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REVIEW ARTICLE

The Role of Caspase Family in Acute Brain Injury: The Potential Therapeutic Targets in the Future

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Abstract: The caspase family is commonly involved in the pathophysiology of acute brain injury (ABI) through complex apoptotic, pyroptotic, and inflammatory pathways. Current translational strategies for caspase modulation in ABI primarily focus on caspase inhibitors. Because there are no caspase-inhibiting drugs approved for clinical use on the market, the development of caspase inhibitors remains an attractive challenge for researchers and clinicians. Therefore, we conducted the present review with the aim of providing a comprehensive introduction of caspases in ABI. In this review, we summarized the available evidence and potential mechanisms regarding the biological function of caspases. We also reviewed the therapeutic effects of caspase inhibitors on ABI and its subsequent complications. However, various important issues remain unclear, prompting further verification of the efficacy and safety regarding clinical application of caspase inhibitors. We believe that our work will be helpful to further understand the critical role of the caspase family and will provide novel therapeutic potential for ABI treatment.

Keywords: Caspase inhibitor, acute brain injury, neuroprotection, neuroinflammation, apoptosis, stroke.

1. INTRODUCTION

Caspases are a family of evolutionarily conserved cysteine proteases that are centrally involved in programmed cell death and inflammatory responses. A wealth of pioneering research has unraveled the distinct roles of caspases in programmed cell death, inflammation, and cellular proliferation in recent years [1-3]. Until now, important advancements in the study of caspase include involvement in both extrinsic and intrinsic apoptotic pathways, participation in pyroptosis and inflammatory responses, and regulation of cellular proliferation and differentiation. The caspase family was also found to participate in tumorigenesis, immunity homeostasis, and aging [4]. Additionally, it has been demonstrated that the caspase pathway is an essential component of the pathophysiological processes of central nervous system (CNS) diseases, including neurodegenerative diseases, traumatic brain injury (TBI), and stroke [5].

Acute brain injury (ABI), including ischemic stroke, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and TBI, is a devastating category of disease and is considered to be a major global health concern with limited approaches for accurate diagnosis and effective therapy [6]. Trends in mortality and morbidity revealed that remains a tough challenge for modern medicine. Despite extensive research, therapeutic strategies remain limited in treating the progressive neurological deficits that occur after ABI [7]. Thus, it is imperative to find novel therapeutic targets to alleviate brain damage in patients with ABI.

Following ABI, a cascade of events amplifies the initial injury, which leads to a subsequent injury with related neuronal cell death. Secondary brain injury after ABI further leads to unfavorable long-term outcomes, although the initial injury may be well-managed. Multiple animal models and experimental studies have revealed the common pathophysiological mechanisms of secondary brain injury after ABI, including cerebral edema, excitotoxicity, oxidative stress, inflammatory responses, and programmed cell death [8]. Among them, caspase-mediated programmed cell death and inflammatory responses were found to be important components of secondary brain injury, which suggests a potential link between pathological molecular mechanisms and prospective targets for clinical therapy. Accumulating evidence has shown that the caspase family plays a controversial and

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multifaceted role in the process of ABI. While several clinical trials exploring the use of caspase inhibitors have been conducted in a variety of disease models, such as neurodegenerative diseases and liver diseases, they are rarely tested in ABI [9]. Thus, a recognition of the roles of caspases in ABI, as well as the effect of caspase modulators, may provide us with a novel therapeutic option for ABI treatment. Considering the interconnections between the caspase pathway and the mechanisms of programmed cell death and inflammation in AB.

A literature review on ABI and caspase was performed using PubMed. The following search terms were used: acute brain injury, subarachnoid hemorrhage, traumatic brain injury, stroke, ischemic stroke, intracerebral hemorrhage, caspase, and caspase inhibitor. We evaluated studies in English language that investigated interventions targeting caspase in ABI. The common process of the caspase activation and therapeutic effects of caspase inhibitor for ABI were summarized in this review.

2. FOCUSED OVERVIEW OF CASPASE FAMILY

2.1. Molecular Structure and Activation Mechanism

Caspases consist of an amino-terminal domain sequentially followed by catalytic subunit, which together comprise the protease domain [1]. The size and composition determine the requirement of cleavage for caspase activation. The amino-terminal regions contain a caspase recruitment domain (CARD) in caspase-1, -2, -4, -5, -9, and -11, or death effector domain (DED) in caspase -8 and -10. Conversely, executioner caspases (-3, -6, and -7) lack amino-terminal pro-domains. Therefore, their activation requires cleavage by initiator caspases (-8, -9, and -10) [10]. Besides, each caspase owns an optimal substrate motif in the catalytic site for specific cleavage [11].

Caspases with long pro-domains (caspase-1, -2, -8, -9, and -11) containing CARD or DED sequences are present as zymogen monomers. When the dimerization was formed, structural changes in the longer inter-subunit linker permitted the exposure of the catalytic site, and the caspases were then activated. Following induced dimerization, initiator caspases may auto-cleave, but this does not result in direct activation. Conversely, caspases with short pro-domains exist as inactive zymogen dimers. The absolute requirement for the activation of these caspases is proteolytic cleavage within a linker [1].

2.2. Functional Classification

According to the functional classification, caspases can be divided into two major subgroups: apoptotic (eliciting cell death) and inflammatory caspases. The apoptotic caspases can be further sub-categorized as an initiator (-8, -9, and -10) or executioner caspases (-3, -6, and -7) according to their order in execution of apoptosis [12]. Initiator caspases act as proteolytic signal amplifiers to activate executioner caspases, which proteolytically cleave various proteins at their target domain to facilitate apoptosis. Caspase-1, -4, -5, -11, and -12 are classified as inflammatory caspases. Each shares a CARD-domain at the amino-terminal and is functionally distinct from apoptotic caspases [13, 14]. Structurally, caspase-2 and -12 share domain architecture with inflammatory caspases. Caspase-2 functions are reportedly cell-cycle related, whereas caspase-12 remains undefined. Moreover, caspase-14 is not categorized as an inflammatory or apoptotic caspase, but it is known to be linked to cell differentiation and warrants further investigation [15, 16].

2.3. Caspase-mediated Apoptosis

Apoptosis is an intrinsic homeostatic and non-lytic process of regulated cell death, which is evolved to dismantle cellular components and remove old and injured cells [10]. Caspases are key hydrolyzed cellular proteins in this complex cascade and are responsible for the characteristic morphological changes, including DNA degradation, cell shrinkage, membrane blebbing, and release of apoptotic bodies. There are two typical apoptotic pathways, intrinsic and extrinsic, both of which execute apoptosis via caspase activation [17].

