INVITED REVIEW

Cerebral ischemia and neuroregeneration

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Abstract

Cerebral ischemia is one of the leading causes of morbidity and mortality worldwide. Although stroke (a form of cerebral ischemia)-related costs are expected to reach 240.67 billion dollars by 2030, options for treatment against cerebral ischemia/stroke are limited. All therapies except anti-thrombolytics (*i.e.*, tissue plasminogen activator) and hypothermia have failed to reduce neuronal injury, neurological deficits, and mortality rates following cerebral ischemia, which suggests that development of novel therapies again st stroke/cerebral ischemia are urgently needed. Here, we discuss the possible mechanism(s) underlying cerebral ischemia-induced brain injury, as well as current and future novel therapies (*i.e.*, growth factors, nicotinamide adenine dinucleotide, melatonin, resveratrol, protein kinase C isozymes, pifithrin, hypothermia, fatty acids, sympathoplegic drugs, and stem cells) as it relates to cerebral ischemia.

Key Words: *cerebral ischemia; melatonin; resveratrol; protein kinase C; pifithrin-α; fatty acids; sympathetic nervous system; neuromodulation therapy; traditional Chinese therapies; stem cell*

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Introduction

Stroke (a form of cerebral ischemia) remains the fifth leading cause of death and disability in the United States. A first or recurrent stroke occurs every 40 seconds, which affects approximately 800,000 people per year (Go et al., 2014). Stroke occurs when blood vessel(s) are interrupted by a blood clot/thrombus or when blood vessel(s) rupture (*i.e.*, hemorrhage) due to arteriovenous malformations or aneurysms. Since the brain is one of the most high-energy consuming organs, the lack of oxygen and nutrient supply elicited by stroke can cause severe brain damage resulting in neurological disorders.

Stroke can be classified into two categories: ischemic (87% of the population) and hemorrhagic stroke (23% of the population) (Ovbiagele and Nguyen-Huynh, 2011). Ischemic stroke is characterized by vascular thrombus formation, interruption of blood supply to the brain, which causes neuronal cell death and neurological deficits, such as learning/memory and locomotor deficiencies (Janardhan and Qureshi, 2004; Li et al., 2013). The middle cerebral artery, the largest branch of the internal carotid artery, is a prevalent site for ischemic stroke, which provides oxygen and nutrient supply to the primary motor, sensory, and speech areas of the brain including the frontal and the lateral surface of the temporal and parietal lobes. Thus, patients with middle cerebral artery occlusions suffer from hemiparesis or monoparesis, hemisensory and visual deficits, dysarthria, and ataxia (Gautier and Pullicino, 1985; No authors listed, 1990).

Another common type of ischemic stroke is transient ischemic attack (TIA or mini-stroke). TIA is characterized by a temporary blockage of cerebral blood flow (CBF), caused by the formation of blood clots and/or atherosclerotic plaques, damaging inner walls of brain vasculature (Eliasziw et al., 2004; Ovbiagele et al., 2008; Coutts, 2017). This form of ischemic stroke does not cause permanent brain damage due to the acute (minutes to hours) nature of the ischemia. However, One-third of TIA patients are expected to have an ischemic stroke within a year indicating that post-TIA care/treatment is paramount to favorable outcomes (Amarenco et al., 2016).

Hemorrhagic stroke is characterized by an aneurysm, arteriovenous malformation, or weakening of blood vessel walls causing rupture in the brain. Untreated hypertension and aging blood vessels are the major risk factors for hemorrhagic stroke. In fact, if hypertension is not properly controlled, patients are 10 times more likely to develop hemorrhagic stroke as compared to normotensive patients (Semple, 1995). An added consequence of hemorrhagic stroke is the elevation of intracranial pressure causing severe brain damage leading to high morbidity and mortality (van Asch et al., 2010; Keep et al., 2012). Hemorrhagic strokes can be further classified into two subtypes: intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) (Grysiewicz et al., 2008; Caceres and Goldstein, 2012). ICH occurs in the brain parenchyma, while SAH is predominately found between the pial and arachnoid space caused by the rupture of cerebral vessels.

Other non-stroke ischemia-related conditions include global ischemia (*i.e.*, cardiac arrest) and small vessel diseases (SVD). Life-threatening medical conditions, such as cardiac arrest, shock, severe hypotension, and asphyxia, result in insufficient blood supply throughout the entire brain (namely global ischemia) to cause neuronal cell death in the vulner-

able CA1 region of the hippocampus and cortex (Kirino, 1982; White et al., 1996; Schaller and Graf, 2004; Nour et al., 2013). Since the neurons in the CA1 region of the hippocampus and cortex play an important role in learning/memory formation, patients with global ischemia suffer severe learning/memory deficits. SVD has been frequently diagnosed in the elderly *via* neuroimaging (*i.e.*, computed tomography and magnetic resonance imaging scans). The pathological progression of SVD includes small cortical infarctions or hemorrhages, microbleeds, white matter attenuation (leukoaraiosis), Virchow-Robin spaces (enlarged perivascular spaces), and brain atrophy (brain volume loss) (Nitkunan et al., 2011; Wardlaw et al., 2013a, b), which are highly related to vascular dementia, cognitive or motor impairments, and depression (Mok et al., 2004; Pantoni and Gorelick, 2014).

