



# Review Cerebral Ischemic Tolerance and Preconditioning: Methods, Mechanisms, Clinical Applications, and Challenges

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### Specialty section:

This article was submitted to  
Stroke,  
a section of the journal  
Frontiers in Neurology

**Received:** 15 March 2020

**Accepted:** 29 June 2020

**Published:** 18 September 2020

### Citation:

Hao Y, Xin M, Feng L, Wang X,  
Wang X, Ma D and Feng J (2020)  
Review Cerebral Ischemic Tolerance  
and Preconditioning: Methods,  
Mechanisms, Clinical Applications,  
and Challenges.  
*Front. Neurol.* 11:812.  
doi: 10.3389/fneur.2020.00812

Stroke is one of the leading causes of morbidity and mortality worldwide, and it is increasing in prevalence. The limited therapeutic window and potential severe side effects prevent the widespread clinical application of the venous injection of thrombolytic tissue plasminogen activator and thrombectomy, which are regarded as the only approved treatments for acute ischemic stroke. Triggered by various types of mild stressors or stimuli, ischemic preconditioning (IPreC) induces adaptive endogenous tolerance to ischemia/reperfusion (I/R) injury by activating a multitude cascade of biomolecules, for example, proteins, enzymes, receptors, transcription factors, and others, which eventually lead to transcriptional regulation and epigenetic and genomic reprogramming. During the past 30 years, IPreC has been widely studied to confirm its neuroprotection against subsequent I/R injury, mainly including local ischemic preconditioning (LIPreC), remote ischemic preconditioning (RIPreC), and cross preconditioning. Although LIPreC has a strong neuroprotective effect, the clinical application of IPreC for subsequent cerebral ischemia is difficult. There are two main reasons for the above result: Cerebral ischemia is unpredictable, and LIPreC is also capable of inducing unexpected injury with only minor differences to durations or intensity. RIPreC and pharmacological preconditioning, an easy-to-use and non-invasive therapy, can be performed in a variety of clinical settings and appear to be more suitable for the clinical management of ischemic stroke. Hoping to advance our understanding of IPreC, this review mainly focuses on recent advances in IPreC in stroke management, its challenges, and the potential study directions.

**Keywords:** cerebral ischemia, ischemic tolerance, ischemic preconditioning, local ischemic preconditioning, remote ischemic preconditioning, cross preconditioning

## INTRODUCTION

Cerebrovascular disease is one of the main diseases that lead to human death and disability worldwide, which endangers the health and life of middle-aged and elderly people (1, 2). About 795,000 new or recurrent cerebrovascular diseases occur every year, among which 87% are ischemic cerebrovascular diseases (1). Ischemic cerebrovascular diseases are mainly cerebral infarctions caused by the interruption of cerebral blood flow due to thrombus, embolism, or other

reasons in the cerebral blood vessels, resulting in energy metabolism depletion and disorders of ion homeostasis; membrane depolarization; inhibition of high-energy phosphates; cellular potassium efflux; and water, sodium, and chloride influx, followed by a subsequent host cascade of mechanisms, including excitotoxicity, calcium overload, oxidative/nitrative stress, free radical generation, apoptosis, and inflammation, which trigger irreversible brain injury (3). Therein, neurons, glial cells, endothelial cells, and their interconnections are severely damaged and trigger each other in a positive feedback loop and eventually lead to damage and death of nerve cells.

The currently approved treatments for acute cerebral ischemia include the venous injection of thrombolytic tissue plasminogen activator (tPA) within 4.5 h and thrombectomy within 24 h after the appearance of neurological symptoms, which, however, could inevitably induce ischemia/reperfusion (I/R) injury (1, 4). However, the narrow therapeutic window and potential side effects limit their clinical application. In the past few decades, researchers have also carried out a large number of experimental studies on cerebral ischemic neuroprotective agents, but the results were not as expected when these agents were used clinically. Therefore, it is necessary to further fully understand the complex cascade mechanism of its pathological process and advance cost-effective and neuroprotective strategies for ischemic stroke treatment.

Being challenged by nutrient and oxygen deprivation, the brain starts potent endogenous defensive mechanisms against the complex deleterious cascade mechanism, which is also an underlying mechanism leading to irreversible lethal ischemic injury (5). Thus, the endogenous defensive mechanisms that protect the brain against ischemic stimuli and recovers from injury become an increasing hot spot. Ischemic preconditioning (IPreC), referring to a non-injurious and sublethal ischemic insult, can mediate complex endogenous protective mechanisms and provide ischemic tolerance and potent protection against a subsequent, otherwise lethal, ischemia (6, 7). IPreC is considered to be a potential and powerful neuroprotective mechanism that can cope with extreme metabolic stress, such as hypoxia or ischemia, which has aroused great interest in neurological experiments and clinical fields (8). In addition, studies have found a variety of physical and pharmacological stimuli can also induce ischemic tolerance (9–13). Over the past decades, researchers have made significant progress in signifying the endogenous mechanisms of IPreC and in applying the above mechanisms of action to routine clinical practice.

## UNDERSTANDING CEREBRAL ISCHEMIC PRECONDITIONING

In the past 30 years, ischemic tolerance, as an effective protective strategy for ischemic diseases, has attracted wide attention and in-depth research. According to the time and process of sublethal ischemic injury and ischemic stroke, ischemic tolerance can be divided into the following three types: (1) ischemic preconditioning (IPreC), when sublethal ischemia insult is performed before ischemic disease; (2) ischemic perconditioning,

when the ischemic stroke occurs and sublethal ischemia insults should be initiated at the same time; and (3) ischemic post-conditioning, when sublethal ischemia insult is implemented after the ischemic stroke. The above three methods may be involved in different endogenous protective mechanisms. In 1986, Murry et al. first described IPreC in myocardial tissue, and most IPreC research focused on enhancing the resistance of the myocardium to subsequent fatal ischemic injury (13, 14). Studies have found that ischemic tolerance caused by IPreC is a common phenomenon and can be observed in various organs and tissues, such as heart, central nervous system (CNS), liver, retina, skeletal muscle, kidney, and intestine (15–17). Among them, tissues that are sensitive to hypoxia, such as myocardium, brain, and kidney, are the most promising targets for clinical application of IPreC (17–19).

Initially, an *in vitro* model of hippocampal slices was used to confirm the adaptability of rat brain tissue to anoxia, which caused wide concern in 1986 (20). In 1989, research showed that brief hypothermia could trigger neuroprotection (21). In 1990, Kitagawa et al. demonstrated that non-lethal ischemic insult could afford sufficient neuroprotection against neuronal death in the hippocampus CA1 region following subsequent lethal ischemic stress (22). In 1991, Kirino et al. also showed protective effect of non-lethal ischemic treatment in a global ischemia model of gerbils (23). During the late 1990s, a large number of research results consistently signified the IPreC-induced neuroprotection against lethal ischemic injury in focal and global cerebral ischemia of different animals (24, 25). One of the disadvantages of IPreC, which cannot be ignored, is that IPreC is capable of leading to serious damage with only small changes in the timing, durations, and location of sublethal ischemic insults (26). Therefore, researchers work tirelessly to find other safe and effective methods to safely induce ischemic tolerance. Remote ischemic preconditioning (RIPreC) is a method in which cerebral ischemic tolerance is induced after a brief short-term I/R duration in distant organs or tissue (27). RIPreC was reported in the myocardium in 1993 (15) and was also confirmed to be neuroprotective against ischemic stroke in 2011 (28).