The extrinsic pathway, also known as the death receptor pathway of apoptosis, is triggered by the activation of caspase-8 through the combination of death ligands and death receptors (DRs) in the target cell membrane [18]. DRs are members of the TNF (tumor necrosis factor) superfamily, whose binding with death ligands results in the recruitment of monomeric procaspase-8 through its death effector domain (DED) to form the death-inducing signaling complex (DISC), where pro-caspase-8 self-catalyzed into active caspase-8 [18-20]. Active caspase-8 activates the apoptotic pathway by cleaving pro-caspase-3 and pro-caspase-7 [21]. Currently known death receptor-ligands primarily include Fas-FasL, TNFR1-TNF, TRAILR1-TRAIL, and TRAILR2-TRAIL [18]. Fas-FasL-mediated apoptosis is the most commonly described. Fas undergoes trimerization and activation after binding to FasL, resulting in the recruitment of the downstream adaptor, Fas-associated death domain (FADD), which then binds to and activates caspase-8 [19]. In TNFR1-TNF-mediated apoptosis, several molecules are required to form the complex to activate caspase-8, including receptor-interacting serine/threonine protein kinase 1 (RIPK1), cellular IAPs (cIAPs), TNFR-associated factor 2 (TRAF2), and TNFR1-associated death domain (TRADD) [19].

The intrinsic pathway, also known as the mitochondrial pathway of apoptosis, is caused by the release of soluble proteins from the mitochondrial intermembrane space induced by various factors of exogenous and endogenous stressors, such as DNA damage, endoplasmic reticulum (ER) stress, and reactive oxygen species (ROS) [18]. Mitochondrial permeability transition plays an important role in the intrinsic pathway, which can be regulated by the B cell lymphoma 2 (BCL-2) protein family [21, 22]. The members of the BCL-2 protein family can be classified as anti-apoptotic proteins, pro-apoptotic proteins, or pro-apoptotic BH3-only proteins. Under normal conditions, the pro-apoptotic protein, BAX, promotes mitochondrial outer membrane permeabilization (MOMP), whereas the anti-apoptotic protein, BCL-2, inhibits MOMP through preventing the activation of pro-apoptotic proteins and BH3-only proteins [21, 23]. MOMP leads to the release of cytochrome c (Cyt-C) into the cytosol. Binding of Cyt-C and nucleotide dATP to apoptotic peptidase activating factor 1 (APAF1) triggers the assembly of the apoptosome complex and facilitates the activation of caspase-9, eventually causing the cleavage of procaspase-3 and procaspase-7 [21, 22].

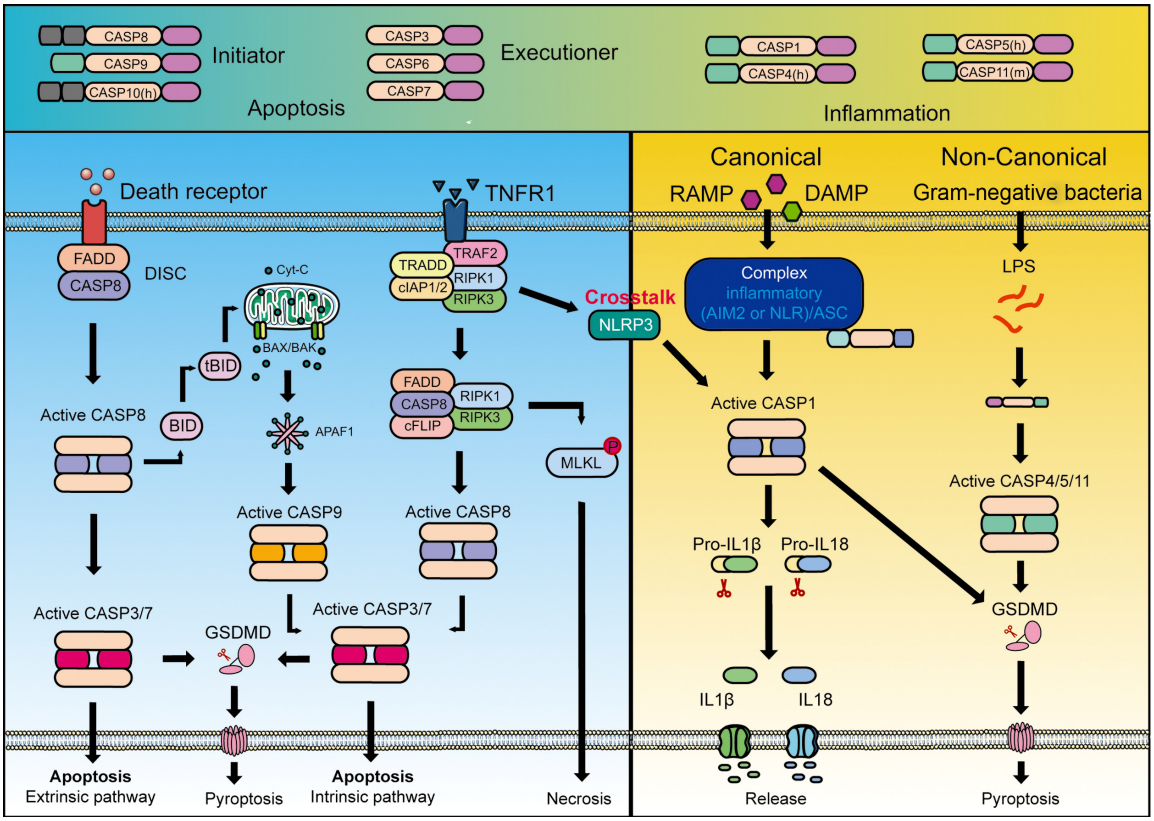

Fig. (1). Overview of apoptotic and inflammatory caspases pathways. Caspases trigger activation of a noninflammatory form of cell death. In extrinsic apoptosis, death receptor activation facilitates recruitment of FADD and caspase-8 to form the death-inducing signaling complex (DISC), which further processes executioner caspases (caspase-3 and -7) to engage apoptosis. In intrinsic apoptosis, intracellular stress stimuli induce the release of cytochrome c (Cyt-C) into the cytosol. The binding of cytochrome c to APAF1 triggers assembly of the apoptosome complex, which facilitates activation of caspase-9. This leads to activation of caspase-3 and -7 to execute apoptosis. Upon ligation of TNF ligand to its receptor (TNFR1), several molecules are required to form the cytoplasmic domain of the receptor (TRAF, TRADD, RIPK1, and IAP). The phosphorylation of mixed lineage kinase domain-like pseudokinase (MLKL) forms pores on the membrane and engages necroptosis. Additionally, apoptotic caspases have been found to be related to the NLRP3 inflammasome-mediated caspase-1 activation. Additionally, recognition of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) by their respective inflammasome-sensors leads to the assembly of a multiprotein complex termed the inflammasome. Consequently, caspase-1 was activated. Caspase-1 directly cleaves its substrates, gasdermin D and the pro-inflammatory cytokines. The N-terminal cleavage fragment of GSDMD forms pores in the cell membrane, thereby mediating pyroptosis. Additionally, the mature IL-1b and IL-18 were released, leading to neuroinflammation. Alternatively, LPS, coming from Gram-negative bacteria, activates the murine caspase-11 or its human orthologs caspases-4 and -5 to initiate gasdermin D-mediated pyroptosis. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

Besides, there exists an intimate communication between intrinsic and extrinsic apoptotic pathways through a proapoptotic BH3-only protein, BID. Activated caspase-8 cleaves BID to tBID, which acts on the proapoptotic BCL-2 antagonist or killer BAK/BAX molecular switch, and leads to MOMP and the release of Cyt-C [21, 22]. Furthermore, defective uptake of apoptotic debris may lead to secondary necrosis, in which rupture of the plasma membrane triggers the release of damage associated molecular patterns (DAMPs) that stimulate inflammatory and immunogenic reactions. The overview of the caspase-mediated apoptosis pathway is shown in Fig. (**1**).

