REVIEW ARTICLE

Neuroprotective effect of ischemic postconditioning against hyperperfusion and its mechanisms of neuroprotection

Seyyed Majid Bagheri[1], Mohammad Allahtavakoli[1,2], Elham Hakimizadeh[1]

[1]Physiology-Pharmacology Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran, [2]Department of Physiology and Pharmacology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

Background: In recent years, stroke and ischemia–reperfusion injury has motivated researchers to find new ways to reduce the complications. Although reperfusion is essential for brain survival, it is like a double-edged sword that may cause further damage to the brain. Ischemic postconditioning (IPostC) refers to the control of blood flow in postischemia–reperfusion that can reduce ischemia-reperfusion injuries. **Materials and Methods:** Articles were collected by searching for the terms: Ischemic postconditioning and neuroprotective and ischemic postconditioning and hyperperfusion. Suitable articles were collected from electronic databases, including ISI Web of Knowledge, Medline/PubMed, ScienceDirect, Embase, Scopus, Biological Abstract, Chemical Abstract, and Google Scholar. **Results:** New investigations show that IPostC has protection against hyperperfusion by reducing the amount of blood flow during reperfusion and thus reducing infarction volume, preventing the blood–brain barrier damage, and reducing the rate of apoptosis through the activation of innate protective systems. Numerous mechanisms have been suggested for IPostC, which include reduction of free radical production, apoptosis, inflammatory factors, and activation of endogenous protective pathways. **Conclusion:** It seems that postconditioning can prevent damage to the brain by reducing the flow and blood pressure caused by hyperperfusion. It can protect the brain against damages such as stroke and hyperperfusion by activating various endogenous protection systems. In the present review article, we tried to evaluate both useful aspects of IPostC, neuroprotective effects, and fight against hyperperfusion.

Key words: Ischemic postconditioning, neuroprotective, reperfusion injury

How to cite this article: Bagheri SM, Allahtavakoli M, Hakimizadeh E. Neuroprotective effect of ischemic postconditioning against hyperperfusion and its mechanisms of neuroprotection. J Res Med Sci 2024;29:31.

INTRODUCTION

Cerebral hyperperfusion or cerebral reperfusion syndrome is a serious complication of restoring blood flow to the brain, which is much higher than the metabolic needs of brain tissue.[1] It was first described by Sundt *et al*. in 1975[2] and occurs in carotid endarterectomy and intracranial stenting and after tissue plasminogen activator (tPA) application which leads to higher cerebral infarction.[3] Studies have shown that reperfusion injury is directly involved in amplifying stroke injury.[4] Various factors, including cytokine release and leukocyte adhesion, as well as damage to the blood–brain barrier (BBB), play a major role in causing these complications.[5] The main symptoms of cerebral reperfusion syndrome appear as unilateral headache, contralateral nerve deficits, and seizures. During acute ischemia, systemic blood pressure increases to compensate for the lack of cerebral blood flow (CBF), which is one of the most common symptoms observed in patients with cerebral ischemia. In this case, the blood pressure usually remains untreated and disrupts the BBB following reperfusion.[6] Ischemia has various complications that cause damage to cells, and these complications are aggravated during reperfusion and cause more damage. The production of free radicals is one of

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_341_22

Address for correspondence: Dr. Mohammad Allahtavakoli, Physiology-Pharmacology Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.
E-mail: mohammadallahtavakoli@yahoo.com

Submitted: 06-May-2022; **Revised:** 13-May-2023; **Accepted:** 27-Jun-2023; **Published:** 11-Jul-2024

the complications that increases during ischemia and causes brain damage during reperfusion.[7] Excessive production of reactive oxygen species (ROS) causes the opening of mitochondrial inner membrane channels called permeability transition pores (PTP) and reduces the endogenous antioxidant capacity and ultimately causes cell death [Figure 1].[8] Inflammation is another complication of ischemia in which leukocytes attach to endothelial cells due to the release of chemotactic signals, thereby disrupting the BBB and penetrating into brain tissue, releasing cytokines that mediate inflammation.[9] In addition, during reperfusion, the complement system [Figure 2] can be activated through classical antibody dependent or the lectin pathway.[10] Several methods have been proposed to minimize the deleterious effects of ischemia/reperfusion, such as the use of antihypertensive drugs such as labetalol and nicardipine,[11] hypothermia,[12] the use of antioxidants such as α-lipoic acid and magnolol,[13] and the use of anti-inflammatory agents.[14] Nevertheless, it seems that common methods are not sufficient in reducing the effects of hyperperfusion and finding new protocols is a subject that is still of interest to researchers. Ischemic postconditioning (IPostC) is emerging as a potentially effective strategy for the treatment of ischemic-reperfusion injury. This method is a nonpharmacological method that has shown positive results in animal experiments in protecting the nervous system and dealing with the negative effects of reperfusion. So far, there have been many studies related to the neuroprotective effects of ischemia postconditioning, and it has been investigated from different aspects of this issue. IPostC can activate various endogenous mechanisms including rCBF, antioxidant system and local anti-inflammatory factors and protect the nervous system by regulating the phosphorylation of multiple pathways such as PKC, mitogen-activated protein kinase (MAPK) and PI3K/Akt.[15] In several studies, the neuroprotective effects of IPostC against ischemia damage have been proven.[16,17] Cerebral ischemia may be caused by cardiac arrest, stroke, severe anemia, aging, systemic hypertension and hypoxia, and metabolic or regulatory disorders. Stroke is one of the severe conditions of ischemia that causes morbidity, cognitive decline, disability, and mortality of a large number of patients worldwide every year.[18] Currently, thrombolytic therapy is not an effective method in the treatment of ischemic stroke due to time limitations. On the other hand, hyperperfusion created after using thrombolytics such as tPA can cause damage to the brain tissue and the BBB. Fortunately, studies have shown that ischemia conditioning can both increase the time period of using thrombolytics and minimize the damage caused by reperfusion.[19] Therefore, neuroprotective effects can be used to reduce the harmful effects of reperfusion caused by the use of thrombolytic drugs. In this review article, an attempt is made to investigate the various aspects of IPostC and its neuroprotective mechanisms as well as prevent the harmful effects of reperfusion.

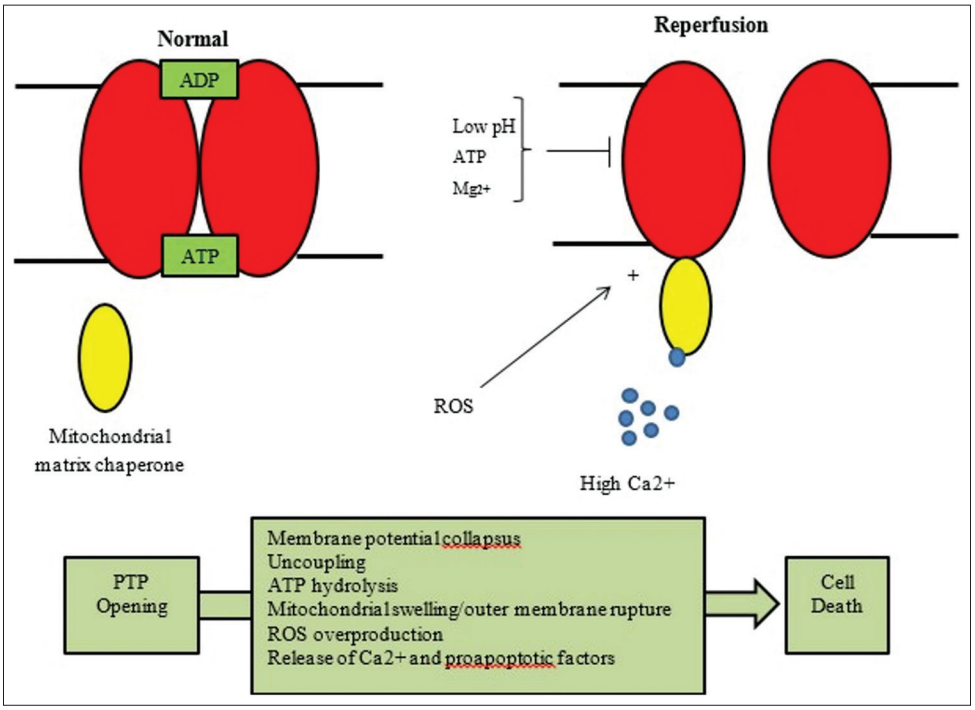

Figure 1: Schematic of the effect of reperfusion on the opening of mitochondrial membrane pores called permeability transition pore (PTP). During reperfusion following prolonged ischemic, the accumulation of Ca2 + in the mitochondrial matrix causes the matrix chaperones to move to the inner mitochondrial membrane, which in turn causes PTP to open

