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Review Article

The Role of Emulsified Isoflurane in Multi-Organ Protection

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ABSTRACT

Aim of review: This review describes the multi-organ protective effects of emulsified isoflurane.

Method: This review examines the recent experimental researches involving emulsified isoflurane-induced preconditioning and postconditioning in multiple organs.

Recent findings: Emulsified isoflurane is a new formulation of isoflurane in lipid emulsion. It enables an intravenous, intraperitoneal injection or oral (rather than the traditional inhalation) route of administration for this anesthetic. Pharmacological preconditioning and postconditioning by using inhalation isoflurane have been demonstrated to be the protective strategies in clinical settings for the high risk patients with various organ dysfunctions. In recent years, there has been increased interest in exploring the protective effect of emulsified isoflurane in multiple organs including heart, brain, kidney, liver and lung, providing potential approaches translating these convincing experimental conditioning effects to clinical practice.

Summary: Emulsified isoflurane could exert strong organ-protective effects. With an understanding of its potential mechanisms, therapeutic approaches may be applied to the future organ-protective properties, transferring convincing experimental evidences into clinical therapies.

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Emulsified isoflurane, a newly developed formulation, combines isoflurane into a lipid emulsion, and can be given intravenously rather than as an inhalant commonly used in the traditional practice for this anesthetic (1, 2). Such a preparation facilitates the intravenous administration of isoflurane and eliminates the need for specific ventilatory circuits. In particular, it delivers anesthetic induction independent of pulmonary function. The evidences for the benefit of volatile anesthetics in multi-organ protection have been repeatedly shown in the recent literatures. Volatile anesthetics target the endothelium, thus, at even lower dose of intravenous administration, their emulsified formulation would clearly facilitate the use of halogenated ethers for organ protection, promoting their clinical advances during diagnostic and interventional procedures for high-risk patients. This review summarizes the role of emulsified isoflurane in different organ protection.

Cardioprotection

The first important report on the cardioprotective effect of emulsified isoflurane backdates to 2004 (3). The researchers found that pretreatment of emulsified

isoflurane protected hearts against infarction similar to ischemic preconditioning in rabbits. In that study, rabbits were treated with intralipid (vehicles for isoflurane) alone or with emulsified isoflurane (6.9%) for 30-minute followed by 30 minutes washout period. The hearts were then subjected to 30 minutes of coronary artery occlusion and 3 hours of reperfusion. Emulsified ethers reduced infarct size by approximately 50% while intralipid had no effect on infarction. Since then, pharmacological researches in different small and large animal species further clarified most of its cardioprotective feature (4). Using a classic preconditioning protocol, emulsified isoflurane was intravenously applied before an ischemia episode. In emulsified isoflurane treated group, better recovery of hemodynamics, less infarction size, accompanied by the suppression of apoptosis were found in rabbit (5, 6) or murine (7) models of ischemia and reperfusion (I/R) injury and myocardial ischemia (8). Inhibition of inflammatory responses including down-regulation of myocardial nuclear factor (NF)-κB and intercellular adhesion molecule-1 (ICAM-1) expression may contribute to the mechanism by which preconditioning with emulsified isoflurane protects against myocardial I/R injury (9-11).

Emulsified isoflurane with its preconditioning effects could be also added to St Thomas organ-preservation solutions. 8% emulsified isoflurane supplemented to cardioplegia solution enhanced cardiac protection and reduced CK-MB leakage and infarct size by 23% in a murine isolated heart ischemia reperfusion injury model (12). This beneficial effect was also found in lower dose of emulsified isoflurane at 1 mmol/L in the same model of I/R injury (13). A proposed "Micelles–lipid raft" model showed the mechanism of the emulsified halogenated ether-induced cardioprotection, which would be separated from its intralipid vehicle. However, high dose of emulsified isoflurane failed to protect hearts, possibly due to insufficient elimination of anesthetics from lung in isolated hearts without pulmonary circuits, resulting in an increasing susceptibility to the toxic effects caused by anesthetics accumulation. Consistently, Xu et al. (14) further tested the effects of different dosages of emulsified isoflurane when adding into cardioplegic solution and found that 1.68 mmol/L emulsified isoflurane could attenuate myocardial I/R injury in isolated rat hearts.