2.4. Caspase-mediated Pyroptosis and Inflammatory Response

In contrast to the apoptotic caspases, inflammatory caspases play critical roles in the innate immune response and promotion of pyroptosis. Pyroptosis is a major form of programmed cell death, which induces the immune response to maintain organismal homeostasis during infection [24]. The human genome encodes inflammatory caspases, including caspase-1, -4, and -5, whereas the mice genome encodes caspases-11 and -12. These caspases can serve as direct sensors to pathogen-encoded molecules, such as lipopolysaccharide (LPS), and then undergo self-oligomerization and autoactivation [25, 26].

Inflammasomes are heterologous oligomeric complexes, which are assembled when pathogen-associated molecular patterns (PAMPs) or other danger signals are sensed by innate immune receptors [27]. There is a variety of inflammasome complexes, such as Nod-like receptor (NLR) family pyrin domain (PYD)-containing 1 (NLRP1), NLRP3, NLRP family CARD domain-containing 4 (NLRC4), absent in melanoma2 (AIM2), and pyrin inflammasome [28-30]. Through

homotypic protein-protein interactions, many inflammasomes recruit apoptosis-associated speck-like protein containing a CARD (ASC), which further recruits caspase-1 by exposing the CARD [31]. It is well-established that caspase-1 is activated in inflammasome, whereas caspase-4, -5, and -11 do not need such multiprotein platforms for activation [32]. Moreover, certain inflammasomes, such as NLRP1 and NLRC4, can directly engage caspase-1 through CARD-CARD interactions without ASC for activation [33]. Assembly of the inflammasome is a critical step to promote caspase-1 activation, as well as induce pyroptosis and the release of inflammatory cytokines.

IL-1β and IL-18 are downstream cytokines of the inflammatory caspase-mediated pathway, which present as immature pro-forms and require cleavage into active cytokines. These cytokines are mainly released through inflammatory caspase-mediated membrane pores and lytic cell death [34, 35]. Thus, caspase-1 is identified as an initial and crucial factor for the maturation and secretion of IL-1β and IL-18 [36]. The overview of the caspase-mediated pyroptosis pathway and inflammatory response is shown in Fig. (**1**).

2.5. Caspases in Cellular Proliferation

Extensive evidence indicates that some caspases influence cell proliferation and tissue regeneration. Caspase-8 plays an important role in T cell homeostasis and immunity. The deletion of caspase-8 in T cells can lead to a substantial reduction in peripheral T cells and an impaired T cell immune response but will promote the development of normal thymocytes [37]. In mice with hepatocyte-specific deletion of caspase-8, the ability to regenerate the liver was significantly enhanced [38]. Caspase-6 was also found to positively regulate B cell proliferation and maintain lymphocyte homeostasis [39]. Additionally, caspase-7 was found to play an important role in osteogenesis. In caspase-7 knockout mice, the bone mineral density and bone volume in certain body parts were reduced [40]. In contrast, caspase-3 may exert opposite effects. An experimental study found that B cells lacking caspase-3 showed excessive proliferation both *in vivo* and *in vitro* [41]. This effect of caspase-3 is related to its cleavage of p21, a cyclin-dependent kinase inhibitor [42].

3. ROLE OF CASPASES IN THE PATHOPHYSIOLOGICAL MECHANISMS OF ABI

Clinical and preclinical studies have indicated that the caspase family is involved in the pathophysiology of many neurological disorders through complex apoptotic, pyroptotic, and inflammatory pathways [43]. Animal models of ABI, including TBI and stroke, have demonstrated caspase-mediated cell death and inflammation in CNS [44, 45]. Both TBI and stroke involve extrinsic and intrinsic pathways of cellular apoptosis, as well as caspase-1-mediated cellular pyrolysis and inflammation, although these mechanisms may vary depending on the type of ABI [43]. We will introduce the multiplex roles of caspases in the following sections.

3.1. Caspases and TBI

TBI refers to a range of brain lesions caused by an array of sharp or dull mechanical forces, including primary and secondary brain injury. In addition to the primary damage to tissues, blood vessels, and cells in CNS caused by mechanical external forces, some secondary molecular mechanisms, including neuroinflammation, excitotoxicity, oxidative damage, and cellular death, cause further brain damage and worsen the prognosis of TBI [46, 47]. Due to the important impact of secondary brain injury on the outcome, a deep understanding of its pathological mechanism is helpful to find a therapeutic target for TBI.

Caspase-mediated apoptosis plays an important role in secondary brain injury after TBI. Following TBI, caspases in both intrinsic and extrinsic apoptotic pathways, as well as an inhibitor of apoptosis (IAPs), are activated. The caspase-8, -9, and -3 were reportedly increased in superficial cortical areas adjacent to the impact site and in the thalamus as early as 1 hour after TBI in rats [48]. Besides, the increase of IAPs (XIAP, cIAP-1 and cIAP-2) was similarly found to be up-regulated with the activation of caspases [48]. The activity of caspases is regulated by the Bcl-2 protein family. The expression of Bcl-2 in the brain increased following TBI, which is related to reduced cell death with a more favorable outcome, while increased expression of BAX may promote cell death [49]. Additionally, apoptosis-related caspases have been shown to be effective biomarkers for predicting the prognosis of patients with TBI. One recent clinical study showed that high blood caspase-8 levels were significantly associated with the mortality of TBI patients [50]. Another study found the correlation between activated caspase-9 and poor neurologic outcome after TBI [51].

Assembly of inflammasome and activation of inflammatory caspases were also found in TBI. In a rat fluid-percussion injury model of TBI, formation of NLRP1 inflammasomes, maturation of caspase-1, and secretion of IL-1β were detected 4 hours after injury [52]. The role of the NLRP3 inflammasome in TBI has also been extensively studied. Some modulators may promote its activation, including NIMA-related kinase 7 (NEK7), β-catenin, and cathepsin [53]. The maturation and activation of caspase-1 lay the foundation for downstream cytolytic death and cascade inflammation.

Moreover, delayed neuronal death is associated with neurological deficits and mortality after TBI, where post-synaptic density (PSD) plays a critical role. PSD molecules are involved in synaptic plasticity processes at glutamatergic synapses [54, 55]. A previous study demonstrated that traumatic neuronal injury was induced by promoting ER stress-associated apoptosis and necroptosis and the aggravation of neuronal death accompanied by caspase-12 [56]. Therefore, caspases might also exert an action on post-synaptic density interacting with glutamatergic transmission.

