Paradigms and mechanisms of inhalational anesthetics mediated neuroprotection against cerebral ischemic stroke

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Abstract

Cerebral ischemic stroke is a leading cause of serious long-term disability and cognitive dysfunction. The high mortality and disability of cerebral ischemic stroke is urging the health providers, including anesthesiologists and other perioperative professioners, to seek effective protective strategies, which are extremely limited, especially for those perioperative patients. Intriguingly, several commonly used inhalational anesthetics are recently suggested to possess neuroprotective effects against cerebral ischemia. This review introduces multiple paradigms of inhalational anesthetic treatments that have been investigated in the setting of cerebral ischemia, such as preconditioning, proconditioning and postconditioning with a variety of inhalational anesthetics. The pleiotropic mechanisms underlying these inhalational anesthetics-afforded neuroprotection against stroke are also discussed in detail, including the common pathways shared by most of the inhalational anesthetic paradigms, such as anti-excitotoxicity, anti-apoptosis and anti-inflammation. There are also distinct mechanisms involved in specific paradigms, such as preserving blood brain barrier integrity, regulating cerebral blood flow and catecholamine release. The ready availability of these inhalational anesthetics bedside and renders them a potentially translatable stroke therapy attracting great efforts for understanding of the underlying mechanisms.

Key words: inhalational anesthetics; cerebral ischemia; preconditioning; proconditioning; postconditioning, neuroprotection, sevoflurane, isoflurane

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Introduction

Stroke, also known as cerebral vascular event, is one of the world's leading causes of mortality and morbidity, especially in the aged population (Donnan et al., 2008; Zhou et al., 2014). There are mainly two pathological types of stroke: ischemic and hemorrhagic (Chen et al., 2014b; Harris et al., 2014; Liu et al., 2014a; Hafez et al., 2015), among which ischemic stroke accounts for about 80% (Thrift et al., 2001; Khanna et al., 2014). Recent clinical studies suggest that neurosurgical procedures, as well as endovascular and cardiovascular surgery (such as carotid endarterectomy, intracranial aneurysm resection, deep hypothermia aortic

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repair) are associated with high risk of perioperative cerebral ischemia/reperfusion injury (Arrowsmith et al., 2000; Kelley, 2001), which may cause irreversible damage to patients' postoperative neurological function (Liu et al., 2014b; Hill et al., 2015). The catastrophic consequence and high risk of cerebral ischemic stroke make it a huge concern for anesthesiologists and perioperative care providers (Lapchak, 2015). The mechanisms of cerebral ischemic injury are complex, possibly involving energy metabolism disorder (Lioutas et al., 2015; Yu et al., 2015), oxygen free radical injury (Bozkurt et al., 2014; Hu et al., 2014; Aras et al., 2015; Zheng et al., 2015), calcium overload (O'Bryant et al., 2014; Pignataro et al., 2014), excitotoxicity (Baxter et al., 2014; Ruan et al., 2014; Song and Yu, 2014), inflammatory reaction (An et al., 2014; Zhou et al., 2014; Petrone et al., 2015; Rossi, 2015; Waje-Andreassen et al., 2015) and apoptosis (Li et al., 2014c; Liu et al., 2014c; Yan et al., 2015). In the recent three decades, an increasing number of studies support the idea that various pharmaceutical agents can provide organ protection (Zhu et al., 2014; dela Pena and Borlongan, 2015; Kandadai et al., 2015; Soliman et al., 2015; Wang et al., 2015) including inhalational anesthetics, which exhibit protective profiles in major organs, such as the heart, brain, lung and liver (Schumacher et al., 2014; Vargas-Martinez et al., 2014; Ferreira et al., 2015; Lourenco et al., 2015; Ohno et al., 2015; Waterford et al., 2015). Moreover, pre-, pro-, and postconditioning by isoflurane or sevoflurane have all been demonstrated to significantly reduce cerebral infarct size and improve recovery of neurological function after cerebral ischemia (McBride et al., 2015). As for the underlying protective mechanism, a great effort has been made to uncover the ambiguous mechanisms and remarkable progress that has been achieved in this field (Deng et al., 2014). The pursuit of further understanding of the mechanism underlying the inhalational anesthetics conferred neuroprotection against cerebral ischemia may potentially move its clinical translation forward and shed new light on the discovery of novel therapeutic targets.