Therapeutic strategies against cerebral ischemia are limited. For example, treatments against hemorrhagic stroke are dependent on surgery (*i.e.*, aneurysm clipping, coil embolization, and arteriovenous malformation repair) to reduce bleeding and intracranial pressure. In terms of ischemic stroke, intravenous thrombolysis with tissue plasminogen activator (tPA) (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995; Kanazawa et al., 2017) is the only FDA approved therapy for the treatment of acute ischemic stroke (Hacke et al., 2008; Zivin, 2009; Farbu et al., 2011; Cheng and Kim, 2015). However, tPA's narrow therapeutic time window (within 4.5 hours after the onset of stroke) significantly reduces its' therapeutic efficacy in the treatment against ischemic stroke. As for treatments against TIA and cardiac arrest, all therapies except hypothermia have failed to reduce neuronal injury. Thus, the goal of the treatments mainly focus on preventing risk factors for TIA and cardiac arrest (*i.e.*, high blood pressure, hyperlipidemia, smoking, and heart disease) indicating that developing novel therapies against cerebral ischemia is greatly needed. We will discuss the mechanisms underlying stroke/cerebral ischemia-induced brain injury as well as current and future novel therapies as it relates to cerebral ischemia.

Mechanisms Underlying Ischemic Brain Injury

Excitotoxicity and apoptosis/necrosis

Glutamate, the most abundant excitatory neurotransmitter in the brain, is a major contributor to cerebral ischemia-induced excitotoxicity (excitatory amino acids-induced neurotoxicity) and subsequent apoptosis/necrosis (Xu et al., 2001; Lai et al., 2014). Adenine triphosphate (ATP) deficiency (energy failure) and glutamate transporter dysfunction following cerebral ischemia can cause an increase in neuronal excitability and subsequent glutamate release and accumulation in the synaptic cleft (Bosley et al., 1983; Benveniste et al., 1984; Drejer et al., 1985; Hagberg et al., 1985; Silverstein et al., 1986; Dawson et al., 2000). This results in excessive activation of N-methyl-D-aspartate receptors (an ionotropic receptor) to cause massive calcium influx and dyshomeostasis in neurons (Berdichevsky et al., 1983; Jancso et al., 1984). Neuronal calcium overload can further activate calpains (calcium-dependent proteases) to cleave apoptotic regulatory proteins (*i.e.*, caspase family), as a result of lysosome-associated apoptosis and necrosis (Bisset, 1978; Schielke et al., 1998; Yamashima, 2004; Li and Yuan, 2008; Mrschtik and Ryan, 2015).

In addition to glutamate-induced cellular excitotoxicity, cerebral ischemia alone can induce overexpression of the death receptor ligands (*i.e.*, tumor necrosis factor (TNF)-α and FasL), as a result of serine/threonine-protein kinase 1-mediated neuronal necroptosis (Holler et al., 2000; Degterev et al., 2005, 2008). Furthermore, enhanced expression of c-Jun N-terminal kinase (JNK, a stress-activated protein kinase) after cerebral ischemia (Irving and Bamford, 2002; Borsello et al., 2003) can activate Fas- and Bim-mediated pro-apoptotic signals (Herdegen et al., 1998; Putcha et al., 2003; Okuno et al., 2004) leading to neuronal cell death.

Reperfusion injury and neuroinflammation

Reperfusion injury occurs when a tissue/organ encounters deprivation of blood supply followed by a restoration of blood flow to the ischemic area (Nour et al., 2013). Following reperfusion, reoxygenation, however, causes secondary injury (Chen and Nunez, 2010; Eltzschig and Eckle, 2011) due to excessive formation of reactive radical oxide species (ROS) and/or peroxynitrite (Peters et al., 1998; Bolanos and Almeida, 1999; Shen et al., 2003; Vitturi and Patel, 2011; Kietadisorn et al., 2012; Li et al., 2012; Olmez and Ozyurt, 2012; Rodriguez et al., 2013) and activation of the immune system (Eltzschig and Eckle, 2011).

In terms of ischemia induced-neuroinflammation, infiltrating immune cells release inflammatory mediators to recruit multiple immune and glia cells. These immunoreactive cells further limit the extent of the injury and restore tissue integrity (Kumar and Loane, 2012; Xanthos and Sandkuhler, 2014). However, excessive activation of microglia can occur following cerebral ischemia resulting in the release of pro-inflammatory cytokines, such as TNF-α, interleukin (IL)-1β, IL-6, IL-12, and interferon (IFN)γ (Schmidt et al., 2005; Hernandez-Ontiveros et al., 2013), as a result of blood brain barrier leakage (Chodobski et al., 2011). Moreover, pro-inflammatory cytokines increases neurotoxic molecules and free radicals (*i.e.*, ROS), reactive nitrogen species, cyclooxygenase-2, and inducible nitric oxide synthase] to cause secondary neuronal cell death (Qin et al., 2007; Erickson and Banks, 2011; Tremblay et al., 2011; Park et al., 2012; Biesmans et al., 2013; Hernandez-Ontiveros et al., 2013; Kabadi and Faden, 2014).

It is interesting to note that the ischemia-induced neuroinflammation mainly occurs in the non-microbial environment. Thus, the host receptor (*i.e.*, toll-like receptors) can be can be activated *via* non-microbial ligands, namely damage-associated molecular patterns (Chen and Nunez, 2010; Eltzschig and Eckle, 2011). These damage-associated molecular patterns, such as high-mobility group box1 protein and ATP are released from the cytoplasm upon tissue injury and/or cell death to initiate series of innate immune responses, as a result of excessive production of proin-

flammatory cytokines/chemokines (Iyer et al., 2009; Chen and Nunez, 2010; McDonald et al., 2010), which causes peroxynitrite- and ROS-mediated lipid peroxidation, DNA damage, and cell dysfunction/death (Garry et al., 2015).