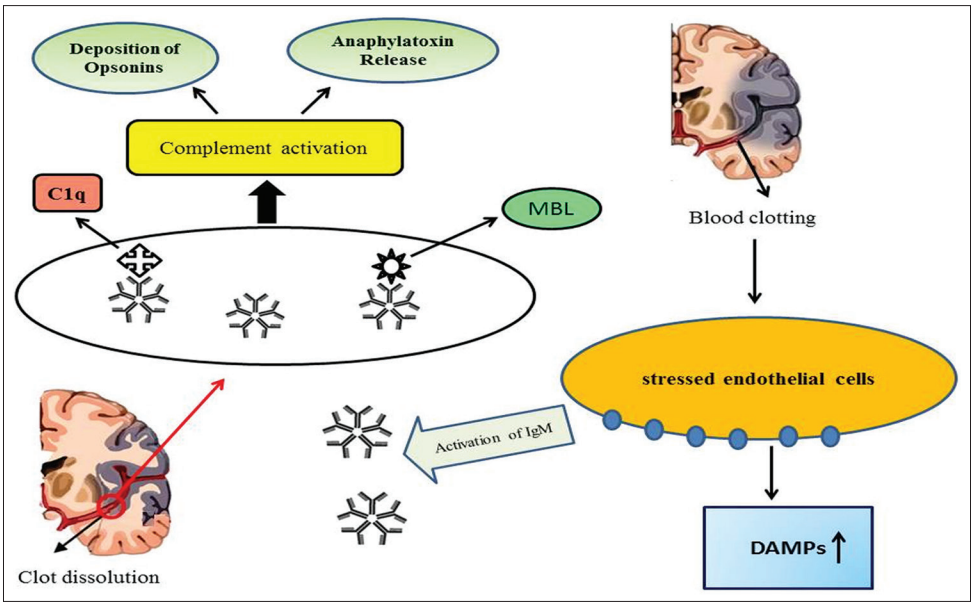

Figure 2: Triggers of complement activation after cerebral ischemia–reperfusion injury. Ischemic insult induces the expression of neoepitopes or danger-associated molecular patterns (DAMPs) on the surface of stressed endothelial cells. The exposed DAMPs are recognized by circulating natural self-reactive antibodies, principally immunoglobulin M (IgM), which triggers complement activation. Although IgM binds C1q, it appears to be the binding of mannose-binding lectin and activation of the lectin pathway that drives ischemia and reperfusion injury in the organ systems examined, including the brain. Complement can be also activated through direct binding of C1q to apoptotic cells, as well as through C-reactive protein-induced complement activation

METHODS

We reviewed articles without a time limit until the end of May 2022 by searching terms including "ischemic and ischemic preconditioning," "ischemic preconditioning and reperfusion," "ischemic preconditioning and neuroprotection," and "ischemic preconditioning and stroke." To investigate the mechanism of the effect of IPostC on neuroprotection, we searched the terms of "ischemic postconditioning" and "anti-apoptotic," "antioxidant," "anti-inflammatory," and "intrinsic protection" effects. Information was collected through searches and studies in electronic databases, including ISI Web of Knowledge, Medline/PubMed, Science Direct, Embase, Scopus, Biological Abstract, Chemical Abstract, and Google Scholar. Duplicate and unrelated articles were removed from the obtained articles, and the abstracts of the articles were collected and sorted. Mendeley was used as a reference manager tool, and only the abstracts of the articles whose full text was available were examined and reported as a review article.

RESULTS

Ischemic postconditioning: A novel neuroprotective strategy

For the first time, Murry *et al*., in 1986, showed that short periods of ischemia with reperfusion before long-term ischemia significantly reduced the size of the infarction in a dog's heart.[20] They called the phenomenon as "ischemic preconditioning." In 2003, Zhao *et al*. showed that comparable protection could be achieved by changing the conditions of reperfusion.[21] After induction of ischemia, they performed short cycles of ischemic-reperfusion of blood flow. The intervention led to a significant reduction in the size of the infarct of the heart, which they called "IPostC." IPostC is the application of a series of short ischemic periods and reperfusion to the ischemic organ after reperfusion which leads to a reduction in infarction in the target tissue, such as the heart and brain.[22] Later, studies showed that ischemia preconditioning, in addition to the heart and brain, can have protective effects on other organs, such as the kidney.[23] The most common use of postconditional ischemia is protection of the nervous system in strokes and subsequent reperfusion.[24] The molecular mechanism of IPostC is complex and includes the expression of various genes and the increase of mRNAs that cause the reduction of cell death. It has even been found that the amount of some microRNAs has increased, which can cause the reduction and destruction of proteins involved in cell death. Weng *et al*. showed that IPostC treatment reduces miR124 levels, indicating that IPostC exerts its brain protection by downregulating miR-124 and reduced neurobehavioral defects and infarct volume percentage significantly.[25] Examination of long-term expression of noncoding RNA in adult rats with focal cerebral ischemia showed that IPostC strongly influenced the expression of noncoding RNAs and mRNAs that are associated with cellular response to ischemia, oxidative stress, and inflammation signals and apoptosis signaling pathways.[26] IPostC also increases protein and mRNA levels of SIRT1 and PGC-1α in ischemic brain tissue,

regulates downstream protein NRF-1, lowers cytochrome C (Cyto C) 1, and improves mitochondrial function, thereby protecting the brain.[27] In addition, it seems that IPostC exerts a neuroprotective effect against I/R injury by reducing the expression of GSK-3β and increasing the level of CREB and BDNF.[28] Numerous studies have confirmed the protective effect of IPostC, as well as its mechanisms in ischemic-reperfusion injury in the brain. A study on rats showed that the use of remote limb ischemia post-conditioning by occluding and releasing the femoral artery 90 minutes after stroke induction, significantly reduced cerebral infarct volume, inflammation, and BBB leakage.[29] Pignataro *et al*. showed that postconditioning ischemia 30 min after reperfusion has a protective effect on the brain.[30] Mobini *et al*. investigated the protective effect of IPostC in female mice, and in five cycles, common carotid arteries were occluded and reopened for 30-s periods. The results showed that the volume of infarction, cerebral edema, and neurological disorders in the postconditional ischemia group decreased significantly compared to the stroke group.[31] Studies have shown that the pattern and method of using IPostC is also important in preventing the harmful effects of Hyperperfusion. Using three different models of postconditioning therapy showed that blockage of the artery in three times 10, 30, and 60 s could reduce the volume of infarct, but only 10 s of blockage reduced brain edema and nerve damage.[32] Typically, one of the most important treatment methods for relieving obstruction in stroke and restoring blood flow in humans is the use of tissue plasminogen activating drug. Applying tPA has a time limit and the maximum should be 4.5 h after ischemic. Concomitant use of IPostC may increase the therapeutic window of tPA. It has been shown that the rapid flow of blood due to the use of tPA increases the damage caused by ischemic, cerebral edema, inflammatory responses, and ultimately, a damage to the brain tissue and the BBB. Esmaeeli-Nadimi *et al*. showed that concomitant use of IPostC with tPA caused a greater reduction in infarct volume, CBF, BBB leakage, inflammation, apoptosis, and improved brain function significantly compared to the tPA group alone.[3] Feng *et al*. showed that neuronal death in CA1 was reduced in the group with IPostC.[33] They found that these beneficial effects were related to improving the antioxidant conditions of the environment and reducing inflammatory factors. It has generally been proved that IPostC can have a protective effect on the nervous system and reduces the volume of infarction by reducing oxidative stress and free radicals or reducing the rate of apoptosis and inflammation.[34] Molecular mechanisms of IPostC are intricate and include stimuli (adenosine, bradykinin, opioids, or nitric oxide [NO]),[35] mediators (protein kinase G and protein kinase C), and end effectors such as PTP and mitochondrial ATP-sensitive potassium channels.[36]

