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Emerging Neuroprotective Strategies for the Treatment of Ischemic Stroke: An Overview of Clinical and Preclinical Studies

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Abstract

Stroke is the leading cause of disability and the second leading cause of death worldwide. With the global population aged 65 and over growing faster than all other age groups, the incidence of stroke is also increasing. In addition, there is a shift in the overall stroke burden towards younger age groups, particularly in low and middle-income countries. Stroke in most cases is caused due to an abrupt blockage of an artery (ischemic stroke), but in some instances stroke may be caused due to bleeding into brain tissue when a blood vessel ruptures (hemorrhagic stroke). Although treatment options for stroke are still limited, with the advancement in recanalization therapy using both pharmacological and mechanical thrombolysis some progress has been made in helping patients recover from ischemic stroke. However, there is still a substantial need for the development of therapeutic agents for neuroprotection in acute ischemic stroke to protect the brain from damage prior to and during recanalization, extend the therapeutic time window for intervention and further improve functional outcome. The current review has assessed the past challenges in developing neuroprotective strategies, evaluated the recent advances in clinical trials, discussed the recent initiative by the National Institute of Neurological Disorders and Stroke in USA for the search of novel neuroprotectants (Stroke Preclinical Assessment Network, SPAN) and identified emerging neuroprotectants being currently evaluated in preclinical studies. The underlying molecular mechanism of each of the neuroprotective strategies have also been summarized, which could assist in the development of future strategies for combinational therapy in stroke treatment.

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DECLARATION OF COMPETING INTERESTS

The authors declare no competing interests.

Keywords

blood-brain barrier dysfunction; clinical trials; comorbidities; excitotoxicity; ischemic stroke; neuroinflammation; neuroprotection; neuroprotective agents; oxidative stress; preclinical studies

1. INTRODUCTION

Cerebrovascular accident or stroke is the second largest cause of death worldwide with an annual mortality rate of about 5.5 million. It is also the leading cause of disability worldwide with 50% of survivors being chronically disabled (Donkor, 2018; Katan and Luft, 2018). New research indicates that the occurrence of stroke is on the increase with one in four people worldwide to experience stroke in their lifetime (Collaborators et al., 2018). An aging population coupled with the burden of accumulating risk factors contributes to such increase in lifetime risk of stroke. In addition, increasing socioeconomic status in the developing countries has led to an epidemic rise in the risk factors for stroke in younger adults (Katan and Luft, 2018). These risk factors include atrial fibrillation, hypertension, hyperlipidemia, hyperhomocysteinemia, diabetes, smoking, lack of physical activity, unhealthy diet, abdominal obesity and alcohol consumption (Boehme et al., 2017; O'Donnell et al., 2016). However, hypertension is by far the most potent risk factor for stroke that accounts for ~54% of all strokes (Benjamin et al., 2019; Boehme et al., 2017; Lawes et al., 2008). Prevalence of hypertension in American adults is estimated to be ~45.4%, with an overall frequency of ~71.8% at age 60 years and older (Benjamin et al., 2019; Dorans et al., 2018). The absolute burden of hypertension in American adults has increased from ~86.6 million in 1999 to ~108 million in 2015 (Dorans et al., 2018). Notably, the global burden of hypertension has increased from 442 million in 1990 to 874 million in 2015, a ~97% increase, and it has been predicted that over the next two decades the incidence of stroke will increase by another ~24.9% (Forouzanfar et al., 2017; Heidenreich et al., 2011; Huffman and Lloyd-Jones, 2017; Kearney et al., 2005). Stroke is primarily classified as ischemic or hemorrhagic in nature. Ischemic stroke is caused by reduction of blood supply to a certain region of the brain due to obstruction of a blood veesel. In contrast, hemorrhagic stroke occurs due to the rupture of a blood vessel in the brain causing bleeding in the brain or the subarachnoid space (Amarenco et al., 2009; Donnan et al., 2008). Several studies have established that ischemic stroke is the most prevalent form of stroke worldwide (Bamford et al., 1991; Donkor, 2018; O'Donnell et al., 2010; Sarfo et al., 2018).

2. PATHOPHYSIOLOGY OF ISCHEMIC STROKE

The progression of ischemic brain damage following impaired blood flow involves the initial development of a core of irreversibly injured necrotic tissue within the affected vascular bed, followed by late phase injury development in the peri-infarct area, a potentially salvageable area surrounding the core (Astrup et al., 1981; Dirnagl et al., 1999; Ramos-Cabrer et al., 2011). The pathophysiology of ischemic brain damage involves the activation of a series of detrimental signaling cascades. Deprivation of oxygen and glucose supply to the brain tissue leads to immediate failure of energy-dependent ion pumps and channels resulting in the release of potentially toxic concentrations of excitatory neurotransmitters and subsequent

death of the vulnerable neurons. The excessive release of the excitatory neurotransmitter glutamate is undoubtedly a prime element initiating the progression of brain damage through activation of N-methyl-D-aspartate (NMDA), Voltage gated (L-type), and quisqualate (Q) post synaptic receptor complexes (Pulsinelli, 1992). The influx of intracellular calcium through these receptors leads to the activation of a series of intracellular signaling cascades (e.g, mitochondrial depolarization, activation of cytosolic phospholipase A2, catalysis of arachidonic acid by cyclooxygenase-2 and activation of NADPH oxidase) resulting in increased free radical generation (Sun et al., 2018). The oxidative and nitrosative stress caused by free radicals are further accelerated by restoration of oxygen supply following reperfusion, inducing lipid peroxidation, protein oxidation and DNA damage during ischemia and reperfusion (Nelson et al., 1992; Sun et al., 2018). Additionally, oxidative stress induced release of damage-associated molecular pattern (DAMP) molecules triggers an inflammatory response involving activation of brain-intrinsic microglia, increased blood-brain barrier (BBB) permeability and peripheral immune cell infiltration (Banjara and Ghosh, 2017; Gulke et al., 2018). Increasing evidences indicate that the post-ischemic inflammation accounts for the secondary progression of brain damage, and the severity of stroke outcome under comorbidities depends on the extent of this inflammatory response (Chamorro et al., 2012; Lakhan et al., 2009; Veltkamp and Gill, 2016; Wang et al., 2007). A simplified overview of the ischemic cascade has been presented in Figure 1.

Despite advances in understanding the pathophysiology of stroke, successful treatment remains a major challenge in clinical medicine. Reperfusion with recombinant tissue plasminogen activator (rtPA) remains the only pharmacological therapy (Cohen et al., 2011; Del Zoppo et al., 2009; Kwiatkowski et al., 1999). In a small number of cases surgical recanalization is also possible (Choi et al., 2006; Cohen et al., 2011; Prabhakaran et al., 2015; Smith et al., 2008). However, rapid reperfusion, although necessary for restoration of brain metabolic activity, is also associated with additional risks (Bai and Lyden, 2015; Khatri et al., 2012; Mizuma et al., 2018). The development of neuroprotection strategies to protect brain cells from both ischemia and reperfusion injury as well as to amplify the time window for thrombolytic treatment is therefore an important goal (Chamorro et al., 2016).

3. PAST CHALLENGES IN DEVELOPING NEUROPROTECTIVE STRATEGIES

Neuroprotectants refers to any agent(s) capable of reducing ischemic brain injury by antagonizing detrimental molecular events in the brain rather than improving cerebral blood flow. Preclinical research for several decades has demonstrated the potential benefit of neuroprotection in experimental stroke models (O'Collins et al., 2006). However translation of such neuroprotective treatments from animal models to humans is yet to yield a positive result (Braeuninger and Kleinschnitz, 2009; Sacchetti, 2008).

Failure to include stroke models with significant comorbidities and sub-optimal design of many of the pre-clinical studies could have contributed to the high failure rate. In many of the earlier studies, neuroprotective agents were tested only in young animals, which do not mimic all aspects of stroke in older humans (Chen et al., 2010a; DiNapoli et al., 2008; Jin et

al., 2004). In only 6% of human patients, stroke occurs in isolation (no comorbidities), and high prevalence of one or more pre-existing comorbidities is known to worsen stroke outcome in patients (Fischer et al., 2006; Gallacher et al., 2014; Guthrie et al., 2012; Karatepe et al., 2008). Moreover, stroke outcome measures in many of these earlier studies have been limited to final infarct size measurement at 24h and relatively limited neurological testing over a short-time period. However, the extent of lesion and functional deficits may vary over prolonged time periods (Colbourne et al., 1999; Virley et al., 2000). As a result, Stroke Therapy Academic Industry Roundtable (STAIR) recommendations now emphasizes a focus on agents with multiple mechanism(s) of action in neuroprotection, assessment of efficacy when treatment is combined with thrombolytic agents, assessment of long-term recovery using non-invasive magnetic resonance imaging and complex sensorimotor and cognitive tasks, as well as inclusion of experimental models of stroke with comorbidities and advanced age in both sexes (Albers et al., 2011; Fisher et al., 2005). From the translational standpoint, it is also important to consider the need for multicenter randomized pre-clinical trials in animal models of stroke (Balduini et al., 2016; Dirnagl and Fisher, 2012; Kellner et al., 2016), similar to what has been adapted in human clinical trials. Preclinical studies that meet these stringent criteria should also be presented in the public domain before moving to clinical trials.

The abundance of failed clinical trials also points toward several caveats/deficiencies in the quality or scope of these trials (Ginsberg, 2008; Xiong et al., 2018). The most important among these caveats is the time of administration of neuroprotective agents. For most of these trials patients were enrolled beyond 4h after stroke onset, which is beyond the optimal time window (4–6h) for efficacious neuroprotection (Saver, 2013). Pre-hospital administration of neuroprotectants in the field by paramedics may allow the therapy to be started at the earliest opportunity and slow down the progression of ischemic brain injury. Low rates of recanalization may have also contributed to the lack of efficacy of neuroprotective agents in earlier clinical trials. In the current thrombectomy era, cotreatment with neuroprotective agents during recanalization could augment the delivery of neuroprotective agents to the targeted brain regions and further enhance the efficacy of stroke therapy. Furthermore, it needs to be considered that all stroke patients may not benefit from a given neuroprotective agent. Also, additional studies are needed to identify serological biomarkers for different subgroups of stroke patients. This information could then be used to determine the efficacy of potential neuroprotective agents in animal models of stroke. Optimal patient selection based on such biomarkers could decrease the likelihood of failure in clinical trials. Thus, a renewed approach towards development of novel neuroprotectants must consider the lessons learned from all the earlier studies, both pre-clinical and clinical, to devise a plausible path to success.

In this review, we have compiled the list of (1) recently completed clinical trials with neuroprotectants performed between 2015 through 2020, (2) ongoing clinical trials, (3) NIH-initiated search for neuroprotectants as part of the Stroke Preclinical Assessment Network (SPAN) and (4) emerging neuroprotectants. We have further discussed the mechanism(s) of action and therapeutic approaches for these potential neuroprotectants.

4. RECENTLY COMPLETED CLINICAL TRIALS FOR STROKE NEUROPROTECTION

Several clinical trials were initiated in the last five years to test the beneficial effects of multiple neuroprotective agents. For most of these agents, some experimental data were available on the mechanism(s) of action, functional outcome following treatment in rodent models of stroke, efficacy in stroke models with comorbidities and use at longer intervals after ischemic injury. As inflammatory mediators play a crucial role in the progression of ischemic brain damage, an important target for these potential neuroprotective agents has been the post-stroke inflammatory pathway, although some of them have diverse effects. In addition, two of these neuroprotective agents targets excitotoxicity and oxidative stress signaling pathway (Table 1).

