Neuronal injuries in cerebral infarction and ischemic stroke: From mechanisms to treatment (Review)

YUNFEI ZHAO[1*], XIAOJING ZHANG[2*], XINYE CHEN[2,3] and YUN WEI[2]

[1]Department of Molecular and Cell Biology, University of California Berkeley, Berkeley, CA 94720, USA; [2]Shanghai Licheng Bio-Technique Co. Ltd.; [3]Shanghai Yiai Biomedical Technology Co. Ltd., Shanghai 201900, P.R. China

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Abstract. Stroke is the leading cause of disabilities and cognitive deficits, accounting for 5.2% of all mortalities worldwide. Transient or permanent occlusion of cerebral vessels leads to ischemic strokes, which constitutes the majority of strokes. Ischemic strokes induce brain infarcts, along with cerebral tissue death and focal neuronal damage. The infarct size and neurological severity after ischemic stroke episodes depends on the time period since occurrence, the severity of ischemia, systemic blood pressure, vein systems and location of infarcts, amongst others. Ischemic stroke is a complex disease, and neuronal injuries after ischemic strokes have been the focus of current studies. The present review will provide a basic pathological background of ischemic stroke and cerebral infarcts. Moreover, the major mechanisms underlying ischemic stroke and neuronal injuries are summarized. This review will also briefly summarize some representative clinical trials and up-to-date treatments that have been applied to stroke and brain infarcts.

Contents

Correspondence to: Dr Xinye Chen, Shanghai Licheng Bio-Technique Co. Ltd., Lane 2999, Hutai Road, Baoshan, Shanghai 201900, P.R. China
E-mail: xinyechen00@163.com

*Contributed equally

Abbreviations: AIS, acute ischemic stroke; MCAO, middle cerebral artery occlusion; BBB, blood brain barrier; NPC, neural precursor cell; NMDARs, N-methyl-D-aspartate receptors; WRAP53, WD repeat containing antisense to TP53; GluN2B, NMDA Receptor 2B; NSCs, neural stem cells; PB, Persian blue; ROS, reactive oxygen species; HPBZs, hollow Prussian blue nanozymes; tMCAO, temporary MCAO; FDA, Food and Drug Administration

Key words: cerebral infarcts, ischemic stroke, neuronal injury, mechanism, clinical management

1. Introduction

Stroke was the leading cause of disabilities and cognitive deficits, and the fifth leading cause of mortality in the USA in 2017 (1). Moreover, ischemic stroke accounted for 5.2% of all deaths worldwide in 2015 (2). The basic pathological cause of ischemic stroke is intravascular thrombosis, which can result in cerebral tissue necrosis and focal neuronal deficits. There are three known leading causes of ischemic strokes: 50% are caused by arteriosclerotic plaques of the cerebral vessels and the rupture of the arteriosclerotic plaque, 20% are caused by cardiogenic cerebral infarction, and 25% are caused by Lacunar infarcts from small vessel lesions (3). Furthermore, the remaining 5% are due to other exceptional cause such as vasculitis and extracranial arterial dissection (4).

Acute ischemic stroke (AIS) is a type of ischemic stroke that can cause severe brain and neuronal damage in a very short time after the ischemic episode (5). Various degrees and types of brain damage are caused by ischemic stroke and cerebral infarcts, including cerebral tissue lesions and structural damage, and neuronal death and deficits, amongst others. Clinical symptoms of these types of damage can be observed in patients with conditions such as Alzheimer's disease (6-11), motor functional deficits (12), impaired intelligence quotient score (13) and multiple cognitive functional deficits (selective attention, working memory, information processing, abstract reasoning and verbal comprehension), amongst others (14-19). According to the findings of numerous studies examining the mechanisms and clinical management of ischemic stroke and cerebral infarction, there are three major mechanisms underlying the neuronal injuries caused by ischemic stroke and cerebral infarcts. Firstly, the loss of neurons induced by ischemia and infarcts is one of the most direct cause of neuronal injuries (20). With regards to this mechanism, researchers have been focusing on the processes of neuroprotection and regeneration, as well as related biomarkers and molecular pathways (20). Secondly, vascular obstruction caused by ischemia excessively produces reactive oxygen species (ROS), and it has been shown that oxidative stress exacerbates neuronal damage and leads to severe functional deficits (21). Pathways reacting to and relieving oxidative stress are widely investigated to help decrease neuronal injuries. Inflammation induced by ischemia is an additional factor that leads to further neuronal damage after

strokes (22). Therefore, effectively manipulating the immune responses may help to reduce neuronal injuries.

