Ischemic Tolerance of the Brain and Spinal Cord: A Review

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Abstract

Ischemic tolerance is an endogenous neuroprotective phenomenon induced by sublethal ischemia. Ischemic preconditioning (IPC), the first discovered form of ischemic tolerance, is widely seen in many species and in various organs including the brain and the spinal cord. Ischemic tolerance of the spinal cord is less familiar among neurosurgeons, although it has been reported from the viewpoint of preventing ischemic spinal cord injury during aortic surgery. It is important for neurosurgeons to have opportunities to see patients with spinal cord ischemia, and to understand ischemic tolerance of the spinal cord as well as the brain. IPC has a strong neuroprotective effect in animal models of ischemia; however, clinical application of IPC for ischemic brain and spinal diseases is difficult because they cannot be predicted. In addition, one drawback of preconditioning stimuli is that they are also capable of producing injury with only minor changes to their intensity or duration. Numerous methods to induce ischemic tolerance have been discovered that vary in their timing and the site at which short-term ischemia occurs. These methods include ischemic postconditioning (IPoC), remote ischemic preconditioning (RIPC), remote ischemic perconditioning (RIPerC) and remote ischemic postconditioning (RIPoC), which has had a great impact on clinical approaches to treatment of ischemic brain and spinal cord injury. Especially RIPerC and RIPoC to induce spinal cord tolerance are considered clinically useful, however the evidence supporting these methods is currently insufficient; further experimental or clinical research in this area is thus necessary.

Key words: delayed tolerance, acute tolerance, remote ischemic preconditioning, spinal cord, brain

Introduction

Ischemic preconditioning (IPC) is a phenomenon in which brief episodes of sublethal ischemia induce robust protection against the deleterious effects of subsequent, prolonged, lethal ischemia (Fig. 1). This phenomenon, initially discovered in the heart by Murry et al. in 1986,5 has been shown to occur in many organ systems, including the brain2-4) and spinal cord.5,6) Subsequently, IPC has been shown to be neuroprotective using many other stimuli, such as hypoxia, hyperoxia, hypothermia, and anesthetics.7) IPC was initially observed within two time windows. The first window, which is known as the rapid or short-term window, appears minutes after preconditioning and lasts for a few hours. The second window, which is known as the delayed or long-term window, appears within a day of preconditioning and is thought to last for a maximum of 7 days after preconditioning.7,8) More recently, various other procedures called ischemic postconditioning (IPoC), remote ischemic preconditioning (RIPC), remote ischemic perconditioning (RIPerC) and remote ischemic postconditioning (RIPoC) were discovered6,7) (Figs. 1 and 2).

Unlike the ischemic tolerance of the brain, most reports of the ischemic tolerance of the spinal cord have come from cardiovascular surgeons or anesthesiologists, and relate to the prevention of ischemic spinal cord injury during aortic surgery.5,6,9) Consequently, neurosurgeons are considered to be less familiar with ischemic tolerance of the spinal cord; however, neurosurgeons sometimes have opportunities to see patients with spinal cord ischemia, such as in spinal infarction or vascular malformation of the spinal cord. Understanding the ischemic tolerance of the spinal
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Ischemic tolerance is acquired by some treatment before invasive ischemia, IPOC (a state in which ischemic tolerance is acquired by some treatment after invasive ischemia), and IPerC (a state in which ischemic tolerance is obtained by some treatment during invasive ischemia).

History of ischemic preconditioning

Mild brain injury made by a small needle at four sites, 1 week before brain ischemia, was demonstrated to increase the number of survivors at 1 week after an ischemic insult in a mouse experimental model. This result by Takahata et al. is considered to be the first report suggesting that anti-ischemic factors are released by the injured brain, or that certain, unknown protective mechanisms against ischemia become active following brain injury.10) The authors speculated that anti-ischemic factors or other unknown protective mechanisms are activated by preconditioning. In 1986, the same year as the Takahata et al. report, Murry et al. observed that four cycles of 5 min of ischemia and reperfusion, prior to a more sustained episode of 40 min of ischemia, considerably reduced myocardial infarction compared with controls.1) This was the first description of an endogenous protective phenomenon called IPC. In 1990, Kitagawa et al. investigated the effects of mild and nonlethal ischemic insult on neuronal death following a subsequent lethal ischemic stress, using a gerbil model of bilateral cerebral ischemia3) (Table 1). Two 2 min ischemic treatments at 1-day intervals, 2 days before 5 min of ischemia, afforded complete protection against neuronal death.3) In 1991, Kirino et al. also demonstrated protective effect of 2 min ischemic treatment 1 day, 2 days and 4 days before 5 min of ischemia using a gerbil model of global ischemia.2) They reported that the protective mechanism involves heat-shock proteins induced by very brief ischemia which renders neurons more tolerant to subsequent ischemia.2) As reported by Murry et al.1) ischemic tolerance that develops within a few hours of a brief ischemic load is called early or rapid IPC, and as reported by Kitagawa et al.3) and Kirino et al.2) ischemic tolerance that develops after 24 hours is called delayed IPC (Fig. 1). 

More recently, various methods to induce ischemic tolerance have been discovered that depend on the timing and site at which short-term ischemia occurs. In 1993, RIPC was reported in the myocardium.11) RIPC is a phenomenon in which increased tolerance to an ischemic insult is induced after a short-term ischemia/reperfusion episode in a distant body tissue or organ, and was also demonstrated to be protective for cerebral ischemia in 201112) (Fig. 2). Furthermore, IPOC, which consists of brief ischemia...
applied during the onset of reperfusion, was reported to be cardioprotective and has subsequently been shown to also be effective against cerebral ischemia (Fig. 1).