Either administering emulsified isoflurane before ischemia or at the onset of reperfusion would be capable of delivering sufficient cardioprotection. The application of emulsified isoflurane at the beginning of reperfusion for 30 minutes conferred strong postconditioning against myocardial I/R injury. It was found to limit infarct size, inhibit apoptosis, increase the expression of Bcl-2, decrease the expression of Bax and cleaved caspase-3, and enhance Bcl-2/Bax ratio (15). Using the same protocol, this research group further demonstrated that emulsified isoflurane limited I/R-induced infarction in a dose-dependent manner and the preservation of mitochondria function and metabolism was involved in its protective phenomenon (16). Similarly, using a protocol of intravenous infusion of emulsified isoflurane during the last 3 minutes of coronary artery occlusion and the first 5 minutes of reperfusion, a 33% reduction of infarct size was reported compared with the control group. In this study, the authors further proved that the protection may be mediated by the activation of JAK-STAT pathway (17). Emulsified isoflurane can preserve cardiac mitochondrial ultrastructure (18), however, the reactive oxygen species (ROS) scavenger can abolish its cardioprotection (19). With the use of glibenclamide, a nonselective adenosine-triphosphate-sensitive potassium (KATP) channel inhibitor, and 5-hydroxydecanoate (5-HD), a selective mitochondrial KATP channel inhibitor, a research group reported that mitochondrial KATP channel activation played a role in the protective effects of emulsified isoflurane postconditioning against myocardial I/R injury in rabbits (20).

Stepwisely, the functional study of emulsified isoflurane has been carried out in vitro, bringing out similar results as shown in vivo. Yang et al. (21) found that the best protective dose of emulsified isoflurane was 1.68 mmol/L in a hypoxia/reoxyenation injury model of cultured neonate rat cardiac myocytes and the beneficial effect of emulsified isoflurane may result from the maintenance of cardiac myocytes morphology (18) and the activation of KATP channel (22). They further showed that pretreatment with

emulsified isoflurane could prevent the leakage of cardiac damage markers as LDH, MDA, and SOD in serum as well as attenuate myocytes injury via activation of PI3K/Akt signal pathways (23) and inhibition of L-type calcium channel, thus reducing the overload of intracellular calcium (24). Meanwhile, emulsified isoflurane produced its anti-apoptotic effect by increasing Bcl-2/Bax ratio (25), lowering apoptotic rates and inhibiting Caspase-3 activities (26, 27) after hypoxia/reoxygenation in cultured myocardial cells of neonatal rats. Interestingly, a study on isolated rat Kupffer cells confirmed these findings by showing that emulsified isoflurane protected against hypoxia/reoxygenation- induced injury by reducing the concentration of ROS, tumor necrosis factor-alpha (TNF-α) and attenuating apoptosis (28).

Neuroprotection

Over the last decade, many investigators have studied the effects of emulsified isoflurane on regional or global ischemia or I/R injury in the brain, and the evidence is encouraging. Hippocampus cornu ammonis 3 pyramid neurons abnormalities were found in lidocaine-induced tonic-clonic seizures and the infusion of emulsified isoflurane could increase the convulsive threshold of lidocaine and preserve neurological function in rats (29). Using a right middle cerebral artery occlusion (MCAO) model, both postconditioning (30) and preconditioning (31) with 8% emulsified isoflurane were shown to have strong neuroprotection by reducing neurologic deficit scores and infarct size against focal cerebral ischemia-reperfusion injury in rats. Wang et al. (32) found that this preconditioning was dose-dependent and emulsified isoflurane can inhibit neuroapoptosis by lowering apoptotic index as well as increasing the expression of Bcl-2 protein and decreasing Bax, cytochrome C and caspase-3 protein expression (33). They further used LY294002, a PI3K inhibitor to block the pharmacological protective effect, suggesting that emulsified isoflurane can attenuate focal cerebral I/R injury induced neuronal-apoptosis in hippocampal CA1 region by activating PI3K/Akt related pathways (34). Besides, Erk activation was also involved in this protection phenomenon (35). In addition, studies also indicated that in hippocampus, emulsified isoflurane may target at adenosine A1 receptor to increase its expression (36) and in ischemia cortex and hippocampus, emulsified isoflurane can inhibit phosphorylated PSD95 (pPSD95) expression (37) and PAF receptor expression (38). Changes in all these above expression of receptors and molecules can lead to the beneficial effect conducted by emulsified anesthetics.