In vivo animal models of ischemic stroke and brain infarcts provide valuable insights into the underlying mechanisms and possible clinical therapies. The middle cerebral artery occlusion (MCAO) model in murine models is most widely used for *in vivo* studies (23). Embolic MCAO models closely mimic human stroke, >80% of which are caused by thrombosis or embolism (24). MCAO produces regenerative occlusion in middle cerebral arteries, and also enables reperfusion without extracranial resection of the occlusion (25). Although the mechanism of such rapid recovery of blood flow differs from the pathophysiology of human strokes, this model can still commendably simulate the clinical application of mechanical thrombolysis (25), which may be more widely applied in patients in the future. In addition, the various models of embolic stroke and spontaneous stroke can most effectively simulate the real condition of human strokes (26,27). Different experimental models have contributed significantly to the current knowledge regarding stroke pathophysiology and its consequences, and each model causes different changes in the cerebral microcirculation and local inflammatory responses after ischemia (26). Nevertheless, these models are accompanied by higher instability regarding the size and location of infarcts. For instance, such instability includes unpredictable stroke attacks in spontaneous stroke models and unpredictable reperfusion conditions in embolic stroke models (23).

The ultimate therapeutic goal for ischemic stroke and brain infarcts is to reduce neuronal injuries by relieving arterial occlusion (recanalization) and recovering cerebral blood flow (reperfusion) (28). The basic hypothesis of the pathophysiological response during AIS treatment is that once the cerebral artery has been occluded, hypo-perfused brain tissues are at risk of permanent infarction, but such tissues can be effectively rescued via the rapid recovery of the blood flow (29). These tissues are known as ischemic penumbras, and preventing the conversion of ischemic penumbra to inversible infarction is the aim of AIS treatment (28). Primary stroke treatment challenges are partly a result of distinguishing the penumbra from the core zone and the penumbra from benign hypoperfusion tissues, which have poor perfusion but without the risk of infarction (30).

2. Pathophysiological processes of ischemia

Investigations into ischemic stroke and neuronal injuries have indicated that neuronal damage is caused by neuron loss, oxidative stress and immune responses (31-33). Various biomarkers and molecular pathways are involved in rescuing neuronal damage caused by ischemic stroke and cerebral infarction.

Neuron protection and regeneration. The survival of neurons influences the stability and completeness of brain functions, and neuron loss directly results in cerebral functional deficits (34). Hence, neuronal protection and regeneration has been the major focus for effectively rescuing cerebral functional deficits. There are various methods to achieve this goal, which include enhancing neuron protection, promoting neuron repair and neuron regeneration, and direct mediation of neuronal survival or death, amongst others. For instance, astrocytes contribute to angiogenesis, neurogenesis, synaptogenesis and axonal remodeling (35). Thus, promoting neurological recovery during the late recovery phase after stroke could provide benefits for neuroprotection. Astrocytes limit lesion extension by exerting anti-excitotoxicity effects and releasing neurotrophins (36). Therefore, the pivotal involvement of astrocyte responses to an ischemic lesion designates them as excellent therapeutic targets to improve the functional outcome following stroke. In addition, the blockade of the GSK-3β-induced degradation of β-catenin, which in turn promotes neuronal survival, represents a key step in the ability of Wnt1 to safeguard midbrain dopaminergic neurons (37). Within the central nervous system, Wnt signaling cascades orchestrate all aspects of neuronal functions, including differentiation, neuron death or survival, axonal extension, synapse formation and plasticity, neurotrophin transcription, neurogenesis and regeneration (38-41).

