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INVITED REVIEW ARTICLE

Cellular signaling pathways and molecular mechanisms involving inhalational anesthetics-induced organoprotection

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Abstract Inhalational anesthetics-induced organoprotection has received much research interest and has been consistently demonstrated in different models of organ damage, in particular, ischemia–reperfusion injury, which features prominently in the perioperative period and in cardiovascular events. The cellular mechanisms accountable for effective organoprotection over heart, brain, kidneys, and other vital organs have been elucidated in turn in the past two decades, including receptor stimulations, second-messenger signal relay and amplification, end-effector activation, and transcriptional modification. This review summarizes the signaling pathways and the molecular participants in inhalational anesthetics-mediated organ protection published in the current literature, comparing and contrasting the 'preconditioning' and 'postconditioning' phenomena, and the similarities and differences in mechanisms between organs. The salubrious effects of inhalational anesthetics on vital organs, if reproducible in human subjects in clinical settings, would be of exceptional clinical importance, but clinical studies with better design and execution are prerequisites for valid conclusions to be made. Xenon as the emerging inhalational anesthetic, and its organoprotective efficacy, mechanism, and relative advantages over other anesthetics, are also discussed.

Keywords Organoprotection · Inhalational anesthetics · Signaling pathway · Molecular mechanism · Conditioning

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Introduction

Ischemia–reperfusion (I/R) injury of vital organs in varying degrees of severity occurs during invasive surgical procedures where there is abrupt cessation and reestablishment of blood flow. Perioperative I/R injury can influence postoperative outcomes and cause even life-threatening complications. Myocardial infarct, dysrhythmia, perioperative stroke, and cognitive/psychological impairment are some of the most common sequelae consequent to I/R injury from cardiovascular and neurosurgical procedures. Perioperative inhalational anesthetic agents can induce inherent adaptive mechanisms to protect the susceptible tissues from the upcoming I/R episode. Inhalational anesthetics given before ischemia or upon reoxygenation, termed anesthetic preconditioning (APC) and anesthetic postconditioning (APostC), have been demonstrated to confer exceptional cardioprotection and neuroprotection in preclinical models. Inhalational anesthetics exhibit practical advantages over other 'stressor' paradigms as the result of their relatively safe administration and rapid onset, as opposed to the brief application of ischemia that would prove difficult and perilous to execute in clinical circumstances, especially for high-risk patients in whom any additional ischemic injury could adversely affect postoperative morbidity and even mortality. Inhalational

anesthetics need not to be confined to surgical procedures if they could prevent I/R injury and confer organoprotection at subanesthesia dosage, and when administrated post hoc. Such applications would be invaluable for patients suffering from cardiovascular pathological conditions when the onset of ischemia could not be anticipated.

The molecular mechanisms involved in inhalational anesthetics-mediated organoprotection have attracted much research interest, and within the past two decades much progress has been made in delineating the subcellular events following inhalational anesthetics exposure. This review aims to explore the established cardioprotective and neuroprotective signaling pathways triggered by inhalational anesthetics, as well as commenting on mechanisms involved in protection of other organs, e.g., kidneys.

Cardiac preconditioning

It has now become apparent that cardiac preconditioning by inhalational anesthetics encompasses two chronological phases. In APC an early/classic preconditioned state occurs immediately after anesthetic exposure, conferring intense cardioprotection against 'reversible' stunning and 'irreversible' infarction after a few hours of sustained ischemia. Key signaling events in early cardiac APC are illustrated in Fig. 1.

More recently, a delayed 'second-window' phase of prolonged cardioprotection occurring 12–24 h after anesthetic administration has been demonstrated in animal studies; it is marked by de novo protein synthesis through transcriptional and translational upregulation. This phase

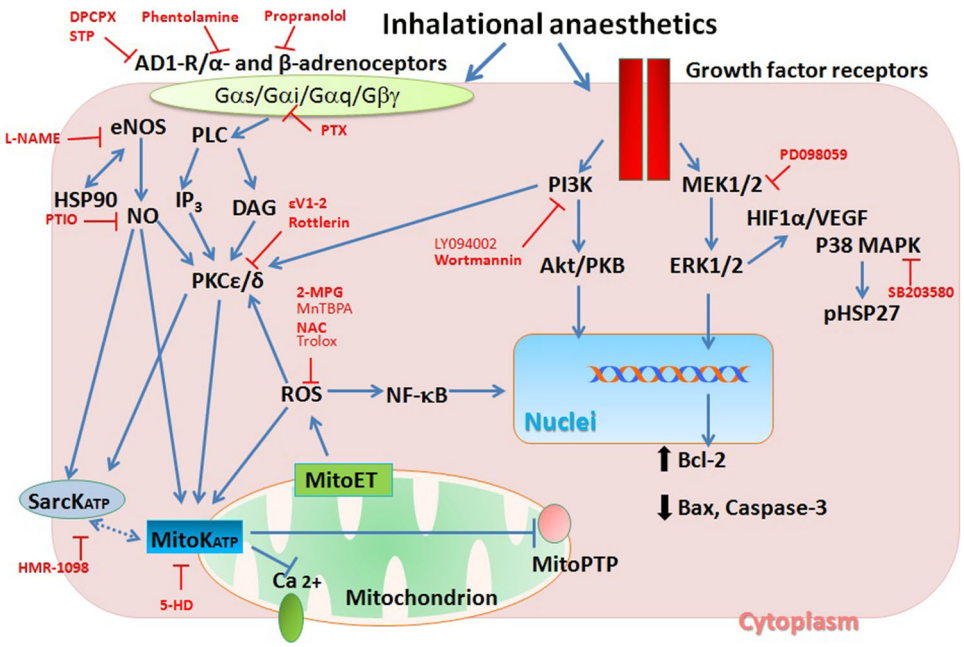

Fig. 1 The signaling events illustrated summarize current knowledge regarding the mechanisms of inhalational anesthetics-mediated cardiac preconditioning. Pharmacological inhibitors employed to study the involvement of each of the signalling components are highlighted in *red*. *Dashed line* depicts the potential 'crosstalk' between mitochondrial and sarcolemmal K_{ATP} channels. Much uncertainty exists with respect to the mitochondrial bioenergetics in cardiac anesthetic preconditioning (APC) that represent interesting research targets for future studies. *2-MPG N*-(2-mercapto propionyl)glycine; *5-HD* 5-hydroxydecanoate, selective blocker of mitoK$_{ATP}$ channels; *AD1-R* adenosine receptor subtype 1; *Akt/PKB* protein kinase B; *Bax* Bcl-associated X protein, proapoptosis protein; *Bcl-2* B-cell lymphoma 2, antiapoptosis protein; *DAG* diacylglycerol; *DPCPX* 8-cyclopentyl-1,3-dipropylxanthine (specific adenosine 1-receptor blocker); *eNOS* endothelial nitric oxide synthase; *ERK1/2 & p38MAPK (MAPK)* mitogen-activated protein kinase; *V1-2* PKCe specific inhibitor; *HIF-α* hypoxic inducible factor α; *HMR-1098* sodium salt of HMR-1883 (1-[5-[2-(5-chloro-*o*-anisamido)ethyl]-2-methoxyphenyl]-sulfonyl-3-methylthiourea, specific blocker of sarcK$_{ATP}$ channels; *HSP27* heat shock protein 27; *HSP90* heat shock protein 90; *IP$_3$* inositol triphosphate; *L-NAME* N^G-nitro-L-arginine methyl ester (eNOS inhibitor); *MEK1/2 (MAPKK)* mitogen-activated protein kinase kinase; *MitoET* mitoET chain (complex I and III); *mitoK$_{ATP}$* mitochondrial potassium (K^+) ATP channels; *mitoPTP* mitochondrial permeability transition pore; *MnTBPA* Mn(III)tetrakis(4-benzoic acid)porphyrine chloride; *NAC N*-acetylcysteine; *NFκB* nuclear factor kappa-light-chain-enhancer of activated B cells, protein complex that controls DNA transcription; phosphorylation of inhibitory component IkB (inhibitor of kappa B) by IKK (IkB kinase) frees p65/p50 subunits to migrate to nucleus to modulate gene transcriptions; *NO* nitric oxide; *PI3K* phosphoinositide 3-kinase; *PKC* protein kinase C, subtypes δ and ε; *PLC* phospholipase C; *PTIO* 2-(4-carboxyphenyl)-4,4′,5,5′-tetramethylimidazole-1-oxyl-3-oxide (nitric oxide scavenger); *PTX* pertussis toxin, Gai protein inhibitor; *ROS* reactive oxygen species; *Rottlerin* PKCδ specific inhibitor; *SarcK$_{ATP}$* sarcolemmal potassium (K+) ATP channels; *SPT* 8-sulfophenyl theophylline (nonspecific adenosine receptor blocker); *VEGF* vascular endothelial growth factor (color figure online)

contrasts to the rapid posttranslational modification and recruitment of signaling kinases of early APC [1].

