Current research progress of isoflurane in cerebral ischemia/reperfusion injury: a narrative review

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Abstract

Cerebral ischemia/reperfusion injury is an important factor leading to poor prognosis in ischemic stroke patients. Therefore, it is particularly important to find effective remedial measures to promote the health of patients to return to society. Isoflurane is a safe and reliable anesthetic gas with a long history of clinical application. In recent years, its protection function to human body has been widely recognized, and nowadays isoflurane for cerebral protection has been widely studied, and the stable effect of isoflurane has satisfied many researchers. Basic studies have shown that isoflurane's protection of brain tissue after ischemia/reperfusion involves a variety of signaling pathways and effector molecules. Even though many signaling pathways have been described, more and more studies focus on exploring their mechanisms of action, in order to provide strong evidence for clinical application. This could prompt the introduction of isoflurane therapy to clinical patients as soon as possible. In this paper, several confirmed signaling pathways will be reviewed to find possible strategies for clinical treatment.

Key words: angiogenesis; cerebral ischemia/reperfusion injury; isoflurane; middle cerebral artery occlusion; vascular endothelial growth factor

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Introduction

With the aging of the population, stroke has a tendency to become the first disease threatening human health, the disability rate and mortality rate of stroke is extremely high, but there is no good treatment.[1] Stroke currently accounts for 55% of the incidence in neuroscience and is the leading cause of physical disability and impairment of consciousness.[2,3] It poses serious health threats and economic pressures for people around the world.[4] At present, most elderly people suffer from insufficient blood supply to the brain due to vascular problems, resulting in ischemic necrosis of the brain tissue, and the incidence of ischemic stroke accounts for the vast majority.[5] Cerebral ischemia can lead to defects such as inflammation, reperfusion injury, and dysfunction. At present, thrombolysis and endovascular intervention are the most effective strategies at the acute phase of ischemic stroke.[6] At present, most views believe that after thrombolytic therapy or thrombectomy, the blood flow of the brain tissue will be restored and the brain tissue will be damaged again.[7] Therefore, a series of problems caused by blood flow recovery in blood vessels need to be solved urgently.[8] Cerebrovascular accident is a terrible event with severe sequelae, which has a tendency to become a major threat to the health of people around the world. Four fifths strokes occur in all patients with ischemic stroke.[9] Because neurons are non-regenerative cells, the necrosis of nerve tissue caused by ischemia and hypoxia is an irreversible event, making stroke the world's leading cause of death and disability.[10] The main treatment of the acute phase of ischemic stroke is recanalization, not only removing toxic metabolites but also replenishing nutrients and oxygen.[11]

Cerebral ischemia/reperfusion (I/R) injury refers to the reflow of blood leads to damage and inflammation to brain. These cascading injuries leave the central nervous system vulnerable, eventually leads to the occurrence of serious adverse events.[12] After cerebral ischemia, cerebral ischemia hypoxia resulting in a large number of brain cell death and neural function defect,[13] primary injury caused by ischemia has been unable to recover, and the secondary brain injury caused by restored blood flow, resulting in the release of various neurotoxic molecules, the expansion of inflammation, cell electrolyte accumulation, brain disorder environment. All of these factors interact to result in a cascade of brain tissue damage, a breakdown of the blood-brain barrier, a weakened nerve function, and ultimately a poor overall prognosis for patients.[14] All injuries cause edema of brain tissue and injury of the extracellular matrix, which may lead to ischemia and rebleeding. Therefore, it is considered that the recovery of microcirculation is the key to save the partial biological function of patients.[15] Existing study has shown that the degree of microcirculation recovery after cerebral ischemia is positively correlated with the overall survival rate of patients.[16] After cerebral ischemia, the body starts the vascular regeneration system. The newly generated capillaries can reduce the blood flow in the low perfusion area, providing a good microenvironment for the repair of nerve cells, attempting to restore and replace the nerve function which has been damaged. However, the body's self-angiogenesis is often insufficient, so we need to look for relevant treatments from this perspective.[17]

Isoflurane (ISO) is a kind of commonly gaseous anesthetic that is often used for sedation and anesthesia in neurosurgery.[18] As the widely used inhalation anesthetic, ISO has been widely

recognized for its safety and neuroprotective effects. In short, short-term and low-concentration ISO therapy has a protective effect on ischemic brain tissue.[19] After cerebral ischemia, the disorder of the central nervous system becomes more and more unpredictable, so it is urgent to find a quick and effective treatment method. As a treatment method, ISO has obvious advantages and is now attracting more and more attention from the majority of scholars. However, the mechanism of brain protection in ISO is unclear.[20] It is worth noting that researches on signal transduction pathways in the central nervous system after ectopic location are limited and worthy of further study. We searched the recent studies on ISO in I/R injury from PubMed to provide potential targets for current treatment.