Impaired axonal regeneration

Besides excitotoxicity, apoptosis/necrosis, reperfusion, and neuroinflammation, impaired axonal regeneration is another major contributor to neuronal cell death following cerebral ischemia. One of the major hallmarks of cerebral ischemia is the inherent glial scar formation. Glial scar (a tissue barrier) is formed by reactive astrocytes, microglia, and infiltrating immune cells to protect survival neurons from the harmful environment (*i.e.*, nitric oxide toxicity and glutamate-induced cellular excitotoxicity) (Reier and Houle, 1988; Fitch and Silver, 1997; Rolls et al., 2009; Huang et al., 2014b). These immunoreactive cells are responsible for trophic and metabolic support (*i.e.*, insulin-like growth factors, nerve growth factors, brain-derived neurotrophic factor, and neurotrophin-3), as well as scavenging excessive accumulation of glutamate, potassium, and other ions after cerebral ischemia (Schwartz and Nishiyama, 1994; Wu et al., 1998; do Carmo Cunha et al., 2007; White et al., 2008; Rolls et al., 2009). However, the immunoreactive cells, in particular astrocytes, become hypertrophic and release chondroitin sulfate proteoglycans (an inhibitory extracellular molecule) in response to cerebral ischemia (McKeon et al., 1991), which restricts axonal regeneration and neuronal survival *via* RhoA/ROCK-mediated pathways (Silver and Miller, 2004; Yiu and He, 2006). In addition to glial scar, myelin (the laminated membrane structure that surrounds the axon) is also responsible for the failure of axonal regeneration. Although myelin has been reported to regulate the axonal cytoskeleton, axon caliber, neurofilament spacing (Yin et al., 1998), and microtubule formation (Hsieh et al., 1994; Nguyen et al., 2009), numerous studies have shown that myelin-associated glycoproteins, such as oligodendrocyte-myelin glycoprotein and nogoA are actually detrimental to axonal regeneration and sprouting after cerebral ischemia (Caroni and Schwab, 1988; McKerracher et al., 1994; Mukhopadhyay et al., 1994).

Novel Neuroregenerative Agents

A stroke lesion can be classified into the ischemic core and the surrounding penumbra (Yuan, 2009), while the irreversible cell death mainly occurs in the ischemic core area. Thus, most of the studies are targeted to prevent neuronal cell death in the hypoperfused penumbra region. We will discuss current and future novel neuroregenerative agents as it relates to cerebral ischemia in subsequent paragraphs. The clinical evidence for each neuroregenerative agent is summarized in the **Table 1**.

Fibroblast growth factors (FGFs)

FGFs are a group of structurally similar polypeptide mitogens, which promote tissue repair, angiogenesis, neurogenesis, axonal growth, embryonic development, and various endocrine signaling pathways. 23 members of FGFs have been isolated (Zechel et al., 2010), while the expression of FGF-2 is significantly increased after various brain injuries including seizures (Riva et al., 1992), transient forebrain ischemia (Takami et al., 1993; Speliotes et al., 1996), and traumatic ischemic brain injury (Christian Alzheimer, 2000-2013). In addition, the FGF-2-deficient mice presented with larger infarct volume (75% more) following experimental brain ischemia, *via* middle cerebral artery occlusion (MCAO) suggesting that FGF-2 had neuroprotective effects against ischemic brain injury (Kiprianova et al., 2004).

The use of FGF-2 has been implicated in several pre-clinical trials of cerebral ischemia. Administration of FGF-2 in rats has been shown to increase the number of neurons and markers for neurogenesis in the hippocampus and dentate gyrus after MCAO (Bethel et al., 1997; Wagner et al., 1999; Cheng et al., 2002; Wang et al., 2008). Subsequent studies by Leker et al, 2007 and Yoshimura et al, 2001 further indicate that up-regulation of FGF-2 *via* adeno-associated viral vectors in the infarct area can increase the number of proliferating cells and motor behavior after MCAO (Yoshimura et al., 2001; Leker et al., 2007). Overall, FGF-2 can enhance neural proliferation/differentiation following cerebral ischemia, which may provide future therapeutic opportunities.

Nicotinamide adenine dinucleotide (NAD)

NAD is a coenzyme of vitamin B3 critical for many biochemical reactions including energy production, ion homeostasis, and biosynthesis of glucose and fatty acids (Ying, 2006; Belenky et al., 2007). Numerous studies indicate that NAD+ (oxidized form) depletion and subsequent ATP loss during/after cerebral ischemia result in energy failure and cell death (Jagtap and Szabo, 2005), which suggests that repletion of NAD+ is beneficial in the treatment against cerebral ischemia.

Zhao et al. (2015) found that overexpression of nicotinamide phosphoribosyltransferase (Nampt, the rate-limiting enzyme for NAD+ biosynthesis) enhanced neurogenesis after MCAO in mice. Additionally, post-treatment of nicotinamide mononucleotide (an intermediate of NAD+ biosynthesis) enhanced neuronal survival and neurogenesis after MCAO (Zhao et al., 2015), while intraperitoneal (IP) injection of nicotinamide (a NAD+ precursor) after MCAO enhanced intracellular NAD+ concentration in the brain. NAD+ derivatives reduced infarct volume *via* sirtuin-1 and sirtuin-2-mediated pathways (Liu et al., 2009; Siegel and McCullough, 2013; Zhao et al., 2015). Overall, the development of novel therapies targeting the Nampt-NAD+ cascade may be valuable against ischemic brain injury.