Early anesthetic preconditioning

Receptors

Inhalational anesthetics-induced cardiac preconditioning is mediated in part by the activation of G protein-coupled receptors, especially those linked to inhibitory G proteins [2, 3]. Adenosine receptor, particularly adenosine type 1 receptor, was shown to initiate inhalational anesthetics-mediated cardioprotection in vivo, in vitro, and in human atrial myocytes [3–5]. Stimulation of α- and β-adrenoceptors was shown to trigger desflurane preconditioning in human atrial trabeculae, as coadministration of the respective antagonists phentolamine and propranolol abolished the postischemic contractile recovery [6]. δ-Opioid receptors, particularly the δ-1 subtype, have been shown to mediate ischemic preconditioning (IPC), and pharmacological preconditioning with δ-opioid receptor agonist DADLE [(D-Ala^2, D-Leu^5)-enkephalin] improved the post-IR force of contraction in human myocardium to a similar extent to IPC [7]. Morphine, a μ-receptor agonist with δ-agonist properties, significantly potentiated the preconditioning effect of isoflurane on rat myocardium. Pretreatment of opioid receptor antagonist naloxone abolished the reduction in infarct size by isoflurane or combined isoflurane/morphine preconditioning, suggesting that opioid receptor stimulation mediates the beneficial effects of inhalational APC [8].

Protein kinase C- and mitogen-activated protein kinase

The putative protein kinase C (PKC) activation pathway requires diacylglycerol as a cleavage product of PIP_2 by phospholipase C that relays APC stimuli from G protein-coupled receptors. Hydrolysis of PIP_2 also results in the production of IP3, which induces the release of Ca^{2+} from the sarcoplasmic reticulum into cytosol to facilitate PKC activation [9]. PI3K/PDK1-dependent activation of PKC has been reported in xenon preconditioning [10].

PKC plays an important role in anesthetic preconditioning, as is demonstrated in many studies. For example, halothane-induced cardioprotection in rabbits was aborted by administration of PKC inhibitor chelerythrine [11], and post-I/R recovery of canine myocardium stunning by isoflurane preconditioning was prevented by PKC inhibitor bisindolylmaleimide [12]. Pretreatment of chelerythrine before I/R also abolished the contractile recovery and the preserved energy state (ATP) by isoflurane preconditioning in isolated hearts [13]. PKCε is extensively implicated in preconditioning mechanisms, but whether it is the exclusive isoform mediating APC has been questioned by many studies [10, 14–16]. By using PKCδ- and PKCε-specific inhibitors rottlerin and PKC-εV1-2, Ludwig et al. underscored the importance of both isoforms in cardioprotection by isoflurane preconditioning in vivo, as coadministration of either inhibitor abrogated the infarct-limiting effect by Iso-PC [17]. PKCε phosphorylation and membrane translocation have also been reported in xenon preconditioning in vivo. The disparate isoform-specific PKC activation could be attributable to the use of different animal species, inhalational anesthetics, and experimental models (in vitro vs. in vivo), as well as variations in preconditioning protocols (frequency and duration). Remarkably, PKC activation in human myocardium has been reported in sevoflurane preconditioned patients undergoing coronary artery bypass graft surgery, detected as translocation of PKCδ to sarcolemma and PKCε to mitochondria, intercalated disks, and nuclei [18]. The use of different detection techniques, e.g., Western blot compared with immunohistochemistry, may account for the different subcellular distributions of PKC isoforms observed in various studies.

ERK1/2(p44/42MAPK) was shown to be crucial for isoflurane preconditioning in vitro [19] and desflurane preconditioning in vivo [20] as ERK1/2 inhibitor LY942002 abrogated the reduced myocardial injury/infarct; however, the two studies reported considerable discrepancy regarding whether ERK1/2 functions as a trigger or a mediator in APC and the temporal relationship between ERK1/2 and PKC. The early and PKC-'independent' ERK1/2 activation observed in Des-PC but not Iso-PC could be attributable to α-adrenergic receptor stimulation, i.e., different mode of actions between these anesthetics or potential mutual modulation between ERK1/2 and PKC in APC signaling. ERK1/2-dependent inductions of HIF-1α and angiogenic vascular endothelial growth factor (VEGF) have been reported in Iso-PC, an antihypoxic response to stimulate coronary collateral development in ischemic myocardium [21].

Phosphor activation of p38MAPK is critical to isoflurane and xenon preconditioning [22], and the cardioprotective mechanism downstream of p38MAPK activation was shown to involve phosphorylation and translocation of HSP27 to the actin network [23], which presumably modifies cytoskeletal structure to confer cardioprotection during I/R.

Other protein tyrosine kinases including Src also contribute to APC-mediated cardioprotection, as coadministration of general PTK inhibitor lavendustin A or Src-specific blocker PP1 opposed the effect of Iso-PC in vivo [17]. Concentration-dependent activation of different kinases has been speculated in Iso-PC, with lower isoflurane concentration favoring PKC signaling, whereas at

higher dosages alternative kinases were likely to mediate signal transduction [24]. It is equally probable that Iso-PC at higher concentrations induced a burst of PKC phosphor activation that was transient and short lived.

Adenosine triphosphate-sensitive potassium (K_{ATP}) channels

K_{ATP} channels play an important role in cardioprotective signaling. Earlier studies emphasized the importance of sarcolemmal K_{ATP} channels, as it was hypothesized that sarcK_{ATP} activation by preconditioning leads to K^+ efflux that shortens action potential and thus attenuates extracellular Ca^{2+} loading. Hyperpolarization and reduced intracellular [Ca^{2+}] render the cardiomyocytes unexcitable, spare oxygen consumption, and prevent hypercontracture and dysrhythmia [9]. However, the association between the extent of action potential shortening and infarct size reduction has been rigorously challenged, but the predominant role of mitoK_{ATP} channels in preconditioning was substantiated with compelling evidence [25]. The putative mechanism by which mitoK_{ATP} channel activation induces cardioprotection involves the inhibition of mitochondrial permeability transition pores (mitoPTP). mitoPTP opening resulting from mitochondrial Ca^{2+} accumulation during I/R forebodes apoptosis; it is characterized by collapse of mitochondrial potential, intermembrane swelling, matrix contraction, respiratory uncoupling, and release of cytochrome *c*/proapoptotic proteins. K^+ influx through opened mitoK_{ATP} channels attenuates mitochondrial Ca^{2+} overloading and hence prevents mitoPTP opening [26]. Sevoflurane preconditioning suppressed mitochondrial [Ca^{2+}] overload during ischemia as well as reducing cardiac infarct upon reperfusion, and pretreatment with mitoK_{ATP} channel blocker 5-HD abolished both effects, indicating that APC elicits cardioprotection via mitoK_{ATP} and its subsequent suppression of mCa^{2+} concentration [27].

Administration of the nonselective K_{ATP} blocker glyburide before coronary artery occlusion in dogs completely abolished the reduced myocardial infarction [28] and myocardial stunning [29] by isoflurane preconditioning. Whether mitochondrial K_{ATP} or sarcolemmal K_{ATP} channels are of greater importance in APC has provoked substantial research interest. In isolated cardiomyocytes, isoflurane or sevoflurane directly activated mitoK_{ATP} channels [30] or potentiated diazoxide-mediated mitoK_{ATP} channel opening [3]. The enhanced postischemic myocyte survival was solely dependent on the mitoK_{ATP} channel, as preexposure to mitoK_{ATP} blocker 5-HD but not sarcK_{ATP} blocker HMR-1098 prevented cytoprotection by Iso-PC/Sevo-PC [3]. Evidence from in vivo or intact heart I/R studies substantiated the pivotal role of mitoK_{ATP} channels in APC, including xenon [31–34]. The exclusive involvement of mitoK_{ATP} channels was corroborated in a study of desflurane-preconditioned human atrial trabeculae, as coadministration of nonselective K_{ATP} blocker glibenclamide or 5-HD but not HMR-1098 abolished the remarkable postischemic contractile improvement [6]. Interestingly, in sevoflurane-preconditioned human trabeculae HMR-1098 partially attenuated the improved contractility [35]. The importance of sarcK_{ATP} channels was reasserted in desflurane-preconditioned canine hearts, as coadministration of glyburide, HMR-1098, or 5-HD similarly aborted the infarct-sparing effect [36]. The controversy with respect to the importance of mitoK_{ATP} and sarcK_{ATP} could be the result of variations among species (rabbit, rat, dog, human), I/R models (myocytes, isolated hearts, open chest), or different mode of actions between volatile anesthetics. It is plausible that sarcK_{ATP} and mitoK_{ATP} channels 'crosstalk' with each other, a phenomenon observed in cardiac ischemic preconditioning. Alternatively, it was speculated that the two channels assume differential roles during early cardiac preconditioning, whereby the reduced myocardial infarct is mediated mainly by mitoK_{ATP} channels (via mitoPTP inhibition), and the functional and mechanical recovery (i.e., heart rate and contractility) is attributable to sarcK_{ATP} channel activation.

mitoK_{ATP} channel opening was shown to be downstream of PKC in IPC [37–39]; however, such temporal relationship has been challenged in APC. For example, two studies have shown that PKC does not translocate to the subcellular compartments after either reactive oxygen species (ROS) scavenging or mitoK_{ATP} blockage in isoflurane and xenon preconditioning in vivo [3, 10]. ROS release was shown to precede PKC activation [14, 40]; thus, mitoK_{ATP} channel opening could indirectly activate PKC by increasing mitochondrial ROS production. To reconcile the perplexing interactions between PKC and mitoK_{ATP} in APC, the initial PKC activation/mitochondrial translocation activates the mitoK_{ATP} channel, prompting ROS release that feeds forward to augment PKC activity to accentuate mitoK_{ATP} opening. In such amplification loop the distinction between upstream regulator and downstream effector diminishes, and several cycles of signal amplifications might be required to attain maximal cardioprotection against subsequent I/R.