Voltage-gated K^+ channel (Kv)2.1/Kv2.2 pathway and neuron protection. Kv2.1 is involved in the neuron apoptosis pathway. Neurons characterized with low functional expression of Kv2.1 are observed to have high resistance against apoptotic stimuli (42). However, overexpression of the C terminal in its homologous Kv2.2 pathway interferes with the Kv2.1 cluster, without affecting other active channels. Such interference leads to neuron protection by blocking the increased current intensity of the K^+ pathway (43,44). In a previous study, it was identified that a seven-amino acid declustering domain, SIDSFTS, induces the dispersion of the Kv2.1 cluster to protect neurons in a murine ischemia-reperfusion model (45). Furthermore, the membrane-permeable derivative, TAT-DP-2, induces Kv2.1 surface cluster dispersal, prevents post-injurious pro-apoptotic potassium current intensity enhancement, reduces infarct size and improves long-term neurological function following stroke (45). The therapeutic peptide derived from TAT-DP-2 is permeable to the blood brain barrier (BBB), providing effective neuron protection in murine models after ischemic stroke *in vivo* (45). Thus, destruction of the Kv2.1 cluster provides neuronal protection (Fig. 1) (45).

WD repeat containing antisense RNA targeting TP53 (WRAP53) mediates neuron repair. It has been shown that WRAP53 expression induces DNA double strand repair in neurons to promote functional recovery after ischemic stroke (46). Moreover, oxygen/glucose deprivation induces excessive production of ROS in murine stroke models, and ROS break DNA double strands in neurons (47). Furthermore, WRAP53 activation promotes DNA repair after its translocation into the nucleus. Knockdown of WRAP53 exacerbates DNA double strand damage, which results in lower resistance to apoptotic stimuli in neurons. By contrast, overexpression of WRAP53 activates DNA double strand repair, and consequently promotes neuron protection and survival (46). Clinical trials have demonstrated that high WRAP53, a telomere-related gene, may be beneficial for healthspan in humans, reversing certain deleterious metabolic consequences of prediabetes (48).

Neural precursor cells (NPCs) mediate astrocyte-neuron conversion. NPCs facilitate the survival, proliferation and

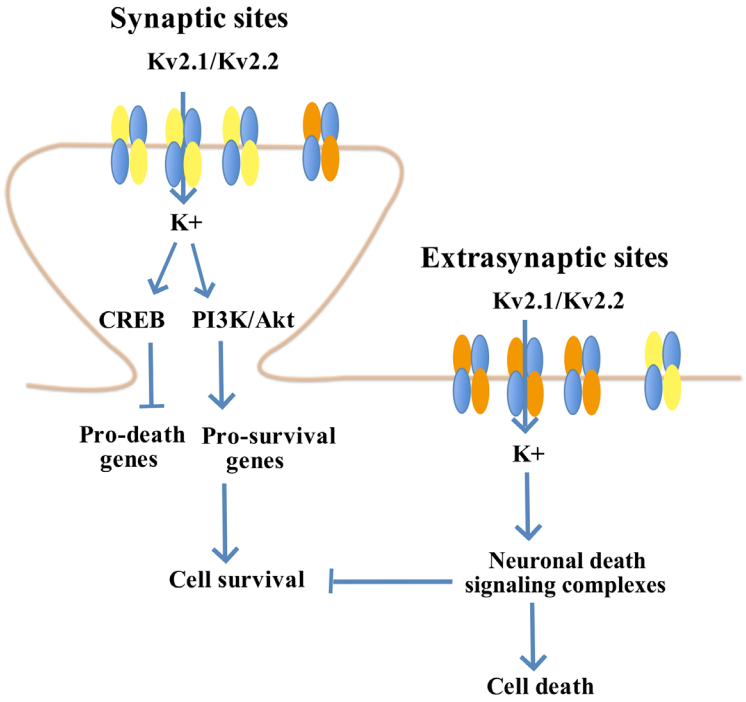

Figure 1. Kv2.1/Kv2.2 pathway in neuron protection. Kv, voltage-gated K^+ channel. CREB, Cyclic AMP response-element binding protein; PI3K/Akt, phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B.

regeneration of neurons in stroke areas and infarct zones in animal models (9-11). Some clinical trials have reported positive results for the use of NPCs in patients (49). Moreover, transplantation of external NPCs is another potential clinical treatment for strokes (6-8). Neurotrophic factors are used to amplify neuron regeneration in adult mammalian brains via embedded neurogenesis, but this only contributes to <1% of the neuron loss caused by ischemic strokes (50-54).