Antiapoptotic effects of ischemic postconditioning

Ischemia–reperfusion increases the rate of apoptosis of nerve cells and new data have shown that IPostC can reduce the rate of apoptosis due to reperfusion. IPostC increases antiapoptotic proteins by changing the factors involved in autophagy, such as LC3/Beclin-1 and p62.[37] Ding *et al*. showed that both ischemic preconditioning and postconditioning reduced neuronal cell death and DNA fragmentation in the CA1 region of the hippocampus. Furthermore, caspase-3, caspase-6, caspase-9, and Bax proteins were decreased but regulated Bcl-2 protein.[38] Meng *et al*. showed that remote IPostC 90 min after occlusion can reduce the area of infarction of brain tissue and this effect is related to reducing Bax expression and increasing Bcl2.[39] IPostC may inhibit apoptosis by activating the TOPK (protein kinase/protein kinase protein-kinase origin-T-LAK cell) pathway while potentiating Akt phosphorylation to protect nerve cells and reduce infarct volume.[40] MAPK signaling pathways are involved in ischemic damage to the brain and play an important role in regulating cell death and apoptosis. MAPKS includes three types of kinases: C-Jun N-terminal kinase, protein kinase mitogen P38 active protein (P38MAPK), and regulated extracellular signal-related kinase (ERK).[41] Liu *et al*. proved that 1–24 h after stroke, ERK1/2 phosphorylation increased intermittently and IPostC could significantly inhibit ERK1/2 expression.[42] IPostC is able to reduce brain damage due to reperfusion ischemic by reducing the P38MAPK-ATF2 pathway which plays a regulatory role for a variety of downstream molecules including ATF2 which may complicate the effects of MAPK on apoptosis and these changes potentially help inhibit apoptosis in neurons.[43] Another important factor in ischemic-reperfusion injury is endoplasmic reticulum (ER) stress. In postconditional ischemia, the ER stress response increases the level of homologous protein C/EBP (CHOP) and releases Bim and Bcl-2, which can disrupt the cell apoptosis pathway[44] [Figure 3]. The mitochondrial proteins Bax and p53 as well as the antiapoptotic proteins Bcl-2 and Bcl XL are also involved in ischemic-reperfusion-induced apoptosis. Sun *et al*. showed that IPostC can protect mitochondria by reducing the synthesis of oxygen-free radicals and increase the expression of Bcl-2 protein, which is located throughout the mitochondrial membrane, thereby reducing cell apoptosis.[45] IPostC also rapidly increases GRP78 expression and EIF2 dephosphorylation, decreases caspase-12 and Bim expression, and increases Bcl-2 expression, all of which prevent cellular apoptosis.[46] IPostC reduces the release of Cyto C into the cytosol, Bax transfer to the mitochondria, and caspase-3 activity, resulting in decreased apoptosis.[47] Nuclear factor-κB (NF-κB) is a known nuclear transcription factor that plays an important role in the regulation of ischemic-induced neuronal apoptosis.[48] Heat shock proteins (Hsps) are also involved in the process of apoptosis

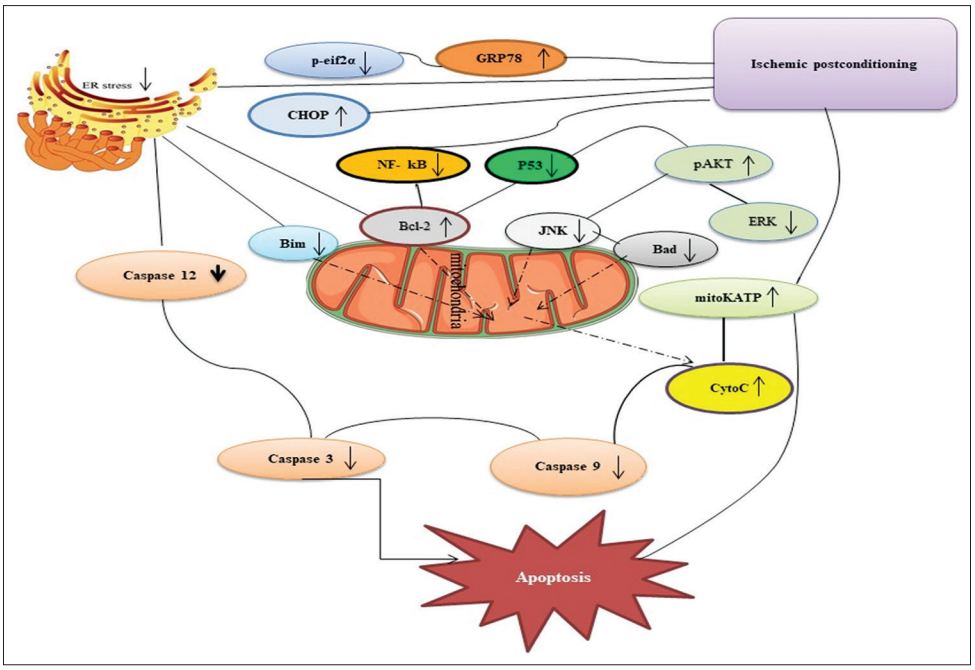

Figure 3: Mechanism of anti-apoptotic effects of ischemic postconditioning. Stress in the endoplasmic reticulum is closely related to mitochondrial function. In fact, ischemic postconditioning causes a kind of stress on the cell, thereby activating the endogenous defense mechanisms and thus protecting the mitochondria. This process reduces apoptosis in nerve cells. P-eif2α: Phospho- eukaryotic initiation factor 2 alpha, GRP78: Glucose-regulated protein78, CHOP: C/EBP homologous protein, ER: Endoplasmic reticulum, Bim: Bcl-2-like protein, Bcl-2: B-cell lymphoma 2, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B-cells, JNK: c-Jun N-terminal kinase, pAKT: Phosphorylated protein kinase B, ERK: Extracellular signal-related kinase, Bad: Bcl-2-associated death promoter, mitokATP: Mitochondrial ATP-sensitive potassium channels, Cyto C: Cytochrome C

and the expression of these proteins increases during IPostC and knockdown Hsp70 reverses the beneficial effects of IPostC.[49] IPostC regulated the expression of Bcl-2, Bax, and caspase-3 to reduce neural apoptosis and inhibit autophagy via the PI3K/Akt/mTOR signaling pathway.[50] Cheng *et al*. showed that IPostC decreased the number of apoptotic cells and protein expression levels of Bcl-2, Bax, NF-κB, and TNF-α and increased the expression of p-STAT3 protein, which indicates that IPostC exerts their protective effects through STAT3 activation.[51] Furthermore, the role of microRNAs in the occurrence of IPostC effects should not be ignored. MicroRNAs such as miR1 and miR133 are increased during IPostC and prevent apoptosis caused by ischemia-reperfusion by decreasing CASP9 protein levels.[52] These observations show that IPostC exerts neuroprotective effects by reducing cellular apoptosis and inhibiting autophagy and protects against brain damage.