Desflurane and isoflurane preconditioning attenuated Ca^{2+}-induced mitoPTP opening, with the reduced Ca^{2+} sensitivity shown to be dependent on PKCε [41] and mitoK_{ATP} channels [42], as coadministration of εV1-2 or 5-HD abolished the delayed mitoPTP opening. Notably, when isoflurane was applied directly to isolated rat mitochondria, neither the delayed opening of mitoPTP nor increased Ca^{2+} threshold was observed. These findings support the end-effector role of mitoPTP in the APC

signaling cascade, being downstream of the interplay between cytosolic PKC and the mitoK$_{ATP}$ channel. Xenon preconditioning also raised the Ca^{2+} concentration required to induce mitochondrial membrane depolarization and an overall suppression of mitoPTP activity [43].

Reactive oxygen species and nitric oxide

The prominence of early ROS generation in acute APC has been evidenced in vitro and in vivo, as coadministration of ROS scavengers during anesthetic preconditioning aborted the infarct-limiting effect of isoflurane, desflurane, and sevoflurane [34, 44–46].

Sevoflurane preconditioning reduced ROS release during reperfusion, and coadministration of ROS scavengers not only abolished cardioprotection but also mitigated the sustained ATP production and re-elevated mitochondrial ROS output during early reperfusion [47, 48]. These findings evidence the paradoxical involvement of ROS in APC-mediated cardioprotection. Moderate induction of mitochondria-derived ROS before ischemia is crucial for triggering APC, presumably via PKC activation/recruitment and mitoK$_{ATP}$ opening; however, the actual cardioprotection by APC is attributable to the suppression of a detrimental ROS burst during I/R that could inflict devastating oxidative myocardial damage. It was hypothesized that inhalational anesthetics induce early mitochondrial ROS release by attenuation of mitochondrial electron transport (mitoET) at complex I or complex III [49], resulting in electron leakages to favor O^{2-} generation. ROS derived from attenuated mitoET could operate in a positive feed-forward loop to further impede mitoET to amplify ROS synthesis [50]. Hypothetically, the opening of mitoK$_{ATP}$ channels by ROS or PKC optimizes K^+ entry to initiate compensatory mitochondrial respiration and preserve ATP output, and the accelerated mitoET flow could minimize electron leakages to switch off ROS formation during I/R.

The pivotal involvement of nitric oxide in early APC has been described in vitro [3] and in vivo [51], with enhanced NO release shown to trigger [52] and mediate [53] APC. Endothelial nitric oxide synthase has been demonstrated as the source of NO during early APC, and its physical association with HSP90 is critical to permit eNOS phosphor activation for early NO production [54].

Antiapoptosis

Apoptotic myocardial deaths characterized by mitochondrial destabilization and nuclear fragmentation contribute to myocardium infarcts and myocyte losses during prolonged cardiac I/R. PI3K/Akt-dependent suppression of cardiac infarct and cardiomyocyte apoptosis was reported in isoflurane preconditioning in vivo. PI3K/Akt-dependent modulation of antiapoptotic and proapoptotic proteins was in part responsible for the potent apoptosis-sparing effect of Iso-PC, characterized by increased Bcl-2, decreased Bax, and enhanced Bad phosphorylation. Iso-PC promoted myocyte survival by maintaining a high Bcl-2/Bax ratio whereas phosphorylation and inactivation of Bad prevented the latter from translocating to mitochondria to form a proapoptotic complex with Bax to sequester Bcl-2. Caspase-3 is the executor of the caspase-dependent apoptotic pathway, and its activation was also downregulated by PI3K/Akt in Iso-PC [55]. PI3K/Akt signaling and its downstream phosphorylation of GSK-3β were also integral to xenon-mediated reduction in cardiac infarct and preservation of mitochondrial respiratory state [43].

ROS-dependent NFκB activation upregulated Bcl-2 expression in sevoflurane-preconditioned hearts before I/R [56]. NFκB activation is both detrimental and protective, and APC could modulate NFκB activity in a time-dependent manner. Zhong et al. [57] showed that Sevo-PC reduced NFκB nuclear translocation during reperfusion and suppressed NFκB-induced inflammatory cytokine expressions, whereas enhanced NFκB activation/translocation before ischemia could be critical to APC-mediated cardioprotection by sparing apoptosis via ROS-NFκB-Bcl-2 signaling [58]. The new publications in this field have been summarized in Table 1.

Delayed APC

Compelling evidence confers a ‘second window’ of cardioprotection by inhalational anesthetics-induced preconditioning [1]. The cardioprotection by delayed APC is triggered by eNOS-derived NO [58, 59] and mitochondrial-derived ROS [60], which activate signaling kinase pathways upstream of the nuclear translocations of various transcriptional factors [61, 62] (NFκB, HIF-α, CREB, and others) to upregulate the expressions of crucial proteins/enzymes of delayed APC, including iNOS [63], COX-2 [62, 64], 12-lipoxygenase [65], caveolin-3, and GLUT-4 [66]. The products from newly synthesized proteins, NO, PGE_2/PGI_2, 12-hydroxyeicosatetraenoic acid, coupled to the enhanced caveolae formation and glucose uptake contribute directly to delayed cardioprotection. Nitric oxide is of great prominence as trigger and mediator in delayed APC [61], and a transition of source from eNOS-derived to iNOS-derived NO was proposed with ‘biphasic’ NO production that sustains intracellular [NO] at a cardioprotective level long after the removal of initial APC stimulation. The transcriptional upregulation of iNOS was shown to be dependent on NFκB; the activation and nuclear translocation required eNOS-derived NO immediately after Iso-PC,

Table 1 Early cardiac preconditioning

Authors	Journal	Species/model	Anesthetic/ pharmacological agents	Protocol	Major findings
Hanouz et al. [44]	A&A	Human atrial trabeculae	SEVO (2 %), DES (6 %), MPG (0.1 mM)	5 min SEVO or DES +/− MPG, 10 min washout, 30 m in hypoxia-1 h reoxygenation	Mechanical and functional preservation of human trabeculae by SEVO/DES-PC against I/R injury involves intracellular ROS
Amour [54]	ALG	Open-chest rabbits	ISO (1MAC), GELD (0.2 mg/kg), RAD (2 mg/kg), L-NAME (10 mg/kg)	30 min ISO +/− GELD, RAD or L-NAME, 15 min memory period, 30 min LAD occlusion-3 h reperfusion	HSP90 and NO are essential to cardioprotection by ISO-PC in vivo
		Human coronary artery endothelial cells and HL-1 cardiomyocytes	ISO (1MAC), GELD (17.8 μM), RAD (20 μM), L-NMMA (1 mM)	3 h GELD or RAD or 12 h L-NMMA, before ISO	ISO-PC leads to HSP90/eNOS association, eNOS activation, and NO production in human endothelial cells
Lu et al. [56]	AJP-Heart	Isolated perfused rat hearts	SEVO (1MAC), 2-MPG (1 mM), 514 (100 μM)	SC-10 min SEVO +/− 2MPG, 20 min washout; 10 min SEVO +/− SC-154, 10 min washout before 1 h IR	SEVO-PC increases Bcl-2 expression before ischemia via ROS-dependent NFκB activation and reduces caspase 3 and cytochrome *c* during I/R
Mio et al. [43]	A&A	Open-chest rats	Xenon (70 %), Wort (0.6 mg/kg)	15 min interspersed Xe-PC +/− Wort, 15 min memory period, 30 min LAD occlusion-2 h reperfusion	Xe-PC enhances Akt/GSK3b phosphorylation and suppresses Ca^{2+}-induced mitoPTP opening to mediate cardioprotection
Pravdic et al. [41]	ALG	Rat ventricular myocytes isolated heart mitochondria	ISO (0.63 mM), CHE (1 μm) rottlerin (0.2 μm), PKCeV1-2 (1 μm) ISO (0.5 mM), CHE (5 mg/kg)	20 min ISO +/− CHE, rottlerin or PKCeV1-2, 5 min washout 30 min ISO +/− 10 min CHE, 15 min washout, heart excision and mitochondria isolation	ISO-PC delays in mitoPTP opening downstream of PKCe activation and mitochondrial translocation
Wang et al. [58]	ESA	Open-chest rats	SEVO (2.5 %), PTN (500 μg/kg)	30 min SEVO +/− PTN, 15 min washout, 30 min LAD-occlusion and 120 min reperfusion	NFκB acts as a trigger and a mediator in SEVO-PC, increasing Bcl-2 expression during PC and reducing TNF-α and ICAM-1 expression during reperfusion
Li et al. [31]	Heart Circ	Lung-isolated perfused immature rabbit hearts	Xenon (75 %), DIAZO (100 μM), HD (100 μM)	5–20 min Xe +/− 5HD or DIAZO, interspersed with washouts, before I/R	Xe-PC attenuates cardiac IR injury through mitoK_{ATP} channel opening