Human urinary kallidinogenase (HUK) is a tissue kallikrein extracted from urine (Savica et al., 2011; Yousef and Diamandis, 2001). It is a glycoprotein that can cleave the low molecular weight protein kininogen to produce the potent vasodilator peptide kinin, which can trigger a series of biological effects (Chao and Chao, 2005). Accumulating evidence indicates that tissue kallikrein is a promising target for the treatment of acute ischemic stroke. Studies in animal models of acute ischemic stroke showed that HUK reduces infarct volume and improves neurological deficits (Chao and Chao, 2006; Wei et al., 2018). The underlying mechanisms involve increased local vasodilation and neuroprotection (Chen et al., 2010b; Emanuelia and Madeddu, 2003; Han et al., 2015; Yang et al., 2017c). HUK confers neuroprotection as an anti-oxidative and anti-inflammatory agent, through suppression of toll-like receptor 4 and the nuclear factor-kappa B (TLR4/NF-κB) signaling pathway that induces the expression of pro-inflammatory genes. It also increases the expression of transforming growth factor beta 1 (TGF-β1), which is known to attenuate neuroinflammation (Cekanaviciute et al., 2014; Dong et al., 2016; Yang et al., 2017c). Additional studies in *ex vivo* models of hypoxic injury have further demonstrated that HUK could inhibit glutamate-induced oxidative injury and neurotoxicity (Liu et al., 2011; Liu et al., 2009). A meta-analysis of 24 small scale randomized controlled trials in acute ischemic stroke with HUK treatment have reported improved neurological function and long-term outcome. However, treatment related adverse events were also observed in 15 trials with transient hypotension being the most common one (Zhang et al., 2012a). For a comprehensive re-evaluation of the safety and efficacy of HUK, a large scale open-label, singlearm, multicenter phase IV trial (NCT02562183) was subsequently designed (Ni et al., 2017). A more recent analysis of pooled data from randomized double-blind placebo-controlled phase IIb and phase III clinical trial have showed that HUK is safe and provides potential clinical benefits as a treatment of acute ischemic stroke regardless of age, sex and comorbidities when treatment is initiated within 48h of symptom onset (Dong et al., 2020b). In addition, a phase IV clinical trial (NCT03431909) to assess the efficacy of HUK in acute ischemic stroke has also been recently completed, but outcome of this trial has still not been reported. HUK has been approved by China‟s State Food and Drug Administration to be used for treatment of mild to moderate stroke (Wu et al., 2017a).

Statins are a group of drugs that inhibit 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, an enzyme involved in cholesterol synthesis (Vaughan et al., 2000). Statins are either fungal-derived (lovastatin, pravastatin and simvastatin) or fully synthetic compounds (atorvastatin, cerivastatin, pitavastatin, rosuvastatin and fluvastatin) (Schachter, 2005). Although the different statins vary in their efficacy for loweing cholesterol, currently they are the most effective agents available for treating hyperlipidemia. They are also effective in decreasing cardiovascular-related morbidity and mortality in individuals with or without coronary artery disease (Lee et al., 2019; Zhou and Liao, 2009). More recently, studies in experimental animal models of stroke have shown that statins can also reduce ischemic infarct size when administered before or after stroke as well as with or without thrombolytic agents (Amin-Hanjani et al., 2001; Balduini et al., 2001; Elkind, 2006; Endres et al., 1998; Gertz et al., 2003; Kawashima et al., 2003; Laufs et al., 2002; Sironi et al., 2003). The efficacy of statins in reducing ischemic brain damage have been shown to be independent of its cholesterollowering ability. In these studies, statins upregulated endothelial nitric oxide synthase (eNOS) in the cerebral vasculature, particularly in the ischemic penumbra, thereby increasing cerebral blood flow and limiting neuronal loss. Treatment with statins also provided protection against post-stroke BBB dysfunction by attenuating the expression of adhesion molecules (Mayanagi et al., 2008; Pruefer et al., 1999; Romano et al., 2000b). In addition, statins have also been shown to confer neuroprotection in the rodent ischemic brain through reduced generation of superoxide radicals and inhibition of NFκB-mediated expression of inflammatory cytokines (Cui et al., 2009; Hong et al., 2006; Kawai et al., 2011; Romano et al., 2000a; Sironi et al., 2006; Weitz-Schmidt, 2002). These pleiotropic effects of statins also account for the reduced infarct size observed in rodent models of ischemic stroke with hypertension (Garcia-Bonilla et al., 2012; Nagotani et al., 2005). Recently, clinical trials have been initiated to evaluate the therapeutic potential of statins in ischemic stroke patients. Phase I clinical trial (NeuSTART) first established the efficacy and feasibility of using lovastatin in stroke patients (Elkind et al., 2008; Elkind et al., 2009). A phase II randomized, blinded and controlled study (NeuSTART2) that was recently completed, assessed the efficacy of short-term administration of a high dose of levostatin (640 mg/day) for 3 days after stroke when compared with patients who were treated with the standard dose of levostatin (80 mg/day) before and after stroke. Functional outcome, inflammatory markers and lipid levels were also assessed 3-months post stroke. However, the outcome of this clinical trial has not yet been published. Another multicenter randomized controlled trial (ASSORT) also completed recently showed that delayed statin therapy (7 days following stroke) was as efficient as statin treatment administered during early acute phase of ischemic stroke (within 24h) in its ability to alleviate physical disability assessed 3-months after stroke onset (Yoshimura et al., 2017).

Edaravone, also known as MCI-186 (3-methyl-1-phenyl-2-pyrazolin-5-one) is a low molecular weight free radical scavenger that can readily cross the blood-brain barrier (Yoshida et al., 2006). Numerous studies in experimental rodent models of ischemic stroke have demonstrated that pre-treatment or post-treatment with edaravone is effective in decreasing infarct volume and improve neurological function (Kitagawa, 2006; Nishi et al., 1989; Shichinohe et al., 2004; Watanabe et al., 1994; Wu et al., 2000). Edaravone exerts its

neuroprotective effects primarily through its anti-oxidant activity (Banno et al., 2005; Higashi, 2009; Lee et al., 2010; Yamamoto et al., 1997). However, the therapeutic potential of edaravone in the treatment of stroke has also been attributed to its ability to regulate additional deleterious cascades, which includes inhibition of lipid oxidation, endothelial expression of nitric oxide synthase by oxidized LDL, inflammatory response caused by the release of high-mobility group box-1 protein from neurons, microglia-induced neurotoxicity and matrix metalloproteinase-9 (MMP-9) activation (Banno et al., 2005; Higashi et al., 2006; Yagi et al., 2009; Yoshida et al., 2005; Zhang et al., 2005). It has also been suggested that edaravone may prevent post-stroke edema by reducing the levels of endothelial growth factor and aquaporin-4 in astrocytes (Kikuchi et al., 2009). Although these findings suggest that edaravone is a multi-target neuroprotective agent that could be beneficial for stroke treatment, information regarding its efficacy in preclinical models with comorbidities and long-term outcome have not been reported. In clinical studies, safety and pharmacokinetic profile evaluation of edaravone have established that it is well tolerated in normal volunteers following administration of a single or multiple doses (Shibata et al., 1998). Analysis of multiple clinical trials evaluating the efficacy of edaravone on embolic, thrombotic and lacunar strokes have also established beneficial effects of treatment with regards to functional outcome and survival parameters, which has been extensively discussed in two earlier review articles (Lapchak, 2010; Rolain et al., 2019). These studies showed that edaravone is most effective when administered within 24h following a stroke, and extended treatment is required for maximum efficacy. However, several adverse side effects of edaravone have also been reported in stroke clinical trials, of which increased renal toxicity is of major concern, although it seems to be reversible in some patients (Edaravone Acute Infarction Study, 2003; Hishida, 2007, 2009; Shinohara et al., 2009). A few clinical studies documented the use of edaravone in combination with thrombolytics and the most intriguing finding from one such study is that treatment with edaravone prior to intravenous administration of thrombolytics reduced intracerebral hemorrhage (Enomoto et al., 2019). Based on these findings edaravone has been approved for the treatment of acute ischemic stroke in Japan, but it is still not considered for standard treatment globally (Kikuchi et al., 2010; Kikuchi et al., 2017; Lapchak, 2010). To further assess its efficacy as a neuroprotective agent, a large-scale clinical trial (NCT02430350) was recently completed to compare the effects of treatment with edaravone alone or in combination with borneol, an anti-inflammatory agent, for which the outcome has still not been reported.

NA-1 (nerinetide; TATNR2B9c) is a cell-permeable peptide comprised of nine COOH-terminal residues of NR2B subunit of NMDA receptor. It interacts with and disrupts the binding of synaptic protein PSD-95 to the NR2B subunit of NMDA receptor and to the PDZ domain of neuronal nitric oxide synthase (nNOS). Disruption of these protein-protein interaction by NA-1 attenuates the neurotoxic signaling cascades downstream of NMDAR activation that includes excessive neuronal calcium ion influx and excitotoxic nitric oxide production (Aarts et al., 2002; Ballarin and Tymianski, 2018; Sattler et al., 1999; Soriano et al., 2008). Thus, NA-1 prevents excitotoxic cell death and subsequent brain damage without blocking normal synaptic function of NMDA receptors. Long-term evaluation of stroke outcomes in rodent and non-human primate models of focal ischemia have further showed that treatment with NA-1, even when administered after the onset of stroke, can reduce

infarct size along with improvement in neurological deficits (Bratane et al., 2011; Cook et al., 2012; Sun et al., 2008). The efficacy and safety of NA-1 was also recently evaluated in a multi-centre, double blind randomized controlled clinical trial (ESCAPE). The study enrolled stroke patients with large vessel occlusion within a 12h treatment window in 48 acute care hospitals in eight countries. The findings show that treatment with a single dose of NA-1 along with endovascular thrombectomy failed to improve long-term stroke outcome when compared with patients receiving pacebo. However, in a sub-population of patients who received NA-1 treatment without any thrombolytics, a lower risk of mortality, significant reduction in infarct volume and improved functional outcome was observed (Hill et al., 2020). The authors hypothesized that in patients receiving both the thrombolytic agent (tPA) and NA-1, it is possible that alteplase was activating proteases that were digesting the drug. As such, further studies with this promising neuroprotectant are necessary to extensively explore its neuroprotective effects.

