mo et al., 2019 |
| EP      | Standardized ginkgo biloba extract Egb 761 | Neuron | Akt | I | NA | Yu et al., 2018b |
| EP      | Docosahexaenoic Acid | Neuron | Mitochondrial dynamics | I | OS, NA | Zhang et al., 2018 |
| EP      | Apelin-13           | Neuron        | ATF6/CHOP   | I | ERSA, BBB | Xu et al., 2018a |
| BSI     | Biochinn A          | Neuron        | Tlr3/Traf/MyD88/NF-κB | I | NA | Wang et al., 2017c |
| EP      | Thioredoxin-interacting protein | Neuron | Mitochondria-dependent pathway | I | NA | Liang et al., 2019 |
| EP      | Phosphodiesterase-4 inhibition | Neuron | Sirt1/Akt pathway | I | NA | Li et al., 2018 |
| EP      | Melatonin           | Neuron        | ROS-Mst1    | I | NA | Shi et al., 2018 |
| EP      | Neutroatin          | All cells     | ChOpi/caspace 3 | I | ERSA | Qi et al., 2018 |
| EP      | Deficiency of tenasin-C | Neuron | Tlr4/NFκB/IL-1β and IL-6 | I | NI, NA | Liu et al., 2018b |
| BSI     | Anti-TNF-α-alpha antibody modified to TNF-α | Neuron | Hypothalamus | I | NA | Ma et al., 2018 |
| EP      | Reservator          | All cells     | Akt/MtOAR pathway | I | NA | Guo et al., 2018 |
| BSI     | p53/microRNA-22     | HEB cell      | IL-6 (α) and caspase-3/8 (β) | I | NI, NA | Yu et al., 2018a |
| EP      | CHOP                | All cells     | ERS-Chop/C-EBPα hepcidin | I | NF | Zhao et al., 2018b |
| EP      | Hydrogen sulfide    | Neuron        | ROS-Mst1    | I | NA | Shi et al., 2017b |
| EP      | Reservator          | Neuron        | Sirt1/p35   | I | NA | Qian et al., 2017 |
| EP      | Mangeforin         | Neuron        | Nf2/HD-1    | I | NI | Wang et al., 2017c |
| BSI     | Mitogen-and stress-activated protein kinase | Neuron and astrocytes | caspase-3 | I | NI, NA | Ning et al., 2017 |
| BSI     | Mdv-1               | Neuron        | PERK/eif2α/CHOP | I | NI, BBB, ERSA | Fan et al., 2017 |
| EP      | ErbB4               | Neuron        | yap/peek3cB | A | NA | Yan et al., 2017 |
| EP      | PCMT1               | Neuron        | Pcm7/mtst1 | I | NA | Shi et al., 2017a |
| Hemolysate | RBHDFN            | Neuron        | Caspase-9, caspase-8, and caspase-3 | I | NA | Li et al., 2017 |
| EP      | Recombinant Netrin-1 | Neuron | Dcc/apply-1/akt | I | NA | Xie et al., 2017 |
| EP      | Apigenin            | Neuron        | Caspase-3   | I | OS, NA | Han et al., 2017b |
| BSI     | X-linked inhibitor of apoptosis | Neuron | Caspase-dependent apoptosis | I | BBB | Gao et al., 2017 |
| EP      | Naringin            | All cells     | Caspase-3 | I | OS, NA | Han et al., 2017a |
| EP      | Methazolamide       | Neuron        | Caspase-3 | I | NA | Li et al., 2016c |
| EP      | Valproic acid       | Neuron        | HsP70/MMps and HsP70/akt | I | BBB, BB | Ying et al., 2016 |
| EP      | CDG1410             | Neuron        | P-Akt/P-Jnk | I | NA, NN | Wu et al., 2016 |
| BSI     | Insulin             | Neuron        | Akt/nur-77 | I | Apoptosis | Dai et al., 2015 |
| BSI     | Metanin             | Neuron        | Nlrp3 | I | NI, NA | Dong et al., 2016 |
| BSI     | Phosphorylation of p53 | Neuron | Race/Radk | I | NA | Feng et al., 2016 |
| BSI     | Rhinacanabin-C      | Neuron        | Nlrp3 | I | NI, NA | Chang et al., 2016 |
| BSI     | A purine antimitabole | Neuron and glia | Tlr2, Tlr4 | I | NA, GA | Chang et al., 2015 |
| BSI     | Sennp3             | Neuron        | Caspase-3 | A | NA | Yang et al., 2015 |
| EP      | Minocycline         | Neuron        | Inflammation and p53 | I | NI, PAA | Li et al., 2016b |

A: Activity; AA: autophagy apoptosis; BBBD: blood-brain barrier disruption; BSI: blood single injection; CVS: cerebral vasospasm; EP: endovascular perfusion; ERS: endoplasmic reticulum stress; ERSA: ERS apoptosis; I: inhibition; MA: mitochondrial apoptosis; NA: neuro-apoptosis; NF: neuron ferroptosis; NF-κB: nuclear factor-κB; NI: neuro-inflammation; Nlrrp3: inflammasome-induce inflammation; Nlrp3: NOD-like receptor thermal protein domain associated protein 3; OA: oligodendroglial apoptosis; OS: oxidative stress; OxyHb: oxyhemoglobin; Paa: p53 associated apoptosis; RBHDFN: recombinant human brain-derived neurotrophic factor; ROS: reactive oxygen species; Tlr: Toll-like receptor.
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