By now, numerous studies have shown that different inducers/stressors can mediate cerebral ischemic tolerance. In addition to classic mechanical IPreC methods, including local ischemic preconditioning (LIPreC) and RIPreC, there are still many types of endogenous or exogenous stimuli that can induce experimental animals, brain tissue slice and cell cultures develop ischemic tolerance, named cross-preconditioning, mainly including chronic hypoxia (29, 30), hyperoxic or oxidative stress (31), hypothermia or hyperthermia (32), pharmacological treatment and chemical agent application (33–37), cortical spreading depression (38, 39), electroacupuncture (40), sports activity (41), and others [(9, 11, 12); Table 1].

### Local Ischemic Preconditioning

LIPreC, one of the earliest mechanical methods for mediating IPreC, can induce cerebral protective tolerance to the subsequent prolonged lethal I/R injury by short-term I/R of the brain tissue (92). Transient ischemic attacks (TIA) and clinical practice of

**TABLE 1** | Representative reported methods of cerebral ischemic preconditioning.

Classic mechanical preconditioning	Local ischemic preconditioning	<i>In vivo</i>	Focal ischemic preconditioning	Global-Global (20, 42–44) Global-Focal (45)
			Global ischemic preconditioning	Focal-Focal (46) Focal-Global (47)
		<i>In vitro</i>	Oxygen–glucose deprivation (48, 49)	
	Remote ischemic preconditioning	Kidney (50, 51), mesenteric artery (52), liver (53), limbs (54–56), etc.		
Cross-preconditioning	Hyperoxic/Hypoxic preconditioning (57–82)			
	Hypothermia and Hyperthermia preconditioning (58–62)			
	Chemical/Pharmacological preconditioning (63–77, 83–87)			
	Other methods, including cortical spreading depression (36, 37), electroacupuncture (88), ketogenic diet (89), exercise (90), transcranial low-level light therapy (91), etc.			

surgical protection in organ transplantation provides convincing evidence for the effectiveness of LIPreC (92–95).

TIAs are caused by thrombosis, embolism, or vasospasm in the blood supply vessels of the brain tissue, which temporarily and non-lethally block the blood supply to the target brain, but do not cause cerebral tissue infarction. TIAs have the same clinical symptoms as ischemic stroke but do not leave permanent neurological impairment (96). Some previous clinical research concerning stroke patients has shown that TIAs can mediate the protective ischemic tolerance of brain tissue to subsequent lethal cerebral ischemia to a certain extent. The results of a case-control study of stroke patients in Germany suggest that the occurrence of previous TIAs can reduce the severity of subsequent lethal ischemic strokes (97). Another study compared the clinical data of stroke patients with or without prior TIAs, and the results show that ipsilateral TIA that lasted for 10–20 min before cerebral ischemia can produce significant ischemic protection (98). Wegener et al. demonstrated that patients with prior TIAs showed smaller initial cerebral diffuse injury and smaller final brain infarct volume within 12 h after the onset of stroke; however, there was no significant difference in the size and severity of hypoperfusion (99). To further explore the protective effects and possible neuroprotective mechanisms of IPreC on subsequent stroke, more clinical and experimental research needs to be conducted (95, 100, 101). Paradoxically, a cohort study involving more than 1,000 stroke patients showed that there was no correlation between prior TIA attacks and disability rates due to subsequent strokes, and the proportion of neurological impairment in stroke patients occurring 1–7 days after TIA onset was even higher (102). Individual heterogeneity among patients and diversity of the etiology of TIAs and subsequent stroke may be two important reasons for the discrepant results of the above studies.

As a means of surgical protection, LIPreC has been studied for many years and made great progress in organ transplantation, trauma, aneurysm surgery, and other fields. It was evaluated whether ischemic tolerance induced by occlusion at the proximal artery for 2 min could reduce the brain tissue damage caused by the subsequent clipping of cerebral aneurysm during the operation in 12 patients with aneurysmal subarachnoid hemorrhage (103). The results showed that the baseline gas

pressure and pH value of the two groups were similar, but the decrease of oxygen pressure and pH value in the IPreC group was slower than that in the control group (103). These results suggest that short-term occlusion of the proximal artery to induce ischemic tolerance may be an effective protective measure in complex cerebrovascular surgery.

### Protection of Local Ischemic Preconditioning

According to previous research results, LIPreC mainly has two temporal protective tolerance windows (13). The first is the short-term window, which is also called the quick window, which usually appears a few minutes after pretreatment. The mechanism is formed by the changes of post-translational modification, and the window of protection is very short, which usually disappears after a few hours. The second window is the long-term window, also known as the delayed window, which usually appears within 1 day of pretreatment and lasts for a maximum of a week after preconditioning (8, 26). The mechanism mainly involves genetic reprogramming and epigenetic modifications, which ultimately involve changes in protein synthesis, and therein, the delay window has more important protective significance for the ischemic brain (104, 105). However, current research perspectives regard that there is usually an unprotected window with little or no neuroprotection between the first window and the second window (104). Recent research evidence suggests that repeated hypoxic preconditioning can even mediate brain tissue to produce a third protective window that lasts up to 8 weeks of which the underlying mechanism may be caused by epigenetic regulation (106, 107).

### Methods of Local Ischemic Preconditioning

There are *in vivo* and *in vitro* means to locally precondition the ischemic brain (42, 43, 108). The *in vivo* methods mainly include focal IPreC and global IPreC, whether it is rapid or delayed ischemic tolerance (26, 42). In focal ischemic preconditioning, ischemic tolerance is caused by a single or several brief interruptions of the middle cerebral artery blood flow for several minutes and subsequent reperfusion in between (8). Global ischemic preconditioning is caused by a single brief occlusion of the two common carotid arteries that supply

the forebrain tissue or all the four cerebral vessels, usually <5 min (8, 42). Within the subsequent protective time window of sufficient ischemic tolerance, the lethal ischemic insults of a longer duration were established thereafter. It should be noted that focal and global ischemia can produce interactive ischemic tolerance, so different preconditioning modes by varying durations of focal and global ischemia insults were established (8). There are mainly four different experimental ischemic duration modes: (1) global ischemic preconditioning through two- or four-vessel occlusion before final global ischemia (22, 44–46), (2) global ischemic preconditioning by four-vessel occlusion before permanent focal ischemia (47), (3) focal ischemic preconditioning by transient middle cerebral artery occlusion (MCAO) followed by permanent MCAO in rats (109), (4) focal ischemic preconditioning induced by unilateral MCAO followed by global ischemia (25, 110). It should be noted that not all combinations of ischemic time and reperfusion time can trigger ischemic tolerance to play a protective role in brain tissue. Ischemic tolerance can be induced by 3–5 min of focal ischemia and at least 5 min of reperfusion but cannot be induced by 1–2 min of focal ischemia (111, 112). Single ischemia-reperfusion treatment can effectively induce ischemic tolerance, but repeated transient ischemia-reperfusion treatment also has an obvious protective effect (17, 48, 49, 113). The safe and effective time collocation of ischemia and reperfusion still needs a lot of follow-up experimental research.