Neuroprotection Paradigms of Inhalational Anesthetics–Preconditioning, Proconditioning and Postconditioning

Inhalational anesthetics can provide neuroprotective effect against brain ischemia by three treatment paradigms according to the timing of intervention: preconditioning, proconditioning and postconditioning. Preconditioning is a process in which a relatively small amount of damage or chemical/pharmacological agent is administered prior to the ischemic insult (Shah and Aizenman, 2014; Stetler et al., 2014). With preconditioning treatment, the ischemic tolerance to the predictable ischemic injury of the brain is increased through a series of mechanisms (Keep et al., 2014). Treatment of inhalational anesthetics during the cerebral ischemic period is termed as proconditioning (Wu et al., 2014). Postconditioning, however, is applied after cerebral ischemic event has developed (Liu et al., 2014c; Khan et al., 2015).

Pre- and postconditioning of isoflurane exhibit neuroprotection consistently but proconditioning remains controversy

A growing number of studies have demonstrated the protective effect of isoflurane against ischemic brain damage both in rodents and *in vitro* (Bickler et al., 2005; Shah and Aizenman, 2014). The preconditioning paradigms differ a lot among different studies. Animals exposed to 1.2% or 2% isoflurane for 1 hour for 5 consecutive days (Sun et al., 2015; Tong et al., 2015), 1.5% isoflurane for 30 minutes (Li et al., 2013) or 1% isoflurane for 4 hours (Zhu et al., 2010) before middle cerebral artery occlusion (MCAO) were all shown to exhibit significantly alleviated neurological deficits and reduced infarct volume. Consistent with the *in vivo* studies, pretreatment with isoflurane 24 hours prior to oxygen glucose deprivation (OGD) injury in primary cortical neurons cultured cells preserved neuronal activity and reduced lactate dehydrogenase (LDH) release (Kapinya et al., 2002; Kaneko et al., 2005).

In a rat MCAO model, postconditioning significantly decreased neurobehavioral deficit scores and infarct volume (Li et al., 2014b). Additionally, isoflurane postconditioning decreased the numbers of PI-positive cells 24 hours after reperfusion compared with the ischemia/reperfusion group (Wang et al., 2016). In cultured human neuron-like cells, isoflurane postconditioning also showed protection against the OGD insult. In terms of the paradigm of isoflurane postconditioning, postconditioning with 1.5%, 2% and 3.0% isoflurane for 1 hour since reperfusion has all been demonstrated as effective in previous animal studies (Lin et al., 2011). Post-treatment with 2% isoflurane for 30 minutes immediately after the 15-minute OGD dose-dependently has been shown to reverse the OGD-induced decrease of 2,3,5-triphenyltetrazolium chloride (TTC) conversion and to improve neurologic outcome after brain ischemia (Lee et al., 2008).

Although the protection of isoflurane pre- and postconditioning against cerebral ischemic stroke has been well documented by many studies, the effectiveness of isoflurane protreatment is still uncertain due to conflicting evidences. Little neuroprotective effect of isoflurane on focal or global cerebral ischemia was observed on the tissue damage and neurological function. In some studies, even worsening effect was detected. For example, isoflurane at

lower concentrations could enact quicker brain protection afterinjury (Lee et al., 2008). Using cultured neurons or rat brain sections, it was suggested that isoflurane proconditioning provided protection against ischemic or other forms of neuronal damage (Lee et al., 2008). Isoflurane proconditioning in rat cerebellum and hippocampal slices decreased neuronal apoptosis at 5 to 14 days after OGD (Robert et al., 2000; Liniger et al., 2001; Breandan et al., 2002; Li et al., 2002). The protective effect of isoflurane was demonstrated to be dose-dependent (Nasu et al., 2006). High concentrations of isoflurane were more likely to attenuate OGD-induced neurotoxicity in rat cortical striatum slices (Toner et al., 2002). Thus, the exact impact of isoflurane proconditioning on ischemic brain injury still merits further investigation.

Divergent effect of sevoflurane pre-, post- and proconditioning on cerebral ischemic injury

As a new inhalational anesthetic that is gaining popularity in clinical anesthesia practice, sevoflurane is increasingly studied in the research of anesthetic treatment against cerebral ischemia. Multiple paradigms of sevoflurane treatment have been proposed.

Preconditioning with the single inhalation of sevoflurane enabled to protect animals from cerebral ischemic insults, while repeated preconditioning of sevoflurane also provided neuroprotection against focal or global brain damage induced by ischemia/reperfusion in short period (3 days) after ischemia (Wang et al., 2011; Wang, 2016). *In vitro* studies consistently reveals the protection of sevoflurane preconditioning (Zheng and Zuo, 2005), as evidenced by attenuated OGD injury and increased the number of surviving neurons in hippocampal slices (Kehl et al., 2004; Wang et al., 2007a, b), and dose-dependently reduced neuronal apoptosis in primary cultured cortical neurons (Wise-Faberowski et al., 2001).