3K3A-activated protein C (APC) is an analogue of the endogenous blood serine protease APC where 3 lysine residues (residues 191–193) were replaced by 3 alanine residues (Zlokovic and Griffin, 2011). APC is derived from the protein C zymogen produced by the liver and it has both anticoagulant and cytoprotective properties (Rezaie, 2010). Earlier studies have established that the vasculoprotective, neuroprotective and anti-inflammatory activities of APC protects neurons and cerebrovascular endothelium from stroke injury (Guo et al., 2009; Shibata et al., 2001; Wang et al., 2009; Zlokovic et al., 2005). However, its anticoagulant activity increases the risk of intracerebral hemorrhage and is a significant side-effect in the clinical application of APC (Nadel et al., 2007). To minimize the risk of bleeding, 3K3A-APC was designed that lacks >90% of the anti-coagulant activity, while maintaining the cytoprotective activies of APC (Guo et al., 2009; Mosnier et al., 2004; Wang et al., 2009; Williams et al., 2012). In animal models of ischemic stroke, treatment with 3K3A-APC has been shown to reduce infarct size and improve functional outcome, even when administered several hours after the onset of the insult (Ellery et al., 2019; Wang et al., 2012). When 3K3A-APC was administered along with tPA, it also eliminated tPA-induced intracerebral hemorrhages and extended the therapeutic time window of treatment with tPA (Wang et al., 2012). In addition, 3K3A-APC has also been shown to be effective in the treatment of stroke in both aged and hypertensive animals (Wang et al., 2013). The mechanisms of 3K3A-APC-mediated neuroprotective and anti-inflammatory activities have been partly elucidated (Griffin et al., 2018). Studies in neuronal cultures have highlighted the requirement of protease activated receptors 1 and 3 (PAR1 and PAR3) in 3K3A-APC mediated attenuation of NMDAR mediated neurotoxicity (Guo et al., 2004). *In vivo* studies have further showed that APC mediated reduction in ischemic infarct volume and intracerebral hemorrhage during combination therapy with tPA requires activation of PAR1-mediated intracellular signaling (Cheng et al., 2006; Liu et al., 2004; Zlokovic and Griffin, 2011). In addition, suppression of NLRP3 inflammasome signaling is also a key contributor to 3K3A-APC‘s anti-inflammatory action (Guo et al., 2016; Guo et al., 2018; Nazir et al., 2017). Based on its strong neuroprotective and anti-inflammatory activities, preclinical safety and pharmacokinetic studies with 3K3A-APC were carried out in both mice and monkeys to ensure the feasibility of 3K3A-APC for stroke therapy in patients (Williams et al., 2012). A phase I clinical trial in healthy volunteers have further established that the drug

is safe up to a maximum dose of 0.54mg/kg without any clinical manifestations of bleeding or bruising (Lyden et al., 2013). A recently completed Phase II clinical trial (RHAPSODY) in moderate to severe ischemic stroke patients, where 3K3A-APC treatment was initiated following tPA infusion or mechanical thrombectomy, also showed that the drug is well tolerated in stroke patients and there is a trend toward lower hemorrhage rate when compared to placebo-treated patients (Lyden et al., 2019). These promising findings have laid the groundwork for additional clinical trials in a larger cohort of stroke patients in the future.

GM6, developed by Genervon Biopharmaceuticals, is a peptide-based multi-target drug that is believed to reduce inflammation and limit neuronal degeneration (Swindell et al., 2018). It is a six amino acid peptide that represents the smallest active site of an endogenous neurotrophin, motoneurotrophic factor (MNTF) that is highly specific for the human nervous sytem and has maximum expression in the ninth week of human fetal development (Di and Huang, 1998; Valko et al., 2018; Yu et al., 2008). Some of its observed functions include motor neuron differentiation, maintenance and survival (Di and Huang, 1998; Di et al., 1997; Yu et al., 2008; Zhou et al., 1994). During injuries and disorders of the central and peripheral nervous sytems, the anti-apoptotic, antioxidative and anti-inflammatory functions of MNTF is thought to create a permissive environment for nerve regeneration and repair (Wang et al., 1995; Yu et al., 2008; Zhou et al., 1997; Zhou et al., 1993). More recent studies have shown that synthetic GM6 has similar activity and demonstrate similar neurotrophic activities as the parent molecule (Chau, 2005; Chau and Ko, 2007). It is anticipated that GM6 have a complex mechanism of action involving activation of multiple receptors and downstream signaling cascades (Yu et al., 2008). However, the exact mechanisms of action of GM6 is yet to be determined. GM6 has also been reported to reduce infarct volume and behavioral deficits in a ischemia/reperfusion injury mouse model (Yu et al., 2008). GM602, a FDA-approved proprietary form of GM6 was recently tested in a phase II clinical trial (GMAIS) to evaluate its efficacy and safety in treatment of ischemic stroke, the outcome of which is yet to be released.

Natalizumab is a humanized antibody against the cell adhesion glycoprotein alpha-4 integrin (CD49d) that is expressed on the surface of lymphocytes and monocytes and facilitates their adhesion to the endothelium (Lobb and Hemler, 1994; Rice et al., 2005). The cellular effect of natalizumab is to block the transmigration of lymphocytes and monocytes into the central nervous system (Rudick and Sandrock, 2004; Tubridy et al., 1999). The effectiveness of targeting alpha-4 integrin for stroke treatment in experimental ischemic stroke models have had mixed outcomes. Some studies have shown that blocking alpha-4 integrin reduces peripheral immune cell infiltration and subsequent reduction in infarct size under both normotensive and hypertensive conditions, while others have failed to show efficacy with treatment (Becker et al., 2001; Langhauser et al., 2014; Liesz et al., 2011b; Llovera et al., 2015; Relton et al., 2001). The results from a clinical trial (ACTION) on the safety and efficacy of a single dose of natalizumab (300 mg) given within 9h of acute ischemic stroke established the safety and feasibility of the study. However, with treatment at this dose the study outcome was negative for the efficacy endpoint (Elkins et al., 2017). Based on these findings, a second clinical trial (ACTION 2) was started in 2016 to evaluate the efficacy of a higher dose of natalizumab in stroke treatment. According to a report from Biogen, the trial

failed to meet the efficay endpoint and the company decided not to pursue further development of natalizumab for stroke treatment.

Vinpocetine is a synthetic ethyl-ester derivative of the alkaloid apovincamine, which is isolated from Vinca minor leaves, commonly known as periwinkle plant (Al-Kuraishy et al., 2020). It was initially developed for the treatment of cerebrovascular diseases. A number of studies in rodent models of stroke have now established the protective effects of vinpocetine against brain damage caused by ischemia (Erdo et al., 1990; Jincai et al., 2014; Rischke and Krieglstein, 1991; Sauer et al., 1988; Wu et al., 2017b; Zhao et al., 2020). The neuroprotective function of vinpocetine has been attributed to multiple mechanisms of action (Zhang et al., 2018). In the brain, vinpocetine improves blood flow through its inhibition of phosphodiesterase 1 (PDE1) that catalyzes the degradation of cAMP and cGMP, two known vasodilators (Al-Kuraishy et al., 2020; Medina, 2011; Paterno et al., 1996; Wu et al., 2017b; Zhang et al., 2018). It also prevents neurotoxic calcium and sodium elevation by inhibiting neuronal voltage-gated sodium channel (Molnar and Erdo, 1995; Sitges et al., 2005; Sitges et al., 2011). In addition, vinpocetine has been shown to attenuate oxidative stress through inhibition of lipid peroxidation and free radical generation (Deshmukh et al., 2009; Santos et al., 2000; Zhao et al., 2020). More recent studies have further demonstrated that vinpocetine is a potent anti-inflammatory agent as an inhibitor of IκB kinase, which plays a critical role in NF-κB-dependent inflammatory response (Jeon et al., 2010; Wang et al., 2014; Wu et al., 2017b; Zhao et al., 2020). Vinpocetine can cross the BBB after oral or intravenous administration (Gulyas et al., 2002a; Gulyas et al., 2002b) and is widely used in many European and Asian countries for prevention of cerebrovascular disorders and cognitive impairments (Wu et al., 2017b; Zhang et al., 2018). It is also available as dietary supplements worldwide (Zhang et al., 2018). However, there is no evidence to support the routine use of vinpocetine in ischemic stroke patients. So far, the safety and feasibility of administering vinpocetine in ischemic stroke patients has been established in a previously conducted pilot study (Feigin et al., 2001). A meta-analysis reviewing the effects of vinpocetine treatment on acute ischemic stroke was inconclusive as most of the studies analyzed did not use double-blinded approaches and randomization. The two studies that used appropriate designs did not show significant differences between groups and were based on small samples (Bereczki and Fekete, 2008). As such, additional clinical trials are still needed to determine if vinpocetine treatment can reduce mortality and improve stroke outcome in surviving patients. A phase II multicenter randomized clinical trial (NCT02878772) in a small number of ischemic stroke patients was recently completed to evaluate the efficacy of vinpocetine on stroke outcome, where treatment was initiated between 4.5h to 48h after after the onset of symptoms. However, the findings of this trial has not been reported yet.

This comprehensive review of the neuroprotective agents assessesd in randomized clinical trials within the last five years highlights important differences in their mechanisms of action. While most of them targeted more than one pathophysiological cascade involved in stroke-induced brain damage, some of them have primarily focused on the inflammatory or excitotoxic pathways. Although the outcome is still unknown for many of these clinical trials, it has been reported that the anti-inflammatory agent, Natalizumab and the anti-excitotoxic agent, NA-1 have failed in phase II and phase III clinical trials, respectively.

Natalizumab primarily reduces peripheral immune cell infiltration without any effect on inflammatory processes involving microglial activation. The failure of Natalizumab indicates that for anti-inflammatory therapies to be successful, it is important to develop strategies that could modulate the activity of both microglia and infiltrating immune cells. Since post-stroke inflammation can be both detrimental and beneficial for infarct resolution, a better understanding of the temporal and spatial dynamics of the pathogenic immune signaling involving both resident microglia and infiltrating immune cells is also necessary for the development of next-generation immune therapies. On the other hand, the failure of NA-1 suggests that drugs that will only prevent excitotoxic neuronal cell death without effecting the non-neuronal cells, which contributes substantially to the post-stroke secondary injury, will also not be successful. Collectively, these two failures highlights the importance of pleiotropic multi-target drugs for stoke treatment.

5. ONGOING CLINICAL TRIALS FOR STROKE NEUROPROTECTION

As our understanding of the mechanisms of acute ischemic stroke continues to advance, a variety of additional drugs with neuroprotective properties have been developed and are being evaluated in ongoing clinical trials (Table 2). Interestingly, most of these neuroprotective agents target multiple aspects of the neurodegenerative cascade and, therefore, might have synergistic effects against ischemic injury.

Ginkgolides are a unique class of diterpenoids isolated from the roots and leaves of the ‘fossil’ tree *Ginkgo biloba* L (Jacobs and Browner, 2000). Ginkgolides A, B, C, J, K, L and M are the pharmacologically active diterpene lactones that have been well characterized (Stromgaard and Nakanishi, 2004; van Beek, 2005). They have many pharmacological activities that include selective and potent antagonism to platelet activating factor (PAF), as well as selective antagonism to the receptors for the neurotransmitters glycine and γ-aminobutyric acid (Ivic et al., 2003; Jensen et al., 2007; Koch, 2005; Zeng et al., 2013). Studies using animal models of both transient and permanent cerebral ischemia have shown that ginkgolides and their derivatives could attenuate neuronal injury and reduce brain infarct size (Lv et al., 2011; Ma et al., 2012; Nada and Shah, 2012; Shu et al., 2016; Sun et al., 2011b; Zhou et al., 2017). Additional studies have indicated that ginkgolides may also facilitate post-stroke recovery in hyperlipidemic rats, indicating its efficacy in experimental stroke models with comorbidities (Fang et al., 2015; Huang et al., 2012). The neuroprotective effects of ginkgolides on cerebral ischemia has been attributed to its antagonism to PAF, reduction in BBB permeability, inhibition of brain edema and inflammation, and scavenging oxygen free radicals (Feng et al., 2019). Clinical trials in stroke patients have also established the safety, feasibility and efficacy of ginkgolides in acute ischemic stroke (Dong et al., 2020a; Li et al., 2017b; Oskouei et al., 2013). Based on these findings, a large scale clinical trial (GIANT) in stroke patients is currently evaluating the efficacy of combined treatment with ginkgolide and intravenous thrombolysis. However, the mechanisms through which ginkgolides confers neuroprotection against ischemic brain injury are still in the early stages of investigation (Feng et al., 2019).