Looking back at the history of ischemic tolerance, this phenomenon was reported first in the myocardium, and subsequently in the central nervous system. Hereafter, we describe the ischemic tolerance of the brain and spinal cord.

**Mechanisms of delayed and rapid ischemic tolerance**

**Brain** Regarding the ischemic tolerance of the brain, there have been many reports of delayed IPC, and its mechanism has also been examined since its discovery. Activation of various receptors and transcription factors, as well as expression of various genes and proteins, are involved in a complicated manner, and exact protective mechanisms are still unknown. However, the current hypothesis is that hypoxic stress, acid stress, and excitatory amino acid stress occur because of moderate ischemia, which results in the activation of transcription factors and the production of genes and proteins that act protectively for neural cells, such as Bcl-2 and Mn-superoxide dismutase (MnSOD).

Furthermore, in a recent study of delayed tolerance, preconditioning with a 30 min middle cerebral artery occlusion (MCAO) reduced cortical and subcortical infarct volume following a 120 min MCAO (test ischemia) 72 h later. This preconditioning-induced neuroprotection disappeared when the mitochondrial ATP-sensitive potassium channels (KATP) channel blocker 5HD (5-hydroxydecanoate) was administered 2 hours before the test ischemia. This result suggests a possible involvement of mitochondrial KATP channels in the development of tolerance to focal cerebral ischemia, even if the preconditioning stimuli also produce some cytoprotective protein. Moreover, thousands of genes were screened using microarray analysis, and genes involved in ischemic tolerance were identified. Preconditioning resulted in transcriptional changes for genes involved in suppressing metabolic pathways and immune responses, reducing ion-channel activity, and decreasing blood coagulation. After the first non-fatal invasion, it seems that gene expression is reprogrammed so that neurons become responsive to decreased blood flow and oxygen limitation, as seen during hibernation when they are subsequently subjected to lethal invasion. As described above, it is becoming clear that ischemic tolerance is not just a case of increased cytoprotective protein levels, as was conventionally thought.

Although many reports have demonstrated that delayed-phase neuroprotection evoked by
preconditioning is evident after 1 week or longer, there have only been a few investigations into rapidly induced tolerance. Nakamura et al. reported that rapid ischemic tolerance may be mediated through an adenosine A1 receptor-related mechanism in a rat focal ischemic model; however, many aspects of rapid tolerance are still uncertain. Furthermore, Perez-Pinzon et al. recently reported that rapid IPC reduced microglial activation after subsequent cerebral ischemia, suggesting that the beneficial effects of IPC may also involve an anti-inflammatory process.

**Spinal cord**

The incidence of neurological deficits after aortic surgery has not changed appreciably over the last 50 years. Both anesthesiologists and vascular surgeons have attempted to resolve this clinically important issue by employing various strategies to prevent ischemic spinal cord injury. Kakimoto et al. used a rabbit model to investigate whether pretreatment with sublethal ischemia of the spinal cord can attenuate neuronal injury after spinal cord ischemia. Rapid IPC protects the spinal cord against neuronal damage 24 h, but not 7 days, after reperfusion in a rabbit model of spinal cord ischemia, suggesting that the efficacy of rapid IPC may be transient. Mechanisms by which rapid IPC can protect the spinal cord early after ischemic injury are unknown. However, three possible mechanisms are as follows. Firstly, adenosine and adenosine triphosphate-sensitive potassium channels may be involved in the acquisition of ischemic tolerance by rapid IPC, as Nakamura et al. reported in a model of cerebral ischemia. Secondly, there may be an involvement of mitochondrial KATP channels in the development of rapid tolerance to spinal cord ischemia. Caparrelli et al. demonstrated that administration of a potent mitochondrial adenosine triphosphate-sensitive potassium channel opener, diazoxide, improved neurologic injury in a model of spinal cord ischemia. Thirdly, Fan et al. reported that rapid IPC may enhance the ischemic tolerance of the spinal cord by increasing spinal cord blood flow and decreasing norepinephrine concentration after lethal ischemia. Further study is required to clarify the mechanisms of the beneficial effects of rapid IPC on the spinal cord.

**Postischemic tolerance (early and delayed)**

**Brain** IPC performed immediately or within 30 min after reperfusion is defined as rapid IPC, whereas that performed hours or days after reperfusion is defined as delayed IPC (Fig. 1). Rapid IPC has been demonstrated as neuroprotective by Zhao et al. and Gao X et al. They confirmed that rapid IPC reduces infarct size when started 10 to 30 s after reperfusion, but does not show any effect if it is started more than 3 min after reperfusion. This extremely short therapeutic time window of rapid IPC may hinder its clinical translation.

The exact mechanism of rapid IPC has not yet been determined, but since rapid IPC is performed immediately after reperfusion, possible mechanisms may include harmful reactions such as free radical products caused by reperfusion and obstacles to various cell signaling pathways. Duanmu et al. reported that rapid IPC upregulates acid-sensing ion channel 2a expression in the rat hippocampus after global brain ischemia, which is considered to promote neuronal tolerance to ischemic brain injury.