3.2. Caspases and Ischemic Stroke

Pathophysiological injuries in ischemic stroke, including tissue infarct, excitotoxicity, spreading depolarization, oxidative stress, inflammation, and cellular death, occur rapidly following the occlusion of cerebral blood vessels [57]. However, tissue damage in the ischemic penumbra, the transition zone between ischemic core and normal tissue, develops relatively slower [58]. Saving the tissue of penumbra is key to the treatment of ischemic stroke.

Apoptosis is the main cell death modality in the penumbra after ischemic stroke. Previous studies have suggested that stroke mainly caused caspase-dependent neuronal apoptosis in the CNS [58]. Multiple factors after ischemic stroke cause the activation of apoptotic pathways, including oxidative stress, calcium overload, and excitotoxicity [58]. The expression of caspases-1, 3, 6, 8, and 9 in the infarct core were found to increase 0.5-1 hour after middle cerebral artery occlusion (MCAO), which continued until 12-24 hours later [58]. In a rat model of MCAO, the overexpression and activation of caspase-3 were observed in neurons of ischemic penumbra as soon as 4 hours after stroke. The overexpression of caspase-3 in astrocytes was recorded 12-24 hours following stroke [59, 60]. In addition, caspases-3, -6, and -7 were upregulated in the penumbra at 1-4 hours after photothrombotic stroke [61]. Cytochrome c appeared in both the ischemic core and penumbra 3 hours after MCAO in rats, which can activate caspase-9 and lead to downstream apoptosis pathways [62, 63]. However, recent evidence has shown that caspase-independent apoptosis was also widespread in CNS and affected non-neuronal cells, such as microglia [59].

Recent studies have emphasized the pyroptotic mechanism in ischemic stroke. After an ischemic stroke or ischemia/reperfusion (I/R) injury, microglia release inflammasomes to activate caspase-1, which causes cellular pyroptosis by cleaving gasdermin D (GSDMD) [64]. Inflammasomes related to ischemic stroke currently under study include NLRP1, NLRP3, NLRC4, *etc.* [65-67]. Inflammasome-mediated microglia pyrolysis can cause the release of intracellular inflammatory content, such as IL-1β and IL-18, thereby aggravating neuroinflammation and brain damage [67].

3.3. Caspases and ICH

ICH is the most common subtype of hemorrhagic stroke. In addition to primary brain injury, secondary brain injury, including cerebral edema, oxidative stress, neuroinflammation, and neuronal death, causes high mortality and morbidity in ICH [68]. Current research mainly focuses on secondary brain injury to find promising therapeutic targets for ICH.

Caspase-dependent cellular death and inflammation are considered important mechanisms of secondary brain injury after ICH. Blood clot components, thrombin, and inflammation initiate cellular apoptosis in CNS after ICH [69]. It is reported that Fas and FasL were overexpressed in the areas immediately surrounding the clot in 6 deceased ICH patients compared to control group patients [70]. The Bcl-2/Bax ratio fell in the ipsilateral hemisphere after ICH, which causes the mitochondrial permeability transition and the release of pro-apoptotic proteins, such as cytochrome c and AIF [71]. Animal experiments indicated that the ultrastructural morphological changes of neuronal mitochondria could be significantly observed at 12 hours after ICH, and the expression of cytochrome c was significantly up-regulated in the brain tissue at 24 hours after ICH [72]. Cytochrome c can combine with APAF1 to form an apoptosome, which causes the activation of caspase-9, and subsequently cleaves and activates caspase-3 [21]. As the executor of apoptosis, caspase-3 can be an effective biomarker for the prognosis of patients with ICH. A clinical study revealed that serum caspase-3 levels were increased in ICH patients and were associated with clinical severity and outcome at 6 months [73]. Recent studies have found that the NLRP3 inflammasome could be activated following ICH, leading to neuroinflammation and aggravating secondary brain injury [74]. The NLRP3 inflammasome cleaves pro-caspase-1 to caspase-1, which not only causes pyroptosis but also activates IL-1β and IL-18 to induce the inflammatory cascade. Inhibition of caspase-1 has been shown to be effective in improving secondary brain injury and neurological function in rats after experimental ICH [75].

3.4. Caspases and SAH

SAH is a severe subtype of stroke, in which approximately 85% of cases are caused by the rupture of intracranial aneurysms. Since the treatment targeting cerebral vasospasm (CVS) did not improve the long-term outcomes of SAH patients, early brain injury (EBI) has become an emerging focus of SAH research [76]. The pathological mechanism of EBI mainly involves excitotoxicity, inflammation, blood-brain barrier (BBB) destruction, oxidative stress, and cellular death [77]. In-depth studies on EBI will help find new therapeutic targets for SAH.

The caspase family plays an important role in EBI after SAH. It has been demonstrated that TNF-α and FasL are upregulated after SAH, which activates death receptors, such as Fas and TNFR1, to cleave pro-caspase-8, thereby triggering the apoptotic cascade [78, 79]. In an animal study, cleaved caspase-8 was significantly increased at 12 hours and peaked at 24 hours after SAH. Inhibition of caspase-8 activation significantly improved EBI and neurological deficits in rats 24 hours after SAH [80]. In experimental SAH, BCL-2/BAX in CNS was found to be reduced 24 hours after SAH, which could promote the release of cytochrome c from the mitochondrial intermembrane space [81]. Cytochrome c activates caspase-9 to cause the mitochondrial-dependent apoptosis cascade. It is worth noting that the death receptor pathway can crosstalk to the mitochondrial pathway through caspase-8-mediated BH3-only Bcl-2 family member (BID) cleavage [21]. In addition, caspase-1, activated by inflammasomes, may cause cellular pyroptosis and promote neuroinflammation in SAH. The inflammasomes that have been proven to be associated with EBI after SAH include NLRP1, NLRP3, AIM2, *etc*. [82-84]. A recent clinical study found elevated caspase-1 activity in CSF of patients with SAH compared to controls. Higher CSF levels of caspase-1 were significantly related to worse functional outcomes in SAH patients [85].

4. TRANSLATIONAL STRATEGIES FOR CASPASE MODULATION IN CNS

DR regulation, genetic manipulation, and catalytic modulation are the three dominant strategies for moderating caspase-mediated pathways [86]. 1) DR regulation: The regulation of DRs affects the activation of the extrinsic pathway of apoptosis. For example, Fas apoptotic inhibitory molecule (FAIM)1, FAIM2, and FAIM3 can inhibit Fas-induced cell death in CNS. These molecules protect neurons from DR-induced apoptosis by interacting with Fas receptor, and are involved in neurite outgrowth and neuronal plasticity [87]. 2) Genetic manipulation: Knockout of relevant caspase genes

can inhibit cell death in the CNS. A study found that caspase-1 gene knockout reduced inflammatory gliosis and neuronal loss in the microenvironment caused by chronic implantation of microelectrodes into the cortices of mice [88]. Genetic knockouts of caspase-1, -3, -6, and -11 were shown to have a neuroprotective effect on stroke [86]. In addition, RNAi-based gene therapy for caspases is also an option. Certain drugs can also regulate the expression of caspases. For example, minocycline inhibits caspase-1 expression and promotes the expression of BCL-2 in stroke [86]. 3) Catalytic inhibitors: In recent decades, caspase inhibitors have served as the principal tools for exploring and manipulating caspase-mediated pathways [86]. There is a wide range of caspase inhibitors, including peptide caspase inhibitors, peptidomimetics, non-peptide caspase inhibitors, and allosteric caspase inhibitors [9]. Based on the optimal substrate motif of an individual caspase, these inhibitors can be modified with synthetic chemical moieties to determine their medicinal properties [86].