Having been transplanted into damaged cortical zones, neural stem cells (NSCs) from the cerebral pituitary chamber are responsible for producing astrocytes rather than neurons (55,56). Furthermore, transplanted external NSCs are associated with various challenges, such as immunological rejection, tumor progression and poor long-term survival (12,49,57-59). In addition, astrocytes can be converted to neurons after ischemic stroke *in vitro* and *in vivo* (13-17,19,60-62). For instance, Chen *et al* (20) reported a 74.3% astrocyte-neuron conversion rate in murine models after stroke. However, the clinical effects of this conversion in patients has not been investigated.

N-methyl-D-aspartate receptor (NMDAR) bidirectional regulation of neuronal survival or death. NMDARs are a crucial regulatory factor of neuron injuries and ischemic stroke. NMDARs serve a double-edged role in the regulation of neuronal survival or death (63-65). Firstly, different subtypes of NMDARs regulate neuronal survival and death (66-68). It has shown that NMDAR antagonists, containing NMDA receptor 2B (GluN2B), relieve the toxicity caused by NMDA in temporary MCAO (tMCAO) models *in vitro* and *in vivo*. However, NMDAR antagonists containing GluN2A aggravate neuronal death rather than relieving its effects (66,68-74). Secondly, the functions of NMDARs vary with their locations. Indeed, NMDARs inside and outside the synapse exert opposite functions (63,75,76). NMDAR downstream mechanisms and pathways are complex (77-81). NMDARs inside and outside of synapses evoke ERK1/2 kinases, but only the NMDARs inside the synapse increase the level of ERK phosphorylation to provide protection for neurons under toxic conditions (80,82). Notably, stimulation of the NMDAR outside the synapse inactivates ERK1/2 (82). Thirdly, NMDARs serve various roles in signaling pathways that modulate neuronal survival and death (64,65). A low concentration of NMDA activates NSCs to exert a neuroprotective response. Furthermore, the PI3K/Akt kinase and MAPK pathways are downstream of NMDARs involved in neuron survival (Fig. 2) (63,83). MAPK signaling pathway members, including p44/42 MAPK (ERK1/2), JNK and p38 MAPK, regulate cell proliferation and differentiation, and the responses to cytokines and stress during protein kinase cascades. However, NMDARs induce neural toxicity by activating NSCs, in the form of the GluN2B-postsynaptic density protein 95-neuronal nitric oxides synthase complex (84,85), GluN2B-death associated protein kinase 1-p53 complex (86,87) or GluN1-PTEN complex (88) (Fig. 3).

Oxidative stress. Heme oxygenase 1 (HO-1) is highly expressed in brain tissues after cerebral injuries, including stroke and infarction, and a high expression level of HO-1 symbolizes the activation of the protective mechanism against oxidative stress (89). Brain injuries are associated with oxidative stress. It has been revealed that Persian blue (PB) nanoparticles effectively eliminate excessive ROS produced by ischemic stroke and cerebral infarcts. PB exerts a similar function to catalase, superoxide dismutase and peroxidase (90,91). Moreover, hollow Prussian blue nanozymes (HPBZs) react and neutralize inflammation caused by immune responses, as well as suppressing neuron apoptosis *in vitro* and *in vivo*. Thus,