1–3-N-Butylphthalide (1-NBP), an active ingredient in the seeds of celery and its racemic form DL-3-N-butylphthalide (DL-NBP) have shown significant neuroprotective effects in

stroke (Abdoulaye and Guo, 2016). NBP exerts its efficacy by targeting several pathways that include reduction in post-ischemic oxidative damage, neuronal apoptosis, mitochondrial dysfunction and inflammation (Chen et al., 2018; Hu et al., 2014; Lan et al., 2015; Li et al., 2018; Wang et al., 2018; Yan et al., 2017; Yang et al., 2019a). Additional studies have indicated that NBP may also facilitate post-stroke recovery by promoting neurogenesis (Sun et al., 2017). These studies have utilized both rodent models of permanent and transient focal cerebral ischemia to evaluate either short-term or long-term efficacy of NBP, and at least two such studies used hypertensive rats to evaluate the efficacy of post-stroke NBP treatment (Liao et al., 2009; Zhang et al., 2012b). Efficacy and safety of NBP have also been evaluated in multiple clinical trials in China and it is clinically-approved as an anti-ischemic drug in China (Abdoulaye and Guo, 2016; Cui et al., 2013; Xu et al., 2019; Zhang et al., 2020; Zhang et al., 2017). It is currently undergoing phase II clinical trial in USA (NCT03539445) as well as a phase III/IV clinical trials in China (NCT03394950) to evaluate its multitargeted effect in ischemic stroke.

BIIB093 is an intravenous (IV) formulation of glibenclamide (also known as glyburide). Glibenclamide is a sulfonylurea class of drugs that has been in clinical use as an oral hypoglycemic agent for the treatment of type 2 diabetes since 1969 (Feldman, 1985; Kurland et al., 2013; Marble, 1971) as it promotes the release of insulin by blocking pancreatic K_{ATP} [sulfonylurea receptor 1 (Sur1)-Kir6.2] channels (Kramer et al., 1995; Panten et al., 1996). Glibenclamide has received renewed attention in the last decade due to its neuroprotective effect in CNS injury, where its principal target is the transient receptor potential melastatin 4 (Trpm4), a non-slecetive cation channel that has been shown to be associated with Sur1 to form the Sur1-Trpm4 channels (Simard et al., 2006; Woo et al., 2013). Sur1-Trpm4 channels have been shown to be upregulated following ischemia in ischemic endothelial cells, neurons and glia, and has been associated with cytotoxic edema, BBB breakdown and formation of vasogenic edema (Mehta et al., 2015). Additional studies have also demonstrated that activated microglia in the ischemic lesion core express Sur1-Kir6.2 channels (Ortega et al., 2012). In a number of preclinical studies using both transient and permanent models of middle cerebral artery occlusion (MCAO) as well as thromboembolic model of ischemic stroke, it has been shown that treatment with glibenclamide significantly reduces ischemic infarct size and hemispheric swelling, even when administered several hours after the onset of stroke (Simard et al., 2006; Simard et al., 2012; Simard et al., 2009). Analysis of long-term outcomes of glibenclamide treatment have showed marked improvements in sensorimotor and cognitive functions, observed one month after stroke onset (Ortega et al., 2013). The effect of glibenclamide was also examined in rodent models of lethal stroke with malignant cerebral edema, where it significantly reduced edema and mortality rate (Simard et al., 2006; Simard et al., 2010). The molecular basis of the neuroprotective effect of glibenclamide has been attributed to its ability to reduce brain edema through inhibition of Sur1-Trpm4 channels, and to reduce neuroinflammation through inhibition of K_{ATP} channel (Kurland et al., 2013). In addition to the preclinical studies, the safety of IV formulation of glibenclamide (BIIB093) has been evaluated in multiple exploratory studies (NCT01132703). Efficacy of IV glibenclamide was also recently evaluated in a randomized, multicenter, prospective, double-blinded, placebo-controlled phase II clinical trial (GAMES-RP) in ischemic stroke patients who were likely to

develop malignant edema (NCT01794182). Although the study did not meet the primary efficacy outcome, treatment with IV glibenclamide did show some promising results for measures of edema/swelling and mortality. Midline shift, an imaging marker of neurological deterioration decreased significantly and plasma MMP-9, a biomarker associated with BBB breakdown was lower in patients treated with IV glibenclamide (Kimberly et al., 2018; Sheth et al., 2016; Sheth et al., 2018). Based on this favorable trend from GAMES-RP trial, a phase III randomized, multicenter, double-blinded, placebo controlled, paral-lelgroup, multi-center study (NCT02864953) is currently evaluating the safety and efficacy of this novel anti-edema neuroprotective agent (Pergakis et al., 2019).

MultiStem cells (HLCM051, Athersys) are a distinct subpopulation of adherent human bone marrow cells obtained from heathy adult donors. Prior studies have shown that these adult progenitor cells are not immunogenic, scalable through long-term tissue culture expansion and have the capacity to exert potent immunomodulatory effects in traumatic brain injury, spinal cord injury and stroke (Bedi et al., 2013; Busch et al., 2011; Jacobs et al., 2013; Jellema et al., 2015; Reading et al., 2015; Walker et al., 2012; Yasuhara et al., 2006). Using animal models of acute ischemic stroke, it has also been shown that intravenous administration of Multistem cells 24h after the onset of the insult reduced brain lesion size and neurological deficits, and suppressed the enrichment of ischemia-induced inflammatory genes in the brain and the spleen (Yang et al., 2017a). However, in mice with surgical splenectomy, treatment with Multistem cells following stroke failed to show efficacy, suggesting that a splenic response attenuates pro-inflammatory modulators in the brain to create a regenerative environment for better recovery from stroke (Yang et al., 2017a). However, the potential mchanisms by which cell therapy might improve the outcome after stroke is still not understood. Nevertheless, a phase II, multicenter double-blinded and randomized clinical trial with Multistem cells was carried out for safety assessment and efficacy outcome in stroke patients treated between 24h and 48h after symptom onset and the study outcome has been published. The findings show that a single intravenous administration of Multistem cells (up to 1200 million cells) is safe and well tolerated in stroke patients. But, no significant improvement was observed at 90 days with treatment (Hess et al., 2017). Two additional clinical trials (TREASURE and MASTERS-2) are now enrolling patients, primarily in North America, Europe and Japan to evaluate efficacy of intervention within an earlier time window (<36h).

Imatinib (Gleevec), is a small molecule tyrosine kinase inhibitor that can target both receptor and non-receptor tyrosine kinases and is currently approved by the United States Food and Drug Administration (FDA) for the treatment of cancer. Its most important targets include PDGFRα (platelet derived growth factor receptor α), Flt-3 (FMS-like tyrosine kinase 3), c-fms (CSF-1R; colony-stimulating factor-1-receptor) and Abl tyrosine kinases. The primary goal of the proposed treatment with imatinib in ischemic stroke is to ameliorate the side-effects of thrombolytic treatment with tPA and extend the time window of treatment with tPA. In pre-clinical models of stroke it has been shown that tPA-induced activation of PDGF-CC, a member of the PDGF family and a potent angiogenic factor, upregulates PDGFRα signaling pathway resulting in BBB dysfunction that contributes to infiltration of peripheral immune cells and inflammation (Fredriksson et al., 2004; Su et al., 2008). In these studies, post-ischemic administration of imatinib (1h) along with a delayed tPA treatment (5h)

resulted in a significant reduction in hemorrhagic complications and infarct volume (Merali et al., 2015; Su et al., 2008). Inhibition of Flt-3 and c-fms tyrosine kinases by imatinib also alleviate post-stroke inflammatory response through reduction of the pro-inflammatory cytokines IL-1β and TNFα and accumulation of macrophages (Gagalo et al., 2015). A Phase II clinical trial in acute ischemic stroke patients with combined imatinib and intravenous thrombolysis treatment has shown that imatinib is safe and may reduce neurological disability in patients (Wahlgren et al., 2017). Based on these findings, a confirmatory Phase III clinical trial (NCT03639922) is currently underway in Sweden.

Exenatide is a synthetic form of the endogenous glucagon-like-peptide-1 (GLP-1), which is a potent gastrointestinal hormone that regulates blood glucose level by inducing the release of insulin from pancreatic beta cells (Drucker and Nauck, 2006; Lovshin and Drucker, 2009). Studies have shown that GLP-1 receptor is expressed throughout the brain and its expression is upregulated in neurons, astrocytes, microglia and cerebral endothelial cells following an acute ischemic insult (Goke et al., 1995; Hamilton and Holscher, 2009). Increasing evidence indicates that administration of exenatide during or after experimental stroke in mice, rats and gerbils may provide neuroprotection and reduce ischemic infarct volume (Briyal et al., 2012; Lee et al., 2011; Li et al., 2009; Marlet et al., 2018). The efficacy of exenatide in attenuating ischemic brain damage has been observed in both non-diabetic and diabetic animals (Darsalia et al., 2012; Marlet et al., 2018). However, such neuroprotective effect was lost if exenatide is administered 3h after stroke (Teramoto et al., 2011). The proposed mechanism of action of exenatide includes downregulation in the expression of hypoxia-inducible factor-1α (Helton et al., 2005; Jin et al., 2014), reduced expression and activity of inducible nitric oxide synthase (Teramoto et al., 2011), reduced neutrophil infiltration (Kuroki et al., 2016) and decreased ROS generation (Li et al., 2016). Exenatide also reduces expression of MMP-9, an enzyme that plays a significant role in cerebral edema by breaking down the extracellular matrix (Kuroki et al., 2016; Madden, 2012). In spite of the extensive studies in animal models of stroke, clinical trials evaluating the efficacy of exenatide in stroke patients are still sparse. Following a successful pilot study evaluating safety and feasibility of exenatide, a phase II clinical trial (NCT03287076) is currently being conducted to evaluate post-stroke hyperglycemia and improvement in neurological outcome after exenatide treatment for 5 days (Muller et al., 2018).