In addition to promoting apoptosis, neuronal DRs are also involved in cell survival, differentiation, and neuronal plasticity [87]. Moderating caspase-mediated pathways through DR regulation may cause a series of serious side effects [89]. Therefore, this strategy has not been widely considered for the regulation of caspases in the CNS.

While therapies based on caspase gene knockout may be an effective strategy, there remains a lack of any clinical testing. Several challenges and obstacles for RNAi-based gene therapy for caspases include insufficient distribution of therapeutic siRNA/miRNA to relevant CNS regions and inefficient delivery towards neurons. Additionally, drug-based knockdown of caspases often lacks complete specificity. For instance, minocycline can inhibit caspase-1 expression during ischemic stroke and can induce Bcl-2 to suppress apoptosis and modify various gene targets [90]. Furthermore, gene therapy might have limited utility, although it may be a potential and effective prophylactic strategy because of the abundant caspase activation that occurs before treatment takes effect.

In recent decades, caspase inhibitors have been the dominant tool to further explore caspase-mediated pathways. Based on the substrate motif of caspase, synthetic inhibitors with additional chemical moieties can prevent reversibility and membrane permeability. Clinical trials have been conducted for the use of peptide caspase inhibitors for psoriasis and liver injury [86]. However, peptide caspase inhibitors are highly promiscuous, and the lack of specificity reduces their overall usefulness in the CNS. Some natural protein biologics, which inhibit caspases and offer higher target specificity, may be a viable alternative to peptide caspase inhibitors. Due to their larger size, most natural biologics require the assistance of some carrier to pass through the plasma membrane, such as Tat and Penetratin1 [86]. Additionally, the presence of the blood-brain barrier (BBB) may limit the entry of these drugs into the CNS. However, effective drug delivery systems, through the use of nanoparticles, polymers, and liposomes, have been suggested [9]. In general, compared to DR regulation and genetic manipulation, caspase inhibitors provide a more promising strategy for caspase modulation in CNS, although there are still no caspase inhibitory drugs approved for clinical use on the market.

5. CASPASE MODULATION AS A NOVEL THERAPEUTIC STRATEGY FOR ABI

Current translational strategies for caspase modulation in ABI are mainly focused on caspase inhibitors. Caspase inhibitors have served as an effective target for cancer treatment because of their inhibitive function on apoptosis, chemoresistance, and immune disorders [91, 92]. Recently, natural compounds and artificially synthetic resources have been developed for the inhibition of caspase-mediated cell death and inflammation in experimental models [93]. A variety of synthetic caspase inhibitors have been developed primarily for research purposes, such as Ac-YVAD-FMK (caspase-4 inhibitor), VX765 (caspase-1 inhibitor) [94, 95], Z-LEHD-FMK (caspase-9 inhibitor) [96], Z-LETD-FMK (caspase-8 inhibitor) [97], Z-VEID-FMK (caspase-6 inhibitor) [98], Z-DEVD-CMK, M867, and MX1122 (caspase-3 inhibitor) [99-101], as well as MMPSI and lsatin-bearing sulfonamides (caspase-3/7 selective inhibitor) [102, 103], and the broad caspase inhibitor (Emricasan, Boc-Asp-FMK, Z-VAD-FMK, Q-VD-OPH, and VX-166) [104-108]. As there are no caspase-inhibiting drugs approved for clinical use on the market, the development of caspase inhibitors remains an attractive challenge for researchers and clinicians. Next, we will categorize and introduce the translational effects of the caspase inhibitors in ABI. Fig. (**2**) shows the mechanisms of caspase inhibitors in ABI.

5.1. Pan-caspase Inhibitor for ABI

Pan-caspase inhibitors are compounds which can inhibit multiple caspases, including Z-VAD-FMK, Q-VD-OPH, and Emricasan. Although natural and synthetic compounds for caspase activation have been highlighted as potential therapeutic agents towards several cancers, the first generation of pan-caspase inhibitors was mainly used *in vitro* and *in vivo* experimental studies [109-122]. Besides, activation of caspase is closely related to ABI, including TBI [48], ischemic stroke [58], and hemorrhagic stroke [71, 72]. As shown in several animal models, pharmacological caspase inhibition is a potential therapeutic strategy for the treatment of these diseases. Z-VAD-FMK is the most frequently studied pan-caspase inhibitor, which binds to the catalytic sites of caspases-3, -8, and -9 to inhibit the apoptotic cascade [106]. Experimental studies have shown that Z-VAD-FMK can decrease apoptotic cell death, inhibit cytokine production, reduce infarct volume, and extend the treatment window in ischemic stroke [113-115]. In SAH, Z-VAD-FMK plays a role in preventing endothelial apoptosis, protecting the BBB, and reducing vasospasm [79, 116]. In addition, Z-VAD-FMK also has a neuroprotective effect in secondary brain injury after TBI [117]. The overall summary of pan-caspase inhibitors studied in ABI is listed in Table **1**.

However, multiple studies have revealed that the pan-caspase inhibitors are highly promiscuous, given that certain caspases play a critical role in synaptic plasticity and microglial activation [118, 119]. The lack of specificity towards therapeutic targets limits the overall usefulness of pan-caspase inhibitors in stroke. Since caspases may be activated in parallel or in a cascade, the pharmacological effect of pan-caspase inhibitors cannot be attributed to the inhibition of single caspase.