Kidney, Lung and Liver Protection

Emulsified isoflurane exerts strong protective effect against myocardial and cerebral I/R injury, using an infusion protocol similar to that used in cardioprotection studies (16), intravenous pretreatment with this anesthetic was also shown to protect kidneys against I/R injury by inhibiting systemic inflammatory responses (as reducing serum creatinine, blood urea nitrogen, cystatin c, TNF-α, and interleukin-6 levels) and improving renal antioxidative ability (39, 40). Lv et al. (41) used a hepatic I/R-induced lung injury model, allowing blood supply of the hepatic artery and portal vein to the left and the median liver lobes to be blocked for 90 minutes after 30 minutes washout period, followed by 240 minutes reperfusion, emulsified isoflurane preconditioning was found to reduce lung injury and inhibit the increase of myeloperoxidase (MPO) activity, TNF-α level, ICAM-1 expression and NF-κB translocation in the lung tissue, indicating that this new anesthetic may be applied for lung protection caused by hepatic surgery, transplantation or hemorrhagic shock. Another group of researchers further demonstrated that, using the hemorrhagic shock model, emulsified isoflurane preconditioning protected against liver and lung injury caused by massive surgical blood loss (42). They found that emulsified isoflurane enhanced rat survival after hemorrhagic shock and decreased the concentration or number of alanine aminotransferase and white blood cells in bronchoalveolar lavage fluid. It also reduced liver and lung apoptosis, decreased MDA and increased SOD activity in the liver and lung mitochondria, suggesting that the potential mechanisms involved in emulsified isoflurane induced organ protection is related to the inhibition of

apoptosis and improvement of antioxidation in mitochondria. Furthermore, emulsified isoflurane pretreatment can ameliorate LPS-induced acute lung injury or lung I/R injury (43) by reducing changes in the concentration of a series of antioxidant radicals or inflammatory molecules including SOD, MDA, MPO, TNF-α and IL-6 (44). The protective effect of pretreatment with emulsified isoflurane was also tested on different models of liver injury. The results are promising. Emulsified isoflurane was shown to protect liver against liver I/R injury by lowering serum concentrations of alanine transaminase, aspartate transaminase, MDA, while increasing SOD, and this effect may be mediated by Kupffer cells (45). Using metallothionein gene deficient mice, Ye et al. (46) showed that metallothionein may be involved in emulsified isoflurane-induced liver protection against I/R injury (Table 1).

Mechanism of Organ Protection

Many studies have evaluated the mechanisms of anesthetics-induced organ protection, among which the cardiac protection gains the subject of intense investigation. Many characteristics of preconditioning and postconditioning with volatile anaesthetics are similar to those of ischaemic preconditioning or postconditioning, including the activation of KATP channels, proteases, nitric oxide (NO), et al. The experimental results either in animals or human cells have been considered together to ascertain volatile anesthetics and their emulsified reagent as the relevant effectors of preconditioning and postconditioning in multiple signaling pathways. Nonetheless, accurate researches of their differences have not yet been fully identified. Of note, emulsified isoflurane also shares the common mechanisms with inhaled isoflurane except for a recent proposed model of "Micelles–lipid raft" by E Lucchinetti et al. indicating the differences between the function sites of the cardiac protective effect. People may question that how could emulsified isoflurane exert their organ protective actions while separating protection signaling from anesthetic effects? In this model, the authors speculated that there were large interfaces between ether-loaded micelles and lipid rafts, which may serve as ether-releasing reservoirs and form a cellular microenvironment promoting protection signaling (47). Similarly, emulsified isoflurane (5, 7) and isoflurane (4) both can induce an acute "memory phase" (>30 minutes), allowing the protective effect get started. Meanwhile, emulsified isofurane (16) and isoflurane (4) both have a dose-dependent protection in an in vivo rat model of regional ischaemia, in which both regents significantly reduced infarct size.