In contrast, delayed IPC is applied a few hours, or even a few days, after reperfusion. In a global ischemia model with induction by 4-vessel occlusion, Burda et al. confirmed that hippocampal neuronal death measured 7 days after global ischemia decreased when delayed IPC was performed for 5 min, 2 days after reperfusion. Other groups have also confirmed this protective phenomenon in similar global ischemia models.

Delayed IPC is thought to regulate the secondary response occurring in the delayed phase after reperfusion injury. For example, it is considered that the mechanism of delayed IPC involves the attenuation of cerebral blood flow decrease and the inflammatory response occurring late after reperfusion, which is also a delayed adverse event after a stroke. In addition, it may promote angiogenesis and neurogenesis. However, it is not known how much the intensification of intrinsic defense mechanisms is involved in the expression of delayed IPC, and further research is needed.

**Spinal cord**

There are several studies into the protective effects of post-conditioning with volatile (inhalation) anesthetics for spinal cord ischemia. However, there are no reports of IPC for ischemic spinal cord injury, possibly because it is difficult to apply clinically because of safety and ethical aspects.

**Cross-tolerance**

Ischemic tolerance induced by something other than brief ischemia is called cross-tolerance. After Kitagawa et al. and Kirino et al. demonstrated delayed ischemic tolerance in a gerbil model of global ischemia, multiple preconditioning stimuli have been reported to induce ischemic tolerance, including hypoxia, hyperoxia, hypothermia, hyperthermia, epidural electrical stimulation, lipopolysaccharide (LPS), diphosphoryl lipid
A (DPL), 3-nitropropionate (3-NP), cortical spreading depression (CSD), morphine and erythropoietin (Table 2). The following are representative items in which cross-tolerance was confirmed experimentally, and that are likely to have a clinical application because of their low invasiveness.

a) **Hyperoxia**

**Brain** Wada et al. reported that in a gerbil forebrain ischemia model, pretreatment of repeated hyperbaric oxygenation (HBO) of 2 atmospheres absolute (ATA) induced delayed ischemic tolerance. They speculated that protection against mitochondrial alterations after ischemia via MnSOD and/or Bcl-2 expression may be related to the induction of ischemic tolerance by repeated HBO pretreatment.

**Spinal cord**

In a rabbit spinal cord ischemia model, delayed tolerance was demonstrated when HBO at 2.5 ATA, 1 hour per day for 5 days, was used as a pretreatment.

b) **Anesthetics**

**Brain** Delayed preconditioning by isoflurane and xenon and rapid preconditioning and postconditioning by sevoflurane are reported to be protective for cerebral ischemic injuries. In a rat MCAO model, there is a dosage-dependent (inhalation concentration) protective effect of isoflurane, inhaled once a day for 5 days until 1 day before ischemia. It is reported that the protective mechanism involves the activation of KATP channels.

Using a neuronal-glial cell coculture, hippocampal slice culture, and an in vivo model of neonatal asphyxia involving hypoxic-ischemic injury to 7-day-old rats, Ma et al. provided evidence for xenon’s preconditioning effect, which may be caused by a phosphorylated cAMP (cyclic adenosine 3’,5’-monophosphate)-response element binding protein (pCREB)-regulated synthesis of proteins that promote survival against neuronal injury.

Codaccioni et al. demonstrated that sevoflurane preconditioning induces rapid tolerance in a rat transient MCAO model. Furthermore, Zhang et al. recently reported that sevoflurane postconditioning may decrease blood and brain oxidative injuries, which in turn may cause tolerance in cerebral ischemia/reperfusion rats.

**Spinal cord**

For spinal cord ischemia, there are several studies of the protective effects of volatile (inhalation) anesthetics. Delayed and rapid preconditioning by isoflurane.

### Table 2 Representative reported items which cross-tolerance was confirmed in brain and spinal cord

|                                | Delayed tolerance | Rapid tolerance | Postconditioning |
|--------------------------------|------------------|----------------|------------------|
| **Brain**                      |                  |                |                  |
| Hyperoxia                      | Wada K 2001      | Codaccioni JL 2009 | Zhang Y 2011     |
| Sevoflurane                    |                  |                |                  |
| Isoflurane                     | Xiong L 2003     |                |                  |
| Xenon                          | Ma D 2006        |                |                  |
| Morphine                       | He Dong 2010     |                |                  |
| LPS                            | Tasaki 1997      |                |                  |
| Erythropoietin                 | Prass K 2002     |                |                  |
| CSD                            | Kobayashi S 1995| Gniel HM 2011  |                  |
| 3-NPA                          | Kuroiwa T 2000   |                |                  |
| DPL                            | Toyoda T 2000    |                |                  |
| Hypothermia                    | Nishio S 2000    | Yunoki M 2002  |                  |
| Hyperthermia                   | Xu 2002          |                |                  |
| **Spinal cord**                |                  |                |                  |
| Electrical stimulation         | Kakinohara 2005  |                |                  |
| Hyperoxigen                    | Dong H 2002      |                |                  |
| Hyperthermia                   |                  | Zhang P 2000   |                  |
| Sevoflurane                    |                  | Ding Q 2009    | Wang Q 2011      |
| Isoflurane                     | Sang H 2006      |                | Park HP 2005     |
| Xenon                          |                  |                | Yang YW 2012     |