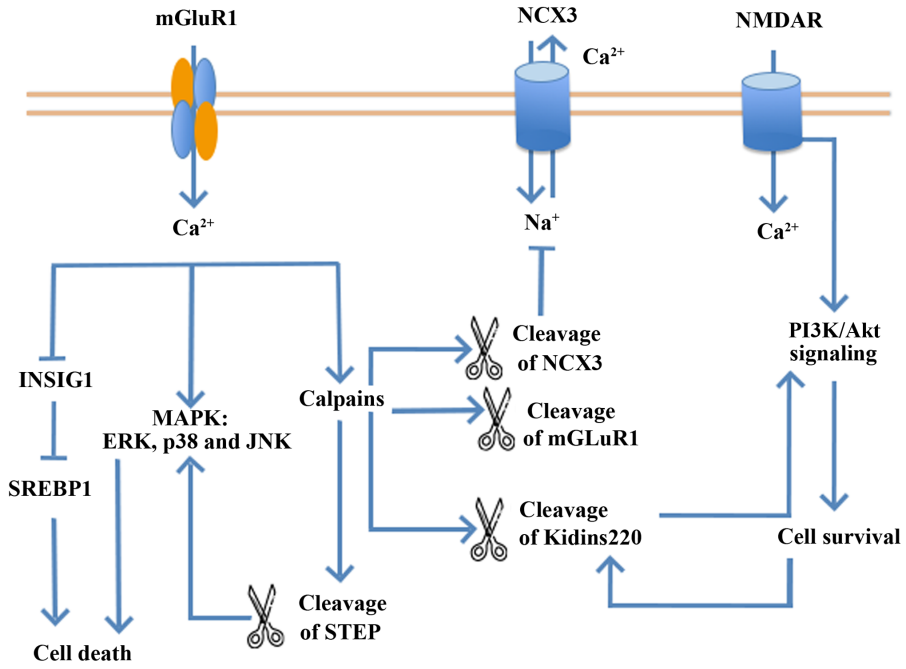

Figure 2. NMDARs mediate bidirectional regulation of neuronal survival or death. NMDAR, N-methyl-D-aspartate receptor; mGluR1, metabotropic glutamate receptor subtype 1; INSIG1, insulin-induced gene 1; SREBP1, sterol regulatory element binding protein 1; STEP, striatal-enriched protein tyrosine phosphatase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; NCX3, sodium-calcium exchanger 3.

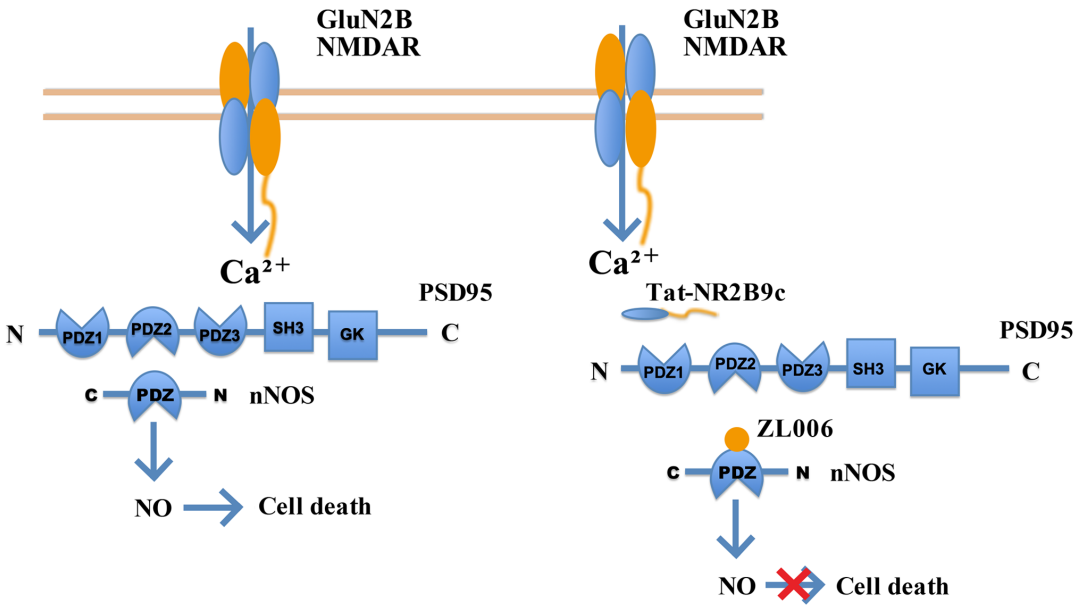

Figure 3. NMDARs induce neural toxicity through the GluN2B-postsynaptic density protein 95-nNOS axis. NMDAR, N-methyl-D-aspartate receptor; GluN2B, NMDAR receptor 2B; nNOS, neuronal nitric oxides synthase; PDZ, PSD95 discs-large and zona occludens-1; Tat-NR2B9c, postsynaptic density 95 blocking peptide; ZL006, a small-molecular inhibitor of the nNOS-PSD-95 interaction; SH3, Src Homology 3; GK, guanylate kinase.

HPBZs increase the tolerance to strokes and minimize neural injuries (92).