Multiple signaling pathways have been involved as mediators of anesthetics-induced organ-protection ligands, as guanine nucleotide-binding proteins (G proteins) ligand and protease (Figure 1). Anesthetics preconditioning and postconditioning both stimulated activation of various receptors and free radicals, followed by transmitting signaling molecules to the coupled G proteins, therefore, resulting in protein kinase activation and ADP phosphorylation, and eventually enhancing KATP channel opening. Isoflurane can activate ROS production, which in turn activates G proteins and mitoKATP channels. Although contradictory reports showed reversed results of the inhibitory effect of G protein by halothane (48), enough evidence has proved that G protein–coupled inwardly rectifying potassium channels were inhibited by volatile anesthetics including halothane, isoflurane and enflurane (49). Although enormous experiments have confirmed the importance of KATP channels in anesthetics-induced organ protection with the use of KATP channel blockers, glibenclamide and 5-HD, further researches are strongly demanded to elucidate their precise roles in the signal transduction pathways. Volatile anesthetics were shown to activate mitoKATP channels (50), whereas, other results indicated that volatile anesthetics targeted at mitoKATP channel via PKC-coupled signaling pathways instead of directly openning mitoKATP channels (51). Therefore, it may be considered that both channel types may equally contribute to multi-organ protection by volatile anesthetics. As an intracellular mediator, protein kinases play a vital role in organ protection upstream of mitoKATP channel, selectively priming the opening of mitoKATP channels through triggering multiple PKC-coupled signaling pathways. It was reported that isoflurane in-

Table 1. Studies of Emulsified Isoflurane on Multiorgan Protection.

Models	Animals	Endpoint	Organ Protection	Dosages	Reference
Myocardial I/R injury	rabbit	infarct size	decrease myocardial infarction	3.5 ml/kg/hour	3
Myocardial I/R injury	rabbit	infarct size	decrease myocardial infarction	emulsified isoflurane to an end-tidal concentration of 0.64%	5, 6
Myocardial I/R injury	rat	infarct size	decrease infarction, improve hemodynamics	4 ml/kg/hour	7, 8, 10, 11, 15-17
Myocardial I/R injury	rabbit	infarct size	decrease myocardial infarction	emulsified isoflurane to an end-tidal concentration of 1.28%	9
Myocardial I/R injury	rat	infarct size	decrease myocardial infarction	0.65 ml of 8% emulsified isoflurane in St Thomas solution	12
Myocardial I/R injury	rat	infarct size	decrease myocardial infarction	5 mmol/L	13
I/R and hypoxia/ reoxygenation injury	rat and myocytes	infarct size	decrease infarction, apoptosis	0.28, 0.56, 1.12, 1.68, 2.24, 2.80 mmol/L	14, 21-27
Hypoxia/reoxygenation injury	rat myocytes	myocardial ultrastructures	preserve myocardial ultrastructures	0.84, 1.68, 2.52 mmol/L	18, 19
Myocardial I/R injury	rat	infarct size	decrease myocardial infarction	1.0 MAC	20
Hypoxia/reoxygenation-induced injury	rat kupffer cells	apoptosis	decrease apoptosis and ROS, TNF-α production	0.05%, 0.1% or 0.2% emulsified isoflurane	28
Lidocaine-induced convulsions	rat	neurological function	preserve neurological function	0.032 ml/kg	29
Focal cerebral ischemia-reperfusion	rat	infarct size	decrease brain infarction	3.5, 7.0, 10.5 ml/kg	30
Focal cerebral ischemia-reperfusion	rat	infarct size	decrease brain infarction	17 ml/kg/hour	31
Focal cerebral ischemia-reperfusion	rat	infarct size	decrease brain infarction	3.5 ml/kg	32
Focal cerebral ischemia-reperfusion	rat	infarct size	decrease brain infarction	7.5 ml/kg	33
Focal cerebral ischemia-reperfusion	rat	neuronal apoptosis	decrease focal cerebral neuronal apoptosis	10.5 ml/kg	34-38
Renal I/R injury	rat	renal inflammation	decrease renal inflammation	1, 2, 4 ml/kg	40
Hepatic I/R-induced lung injury	rat	MPO expression	decrease MPO expression	8 ml/kg	41
Hemorrhagic Shock	rat	survival rate	decrease death rate and protect lung and liver	4 ml/kg	42
LPS induced lung injury	rat	lung W/D ratio, MPO expression	ameliorate lung damage	4 ml/kg/hour , 5 ml/kg/hour	43, 44
Hypoxia/reoxygenation-induced injury	rat	apoptosis	inhibit apoptosis	0.1% or 0.2% emulsified isoflurane	45
Liver I/R injury	rat	ALT, AST concentration	decrease ALT, AST	6 ml/kg/hour	46