Melatonin (N-acetyl-5-methoxy tryptamine)

Melatonin, a hormone synthesized and released from the pineal gland, plays a crucial role in the regulation of sleep and wake cycles (Reiter, 1991). Thus, melatonin has been widely used for the treatment of sleep disorders including insomnia, delayed sleep phase syndrome, and rapid eye movement sleep behavior disorder (Laudon and Frydman-Marom, 2014; Tordjman et al., 2017; Xie et al., 2017). Interestingly,

Table 1 Neuroregenerative agents in cerebral ischemia

Agents	Pre-clinical trials	Clinical trials/uses	Applications
Fibroblast growth factors	Kiprianova et al., 2004; Bethel et al., 1997; Wagner et al., 1999; Cheng et al., 2002; Wang et al., 2008; Yoshimura et al., 2001; Leker et al., 2007	N/A	MCAO-induced ischemic brain injury
Nicotinamide adenine dinucleotide	Jagtap and Szabo, 2005; Liu et al., 2009; Siegel and McCullough, 2013; Zhao et al., 2015	N/A	MCAO-induced ischemic brain injury
Melatonin (N-acetyl-5-methoxy tryptamine)	Pei et al., 2003; Kilic et al., 2004; Koh, 2008; Kim and Lee, 2014	N/A	MCAO-induced ischemic brain injury; bilateral common carotid arteries occlusion-induced transient cerebral ischemia
Resveratrol	Tsai et al., 2007; Dong et al., 2008; Fang et al., 2015; Kizmazoglu et al., 2015; Narayanan et al., 2015; Koronowski et al., 2015; He et al., 2017	N/A	MCAO- and bilateral common carotid artery occlusion-induced cerebral ischemia
Protein kinase C (PKC) isozymes, δPKC and εPKC	Raval et al., 2003; Gonzalvez et al., 2005; He et al., 2007; Shimohata et al., 2007a, b; DeFazio et al., 2009; Ghibelli and Diederich, 2010; Dave et al., 2011; Lin et al., 2012	N/A	Oxygen and glucose deprivation; ACA- and bilateral carotid artery occlusion-induced cerebral ischemia
Pifithrin-α	Culmsee et al., 2001; Zhang et al., 2016	N/A	MCAO-induced ischemic brain injury
Hypothermia	Busto et al., 1987; Dietrich et al., 1990, 1991, 1993, 1994; Morikawa et al., 1992; Globus et al., 1995; Hall, 1997; Prakasa Babu et al., 2000; Kollmar et al., 2007; Zhao et al., 2007; Li and Wang, 2011; Yenari and Han, 2012; Lee et al., 2016; Jiang et al., 2017	Schwab et al., 1998; Els et al., 2006; Hong et al., 2014	MCAO- and bilateral common carotid artery occlusion-induced cerebral ischemia; traumatic brain injury; patients with middle cerebral artery infarction
Fatty acids	Lin et al., 2008, 2014	N/A	MCAO- and ACA-induced cerebral ischemia
Attenuation of sympathetic nervous system	Lee et al., 2017	Treggiari et al., 2003	ACA-induced cerebral ischemia; aneurysmal subarachnoid hemorrhage
Neuromodulation therapy	Adkins-Muir and Jones, 2003; Kleim et al., 2003; Plautz et al., 2003; Teskey et al., 2003	Naeser et al., 2005; Kirton, 2017; Lindenberg et al., 2010; Cazzoli et al., 2012; Bonni et al., 2014; Yamada et al., 2014; Lee and Lee, 2015; Triccas et al., 2015; Allman et al., 2016; Rocha et al., 2016; Kirton, 2017	MCAO-induced cerebral ischemia; patients with ischemic stroke
Traditional Chinese therapy	Wang et al., 2002; Cai et al., 2007; Chen et al., 2008, 2015; Ma and Luo, 2008; Wang and Jiang, 2009; Lang et al., 2011; Kim et al., 2013a, b, 2014; Xie et al., 2013; Xin et al., 2013b ; Huang et al., 2014a, 2017; Mu et al., 2014; Shen et al., 2014; Lu et al., 2016	Tan et al., 2013; Huang et al., 2014c; Mu et al., 2014; Liu et al., 2015; Zhang et al., 2015; Lu et al., 2016; Li et al., 2017; Yang et al., 2017; Wang et al., 2017	MCAO-induced cerebral ischemia; patients with acute stroke
Stem cell therapy	Goldman and Nottebohm, 1983; Gage, 2000; Li et al., 2000; Anderson, 2001; Chen et al., 2001; Doetsch et al., 2002; Arvidsson et al., 2002; Chen et al., 2003; Dempsey et al., 2003; Picard-Riera et al., 2004; Ryan et al., 2005; Kobayashi et al., 2006; Leker et al., 2007; Chojnacki and Weiss, 2008; Liauw et al., 2008; Yoo et al., 2008; Daadi et al., 2009; Jin-qiao et al., 2009	Kondziolka et al., 2000, 2005; Riera et al., 2004; Bliss et al., 2010; Zhao et al., 2012; Ankrum et al., 2014; Trounson and McDonald, 2015; Azad et al., 2016; Polymeri et al., 2016	MCAO-induced cerebral ischemia; patients with acute stroke

N/A: Not applicable; MCAO: middle cerebral artery occlusion; ACA: asphyxial cardiac arrest.

recent studies suggest that melatonin provides other non-sleep/wake cycle related pharmacological effects, such as anti-nitric oxide (NO) production, anti-oxyradicals, and anti-peroxynitrite effects (Poeggeler et al., 1994; Pozo et al., 1994; Gilad et al., 1997; Cuzzocrea et al., 2000). Oxyradicals, NO, and peroxynitrite play a crucial role in the pathological progression of neuronal cell death following cerebral ischemia (Beckman et al., 1990; Crow and Beckman, 1995), which suggests that melatonin may provide neuroprotection against cerebral ischemia.