CSD: Cortical spreading depression, DPL: diphosphoryl lipid A, LPS: lipopolysaccharide, 3-NPA: 3-nitropropionic acid.
rapid preconditioning and postconditioning by sevo-
flurane,9,52 and postconditioning by xenon47,53 are all
reported to be protective for ischemic spinal injury.
In one study, rabbits received preconditioning with
3.7% sevoflurane in 96% oxygen for 30 min, and at
1 h after preconditioning the animals were subjected
to spinal cord ischemia/reperfusion induced by infra-
renal aorta occlusion. Sevoflurane preconditioning
induced rapid tolerance to spinal cord ischemia/
reperfusion in rabbits, and this tolerance may have
been mediated through the activation of extracellular
signal-regulated kinase (ERK).52 Using a rabbit spinal
cord ischemia model, Wang et al. reported a benefi-
cial effect when 3.7% sevoflurane was inhaled for
10 min from the time of reperfusion following 20 min
of spinal cord ischemia.9 An increase in superoxide
dismutase and catalase activity was demonstrated as
the mechanism for these beneficial effects.

In a rat spinal cord ischemia model, inhalation of
50% xenon (and 50% oxygen) for 60 min immediately
after spinal cord ischemia for 20 min resulted in a
neuroprotective effect compared with controls. An
improvement in the functional score and a decrease
in the number of apoptotic cells in the spinal cord
anterior horn were confirmed.53 Thus, a number of
studies have shown that inhalation anesthetics are
effective for spinal cord protection. However, there has
been no evidence of these effects in clinical research.

c) Epidural electrical stimulation
Spinal cord In 2005, Kakinohana et al. confirmed
delayed ischemic tolerance of the spinal cord
induced by epidural electrical stimulation in a rat
transient aortic occlusion model.37 Electrical stimuli
on the epidural space surrounding the spinal cord
is already an established treatment in pain clinics
and can be performed safely. There is no report of
cross-tolerance by epidural stimulation in the brain.

d) Hypothermia
Brain Hypothermic preconditioning elicits both
delayed and rapid forms of tolerance to focal ischemic
injury.33,34 Hypothermia is already an approved
clinical procedure for intraischemic and postischemic
therapy, and it is therefore possible that hypothermia
could be a clinically useful conditioning stimulus
to limit injury elicited by anticipated periods of
ischemia. There is no report of cross-tolerance by
hypothermia in the spinal cord.

Remote tolerance
Various types of preconditioning stimuli have
been used to protect the brain and spinal cord.
A disadvantage involved in many preconditioning
stimuli is that they may cause damage with only
minor changes in their intensity or duration.7
RIPC is a phenomenon in which ischemic toler-
ance develops in target organs, caused by ischemic
injury induced in organs or parts of the body
away from the target organ. In RIPC, subthreshold
ischemia can be performed more safely by avoiding
important organs such as the brain and the heart,
and thus a clinical application is more likely
than with conventional preconditioning. IPC and
postconditioning of the central nervous system
were reported 4 and 5 years after IPC and postcon-
ditioning of the myocardium were reported,
respectively.1–3,13,14 However, RIPC of the spinal
cord was reported more than 10 years after RIPC of
the myocardium was reported.11,54 This may mean
that the effects of RIPC are difficult to detect in
the central nervous system.

Similar to direct IPC, a protective effect of delayed
and rapid preconditioning and postconditioning have
been reported in RIPC.12,54–56 Furthermore, in RIPC a
subthreshold ischemia during cerebral ischemia is
possible, known as perconditioning12 (Fig. 1). For
RIPC, the following three mechanisms are considered,
(1) a brief ischemic stimulation of distant organs is
transmitted to the target organs via the autonomic
nervous system; (2) a pathway in which humoral
factors such as adenosine are released in remote organs
and carried to target organs, or (3) a brief ischemic
stimulation of distant organs causes a systemic anti-
inflammatory reaction, which in turn increases produc-
tion of interleukin 10 and suppresses production of
Tumor Necrosis Factor α (TNFα), which consequently
protects the target organ.7

Brain
Delayed and rapid RIPC have been demonstrated to
reduce infarct size in a focal and global ischemia model
(Table 1). Hahn et al. demonstrated a protective effect
of remote perconditioning by transient limb ischemia
in a model of regional brain ischemia/reperfusion
injury.12 Furthermore, Ren et al. demonstrated that
remote postconditioning performed immediately after
reperfusion markedly reduces infarct size by rat focal
ischemia model.56 In addition, delayed remote postcon-
ditioning initiated as late as 3 hours after reperfusion,
though not 6 hours, robustly reduces infarct size.56
These results suggest that remote postconditioning
provides a wide therapeutic time window for clinical
translation.

Spinal Cord
In the area of remote preconditioning against spinal
ischemia, there are only a few studies demonstrating
that limb ischemia reduces ischemic spinal injury.
Dong et al. studied the effects of limb RIPC in spinal
cord ischemia in New Zealand White rabbits. All rabbits were subjected to 20 min of spinal cord ischemia by aortic occlusion. Thirty minutes before the ischemia, rabbits were subjected to sham intervention or riPC using bilateral femoral artery occlusion. RIPC was confirmed to improve neurologic function and reduced histological damage, which was associated with increased endogenous antioxidant activity.57