Existing Signaling Pathways and Brief Mechanism

Sonic hedgehog/Gli signaling pathway

After I/R injury, angiogenesis is the key factor leading to good recovery. Angiogenesis requires the synergistic action of many cytokines. Angiogenesis is a synergistic function of multiple cytokines and signal transduction pathways, among which transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF) and CD34 are the most critical ones.[21] Modern medical research shows that sonic hedgehog (Shh)/Gli signaling pathway plays an important role in almost every process of mammalian growth and development.[22] ISO can regulate the production of VEGF and CD34 through Shh/Gli signaling pathway.[21] In other words, ISO treatment can promote the formation of new blood vessels after I/R, and further improve the microvascular network of the central nervous system. After ISO treatment, infarction area of rats was reduced and neurological function score was improved. However, there was no difference in injury changes of rats compared with the control group after Shh inhibitor was given, indicating that ISO can achieve cerebral protection through Shh/Gli pathway[21] (**Figure 1**).

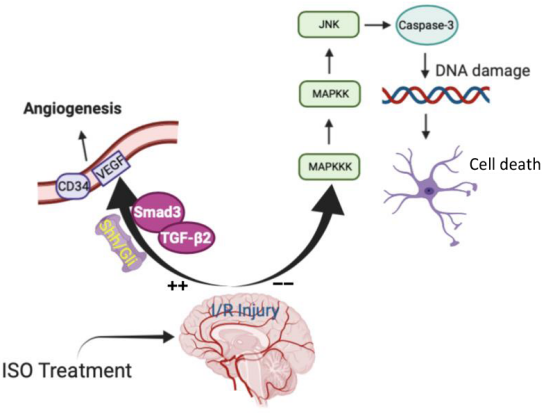

Figure 1: Mechanism of ISO in cerebral I/R injury.
Note: After ISO treatment, Shh/Gli and TGF-β2/Smad3 pathway can promote the production of cytokines such as VEGF and CD34, promoting angiogenesis, and restoring blood supply and oxygen to the brain. On the other side, ISO could reduce the death of cells in anoxic area and protect brain tissue by inhibiting MAPKKK, MAPKK, JNK. I/R: Ischemia/reperfusion; ISO: isoflurane; JNK: c-Jun N-terminal kinase; MAPKK: mitogen-activated protein kinase kinase; MAPKKK: mitogen activated protein kinase kinase kinase; Shh: sonic hedgehog; Smad3: mothers against decapentaplegic homolog 3; TGF-β2: transforming growth factor-β2; VEGF: vascular endothelial growth factor.

TGF-β2/mothers against decapentaplegic homolog 3 signaling pathway

ISO was shown to up-regulate TGF-β2 expression in the hippocampus and cortex after I/R, while phosphorylated mothers against decapentaplegic homolog 3 (Smad-3) expression was also increased. These results suggest that ISO treatment is likely to activate the TGF-β2/Smad3 signaling pathway.[23] TGF-β2 has been recognized as a necessary protective molecule of the central nervous system, and experiment has confirmed the protective effect of TGF-β2.[24] The TGF-β2/Smad3 signaling pathway participates in and regulates the expression of VEGF and CD34, promoting the repair of cerebral microvascular network after I/R. In summary, ISO can promote the formation of new blood vessels through T cell receptor signaling pathway and reduce brain injury. In addition, other studies have shown that the expression of TGF-β2 protein in neurons of animals with chronic ischemia can be continuously increased, which is helpful for the body to fight against transient ischemic attack[25] (**Figure 1**).