There are currently a variety of *in vitro* IPreC methods, of which oxygen-glucose deprivation (OGD) is the most widely used model (114). The OGD model established by neural cell line culture and brain tissue is a particularly useful tool for studying its tolerance mechanism under *in vitro* conditions and is beneficial to exclude the influence of systemic factors after stroke (114, 115). Studies have shown that, after being exposed to OGD pretreatment for a short period of time, the cortical culture of murine brain tissue was subsequently exposed to OGD for a longer time, and the death of cortical neurons was reduced by 30–50%, but this protective effect only lasts between 7 and 72 h (115).

### Mechanisms of Local Ischemic Preconditioning

In most cases, various forms of pretreatment stimulation can trigger endogenous protection or regeneration mechanisms through various signaling molecules and mechanism pathways, thereby generating protective ischemic tolerance from subsequent cerebral ischemic injury (26). IPreC involves a complex and interacting protective cascade mechanism, which can effectively reduce nerve cell damage after subsequent lethal stimuli. The induction of protective ischemic tolerance by IPreC is usually specific to the applied preconditioning stimuli and also related to the applied durations (5, 8, 26, 105). Existing research results support the view that energy depletion, ion disorders, excitatory amino acid toxicity, and lactic acid generation can occur immediately after an appropriate non-lethal ischemic attack, thereby activating the transcription factors and promoting protein synthesis that plays a protective role in neural cells (5, 116–121). Moreover, microarray analysis identified that gene expression is reprogrammed (122), and epigenetic modifications and post-transcription translation

levels also changed significantly (121), mediating the protective phenotype so that neurons become responsive to the subsequent lethal ischemic attack.

### Hypoxia inducible factor

Hypoxia conditions can trigger the generation of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), which is an oxygen-sensitive transcription factor. It can be significantly upregulated after cerebral ischemia and then participate in regulating the expression of various genes, thereby triggering various physiological responses (123–129). IPreC has different effects on the expression of HIF-1 $\alpha$  in different cells, and it can increase the expression of HIF-1 $\alpha$  in neurons quickly and transiently but slowly and continuously in astrocytes (130). It has been reported that the inhibition of prolylhydroxylase 2 (PHD2), which can promote the degradation of HIF-1 $\alpha$  depending on the oxygen level, can promote the expression of neuronal HIF-1 $\alpha$ , and is not involved in the induction of ischemic tolerance (131). However, astrocytic HIF-1 $\alpha$  was independent of PHD2, which allows astrocytes to cause long-lasting HIF-1 $\alpha$  expression and was rather essential for induction of ischemic tolerance efficiently (132). IPreC can also attenuate neuronal death induced by ischemic insults in the gerbil hippocampal CA1 region (CA1) throughout upregulation of HIF-1 $\alpha$ , which enhances vascular endothelial growth factor (VEGF) expression and nuclear factor-kappa B (NF- $\kappa$ B) activation (125).

### Glutamate pathway

Glutamate excitotoxicity is a chief mechanism of action in nerve cell injury following stroke (133, 134). After ischemia, lack of oxygen supply can decrease adenosine triphosphate (ATP) levels and increase glutamate levels significantly, which can overactivate the N-methyl-D-aspartate (NMDA) receptor and result in excessive calcium influx, impaired synaptic plasticity, and accumulation of glutamate (133, 135, 136). In neuronal cortical cultures, glutamate preconditioning can mediate ischemic tolerance while antagonists of NMDA and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor can eliminate the protective effect of glutamate pretreatment preconditioning (104, 106). Appropriate moderate activation of NMDA receptors is necessary to induce ischemic tolerance; studies have shown that this mechanism may involve NF- $\kappa$ B and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) pathways (137–139). It has been reported that activation of the NMDA receptor can inhibit the activation of stress-activated c-Jun N-terminal kinase (JNK) and protein kinase B (Akt), promote the activation of extracellular signal-regulated kinase (ERK1/2), and regulate the activity of normal cyclin adenosine monophosphate (cAMP) responsive element binding (CREB) activity, which may be key signaling molecules that mediate protective tolerance (140–142).

Other studies have also shown the specific overexpression of GLT-1 in astrocytes (35–38). Studies have shown that p38 mitogen-activated protein kinase (p38 MAPK) is involved in the regulation of GLT-1 upregulation during the induction of ischemic tolerance.

Upregulation of astrocyte glutamate transporter-1 (GLT-1) was found to assist in inducing cerebral ischemic tolerance (143).

Research evidence indicates that IPreC can inhibit the increase in extracellular glutamate after OGD, promote the uptake of extracellular glutamate, and increase the GLT-1 expression in rat cortical cultures (144). Other research results showed that astrocytes GLT-1 overexpression had significant neuroprotective effects (35–38). Research has shown that p38 mitogen-activated protein kinases (p38 MAPK) played an important role in the induction of GLT-1 upregulation during ischemic tolerance mediation (145). Gap junctions (GJs), composed of connexin 43 (Cx43), are found at the corresponding position where adjacent astrocytes contact each other and form channels that allow the molecular exchange and information transfer between astrocytes. Recent studies have shown that astrocytes can release excessive glutamate through GJs after ischemia, which may promote the expansion of the infarct core and the surrounding penumbra area (146, 147). It has been demonstrated that IPreC can block GJs between astrocytes and decrease the extracellular glutamate content and reduce reactive oxygen species (ROS) injury in astrocytes, resulting in less neuronal damage (148).

#### **Nitric oxide synthase**

For both *in vivo* and *in vitro* models of IPreC, nitric oxide (NO) is a crucial member, but the exact mechanism of action remains unclear. In cortical cultures, activation of neuronal nitric oxide synthase (NOS) and subsequent other neuroprotective mechanisms may be an important part of a series of signaling cascades during OGD preconditioning (149). Anoxia preconditioning can protect rat hippocampal slices against the subsequent fatal anoxic injury, and interestingly, the NOS inhibitor (7-nitroindazole) can abolish the above protective effects (150). It was found that inducible NOS was involved in the neuroprotective tolerance induced by IPreC in both *in vivo* and *in vitro* conditions (141, 151–153). In addition, in endothelial NOS (eNOS) and neuronal NOS knockout mice, IPreC did not reduce the infarct volume of brain tissue in the focal ischemia model compared with the preconditioned wild-type counterpart (151). Recently, eNOS is considered to be a neurovascular protection mediator against vasospasm caused by subarachnoid hemorrhage, indicating that IPreC may also have a protective effect on other forms of stroke (154).