**Clinical uses of preconditioning**

**Brain** The effects of IPC on cerebral and myocardial infarction have not been fully investigated because they cannot be predicted based on their nature. The effects of IPC have therefore been mainly studied for cardiovascular surgery, with studies designed to compare prognosis and complications. Although some studies showed effectiveness of IPC, others showed ineffectiveness; the effect of IPC on human myocardium is inconsistent.58-60 In the brain, there have also been studies comparing prognosis and complications using IPC for carotid endarterectomy, but there are relatively few reports compared to those of cardiovascular surgery60,61 The lack of studies is mainly because causing ischemia in a brain with a high risk of cerebral infarction is dangerous. Nevertheless, a retrospective study revealed that patients who have a transient cerebral ischemic attack (TIA) before cerebral infarction had better prognosis after cerebral infarction than patients who did not have a TIA.62,63 It is therefore thought that ischemic tolerance occurs in humans if the conditions match well. The effectiveness of RIPC, a procedure that resolves the risk of causing cerebral infarction by preconditioning stimuli, was first reported in the human brain in 2012.64 This study aimed to evaluate the preventive effect of short-term repetitive RIPC on the recurrence of stroke in symptomatic atherosclerotic intracranial artery stenosis (IAS) patients. In this study, 103 cerebral ischemia patients with high-risk vascular stenosis within 30 days of onset were divided into two groups (a control and an RIPC group). In the RIPC group, patients received brief ischemia and reperfusion of the bilateral upper limbs 5 times. This procedure was performed twice a day for 300 consecutive days and the incidence of recurrent stroke was compared with the control group.

In the control group, the recurrence rate of stroke was 23.3% and 26.7% at 90 days and 300 days, respectively. In the RIPC group, the incidence of recurrent stroke dropped to 5% and 7.9% at 90 days and 300 days (P < 0.01), respectively.64

In recent years, the concept of IPC has been applied to prevent secondary damage at the site of acute treatment of stroke.65-70 For example, it was recently reported that in patients receiving thrombolysis in the acute phase of stroke, the survival rate 1 month after onset increased when RIPC was performed during transport to the hospital.68 Delayed cerebral ischemia (DCI) occurs due to vasospasm after a subarachnoid hemorrhage (SAH), and this may be a situation that is suitable for confirming the effects of IPC clinically.71,72 It is reported that in patients receiving RIPC after a subarachnoid hemorrhage, the mean velocity of the middle cerebral artery decreased, the ratio of lactic acid:pyruvic acid decreased, and the glycerol level decreased, and these effects lasted up to 2 days.73

As treatment of unruptured aneurysms, such as clipping and coil embolization, may cause brain damage by transient arterial occlusion, for example, this is also considered to be a suitable medical situation for examining the effect of RIPC clinically. Tulu et al. investigated whether RIPC before treatment of an unruptured aneurysm alleviates brain damage, by measuring serum biomarkers or performing brain magnetic resonance imaging (MRI) after surgery. The results of this trial, however, did not give a clear answer as to whether RIPC before treatment of unruptured aneurysms is useful for protecting the brain from ischemia.70

**Spinal cord**

As mentioned previously, RIPC may protect the spinal cord from ischemic injury; however, there are only a few studies that have investigated whether preconditioning reduces ischemic spinal injury. Hu et al. conducted a randomized clinical trial to assess the effect of RIPC on neurologic outcome in patients undergoing spine surgery. Forty patients with cervical myelopathy who underwent selective decompression surgery were divided into either an RIPC group (n = 20) or a control group (n = 20) and the therapeutic effect was investigated. Recovery rate after surgery was better in the RIPC group than in the control group (P < 0.05).69

**Summary of current status of research for spinal cord ischemic tolerance**

Spinal cord ischemic tolerance induced by rapid IPC, delayed IPC, and rapid RIPC has been reported from between several years to 10 years after it was reported in the brain.5,6,57 However, no experimental reports of iPoC, RIPC, or ROPerC have been confirmed in the spinal cord, and we think they are worth examining in the future (Table 1). Clinically, tolerance induced by RIPC is considered useful particularly for the spinal cord. A clinical trial confirmed the usefulness of RIPC in spinal surgery69; however, the number of clinical trials for spinal diseases is few compared with that of cerebral diseases.60-73 Clinical trials should thus...
be further promoted, including for procedures that are thought to be more clinically useful, such as RIPoC and RIPerC. With respect to cross tolerance, there are many reports of spinal cord tolerance induced by inhalation anesthetics compared with similar reports in the brain. It is important for physicians performing spinal cord surgery to summarize and understand such knowledge.

**Conclusion**

This review of the literature has summarized current knowledge of the ischemic tolerance of the brain and spinal cord. One drawback of preconditioning stimuli is that they are also capable of producing injury with only minor changes in their intensity or duration. However, IPOC and RIPC have been reported to be neuroprotective, and the possibility of clinical applications is expanding.

Further experimental or clinical research into the use of conditioning methods to induce spinal cord tolerance, such as RIPerC and RIPoC, are especially necessary because these methods are considered clinically useful, but currently have insufficient reported evidence to support their use.

**Conflicts of Interest Disclosure**

The authors have no personal, financial, or institutional conflicts of interest regarding any of the drugs, materials, or devices in this article. The authors who are members of the Japan Neurosurgical Society (JNS) have registered online and filled out the Self-reported COI Disclosure Statement Forms through the JNS members’ website.