Poly (ADP-ribose) polymerase-1 (PARP-1), a DNA repair enzyme that is known to be overactivated in brain cells during ischemia causes cellular injury by inducing cellular NAD^+ and ATP depletion, mitochondrial dysfunction, reactive oxygen species (ROS) generation, apoptosis inducing factor activation and inflammation (Koh et al., 2004; Moroni, 2008; Strosznajder et al., 2010; Takahashi et al., 1999; Tanaka et al., 2005). Multiple PARP inhibitors have been identified till date that could have diverse effects on ischemia/reperfusion induced brain damage (Berger et al., 2018). Emerging evidence now indicate that JPI-289 (also known as amelparib), a highly-specific, potent and water soluble PARP-1 inhibitor could be a potential neuroprotective agent for treatment of acute ischemic stroke. An ex vivo study in a neuronal culture model of oxygen-glucose deprivation (OGD) has shown that treatment with JPI-289 confers neuroprotection by attenuating OGD-induced depletion of ATP and NAD^+ levels, and caspase-3 activation (Kim et al., 2017). Additional studies in rodent models of permanent and transient focal cerebral ischemia have shown that

early treatment with JPI-289 can reduce infarct volume and improve functional outcomes by modulating the post-ischemic immune response (Kim et al., 2018; Noh et al., 2018). It has also been reported that the efficacy of various PARP inhibitors in rodent models of stroke is preferentially observed in male mice and is also dependent on the age of the animals (Chen et al., 2020; Eliasson et al., 1997; Hagberg et al., 2004; McCullough et al., 2005; Yuan et al., 2009). However, such gender- and age-dependent differences in the efficacy of JPI-289 for stroke treatment have not been studied yet. A phase I randomized, double-blinded and placebo-controlled clinical trial in Korea has also established the safety and tolerability of multiple doses of JPI-289 in healthy human volunteers (Han et al., 2017). A phase II clinical trial (NCT03062397) is currently being conducted in Korea to evaluate its efficacy in the treatment of ischemic stroke.

Neu2000 is a synthetic derivative of aspirin (acetylsalicylic acid) and the anti-inflammatory drug sulfasalazine (Gwag et al., 2007). It is a dual neuroprotectant targeting both NMDA receptors and free radicals (Cho et al., 2010). Ex vivo studies have shown that Neu2000 is a moderate, uncompetitive and reversible NMDA receptor antagonist with NR2B-subtype specificity and fast binding kinetics (Gwag et al., 2007; Noh et al., 2009). In addition it also blocks free radical injury as a potent cell permeable spin trapping molecule (Cho et al., 2010; Gwag et al., 2007). Randomized and blind experiments in pre-clinical models of transient ischemic stroke have also established the efficacy of Neu2000 in reducing infarct size and improving long-term neurological functions, when administered within 8h of reperfusion (Gwag et al., 2007). In permanent occlusion models, dual injection of Neu2000 at 2h and 16h after the onset of stroke also resulted in significant attenuation of infarct volume (Lee et al., 2007). A phase I double-blinded and randomized clinical trial in a small group of young and elderly volunteers have now established the safety, tolerance and pharmacokinetics of Neu2000 (Cho et al., 2009). A phase II multi-center, randomized and double-blinded clinical trial (NCT02831088) is currently focusing on the efficacy and safety of this neuroprotectant (Hong et al., 2018).

Remote ischemic conditioning (RIC) is based on the concept that repetitive and transient mechanical obstruction of blood vessel at a limb distal from the brain would initiate signals that could increase blood flow to the brain and trigger anti-oxidative, anti-inflammatory, and mitochondria modulatory protective mechanisms in the brain (Hess et al., 2015; Yang et al., 2019b; Zhou et al., 2018). Multiple pre-clinical studies have demonstrated the efficacy of RIC in reducing infarct size and improving functional outcome in rodent models of ischemic stroke (Doeppner et al., 2018; Liu et al., 2014b; Malhotra et al., 2011; Ren et al., 2009; Sun et al., 2012; Wei et al., 2012). In these studies, RIC was induced either by femoral artery occlusion or by manual inflation of a blood pressure cuff on the hindlimb and adminstration of RIC prior to, during, or after stroke were all effective in reducing post-stroke infarct size and brain injury. RIC therapy has also been shown to reduce mortality with intravenous thrombolysis treatment and is effective in both sexes (Hoda et al., 2014; Hoda et al., 2012). However, the exact mechanisms of neuroprotection with RIC therapy are yet unknown. It has been postulated that both circulating mediators and neural mechanisms have central roles in RIC-mediated neuroprotection (Hess et al., 2015; Yang et al., 2019b). In addition to the preclinical evidence, feasibility and safety of RIC as well as the beneficial effects of RIC in ischemic stroke have been observed in several early stage clinical studies (England et al.,

2017; Hougaard et al., 2014; Zhao et al., 2018). However, a more recent pilot study in a multicenter randomized trial showed that RIC during or after reperfusion did not reduce brain infarction at 24h after symptom onset (Pico et al., 2020). Several ongoing (Table 2) and recently completed (SERICT-AIS, ReCAST-2) clinical trials are now focusing on the benefits of conditioning following single application of RIC in a prehospital setting or repeated application of RIC for the first 1–2 weeks after an ischemic insult in stroke patients.

6. NINDS/NIH INITIATIVE FOR THE DEVELOPMENT OF NEUROPROTECTIVE STROKE THERAPIES

To accelerate the progress of translational studies for acute neuroprotection in stroke, the National Institute of Neurological Disorders and Stroke (NINDS) in the USA recently announced support for the Stroke Preclinical Assessment Network (SPAN; RFA-NS-18–034). The primary goal of this new approach is to consider highly promising neuroprotective agents or interventions as adjunctive therapies along with or prior to endovascular thrombectomy, to extend the time window for additional intervention and improve functional outcomes. Specifically, six promising therapeutic agents that have been approved by U.S. Food and Drug Administration for treatment in other diseases have been selected for evaluation of efficacy in stroke treatment. These agents will be evaluated simultaneously at multiple sites in experimental animal models of stroke with comorbidities and advanced age in both sexes. These multi-center double-blinded preclinical trials could accelerate the identification of the most promising neuroprotective approaches for future clinical trials. In this section we have summarized the existing literature on these selected neuroprotective agents / interventions (Table 3).

Fasudil (AT877 or HA-1077) is an inhibitor of Rho-kinase (ROCK), a downstream target of the small GTP-binding protein Rho. Activation of Rho/ROCK signaling pathway is substantially involved in the pathogenesis of coronary and cerebral vasospasm (Sato et al., 2000; Shimokawa et al., 1999). ROCK activation is also involved in all stages of the inflammatory process (Dong et al., 2010). Thus ROCK inhibitors like fasudil are potential targets for the the treatment of various cardiovascular and central nervous system (CNS) disorders. Fasudil is approved in Japan since 1995 for treatment of cerebral vasospasm. However, it is not yet approved by the FDA for treatment in USA. Fasudil has also shown promise in the attenuation of ischemic brain damage in animal models of MCAO, particularly by decreasing inflammatory response through reduced neutrophil and monocyte infiltration, reduced oxidative damage and improving regional cerebral blood flow (Mueller et al., 2005; Rikitake et al., 2005; Satoh et al., 1996; Satoh et al., 1999; Satoh et al., 2002). However, in spontaneously hypertensive rats treatment with fasudil failed to attenuate ischemic brain damage (Chan and Cipolla, 2017). The safety and usefulness of fasudil in the treatment of stroke patients has also been evaluated in phase III clinical trails (Shibuya et al., 2005). It has been reported that the trial was terminated because of less than anticipated clinical efficacy of the drug (Fukuta et al., 2016). The lack of optimal efficacy of fasudil in clinical trials has been attributed to its short half-life in circulation and poor ability to penetrate the BBB (Mueller et al., 2005). To enhance the bioavailability of fasudil in the brain, in a novel approach, fasudil was encapsulated in the water phase of PEGylated

liposomes (liposomal fasudil). Intravenous administration of liposomal fasudil allowed increased release of fasudil in the ischemic region resulting in suppression of neutrophil infiltration and brain cell damage in the MCAO rat models (Fukuta et al., 2016). Combination therapy with tPA in a photochemically induced thrombosis model of stroke, where fasudil was administered prior to tPA treatment also showed decreased intracerebral hemorrhage and increased protection as compared with tPA treatment along with free fasudil or separate treatment with each drug (Fukuta et al., 2017). These findings suggest that liposomal fasudil treatment prior to tPA could reduce the risk of tPA-derived cerebral hemorrhage and extend the time window of tPA treatment. This also implies that liposomal drug delivery system could be a better alternative for stroke therapy with fasudil.

Fingolimod (FTY720) is derived from an atypical amino acid myriocin produced from the fungus *Isaria sinclairii*, otherwise known as winter-insect and summer plant that is commonly used in traditional Chinese medicine. It is an orally bioavailable lipophilic drug that readily crosses the BBB (Tamagnan et al., 2012) and has been approved by the FDA in 2018 for use in both adolescent and adult patients suffering from multiple sclerosis. In rodent models of transient ischemia, fingolimod has been shown to reduce infarct size and neurological deficits, when administered either before or after the insult (Liu et al., 2013). Fingolimod is structurally similar to the membrane lipid sphingosine (Paugh et al., 2003) and the phosphorylated and active form of fingolimod (fingolimod-phosphate) is analogous to sphingosine-1-phosphate (S1P). The mechanism of action of fingolimod involves its binding to S1P receptors present on lymphocytes causing degradation of the receptor, thereby preventing lymphocyte release from lymphoid tissue (Pham et al., 2008). This decrease in circulating lymphocytes following treatment with fingolimod reduces post-stroke lymphocyte infiltration in the brain resulting in attenuation of post-ischemic inflammatory response and neurotoxicity (Czech et al., 2009; Kraft et al., 2013; Liesz et al., 2011a; Wei et al., 2011). In addition, fingolimod enhances neuroprotection through protein kinase B mediated phosphorylation and inactivation of FOXO3a, a transcription factor that causes oxidative stress (Safarian et al., 2015). The safe use of this drug in patients has already been established in clinical trials involving multiple sclerosis patients, although administration of fingolimod in stroke patients resulted in sustained lymphopenia that persisted for more than 7 days and resolved by day 30 (Fu et al., 2014; Willis and Cohen, 2013). A non-randomized clinical trial in a small group of ischemic stroke patients administered with three oral doses of fingolimod (0.5 mg daily) showed no significant decrease in lesion volume at day 7 compared to placebo treated group (Fu et al., 2014). However, beyond day 7, lesion volume did not increase any further in the fingolimod treated group, although lesion volume continued to increase in the placebo treated group. Significant improvement was also observed in neurological function with fingolimod treatment throughout the 90-day period of the study. Another small randomized study assessed the efficacy of fingolimod when administered prior to treatment with tPA (Zhu et al., 2015). Such combination therapy decreased lesion volume, reduced hemorrhagic transformation and improved functional outcome when compared to tPA treatment alone, suggesting a beneficial role of fingolimod both with and without tPA.

RIC or remote ischemic conditioning has been discussed in more details above (section 5). It involves a series of brief mechanical occlusions and reperfusions of blood vessels at a limb

distal to the brain, and exerts its effects through activation of endogenous neuroprotective mechanisms (Ma et al., 2017). This approach is currently being evaluated in multiple ongoing clinical trials in addition to the preclinical studies through the SPAN initiative.