#### **Immune system**

Under an ischemia condition, a large number of inflammatory cells (such as microglia, lymphocytes, neutrophils, etc.) are recruited to the infarct area, mediating inflammatory damage to the brain tissue (155–158). The non-catalytic Toll-like receptor (TLR) signaling pathway can induce the transcription factor NF- $\kappa$ B to mediate the transcription of cytokines and chemokines by recognizing foreign signaling molecules, thereby initiating immune responses and establishing an inflammatory cascade, thereby causing secondary inflammation damage (158–161). The mechanism by which IPreC exerts neuroprotection is mainly through the promotion of anti-inflammatory molecules or inhibiting the expression of pro-inflammatory molecules. IPreC can reduce cerebral ischemic injury mainly through inhibiting TLR4/NF- $\kappa$ B signaling, enhancing interferon regulatory factor-dependent signaling, and inhibiting TLR4/myeloid

differentiation factor 88 (MyD88) signaling, which resulted in an anti-inflammatory phenotype (162–164). It is reported that astrocytic TLR3 signaling plays an important role in IPreC-induced ischemic tolerance, which increases interferon secretion but decreased IL-6 secretion, resulting in suppression of the post-ischemic inflammatory response (160). Pérez-Pinzón et al. (165) reported that rapid IPreC can inhibit the activation of microglia after cerebral ischemia, mediating ischemic tolerance by exerting an anti-inflammatory effect. Chemokines promoting the migration of inflammatory cells play a vital role in the recruitment of inflammatory cells to ischemic brain tissue after ischemia, which direct the progression of inflammatory processes in stroke (165–167). The enhanced ability of IPreC-induced microglia to release chemokines can mediate the migration of leukocyte to protect the ischemic cells (168). In addition, IPreC can also mediate through the activation of cell surface chemokine receptor 2 to exert a neuroprotective effect (169).

#### **Enzymes and receptors**

sublethal cerebral ischemic insult can activate enzymes, which are the other group of proteins activated in IPreC. Studies have shown that the activation of Akt mediated by IPreC can negatively regulate the JNK signaling pathway (170). The physiological function of cyclooxygenase-2 (COX-2) is to promote the oxidation of arachidonic acid to prostaglandin, which plays an important role in the inflammatory damage after ischemia (171). Downregulation of COX-2 in IPreC was previously reported in gerbils, which means obstruction of the COX-2 pathway might be a therapeutic strategy in cerebral ischemia (172). IPreC can maintain or even increase the content of kynurenic acid (KYNA) in pyramidal neurons of the hippocampal CA1 area, which indicates that IPreC-induced increase in KYNA expression is related to endogenous cerebral ischemic tolerance (173). The increase of adenosine after stroke is regarded to be neuroprotective, and the expression of adenosine receptors was increased after IPreC (174). Nakamura et al. reported that the adenosine A1 receptor may be related to rapid ischemic tolerance in rat focal ischemia (167). Adenosine kinase (ADK) can inhibit the expression of adenosine, and under-expression of cerebral ADK in transgenic mice can induce cortical protection, suggesting a promising target for developing a stroke therapy (174).

The physiological function of monocarboxylate transporter 4 (MCT4) is mainly involved in transferring monocarboxylates across phospholipid membranes, and recent studies have shown that it is related to cerebral ischemic injury. It was reported that IPreC elevated or maintained the expression of MCT4 in astrocytes and protected pyramidal neurons from ischemic damage in the ischemic CA1 region (175). It has been discovered that the accumulation of unfolded proteins in the endoplasmic reticulum (ER) lumen occurs in cerebral nerve cells during reperfusion following global or focal cerebral ischemia (176, 177). IPreC can inhibit ER stress-induced apoptosis and play a positive role in the protection of following focal cerebral I/R injury (178). Downregulation of adenosine monophosphate-activated protein kinase (AMPK) contributes toward delayed ischemic tolerance in a MACO model in male mice (179). The endogenous

protection mechanisms of IPreC may also involve  $\text{Na}^+/\text{Ca}^{2+}$  exchangers (NCXs). HIF-1 can increase the expression of NCX-1 and Akt signaling participating in mediating the expression of NCX-3 (180). Finally, many key players such as HIF-2 $\alpha$ , silent information regulator protein 1, and CREB are also important parts of the preconditioning cascade (142, 181).

### **Autophagy and apoptosis**

Autophagy, a process of internalizing and digesting damaged organelles or misfolded proteins to produce metabolic substrates for cell recycling, is believed to be one of the most important mechanisms in IPreC-induced tolerance (182–184). Studies have shown that ischemic injury can activate autophagy, and the activation of autophagy was related to neuroprotection (184). IPreC can activate autophagy, and 3-MA can abolish the IPreC-induced ischemic tolerance while rapamycin potentiates the IPreC-induced ischemic tolerance (185). In contrast to the neuroprotective function of autophagy, apoptosis mediated cell death in I/R injury, mainly through the caspase-3-dependent apoptosis pathway (186). Cerebral ischemia can mediate the overexpression of caspase-3, and IPreC can attenuate this overexpression during ischemia (187). Interestingly, three episodes of IPreC can activate autophagy and exert neuroprotection against apoptosis in the following ischemia (187). Therefore, apoptosis may be the therapeutic target, and inducing autophagy could be expected to become an important protective strategy. Recent studies have shown that bone morphogenetic protein 7 (BMP-7), an important regulator of cartilage and bone formation, is also involved in DNA synthesis and astrocyte differentiation in the rat midbrain (188). Studies have found that BMP-7 participates in IPreC-mediated endogenous protective mechanisms to induce ischemic tolerance (189). Inhibition of BMP-7 can attenuate apoptosis via inhibiting Bcl-2 and promoting cleaved caspase-3 (189). Moreover, BMP-7-mediated IPreC-induced neuroprotection may be through activation of p38 MAPK signaling pathway (190).

### **Energy metabolism**

With the impaired delivery of glucose and oxygen in ischemia, the energy metabolism pattern of the brain changed from oxidative phosphorylation to excessive glycolysis, thereby promoting the rapid generation of ATP to meet energy expenditure (191). However, excessive glycolysis increased the production of lactic acid and ROS, which promoted the expansion of the ischemic penumbra (192, 193). IPreC can subdue post-ischemic hyperglycolysis and promote the utilization of  $\beta$ -hydroxybutyrate and provide a well-adapted metabolic background (192). A number of studies revealed that IPreC-related metabolic flexibility was associated with the downregulation of AMPK-mediated glucose transporter-1 and decreased the mRNA levels of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits (194).

Nuclear erythroid 2-related factor 2 (Nrf2) protein can reduce oxidative stress damage by upregulating the transcription of antioxidant-related protein under pathological conditions in astrocytes and may be a novel key player in nuclear-mitochondrial interaction and IPreC-mediated neuroprotection

(195). Novel evidence indicates that Nrf2 plays an important role in oxidative phosphorylation supercomplex association, and the absence of Nrf2 can reduce IPreC-induced protection in astrocyte cultures (196, 197). Glucokinase (GK) and glucokinase regulatory protein (GKRP) may be involved in protecting neurons in the ischemic CA1 region (198). Certain studies have suggested that IPreC can significantly enhance the immunoreactivity of GK and GKRP in neurons of the CA1 region after 5 min of I/R, suggesting that an important mechanism for IPreC to promote the survival of neurons in CA1 region under ischemic conditions may be to maintain the expression of GK and GKRP (199).