Antioxidant property of ischemic postconditioning

Ischemia–reperfusion increases free radicals and produces reactive oxygen mediators.[53] Important features of oxidative stress that cause damage to the lipid and protein compounds of the nerve membrane include overproduction or inadequate clearance of ROS.[54] Mitochondria are the main source of ROS production in neurons.[55] A large number of ROS are also produced during restoring blood flow, causing oxidative stress damage. Accordingly, the use of ascorbic acid can reduce the volume of infarction in the stroke model.[24] IPostC defense mechanisms are the same in the heart and brain, although the effects of postconditioning on ROS may be controversial.[56] IPostC can cause neuroprotective effects by reducing oxidative stress or increasing antioxidant enzymes. IPostC increases the enzyme superoxide dismutase (SOD)[57] and is also able to decrease malondialdehyde.[58] In addition, IPostC increases acetylcholine[59] and NO synthesis and inhibits oxidative stress.[60] It can also reduce ROS production after ischemia-reperfusion and increase endogenous antioxidant activity and prevent lipid and protein oxidation and thus protect the nervous system.[61] IPostC could improve the activity of the antioxidant enzymes such as SOD and catalase.[62] The main source of these enzyms in ischemic injury conditions is nicotine amide-adenine phosphate dinucleotide phosphate (NADPH) oxidase, especially in neutrophils.[63] IPostC can reduce the neutrophil activity of NADPH oxidase that they have protective effects against I/R brain damage.[64] This action may be related to the regulation of NADPH oxidase activity in neutrophils by the MyD88/TRAF6/p38-MAPK pathway.[65]

Anti-inflammatory effects

There are plenty of evidence from clinical and animal studies that pro-inflammatory cytokines increase during ischemia and can damage nerve cells during reperfusion.[66] Elevated levels of cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1),

interleukin-6 (IL-6), and interferon-gamma, have been observed after the onset of ischemia.[67] Xing *et al*. showed that glutathione decreased and myeloperoxidase (MPO) as well as inflammatory markers increased during cerebral ischemic/reperfusion in mice.[68] Chemokines and intercellular adhesion molecules (ICAM-1) cause leukocytes to attach to endothelial cells, enabling these cells to leave the bloodstream and enter the ischemic region of the brain. Numerous evidence and studies suggested that IPostC improves stroke damage and reperfusion by reducing inflammatory factors and chemokines. Tahamtan *et al*. investigated the effect of IPostC on the expression of CXCL1, CXCL10, and CXCL12. Results showed that IPostC reduced the expression of inflammatory chemokines CXCL1 and CXCL10 in the hippocampus of rats after reperfusion but had no effect on the expression of CXCL12.[69] Xing *et al*. demonstrated that rapid IPostC could reduce MPO activity and expression of IL-1β, TNFα, and ICAM-1 and prevent the accumulation of leukocytes in the cerebral cortex as well. These studies also confirm the positive role of IPostC, which may prevent the invasion of inflammatory agents and block the secretion of cytokines and pro-inflammatory chemokines.[68] Li *et al*. found that IL-1β and IL-6 levels were reduced in both proximal and remote postconditioning.[70] Hwang *et al*. observed that IPostC improves the number of peripheral blood immune cells and reduces the number of microglia, macrophages, and T and B lymphocytes in the ischemic brain.[71] Although the number of immune cells in the peripheral blood and spleen was increased by IPostC, no change was observed in the bone marrow immune cell population by IPostC. Activation of NF-κB during reperfusion ischemic causes the high release of downstream inflammatory cytokines, including IL-1β, IL-6, and TNF-α.[72] IPostC significantly reduces NF-κβ/p65. Toll-like receptor (TLR) pathways are the main signaling pathways responsible for regulating endogenous or exogenous inflammation,[73] and the TLR4 pathway has an important role in the pathology of stroke.[74] Wang *et al*. showed that the neuroprotective effect of IPostC was associated with the inhibition of neuroinflammation by inhibiting the TLR2 and TLR4 pathways, which reduce the production of the pro-inflammatory cytokine IL-1β.[75] The TLR4/NF-κB pathway also plays a key role in the inflammatory response to ischemic-reperfusion injury [Figure 4]. Qi *et al*. suggested that IPostC may protect the brain against the harmful effects of ischemic and stroke by suppressing the TLR4/NF-κB pathway.[76] During inflammation, peripheral immune cells, including monocytes and lymphocytes, penetrate the ischemic region of the brain and contribute to further brain damage through the neurotoxic effects of glutamate. By activating NMDA receptors expressed by surrounding neurons, these cells can penetrate the brain and release glutamate and cause neurotoxicity;[77] however, the use of antagonists of NMDA receptors could have protective effects against ischemia.[78] Studies have shown that the protective effects of IPostC on ischemic and subsequent reperfusion may partly be due to the inhibition of macrophage accumulation in the brain, thereby reducing the adverse effects of glutamate on the nervous system through reduction of NMDA receptor.[79]

Innate protection

IPostC conventionally refers to a series of brief blood vessel occlusions and reperfusions, which can induce an endogenous neuroprotective effect and reduce cerebral ischemia/reperfusion injury.[80] Endogenous neuroprotective mechanisms in neurons can be classified into several categories. Neurotrophic factors and enzymatic and nonenzymatic mechanisms of ROS inhibition are major and well-known factors in neuronal homeostasis. In addition, incorrect protein degradation systems (e.g., autophagy) and mechanisms of gene expression control are gaining increasing attention and are potentially interesting goals for the treatment and/or prevention of neurodegeneration.[81] The innate protection mechanism of IPostC is through improving brain blood flow, reducing oxidative stress, inhibiting apoptosis, reducing brain edema, improving mitochondrial function, regulating autophagy and also regulating Akt, MAPK and PKC signaling pathways[82] [Figure 5]. Naturally, nerve cells use the body's immune systems to prevent cell death and damage. Numerous studies have shown that the brain can adapt to traumatic events such as ischemia. As a result, it improves cell resistance in the event of more serious damage in the future.[83] To achieve adaptation, a coordinated response must be established at the cell surface, and if the stimulus is beyond tolerance, the cells may be doomed to destroy. Establishing ischemic tolerance by exposure to stressors, which can be induced by preconditioned or postconditional ischemia, is a powerful mechanism for stimulating endogenous processes to protect neurons.[84] García-Bonilla *et al* showed that reprogrammed monocytes can stimulate endogenous activity and protect the brain. They migrate from the spleen to the brain and suppress inflammation after ischemia and invasive of neutrophils into the brain parenchyma.[85] The PI3K/Akt pathway is one of the important intermediary pathways in signal transmission that causes endogenous protection in the cell by inhibiting apoptosis. In IPostC, many targets and processes are regulated by the PI3K/Akt pathway. Recently, downstream targets of Akt involved in IPostC-induced neuroprotection have been reported. Animal studies propose that IPostC increases endothelial nitric oxide synthase synthesis and activates the PI3K/Akt signal transduction pathway, consequently protects vascular endothelial cells, and regenerates blood vessels.[86] Some studies have shown that IPostC can reduce cerebral ischemia injury through protective mechanisms that increase CBF after reperfusion.