**References**

1) Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 74: 1124–1136, 1986
2) Kirino T, Tsujita Y, Tamura A: Induced tolerance to ischemia in gerbil hippocampal neurons. *J Cereb Blood Flow Metab* 11: 299–307, 1991
3) Kitagawa K, Matsumoto M, Tagaya M, et al.: ‘Ischemic tolerance’ phenomenon found in the brain. *Brain Res* 528: 21–24, 1990
4) Chen J, Graham SH, Zhu RL, Simon RP: Stress proteins and tolerance to focal cerebral ischemia. *J Cereb Blood Flow Metab* 16: 566–577, 1996
5) Abraham VS, Swain JA, Forgash AJ, Williams BL, Musulin MM: Ischemic preconditioning protects against paraplegia after transient aortic occlusion in the rat. *Ann Thorac Surg* 69: 475–479, 2000
6) Kakimoto M, Kavaguchi M, Sakamoto T, et al.: Evaluation of rapid ischemic preconditioning in a rabbit model of spinal cord ischemia. *Anesthesiology* 99: 1112–1117, 2003
7) Stetler RA, Leak RK, Gan Y, et al.: Preconditioning provides neuroprotection in models of CNS disease: paradigms and clinical significance. *Prog Neurobiol* 114: 58–83, 2014
8) Dirmagl U, Becker K, Meisel A: Preconditioning and tolerance against cerebral ischemia: from experimental strategies to clinical use. *Lancet Neurol* 8: 398–412, 2009
9) Wang Q, Chen Q, Ding Q, et al.: Sevoflurane postconditioning attenuates spinal cord reperfusion injury through free radicals-mediated up-regulation of antioxidant enzymes in rabbits. *J Surg Res* 169: 292–300, 2011
10) Takahata Y, Shimoji K: Brain injury improves survival of mice following brain ischemia. *Brain Res* 381: 368–371, 1986
11) Przyklenk K, Bauer B, Ovize M, Kloner RA, Wiltzaker P: Regional ischemic ‘preconditioning’ protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 87: 893–899, 1993
12) Hahn CD, Manlhiot C, Schmidt MR, Nielsen TT, Redington AN: Remote ischemic per-conditioning: a novel therapy for acute stroke? *Stroke* 42: 2960–2962, 2011
13) Zhao ZQ, Corvera JS, Halkos ME, et al.: Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 285: H579–H588, 2003
14) Wang JY, Shen J, Gao Q, et al.: Ischemic postconditioning protects against global cerebral ischemia/reperfusion-induced injury in rats. *Stroke* 39: 983–990, 2008
15) Pignataro G, Meller R, Inoue K, et al.: In vivo and in vitro characterization of a novel neuroprotective strategy for stroke: ischemic postconditioning. *J Cereb Blood Flow Metab* 28: 232–241, 2008
16) Steiger HJ, Hänggi D: Ischaemic preconditioning of the brain, mechanisms and applications. *Acta Neurochir (Wien)* 149: 1–10, 2007
17) Kitagawa K: Ischemic tolerance in the brain: endogenous adaptive machinery against ischemic stress. *J Neurosci Res* 90: 1043–1054, 2012
18) Yoshida M, Nakakimura K, Cui YJ, Matsumoto M, Sakabe T: Adenosine A(1) receptor antagonist and mitochondrial ATP-sensitive potassium channel blocker attenuate the tolerance to focal cerebral ischemia in rats. *J Cereb Blood Flow Metab* 24: 771–779, 2004
19) Stenzel-Poore MP, Stevens SL, Xiong Z, et al.: Effect of ischaemic preconditioning on genomic response to cerebral ischaemia: similarity to neuroprotective strategies in hibernation and hypoxia-tolerant states. *Lancet* 362: 1028–1037, 2003
20) Pérez-Pinzón MA, Xu GP, Mumford PL, Dietrich WD, Rosenthal M, Sick TJ: Rapid ischemic preconditioning protects rats from cerebral anoxia/ischemia. *Adv Exp Med Biol* 428: 155–161, 1997
21) Nakamura M, Nakakimura K, Matsumoto M, Sakabe T: Rapid tolerance to focal cerebral ischemia in rats is attenuated by adenosine A1 receptor antagonist. J Cereb Blood Flow Metab 22: 161–170, 2002

22) Pérez-Pinzón MA, Vitro TM, Dietrich WD, Sick TJ: The effect of rapid preconditioning on the microglial, astrocytic and neuronal consequences of global cerebral ischemia. Acta Neuropathol 97: 495–501, 1999

23) Caparrelli DJ, Cattaneo SM, Betha BT, et al.: Pharmacological preconditioning ameliorates neurological injury in a model of spinal cord ischemia. Ann Thorac Surg 74: 838–844; discussion 844–845, 2002

24) Fan T, Wang CC, Wang FM, et al.: Experimental study of the protection of ischemic preconditioning to spinal cord ischemia. Surg Neurol 52: 299–305, 1999

25) 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 26: 1114–1121, 2006

26) Gao X, Ren C, Zhao H: Protective effects of ischemic postconditioning compared with gradual reperfusion or preconditioning. J Neurosci Res 86: 2505–2511, 2008

27) Duanmu WS, Cao L, Chen JY, Ge HF, Hu R, Feng H: Ischemic postconditioning protects against ischemic brain injury by up-regulation of acid-sensing ion channel 2a. Neural Regen Res 11: 641–645, 2016

28) Burda J, Danielisová V, Némethová M, et al.: Delayed postconditioning initiates additive mechanism necessary for survival of selectively vulnerable neurons after transient ischemia in rat brain. Cell Mol Neurobiol 26: 1141–1151, 2006