Tocilizumab is a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor. It is an immunosuppressive drug that inhibits the pro-inflammatory effects of IL-6 and has been approved by the FDA for the treatment of autoimmune disease, such as rheumatoid arthritis (Rubbert-Roth et al., 2018; Tanaka et al., 2014). In the classical IL-6 signaling pathway, binding of IL-6 to its receptor activates the Janus-activated kinase / signal transducer and activator of transcription (JAK/STAT) pathway resulting in phosphorylation and subsequent activation STAT3, which then translocates to the nucleus and upregulates genes responsible for inflammation and apoptosis (Scheller et al., 2011; Wang and Sun, 2014). As higher serum levels of IL-6 in stroke patients correlate with larger infarct size and worsening functional outcome (Smith et al., 2004; Waje-Andreassen et al., 2005), there is substantial interest in evaluating the efficacy of treatment with tocilizumab on stroke outcome. However, the effect of IL-6 inhibition on the pathogenesis of ischemic stroke remains controversial. Intravenous administration of anti-IL-6 receptor antibody after the onset of transient MCAO has been shown to exacerbate ischemic brain injury at 24h of reperfusion (Yamashita et al., 2005). Consistent with this finding, intracerebro-ventricular injection of recombinant IL-6 has been shown to reduce early ischemic brain damage in an animal model of permanent MCAO (Loddick et al., 1998). In a separate group of studies, evaluation of the ischemic infarct size between wild-type and IL-6 knockout mice showed that acute stroke outcome (24h) did not differ between the genotypes (Clark et al., 2000; Gertz et al., 2012; Herrmann et al., 2003). The study by Gertz et al (2012) further demonstrated an exacerbation of ischemic lesion volume and worsening of sensori-motor function in IL-6 knockout mice after 4 weeks. In contrast, a study where IL-6 receptor mediated signaling was inhibited with tocilizumab administered 4h after the onset of MCAO in mice showed significant reduction in infarct size, improvement in sensorimotor function and attenuation of microglial activation (Hudobenko et al., 2017). A second study in aged male and female mice have further indicated that amelioration of transient MCAO-induced ischemic brain damage, mortality and behavioral deficit by tocilizumab treatment requires sex-specific dosing, with a 5-fold higher dose requirement for females (Hudobenko et al., 2019).

Uric acid, a product of purine metabolism is a powerful endogenous antioxidant in the circulation (Pasalic et al., 2012). However, high serum uric acid levels (hyperuricemia) is neurotoxic as a pro-oxidant and may increase the risk of stroke morbidity and mortality (Chamorro and Planas, 2004; Kanellis and Johnson, 2003; Li et al., 2014; Li et al., 2015). Despite this controversy, earlier studies have shown that physiologically relevant concentrations of uric acid confers neuroprotection to cultured neurons from glutamate-induced (excitotoxic) or peroxynitrite-induced (nitrosative) cell death by scavenging ROS and suppressing lipid peroxidation (Gursoy-Ozdemir et al., 2004; Justicia et al., 2017; Romanos et al., 2007; Squadrito et al., 2000). The neuroprotective effects of uric acid has also been attributed to its role in elevating nuclear expression of nuclear factor E2-related factor 2 (Nrf2) protein, an essential transcription factor that regulates the transcription of multiple antioxidant and detoxifying genes (Kanninen et al., 2015; Nakka et al., 2016; Ya et

al., 2018). In animal models of transient ischemic insult, exogenous administration of uric acid has been shown to attenuate ischemic brain damage and behavioral deficits by reducing lipid, protein and DNA peroxidation as well as post-ischemic infiltration of neutrophils (Chamorro et al., 2014; Justicia et al., 2017; Onetti et al., 2015; Romanos et al., 2007; Ya et al., 2018; Yu et al., 1998). The efficacy of uric acid in reducing stroke-induced brain damage was more pronounced following cotreatment with tPA, suggesting that combination therapy extends the benefits of tPA treatment alone (Romanos et al., 2007). In animal studies, uric acid treatment was also effective in improving stroke outcome in both males and females (Aliena-Valero et al., 2018; Dhanesha et al., 2018). In a randomized, double-blinded, placebo-controlled, phase III clinical trial (URICO-ICTUS), uric acid has been shown to be safe and improve outcomes in stroke patients when administered along with tPA, as well as in patients receiving both intravenous tPA and mechanical thrombectomy (Amaro et al., 2016; Amaro et al., 2019; Chamorro et al., 2017; Chamorro et al., 2004).

Veliparib (ABT-888) is another PARP-1 inhibitor that has similar mechanism of action as JPI-289 (amelparib) described above (section 5). Veliparib has good oral bioavailability, can cross the BBB and is well tolerated in cancer patients (Donawho et al., 2007; Reck et al., 2017). It has been granted “orphan drug designation” by FDA in 2016 for treatment of advanced squamous non–small cell lung cancer. However, its efficacy in attenuating ischemic brain damage in preclinical animal models of stroke or clinical trials in stroke patients has not been evaluated yet.

7. EMERGING NEUROPROTECTANTS FOR STROKE TREATMENT

It is now expected that development of future strategies for stroke therapy would require novel approaches for selection of neuroprotective agents. Such approaches should emphasize on agents that can readily cross the BBB as well as target the upstream components or multiple aspects of the ischemic cascade. In this section we have evaluated the therapeutic potential of two emerging peptide-based agents, a pharmacological compound and several epigenetic factors as future neuroprotective strategies to reduce the impact of ischemic brain injury (Table 4).

Adropin is a recently identified small polypeptide (4.9 kDa) encoded by the Energy homeostasis gene (*Enho*), which is expressed in multiple organs including the brain (Aydin et al., 2013; Kumar et al., 2008; Wong et al., 2014). Multiple functions of adropin includes its ability to regulate glucose and lipid homeostasis and insulin sensitivity (Aydin, 2014; Kumar et al., 2008). It also enhances mitochondrial function and plays a role in fatty acid oxidation (Gao et al., 2015). Furthermore, adropin has beneficial effects on endothelial cell function by reducing permeability through activation of endothelial nitric oxide synthase (eNOS) signaling pathways (Lovren et al., 2010). Emerging evidences indicates that adropin level is significantly downregulated in rat brain microvascular endothelial cells exposed to hypoxia and low glucose, resulting in increased paracellular permeability, while treatment with synthetic adropin attenuates the increased endothelial permeability (Yang et al., 2016). This would imply that adropin could be protective against endothelial barrier dysfunction during ischemia. Consistent with the above finding, more recent studies in animal models of cerebral ischemia have shown significant reduction in adropin level, which is accompanied

with a larger infarct size. Treatment with synthetic adropin reduced infarct size through eNOS activation and reduced oxidative damage (Yang et al., 2017b; Yang et al., 2020). The role of adropin-mediated activation of eNOS signaling pathway in neuroprotection against cerebral ischemia was further confirmed using adropin overexpressing transgenic mice (AdrTg), adropin knockout mice (*Enho*−/−) and eNOS knockout mice (eNOS−/−) subjected to cerebral stroke. This later study showed significant reduction in ischemic brain damage in AdrTg mice when compared to wild-type control. Conversely, adropin deficient mice had larger strokes compared to wild-type littermate controls. Pharmacological treatment with synthetic adropin significantly reduced infarct size and protected against stroke-induced BBB damage. This protective effect of adropin was completely abolished in eNOS−/− mice (Yang et al., 2020), suggesting that eNOS is involved in the underlying mechanisms of protection by adropin in stroke. Understanding the long-term effects of adropin treatment on stroke outcomes and the underlying signaling mechanism(s) could therefore offer a novel therapeutic strategy for the treatment of ischemic brain damage.

The tyrosine phosphatase STEP, also known as Ptpn5, is an intracellular phosphatase that is expressed specifically in the central nervous system (Boulanger et al., 1995; Lombroso et al., 1993), and whose specific targets and functions are beginning to emerge. STEP is expressed in the neurons of the striatum, cortex, hippocampus and related structures, and its substrate affinity is regulated through phosphorylation/dephosphorylation of a serine residue in the conserved regulatory domain termed the KIM (kinase interacting motif) domain (Bult et al., 1997; Paul et al., 2003; Paul et al., 2000; Poddar et al., 2010; Pulido et al., 1998). STEP can dephosphorylate and inactivate several key neuronal signaling proteins that includes the extracellular signal-regulating kinase 1 and 2 (ERK1/2), stress activated protein kinases p38, the Src family tyrosine kinases Fyn and Pyk2, NR2B-subunit of NMDARs and GluA2 and GluA3 subunit of AMPA receptors (Nguyen et al., 2002; Paul et al., 2003; Poddar et al., 2010; Poddar et al., 2016; Snyder et al., 2005; Won et al., 2019; Xu et al., 2012). Aberrant increase in the activation of these proteins during an ischemic insult plays a role in excitotoxicity, oxidative stress and inflammatory response. As an inhibitor of the activity of these proteins, STEP has the potential to target multiple aspects of the ischemic cascade to confer neuroprotection. Indeed, in cell culture models of excitotoxicity and oxygen glucose deprivation, dephosphorylation and subsequent activation of STEP has been shown to contribute to neuroprotection (Deb et al., 2013; Poddar et al., 2010). Using a rat model of transient focal ischemia, it has also been shown that rapid activation of STEP during the ischemic insult provides initial neuroprotection, while degradation of active STEP over time leads to secondary activation of deleterious processes, resulting in progression of ischemic brain damage (Poddar et al., 2010). Another potentially important finding is that STEP activity decreases with age-associated increase in oxidative stress (Deb et al., 2011; Rajagopal et al., 2016), suggesting that the loss of this protective response may be a contributing factor for the increased susceptibility of the aging brain to ischemic brain damage (Howard et al., 1987; Nakayama et al., 1994). Consistent with this interpretation, studies in STEP knockout (KO) mice further showed that the loss of endogenous STEP leads to exacerbation of ischemic brain injury as observed 24h after a mild ischemic insult. Based on these observations, additional studies developed a novel brain-permeable STEP-derived peptide (STEP-mimetic) that is resistant to degradation (Deb et al., 2013). Intravenous

administration of this peptide in a rat model of ischemic stroke was not only effective in limiting stroke injury and functional deficits but also facilitated long-term recovery, even when administered 6h after the onset of the insult (Deb et al., 2013; Poddar et al., 2019). Studies in STEP KO mice further showed that restoration of the STEP signaling pathway with the administration of the STEP-mimetic could also attenuate the exacerbation of ischemic brain injury in the absence of endogenous STEP (Deb et al., 2013). These findings highlight the importance of STEP in neuroprotection against ischemic brain injury. Establishing the efficacy of the STEP-mimetic in attenuating ischemic brain damage in animals models with comorbidities and understanding the molecular basis of this neuroprotection would help promote the STEP-mimetic as a novel therapeutic strategy for stroke treatment.