Sevoflurane postconditioning also yields protection against cerebral ischemia consistently. Postconditioning with sevoflurane significantly decreased apoptotic cell counts at 3 days (Kim et al., 2016) and preserved the CA1 neuron histology and reduced necrotic or apoptotic cells at 7 days after global cerebral ischemia in rats (Seo et al., 2013). In this study, the postconditioning paradigms ranged from single treatment of 10 minutes after transient global ischemia to two repeats of 5 minutes treatment of 2.5% sevoflurane and a subsequent washout time of 10 minutes after ischemia (Seo et al., 2013). *In vitro* experiments demonstrated that postconditioning with sevoflurane decreased the release of LDH and reduced OGD injuries of human neuroblastoma cell line at the early phase of reperfusion (Lin et al., 2011). It also attenuated ischemic injury of the neurons in the CA1 region of rat hippocampus after OGD and reperfusion (Peng et al., 2011).

Sevoflurane preconditioning is somehow comparable to sevoflurane anesthesia in surgical patients. In addition to its anesthetic effect, sevoflurane treatment also shows protection in OGD-induced rat brain slices (Toner et al., 2001). However, *in vivo* studies investigating sevoflurane preconditioning in cerebral ischemic animals models are still lacking. With a number of advantages over isoflurane, sevoflurane is widely used in clinical anesthesia nowadays. Considering the large number of surgical patients receiving sevoflurane anesthesia, it would be intriguing to know whether sevoflurane treatment can confer neuroprotection against cerebral ischemia.

Desflurane preconditioning is potentially neuroprotective

Desflurane is a highly fluorinated methyl ethyl ether used in clinical anesthesia. It is gaining popularity because of its extremely low blood-gas solubility which allows fast induction and fast emergence while used in general anesthesia (Shan et al., 2015). Although studies on neuroprotective effect of desflurane preconditioning, postconditioning and proconditioning in cerebral ischemia are still limited, studies in cerebral ischemic related animal models, such as circulatory arrest or cardiopulmonary bypass, suggest the potential neuroprotective effect of desflurane preconditioning. The neuroprotective effect of desflurane has been demonstrated in focal cerebral ischemia in rats and also in newborn pigs under deep hypothermic circulatory arrest (Haelewyn et al., 2003; Tsai et al., 2004). In neonatal rats with incomplete cerebral ischemia and low-flow cardiopulmonary bypass, neurologic function was improved with desflurane anesthesia (Kurth et al., 2001). Desflurane postconditioning was suggested as protective in an *in vitro* study showing that LDH release at 1 hour after OGD was reduced by desflurane postconditioning in the human neuroblastoma cell line (Lin et al., 2011). Considering the increasing popularity of desflurane in clinical anesthesia, it would be intriguing to investigate the protective effect of pre-, post- and preconditioning of desflurane in cerebral ischemic injury.

Other inhalational anesthetics

Besides the above mentioned anesthetic agents, there are also some other inhalational anesthetics that have been shown to be protective in cerebral ischemia. Halothane, as a classic volatile anesthetic, was demonstrated to attenuate cerebral ischemic injury both in cats and rodents 16 hours to 7 days after ischemia and hypoxia (Zausinger et al., 2002; Haelewyn et al., 2003). Xenon is a colorless, dense, odorless noble gas that has recently been used as an inhalation anesthetic in clinical practice. Several studies have shown that xenon has a beneficial effect on rodent cardiopulmonary

bypass and other brain injury models of neuronal damage and neurological damage (Kitano et al., 2007). Post-MCAO administration of xenon showed reduced cortical damage in animal models (David et al., 2003; Abraini et al., 2005). However, there's also conflicting evidence showing that xenon exacerbates ischemic brain damage and neurological deterioration in the model of rat cardiopulmonary bypass combined with cerebral air embolization (Jungwirth et al., 2006).

Taken together, a great body of evidence has confirmed the protection of pre- and postconditioning of the two commonly used inhalational anesthetics, isoflurane and sevoflurane against cerebral ischemic injury, but the impact of proconditioning of these two anesthetics still remains ambiguous. The impact of desflurane on cerebral ischemic injury is also uncertain and thus warrants further investigation.