IP injection and/or oral treatment of melatonin has been shown to reduce infarct volume and neuronal cell death (Pei et al., 2003; Kilic et al., 2004; Koh, 2008) after MCAO. Administration of melatonin (*via* IP) 30 minutes before bilateral common carotid arteries occlusion-induced transient cerebral ischemia alleviates neuronal cell death in the CA1

and CA2 regions of the hippocampus (Kim and Lee, 2014). Mechanisms underlying melatonin-induced neuroprotection after cerebral ischemia are highly complicated and remains to be elucidated. Kilic et al., (2004) reported that melatonin prevents cerebral ischemia-induced brain injury *via* inhibition of endothelin converting enzyme-1, while others' suggest that melatonin reduces ischemic brain injury *via* inhibition of matrix metalloproteinase-9 (Kim and Lee, 2014) or enhanced MEK/ERK/p90RSK/Bad signaling cascade (Koh, 2008). In summary, melatonin may be used to combat cerebral ischemia by inhibition of oxyradicals/peroxynitrite production, endothelin biosynthesis, and promote MEK/ERK-mediated cell proliferation and differentiation.

Resveratrol

Resveratrol, 3,5,4′-trihydroxy-trans-stilbene, is a poly-phenol found in red wine, grapes, chocolate, and many plants, such as knotweeds and pine trees. Numerous studies have shown that resveratrol has multifactorial effects including anti-inflammation and anti-oxidation, which suggests that the use of resveratrol may provide benefits in the treatment against cerebral ischemia. Many studies conducted in experimental brain ischemia further suggest that administration of resveratrol (0.1 μg/kg to 40 mg/kg) reduced infarct volume following MCAO- and bilateral common carotid artery occlusion-induced cerebral ischemia (Tsai et al., 2007; Dong et al., 2008; Fang et al., 2015; Kizmazoglu et al., 2015; Narayanan et al., 2015; He et al., 2017).

Mechanisms underlying resveratrol-induced neuroprotection against cerebral ischemia are multifactorial. Tsai et al. (2007) reported that resveratrol reduced MCAO-induced infarction by inhibition of inducible nitric oxide synthase (iNOS) production, while upregulation of endothelial nitric oxide synthase (eNOS) expression. Other studies suggest that resveratrol attenuates ischemic brain injury *via* inhibition of myeloperoxidase levels, pyrin domain-containing 3 inflammasome formation, cerebral TNF-α production, and markers for apoptosis (*i.e.*, Bcl-2, Bax, p53, and annexin V) (Fang et al., 2015; Kizmazoglu et al., 2015; He et al., 2017). Furthermore, resveratrol activates nuclear erythroid 2-related factor 2- and sirtuin-1-mediated pathways to enhance neuronal survival in response to cerebral ischemia (Koronowski et al., 2015; Narayanan et al., 2015) indicating that resveratrol is a potential candidate in the treatment of cerebral ischemia.

Protein kinase C (PKC) isozymes, δPKC and εPKC

Enhanced expression of δPKC after cerebral ischemia (Shimohata et al., 2007b; Dave et al., 2011) can initiate phosphorylation of mitochondrial phospolipid scramblase 3 (PLSCR3) (He et al., 2007), dephosphorylation of Bad, and formation of Bax/Bak pores, as a result of cytochrome c release and mitochondria-mediated apoptosis (Gonzalvez et al., 2005; He et al., 2007; Ghibelli and Diederich, 2010). Subsequent studies by Lin et al. (2012) further suggest that inhibition of δPKC *via* δPKC specific inhibitor, δV1-1, can alleviate neuronal cell death and CBF derangements, which suggest the neuroprotective effects of δPKC inhibition after cerebral ischemia. Unlike the detrimental role of δPKC in ischemic brain injury, εPKC (another PKC isozyme) expression is actually enhanced during therapeutic hypothermia and ischemic preconditioning, which suggest εPKC's possible neuroprotective role in ischemic brain injury (Raval et al., 2003; Shimohata et al., 2007a).

The Perez-Pinzon research group further investigated the activation of εPKC following oxygen and glucose deprivation (an *in vitro* ischemia injury model) can reduce GABAA receptor-mediated excitotoxicity in the hippocampal neurons (DeFazio et al., 2009). Furthermore, pretreatment of specific εPKC activator, ψεRACK, can attenuate CBF derangements and neuronal cell death elicited by asphyxial cardiac arrest (ACA)- and bilateral carotid artery occlusion-induced cerebral ischemia, which suggests that development of novel therapies to inhibit δPKC but activate εPKC may provide potential benefits in the treatment against cerebral ischemia.

Pifithrin-α (PFT-α)

Recent studies suggest that the tumor suppressor protein p53-induced apoptosis plays a crucial role in neuronal cell death after cerebral ischemia (Broughton et al., 2009; Hong et al., 2010). Culmsee et al. (2001) thus developed a synthetic p53 inhibitor, PFT-α, to evaluate the therapeutic potentials of p53 inhibition on ischemic brain injury. They found that IP injection of PFT-α 30 minutes before MCAO can reduce neuronal cell death in the CA1 region of the hippocampus, which suggests that the use of PFT-α may have therapeutic potential against cerebral ischemia in the near future. Mechanisms underlying PFT-α-induced neuroprotection after cerebral ischemia remains to be elucidated. Zhang et al. (2016) reported that PFT-α can stimulate angiogenesis and neurogenesis after MCAO, while other studies suggest PFT-α reduces infarct volume and neurological and locomotor deficits *via* vascular endothelial growth factor-mediated pathways.