### **Blood-brain barrier permeability**

Blood-brain barrier (BBB) injury occurs soon after cerebral ischemia (200, 201), which allows infiltration of immune cells and inflammatory factors and leads to brain edema and hemorrhagic transformation (202). Tight junctions (TJs) and adherens junctions (AJs), located between adjacent endothelial cells of the BBB, is critical for BBB integrity (201). The transmembrane TJs and AJs are mainly composed of claudin-5 and cadherin 5, which are involved in regulating paracellular permeability (201). IPreC can maintain the BBB permeability by directly upregulating the TJs protein claudin 5 and the AJ protein cadherin 5 (109, 203). IPreC-induced cytokines, such as TNF- $\alpha$  and interleukin 1 $\beta$  (IL-1 $\beta$ ), may affect BBB permeability (106). IPreC can mediate TJs and angiogenic factors levels via activating ERK1/2, implying an essential role of ERK1/2 in paracellular permeability in IPreC (106). Other studies showed that the underlying mechanisms of IPreC-mediated BBB protection involve VEGF, Nrf2, or inflammatory pathways (109, 201).

### **Electrophysiology**

Research indicated that MCAO impaired the expression of long-term potentiation (LTP) in the hippocampal CA1 region (204). Moreover, the LTP magnitude remained at a relatively low level 4 months after permanent MCAO (57). IPreC can dramatically increase the neurotransmitter content in presynaptic neurons to promote basal synaptic transmission without obvious adverse effects on the LTP induction (205).

### **Transcriptional regulation**

Recent research on IPreC-related ischemic tolerance has shed light on the modifications at gene level. HIF-1 can promote the transcription of survival genes after ischemic injury (123, 124). After hypoxic stress occurs, HIF-1 $\alpha$  and HIF-1 $\beta$  combine to form a heterodimer HIF-1, and then the heterodimer binds to the hypoxic response element on the target genes to form a transcription complex that promotes the transcription of VEGF, erythropoietin (EPO), and glucose transporters (123, 170, 206). Studies have found that the HIF-2 $\alpha$  subunit in astrocytes can promote the transcription of EPO mRNA (207); however, the HIF-2 $\alpha$ -mediated transcriptional regulation signaling cascade in IPreC has not been deeply explored (207, 208). Transcription factor activator protein 1 (AP-1), composed of c-Jun and c-Fos, is a dimeric protein that functions in both neuroprotection and cell death (209). *In vivo* experiments indicate that the early activation of AP-1 and its enhanced binding affinity to DNA are involved

in the neuroprotection induced by IPreC (210). In addition, JNK and Akt signaling pathways are also involved in IPreC-mediated transcriptional regulation (211, 212).

### **Genomic reprogramming**

Clarifying the changes in gene expression profiles in neuroprotective phenotypes after ischemia can help to understand IPreC-induced tolerance (122). It is worth mentioning that IPreC-induced changes in gene expression profiles include not only upregulation of genes related to neuronal protection and regeneration and also inhibition of genes related to degenerative pathways during ischemic injury (122). Various regulatory molecules and processes, for example, transcription factors and a large number of post-translational modifications, jointly participate in the change of gene expression profiles induced by IPreC (213). GeneChip technology was used to identify genomic reprogramming induced by IPreC, and molecules involved in inducing ischemic tolerance, such as heat shock protein 70 (HSP-70) and transforming growth factor (TGF)- $\alpha$  were confirmed (213). DNA microarray technology, an efficient method for studying differential gene expression patterns of ischemic tolerance, were used to imply the genetic profile in IPreC-stimulated rat hippocampal slices and mouse cortex (118, 214), by which the genes related to cell survival and regeneration (such as HIF, insulin-like growth factor, etc.) are upregulated, and region-specific expression patterns can be observed apparently (215).

### **Epigenetic reprogramming**

Existing evidence indicates that IPreC-mediated ischemic tolerance involves epigenetic reprogramming in neuronal cells, and microRNA (miRNA) plays an important role in this process. The results of Dharap and Centeno et al. showed that IPreC can mediate downregulation of 25 miRNAs and upregulation of 26 miRNAs in rat cortex, and 20 of these miRNAs maintained expression changes within 3 days (150). Atochin et al. (151) analyzed miRNAs transcription in mouse cortex and found that IPreC could upregulate miRNAs expression while lethal ischemia downregulated miRNA expression. The results of bioinformatic analysis of IPreC-mediated miRNAs expression profiles indicated that IPreC preferentially regulates miRNAs targeting transcriptional regulators (216). miR-132, which regulates methyl CpG binding protein 2 (MeCP2) expression, is one of the most notable downregulated miRNAs in the IPreC brain, and MeCP2 protein expression was increased while knocking out MeCP2 in transgenic mice abolished the IPreC-induced tolerance (151).

Although LIPreC does reduce reperfusion injury and related systemic consequences, its main disadvantages are direct injury by invasive operation on the target organ and mechanical damage to the main vascular structure. Moreover, it is difficult to predict when an ischemic event will occur, and therefore, it is not clinically possible to perform ischemic pretreatment within the effective protection time window. The disadvantages limit its clinical application.

## **Remote Ischemic Preconditioning**

RIPreC is a systemic protective strategy in which one or more cycles of ischemia and reperfusion durations in the target organ or tissues could confer protection against subsequent more severe ischemia insults in distant organs or tissues (217). RIPreC was first introduced in an animal cardiac study by Przyklenk et al. and first demonstrated in global cerebral ischemia model in rats (15). Experimental and clinical studies have demonstrated that RIPreC can induce cerebral tolerance to ischemic injury, augment cerebral perfusion status, reduce the risk of cerebral infarction, reduce TIA recurrence, promote the formation of cerebral collaterals, and increase the recovery rate (218–220). Subsequent studies confirmed that RIPreC decreases the infiltration of circulating leukocytes and provided a degree of cerebral protection (221). A large experimental animal model, has shown significantly better electroencephalogram results, better behavioral scores and histopathological scores in the RIPreC group 7 days post-operation (222). Additionally, patients undergoing carotid endarterectomy or patients undergoing elective cervical decompression surgery also benefitted from RIPreC (50, 219).

### **The Organs or Tissues for Performing Remote Ischemic Preconditioning**

It has been evaluated that many organs or tissues, such as kidney (51, 52), mesenteric artery (53, 54), liver (55, 56), and limbs (223–225), can be considered as remote conditioned sites. Obviously, the most convenient and safest strategy of performing RIPreC should be on limbs when this preconditioning strategy is considered to be clinically used (28). Remote ischemic limb(s) preconditioning (limb-RIPreC), usually via binding the cuff to the distal limb(s) and inflating the cuff to a pressure that blocks the blood perfusion of the limb(s), has been used to effectively induce ischemic tolerance against subsequent I/R damage in animal experiments (223) and clinical trials over decades (28, 226). It has been found that acute ischemic stroke patients with a history of peripheral vascular disease (PVD) have significantly smaller infarct volumes, better clinical outcomes, and a lower mortality rate than those without PVD (227), also confirming the efficiency of limb-RIPreC.