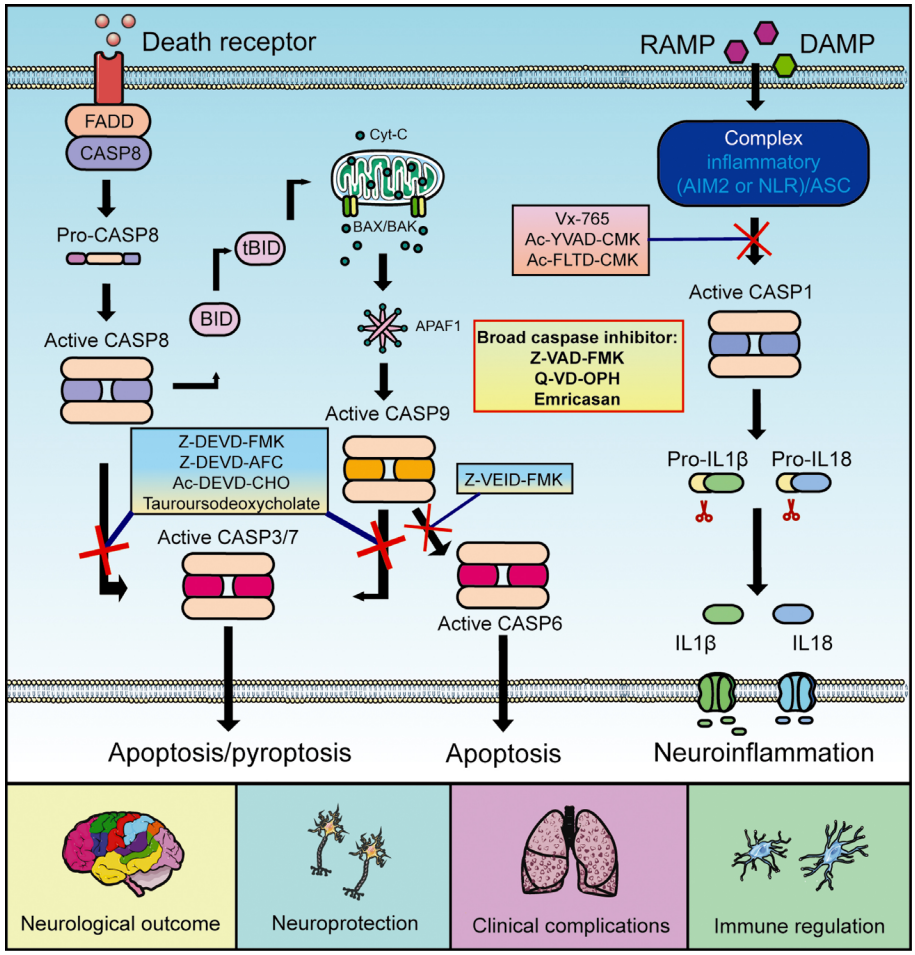

Fig. (2). Caspase inhibitors selectively targeting caspase pathways and clinical effects. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

5.2. Inflammatory Caspase Inhibitor for ABI

Inflammatory caspases include caspase-1, -4, -5, and -11, which have been known to induce pyroptosis and proinflammatory cytokine release, such as IL-1β and IL-18. Several studies have demonstrated an upregulation of caspase-1 following ABI [85, 120-122]. Thus, targeting caspase-1 represents a potentially effective approach for anti-neuroinflammation in ABI. Ac-YVAD-CMK, Z-WEHD-FMK, and Vx-765 were all selective inhibitors of caspase-1 and their anti-inflammatory functions were demonstrated both *in vitro* and *in vivo*. In recent decades, genetically modified caspase-deficient animals (*e.g.*, caspase-1 and -11) and pharmacological inhibition with pan- or selective caspase inhibitors have been used in a variety of preclinical studies and have demonstrated that suppressing the activity of caspases improves neurological deficits in ABI. For example, they were found to provide neuroprotection in penumbral regions following ischemic stroke [123-127].

Vx-765, a pro-drug of VRT-043198, is a highly potent selective small molecular inhibitor towards caspase-1, which can be delivered to the BBB [128]. It has been shown that pharmacological inhibition of caspase-1 *via* vx-765 (50 mg/kg, i.p. for 3 days) significantly decreased brain infarct volume, ameliorated cerebral I/R injury, and improved neurobehavioral performance through suppressing the inflammatory response and by inducing a shift in microglial phenotype [129]. Ac-YVAD-CMK, an irreversible caspase-1 inhibitor (25 mg/kg, i.p. for 10 days), can attenuate hyperoxia-induced lung and brain injury *via* downregulation of NLRP1 inflammasome, and decreases atrophy of SGZ and SVZ [130]. Ac-YVAD-CMK (200ng, i.c.v. 1 h before or after trauma) can also confer tissue protection following TBI by reducing formation of ROS [117]. In conclusion, as is shown in Table **2**, the caspase-1 inhibitor may be a potential therapeutic strategy for ABI.

5.3. Initiator Caspase Inhibitor for ABI

Caspase-8 and caspase-9 serve as initiator caspases in the extrinsic and intrinsic apoptotic pathways, respectively. Initiator caspase inhibitors are a class of compounds that inhibit the initiator caspases, including selective caspase-8 inhibitor and caspase-9 inhibitor. Z-IETD-FMK, a selective caspase-8 inhibitor (0.5, 1, and 2 mg/kg, i.c.v.), has been demonstrated to improve spatial learning and memory abilities, as well as reduce cytokines and pyroptosis in rat perforation models [80]. It can also decrease the neuropathological consequences after middle cerebral artery occlusion (50 nM, i.c. at Day 3 and 10) [131]. Z-LEHD-FMK is a selective caspase-8 inhibitor that inhibits the initiation of the intrinsic pathway of apoptosis. In a rat brain I/R model, the use of Z-LEHD-FMK (4.8 μg, i.c.v. 15 min after reperfusion) reduced total

Table 1. Summary of pan-caspase inhibitors in ABI.

Inhibitor	ABI Type	Therapeutic Effects	Year	Refs.
Z-VAD-FMK	Ischemic stroke	Putatively blocked apoptotic cell death and inhibited cytokine production	1998	Ma [113]
Z-VAD-FMK	Ischemic stroke	Reduced CA1 injury after global ischemia	2000	Li [137]
Z-VAD-FMK	Ischemic stroke	Extended the short treatment window for ischemic stroke	2001	Ma [114]
Z-VAD-FMK	Ischemic stroke	Showed neuroprotective activity given immediately after MCAO	2002	Skifter [156]
Z-VAD-FMK	Ischemic stroke	Increased reduction of infarct volume	2007	Elgin [115]
Z-VAD-FMK	SAH	Reduced BBB permeability, relieved vasospasm, abolished brain edema, and improved neurological outcome	2004	Park [116]
Z-VAD-FMK	SAH	Prevented endothelial apoptosis and reduced angiographic vasospasm	2004	Zhou [79]
Z-VAD-FMK	SAH	Prevented endothelial apoptosis and reduced angiographic vasospasm	2004	Park [116]
Z-VAD-FMK	SAH	Prevented SAH-induced vasospasm through inflammatory reaction	2007	Keiichi [157]
Z-VAD-FMK	SAH	prevented apoptosis and Neurogenic pulmonary edema	2011	Hidenori [146]
Z-VAD-FMK	TBI	Reduced trauma-mediated brain tissue injury	1999	Fink [117]
Z-VAD-FMK	TBI	Improved performance on motor and spatial learning tests	2002	Knoblach [158]
Z-VAD-FMK	TBI	Reduced lesion volume	2006	Alessandri [159]
Q-VD-OPH	ischemic stroke	prolonged survival time and attenuate neurological dysfunction	2007	Sylvain [160]
Q-VD-OPH	ischemic stroke	Reduced infarct volume	2007	Reshef [161]
Q-VD-OPH	ischemic stroke	Reduced ischemic brain damage and stroke-induced programmed cell death	2007	Johann [147]
Q-VD-OPH	ischemic stroke	Reduced total brain tissue loss and ameliorated the loss of sensorimotor function	2014	Han [162]
Emricasan	ischemic stroke	Reduced I/R injury	2018	Tian [163]

infarction volume by 49% and improved neurological outcome by 63%, showing a strong neuroprotective effect [132].