29) Zhou C, Tu J, Zhang Q, et al.: Delayed ischemic postconditioning protects hippocampal CA1 neurons by preserving mitochondrial integrity via Akt/GSK3β signaling. Neurochem Int 59: 749–758, 2011

30) Lehotský J, Burda J, Danielisová V, Gottlieb M, Kaplán P, Saniová B: Ischemic tolerance: the mechanisms of neuroprotective strategy. Anat Rec (Hoboken) 292: 2002–212, 2009

31) Miller BA, Perez RS, Shah AR, Gonzales ER, Park TS, Gidday JM: Cerebral protection by hypoxic preconditioning in a murine model of focal ischemia-reperfusion. Neuroreport 12: 1663–1669, 2001

32) Wada K, Miyazawa T, Nomura N, Tsuzuki N, Nawashiro H, Shima K: Preferential conditions for and possible mechanisms of induction of ischemic tolerance by repeated hyperbaric oxygenation in gerbil hippocampus. Neurosurgery 49: 160–166, 2001

33) Nishio S, Yunoki M, Chen ZF, Anzivino MJ, Lee KS: Ischemic tolerance in the rat neocortex following hypothermic preconditioning. J Neurosurg 93: 845–851, 2000

34) Yunoki M, Nishio S, Ukita N, Anzivino MJ, Lee KS: Hypothermic preconditioning induces rapid tolerance to focal ischemic injury in the rat. Exp Neurol 181: 291–300, 2003

35) Zhang P, Abraham VS, Kraft KR, Rabchevsky AG, Scheff SW, Swain JA: Hyperthermic preconditioning protects against spinal cord ischemic injury. Ann Thorac Surg 70: 1490–1495, 2000

36) Xu H, Aibiki M, Nagoya J: Neuroprotective effects of hyperthermic preconditioning on infarcted volume after middle cerebral artery occlusion in rats: role of adenosine receptors. Crit Care Med 30: 1126–1130, 2002

37) Kakinohana M, Harada H, Mishima Y, Kano T, Sugahara K: Neuroprotective effect of epidural electrical stimulation against ischemic spinal cord injury in rats: electrical preconditioning. Anesthesiology 103: 84–92, 2005

38) Tasaki K, Ruetzler CA, Ohtsuki T, Martin D, Nawashiro H, Hallenbeck JM: Lipopolysaccharide pre-treatment induces resistance against subsequent focal cerebral ischemic damage in spontaneously hypertensive rats. Brain Res 748: 267–270, 1997

39) Toyoda T, Kassell NF, Lee KS: Induction of tolerance against ischemia/reperfusion injury in the rat brain by preconditioning with the endotoxin analog diphosphoryl lipid A. J Neurosurg 92: 435–441, 2000

40) Kuroiwa T, Yamada I, Endo S, Nakamata Y, Ito U: 3-Nitropropionic acid preconditioning ameliorates delayed neurological deterioration and infarction after transient focal cerebral ischemia in gerbils. Neurosci Lett 283: 145–148, 2000

41) Kobayashi S, Harris VA, Welsh FA: Spreading depression induces tolerance of cortical neurons to ischemia in rat brain. J Cereb Blood Flow Metab 15: 721–727, 1995

42) Gniel HM, Martin RL: Cortical spreading depression-induced preconditioning in mouse neocortex is lamina specific. J Neurophysiol 109: 2923–2936, 2013

43) Dong H, Ji X, Wang D, Ren Y, Wang S, Song J: Effect of morphine preconditioning on neuronal apoptosis following cerebral ischemia/reperfusion injury. Neural Regen Res 5: 1144–1149, 2010

44) Prass K, Ruscher K, Karsch M, et al.: Desferrioxamine induces delayed tolerance against cerebral ischemia in vivo and in vitro. J Cereb Blood Flow Metab 22: 520–525, 2002

45) Dong H, Xiong L, Zhu Z, Chen S, Hou L, Sakabe T: Preconditioning with hyperbaric oxygen and hypoxia induces tolerance against spinal cord ischemia in rabbits. Anesthesiology 96: 907–912, 2002

46) Xiong L, Zheng Y, Wu M, et al.: Preconditioning with isoflurane produces dose-dependent neuroprotection via activation of adenosine triphosphate-regulated potassium channels after focal cerebral ischemia in rats. Anesth Analg 96: 233–237, 2003

47) Ma D, Hossain M, Pettet GK, et al.: Xenon preconditioning reduces brain damage from neonatal asphyxia in rats. J Cereb Blood Flow Metab 26: 199–208, 2006