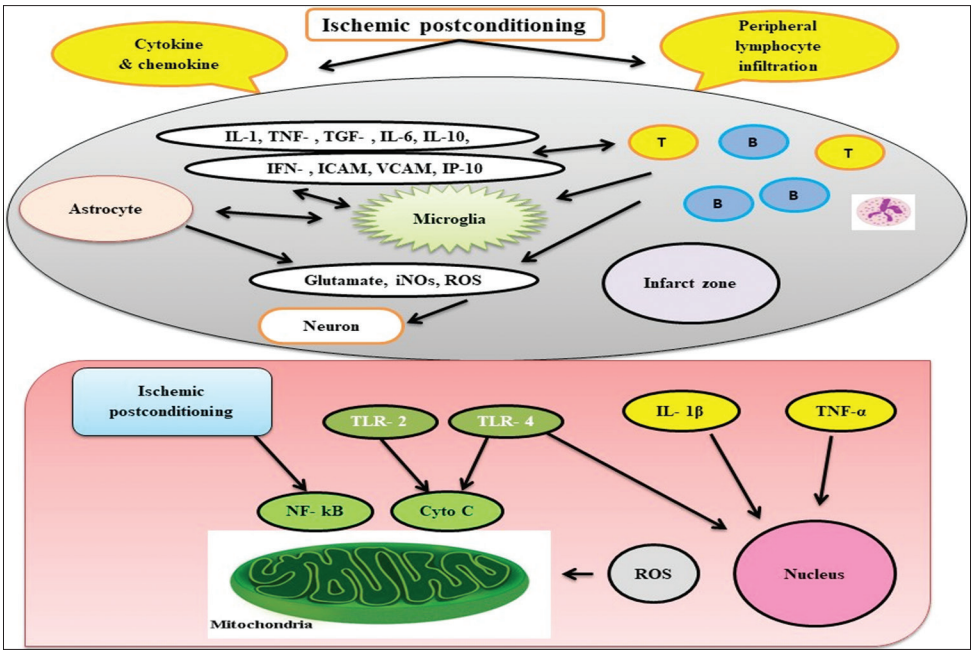

Figure 4: Mechanism of anti-inflammatory effects of post-conditional ischemic. Ischemic postconditioning stimulates endogenous defense mechanisms. Decreased mitochondrial cytochrome C leads to suppression of the immune system, which in turn reduces the levels of inflammatory cytokines and chemokines. IL-1β: Interleukin-1 beta, TNF-α: Tumor necrosis factor-alpha, TLR-2: Toll-like receptor 2, TLR-4: Toll-like receptor 4, Cyto C: Cytochrome C, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B-cells

The laser-Doppler flow meter has shown that regional hippocampal blood flow increased after IPostC.[87] Lu *et al*. showed that the protective mechanism of IPostC may be associated with increased expression of vascular endothelial growth factor and rCBF.[88] Endothelial and astrocytes are two groups of cells in the nervous system that play a protective role by suppression of transcription of inflammatory mediators such as NF-κB, inhibiting free radicals, glycogen storage, and erythropoietin production. By regulating the expression of P-selectin, ICAM 1 and E-selectin, IPostC increases the migration of white blood cells and leads to a decrease in inflammation and thus protects the brain against ischemia-reperfusio.[66] Autophagy is a way to maintain intracellular homeostasis, which causes the destruction of macromolecules or cell organelles. In ischemia–reperfusion conditions, autophagy causes an increase in brain injury, which indicates that autophagy plays different roles in cerebral ischemia and subsequent reperfusion.[89] It has been reported that inhibition of autophagy by IPostC method can significantly induce neuroprotection by decreasing LC3 and Beclin-1 and increasing p62.[37] Together, these studies suggest that organisms/cells have endogenous protective mechanisms, and boosting them may be an effective therapeutic strategy.

DISCUSSION

IPostC has been introduced as a promising neuroprotective strategy against stroke and ischemic/reperfusion. Experimental models have been used to successfully demonstrate the attenuation of organ damage, including heart, spinal cord, brain, kidney, liver, muscle, lung, and intestine. The mechanisms of postconditioning are not yet fully understood but appear to involve multiple signaling pathways and molecules, including protein kinases, ROS, pro-inflammatory cytokines, and NO, as well as changes in mitochondrial function. On the other hand, IPostC relieves ischemia/reperfusion injury by reducing the size of cerebral infarction, neuropathic apoptosis, and nerve defects and increases SOD activity and decreases MDA content in brain tissue.[90] This phenomenon can effectively reduce nerve mortality cells and the size of cerebral infarction and maintain BBB integrity, improve cerebral circulation and metabolism, and increase cerebral ischemic tolerance.[80] In addition, postconditioning can be mimicked using anesthetics or other pharmacological agents as stimuli to protect against ischemia/reperfusion injury.[24] New evidence shows that ischemic preconditioning can exert its protective effects through the PI3K/Akt2 pathway, which plays an important role in regulating cell growth, apoptosis, and cell proliferation.[91] In addition, the PI3K/Akt2 pathway is an important regulator of antiapoptotic protection after ischemic conditioning.[92] Therefore, IPostC by activating intracellular mechanisms and expression of antiapoptotic genes, reduction of oxidative stress, and the prevention of the release of inflammatory factors minimizes long-term damage to neurons and other parts of nerve tissue such as microglia. These interventions are suitable for not only acute ischemia treatment but also primary and secondary stroke prevention. However, there is still a long way to go

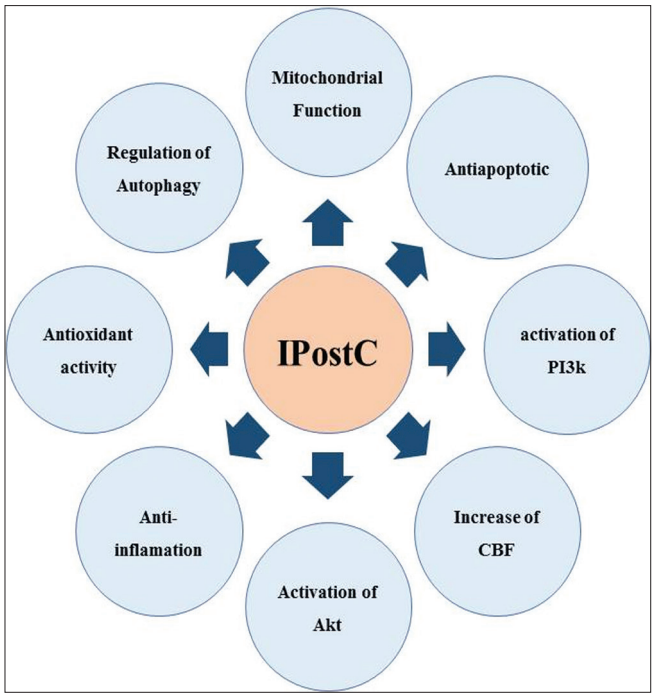

Figure 5: Schematic diagram illustrating the impact of endogenous neuroprotective mechanisms on neuron rescue after injury

from basic research to the clinical application of IPostC. To use this method in the clinic, some points should be considered. Currently, there are many models and methods to study the mechanism of IPostC, and this method has not been standardized yet. Furthermore, most studies have investigated the acute effects of IPostC, whereas late animal experiments should be performed in older mice. Existing research on the treatment of IPostC is mostly focused on the acute stage of cerebral infarction, and there are few studies on the treatment process of IPostC. We hope that by studying the course of IPostC treatment, these studies will be useful and usable for clinical application.