with maximal iNOS expression and activity only observable 24 and 48 h after exposure to inhalational anesthetics. An interesting side note to delayed APC is its reported gender specificity in rabbits [63], when distant isoflurane treatment was only cardioprotective in males but not females when compared with respective controls. It was speculated that the significantly elevated basal eNOS expression in females, resulting from estrogen, readily confers additional protection over myocardial infarction, and preconditioning with APC may fail to benefit female rabbits further as it did with male rabbits. Gender-specific organoprotection by inhalational anesthetics warrants further investigation, with different anesthetics of different concentrations tested on different animal models of both genders. Once confirmed in humans, the gender specificity of inhalational anesthetics-induced organoprotection during I/R will propel the development of a gender-tailored anesthesia regime to optimize perioperative organoprotection in male and female patients. The new publications in this field have been summarized in Table 2.

Cardiac postconditioning

Oxygen starvation damages cardiomyocytes through ATP depletion and acidosis; however, acute reperfusion is equally if not more destructive, giving rise to 'lethal reperfusion injury' that superimposes upon ischemic damage. Inhalational anesthetics are powerful 'preconditioning' agents; their more recent application during early reperfusion, termed 'anesthetic postconditioning' (APostC), has been reported to effectively mitigate reperfusion injury, and this has been well reviewed previously [67]. APostC is of greater clinical and practical relevance

Table 2 Delayed cardiac preconditioning

Author	Journal	Model	Anesthetics/ pharmacological agents	Protocol	Major findings
Tsutsumi et al. [65]	AJP-Heart	Isolated mouse hearts	ISO (lMAC), BAL (3 mg/kg)	30 min ISO in vivo, 24 h later heart perfusion +/− BAL, before 30 min ischemia-2 h reperfusion	ISO-PC increases 12-LO expression over 24 h to mediate delayed cardioprotection
Chen et al. [61]	Shock	Open-chest rats	ISO (2.5MAC), L-NAME (0.86 mg/kg/min for 15 min), DDTC (150 mg/kg), SMT (0.375 mg/kg/min for 30 min)	l h ISO +/− L-NAME, DDTC or SMT, 24 h before 30 min CAO-2 h reperfusion	ISO-PC depends on early NO production and NFκB activation, which upregulates iNOS expression to permit delayed NO generation after 24 h
Feng et al. [62]	Card R	Isolated perfused rat hearts (healthy vs. postinfarct remodeled)	ISO (1.5MAC), CEL(0.1 μM or 1 μM), NS-398 (5 μM), CDC (0.5 μm)	90 min ISO in vivo, 24 h or 48 h later heart perfusion +/− CEL, NS-398 or CDC, before 40 min global ischemia-90 min reperfusion	Delayed ISO-PC upregulates COX2 to promote HIFa and CREB nuclear translocation in healthy hearts, but these pathways are hindered in diseased hearts
Tsutsumi et al. [66]	ALG	Open-chest mice, WT vs. Cav-1 or Cav-3 KO mice cardiac myocytes	ISO (1MAC) ISO (1.4 %), M[beta]CD (1 mm)	30 min ISO 24 h before 30 min CAO-2 h-reperfusion 30 min ISO, 24 h before 30 min ischemia-l h reoxygenation, +/− M[beta]CD before ISO or before I/R	Caveolin-3 membrane translocation; association with GLUT 4 and formation of caveolae mediate, but do not trigger, delayed cardioprotection by ISO-PC

than preconditioning, as the precise onset of coronary artery occlusion, in contrast to during surgical procedures, could not be anticipated in pathological conditions, i.e., acute myocardial infarction; thus, interventions before ischemia would not be feasible to attempt. However, reperfusion timing is largely predictable and controllable, and by administering inhalational anesthetics 'post hoc' upon reperfusion myocardial damage could be reduced [67].

The mitochondrial-permeability-transition pore is the end effector downstream of mitoK$_{ATP}$ activation in early APC; its inhibition is also paramount to APostC. Pretreatment with the mitoPTP opener atractyloside completely abrogated the reduced cardiac infarction by isoflurane postconditioning in vivo, whereas coadministration of mitoPTP inhibitor cyclosporine A halved the dosage of Iso-PostC without compromising cardioprotection. Importantly, mitoK$_{ATP}$ blockage abolished the reduction in size of infarctions produced by Iso-PostC and combined CsA/Iso-PostC treatment, suggesting that the interaction between mitoK$_{ATP}$ and mitoPTP is crucial to APostC-mediated cardioprotection [68]. Inhibition of mitoK$_{ATP}$ with 5-hydroxydecanoate (5-HD) also abolished the additive cardioprotection produced by combining sevoflurane preconditioning and postconditioning [69]. Aside from mitoK$_{ATP}$, activation of the mitochondrial large-conductance Ca^{2+}-activated potassium channel (BK_{Ca}^{2+}) also mediated desflurane postconditioning, probably by triggering mitochondrial ROS production [70]. The temporal relationship between BK_{Ca}^{2+} and mitoPTP remains controversial; the most recent study demonstrated that the mitoPTP opener atractyloside only partially blocked the cardioprotection by BK_{Ca}^{2+} activator NS1619, suggesting the opening of BK_{Ca}^{2+} in APostC could be independent of the status of mitoPTP, and mitoPTP may not necessarily act downstream of BK_{Ca}^{2+}.

Several signaling pathways converge at the level of mitoPTP to prohibit its opening and attenuate reperfusion injury. Recruitment of the prosurvival PI3K/Akt pathway is principal to isoflurane postconditioning as co-administration of PI3K/Akt inhibitors Wortmannin/LY294002 abolished the reduced cardiac infarction, apoptosis, and cytochrome *c* release [71–73]. As a phosphorylation target of PI3K/Akt, the obligatory role of eNOS in Iso-PostC was confirmed. Using eNOS inhibitor L-NAME or eNOS$^{-/-}$ knockout mice, suppression of myocardial infarct and improvement in cardiac function were shown to be eNOS dependent [74] because of the eNOS-dependent inhibition of mitoPTP opening to Ca^{2+}. ERK1/2-mTOR-p70s6K signaling was demonstrated to be as critical as PI3K/Akt in APostC [75], when coadministration of MEK1 inhibitor PD098059 or p70s6K inhibitor rapamycin abrogated the infarct-limiting effect of Iso-PostC in vivo. Enhanced phosphorylation of ERK1/2 and p70s6K was observed in Sevo-PostC, concurrent with ERK-dependent suppression of cytochrome *c* release and cardiac infarct [76].

Phosphor inactivation of 'master-switch' kinase glycogen synthase-kinase (GSK)-3β by upstream kinases, including PI3K/Akt, MAPK, PKC, and p70s6K, represents the proximal and obligatory event to attenuated mitoPTP

opening. Iso-PostC in vivo was characterized by PI3K-dependent Akt and GSK3β phosphorylation and the attenuation of mitoPTP opening [77]; the infarct-limiting effect of subthreshold Iso-PostC was also potentiated when GSK-3β inhibitor SB16763 was coadministered [78].

Bcl-2 is critical to Iso-PostC and acts upstream of mitoPTP by prohibiting mitoPTP opening, hence limiting myocardial infarct/apoptosis [79]. Furthermore, the suppressed nuclear activation of pro-caspases 9 and 3 by Sevo-PC was shown to be PI3K/Akt- and ERK1/2 dependent [80].

Thus, it appears that antiapoptotic prosurvival kinase cascades exemplified by PI3K/Akt and ERK1/2(p44/42MAPK) following APostC could favorably affect the transition state of mitoPTP via GSK-3β and directly modulate antiapoptotic and proapoptotic proteins to confer cardioprotection during reperfusion. mitoK$_{ATP}$ channel activation and mitoPTP inhibition are common to both APC and APostC; however, the temporal relationships between mitoPTP and mitoK$_{ATP}$/mitoBKCa in APostC are complicated (Fig. 2) and remain to be clarified.

Morphine was shown to potentiate isoflurane postconditioning in vivo [73], and blockage of the δ-1 opioid receptor with naloxone completely abolished the reduced infarction size by 1MAC Iso-PostC or morphine combined with subthreshold concentration of isoflurane. Therefore, similar to cardiac preconditioning, postconditioning with inhalational anesthetics is also achieved via stimulation of opioid receptors and their downstream targets. The new publications in this field have been summarized in Table 3.