Pleiotropic Mechanisms Involved in Inhalational Anesthetic-Induced Neuroprotection

Modulating excitotoxicity glutamate release plays a role in pre-, pro-, and postconditioning of inhalational anesthetic treatments

Preconditioning of inhalational anesthetics inhibits glutamate release

Some studies have shown that prior to cerebral ischemia, the administration of inhalational anesthetic produces neuroprotective effects by inhibiting glutamate release (Bickler et al., 1995). In a rat global cerebral ischemia model, sevoflurane enabled reduction of the concentration of glutamate in the brain. Isoflurane preconditioning decreased Purkinje neuronal damage induced by glutamate excitotoxicity in the rat cerebellar slice. Moreover, the use of a specific glutamate transporter inhibitor during OGD reversed this effect (Zheng and Zuo, 2003, 2005). Thus the impact of glutamate release of preconditioning of isoflurane may contribute to its protection against cerebral ischemia.

Proconditioning of inhalational anesthetics inhibits glutamate release and antagonizes the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors

After cerebral ischemia, there is increased glutamate release, which activates AMPA and NMDA receptors, thus cell excitotoxicity and neuronal injury ensues (Lai et al., 2014; Leng et al., 2014). Inhalational anesthetics can inhibit the glutamate release trigger by cerebral ischemia. It was demonstrated that sevoflurane reduced the glutamate concentration in the ratcortex and hippocampus after global cerebral ischemia (Engelhard et al., 2003). Administration of halothane, isoflurane, sevoflurane and enflurane reduced the release of glutamate in the rat brain slices exposed to hypoxia, chemical hypoxia and OGD (Bickler et al., 1995; Eilers and Bickler, 1996; Toner et al., 2001).

In addition to the inhibition on the glutamate release, inhalational anesthetics also antagonize the AMPA and NMDA receptors, which can be activated by glutamate after ischemic injury. Studies have found that in both the cerebellar and the mouse cortex brain slices, administration of isoflurane attenuated excitotoxicity both during and after administration of AMPA (Li et al., 2002). Halothane attenuates AMPA receptor-mediated excitatory responses more profoundly compared with xenon, cyclopropane, enflurane, isoflurane and desflurane (Pirot et al., 1995) Besides the AMPA receptor, halothane and sevoflurane inhibited the NMDA receptor (Solt et al., 2006). Isoflurane and sevoflurane antagonized NMDA excitotoxicity and NMDA-gated currents in hippocampal slices, cultured cortical neurons, and neuron-glial mixed cell cultures (Beirne et al., 1998; Harada et al., 1999; Kimbro et al., 2000; Kudo et al., 2001; Ming et al., 2002). Thus, attenuating the excitotoxicity by inhibiting the AMPA and NMDA signaling plays a role in the inhalational anesthetic-conferred neuroprotection (**Figure 1**).

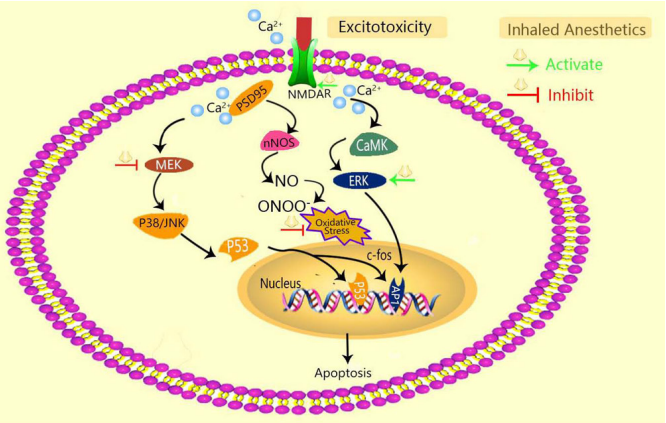

Figure 1: Modulation of cell excitotoxicity plays a role in the neuroprotection of inhalational anesthetics against cerebral ischemia.
Note: Inhalational anesthetics attenuate the cell cytotoxicity induced by cerebral ischemia *via* inhibiting the glutamate release and activation of AMPA and NMDA receptors. It thus increases the activity of nNOS and the concentration of Ca^{2+}, activating the MAPK-ERK pathway. Consequently, it decreases oxidative stress injury and promotes neuron survival after ischemia. On the other hand, it opens and promotes the KATP activity in mitochondria, which reduces cerebral cell death. AMPA: α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA: N-methyl-D-aspartate; NMDAR: N-methyl-D-aspartate receptor; nNOS: neuronal nitric oxide synthase; MAPK-ERK: mitogen-activated protein kinases-extracellular regulated protein kinase; CaMK: calcium/calmodulin-dependent protein kinase; PSD95: postsynaptic density protein 95; MEK: mitogen-activated extracellular signal-related kinase kinase.

Postconditioning of inhalational anesthetics both modulates the excitatory and inhibitory amino acids

Postconditioning with sevoflurane significantly increased excitatory amino acids (aspartic acid, glutamic acid) and decreased inhibitory amino acids (GABA) in a concentration-dependent manner and consequently ameliorated OGD-reperfusion injury in the rat hippocampus (Peng et al., 2011). Current evidence in this regard is relatively limited and further studies are needed to confirm the protection of inhalational anesthetic postconditioning.