Verapamil is a phenylalkylamine and a member of the non-dihydropyridine class of calcium channel blockers (Bergson et al., 2011). It is primarily a L-type calcium channel blocker with higher affinity for depolarized channels rather than resting channels, which prevents the contraction of vascular smooth muscle cells causing vasodilation throughout peripheral circulation thus alleviating angina (Bergson et al., 2011). Verapamil is currently approved by the FDA for the treatment of hypertension, angina and arrhythmia (Frishman and Charlap, 1983; McTavish and Sorkin, 1989). Intra-arterial verapamil administration is also thought to be effective for treatment cerebral vasopasm, a common complication of aneurysmal subarachnoid hemorrhage (Keuskamp et al., 2008; Mikeladze et al., 2013; Stuart et al., 2011). Earlier studies on the application of verapamil for stroke treatment in animal models have mixed outcome depending on the animal model of stroke and the post-stroke time of intervention (Berger et al., 1984; Roy et al., 1985; Ueda et al., 1989; Wauquier et al., 1989). However, in more recent studies intra-arterial administration of verapamil following recanalization in a mouse model of focal cortical ischemia showed significant reduction in infarct volume and improvement in functional outcome (Fraser et al., 2017; Maniskas et al., 2016). Most importantly, these studies also showed that verapamil treatment did not have any effect on cerebral perfusion, implying that the protective mechanisms of action in stroke is independent from its vasodilatory effects. Although the exact mechanism of action of verapamil in stroke treatment is still not understood the authors postulated that through its inhibition of L-type calcium channels verapamil could reduce excitotoxic damage. Further support for this hypothesis comes from *in vitro* studies where verapamil administration to neurons in culture following OGD prevented neuronal injury in a dose-dependent manner (Fraser et al., 2017). In the same study, a phase I trial (SAVER-I) evaluating the feasibility and safety of intra-arterial administration of verapamil in human patients showed that at a clinically applicable dose range, intra-arterial administration of verapamil following thrombectomy is safe and feasible. These findings not only establish the feasibility of developing of verapamil as a new neuroprotectant for stroke therapy but also highlight the importance of intra-arterial delivery of neuroprotectants for stroke treatment.

The neuroprotectants identified till date for stroke therapy are involved in regulating intracellular signaling pathways to reduce post-stroke edema, excitotoxicity, oxidative stress, inflammation and apoptosis. In addition to pursuing these conventional therapeutic approaches current attention has shifted towards the identification of epigenetic factors that might influence the etiology and progression of stroke (Ng et al., 2018). MicroRNAs

(miRNAs) are emerging as an important player in the field of epigenetics and are involved mainly with message translation rather than with gene transcription. They are the best characterized sub-class of non-coding RNAs and the sequences coding for miRNAs often arise from intronic DNA and regulate the gene products coded by adjacent exons. They can regulate mRNA translation by binding to and retarding or accelerating their degradation. In addition, miRNA binding to mRNA can block message translation (Krupinski and Slevin, 2013). MicroRNAs appears to modulate different aspects of stroke pathophysiology, including excitotoxicity, oxidative stress, inflammation and BBB dysfunction, and several miRNAs that are neuroprotective tend to be downregulated in stroke, while miRNAs that could promote neurotoxic signaling tend to be upregulated (Khoshnam et al., 2017; Ng et al., 2018). With the development of synthetic miRNAs that could either mimic the function of biological miRNAs (agomirs) or inhibit the function of specific miRNAs (antagomirs), it is now possible to evaluate the efficacy of upregulating or downregulating miRNA levels in promoting neuroprotection in stroke. Based on the current literature, here we have highlighted the role of several promising miRNAs as potential neuroprotective agents in cerebral ischemic stroke (Table 4).

Post-ischemic down regulation of the glutamate transporter-1 (GLT-1) has been associated with the accumulation of glutamate and neuronal excitotoxicity. It has now been shown that expression of miR-29a and miR-223 are involved in regulating post-ischemic excitotoxicity and cell death. Intravenous administration of miR-29a agomir following reperfusion protects astrocytes and preserves astrocyte GLT-1 level by targeting the pro-apoptotic protein PUMA (p53 upregulated modulator of apoptosis). Overexpression of mir-223 also controls neuronal injury by reducing the levels of the GluR2 subunit of AMPA receptors and NR2B-subunit of NMDA receptors (Harraz et al., 2012; Ouyang et al., 2013; Tuo et al., 2017).

Studies have also shown that miR-424, miR-99a, miR-23a-3p agomirs as well as miR-106b-5p antagomir protects against ischemic brain injury by reducing oxidative stress. miR-424 levels has been shown to decrease in plasma of patients with acute ischemic stroke as well as in plasma and ipsilateral brain tissue of mouse after ischemic stroke. Accordingly, treatment with miR-424 decreases cerebral infarct volume by increasing the expression and activation of superoxide dismutase (SOD), manganese SOD (MnSOD) and the redox sensitive transcription factor Nrf2. It also suppresses microglial activation and TNFα production (Liu et al., 2015; Zhao et al., 2013). The level of miR-99a, a suppressor of tumorigenicity, has also been observed to be significantly downregulated in the plasma of acute ischemic stroke patients. Furthermore, the neuroprotective role of miR-99a was demonstrated in a mouse model of transient MCAO, where intracerebroventricular injection of miR-99a agomir immediately after MCAO reduced both infarct volume and neural apoptosis (Li et al., 2011; Sun et al., 2011a; Tao et al., 2015). Mechanistic studies further showed that miR-99a can alleviate oxidative stress injury and promote neural survival following stroke. Similarly, another suppressor of tumorigenicity miR23a-3p has been shown to reduce ischemic infarction volume and lessen oxidative stress when miR23a-3p agomir is injected intracerebroventricularly immediately after MCAO (Chen et al., 2019; Ding et al., 2019; Zhao et al., 2014). On the other hand, miR-106b-5p, which functions as a tumor promoter has also been reported to be a major contributor of oxidative stress and cerebral ischemic injury (Li et al., 2017a; Liu et al., 2014a; Xiang et al., 2015). Furthermore,

miR-106b-5p antagomir has been shown to significantly decrease ischemic infarct volume and neurological deficits. At the mechanistic level, miR-106b-5p antagomir reduced malondialdehyde content, restored SOD activity, increased the expression of Mcl-1, an anti-apoptotic member of the Bcl-2 family, and decreased the expression of Bax in the ischemic cortex (Li et al., 2017a).

Micro RNAs that have been implicated in the regulation of inflammation during stroke includes miR-124, miR-let-7c-5p and miR-181a. miR124 is almost exclusively expressed in the CNS (Lagos-Quintana et al., 2002; Landgraf et al., 2007). Post-ischemic administration of miR-124 has been shown to reduce infarct size at 24h after MCAO by modulating polarization of activated microglia and infiltrating macrophages towards the anti-inflammatory M2 phenotype (Hamzei Taj et al., 2016; Sun et al., 2013). miR-let-7c is another important regulator of macrophage polarization (Banerjee et al., 2013). Recent studies have shown that the level of miR-let7c-5p, a member of the let-7c family, is significantly decreased in the plasma of patients with ischemic stroke as well as in the plasma and ipsilateral brain tissue of mice subjected to MCAO/reperfusion (Ni et al., 2015). The study further showed that intracerebroventricular injection of miR-let7c-5p agomir decreased the infarct volume through inhibition of microglial activation and attenuated neurological deficits (Ni et al., 2015). Expression of miR-181a, which is enriched in the brain, has been shown to increase in the ischemic core following stroke and was associated with decrease in the level of GRP78, a master regulator of endoplasmic reticulum stress with antiapoptotic properties. Conversely, reducing the level of miR-181a with an antagomir reduced ischemic injury and was associated with increase in GRP78 level (Lee, 2005; Miska et al., 2004; Ouyang et al., 2012). Additional studies further showed that the reduction in brain infarct size following post-stroke treatment with miR-181a antagomir was associated with reduced NF-κB activation, microglial activation and leukocyte infiltration (Xu et al., 2015). The findings imply that reducing or blocking miR-181a protects the brain from both oxidative stress and inflammatory response following ischemia.

The role of microRNAs in BBB dysfunction following ischemic stroke is also evident from emerging studies. Two highly conserved microRNAs, miR-15a and miR-16–1 binds to common mRNA targets forming a structural and functional cluster termed as the miR15a/16–1 cluster (Calin et al., 2008; Klein et al., 2010). The cluster was first identified in human leukemia (Calin et al., 2008) and more recently dysregulation of miR-15a/16–1 levels in plasma of stroke patients has been reported (Tan et al., 2009). Subsequent studies in animal models of stroke showed significant increase in the level of both miR-15a and miR-16–1 in the ipsilateral hemisphere (Yang et al., 2017d). Utilizing miR-15a/16–1 knockout mice and pharmacological intervention with miR15a/16–1 antagomirs, the study further established that miR15a/16–1 in the brain negatively regulates the outcome of stroke by promoting inflammatory response and inhibiting the antiapoptotic genes bcl-2 and bcl-w. In an additional study, experimentally induced stroke in mice with an endothelial cell selective deletion of miR15a/16–1 showed a smaller infarct size, reduced BBB leakage and decreased infiltration of peripheral immune cells (Ma et al., 2020). Together, the above findings not only expand our understanding of the roles of miRNAs in stroke, but also identify a new direction for the development of future neuroprotective strategies.

8. CONCLUSION

It is evident from the existing literature that a large number of therapeutic agents have either undergone clinical trials or currently being assessed in pre-clinical studies for evaluation of efficacy in acute ischemic stroke. In spite of this extensive effort, the development of clinically effective neuroprotective agents is still elusive. Stroke is a complex disorder and our current understanding of the mechanistic basis indicates simultaneous and sequential activation of multiple detrimental signaling cascades in both the core and the penumbra. Moreover, with the advent of new technologies such as proteomics, metabolomics and RNA sequencing, new molecular events involved in ischemic brain damage are still emerging. Development of therapeutic agents that target a single event in the ischemic cascade may not be effective in spite of successful inhibition of the specific target. It is therefore essential to focus primarily on pleiotropic, multi-target agents that could intervene at multiple levels of the ischemic cascade to confer neuroprotection. However, identification of such agents could be a daunting task and could also be impossible. In addition, toxicity of such pleiotropic drugs could also be an issue. A clinically useful alternative could therefore be the development of combinational therapy. This would include multiple therapeutic compounds that could target both complementary and synergistic pathways in the acute stage, based on our knowledge of the distinct temporal profile of the progression of ischemic cascade. Development of such optimal therapies by combining neuroprotective agents that are currently undergoing clinical/pre-clinical assessment holds promise and it is only a matter of time before further advancement in stroke research yields a breakthrough.