Other Neuroregenerative Factors/Agents

Hypothermia

The normal body core temperature is near 37°C in humans, while hypothermia is defined as body core temperature below 35°C. Hypothermia can be a medical emergency if the body temperature falls below 32°C or less, which results in multiple organ failure and even death. However, Busto et al. (1987) first discovered that moderate decrease of brain temperature provides neuroprotection against experimental brain ischemia. In Busto et al's studies, the rat brain temperature was maintained at 36, 33, or 30°C following four-vessel or bilateral carotid artery occlusion-induced cerebral ischemia. They found that hypothermia treatment (at 33 and 30°C) significantly reduced neuronal metabolic demand and glutamate release, ultimately attenuating neuronal cell death in the CA1 region of the hippocampus after cerebral ischemia (Busto et al., 1987; Dietrich et al., 1993). Busto et al's landmark findings were further established by a different experimental brain ischemia including MCAO and traumatic brain injury (Morikawa et al., 1992; Dietrich et al., 1994; Kollmar et al., 2007; Li and Wang, 2011) suggesting

that hypothermia is actually beneficial in the treatment of general cerebral ischemia.

In addition to experimental brain ischemia, moderate hypothermia has been shown to significantly reduce intracranial pressure, cerebral edema, and neurological deficits in patients with severe middle cerebral artery infarction (Schwab et al., 1998; Els et al., 2006; Hong et al., 2014). Multiple factors are involved in hypothermia-mediated neuroprotection after cerebral ischemia. Hypothermia inhibits glutamate-induced excitotoxicity (Busto et al., 1987; Zhao et al., 2007; Yenari and Han, 2012), while reducing the production of superoxide, peroxynitrite, hydrogen peroxide, and hydroxyl radicals to relieve oxidative stress after cerebral ischemia (Globus et al., 1995; Hall, 1997; Yenari and Han, 2012). Furthermore, hypothermia has also been reported to reduce apoptosis, autophagy, and inflammation (Prakasa Babu et al., 2000; Lee et al., 2016; Jiang et al., 2017), as well as blood-brain barrier leakage and brain metabolism after cerebral ischemia (Busto et al., 1987; Dietrich et al., 1990; Dietrich et al., 1991), which suggests that the use of hypothermia during/after cerebral ischemia provides high therapeutic potential in the treatment of patients with stroke or other central nervous system disorders.

Fatty acids

Saturated fatty acids were traditionally considered as a "detrimental" class of fatty acids, which can increase the risk of cardiovascular diseases. Lin et al. (2008, 2014) however, found palmitic acid methyl ester (PAME) released from the sympathetic nervous system is a novel vasodilator and CBF mediator. Since hypoperfusion (decrease in CBF) following cerebral ischemia plays a crucial role in the pathological progression of neuronal cell death and neurological deficits, the vasodilatory properties of PAME suggest its therapeutic potential in the treatment against cerebral ischemia. Subsequent investigations by Lin's research group further indicate that pre-treatment of PAME increased CBF and neuronal viability after MCAO and ACA (Lin et al., 2014), which suggests that PAME is a novel neuroprotective agent against cerebral ischemia.

Attenuation of sympathetic nervous system

Autonomic dysregulation after cardiac arrest can be detrimental to the brain. Lee et al, 2017 first reported that excessive activation of perivascular sympathetic nervous system in the brain is one of the major causes of hypoperfusion, neuronal cell death, and neurological deficits after ACA-induced cerebral ischemia (Lee et al., 2017). Thus, surgical interruption of perivascular sympathetic nerves *via* decentralization of superior cervical ganglion (a sympathetic ganglion that innervates cerebral arteries) can alleviate ACA-induced hypoperfusion and brain injury (Lee et al., 2017). Interestingly, interruption of cervical sympathetic chain *via* bolus injection of bupivacaine and clonidine (ganglionic and α2 blocker, respectively) in the superior cervical ganglion has been shown to reduce neurological deficits after aneurysmal subarachnoid hemorrhage in humans (Treggiari et al., 2003), which suggests that developing novel therapies target on the perivascular sympathetic nervous system may be beneficial.

Neuromodulation therapy

Neuromodulation therapy is a novel technique that utilizes implantable neuromodulatory device/stimulator to deliver electrical or magnetic stimuli directly upon injured neurons. There are growing evidences suggest that neuromodulation therapies can promote functional recovery, in particular locomotor function after stroke. For example, the use of repetitive transcranial magnetic stimulation (TMS) (at ~1 and ~10 Hz) to stimulate motor cortex has been shown to enhance motor function after experimental ischemia (Adkins-Muir and Jones, 2003; Kleim et al., 2003; Plautz et al., 2003; Teskey et al., 2003; Naeser et al., 2005; Kirton, 2017). In addition to experimental ischemia, recent clinical studies suggest that non-invasive brain stimulation *via* transcranial direct current stimulation (tDCS) or theta burst stimulation (TBS, a neuromodulatory device that provides continuous theta frequency low-intensity stimuli into target brain regions) can facilitate motor and language recovery after chronic stroke (Lindenberg et al., 2010; Cazzoli et al., 2012; Bonni et al., 2014; Yamada et al., 2014; Lee and Lee, 2015; Triccas et al., 2015; Allman et al., 2016; Rocha et al., 2016; Kirton, 2017). Since over 70% of stroke survivors suffer from gait abnormalities, one of the major therapeutic challenges for stroke survivors is gait rehabilitation indicating that neuromodulation therapy's potential in the treatment of cerebral ischemia.