### **Protection of Remote Ischemic Preconditioning**

Similar to LIPreC, the results from clinical trials concerning the protection of RIPreC considered that there might be a first window (also called early, short window) and second window (also called later, prolonged window) of RIPreC (228). The neuroprotection of the first window occurs soon after pretreatment and is maintained for about 4 h (228). Ren et al. reported that limb-RIPreC via three cycles of 15 min femoral occlusion and reperfusion durations significantly reduced cerebral ischemic injury after 30 min of bilateral common carotid artery occlusion in rats (225), the same as the results of Wei et al. (229). Hu et al. (223) showed that performing limb-RIPreC 1 h before MCAO can obviously protect the subsequent cerebral ischemic injury in rats. Once believed to start 24 h after preconditioning (228), the later phase was corrected to start 12 h after preconditioning (225) and last for at least 48 h (228). Animal

studies showed that RlPreC started 24 (230) and 48 h (225) prior to brain ischemia were both protective. Malhotra et al. also showed that RlPreC can't mediate protection when performed 48 h before brain ischemia onset (230).

### Mechanisms of Remote Ischemic Preconditioning

At present, there is no unified view on the underlying mechanism of the protective effect transport to the target organ and the identity of the tolerance-inducing signal in the brain. There are three theories about the mechanism by which the protective effect mediated by ischemic preconditioning of distant organs or tissues is transferred to the brain tissue to protect the brain tissue against subsequent ischemic injury. It should be pointed out that these three theories are not mutually exclusive. The first theory holds that the transmission of neuroprotection is mainly mediated by various humoral factors in the blood circulation system. The second theory is that the autonomic nervous system plays an important role in the transmission of neuroprotection, and the last one is the immune pathway involving circulating cytokines, chemokines, and immune cells (231). After the protective effect is transmitted to the brain through the above three pathways, the ischemic tolerance is initiated through a common signaling pathway (Figure 1).

#### Humoral pathway

The humoral pathway is considered to exist because of two reasons: (1) a period of reperfusion is needed after ischemia in the preconditioned site during the RlPreC durations, suggesting that the protective factors need to be transported via circulation to the target organs from the conditioned site, and (2) the blood cross-circulation model identified the existence of protective humoral factors (232, 233). Similarly, Shimizu et al. (232) reported that treating the naive hearts with the blood from rabbits or humans after receiving RlPreC treatment can protect the naive recipient hearts against subsequent I/R injury, and the protective effect could be mediated by molecules <15 kDa. Research had identified that interleukin, prostaglandins, stromal cell-derived factor-1 $\alpha$ , TNF- $\alpha$ , bradykinin-2, adenosine, opioids, NO, EPO, rich secretory protein 3, HSP, catecholamines, heme oxygenase-1, miRNA-144, etc. as possible candidate transfer factors (234, 235). The related signaling pathways or molecular targets of those humoral factors include G-protein cell surface coupled receptors, protein kinase C, Notch1, ERK1/2, JNK1/2, p38 MAPK, and signal transducer and activator of transcription 5 (STAT5) (16, 19, 236).

#### Nerve pathway

Increasing evidence from experiments about ischemic stroke confirms that a neuronal pathway is involved in the RlPreC protection transmission from the remote conditioned organ to the brain. Research inducing limb-RlPreC in MCAO rats by different methods demonstrated that a ganglion blocker (hexamethonium) could abrogate the neuroprotection of RlPreC (229, 237). Research by Mastitskaya et al. (237) suggests that the dorsal motor neurons of the vagus in the brain stem participated in RlPreC-mediated cardioprotection, and stimulation of these neurons can produce the same protective

effect as RlPreC, indicating that the vagal preganglionic neurons are involved in the neural transmission mechanism. Activation of parasympathetic efferent nerves was neuroprotective, and vagal stimulation reduced cerebral infarct size (238). Animal research has reported that transection of the femoral nerve or spinal cord can abolish the protective effect of RlPreC in rabbits (239). Interestingly, the protective effects of RlPreC seem to be attenuated in patients with neuropathy, implicating the dependence on intact neural pathways (237).

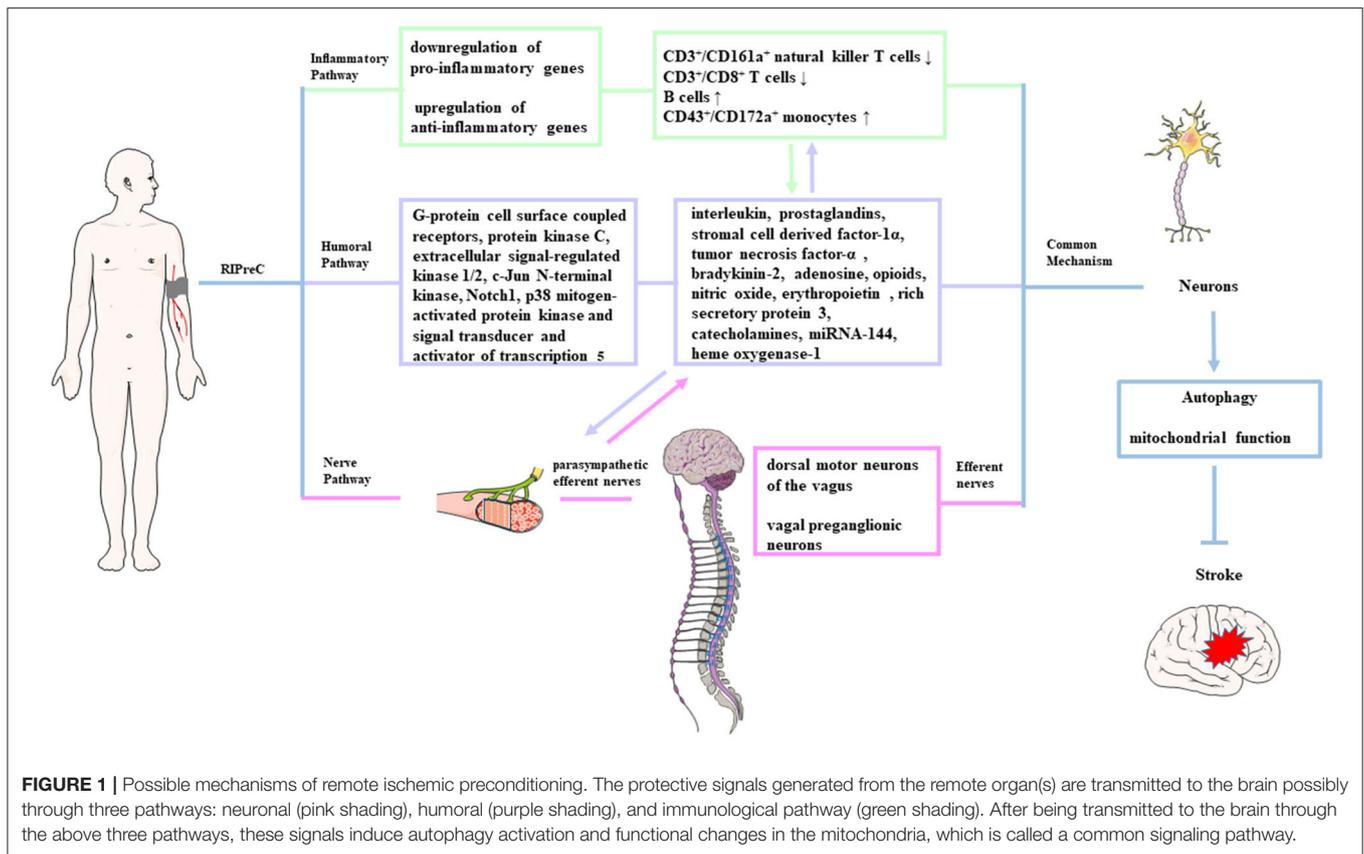
However, the neuroprotective effect of RlPreC in mice was partially abolished when the femoral nerve or sciatic nerve was scathed, indicating the interaction of neural and humoral pathways (239). The neuronal mechanism may work in combination with the humoral pathway: The release of endogenous humoral factors from the conditioned organ first activated the afferent nerves in the conditioned organ and then activated the efferent nerves terminating at the target organ to induce neuroprotection. For example, limb-RlPreC allowed the preconditioned limb(s) to release autacoids that can activate neural pathways (240, 241). Animal studies showed that the release of humoral factors caused by limb-RlPreC would be abolished by femoral nerve transection and the release of protective humoral factors can be induced by femoral nerve stimulation, indicating that the integrity of neural pathway is an important prerequisite for the production of humoral factors (240, 242, 243).