Signaling pathways involved in the anti-apoptotic effect of inhalational anesthetics in cerebral ischemia

Preconditioning induced anti-apoptosis

Apoptosis is one of the important cell death signaling following cerebral ischemia (Hosaka and Hoh, 2014) and anti-apoptosis is one of the pivotal common mechanisms underlying the inhalational anesthetic-afforded neuroprotection against ischemic injury, including pre-, pro- and postconditioning.

It was demonstrated that halothane and isoflurane intervention before OGD could attenuate neuronal apoptosis in a dose-dependent manner in rat cortical neurons (Wise-Faberowski et al., 2001). Isoflurane-induced ischemic tolerance is mediated by the activation of p38 mitogen-activated protein kinases (MAPK). Because p38MAPK inhibitor can reverse the preconditioning effect of isoflurane in rat permanent MCAO model, the activation of p38MAPK can mimic the pretreatment of isoflurane (Zheng and Zuo, 2004). Pre-intervention with sevoflurane markedly decreased activation of caspase3 and apoptosis inducing factor, and robustly suppressed pro-apoptotic protein and increased anti-apoptotic protein in Bcl-2 super family in the rat MCAO model (Zhu et al., 2016). Furthermore, preconditioning with sevoflurane attenuated the activation of JNK and p53 pathway (Wen et al., 2016). The above evidence suggest that suppression of apoptotic responses may contribute to the neuroprotection of inhalational anesthetic preconditioning against focal ischemic brain injury (Wang et al., 2016) (**Figure 2**).

Proconditioning of inhalational anesthetics attenuates neuronal apoptosis by modulating Bax expression

Mounting evidence suggest that inhalational anesthetics are able to modulate the neuronal cell apoptosis thus exert its neuroprotective effect (Leung et al., 2014). It reduces the expression of apoptosis-inducing protein Bax at 4 hours after ischemia, while p53, Bcl-2 and Mdm-2 show no changes (Engelhard et al., 2004). Isoflurane attenuates neuronal apoptosis 24 hours after focal cerebral ischemia in rats (Kawaguchi et al., 2004).

Postconditioning of inhalational anesthetics modulates the post-stroke apoptosis in multiple pathways

Several signalings have been suggested in the anti-apoptotic effect of inhalational anesthetic postconditioning, including JAK-STAT pathway, Bcl-2 and glycogen synthase kinase (GSK) 3β pathway (**Figure 2**). Sevoflurane postconditioning reduced apoptosis by increasing phosphorylated Janus kinase (p-JAK) and phosphorylated signal transducer and activator of transcription (p-STAT) expression after transient global ischemia in rats, and the Janus kinase- signal transducer and activator of transcription (JAK-STAT) inhibitor, AG490 reversed the beneficial anti-apoptotic effects of sevoflurane postconditioning, suggesting that the JAK-STAT pathway may be involved in the anti-apoptotic mechanism of sevoflurane postconditioning (Kim et al., 2016). Postconditioning with 2.5% sevoflurane in rats alleviated ischemic damage against global cerebral ischemic insults by suppressing Bax and and increasing Bcl2 expression.(Seo et al., 2013). Isoflurane postconditioning also robustly increased the phosphorylation of GSK3β at Ser9 in SH-SY5Y cells 1 hour after the OGD. In addition, GSK3β inhibitors reduced OGD and triggered LDH release. The combination of GSK3β inhibitors and isoflurane postconditioning did not present a greater protective effect than isoflurane post-conditioning alone (Lin et al., 2011).

Taken together, anti-apoptosis represents one of the critical common mechanisms underlying the inhalational anesthetic conferred neuroprotection against cerebral ischemia. Compared to pre- and postconditioning, studies in proconditioning of inhalational anesthetics are relatively limited. Further mechanistic investigations in this regard are warranted.

Targeting inflammation by the inhalational anesthetics in cerebral ischemic injury

Suppressing inflammation and affecting the related molecular signaling pathway by preconditioning of inhalational anesthetics

Our previous study found that pretreatment with sevoflurane inhibited the activation of microglial cells in the early stage of cerebral ischemic injury, decreased the expression of inflammatory factors such as cyclooxygenase-2 (COX-2), interleukin 6 (IL-6), interleukin-1α (IL-1α), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and inducible nitric oxide synthase (iNOS), and suppressed the activation of its upstream transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), leading to significantly improved neurological function after ischemic brain injury in rats (Wang et al., 2011). We further confirmed that the role of sevoflurane was directly mediated by its anti-inflammatory effects, but not from other pathways to reduce secondary injury after the brain injury (Wang et al., 2011) (**Figure 3**).