Traditional Chinese therapies

Traditional Chinese therapies (*i.e.*, plant-based medicines and acupuncture) are considered novel therapies against stroke/cerebral ischemia due to their multifactorial effects (*i.e.*, anti-inflammation and anti-oxidation). For example, Buyang Huanwu decoction (BHD) is derived from extracts from various Chinese herbs, including Radix Astragali (the root of *Astragalus membranaceus*), Radix Angelicae Sinensis (the root of *Angelica sinensis*), Radix Paeoniae Rubra (chishao, the root of *Paeonia lactiflora* Pall), Chuanxiong Rhizoma (the root and rhizome of *Ligusticum chuanxiong* Hort), Semen Persicae (taoren, the seeds of *Amygdalu spersica*), Flos Carthami (the flower of *Carthamus tinctorius* L, and Pheretima [the body of *Pheretima aspergillum* (earth worm)] (Mu et al., 2014). Numerous studies have shown that BHD can reduce cerebral ischemia-induced neuronal damage by inhibiting excitotoxicity, inflammation, and apoptosis (Chen et al., 2008; Wang and Jiang, 2009), while promoting angiogenesis (Shen et al., 2014), proliferation, differentiation, and migration of neuroprogenitor cells (NPCs) to the infarct area (Cai et al., 2007).

In addition to BHD, Dragon's blood dropping pills (the red resin from *Dracaena cochinchinensis*) and Bilobalide (EGb 761, a ginkgo biloba extract) have also been shown to alleviate cerebral water content, oxidative stress, and glutamate release in the infarct area following MCAO, thus reducing excitotoxicity, infarct volume, and neurological deficits (Lang et al., 2011; Xin et al., 2013b). Furthermore, clinical studies suggest that flower extracts, including *Dengzhan Xixin* (erigeron

breviscapus, a Chinese daisy) and *Dengzhanhua* can enhance acute stroke patients' CBF, plasma viscosity, and platelet adhesion to improve neurological function (Huang et al., 2014c; Li et al., 2017; Wang et al., 2017).

In additional to the aforementioned traditional Chinese medicines, acupuncture has also been considered as a complementary and alternative therapies for stroke patients in Asian countries. Acupuncture can be divided into traditional acupuncture and electro-acupuncture. The traditional acupuncture utilizes thin metal needles to stimulate acupuncture points over the body, while electro-acupuncture combines traditional acupuncture with modern electrotherapy to enhance stimulations to acupuncture points. Acupuncture has been shown to ameliorate neuronal cell death, neurological deficits, and brain edema following MCAO (Lu et al., 2016). In addition to experimental stroke models, recent clinical studies suggest that acupuncture can reduce disability rates, while enhance stroke patients' activities of daily living evaluated by Barthel Index, National Institutes of Health Stroke Scale, and Revised Scandinavian Stroke Scale (Tan et al., 2013; Liu et al., 2015; Yang et al., 2017). Furthermore, a multicenter randomized controlled trial from 862 stroke patients suggests that patients received acupuncture therapies 5 times per week for 3 to 4 weeks have higher survival rate than patients without acupuncture treatments (Zhang et al., 2015), which suggest acupuncture's potential in the treatment against stoke/cerebral ischemia.

Multiple pathways are involved in acupuncture-mediated neuroprotective effects following cerebral ischemia. Huang et al. (2017) reported that acupuncture enhances IκB-α expression to reduce NF-κB-mediated inflammation. Kim et al. (2013b) and Wang et al. (2002), however, suggest that acupuncture can inhibit apoptotic signaling cascade *via* enhancing Akt, Bcl-2, Bcl-xL, and cIAP1/2, while reducing apoptotic mediators (*i.e.*, death receptor 5 and caspases-3, -8, and -9). In addition to acupuncture's anti-inflammatory and anti-apoptotic effects, Kim et al. (2014) reported that acupuncture promotes astrocytes and neuronal progenitor cells proliferation *via* Wnt/β-catenin- and ERK1/2-mediated pathways (Xie et al., 2013; Huang et al., 2014a; Chen et al., 2015), as a result of brain-derived neurotrophic factor/vascular endothelial growth factor (VEGF)-mediated neurogenesis (Kim et al., 2014). Furthermore, acupuncture enhances post-ischemia CBF by promoting VEGF and angiogenin-1-mediated angiogenesis (Ma and Luo, 2008), as well as enhanced release of vasoactive mediators (*i.e.*, acetylcholine and nitric oxide) (Kim et al., 2013a) after cerebral ischemia. Overall, traditional Chinese therapies (*i.e.*, plant-based medicines and acupuncture) can inhibit cerebral ischemia-induced excitotoxicity, inflammation, and apoptosis, while promoting angiogenesis and cerebral blood flow after cerebral ischemia. The use of traditional Chinese traditional may provide therapeutic opportunities against cerebral ischemia.

Stem cell therapy

In addition to the above mentioned neuroregenerative agents, stem cell therapy is also a promising option for patients with stroke/cerebral ischemia due to stem cells' self-regenerative, differentiating, and multifunctional properties (Trounson and McDonald, 2015). Stem cell therapies can be divided into endogenous and exogenous therapies. The endogenous therapies utilize neurotrophic and growth factors, such as epidermal growth factor, glial cell-derived neurotrophic factor, FGF-2, insulin-like growth factor-1, and brain-derived neurotrophic factor (Dempsey et al., 2003; Kobayashi et al., 2006; Leker et al., 2007; Jin-qiao et al., 2009) to enhance vascular regeneration and brain synaptic plasticity, while it stimulates the reparative abilities of the endogenous neural stem cells (NSCs) in the injured dentate gyrus and subventricular zone (SVZ) (Picard-Riera et al., 2004), thus reducing lesion size and locomotor deficits. On the contrary, exogenous therapies use tissue extraction, *in vitro* cultivation, and subsequent stem cell transplantation into damaged brain regions caused by stroke/cerebral ischemia (Azad et al., 2016).