5.4. Executioner Caspase Inhibitor for ABI

At the final stage of both the extrinsic apoptotic and the intrinsic apoptotic pathways, the executioner caspases, such as caspase-3, -6, and -7, cleave various substrates, resulting in cell shrinkage, membrane blebbing, nuclear DNA fragmentation, and nuclear condensation, which are morphological and functional characteristics of apoptosis [133]. Over recent decades, a variety of studies have focused on the detection of caspase-3 following ABI, which is the main apoptotic executor. Caspase-7 is located on chromosome 10q25.3, which has been identified as a susceptibility locus for ischemic stroke and ICH [134]. Caspase-6, described as both an initiator and effector caspase, can cleave certain caspases, including caspase-2, -3, and -8, playing a critical role in the pathogenesis of stroke, Huntington's disease, and Alzheimer's disease [135, 136]. Currently, the executioner caspase inhibitors understudy in ABI mainly include Z-DEVD-FMK, Ac-DEVD-CHO, Z-DEVD-AFC, tauroursodeoxycholate, and Z-VEID-FMK.

Z-DEVD-FMK is a specific and irreversible caspase-3 inhibitor, which has been tested in the therapy of multiple types of ABI in animal models [137]. In tMCAO rat models of ischemic stroke, the use of Z-DEVD-FMK (320 ng, i.c.v. immediately after ischemia;1.5 μg, i.c.v. 30 min before and 2 h/ 24h after ischemia) could significantly inhibit apoptosis, reduce infarction volume, and extend the treatment window [113, 137, 138]. Following TBI, Z-DEVD-FMK (160 ng, i.c.v. at 30 min before and at 6 and 24 h after TBI) has also been found to play an important neuroprotective role in secondary brain injury [139-141]. In addition, it has been demonstrated that Z-VEID-FMK, the selective caspase-6 inhibitor (50 nM, i.c. at Days 3 and 10), can decrease the neuropathological consequences and is an effective strategy for neuroprotection in stroke [131]. The overall summary regarding the study of executioner caspase inhibitors in ABI is listed in Table **3**.

Table 2. Summary of inflammatory caspase inhibitor in ABI.

Inhibitor	Target	ABI Type	Therapeutic Effects	Year	Refs.
Vx-765	Caspase-1	Ischemic stroke	Protected against MCAO injury and attenuated microglia mediated neuroinflammation	2019	Li [129]
Vx-765	Caspase-1	Ischemic stroke	attenuated brain edema, minimized hemorrhagic transformation, and improved neurological outcome	2021	Chen [164]
Vx-765	Caspase-1	Ischemic stroke	Improved ischemia-associated BBB permeability and integrity by suppressing pyroptosis activation	2021	Liang [165]
Vx-765	Caspase-1	TBI	Decreased blood-brain barrier (BBB) leakage, apoptosis, and microglial polarization	2020	Sun [166]
Ac-YVAD-CMK	Caspase-1	Ischemic stroke	Improved cognitive function and reversed brain volume in the hippocampus	2020	Hyunha [149]
Ac-YVAD-CMK	Caspase-1	Brian injury	Prevention of lung and brain injury in preterm infants	2019	Fredrick [130]
Ac-YVAD-CMK	Caspase-1	TBI	Reduced trauma-mediated brain tissue injury	1999	Fink [117]
Ac-YVAD-CMK	Caspase-1	TBI	alleviated TBI-induced BBB leakage, brain edema, loss of tight junction proteins, and the inflammatory response	2018	Ge [167]
Ac-YVAD-CMK	Caspase-1	ICH	Protected the brain against ICH-induced injury, and the exerted neuroprotective effect may result from anti-inflammation-induced blood-brain barrier protection.	2010	Wu [95]
Ac-YVAD-CMK	Caspase-1	ICH	Inhibited pyroptosis, decreased the secretion or activation of inflammatory factors, and affected the polarization of microglia	2018	Lin [168]
Ac-YVAD-CMK	Caspase-1	ICH	Reduced the release of mature IL-1β/IL-18 in perihematoma, improved the behavioral performance, and alleviated microglia in perihematoma region	2019	Liang [75]
Ac-YVAD-CMK	Caspase-1	SAH	Attenuated the mature IL-1β induction and prevented early brain edema	2009	Takumi [169]
Ac-YVAD-CMK	Caspase-1	SAH	Inhibited lung cell apoptosis and neurogenic pulmonary edema	2009	Hidenori [145]
Ac-YVAD-CMK	Caspase-1	SAH	Inhibited lung cell apoptosis and neurogenic pulmonary edema	2009	Suzuki [145]
Ac-YVAD-CMK	Caspase-1	SAH	Attenuated brain edema, and improved neurological function	2017	Li [170]
Ac-FLTD-CMK	Caspase-1/11	TBI	Suppressed pyroptosis and protected mice against TBI	2021	Wang [171]

5.5. Other Caspase Inhibitors for ABI

Caspase-2 harbors structural hallmarks of initiator caspases and has been demonstrated to mediate reactive oxygen species (ROS) and DNA damage [142]. In addition, caspase-2 is also associated with the activation of caspase-1 and its downstream signaling. A previous study reported that caspase-2 levels were elevated in the brain (ischemia/reperfusion) I/R mode. Z-VDVAD-FMK served as a specific caspase-2 inhibitor, and it blocked the apoptotic process of cerebral neurons in the mouse MCAO model [143].

5.6 Role of Caspase Inhibitors on Complications Following ABI

In addition to their neuroprotective effect in ABI, caspase inhibitors also have a positive effect on the systemic complications following ABI. Severe SAH is likely to be complicated by cardiopulmonary dysfunction, such as neurogenic pulmonary edema (NPE). NPE is estimated to occur in approximately 2-29% of SAH patients. NPE is known as a severe life-threatening complication after CNS disorders, such as SAH or severe TBI [144]. Several studies have

Table 3. Summary of executioner caspase inhibitor in ABI.