Immune responses. Stroke interrupts the blood flow into the brain. The pathophysiology of stroke involves a progressive systematic response after brain damage (93). Animal stroke models (94) and clinical patients (95) show dynamic BBB rupture. The BBB fracture induced by stroke initiates a series of pathological responses. The hyperinflammatory responses caused by strokes include increased levels of inflammatory cells, cytokines and chemokines in the circulating blood (96). Recently, it has been shown that infarct sizes are effectively decreased and that a promising recovery of neural injuries occurs at 6.5-7 h after the stroke in an animal model of tMCAO (22). The intervention used in this model was blood substitution therapy to replace the blood of mice suffering from strokes with the whole blood from healthy infant mice (22). The possible underlying mechanisms in this therapy may be as follows: Firstly, the brain antigens released after the rupture of the BBB may activate the immune system after stroke.

Therefore, replacing the blood in mice with strokes may reduce the amount of brain antigens in the circulating blood to alleviate the immune responses after stroke. Secondly, replacing the blood in mice with strokes effectively reduces the number of activated leukocytes. Thus, large amounts of harmful signals in circulating blood after stroke, including cytokines, chemokines and proteases, are decreased. Finally, new replacement blood may provide oxygen and various other neuroprotective factors.

Platelet microvesicle (PMV) intervention and microRNAs (miRNAs/miRs). The molecular mechanism of neuronal damage caused by ischemic stroke and cerebral infarction is complex. In addition to the molecular processes previously mentioned, multiple other factors also provide new insights into the treatment of stroke. Recently, PMVs have been found to significantly improve the recovery of neurological function in mice with cerebral infarction and promote angiogenesis at the infarction edge (97). The procoagulant and proinflammatory phenotype of circulating PMVs may contribute to acetylsalicylic acid treatment failure in patients with convalescent stroke (98).

Accumulating evidence has shown that exosomal miRNAs are one of the most important factors involved in the pathogenesis of stroke. Exosomal miRNAs are used as non-invasive biomarkers in stroke diagnosis and for monitoring the response during therapy (99). Antagomirs (anti-miRNAs) are an effective treatment method to enhance neuronal survival in various animal models, for example, administration of an antisense oligonucleotide inhibitor of miR-129-5p to an amyotrophic lateral sclerosis animal model, SOD1 (G93A) mice, resulted in a significant increase in survival and improved the neuromuscular phenotype in treated mice (100); and some miRNAs show therapeutic effects in stroke (101). These miRNAs affect the pathways induced by stroke, including leukocyte extravasation signaling, NF-κB signaling, Toll-like receptor signaling and the prothrombin activation pathway (102). For instance, miR-122, miR-9, miR-298 and miR-155-5p participate in brain injury after stroke by targeting different genes involved in the NF-κB signaling pathway (103-106). Thus, miRNAs are crucial in stroke progression, diagnosis, therapy and prognosis.

3. Clinical management

At present, thrombolytic therapy is the most widely applied treatment for ischemic stroke and brain infarction (107). The basic principle of thrombolysis is to recanalize and reperfuse cerebral arteries using thrombolytic drugs and mechanical thrombectomy devices, eventually leading to the partial recovery of brain tissues and neural functions (108). The clinical effectiveness of intravenous thrombolytic therapy has been established for patients within 4.5 h of stroke onset. However, numerous patients experience complicated situations, such as proximal artery occlusion, >4.5 h of stroke onset and contraindication of systemic thrombolysis due to recent major surgeries or active hemorrhage. Such patients are not suitable for intravenous thrombolysis therapy (109). Therefore, a recent review indicated that several studies and clinical trials have focused on catheter or artery-based treatments that directly remove occlusions in blood vessels and recover the blood flow (28).

Intravenous thrombolysis. Clinical trials funded by the United States Natural Institute of Neurological Diseases and Stroke and the European Acute Stroke Study have shown that intravenous thrombolysis has strong effects in patients with mild symptoms or no disability, and that intravenous thrombolysis has more benefits than limitations in patients with a full range of disabilities (110,111). For instance, treatment with tissue plasminogen activator in the 3- to 4.5-h window confers benefit on approximately half as many patients as treatment for <3 h, with no increase in the conferral of harm; ~1 in 6 patients has a better outcome and 1 in 35 has a worse outcome as a result of therapy. Previous studies (112-114) have established intravenous thrombolysis as the standard therapy for patients with AIS within 3 h of stroke onset. Intravenous thrombolysis is beneficial for all levels and subtypes of strokes (115), and 35-40% of patients displayed a good therapeutic outcome. However, only 10-15% of internal carotid artery occlusions and 25-50% of proximal MCAO were alleviated by intravenous thrombolysis therapy alone. These data indicated that the proximal artery occlusion (internal carotid artery and MCAO) may be resistant to intravenous thrombolysis therapy alone (116,117). Proximal artery occlusion leads to one-third of AIS cases with severe stroke symptoms and has the negative outcome of ineffective reperfusion (118). Thus, several large-scale clinical trials have been focusing on identifying other substitutional or adjunctive therapies based on intravenous thrombolysis to improve recanalization and the reperfusion rate.