Neurol Med Chir (Tokyo) 57, November, 2017
48) Codaccioni JL, Velly LJ, Moubarak C, Bruder NJ, Pisano PS, Guillet BA: Sevoflurane preconditioning against focal cerebral ischemia: inhibition of apoptosis in the face of transient improvement of neurological outcome. *Anesthesiology* 110: 1271–1278, 2009
49) Zhang Y, Zhang FG, Meng C, et al.: Inhibition of sevoflurane postconditioning against cerebral ischemia reperfusion-induced oxidative injury in rats. *Molecules* 17: 341–354, 2011
50) Sang H, Cao L, Qiu P, et al.: Isoflurane produces delayed preconditioning against spinal cord ischemia injury via release of free radicals in rabbits. *Anesthesiology* 105: 953–960, 2006
51) Park HP, Jeon YT, Hwang JW, et al.: Isoflurane preconditioning protects motor neurons from spinal cord ischemia: Its dose-response effects and activation of mitochondrial adenosine triphosphate-dependent potassium channel. *Neurosci Lett* 387: 90–94, 2005
52) Ding Q, Wang Q, Deng J, et al.: Sevoflurane preconditioning induces rapid ischemic tolerance against spinal cord ischemia/reperfusion through activation of extracellular signal-regulated kinase in rabbits. *Anesth Analg* 109: 1263–1272, 2009
53) Yang YW, Lu JK, Qing M, et al.: Post-conditioning by xenon reduces ischemia-reperfusion injury of the spinal cord in rats. *Acta Anaesthesiol Scand* 56: 1325–1331, 2012
54) Zhao HG, Li WB, Li QJ, et al.: Limb ischemic preconditioning attenuates apoptosis of pyramidal neurons in the CA1 hippocampus induced by cerebral ischemia-reperfusion in rats. *Sheng Li Xue Bao* 56: 407–412, 2004.
55) Ren C, Gao X, Steinberg GK, Zhao H: Limb remote-preconditioning protects against focal ischemia in rats and contradicts the dogma of therapeutic time window for preconditioning. *Neuroscience* 151: 1099–1103, 2008
56) Ren C, Yan Z, Wei D, Gao X, Chen X, Zhao H: Limb remote ischemic postconditioning protects against focal ischemia in rats. *Brain Res* 1288: 88–94, 2009
57) Dong HL, Zhang Y, Su BX, et al.: Limb remote ischemic preconditioning protects the spinal cord from ischemia-reperfusion injury: A newly identified nonneuronal but reactive oxygen species dependent pathway. *Anesthesiology* 112: 881–891, 2010
58) Wang S, Li H, He N, et al.: Impact of remote ischaemic preconditioning on major clinical outcomes in patients undergoing cardiovascular surgery: A meta-analysis with trial sequential analysis of 32 randomised controlled trials. *Int J Cardiol* 227: 882–891, 2017
59) King N, Dieberg G, Smart NA: Remote ischaemic pre-conditioning does not affect clinical outcomes following coronary artery bypass grafting. A systematic review and meta-analysis. *Clinical Trials and Regulatory Science in Cardiology* 17: 1–8, 2017
60) Healy DA, Boyle E, McCartan D, et al.: A multicenter pilot randomized controlled trial of remote ischemic preconditioning in major vascular surgery. Preconditioning Shields Against Vascular Events In Surgery (Preconditioning Saves) trial group. *Vasc Endovascular Surg* 49: 220–227, 2015
61) Walsh SR, Nouraei SA, Tang TY, Sadat U, Carpenter RH, Gaunt ME: Remote ischemic preconditioning for cerebral and cardiac protection during carotid endarterectomy: results from a pilot randomized clinical trial. *Vasc Endovascular Surg* 44, 434–439, 2010
62) Moncayo J, de Freitas GR, Bogousslavsky J, Altieri M, van Melle G: Do transient ischemic attacks have a neuroprotective effect? *Neurology* 54: 2089–2094, 2000
63) Wegener S, Gottschalk B, Jovanovic V, et al.; MRI in Acute Stroke Study Group of the German Competence Network Stroke: Transient ischemic attacks before ischemic stroke: Preconditioning the human brain? A multicenter magnetic resonance imaging study. *Stroke* 35: 616–621, 2004.
64) Meng R, Asmro K, Meng L, et al.: Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. *Neurology* 7918: 1853–1861, 2012
65) Hu S, Dong HL, Li YZ, et al.: Effects of remote ischemic preconditioning on biochemical markers and neurologic outcomes in patients undergoing elective cervical decompression surgery: a prospective randomized controlled trial. *J Neurosurg* *Anesthesiol* 22: 46–52, 2010
66) Jensen HA, Loukogeorgakis S, Yannopoulos F, et al.: Remote ischemic preconditioning protects the brain against injury after hypothermic circulatory arrest. *Circulation* 123: 714–721, 2011
67) Connolly M, Bilgin-Freiert A, Ellingson B, et al.: Peripheral vascular disease as remote ischemic preconditioning, for acute stroke. *Clin Neurol Neurosurg* 115: 2124–2129, 2013
68) Hougaard KD, Hjort N, Zeidler D, et al.: Remote ischemic preconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke. *Stroke* 45: 159–167, 2014
69) Weih M, Kallenberg K, Bergk A, et al.: Attenuated stroke severity after prodromal TIA: a role for ischemic tolerance in the brain? *Stroke* 30: 1851–1854, 1999
70) Tüllü S, Mulino M, Pinggera D, et al.: Remote ischemic preconditioning in the prevention of ischemic brain damage during intracranial aneurysm treatment (RIPAT): study protocol for a randomized controlled trial. *Trials* 16: 594, 2015
71) Koch S, Gonzalez N: Preconditioning the human brain: proving the principle in subarachnoid hemorrhage. *Stroke* 44: 1748–1753, 2013
72) Ostrowski RP, Zhang JH: Preconditioning for SAH. In Gidday JM, Perez-Pinzon MA, Zhang JH (eds): Translational Neuroprotection by Pre- and Postconditioning, Springer Series in Translational Stroke Research. New York, Springer, 2013. pp. 291–308

73) Gonzalez NR, Hamilton R, Bilgin-Freiert A, et al.: Cerebral hemodynamic and metabolic effects of remote ischemic preconditioning in patients with subarachnoid hemorrhage. Acta Neurochir Suppl 115: 193–198, 2013

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