CONCLUSION

Several studies have been conducted on the neuroprotective effects of ischemia post-conditioning and most of them have confirmed the protective effects of this method. This method can be very helpful in the treatment of strokes and prevent further damage caused by reperfusion during the treatment process. This method is a non-invasive and non-pharmacological method, so more additional studies should be done so that it can be used as a therapeutic method as soon as possible in the treatment of ischemia and strokes.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Farooq MU, Goshgarian C, Min J, Gorelick PB. Pathophysiology and management of reperfusion injury and hyperperfusion syndrome after carotid endarterectomy and carotid artery stenting. Exp Transl Stroke Med 2016;8:7.
2. Sundt TM Jr., Sharbrough FW, Piepgras DG, Kearns T, Messick JM Jr., O'fallon WM. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy, with results of surgery and hemodynamics of cerebral ischemia. Surv Anesthesiol 1982;26:200-1.
3. Esmaeeli-Nadimi A, Kennedy D, Allahtavakoli M. Opening the window: Ischemic postconditioning reduces the hyperemic response of delayed tissue plasminogen activator and extends its therapeutic time window in an embolic stroke model. Eur J Pharmacol 2015;764:55-62.
4. Mandalaneni K, Rayi A, Jillella DV. Stroke reperfusion injury. In: StatPearls. St. Petersburg, Florida, United States: StatPearls Publishing; 2022.
5. Bernstein DL, Zuluaga-Ramirez V, Gajghate S, Reichenbach NL, Polyak B, Persidsky Y, *et al*. miR-98 reduces endothelial dysfunction by protecting blood-brain barrier (BBB) and improves neurological outcomes in mouse ischemia/reperfusion stroke model. J Cereb Blood Flow Metab 2020;40:1953-65.
6. Adhiyaman V, Alexander S. Cerebral hyperperfusion syndrome following carotid endarterectomy. J Assoc Physicians 2007;100:239-44.
7. Ferrari RS, Andrade CF. Oxidative stress and lung ischemia-reperfusion injury. Oxid Med Cell Longev 2015;2015:590987.
8. Leung AW, Halestrap AP. Recent progress in elucidating the molecular mechanism of the mitochondrial permeability transition pore. Biochim Biophys Acta 2008;1777:946-52.
9. Tuttolomondo A, Daidone M, Pinto A. Endothelial dysfunction and inflammation in ischemic stroke pathogenesis. Curr Pharm Des 2020;26:4209-19.
10. Rahmani MR, Shamsizadeh A, Moghadam-Ahmadi A, Kaeidi A, Allahtavakoli M. Monoacylglycerol lipase inhibitor, JZL-184, confers neuroprotection in the mice middle cerebral artery occlusion model of stroke. Life Sci 2018;198:143-8.
11. Pagliaro P, Penna C. Hypertension, hypertrophy, and reperfusion injury. J Cardiovasc Med (Hagerstown) 2017;18:131-5.
12. Hassanipour M, Zarisfi M, Ehsani V, Allahtavakoli M. Whole body hypothermia extends tissue plasminogen activator treatment window in the rat model of embolic stroke. Life Sci 2020;256:117450.
13. Bazmandegan G, Boroushaki MT, Shamsizadeh A, Ayoobi F, Hakimizadeh E, Allahtavakoli M. Brown propolis attenuates cerebral ischemia-induced oxidative damage via affecting antioxidant enzyme system in mice. Biomed Pharmacother 2017;85:503-10.
14. Zhu P, Li JX, Fujino M, Zhuang J, Li XK. Development and treatments of inflammatory cells and cytokines in spinal cord ischemia-reperfusion injury. Mediators Inflamm 2013;2013:701970.
15. You J, Feng L, Xin M, Ma D, Feng J. Cerebral ischemic postconditioning plays a neuroprotective role through regulation of central and peripheral glutamate. Biomed Res Int 2018;2018:1-12.
16. Miao W, Yan Y, Bao TH, Jia WJ, Yang F, Wang Y, *et al.* Ischemic postconditioning exerts neuroprotective effect through negatively regulating PI3K/Akt2 signaling pathway by microRNA-124. Biomed Pharmacother 2020;126:109786.
17. Li Z, Chen H, Lv J, Zhao R. The application and neuroprotective mechanisms of cerebral ischemic post-conditioning: A review. Brain Res Bull 2017;131:39-46.