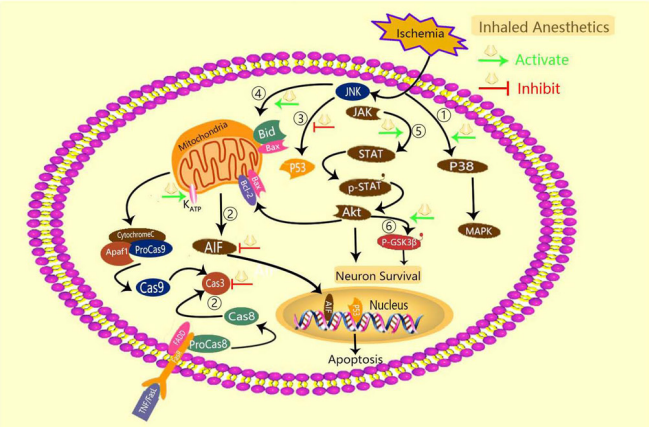

Figure 2: The anti-apoptotic signaling pathways are involved in the neuroprotection of inhalational anesthetics against cerebral ischemia.
Note: Inhalational anesthetics exerts anti-apoptotic effects through several classical apoptotic pathways: 1) isoflurane preconditioning activates the p38-MAPK pathway, which subsequently inhibits cell apoptosis and promotes cell survival; 2) sevoflurane preconditioning attenuates neuronal apoptosis by decreasing the activation of caspase 3 and AIF, and thus robustly suppresses pro-apoptotic protein and increases anti-apoptotic protein in Bcl-2 super family; 3) sevoflurane preconditioning attenuates the activation of JNK and p53 pathway; 4) inhalational anesthetic proconditioning reduces the expression of Bax, which can induce neuronal apoptosis after ischemia; 5) sevoflurane postconditioning increases JAK-STAT signaling, which is an anti-apoptotic pathway; 6) isoflurane postconditioning increases the phosphorylation of GSK3β to exert the anti-apoptotic effect. MAPK: Mitogen-activated protein kinases; AIF: apoptosis inducing factor; JNK: c-Jun N-terminal kinases; (p-) STAT: (phosphorylated) signal transducer and activator of transcription; (p-) GSK3β: (phosphorylated) glycogen synthase kinase3β; JAK: Janus kinase; Cas9: caspase9.

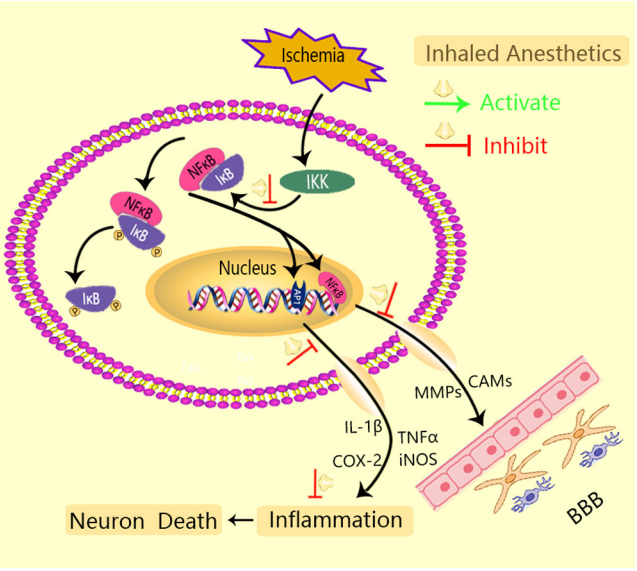

Figure 3: Neuroprotection of inhalational anesthetics in cerebral ischemia bytargeting inflammation.
Note: Inhalational anesthetics have profound impact on the inflammatory responses induced by cerebral ischemia. Inhalational anesthetic preconditioning inhibits the activation of microglia and suppresses the activation of NFκB, thus decreasing the expression of a variety of inflammatory cytokines, such as COX-2, IL-6, IL-1α, IL-1β and TNFα. The preservation of BBB also contributes to the anti-inflammatory responses of inhalational anesthetics by reducing the levels of MMPs and CAMs. COX-2: Cyclooxygenase-2; IL-6: interleukin 6; IL-1α: interleukin-1α; IL-1β: interleukin-1β; TNFα: tumor necrosis factor-α; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; MMPs: matrix metalloproteinases; CAMs: cell adhesion molecules; BBB: blood-brain-barrier; iNOS: inducible nitric oxide synthase; IkB: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; IKK: IkB kinase.

iNOS has been suggested to play a critical role in the protective effect of inhalational anesthetics preconditioning (Tanaka et al., 2004). Furthermore, the neuroprotection of isoflurane against ischemic neuronal injury was dependent on iNOS (Kapinya et al., 2002; Zheng and Zuo, 2004). However, this may not be the case in halothane preconditioning, because using nonspecific nitric oxide synthase (NOS) inhibitors at 2 hours after transient focal cerebral ischemia in rats did not alter the pretreatment effect of halothane (Drummond et al., 2005).