#### Inflammatory pathway

It has been reported that RlPreC has a systemic anti-inflammatory influence via suppression of proinflammatory genes in immune cells. Microarray analysis of blood samples showed downregulation of proinflammatory genes and upregulation of anti-inflammatory genes within 15 min of RlPreC and at 24 h after preconditioning, confirming that limb-RlPreC inhibited systemic inflammation (244). RlPreC can also reduce circulating neutrophil activation, inhibit the release of proinflammatory cytokines, and downregulate the expression of adhesion molecules in healthy adults (245). Recently, it was reported that RlPreC resulted in the reduction of CD3<sup>+</sup>/CD161a<sup>+</sup> natural killer T cells and CD3<sup>+</sup>/CD8<sup>+</sup> T cells and elevation in the percentage of B cells and CD43<sup>+</sup>/CD172a<sup>+</sup> monocytes in circulation (246). Interestingly, the inflammation changes are associated with improved neurological functions, implying the direct evidence that the immune pathway participates in RlPreC-induced neuroprotection (246). It was suggested that the activation of immune cells and regulation of inflammatory genes were related to the release of endogenous opioids; therefore, the immunological pathway is also linked to the humoral pathway (247).

#### Final common mechanism

Based on the above evidence, we can conclude that the three neuroprotection transmission pathways via humoral, neural, and inflammatory mechanisms may be a relationship of mutual influence and promotion in RlPreC. After being transmitted to the brain, these protective signals had a final common pathway to induce ischemic tolerance. Autophagy can promote the



degradation of damaged organelles and accumulated misfolded proteins to produce metabolic substrates to meet the energy consumption of the brain tissue after ischemic injury (248). There is a view that the autophagy regulation may be an important process in mediating the protective phenotype after neuroprotection was transmitted to the brain tissue. It was reported that limb-RIPrEC activated autophagy and promoted the survival of neurons in rat spinal within 24 h after I/R injury (248). IPrEC-mediated autophagy can promote the removal of harmful substances and inhibit the neurotoxic cascade to play a neuroprotective role, such as upregulation of B-cell lymphoma 2 (Bcl-2) and HSP-70, reduction in cytochrome c release, and inhibition of caspase-3 activity (249). Park et al. found that the activity of autophagy in the penumbra was enhanced, which was obviously related to the neuroprotective effect of RIPrEC in cerebral ischemia (249). RIPrEC can also increase the resistance of cells to ischemic insults by maintaining mitochondrial structural and functional integrity, decreasing mitochondrial degradation and consequently reducing apoptosis to achieve neuroprotection (250). The possible mechanism of autophagy in IPrEC-mediated neuroprotection still needs further research.

Despite the efficiency of RIPrEC, there are still issues that cannot be ignored. First, animal experiments tend to perform RIPrEC operations on the hind limb(s) of experimental animals (78, 223, 225) while clinical trials would choose the upper limb(s) of the subjects (28, 218); it is still unknown whether

the neuroprotective effects mediated by the precondition of the upper limbs and lower limbs (hind limbs) are different. Second, we still cannot confirm how many limbs and cycles of RIPrEC should be involved to acquire the optimal efficiency because the number of restrained limbs, duration of ischemia in each cycle, and number of cycles of RIPrEC were different among published articles. An animal study by Ren et al. (225) indicated that three cycles of limb preconditioning could induce stronger neuroprotection than two cycles. Therefore, increasing the number of preconditioned limbs and the cycles of preconditioning ischemia/reperfusion durations may enhance the protective effect of RIPrEC.

## Cross-Preconditioning

For ethical reasons, it is not allowed to repeatedly block the cerebral arteries to mediate neuroprotection through ischemic preconditioning in humans; cross-preconditioning, induced by stressors or stimuli other than ischemia, such as hyperoxia/hypoxia, hypothermia or hyperthermia, chemical/pharmacological pretreatment, cortical spreading depression, electroacupuncture, excise, et al. (29, 38, 58, 105, 205), has gradually become a new research hot spot hoping to develop a new IPrEC strategy in humans. Interestingly, research suggests that many stresses or stimuli seem to mediate protective tolerance through a common signaling pathway (105).

### Hyperoxic and Hypoxic Preconditioning

In MCAO models of rats and mice, hyperoxia was shown to induce ischemic tolerance via genetic reprogramming (59). Regular normobaric hyperoxia (95% O<sub>2</sub>) treatment in rodents can reduce the infarct volume of brain tissue and exert obvious neuroprotective effects after cerebral ischemic injury (60). Hyperbaric oxygenation (HBO) was found to induce ischemic tolerance by reducing cellular apoptosis (61) and downregulating the expression of COX-2 in global ischemia model of rats and murine (60). Studies have shown that the NF- $\kappa$ B signaling pathway and its regulated target gene transcription could be activated by exposure to intermittent and long-term normobaric hyperoxia preconditioning conditions in rats (206). Repetitive hypoxic preconditioning induced sustained endogenous tolerance to stroke in a mouse model of stroke, characterized by upregulation of chemokine (C-X-C motif) ligand 12 at the BBB and inhibition of leukocyte-endothelial adherence, contributing to the endogenous, anti-inflammatory phenotype (62).

### Hypothermia and Hyperthermia Preconditioning

Hypothermia treatment, widely used in surgical procedures and other clinical practice, is safe and practical based on evidence from randomized clinical trials (63, 64). In focal ischemic models, hypothermia preconditioning can confer rapid tolerance; however, merely increasing the duration of the preconditioning stimulation did not significantly enhance the neuroprotective effect (64). The underlying mechanism of the prolonged ischemic tolerance induced by hypothermia supposedly depends on protein synthesis (64, 65). Hyperthermia can also bring about protection against cerebral ischemia in rodent. Hyperthermia preconditioning conducted through a hot water bath in newborn rats with brain temperatures increased to 41.5–42°C, reduced neuronal damage after 2 h hypoxic ischemic insult (66). Additionally, exposure to hyperthermia (38–40°C) for 6 h protected astrocytes against cerebral I/R injury in mice (67).