Mechanisms underlying endogenous stem cell therapies against cerebral ischemia are highly complicated and remains to be elucidated (Arvidsson et al., 2002). Endogenous activation of neural stem cells (NSCs) in the subgranular zone (SGZ) and SVZ after cerebral ischemia have been shown to produce neurotrophic factors (*i.e.*, brain-derived neurotrophic factor), which reduce inflammation, while promoting angiogenesis *via* activation of pro-angiogenic complexes, such as netrin-4, laminins, and integrins (Goldman and Nottebohm, 1983; Anderson, 2001; Doetsch et al., 2002; Staquicini et al., 2009), thus reducing brain injury elicited by hypoxia/ischemia. Additionally, the activated NSCs after cerebral ischemia can produce and secrete thrombospondins to promote synaptic regeneration and axonal sprouting (Liauw et al., 2008).

In terms of exogenous stem cell therapies, NPCs, bone-marrow derived stromal cells (BMSCs), and immortalized cell lines have been widely used in the treatment of cerebral ischemia (Bliss et al., 2010). Transplantation of NPCs following ischemic stroke results in the migration of mature and immature neurons towards the injured brain regions, as a result of long-term cell survival, electrical balance, synaptic plasticity recovery (Daadi et al., 2009; Clarkson et al., 2010; Darsalia et al., 2011; Bacigaluppi et al., 2016), and functional outcome improvement (*i.e.*, sensorimotor and memory) (Jin et al., 2010). The major advantage of the NPCs therapy is NPCs' self-differentiate abilities into astrocytes, neurons, and oligodendrocytes (Gage, 2000; Chojnacki and Weiss, 2008). However, NPCs are commonly associated with teratoma formation due to their endless self-renewing ability (Rong et al., 2012), which reduces NPCs' therapeutic efficacy in the treatment of cerebral ischemia indicating that further studies are necessary to evaluate safety and efficacy of NPCs in the treatment against cerebral ischemia.

BMSCs are another type of multipotent stem cells with high-differentiation and migration (Polymeri et al., 2016). BMSCs' anti-inflammatory, immune suppressive, and low tissue rejection properties (Ryan et al., 2005; Zhao et al., 2012; Ankrum et al., 2014) provide therapeutic potential in

the treatment against cerebral ischemia. *In vivo* studies have shown that implantation of BMSCs in rats after cerebral ischemia results in an increase in axonal sprouting (Li et al., 2000), neurogenesis, and angiogenesis (Chen et al., 2001, 2003; Yoo et al., 2008; Xin et al., 2013a), thus reducing brain injury, neuronal cell death, and neurological deficits (Chen et al., 2003; Zheng et al., 2010; Xin et al., 2013a). Mechanisms underlying BMSCs-induced neuroprotection remains unclear. Previous studies, however, suggest that trophic factors (*i.e.*, brain-derived neurotrophic factor) released from BMSCs after cerebral ischemia are the major contributors to BMSCs-induced angiogenesis and regrowth/repair of nerve tissue (Bao et al., 2011). Additionally, BMSCs have also been reported to reduce the expression of axonal-growth inhibitory proteins (*i.e.*, Rho-associated and coiled-coil-containing protein kinase 2) (Song et al., 2013), thus enhancing axon growth and formation following cerebral ischemia.

In addition to NPCs and BMSCs, recent studies also focus on investigating the therapeutic potential of immortalized cell lines as another option for cerebral ischemia treatment due to immortalized cell lines' ability to proliferate indefinitely (Kondziolka et al., 2000, 2005; Stroemer et al., 2009). Furthermore, immortalized cell lines can differentiate into oligodendroglial and endothelial cells to promote/restore endogenous neurogenesis in the SVZ after cerebral ischemia (Stroemer et al., 2009). Thus, treatment with immortalized cell lines (*i.e.*, CTX0E03) can enhance functional sensorimotor recovery (evaluated *via* bilateral asymmetry and rotameter test) after cerebral ischemia elicited by MCAO. Since immortalized cell lines are mainly derived from tumor cells and contain oncogenes, the major drawback of immortalized cell lines is their propensity to form tumors. Although results from several Phase I and II clinical trials suggest that implantation of Ntera2/D1 neuron-like cells, another immortalized cell line derived from teratocarcinoma, has no adverse effects in stroke patients (Kondziolka et al., 2000, 2005), more studies are needed to evaluate the safety and efficacy of the immortalized cell lines in the treatment against cerebral ischemia.

Conclusions

Despite improved education (*i.e.*, dietary), psychological care, and better therapeutic treatments [*i.e.*, less door-to-needle time for plasminogen activator], cerebral ischemia is still one of the leading causes of morbidity and mortality worldwide (Lopez et al., 2006; Feigin et al., 2009). The stroke-related costs are expected to reach 240.67 billion by 2030 according to the American Heart Association (Ovbiagele et al., 2013) indicating that developing novel therapies that can effectively alleviate post-stroke long-term disability is greatly needed. Although more studies are needed to evaluate the safety and efficacy of the novel neuroregenerative agents as we have already discussed, agents that have been investigated in clinical studies, such as hypothermia, bolus injection of bupivacaine and clonidine in the superior cervical ganglion, neuromodulation therapy, stem cell and traditional Chinese therapies should be considered for treatment against stroke and general ischemia.

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