Inhalational anesthetic postconditioning protects against ischemic brain injury via inhibiting inflammatory cytokines

Isoflurane postconditioning led to greater accumulation of hypoxia-inducible factors (HIF-1α) and iNOS gene expression, inducing augment of HIF-1α transcriptional activity and co-localization of HIF-1α and iNOS and thus propagating the inflammatory response. Accordingly, silencing of HIF-1α attenuated the accumulation of iNOS and the protective effects of isoflurane post-conditioning in the primary cortical neuron cultures. These findings suggested the involvement of HIF-1α in the attenuation of iNOS during tolerance against cerebral ischemia caused by isoflurane postconditioning (Fang Li et al., 2012). Serum levels of proinflammatory cytokines including TNF-α and IL-1β were higher in the control group when compared with the sevoflurane groups 2 hours after ischemia (Seo et al., 2013). These data suggest postconditioning with sevoflurane exerts the neuroprotective effect by suppressing the inflammation triggered by primary ischemic insults and induced secondary neuronal damage.

Taken together, the anti-inflammatory effect of pre- and postconditioning of inhalational anesthetics has been identified by the above mentioned evidences. However, the evidence regarding the anti-inflammation of proconditioning of inhalational anesthetics is still lacking, which is an important question that deserves further investigation (**Figure 3**).

Regulating of the ion channels by the inhalational anesthetics in the protection against cerebral ischemia

Preconditioning of inhalational anesthetics regulates calcium and potassium channels in their protection against cerebral ischemia

Ca^{2+} concentration in the brain plays an important role in NMDA receptor activation (Raval et al., 2003; Song and Yu,

2014), opening of voltage-gated Ca^{2+} channels (Bickler and Fahlman, 2004; Shenoda, 2015). Isoflurane preconditioning may regulate the calcium-binding protein calmodulin and activate the MAPK-extracellular regulated protein kinase (ERK) pathway by increasing intracellular calcium concentration in hippocampal neurons in rat OGD model (Bickler et al., 2005). Likewise, isoflurane preconditioning was shown to maintain the calcium/calmodulin-dependent protein kinase II activity in a dog cardiac arrest model (Blanck et al., 2000).

In addition to the regulation on calcium channels and calcium-binding proteins, inhalational anesthetics preconditioning also activates ATP-sensitive potassium channel (KATP). KATP exists in the brain and brain circulation, there are two types: sarcolemma and mitochondria (McCully and Levitsky, 2003; Chen et al., 2014a). These channels, especially the mitochondrial KATP, play important roles in reducing or delaying cerebral cell death (Ockaili et al., 1999). Inhalational anesthetics preconditioning provides neuroprotection against ischemic brain tissue by opening and activating KATP (Obal et al., 2005). The neuroprotection can be reversed by either glibenclamide or 5-hydroxydecanoic acid, two mitochondrial KATP blockers (Xiong et al., 2003; Kehl et al.; Kaneko et al., 2005; Wang et al., 2007b). Isoflurane also activates KATP by activating adenosine A1 receptors and thus provides neuroprotection against focal cerebral ischemic in rats (Liu et al., 2006) (**Figure 1**).

Involvement of adenosine 5'-triphosphate-sensitive potassium channel in the postconditioning of inhalational anesthetic conferred protection

Lee et al. (2008) demonstrated application of 2% isoflurane for 30 minutes started at 10 minutes after the OGD reduced the OGD-decreased TTC conversion. The presence of glibenclamide, a general adenosine 5'-triphosphate-sensitive potassium channel blocker, or 5-hydroxydecanoic acid, a mitochondrial adenosine 5'-triphosphate-sensitive potassium channel blocker, during the application of 2% isoflurane abolished the isoflurane preservation of TTC conversion, suggesting the adenosine 5'-triphosphate-sensitive potassium channel plays an important role in the isoflurane postconditioning afforded protection against neuronal injury in the OGD model.