### Chemical/Pharmacological Preconditioning

The underlying mechanism of chemical/pharmacological preconditioning and their neuroprotective potential as strategies for clinical prevention and treatment of cerebral ischemia are gradually being explored (68–72). Isoflurane, halothane, and other inhalational anesthetics could lead to a subsequent protective phenotype against subsequent ischemic injury via promoting the antagonism of NMDA and AMPA receptors (68, 73). For example, adult male rats with 2% isoflurane inhalation preconditioning for half an hour showed smaller brain infarct sizes after focal ischemia (79). It is considered that sevoflurane possesses smaller infarct sizes and better motor coordination after ischemia (73). Halothane has no clinical feasibility due to the likelihood of hepatotoxicity and other systemic side effects although it could be potentially neuroprotective (73). Using combined inhaled anesthetics might be an alternative for extended neuroprotection (80). Low dose of lipopolysaccharide (LPS) preconditioning can later impart ischemic tolerance in the brain in rats (81, 82). Exposure to

LPS for 4 consecutive days could significantly reduce neuronal death in mice (74). Interestingly, although LPS functioned by suppressing TNF- $\alpha$  signaling, TNF- $\alpha$  is also a necessary prerequisite for LPS-mediated neuroprotection, predicting the dual roles of TNF- $\alpha$  in LPS-mediated neuroprotection (75–77, 81, 83). Exogenous agents that protect the tricarboxylic acid cycle energy metabolism pathway can effectively induce neuroprotection. The pretreatment of chemical reagents to inhibit oxidative phosphorylation of neurons in the CA1 region of the hippocampus slices in rats can significantly reduce the oxidative stress damage mediated by a large amount of oxygen free radicals generated after hypoxia (84). Transient ischemic stimulation resulted in the release of adenosine and activates the ATP-sensitive K<sup>+</sup> channels in the brain to mediate neuroprotection, and pharmacological preconditioning with adenosine receptor agonist can mimic the neuroprotective effects (85). 5-methoxyindole-2-carboxylic acid preconditioning contributed to the neuroprotective effects through regulating the Nrf2 signaling, which decreased dihydroipoamide dehydrogenase activity and increased nicotinamide adenine dinucleotide: ubiquinone oxidoreductase-1 expression (86). Research results indicated that 3-nitropropionic acid preconditioning mediated obvious neuroprotection after cerebral ischemia in rats (87). However, nitrous oxide preconditioning had little or no neuroprotective effect in focal or global ischemia models, it may even repress the neuroprotective effects when used in conjugation with other inhalational anesthetics (73). Jackson et al. (88) preconditioned rats with daily metformin treatments for 2 weeks before transient forebrain global ischemia. They found that metformin preconditioning increased mitochondrial biogenesis and reduced apoptotic cell death (88). Research showed that dexmedetomidine preconditioning could protect against global cerebral ischemic injury following cardiac arrest and was associated with increased HIF-1 $\alpha$  and VEGF expression (89). Preconditioning with recombinant high-mobility group box 1 (rHMGB1) can protect the brain against ischemic damage, which is associated with activated TLR4/interleukin-1R-associated kinase-M signaling in microglia. The lipid kinase sphingosine kinase 2 (SPK-2), an important mediator of ischemic tolerance induced by isoflurane and hypoxia preconditioning (90), can upregulate sphingosine-1-phosphate that promoted the expression of chemokine (C-C motif) ligand 2 to mediated tolerance (91). Several *in vivo* studies have shown that metformin and estrogen involve in preconditioning neuroprotection (251).

### Other Methods of Preconditioning

Continuous electroacupuncture pretreatment can reduce infarct size and improve motor function after ischemia in mice (252). CSD preconditioning of rat brain can resist I/R damage and elicit improved prognosis by activating AMPK-mediated autophagy (38). A 3-week preconditioning period with a ketogenic diet elevated extracellular adenosine levels, improved rCBF, and increased HIFs and HIF-regulated genes in mice with MCAO (253). Other ischemic tolerance-inducing stimuli include exercise and transcranial low-level light therapy (254, 255).

## CLINICAL USES AND CONCERNS

IPreC strategies involve the application of non-lethal but noxious stressors or stimuli, but an inevitable problem is that preconditioning stimuli also have the potential to cause fatal damage. Therefore, preconditioning strategies applied to clinical patients must ensure their security and effectiveness. In spite of its apparent popularity and the largely flourishing trials in the experimental and clinical scenario, the next challenge of research in the area of ischemic neuroprotection is to find the most effective IPreC method, concerning the time window and proper dosage for clinical application.

At present, the results of studies on the protective effect of RIPreC in cerebral ischemia are not consistent: Some studies have shown the effectiveness of LIPreC, and some results are contrary to the above results (27, 256, 257). Limb-RIPreC is seen as a more promising neuroprotective strategy in terms of better tolerance and improved safety of the brain to I/R injury (218, 258, 259), and limb-RIPreC might be the future choice of clinical ischemic adjuvant treatment. For example, subarachnoid hemorrhage (SAH) can lead to delayed cerebral ischemia due to vasospasm, which is considered to be a suitable clinical situation for RIPreC (260). It is reported that the glycerol level and the ratio of lactic acid:pyruvic acid all decreased in SAH patients receiving limb-RIPreC, and these neuroprotective effects lasted up to 2 days (28, 261). Recently, it was found that, in patients with symptomatic atherosclerotic intracranial arterial stenosis, bilateral arm IPreC could reduce the occurrence of stroke (218). Cross-preconditioning provides new ideas for clinical ischemia treatment, especially chemical/pharmacological pretreatment strategies. For example, inhaled anesthetics can effectively mediate neuroprotection and have been already used in surgical procedures (262). Further experimental or clinical research on the mechanism of IPreC-induced cerebral ischemic tolerance are especially necessary.

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## CONCLUSION

Proper stimulus can trigger ischemic tolerance; however, it should be noted that there is no clear line between preconditioning stimuli and lethal stimuli. For safe and regular development of ischemic tolerance, various mutually cross-linked factors that influence the deleterious effect of IPreC need special attention, for example, the endogenous signaling pathways for neuronal survival, the exact window of protection after the final insult, the duration of tolerance, the safety margin, and possible side effects in patients. Every IPreC stimulus has its advantages as well as limitations, and choosing the most effective preconditioning inducer for clinical use is not always easy. Extensive studies with different combinations of stimulus should be conducted, especially cross-preconditioning, and the strategy of RIPreC combined with chemical or pharmacological pretreatment might be the future trend in clinical practice as they seem to hold more promise for combating stroke and related neurological disorders.

## AUTHOR CONTRIBUTIONS

MX and YH: designing and writing original draft. LF, XiW, and XuW: drawing. DM and JF: writing review and editing. All authors contributed to manuscript revision, read, and approved the submitted version.

## FUNDING

This work of the authors was supported by the National Science Foundation of China, Grant Nos. 81771257 and 81701158; the science and technology planning project of Jilin Province, Grant Nos. 20180101161JC and 20180520134JH; and National Key R&D Program of China, Grant Nos. 2017YFC1308401 and 2017YFC0110304.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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