duced the translocation of PKC-δ and PKC-ε to sarcolemmal and mitochondrial membranes while selective translocation of PKC-δ to mitochondria and nuclei and PKC-ε to sarcolemmal membranes (52). Protein tyrosine kinases (PTKs) and mitogen- activated protein kinases (MAPKs) also shared the importance of alternative signaling elements of the signal transduction during this protective phenomenon as Src PTK and ERK1/2, subfamily of MAPK, were both proved to have participated in the aesthetics-induced organ protection (53, 54).

Studies have also indicated the critical role of NO, as a unique bioactive signaling messenger

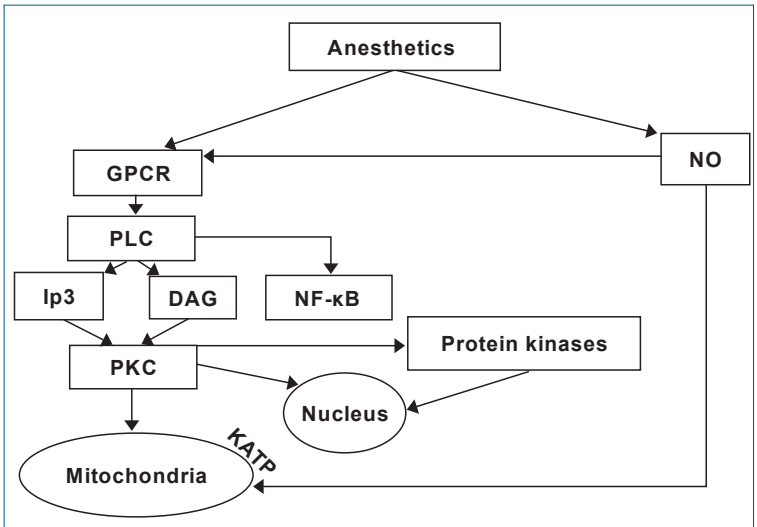

Figure 1. Multiple Signal Molecules and Protein Kinases Involved in Anesthetic-Induced Organ-Protection.

in target cells. NO directly activated mitoKATP, successfully brought the cardioprotective effects in preconditioning or postconditioning in coronary endothelial cells and rat ventricular myocytes, supporting its position of a trigger or subsequently as the mediator in organ protection (55). Apoptosis, a highly regulated, controlled process whereby the cell commits suicide without inducing an inflammatory response, plays an important role in various types of injury and is controlled by the complex interaction of numerous pro-survival and pro-death signals including Bcl-2, Bax or Caspase families. Using a selective Bcl-2 inhibitor (HA14-1), the protection was abolished from hypoxia-reoxygenation injury produced by isoflurane (56). Similarly, emulsified isoflurane also protected organs by inhibiting apoptosis in various disease models (7, 8, 15). Taking together, these data provided further evidence that anesthetics either in vapor or emulsified form, favorably modulated apoptosis and this beneficial effect eventually led to massive organ protective effects. Moreover, the role of mitochondria was also confirmed in the process of protection, as evidence has shown that both volatile isoflurane or emulsified isoflurane protected hearts against ischemic injury via preserving mitochondrial function. Furthermore, emulsified isoflurane also ameliorated mitochondrial bioenergetic properties as well as inhibiting mPTP opening (16).

Emulsified isoflurane has been shown in abundant experimental studies to produce multi-organ protection. The beneficial effect of emulsified isoflurane in clinical settings is less robust and further large randomized controlled trials are required to elucidate this question. It may have the possible potency of improving clinical outcomes and health economics following general or regional surgeries, and reducing intensive care and hospital stay.

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