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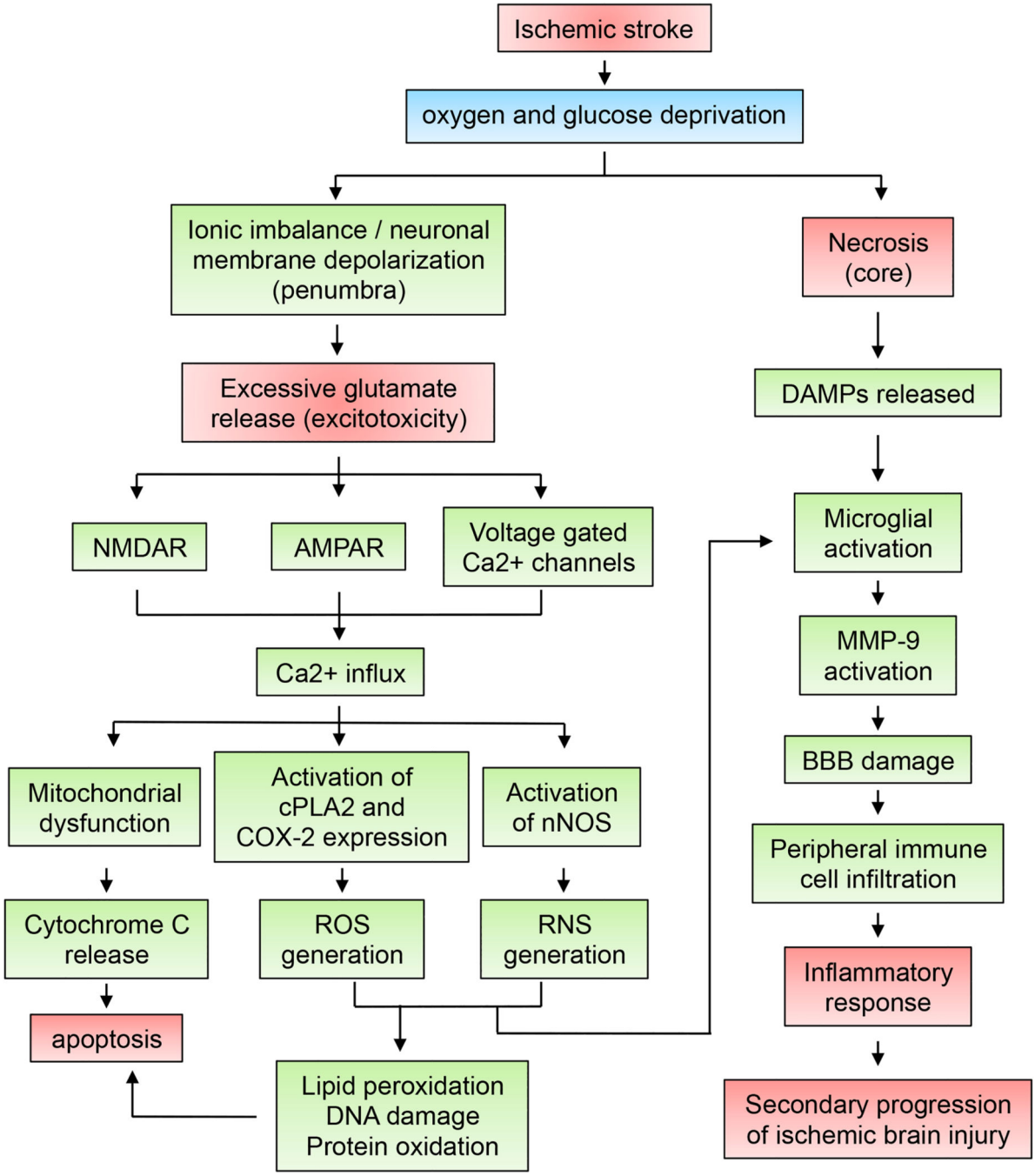

Figure 1.

Schematic representation of ischemia induced signaling cascade in the brain that leads to necrosis, neurotoxicity and inflammation, which contributes to progression of ischemic brain injury. Abbreviations: DAMPs: damage-associated molecular patterns; NMDAR: N-methyl-D-aspartate receptor; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; cPLA2: cytosolic phospholipase A2; COX2: cyclooxygenase-2; nNOS: neuronal

nitric oxide synthase; ROS: reactive oxygen species; RNS: reactive nitrogen species; BBB: blood-brain barrier.

Table 1:

Recently completed (last 5 yeas) clinical trials to assess neuroprotection in ischemic stroke.

Agent	Trial Name	Trial No./Phase/ Location	Time of intervention (post-stroke)	Proposed mechanisms of neuroprotection
Human urinary kallidinogenase (HUK)	-	NCT03431909 Phase IV China	Within 72h	Anti-oxidative and anti-inflammatory agent
Statins	ASSORT	NCT02549846 Phase IV Japan	Within 24h of admission; Atorvastatin (20mg), or Pitavastatin (4mg) or Rosuvastatin (5mg)	Pleiotropic effect with anti-inflammatory and anti-oxidant activity; reduces BBB dysfunction and enhances cerebral blood flow
	NeuSTART2	NCT01976936 Phase II USA	Within 0h to 24h of symptom onset; Lovastatin - 640mg/day for 3 days	
Edaravone	-	NCT02430350 Phase III China/Japan	Every 12h for 2 weeks (37.5mg / dose)	Potent anti-oxidant with other neuroprotective properties
NA-1 (nerinetide)	ESCAPE	NCT02930018 Phase III Canada & USA	As soon as they meet the enrollment criteria, within 12h (2.6 mg/kg)	Targets NMDA receptor mediated excitotoxicity
3K3A-APC	RHAPSODY	NCT02222714 Phase II USA	Within 30min to 120min of tPA infusion or mechanical thrombectomy; q12h,5 doses in 3 days; (120μg, 240μg, 360μg or 540μg/kg)	Anti-inflammatory agent that also suppresses intracerebral hemorrhage
GM602	GMAIS	NCT01221246 Phase II USA	Within 18h; three consecutive daily doses (320mg or 480mg)	Multi-target drug with anti-inflammatory, antioxidative and antiapoptotic properties
Natalizumab	ACTION2	NCT02730455 Phase II Europe & USA	Within 9h or 9-24h Dose - 300mg or 600mg IV	Anti-inflammatory agent
Vinpocetine	-	NCT02878772 Phase II China	Between 4.5h to 48h after symptom onset and 1h (30mg)	Cerebral vasodilator with anti-oxidative and anti-inflammatory properties

Table 2:

Ongoing clinical trials to assess neuroprotection in ischemic stroke.

Agent	Trial Name	Trial No./Phase/ Location	Time of intervention (post-stroke)	Proposed Mechanisms
Ginkgolide	GIANT	NCT03772847 China, Phase IV	To be administered along with tPA	Reduces BBB permeability, ER stress, inflammation and oxidative stress
Butylphthalide (NBP)	-	NCT03394950 Phase IV, China	Within 4.5h; infusion for 14 days; 25mg/day	Reduces oxidative damage, inflammation, apoptosis and mitochondrial dysfunction
	EBCAS	NCT03539445 Phase III, China	Within 6h: 100ml twice/day for 14 days; 60mg/day from day 15 to day 90	
	-	NCT02905565 Phase II, USA	Within 12h; for 30 days; 800mg/day	
BIIB093 (IV Glibenclamide)	CHARM	NCT02864953 USA, Phase III	Bolus within 10h followed by continuous intravenous infusion for 72h.	Reduces edema and inflammation
HLCM051 (Multi Stem)	MASTERS-2	NCT03545607 USA, Phase III	Within 18-36h; 1.2 billion HLCM051 cells	Reduces peripheral inflammatory response
	TREASURE	NCT02961504 Japan, Phase II/III	Within 18-36h; 1.2 billion HLCM051 cells	
Imatinib	-	NCT03639922 Phase III Sweden	Within 8h; for 6 days; 800mg/day	Ameliorates neuroinflammation by preserving BBB integrity.
Exenatide (GLP-1R agonist)	TEXAIS	NCT03287076 Australia, Phase II	Within 9h; 5 μg, twice daily for 5 days	Reduces oxidative stress, inflammation and edema
JPI-289 (Amelparib)	_	NCT03062397 Phase II, Korea	Within 24h (low or high dose)	Attenuates NAD and ATP depletion, mitochondrial dysfunction and immune response
Neu2000	SONIC	NCT02831088 Korea, Phase II	Within 8h (750mg); nine follow-up infusion at 12h intervals (500mg)	NR2B-selectve NMDA receptor antagonist and antioxidant
Remote ischemic conditioning (RIC)	RIC-ACS	NCT03868007 China	Within 4h, twice daily for 14 days	Triggers anti-oxidative, anti-inflammatory, and mitochondria modulatory protective effects
	RICAMIS	NCT03740971 China	Within 48h, twice daily	
	RESIST	NCT03481777 Denmark	After 6h, twice daily for 7 days	
	REMOTECAT	NCT03375762 Spain	Within 8h, prehospital setting - single treatment	

Table 3:

Evaluation of potential neuroprotectants through Stroke Preclinical Assessment Network (SPAN) in USA

Treatment	Mechanisms	References
Fasudil	A Rho-kinase inhibitor that reduces peripheral immune cell infiltration and oxidative stress. It also enhances cerebral blood flow.	Fukuta et al., 2016 Shibuya et al., 2005 Chan et al., 2017 Fukuta et la., 2017
Fingolimod	A sphingosine-1-phosphate receptor inhibitor that ameliorates peripheral immune cell infiltration and oxidative stress.	Li et al., 2017 Dang et al., 2020 Shang et al., 2020 Chamorro et al., 2016 Tian et al., 2018
Remote Ischemic Conditioning (RIC)	A series of transient occlusion and reperfusion of blood vessels at a limb distal to the brain triggers neuroprotective effects in the brain. Exact mechanisms are unknown.	Ren et al., 2011 Malhotra et al., 2011 Wei et al., 2012 Sun et al., 2012 Doeppner et al., 2018
Tocilizumab	An immunosuppressive drug that ameliorates immune response by blocking IL-6 receptor.	Wang et al., 2016 Hubodenko et al. 2017 Hubodenko et al., 2019
Uric acid	An antioxidant that suppresses ROS generation, lipid peroxidation and elevates nuclear expression of Nrf2	Aamaro et al., 2019 Chamorro et al., 2004 Ya et al., 2018 Valero-Aliena et al., 2018 Dhanesha et al., 2018 Laredo et al., 2016
Veliparib	PARP-1 inhibitor that can regulate NAD^+ and ATP depletion, mitochondrial dysfunction and immune response	Hamby et al., 2007 Takahashi et al., 1997 Berger et al., 2018

Table 4:

Emerging approaches for neuroprotection in ischemic stroke

Treatment	Mechanisms	References
Adropin	Ameliorates neurovascular dysfunction to confer neuroprotection	Yang et al., 2020 Shahjouei et al., 2016 Altintas et al, 2016
STEP-mimetic	Targets excitotoxic signaling cascade downstream of NMDARs to confer neuroprotection	Poddar et al., 2019 Deb et al., 2013 Poddar et al 2010
Verapamil	Reduces excitotoxic damage as a L- type calcium channel blocker (and vasodilator)	Fraser et al., 2017; Maniskas et al., 2016
Micro RNAs:		
microRNA-29a	Reduces excitotoxicity by preserving astrocytic glutamate transporter-1 level	Ouyang et al., 2013 Tuo et al., 2017
microRNA-223	Reduces excitotoxicity by regulating expression of NR2B-NMDAR and GluR2-AMPAR	Harraz et al., 2012
microRNA-424	Reduces oxidative stress by enhancing expression of SOD, MnSOD and Nrf2	Zhao et al., 2013 Liu et al., 2015
microRNA-99a	Reduces oxidative stress and neuronal apoptosis	Tao et al., 2015; Zhao et al., 2017
microRNA-23a-3p	Reduces oxidative stress by enhancing expression of MnSOD and reducing nO and 3-NT production	Zhao et al., 2014
microRNA-106b-5p (antagomir)	Reduces oxidative stress by restoring SOD activity and increasing the expression of Mcl-1	Li et al., 2015, 2017
microRNA-124	Reduces inflammation by promoting anti-inflammatory M2 phenotype of microglial/macrophage	Taj et al., 2016 Sun et al., 2013
microRNA-let-7c-5p	Reduces inflammation by inhibiting microglial activation	Ni et al., 2015
microRNA-181a (antagomir)	Reduces inflammation by inhibiting NF- kB activation, microglial activation, leukocyte infiltration and decrease in level of GRP78, an ER stress regulator	Ouyang et al., 2012 Xu et al., 2015
microRNA 15a/16-1 (antagomir)	Reduces BBB dysfunction, inflammatory response and apoptosis	Yang et al., 2017 Ma et al., 2020