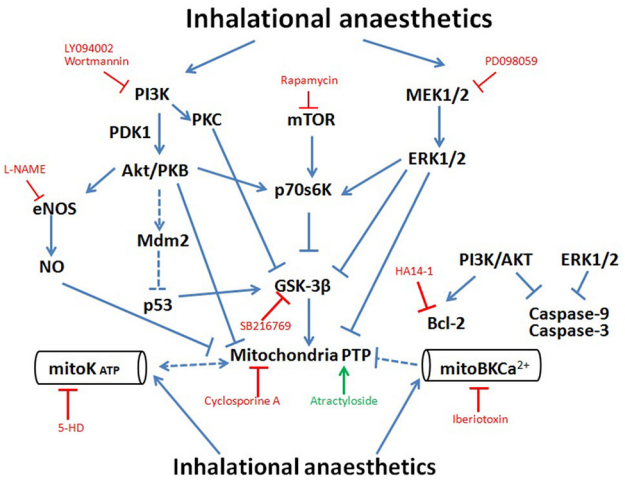

Fig. 2 A schematic illustration of the signaling events occurring in cardiac postconditioning by inhalational anesthetics. Pharmacological inhibitors of respective pathways/components are labeled in *red*, and mitoPTP opener is highlighted in *green*. *Dashed lines* represent hypothetical pathways in cardiac APostC. The PI$_3$K-Mdm2-p53 pathway is of particular interest. p53 was shown to bind to GSK-3β to stimulate mitochondrial permeability transition. p53 can be down-regulated via PI$_3$K/Akt-mediated phosphorylation of Mdm2 that sequesters p53 and induces its degradation. Inhibition of proapoptotic p53 by pifithrin-α enabled cardioprotection by isoflurane postconditioning at subthreshold dosage [136]. *5-HD* 5-hydroxydecanoate, selective blocker of mitoK$_{ATP}$ channels; *Akt/PKB* protein kinase B; *Bcl-2* B-cell lymphoma 2, antiapoptosis protein; *eNOS* endothelial nitric oxide synthase; *ERK1/2* mitogen-activated protein kinase; *GSK3β* glycogen synthase kinase 3b; *HA14-1* 2-amino-6-bromo-α-cyano-3-(ethoxycarbonyl)-4*H*-1-benzopyran-4-acetic acid ethyl ester, cell-permeable inhibitor of Bcl-2 protein; *L-NAME* N^G-nitro-L-arginine methyl ester, eNOS inhibitor; *Mdm2* mouse double minute 2 homologue, a negative regulator of tumor suppressor p53; *MEK1/2* mitogen-activated protein kinase kinase; *mitoBKCa*$^{2+}$ mitochondrial large-conductance calcium-activated potassium channels; *mitochondrial PTP* mitochondrial permeability transition pore; *mitoK$_{ATP}$* mitochondrial potassium (K^+) ATP channels; *mTOR* mammalian target of rapamycin; *NO* nitric oxide; *p53* tumor suppressor protein; *p70s6K* p70s6 kinase, a serine/threonine kinase that phosphorylate S6 ribosomal protein; *PDK-1* phosphoinositide-dependent protein kinase-1, a master kinase that activates many phosphorylation pathways; *PI3K* phosphoinositide 3-kinase; *PKC* protein kinase C (color figure online)

Neuroprotection

Perioperative stroke following neurosurgical and cardiovascular procedures has significant impact on postoperative outcome. The potential benefits of intraoperative and postoperative inhalational anesthetic administration to provide neuroprotection and to mitigate neurological sequelae have been investigated. Administration of inhalational anesthetics beyond surgical settings, if they attenuate ischemic injury, can confer neuroprotection at subanesthetic dosages when given post hoc; this would be of great value clinically in neurological injuries, e.g., stroke, head trauma, and perinatal asphyxia/encephalopathy [81–83].

ATP depletion imminent to cerebral ischemia disrupts ATP-dependent ion channels, resulting in neuronal depolarization and uncontrolled synaptic release of excitatory neurotransmitter glutamate. The excessive glutamate release and glutamate-receptor stimulation give rise to ischemia-induced excitotoxicity, producing depolarization of postsynaptic neurons and inducing Na^+/Ca^{2+} influx via voltage-gated ion channels, compounded by further cation overloading via NMDA- and AMPA-glutamate receptors. The disruption/reversal of ATP-dependent reuptake of glutamate could aggravate ischemia-induced excitotoxicity. Ischemic neuronal injury is a dynamic process consisting of two phases. Abrupt increase of cytosolic Ca^{2+} hyperactivates Ca^{2+}-dependent enzymes, culminating in acute excitotoxic necrotic death in the core of the cerebral infarct; this is followed by ongoing neuronal loss in the penumbral regions largely by apoptosis, entailing the activation of caspases and mitochondrial release of proapoptotic factors [82, 84]. All the excitotoxic events in the pathogenesis of cerebral ischemia represent potential

Table 3 Cardiac postconditioning

Author	Journal	Model	Anesthetics/ pharmacological agents	Protocol	Major findings
Weihrauch et al. [73]	A&A	Open-chest rabbits	ISO (0.5 or 1 MAC), Wort (0.6 mg/kg), NAL (6 mg/kg), MOR (0.05 or 0.1 mg/kg)	ISO +/− morphine 3 min before and 2 min after reperfusion, +/− Wort or NAL, before 30 min LAD occlusion-3 h reperfusion	ISO-PostC and morphine confer additive cardioprotection that is dependent PI3K signaling and opioid receptor activation
Krolikowsk et al. [75]	CJA	Open-chest rabbits	ISO (1 MAC), PD098059 (2 mg/kg), RAP (0.25 mg/kg), L-NAME (10 mg/kg), AG (300 mg/kg), 7-NI (50 mg/kg)	ISO 3 min before and 2 min after reperfusion during 30 min LAD occlusion-3 h reperfusion, +/− PD098059, RAP, L-NAME, AG, or 7-NI	ERKl/2-p70s6 K signaling and eNOS-dependent NO production are central to cardioprotection by ISO-PostC
Venkatapuram et al. [136]	A&A	Open-chest rabbits	ISO (0.5 or 1 MAC), PFTa (1.5 or 3 mg/kg), Wort (0.6 mg/kg), ATR (5 mg/kg)	ISO 3 min before and 2 min after reperfusion, +/− PFTa, +/− Wort or ATR, before 30 min LAD occlusion-3 h reperfusion	Inhibition of antiapoptotic p53 potentiates ISO-PostC cardioprotection via a mitoPTP-dependent mechanism
Chen et al. [76]	APS	Isolated perfused rat hearts	SEVO (vol 3 %), PD98059 (20 μmol/l)	15 min SEVO +/− PD98059 at onset of reperfusion, during 30 min ischemia-90 min reperfusion	SEVO-PostC depends on ERK1/2 signaling with increased ERK and p70s6K phosphorylation and suppressed release of cytochrome *c*
Ge et al. [74]	ALG	Open-chest mice, WT vs. eNOS KO isolated perfused mice hearts	ISO (0.5, 1 or l.5 MAC) e ISO (0.5, 1 or 1.5 MAC), L-NAME (30 μm)	ISO 5 min before and 3 min after reperfusion. during 30 min CAO-2 h reperfusion ISO-PostC +/− 20 min L-NAME before ischemia or upon reperfusion	eNOS and eNOS-derived NO acts as trigger and mediator to delayed ISO-PostC Delayed mitoPTP opening by ISO-PostC is also eNOS dependent
Inamura et al. [80]	JA	Isolated guinea pig heart	SEVO (vol 2 %), PD98059 (20 μmol/l), LY294002 (15 μmol/l)	2 min SEVO upon reperfusion, +/− 10 min PD9805S or LY294002, before 30 min ischemia-2 h reperfusion	SEVO-PostC are dependent on activation of PI3K/Akt and ERK1/2 pathways to suppress caspase activities
Stumpner et al. [70]	BJA	Open-chest mice	DES (1MAC), NS1619 (l μg/g), IbTx (0.05 μg/g), ATR (25 μg/g), CsA (10 μg/g), NAC(150 μg/g)	18 min DES starting 3 min before reperfusion, +/− NS1619, IbTx, ATR, or CsA during 45 min IR	Cardioprotection by DES-PostC is mediated through $BKCa^{2+}$ activation and mitoPTP inhibition

targets of inhalational anesthetics to exert neuroprotection (Fig. 3).