18. Dietz RM, Dingman AL, Herson PS. Cerebral ischemia in the developing brain. J Cereb Blood Flow Metab 2022;42:1777-96.
19. Mohammadi M, Mobini M, Mashayekhi F, Allahtavakoli M, Kaeidi A, Hassanshahi J, *et al.* Ischemic post-conditioning is neuroprotective even at delayed tPA administration after embolic stroke in female rats. Iran J Basic Med Sci 2021;24:1676-82.
20. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. Circulation 1986;74:1124-36.
21. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, *et al*. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: Comparison with ischemic preconditioning. Am J Physiol Heart Circ Physiol 2003;285:H579-88.
22. Zhao H. The protective effect of ischemic postconditioning against ischemic injury: from the heart to the brain. J Neuroimmune Pharmacol 2007;2:313-8.
23. Samadi M, Tabibian F, Moradzadeh K, Nassiri SM, Gheisari Y. Evaluating the effect of remote ischemic preconditioning on kidney ischemia-reperfusion injury. J Res Med Sci 2020;25:6.
24. Zhao H. The protective effects of ischemic postconditioning against stroke: From rapid to delayed and remote postconditioning. Open Drug Discov J 2011;5:138-47.
25. Weng H, Shen C, Hirokawa G, Ji X, Takahashi R, Shimada K, *et al.* Plasma miR-124 as a biomarker for cerebral infarction. Biomed Res 2011;32:135-41.
26. Ma W, Li CY, Zhang SJ, Zang CH, Yang JW, Wu Z, *et al.* Neuroprotective effects of long noncoding RNAs involved in ischemic postconditioning after ischemic stroke. Neural Regen Res 2022;17:1299-309.
27. Zhou Y, Wang S, Li Y, Yu S, Zhao Y. SIRT1/PGC-1α signaling promotes mitochondrial functional recovery and reduces apoptosis after intracerebral hemorrhage in rats. Front Mol Neurosci 2017;10:443.
28. Ramagiri S, Taliyan R. Remote limb ischemic post conditioning during early reperfusion alleviates cerebral ischemic reperfusion injury via GSK-3β/CREB/BDNF pathway. Eur J Pharmacol 2017;803:84-93.
29. Ren C, Gao M, Dornbos D 3rd, Ding Y, Zeng X, Luo Y, *et al.* Remote ischemic post-conditioning reduced brain damage in experimental ischemia/reperfusion injury. Neurol Res 2011;33:514-9.
30. Pignataro G, Meller R, Inoue K, Ordonez AN, Ashley MD, Xiong Z, *et al. In vivo* and *in vitro* characterization of a novel neuroprotective strategy for stroke: Ischemic postconditioning. J Cereb Blood Flow Metab 2008;28:232-41.
31. Mobini M, Rezazadeh H, Shamsizadeh A, Ehsani V, Hakimizadeh E, Amir-Esmaili S, *et al*. Protective effect of delayed ischemic postconditioning on embolic stroke complications in female rat. J Kerman Univ Med Sci 2014;21:230-9.
32. Rezazadeh H, Hoseini Kahnuee M, Roohbakhsh A, Shamsizadeh A, Rahmani MR, Bidaki R, *et al.* Neuroprotective consequences of postconditioning on embolic model of cerebral ischemia in rat. Iran J Basic Med Sci 2013;16:144-9.
33. Feng C, Luo T, Qi L, Wang B, Luo Y, Ge P. Ischemic postconditioning alleviates neuronal injury caused by relief of carotid stenosis in a rat model of cerebral hypoperfusion. Int J Mol Sci 2012;13:13338-51.
34. Saad MA, Abdelsalam RM, Kenawy SA, Attia AS. Ischemic preconditioning and postconditioning alleviates hippocampal tissue damage through abrogation of apoptosis modulated by oxidative stress and inflammation during transient global cerebral ischemia-reperfusion in rats. Chem Biol Interact 2015;232:21-9.
35. Kaur S, Jaggi AS, Singh N. Molecular aspects of ischaemic postconditioning. Fundam Clin Pharmacol 2009;23:521-36.
36. Jang YH, Kim JH, Lee YC. Mitochondrial ATP-sensitive potassium channels play a role in reducing both myocardial infarction and reperfusion arrhythmia in remote ischemic preconditioned hearts. Anesth Pain Med 2017;7:e42505.
37. Gao L, Jiang T, Guo J, Liu Y, Cui G, Gu L, *et al.* Inhibition of autophagy contributes to ischemic postconditioning-induced neuroprotection against focal cerebral ischemia in rats. PLoS One 2012;7:e46092.
38. Ding ZM, Wu B, Zhang WQ, Lu XJ, Lin YC, Geng YJ, *et al*. Neuroprotective effects of ischemic preconditioning and postconditioning on global brain ischemia in rats through the same effect on inhibition of apoptosis. Int J Mol Sci 2012;13:6089-101.
39. Meng X, Li Y, Zhang J, Jiang X, Tian X, Zhao J. Effects of limb remote postconditioning on apoptosis and long-term neurological outcomes of focal cerebral ischemia/reperfusion injury in rats. J Diabetes Metab 2015;6:2.
40. Gao X, Zhang H, Takahashi T, Hsieh J, Liao J, Steinberg GK, *et al.* The Akt signaling pathway contributes to postconditioning's protection against stroke; the protection is associated with the MAPK and PKC pathways. J Neurochem 2008;105:943-55.
41. Li H, Zhou S, Wu L, Liu K, Zhang Y, Ma G, *et al.* The role of p38MAPK signal pathway in the neuroprotective mechanism of limb postconditioning against rat cerebral ischemia/reperfusion injury. J Neurol Sci 2015;357:270-5.
42. Liu X, Zhao S, Liu F, Kang J, Xiao A, Li F, *et al.* Remote ischemic postconditioning alleviates cerebral ischemic injury by attenuating endoplasmic reticulum stress-mediated apoptosis. Transl Stroke Res 2014;5:692-700.
43. Xing B, Chen H, Zhang M, Zhao D, Jiang R, Liu X, *et al*. Ischemic postconditioning inhibits apoptosis after focal cerebral ischemia/reperfusion injury in the rat. Stroke 2008;39:2362-9.
44. Yuan Y, Guo Q, Ye Z, Pingping X, Wang N, Song Z. Ischemic postconditioning protects brain from ischemia/reperfusion injury by attenuating endoplasmic reticulum stress-induced apoptosis through PI3K-Akt pathway. Brain Res 2011;1367:85-93.
45. Sun K, Liu ZS, Sun Q. Role of mitochondria in cell apoptosis during hepatic ischemia-reperfusion injury and protective effect of ischemic postconditioning. World J Gastroenterol 2004;10:1934-8.
46. Hu L, Wang J, Zhu H, Wu X, Zhou L, Song Y, *et al*. Ischemic postconditioning protects the heart against ischemia-reperfusion injury via neuronal nitric oxide synthase in the sarcoplasmic reticulum and mitochondria. Cell Death Dis 2016;7:e2222.
47. Bours V, Bentires-Alj M, Hellin AC, Viatour P, Robe P, Delhalle S, *et al*. Nuclear factor-kappa B, cancer, and apoptosis. Biochem Pharmacol 2000;60:1085-9.
48. Liang J, Luan Y, Lu B, Zhang H, Luo YN, Ge P. Protection of ischemic postconditioning against neuronal apoptosis induced by transient focal ischemia is associated with attenuation of NF-κB/p65 activation. PLoS One 2014;9:e96734.
49. Zhan L, Liu L, Li K, Wu B, Liu D, Liang D, *et al.* Neuroprotection of hypoxic postconditioning against global cerebral ischemia through influencing posttranslational regulations of heat shock protein 27 in adult rats. Brain Pathol 2017;27:822-38.
50. Xie R, Wang P, Cheng M, Sapolsky R, Ji X, Zhao H. Mammalian target of rapamycin cell signaling pathway contributes to the protective effects of ischemic postconditioning against stroke. Stroke 2014;45:2769-76.
51. Cheng Z, Li L, Mo X, Zhang L, Xie Y, Guo Q, *et al.* Non-invasive remote limb ischemic postconditioning protects rats against focal cerebral ischemia by upregulating STAT3 and reducing apoptosis. Int J Mol Med 2014;34:957-66.
52. He B, Xiao J, Ren AJ, Zhang YF, Zhang H, Chen M, *et al.* Role of miR-1 and miR-133a in myocardial ischemic postconditioning. J Biomed Sci 2011;18:22.
53. Abuja PM, Albertini R. Methods for monitoring oxidative stress,