Distinct mechanisms identified respectively in pre-, pro- or postconditioning of inhalational anesthetics affording neuroprotection against cerebral ischemia

Sevoflurane preconditioning preserves the integrity of blood-brain-barrier (BBB) after cerebral ischemic injury

Both ischemic and hemorrhagic strokes are associated with BBB disruption which results in vascular edema and blood extravasation. The expression and activation of matrix metalloproteinases (MMPs) has been repetitively suggested as a critical player in BBB disruption (Merali et al., 2015; Reuter et al., 2015). Sevoflurane preconditioning administered 24 hours before transient MCAO protected BBB by suppression of cell adhesion molecules (CAMs) and MMPs after ischemia. Evans blue extravasation and electron microscopy results both showed that sevoflurane pretreatment markedly improved BBB integrity and neurological outcomes after ischemia. Sevoflurane preconditioning upregulated intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), MMP-2, MMP-9 thus robustly suppressed ischemia-induced degradation of occludins (Yu et al., 2011) (**Figure 3**).

The regulation of cerebral blood flow and brain metabolic rate of inhalational anesthetics in ischemic brain injury

The administration of inhalational anesthetic has profound impact on the cerebral blood flow (Fumagalli et al., 2014). Inhalational anesthetics has been found to dose-dependently increase the CBF in humans (Schlunzen et al., 2006), experimentally in rabbits (Scheller et al., 1986) and monkeys (Li et al., 2014a). Likewise, the impact of inhalational anesthetics on brain metabolic rate (CMR) may contribute to their neuroprotection against ischemic injury. Almost all inhalational anesthetics can reduce the metabolic rate when the energy supply to the brain is reduced in the case of cerebral ischemia (Warner, 2004). It was suggested that the CMR reduction might be associated with the attenuation of brain injury by inhalational anesthetics. Isoflurane exhibited stronger reduction in CMR as compared to halothane (Verhaegen et al., 1992), and meanwhile the isoflurane treated animals developed less severe brain damage following global cerebral ischemia (Nellgard et al., 2000). However, other studies also showed that there were differences among CMR, brain histology and neurological functions in cerebral ischemic models, which could possibly be attributed to the impact of inhalational anesthetics on brain energy (high-energy phosphate) storage (Sano et al., 1992). Cerebral ischemic dogs treated with inhalational isoflurane had higher storage of ATP and creatine phosphate compared to the controls. Thus the lactate accumulation was also reduced, suggesting the neuroprotective effect of isoflurane is partially mediated by inhibition of brain metabolism (Newberg and Michenfelder, 1983). The recovery of ATP and intracellular pH in halothane anesthesia occured significantly later than that in sevoflurane and isoflurane anesthesia in the rat model of ischemia/reperfusion injury (Nakajima et al., 1997). Therefore, distinct impact of inhalational anesthetics on brain energy storage might contribute to the distinct protection of these anesthetics on the neuroprotection against ischemia.

Inhalational anesthetics reduces catecholamine release both in the brain and circulation after cerebral ischemia

The acute release of catecholamine after cerebral ischemia exacerbates the progression of brain injury (Bhardwaj et al., 2001). Isoflurane can reduce the release of dopamine, epinephrine, and phenylephrine in brain tissue and also the level of epinephrine and phenylephrine in the circulation. Sevoflurane can reduce the release of dopamine, epinephrine and phenylephrine in the brain tissue and the release of norepinephrine in the circulation, but has no effect on adrenaline. Desflurane and N_2O reduced the release of norepinephrine and epinephrine in the circulation (Miura et al., 1999; Engelhard et al., 2003). Therefore, reducing catecholamine release may represent one of the underlying mechanisms of inhalational anesthetic afforded protection against cerebral ischemia.

Conclusions

In summary, the efforts on the inhalational anesthetic treatment research in the recent years have led to a better understanding in their neuroprotection against cerebral ischemia. Multiple paradigms have been demonstrated to be protective and potentially translatable into clinical stroke therapy. The mechanisms underlying different paradigms of inhalational anesthetic treatments may converge in some common pathways, such as anti-excitotoxicity, anti-inflammation, anti-apoptosis and et al. While some of the mechanisms are so far exclusively identified in specific paradigms, such as the blood flow and brain metabolism regulation and catecholamine regulation. All above new findings have reshaped our understanding of inhalational anesthetic treatment in cerebral ischemic stroke. There are still a great amount of unknowns which merit further investigation. In addition to the bench side researches, large-scale clinical studies would be of great interest to determine the neuroprotective effects of inhalational anesthetics in cerebral ischemic stroke patients.

Author contributions

HW and PL contributed equally to this work. HW and YG designed this paper. HW, PL, NX, MC, and LZ wrote the paper. PL, WY, and YG reviewed this paper.

Conflicts of interest

None declared.

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