Glutamatergic and GABA neurotransmissions

In an oxygen-glucose-deprivation (OGD) study where NMDA-receptor activation was solely responsible for the acute neuronal injury, isoflurane significantly reduced neuronal loss/damage to the same extent as the NMDA-receptor antagonist MK-801 [85]. Isoflurane anesthesia suppressed excitotoxic cerebral damage from NMDA/AMPA intracortical injections in vivo [86, 87]. The potent NMDA antagonist xenon also reduced NMA-induced cerebral excitotoxicity in rats [88]. Inhalational anesthetics prevented hypoxia-evoked glutamate release in vitro and attenuated ischemia-induced increase in cerebral glutamate in vivo [81]. Inhalational anesthetics have also been shown to promote glutamate reuptake by astrocytes [84] and to upregulate expression of sodium-dependent excitatory amino acid transporter EAAC1 in vitro [89]. Blockage of glutamate transporter mitigated isoflurane-mediated neuroprotection in rat cerebellar slices following OGD [90]. To summarize, inhalational anesthetics could antagonize ischemia-induced glutamatergic excitotoxicity by (1) direct antagonism toward postsynaptic AMPA/NMDA receptors, (2) reduction in pre- and extrasynaptic glutamate release, and (3) promotion of glutamate reuptake and clearance.

Activation of $GABA_A$ receptor results in Cl^- influx and membrane hyperpolarization, the primary mechanism by which many pharmacological agents, including isoflurane,

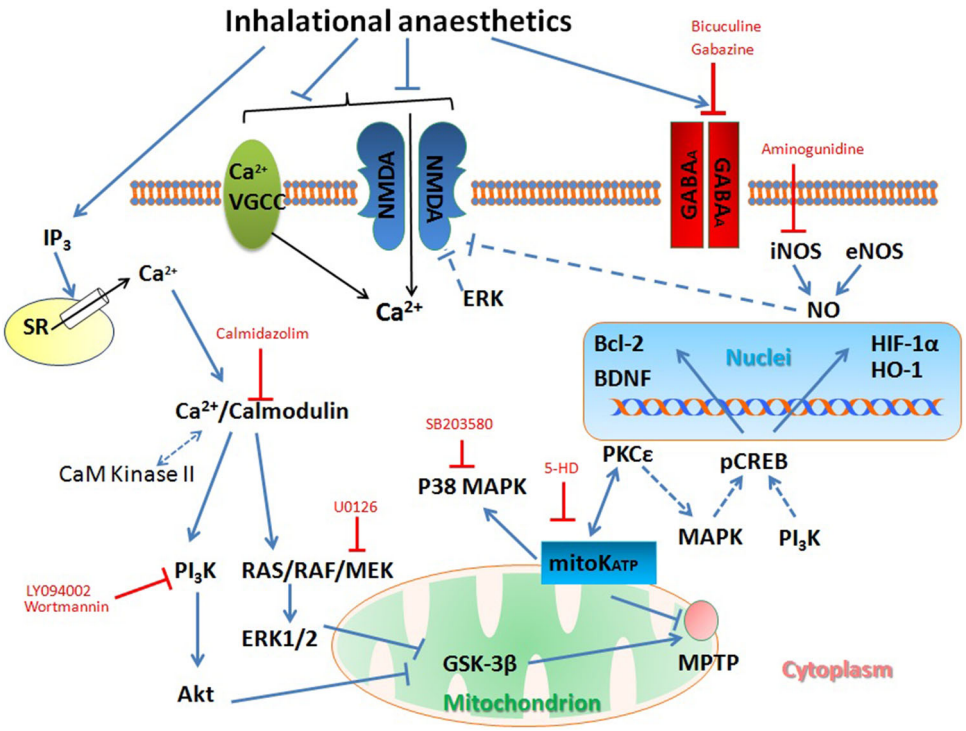

Fig. 3 A schematic overview of the signal transductions in inhalational anesthetics-mediated neuroprotection. Pharmacological inhibitors used to study the various signaling components are in *red*. Mild intracellular Ca^{2+} increase phosphor-activates Ca^{2+}-dependent prosurvival and antiapoptotic pathways following the activation of Ca^{2+}/calmodulin complex. PI_3K/Akt and ERK1/2 could phosphor-inactivate GSK-3β to attenuate mitochondrial permeability transition, or differentially modulate antiapoptotic and proapoptotic proteins, as well as to manipulate gene expression to favor neuronal survival during ischemia. NO and ERK have been shown to attenuate NMDA-receptor mediated Ca^{2+} influx and could potentially contribute to inhalational anesthetics-mediated NMDA antagonism (*dashed line*). eNOS could be responsible for the early production of NO for acute neuroprotection against ischemia. Ca^{2+}/calmodulin-dependent kinase II is one of the most abundant neuronal protein kinases; its role in ischemic brain injury is poorly understood and contradictorily defined [96, 135]. IP_3-Ca^{2+}-CaMKII signaling represents a potential neuroprotective mechanism by inhalational anesthetics (*dashed line*) (color figure online)

exert anaesthesia and analgesia. Isoflurane-mediated neuroprotection is also dependent on $GABA_A$ receptor activation, as coadministration of $GABA_A$-receptor antagonist bicuculline or gabazine during OGD abolished the attenuated neuronal death and LDH release [91, 92].

Ca^{2+} homeostasis and calcium-dependent signaling pathways

Isoflurane anesthesia significantly reduced glutamate receptor-mediated Ca^{2+} influx in rat cortical slices stimulated with NMDA, L-glutamate, or ischemia [93]. Paradoxically, moderate increase in intracellular $[Ca^{2+}]$ could be neuroprotective. Hippocampal slices treated with isoflurane during stimulated 'ischemia' sustained $[Ca^{2+}]_i$ within 30–100 nm, contrasting with the striking surge of $[Ca^{2+}]_i$ to 2 μm in controls. It was postulated that isoflurane inhibits NMDA receptor-mediated Ca^{2+} overloading and increases inositol triphosphate (IP3)-dependent Ca^{2+} release from intracellular sources during ischemia, thus conferring neuroprotection by maintaining $[Ca^{2+}]_i$ within survival limits and also into a range where phosphor activation of prosurvival pathways is feasible. Isoflurane-induced Ca^{2+} release from the sarcoplasmic reticulum was shown to phosphor-activate Ras-Raf-MEK-ERK signaling and reduce neuronal death, and inhibition of MEK1/ERK eliminated isoflurane-mediated neuroprotection [94]. Delayed isoflurane preconditioning also requires moderate intracellular Ca^{2+} release and Ca^{2+}-dependent signaling, as inhibition of calmodulin, prosurvival MEK1/ERK, or antiapoptotic PI3K/Akt individually abrogated suppressed neuronal death by delayed Iso-PC in vitro [95]. Calmodulin as an important Ca^{2+} sensing/binding protein is linked to the activation of MAPK, PKB/Akt, and Ca^{2+} calmodulin-dependent kinase II (CaMKII), a critical neuronal regulatory enzyme that is lost rapidly after ischemia and the abundance of which has been shown to inversely correlate with neurological deficits in a canine model of global ischemia [96].

P38MAPK and protein kinase C

Phosphor activation of p38MAPK is obligatory for delayed isoflurane preconditioning as coadministration of p38MAPK inhibitor completely abrogated the reduced cerebral infarction and neurological deficit following focal ischemia [97]. Enhanced p38MAPK phosphorylation was also observed in sevoflurane preconditioning in vivo and persisted for up to 72 h post reperfusion [98]. Preinfusion of 5-HD prevented Sevo-PC-induced p38MPAK phosphorylation and PKCε membrane translocation [99], suggesting mitoK_{ATP} is upstream of signaling kinase activations; however, potential PKC-mitoK_{ATP} 'crosstalk' as in cardiac APC is more likely.

Adenosine triphosphate-sensitive potassium channels

K_{ATP} channel activation is critical to isoflurane preconditioning 24 h before cerebral ischemia in rats, as pretreatment with the K_{ATP} blocker glibenclamide completely abrogated the reduced infarct size and the improved neurological performance [100]. By coadministration of mitoK_{ATP} blocker 5-HD, the mitochondrial K_{ATP} channel was ascertained to be chiefly responsible for APC-mediated neuroprotection in vitro or in vivo, early or delayed, by isoflurane or sevoflurane [89, 101, 102]. mitoK_{ATP} channel activation is also crucial for isoflurane and sevoflurane postconditioning against OGD in vitro [103] and focal ischemia in vivo [98, 99]. However, K_{ATP} channel blockage did not modify the reduced Purkinje neuronal damage by isoflurane in rat cerebellar slices [90], suggesting regional differences in the mechanisms of inhalational anesthetics-induced neuroprotection, i.e., cerebral versus cerebellar ischemia.

Inducible nitric oxide synthase and nitric oxide

Isoflurane preconditioning induced iNOS expression in adult [104] and neonatal [105] rat cerebral cortices 6–24 h after isoflurane exposure. Preadministration of the iNOS inhibitor aminoguanidine (AG) completely abolished the suppressed cerebral infarct/brain loss by distant Iso-PC, indicating that iNOS- and iNOS-derived NO are obligatory components to delayed neuroprotection by APC. eNOS could be responsible for the early production of NO for acute neuroprotection against ischemia, as iNOS expression was not elevated until 6 h after inhalational anesthetic exposure, suggesting its role in delayed but not early preconditioning.