lipid peroxidation and oxidation resistance of lipoproteins. Clin Chim Acta 2001;306:1-17.
54. Ott M, Gogvadze V, Orrenius S, Zhivotovsky B. Mitochondria, oxidative stress and cell death. Apoptosis 2007;12:913-22.
55. Allahtavakoli M, Amin F, Esmaeeli-Nadimi A, Shamsizadeh A, Kazemi-Arababadi M, Kennedy D. Ascorbic acid reduces the adverse effects of delayed administration of tissue plasminogen activator in a rat stroke model. Basic Clin Pharmacol Toxicol 2015;117:335-9.
56. Nemethova M, Danielisova V, Gottlieb M, Kravcukova P, Burda J. Ischemic postconditioning in the rat hippocampus: Mapping of proteins involved in reversal of delayed neuronal death. Arch Ital Biol 2010;148:23-32.
57. Han R, Zhang G, Qiao X, Guo Y, Sun L, Li J, *et al.* α7 nicotinic acetylcholine receptor mediates the neuroprotection of remote ischemic postconditioning in a rat model of asphyxial cardiac arrest. J Surg Res 2020;246:6-18.
58. Liu K, Yan M, Zheng X, Yang Y. The dynamic detection of NO during the ischemic postconditioning against global cerebral ischemia/reperfusion injury. Nitric Oxide 2014;38:17-25.
59. Buchholz B, Donato M, D'Annunzio V, Gelpi RJ. Ischemic postconditioning: Mechanisms, comorbidities, and clinical application. Mol Cell Biochem 2014;392:1-12.
60. Zhao H, Sapolsky RM, Steinberg GK. Interrupting reperfusion as a stroke therapy: Ischemic postconditioning reduces infarct size after focal ischemia in rats. J Cereb Blood Flow Metab 2006;26:1114-21.
61. Ritzel RM, Pan SJ, Verma R, Wizeman J, Crapser J, Patel AR, *et al.* Early retinal inflammatory biomarkers in the middle cerebral artery occlusion model of ischemic stroke. Mol Vis 2016;22:575-88.
62. Shen J, Bai XY, Qin Y, Jin WW, Zhou JY, Zhou JP, *et al*. Interrupted reperfusion reduces the activation of NADPH oxidase after cerebral I/R injury. Free Radic Biol Med 2011;50:1780-6.
63. Chen G, Ye X, Zhang J, Tang T, Li L, Lu P, *et al.* Limb remote ischemic postconditioning reduces ischemia-reperfusion injury by inhibiting NADPH oxidase activation and MyD88-TRAF6-P38MAP-kinase pathway of neutrophils. Int J Mol Sci 2016;17:1971.
64. Allahtavakoli M, Jarrott B. Sigma-1 receptor ligand PRE-084 reduced infarct volume, neurological deficits, pro-inflammatory cytokines and enhanced anti-inflammatory cytokines after embolic stroke in rats. Brain Res Bull 2011;85:219-24.
65. Jafarinaveh HR, Allahtavakoli M, Rezazadeh H, Kazemi Arababadi M, Taghavi MM, Shamsizadeh A, *et al.* Proinflammatory cytokines in the embolic model of cerebral ischemia in rat. Iran J Allergy Asthma Immunol 2014;13:125-30.
66. Joo SP, Xie W, Xiong X, Xu B, Zhao H. Ischemic postconditioning protects against focal cerebral ischemia by inhibiting brain inflammation while attenuating peripheral lymphopenia in mice. Neuroscience 2013;243:149-57.
67. Xie R, Wang P, Ji X, Zhao H. Ischemic post-conditioning facilitates brain recovery after stroke by promoting Akt/mTOR activity in nude rats. J Neurochem 2013;127:723-32.
68. Xing B, Chen H, Zhang M, Zhao D, Jiang R, Liu X, *et al*. Ischemic post-conditioning protects brain and reduces inflammation in a rat model of focal cerebral ischemia/reperfusion. J Neurochem 2008;105:1737-45.
69. Tahamtan M, Shamsizadeh A, Allahtavakoli M, Nami M, Mohammadi N, Hassanshahi G. Differential expression of CXCL1, CXCL10, and CXCL12 in response to cerebral ischemic postconditioning in rat brain. J Adv Med Sci Appl Technol 2017;3:197-204.
70. Li P, Su L, Li X, Di W, Zhang X, Zhang C, *et al.* Remote limb ischemic postconditioning protects mouse brain against cerebral ischemia/reperfusion injury via upregulating expression of Nrf2, HO-1 and NQO-1 in mice. Int J Neurosci 2016;126:552-9.
71. Hwang JW, Jeon YT, Lim YJ, Park HP. Sevoflurane postconditioning-induced anti-inflammation via inhibition of the toll-like receptor-4/nuclear factor kappa B pathway contributes to neuroprotection against transient global cerebral ischemia in rats. Int J Mol Sci 2017;18:2347.
72. Hakimizadeh E, Kazemi Arababadi M, Shamsizadeh A, Roohbakhsh A, Allahtavakoli M. The possible role of toll-like receptor 4 in the pathology of stroke. Neuroimmunomodulation 2016;23:131-6.
73. Zhang J, Benveniste H, Klitzman B, Piantadosi CA. Nitric oxide synthase inhibition and extracellular glutamate concentration after cerebral ischemia/reperfusion. Stroke 1995;26:298-304.
74. Allahtavakoli M, Shabanzadeh A, Roohbakhsh A, Pourshanazari A. Combination therapy of rosiglitazone, a peroxisome proliferator-activated receptor-gamma ligand, and NMDA receptor antagonist (MK-801) on experimental embolic stroke in rats. Basic Clin Pharmacol Toxicol 2007;101:309-14.
75. Wang PF, Xiong XY, Chen J, Wang YC, Duan W, Yang QW. Function and mechanism of toll-like receptors in cerebral ischemic tolerance: From preconditioning to treatment. J Neuroinflammation 2015;12:1-15.
76. Qi W, Zhou F, Li S, Zong Y, Zhang M, Lin Y, *et al.* Remote ischemic postconditioning protects ischemic brain from injury in rats with focal cerebral ischemia/reperfusion associated with suppression of TLR4 and NF-κB expression. Neuroreport 2016;27:469-75.
77. Morisaki Y, Nakagawa I, Ogawa Y, Yokoyama S, Furuta T, Saito Y, *et al.* Ischemic postconditioning reduces NMDA receptor currents through the opening of the mitochondrial permeability transition pore and K(ATP) channel in mouse neurons. Cell Mol Neurobiol 2022;42:1079-89.
78. Hayashi-Takagi A, Yagishita S, Nakamura M, Shirai F, Wu YI, Loshbaugh AL, *et al.* Labelling and optical erasure of synaptic memory traces in the motor cortex. Nature 2015;525:333-8.
79. Bouayed J, Bohn T. Exogenous antioxidants – Double-edged swords in cellular redox state: Health beneficial effects at physiologic doses versus deleterious effects at high doses. Oxid Med Cell Longev 2010;3:228-37.
80. Li CY, Ma W, Liu KP, Yang JW, Wang XB, Wu Z, *et al.* Advances in intervention methods and brain protection mechanisms of *in situ* and remote ischemic postconditioning. Metab Brain Dis 2021;36:53-65.
81. Wei Y, Gong J, Yoshida T, Eberhart CG, Xu Z, Kombairaju P, *et al.* Nrf2 has a protective role against neuronal and capillary degeneration in retinal ischemia-reperfusion injury. Free Radic Biol Med 2011;51:216-24.
82. Khan ZA, Sumsuzzman DM, Choi J, Kamenos G, Hong Y. Pre- and post-conditioning with poly I: C exerts neuroprotective effect against cerebral ischemia injury in animal models: A systematic review and meta-analysis. CNS Neurosci Ther 2022;28:1168-82.
83. Kirino T. Ischemic tolerance. J Cereb Blood Flow Metab 2002;22:1283-96.
84. Gidday JM. Cerebrovascular ischemic protection by pre-and post-conditioning. Brain Circ 2015;1:97.
85. Garcia-Bonilla L, Brea D, Benakis C, Lane DA, Murphy M, Moore J, *et al*. Endogenous protection from ischemic brain injury by preconditioned monocytes. J Neurosci 2018;38:6722-36.
86. Han D, Zhang S, Fan B, Wen LL, Sun M, Zhang H, *et al.* Ischemic postconditioning protects the neurovascular unit after focal cerebral ischemia/reperfusion injury. J Mol Neurosci 2014;53:50-8.
87. Kin H, Zatta AJ, Lofye MT, Amerson BS, Halkos ME, Kerendi F, *et al.* Postconditioning reduces infarct size via adenosine receptor activation by endogenous adenosine. Cardiovasc Res 2005;67:124-33.
88. Lu Y, Xiong J, Yin B, Wen J, Liu L, Geng D. The role of

three-dimensional pseudo-continuous arterial spin labelling in grading and differentiating histological subgroups of meningiomas. Clin Radiol 2018;73:176-84.
89. Zhang X, Yan H, Yuan Y, Gao J, Shen Z, Cheng Y, *et al*. Cerebral ischemia-reperfusion-induced autophagy protects against neuronal injury by mitochondrial clearance. Autophagy 2013;9:1321-33.
90. Li L, Zhi D, Cheng R, Li J, Luo C, Li H. The neuroprotective role of SIRT1/PGC-1α signaling in limb postconditioning in cerebral ischemia/reperfusion injury. Neurosci Lett 2021;749:135736.
91. Zhang B, Liu Y, Li Y, Zhe X, Zhang S, Zhang L. Neuroglobin promotes the proliferation and suppresses the apoptosis of glioma cells by activating the PI3K/AKT pathway. Mol Med Rep 2018;17:2757-63.
92. Dai RY, Chen SK, Yan DM, Chen R, Lui YP, Duan CY, *et al*. PI3K/Akt promotes GRP78 accumulation and inhibits endoplasmic reticulum stress-induced apoptosis in HEK293 cells. Folia Biol (Praha) 2010;56:37-46.