Inhibitor	Target	ABI Type	Therapeutic Effects	Year	Refs.
Z-DEVD-FMK	Caspase-3	Ischemic stroke	putatively block apoptotic cell death and inhibit cytokine production	1998	Ma [113]
Z-DEVD-FMK	Caspase-3	Ischemic stroke	Prolonged protection and extended treatment window	1998	Fink [138]
Z-DEVD-AFC	Caspase-3	Ischemic stroke	Prolonged protection and extended treatment window	1998	Fink [138]
Z-DEVD-FMK	Caspase-3	Ischemic stroke	Reduce infarction volume	2000	Li [137]
Z-DEVD-FMK	Caspase-3	Ischemic stroke	combining caspase inhibitors and bFGF lengthens the treatment window for the second treatment, plus lowers the dosage requirements for neuroprotection	2001	Ma [114]
Z-DEVD-FMK	Caspase-3	Ischemic stroke	Attenuate ischemia-induced Abeta formation by reducing BACE1 production and activity	2008	Xiong [172]
Z-DEVD-FMK	Caspase-3	Ischemic stroke	Inhibit apoptosis and delayed the necrosis of brain tissue	2015	Sun [173]
Z-DEVD-FMK	Caspase-3	TBI	reduce post-traumatic apoptosis and associated neurological dysfunction	1997	Yakovlev [139]
Z-DEVD-FMK	Caspase-3	TBI	Inhibit brain tissue loss and downstream biochemical events that execute programmed cell death	2000	Clark [140]
Z-DEVD-FMK	Caspase-3	TBI	Neuroprotection through inhibition of calpain-related necrotic cell death	2004	Knoblach [141]
Ac-DEVD-CHO	Caspase-3	SAH	prevented endothelial apoptosis and reduced angiographic vasospasm	2004	Zhou [79]
Tauroursodeoxycholate	Caspase-3/12	Ischemic stroke	improved neurological function and reduce infarct size	2002	Rodrigues [174]
Tauroursodeoxycholate	Caspase-3/12	ICH	reduces apoptosis and protects neurons from acute hemorrhagic stroke	2003	Rodrigues [175]
Tauroursodeoxycholate	Caspase-3/12	SAH	attenuated neuronal apoptosis and improve neurological functions	2020	Wu [176]
Tauroursodeoxycholate	Caspase-12	SAH	prevents EBI and improves the outcome	2020	Chen [177]
Tauroursodeoxycholate	Caspase-3	SAH	alleviates early brain injury following SAH via inhibiting apoptosis	2014	Yan [178]
Z-VEID-FMK	Caspase-6	Ischemic stroke	decreases the neuropathological consequences of cerebral or retinal infarction	2015	Shabanzadeh [131]

demonstrated that caspase-1 or pan-caspase inhibitors can inhibit lung cell apoptosis and prevent NPE in mice SAH l models [145, 146]. In addition, the administration of pan-caspase inhibitors reportedly prevented endothelial apoptosis, which can significantly reduce or relieve CVS after SAH [79, 116]. Furthermore, previous studies provide evidence that the blockade of caspase activation may have further beneficial effects on ischemic stroke outcomes by reducing the susceptibility to infectious complications and seizure activity [131, 147].

Post-stroke cognitive impairment (PSCI) is also considered one of the main complications of the chronic phase of ABI [148]. It will take at least 6 months to be diagnosed with PSCI; thus, an effective therapeutic strategy during the early period is required. Neuroinflammation is a major contributor to cell death in the pathophysiology of ABI, which likely shows a detrimental effect on cognitive function. A previous study has demonstrated that impaired inflammatory mechanisms are likely the factor leading to PSCI and caspase-1 inhibitor significantly improved cognitive function and

Table 4. Caspase inhibitor on complications following ABI.

Inhibitor	Target	ABI Type	Therapeutic Effects	Year	Refs.
Ac-YVAD-CMK	Caspase-1	SAH	Inhibit lung cell apoptosis and neurogenic pulmonary edema	2009	Suzuki [145]
Ac-YVAD-CMK	Caspase-1	ischemic stroke	improved cognitive function and reduce PSCI	2020	Hyunha [149]
Z-VAD-FMK	Pan-caspase	SAH	prevented apoptosis and Neurogenic pulmonary edema	2011	Hidenori [146]
Z-VAD-FMK	Pan-caspase	SAH	Reduce BBB permeability, relieve vasospasm, abolish brain edema	2004	Park [116]
Z-VAD-FMK	Pan-caspase	SAH	prevented endothelial apoptosis and reduced angiographic vasospasm	2015	Zhou [79]
Q-VD-OPH	Pan-caspase	ischemic stroke	Anti-bacterial infection	2007	Braun [147]
Z-IETD-FMK	Caspase-8	Ischemic stroke	Reduce seizure activity	2015	Shabanzadeh [131]

reversed brain volume in the hippocampus in stroke mice [149]. The beneficial effects of caspase inhibitors on complications following ABI are listed in Table **4**.

CONCLUSION

ABI is a multifaceted and devastating disease with high mortality and morbidity, considered major global health concerns with very limited approaches for accurate diagnosis and effective therapy. Cumulative evidence reveals important roles of the caspase family in the secondary brain injury that occurs following ABI, which are potential therapeutic targets for improving long-term outcomes of ABI patients. Studies have also shown that some caspases are effective biomarkers for poor outcomes in patients with ABI. Therapies targeting caspases have shown potential in some animal experiments. In the present review, caspase inhibitors were carefully examined to provide novel research directions for future studies, emphasizing the prospect of developing potent caspase inhibitors with properties and efficacy to serve as a novel therapeutic target for ABI. However, there is still no clear evidence that caspase inhibitors can be offered to ABI patients.

Moreover, there is the another potential therapeutic target for ABI. Coenzyme Q10 (CoQ10) is a strong antioxidant playing a role in membrane stabilization [150]. CoQ10 can reduce apoptotic cell death, attenuate ATP decrease, and DNA fragmentation induced by all apoptotic stimuli, which made it a potential strategy in brain injury, stroke and cerebral ischemia [151-153]. It seems that the main CoQ10 biological role is that of ensuring the electron transfer through the electron transport chain (ETC; respiratory chain) and not only that of acting as an antioxidant [154]. Notably, CoQ10 takes part in the inhibition of mitochondrial depolarization, cytochrome c release, and caspase 9 activation [155]. Thus, it may obtain more benefits of the combination of both Coq10 targeting and caspase inhibitor. The efficacy and safety of this treatment require further verification. More research is necessary to explore new directions for targeting the caspase family in the treatment of ABI.

LIST OF ABBREVIATIONS

ABI = Acute brain injury
SAH = Subarachnoid hemorrhage
ICH = Intracerebral hemorrhage
TBI = Traumatic brain injury
CNS = Central nervous system
CARD = Caspase recruitment domain
DED = Death effector domains
FADD = FAS-associated death domain
DISC = Death-Inducing Signaling Complex
TNFR1 = TNF receptor 1
RIPK1 = Serine/threonine protein kinase 1
cIAPs = Cellular IAPs
TRAF2 = TNFR-associated factor 2
TRADD = TNFR1-associated death domain
ER = Endoplasmic reticulum
ROS = Reactive oxygen species
Apaf-1 = Apoptotic peptidase activating factor 1
MOMP = Mitochondrial outer membrane permeabilization
Cyt-C = Cytochrome c
BH3 = BCL-2 homology 3
BID = BH3-interacting domain death agonist
BAX = BCL-2-associated X
DAMPs = Damage associated molecular patterns
LPS = Lipopolysaccharide
PAMPs = Pathogen-associated molecular patterns
NLRP1 = Nod-like receptor family pyrin domain-containing 1

NLRC4 = NLRP family CARD domain-containing 4

AIM2 = Absent in melanoma2

IAP = Inhibitor of apoptosis

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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

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