Antiapoptosis

Delayed isoflurane preconditioning conferred gender-specific neuroprotection against focal ischemia in male mice and was associated with male-specific Akt phosphorylation. Furthermore, Iso-PC was only neuroprotective in wild-type (WT) but not $Akt1^{-/-}$ knockout (KO) males, indicating that Akt activation is fundamental to APC-mediated neuroprotection [106]. Delayed xenon preconditioning is neuroprotective regardless of gender, associated with comparable upregulation of Akt phosphorylation and HIF-1α expression in male and female mice [107]. These findings suggest divergent mechanisms upstream of Akt between Iso-PC- and Xe-PC-mediated neuroprotection. PI3K/Akt activation was shown to be obligatory to reduced cerebral infarct and neurological deficits by sevoflurane postconditioning [108], in part by attenuating neuronal apoptosis via Bcl-2 upregulation and p53/Bax suppression. Isoflurane preconditioning also attenuated penumbral apoptosis via Bcl-2-dependent inhibition of cytochrome *c* release [109]. Furthermore, enhanced phosphorylation of Akt and mitochondrial GSK-3β was reported in isoflurane postconditioning, concomitant with delayed mitochondrial permeability transition [110], mirroring the PI_3K/Akt-GSK3β-mitoPTP signaling axis reported in cardiac APostC.

Transcriptional upregulation of neuroprotective proteins Bcl-2 and brain-derived neurotropic factor (BDNF) could be dependent on CREB, which upon phosphorylation forms an active transcription complex with CREB-binding protein (CBP) in the nucleus, and a PKC-MAPK-pCREB-Bcl-2/BDNF signaling axis was proposed to mediate enhanced neuronal survival by xenon preconditioning [111]. It was also reported that combined xenon/sevoflurane preconditioning could phosphor activate CREB via PI3K/Akt to upregulate Bcl-2 and BDNF transcriptions [112]. The new publications in this field have been summarized in Table 4.

Renoprotection

Renoprotection by xenon [113] and isoflurane preconditioning [114] before ischemic renal injury or acute renal failure were demonstrated to be HIF-1α dependent. Xe-PC increased HIF-1α expression in an mTOR-dependent manner via translational upregulation, preceding enhanced transcriptions of HIF-1α-regulated genes including VEGF and erythropoietin, which are known to promote angiogenesis, erythrogenesis, and tubular regeneration [113]. Xe-PC enhanced human tubular cell viability that was associated with enhanced Akt phosphorylation and HIF-1α/Bcl-2 expression [115]. Sevoflurane preconditioning exerted antiinflammatory and antinecrotic protection over human tubular cells, and the attenuated necrosis was shown to be dependent on PI3K/Akt and ERK1/2 and the induction of downstream HSP70 [116]. Sevoflurane-mediated

Table 4 Neuroprotection

Author	Journal	Model	Anesthetics/pharmacological agents	Protocol	Major findings
Kitano et al. [106]	JCBFM	Young and middle-aged male and female mice, WT and Aktl KO	ISO (1 %)	4 h ISO, 24 h before 2 h transient MCAO-reperfusion	ISO-PC affords male-specific neuroprotection partially from sex differences in Akt activation and basal NIPK expression Neuroprotection by ISO-PC in males is Aktl dependent
Li et al. [109]	EJP	Intact adult rats	ISO (2 %)	30 min ISO 24 h before permanent MCAO	ISO-PC reduced cortical neuron death in ischemic penumbra through upregulation of Bcl-2 and reduced mitochondrial cytochrome *c* release
Luo et al. [112]	ALG	Neuronal or neuronal-glial cocultures Intact neonatal mice	Xe (25–75 %), SEVO (0.67–3.3 %), Xe (12.5 %)/ SEVO (0.67 %), Wor (100 nM) Xe (75 %), SEVO (1.5 %), Xe (20 %)/SEVO (0.75 %)	2 h Xe and/or SEVO, +/− Wort pretreatment, 24 h before 75 min OGD-reperfusion 2 h Xe and/or SEVO, 4 h before 90 min right common carotid artery ligation	Xe and/or SEVO-PC confer delayed neuroprotection that is dependent on PI3K signaling and involves CREB phosphor-activation
Limatola et al. [107]	Neuroscience	Male and female adult mice	Xenon (70 %)	2 h Xe, 24 h before l h transient MCAO-recovery	Xe-PC at sub-MAC concentration affords delayed neuroprotection in both sexes and induces time-dependent activation of HIFa and Akt
Li et al. [110]	Neuroscience	Intact adult rats primary rat cortical culture	ISO (2 %) ISO (2 %), LY294002 (10 μM)	l h ISO anesthesia after 90 min transient right MCAO-reperfusion 1 h ISO after 1 h OGD, +/− 1 h LY294002 before OGD	ISO-PostC attenuates IR-induced opening of mitoPTP, and the reduced mitochondrial permeability could be downstream of PI3K/Akt signaling
Ye et al. [98, 99]	Neurol Sci, Mol Biol Rep	Intact adult rats	SEVO (2.4 %), 5-HD (40 mg/kg)	1 h SEVO anesthesia +/− 30 min 5HD, 15 min washout, 24 h before 2 h MCAO	Delayed neuroprotection by SEVO-PC depends on mitoK_{ATP} channel opening and downstream p38MAPK phosphor-activation, and PKC phosphorylation and membrane translocation

antinecrosis and antiinflammation during renal I/R was only evident in WT but not TGFβ1$^{+/-}$ or SMAD$^{-/-}$ mice [117], indicating that TGFβ1-SMAD signaling is essential for APC-mediated renoprotection.

An emerging field of xenon-mediated renoprotection concerns its efficacy against renal I/R injuries associated with allograft transplantation, or engraftment after prolonged hypothermic ischemic graft storage [118–121]. The preservation of posttransplant renal function and morphology could be attributed to xenon-induced cell proliferation and suppression of inflammation and apoptosis [119]. Activation of the mitogenic insulin-like growth factor receptor (IGFR)/mTOR/HIF-1α pathway [119] and antiapoptotic PI3K/Akt/mTOR phosphorylation cascade [118] in xenon-conditioned human HK2 cells was demonstrated to mediate the salubrious effects of the noble gas, through robust upregulation of various protective proteins, including HIF-1α, Bcl-2 [120], VEGF [118], HSP70, and HO-1 [121]. Bcl-2 and HSP70 were proposed to play a central role in the maintenance of mitochondrial and nuclear structural integrity, evidenced by the inhibited release of apoptotic cytochrome *c* and AIF and proinflammatory HMGB-1 [120]. The immunomodulatory effects of xenon also contributed to enhanced graft recovery and survival when NFκB activation, cytokine synthesis [118], and immune cell infiltration [121] were potently suppressed. It was suggested that as xenon prohibited nuclear HMGB-1 release, it could no longer interact with

Table 5 Renoprotection

Author	Journal	Model	Anesthetics/ pharmacological agents	Protocol	Major findings
Lee et al. [117]	AJP-renal	Male adult mice, TGFβ1+/ +or +/− , SMAD3+/+ or −/−	SEVO (1MAC), TGFβ1-Ab (250 μg)	SEVO anesthesia +/− TGFb1-Ab, before right nephrectomy +/− 30 min left renal ischemia, followed by 3 h recovery	Renoprotection against I/R injury in vivo, and necrosis and inflammation in vitro, are dependent on TGFβ-1/SMAD3 signaling that suppresses NFκB nuclear translocation
Zhao et al. [118]	AJT	Human proximal tubular cells • Lewis-to-Lewis (isograft) and Lewis-to-Fisher (allograft) rat kidney transplantation	Xe (70 %), HIFa-siRNA (20 nM) • Xe (70 %), HIFa-siRNA (200 μg)	2 h Xe 24 h before or after 24 h hypothermia-hypoxia, +/− 6 h sIRNA pretreatment 2 h donor Xe-PC 24 h before graft retrieval, or 2 h recipient Xe-PostC after grafting, +/− HIFa siRNA; cold-ischemia graft storage for 16 or 24 h	Renoprotection against cold-ischemia graft injury by Xe-PC or Xe-PostC is dependent on HIFa
Zhao et al. [119]	Kl	Human proximal tubular cells Fisher-to-Lewis (allograft) rat kidney transplantation	Xe (70 %), RAP (50 nmol/l), HIFa-siRNA (20 nmol/l), IGFIR-Ab (l μg/ml) Xe (70 %)	2 h Xe 24 h before, or after 16 h hypothermia-hypoxia, +/− RAP, HIFa siRNA, or IGFIR-Ab 2 h donor Xe-PC Xe 24 h before retrieval or 2 h recipient Xe-PostC after grafting; graft cold ischemia storage 0–16 h	Xe treatment enhanced cell proliferation via IGFIR and mTOR/HIFa signaling, and suppressed inflammatory response and immune cell infiltration, to promote graft recovery and prolonged survival
Zhao et al. [120]	FASEB J	Lewis-to-Lewis rat kidney transplantation Human proximal tubular cells/HK2	Xe (70 %) Xe (70 %), HSP70-siRNA (20 nM)	Ex vivo: 24 or 48 h hypoxia-hypothermia graft storage +/− Xe, before transplantation 24 h hypothermia-hypoxia +/− Xe, +/− 6 h HSP70-siRNA pretreatment	Xe upregulates Bcl-2 and HSP70 in renal grafts to promote survival and repair, and inhibits mitochondrial release of proapoptotic factors and nuclear release of proinflammatory HMGB1
Zhao et al. [121]	FASEB J	Human proximal tubular cells/HK2 Norway brown-to-Lewis (allograft) rat kidney transplantation	Xe (70 %), HOl-siRNA (20 nM), HSP70-siRNA (20 nM) Xe (70 %)	2 h Xe 24 h before or after 24 h hypothermia-hypoxia, +/− 6 h siRNA before Xe exposure 2 h donor Xe-PC 24 h before organ retrieval, or 2 h recipient Xe-PostC after engraftment; graft cold-ischemia storage up to 24 h	Xe-PC and Xe-PosiC protect against acute renal graft injury through OH-1 and HSP70 upregulation and suppressed NFκB activation, MHC II expression, and immune cell infiltration