Arterial thrombolysis. Arterial thrombolysis consists of chemical thrombolysis and mechanical thrombectomy, and the use of intravenous therapy prior to mechanical thrombectomy has been recently questioned (118). The clinical efficacy and safety of arterial thrombolysis with the selective thrombolytic recombinant-pro-urokinse (r-proUK) has been investigated in two randomized acute stroke treatment trials, namely PROACT I and PROACT II (119). It has been shown that patients treated with such therapy experience the risk of cerebral hemorrhage. Moreover, the outcome of combining arterial thrombolysis with other agents as therapy remains unclear. Therefore, the Food and Drug Administration (FDA) did not grant the clinical application of arterial r-proUK. Nevertheless, a recent study reported that r-proUK promoted thrombolysis and recanalization, with a decreased risk of cerebral hemorrhage, and thus, this treatment exerted protective effects on cerebral ischemia in rabbits (120).

Different from recently developed chemical thrombolysis, mechanical thrombectomy has been widely applied in the clinic (121). The FDA granted permission of several mechanical thrombectomy devices based on positive results yielded by numerous large-scale clinical trials (122). These devices can effectively recanalize proximal artery occlusion with an acceptable rate of complications (123,124). Indeed, any type of intracerebral hemorrhage was observed less frequently in the mechanical thrombectomy alone group compared with that in the group using the combination of intravenous thrombolysis with mechanical thrombectomy (125). However, the mechanical thrombectomy alone group failed to show a favorable functional outcome among patients with acute large vessel occlusion stroke compared with the combined group. Furthermore, a recent finding supported the hypothesis that

intravenous therapy before mechanical thrombectomy does not influence the prognosis of patients with stroke (126).

Pre-clinical magnetic resonance imaging. Trials of novel recanalization methods based on MRI tool selection of patients are ongoing. Unless a specific lesion site is taken into account, functional deficits due to medium-sized infarcts are difficult to predict (127). Accurate information regarding the location of the lesion and the progression of the disease is crucial for clinic therapy. Therefore, promising neuroprotective compounds in the pre-clinical phase can be subsequently dismissed for ineffectiveness in large-scale clinical trials due to inaccurate information. Infarction of the internal capsule (IC) may be associated with motor impairment and poor prognosis in patients with stroke (128). Pre-clinical MRI information regarding volume size and the precise location of the lesion into the IC is required for subsequent therapy. Moreover, the state of neurological damage according to MRI, as well as the destruction of axonal structures and pathological changes according to immunostaining, provide information for the precise injection site of neuroprotective drugs (129). Thus, combined MRI and histological methods provide a powerful method of assessing neuronal damage during cerebral ischemia therapy (129).

4. Conclusion and future perspectives

Ischemic stroke leads to severe outcomes, including cerebral infarcts, permanent brain damage and neural functional deficits. Therefore, decreasing and preventing neural injuries caused by stroke and infarctions has been the focus of mechanistic and therapeutic studies. The current review summarized the pathophysiology, molecular mechanisms, animal models, and clinical management and therapies in ischemic strokes. The related molecular mechanisms in clinical trials should be further investigated. The American Heart Association has suggested that arterial thrombolysis is an acceptable alternative therapy for strokes. Multiple stroke centers provide arterial thrombolysis for patients experiencing a major acute stroke attack within 6 h. However, the molecular mechanism underlying arterial thrombolysis remains to be fully investigated.

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Authors' contributions

YZ and XZ wrote the manuscript. YZ, XZ, YW and XC searched the relevant literature. XC and YW critically reviewed the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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