Wnt/β-catenin signaling pathway

The importance of Wnt/β-catenin signaling pathway in central nervous system genesis, development, differentiation has been widely recognized.[26] After I/R injury, the expression of Wnt3a, β-catenin and cyclin D1 proteins were inhibited, related proteins in the pathway were activated and increased after ISO treatment. Meanwhile, after activation of this pathway, unphosphorylated β-catenin entered the nucleus to regulate the expression of related molecules such as VEGF and apoptosis related proteins.[27]

c-Jun N-terminal kinase signaling pathway

Mitogen activated protein kinase kinase kinase is activated after cerebral I/R injury, then mitogen-activated protein kinase kinase is activated as well, finally the c-Jun N-terminal kinase (JNK) is included in the JNK signaling pathway is activated. The activated JNK has two main functions. First, JNK can up-regulate the expression of pro-apoptotic proteins and activate the apoptosis pathway of the death receptor.[28] Secondly, JNK regulates the activity of members of the Bcl-2 family through mitochondria-mediated apoptosis. These two pathways eventually activate caspase-3. Caspase-3 activated by these two pathways activates caspase-activated DNase, which cuts nuclear DNA repair enzyme poly(DP-ribose) polymerase, leading to irreversible nuclear DNA damage and ultimately apoptosis.[29] The experimental results showed that the phosphorylation level of JNK protein increased gradually after I/R injury, while 1.5% ISO post-treatment obviously reduced the effect. It was surprising that, at the level of 4.5% of the ISO post-adaptation group, it increased. After injection of JNK blocker SP600125, the brain I/R injury was significantly reduced. This result indicates that JNK signal is involved in the protective effect of ISO adaptation on brain I/R injury (**Table 1**).[30,31] JNK is an important signaling pathway in the downstream of TGF-β1. TGF-β1 inhibitor LY2157299 treatment distinctly enhanced JNK phosphorylation. No significant brain protective effect was observed after 1.5% ISO treatment. The expression levels of TGF-β1 and phosphorylated Smad2/3 significantly increased after JNK-specific inhibitor (SP600125)

Table 1: The effect of ISO postconditioning

Animal	Model	Intervention	Conclusion
Rat	Focal cerebral I/R injury	ISO was delivered with the vehicle air (30% O_2 and 70% medical air)	ISO promotes angiogenesis, reduces brain cell death after cerebral I/R, and improves recovery.[21]
Rat	Cerebral I/R injury	ISO (1.5%) was administered for 1 h after immediate reperfusion	ISO reduces infarct volume after cerebral I/R injury and minimizes the cell death.[23]
Rat	MCAO	Rats in ISO groups inhaled different concentrations of ISO (1.5%, 3.0%, and 4.5%) for 60 min	The results showed that 1.5% isoflurane postconditioning significantly reduced the cerebral infarct volumes and improved the neurobehavioral deficit scores.[30]
Mouse	BCCAO	ISO preconditioning (98% O_2 and 1.2% ISO) at a rate of 1 h/d for 5 d	ISO preconditioning significantly improved the TMS and reduced neuronal degeneration after cerebral I/R.[31]

Note: BCCAO: Bilateral common carotid artery occlusion; I/R: ischemia reperfusion; ISO: isoflurane; MCAO: middle cerebral artery occlusion; TMS: total motor score.

was applied. Cell death was reduced in 1.5% ISO treatment group, suggesting that TGF-β1 and JNK signaling pathways have adverse effects on the post-I/R brain tissue (**Figure 1**).

Notch signaling pathway

Notch signaling pathway is highly conserved and widely expressed in the animal kingdom. In terms of function, Notch plays an important role in cell self-renewal, individual growth and development as well as a series of physiological and pathological processes.[32] Notch is associated with differentiation, maturation, regeneration and functional maturation of intracranial cells in the central nervous system, and is closely related to neurodegenerative diseases.[33] Notch signaling pathway is actively involved in the dynamic changes of cell structure and nervous system function throughout its life cycle. By observing the changes of notch intracellular domain, notch-1 and split-1 expression enhancement factors, it was found that inhaling ISO can activate notch signaling pathway in advance and advance the peak value of Notch signal to 24 hours after reperfusion. The activation of Notch pathway is of great significance in reducing brain injury and cell death after I/R.[31]

Conclusions and Prospects

As an inhalational anesthetic gas, ISO can play an important role in the treatment of cerebral I/R injury. Existing studies have shown that these effects are safe and reliable with basic experimental support. Due to the high disability rate and mortality rate of cerebrovascular disease, it is urgent to find effective approaches. It can be predicted that the high therapeutic value of ISO will certainly enter the clinic for clinical treatment as soon as possible, which will greatly alleviate the current shortage of treatment approaches.

Author contributions
SJC were responsible for writing the manuscript. XQY and QX were responsible for its revision. HFL and GC were responsible for its drafting and revision. All the authors read and approved the final version of the manuscript for publication.
Conflicts of interest
None.

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