Toll-like-receptor 4 to induce NFκB transactivation, thus avoiding an inflammatory and immunogenic cascade that would result in allograft rejection. The new publications in this field are summarized in Table 5.

Clinical evidence and implications

Cardioprotection

Two meta-analytic studies failed to show improvements in primary clinical outcomes, e.g., hospital mortality and myocardial infarction, between coronary artery bypass grafting (CABG) patients who received either inhalational or intravenous anesthesia [122], albeit visible improvements in secondary endpoint marks, such as reduced cardiac troponin I release. However, when only desflurane and sevoflurane anesthesia are concerned, the postoperative risk of all-cause mortality and acute myocardial infarct is remarkably lower compared with IV anesthesia during on-pump CABG [123] (0.4 % vs. 1.6 % and 2.4 % vs. 5.1 %), together with reduced TnI leakage and ICU stay. Perioperative medications and comorbidities could influence the efficacy of inhalational anesthetic-mediated cardioprotection; certain anesthetics were shown to interfere with K_{ATP} channel activity, and in diabetic and hypercholesterolemic animals cardioprotection by preconditioning was considerably attenuated. Moreover, a post-infarct remodeled heart is likely to be less receptive to and amendable by inhalational anesthetic preconditioning.

Neuroprotection

Sevoflurane anesthesia during on-pump CABG did not confer superior neuroprotection to propofol, as the incidence of cognitive dysfunction 6 months post operation was comparable between patients who received either anesthetic [124]. Disturbingly, isoflurane as a GABA-receptor agonist when administered alone, or in combination (midazolam/N_2O), has been reported to induce neurodegenerative apoptosis in neonatal rodent brains during the critical period of synaptogenesis, adversely affecting perinatal neuronal development and inflicting long-term behavioral and neurocognitive impairment [125]. Its effect was even enhanced by nociceptive stimuli [126]. However, anesthetic(s)-induced neuronal apoptosis in the developing brain does not directly translate into equivalent neurotoxicity in clinical pediatric anesthesia, and hence this area of research warrants further studies both preclinically and clinically [127].

Renoprotection

Use of cardiopulmonary bypass (CBP) during CABG can cause systemic inflammation and embolism to the whole body, leading to multiorgan dysfunctions. Acute renal failure represents the most prominent noncardiac complication during CABG with CPB, with acute renal failure (ARF) incidence as high as 16 % and an associated mortality of 13 %. Sevoflurane anaesthesia during on-pump CABG lowered serum cystatin C, an indicator of preserved glomerular filtration rate [18]. However, when the incidence of postoperative acute kidney injury was assessed, inhalational anesthetics did not confer superior renoprotection in CBP-based open heart surgery (CABG, valve surgery, aortic surgery, and combined) compared to opioid anesthetics [128].

Future prospects

The noble gas xenon as an emerging inhalational anesthetic exhibits several advantages, notably its rapid induction and emergence compared with equi-MAC nitrous oxide/isoflurane and nitrous oxide/sevoflurane anaesthesia, and most remarkably its cardiovascular stability, a trait proven to be clinically useful in high-risk/compromised patients during cardiac operations [129]. Xenon-mediated cardioprotection against I/R injury is well documented in animal studies as preconditioning or postconditioning [130], giving rise to the potential use of xenon for attenuating perioperative cardiac I/R injury, and post hoc in acute myocardial infarct patients.

Xenon was demonstrated to be an exceptional neuroprotectant during I/R, CBP, and glutamate receptor stimulation-induced neuron injury in vitro and in vivo, even at subanesthetic concentrations [129, 131–133]. Remarkably, xenon mitigated whereas N_2O aggravated isoflurane-induced cerebral apoptosis in neonatal rodents, albeit both are NMDA-receptor antagonists [134]. The neurotoxicity-free profile and apoptosis-mitigating effect of xenon in neonatal animals make it a desirable agent to be incorporated into current pediatric/obstetric anesthesia and perinatal care practice to preempt ischemic neuronal injury in newborns. Well-organized and adequately powered clinical trials with primary, tangible, and reproducible endpoints are warranted to ascertain the cardioprotective, neuroprotective, and renoprotective efficacy of xenon in different clinical settings.

Conclusion

It has become apparent that some of the fundamental organoprotective mechanisms of inhalational anesthetics are conserved between vital organs, including the recruitment of prosurvival kinase cascades, release of free radicals, opening of mitochondrial K_{ATP} channels/modulation of mitochondrial permeability transition, and alteration of gene expression. However, to what extent the molecular evidence obtained from animal studies could be extrapolated and translated to humans is questionable and requires further verification. Nonetheless, a comprehensive understanding of the intracellular mechanisms would invariably propel the clinical application of inhalational anesthetics, along with improving knowledge of the different administration paradigms (pre-/postconditioning), and could permit tailored and optimized administration protocols under different clinical scenarios.

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Conflict of interest Authors claim no conflict of interest.

Appendix

Appendix-Abbreviations used in the tables

2-MPG	*N*-(2-Mercapto propionyl)glycine, free radical ROS scavenger
5-HD	5-Hydroxydecanoate, selective mitochondrial K_{ATP} channel antagonist
7-NI	7-Nitroindazole, selective neuronal NOS inhibitor
AG	Aminoguanidine, selective iNOS inhibitor
AIP	Autocamtide-2-related inhibitory peptide, specific peptide inhibitor of calmodulin kinase II
APV	(2R)-Amino-5-phosphonovaleric acid, specific NMDA receptor antagonist
ATR	Atractyloside, mitochondrial permeability transition pore opener
BAL	Balcalein, selective 12-lipoxygenase inhibitor
CDC	Cinnamyl-3,4-dihydroxy cyanocinnamate, selective 12-lipoxygenase inhibitor
CEL	Celecoxib, selective COX-2 inhibitor
CGS-21680	Selective agonist of adenosine A2A receptor
CHE	Chelerythrine, PKC inhibitor that affects cellular PKC translocation
CsA	Cyclosporine A, specific mitochondrial permeability transition pore inhibitor
DDTC	Diethyldithiocarbamate, NFκB inhibitor
DIAZO	Diazoxide, specific mitoK_{ATP} channel opener
GELD	Geldanamycin, specific HSP90 inhibitor
GLB	Glyburide, nonselective K_{ATP} channel inhibitor
IbTX	Iberiotoxin, selective BK_{Ca} inhibitor
KN93	Specific inhibitor of calmodulin kinase II
L-NAME	N^G-nitro-L-arginine methyl ester (L-NAME), nonselective nitric oxide synthase inhibitor
L-NMMA	*N*-G-mono-methyl-L-arginine monoacetate, methyl-derivative of arginine and a NOS inhibitor
LY294002	Specific PI3K inhibitor
M[beta]CD	Methyl-[beta]-cyclodextrin, depletes membrane cholesterol and disrupts caveolae
MOR	Morphine
NAC	*N*-Acetyl-L-cysteine, antioxidant and free radical scavenger
NAL	Naloxone, nonselective opioid receptor antagonist
NS-398	*N*-2-Cyclohexyloxy-4-nitrophenyl-methanesulphonamide, selective COX-2 inhibitor
NS1619	Selective BK_{Ca} activator
PD98059	Specific inhibitor of MEK1 and ERK1/2
PFT-α, pifithrin-α	Specific p53 inhibitor
PKC3V1-2	PKC-ε-specific inhibitor
PTN	Parthenolide, NFκB inhibitor
RAD	Radicicol, specific HSP90 inhibitor
RAP	Rapamycin, specific mTOR/p70s6K inhibitor
Rottlerin	PKC-δ-specific inhibitor
SC-514	Selective IKK-2/beta inhibitor to activate NFκB
SMT	*S*-Methylisothiourea, selective iNOS inhibitor
Wort	Wortmannin, specific PI3K inhibitor

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