Volatile anesthetic-induced cardiac preconditioning

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Abstract

Pharmacological preconditioning with volatile anesthetics, or anesthetic-induced preconditioning (APC), is a phenomenon whereby a brief exposure to volatile anesthetic agents protects the heart from the potentially fatal consequences of a subsequent prolonged period of myocardial ischemia and reperfusion. Although not completely elucidated, the cellular and molecular mechanisms of APC appear to mimic those of ischemic preconditioning, the most powerful endogenous cardioprotective mechanism. This article reviews recently accumulated evidence underscoring the importance of mitochondria, reactive oxygen species, and K_{ATP} channels in cardioprotective signaling by volatile anesthetics. Moreover, the article addresses current concepts and controversies regarding the specific roles of the mitochondrial and the sarcolemmal K_{ATP} channels in APC.

Key words K_{ATP} channel · Mitochondria · Myocardium · Preconditioning · Volatile anesthetics

Introduction

Cardiovascular disease remains a major healthcare problem in the United States and in many other developed countries. This disease significantly affects the clinical outcome of both cardiac and noncardiac surgery. It has been well documented that perioperative myocardial ischemia and infarction are the leading cause of morbidity and mortality following anesthesia and surgery. A high incidence of myocardial ischemia and infarction, congestive heart failure, and dysrhythmias encountered during the intra- or postoperative periods has incited research efforts to develop protective interventions for decreasing the cardiac risk in patients with cardiovascular disease. Parallel to the most

powerful endogenous cardioprotective mechanism of ischemic preconditioning [1], pharmacological preconditioning with volatile anesthetics, or anesthetic-induced preconditioning (APC), emerged as a considerably less risk-bearing but equally effective cardioprotective intervention [2]. From that period of time, experimental and clinical research has focused on elucidating the mechanisms of APC in the hope of finding the anesthetic agent most beneficial for patients with coronary artery disease. Extensive research conducted in many laboratories throughout the world has advanced our understanding of the mechanisms of anesthetic preconditioning, a phenomenon whereby a brief exposure to volatile anesthetic agents protects the heart from the consequences of subsequent prolonged ischemic insult. It is now recognized that the cellular signaling of APC involves protein kinase C (PKC), protein tyrosine kinase (PTK), mitogen-activated protein kinases (MAPK), protein kinase B (Akt), mitochondria, and last but not least, the ion channels, in particular the mitochondrial and the sarcolemmal K_{ATP} channels. The mechanisms of APC have been the subject of several detailed review articles [3–12]. The current review will focus on recent findings regarding subcellular constituents that are thought to be essential for the cardioprotective effects of APC: the mitochondria with their reactive oxygen species (ROS) production, the putative mitochondrial K_{ATP} channels, and the sarcolemmal K_{ATP} channels (Fig. 1).

Mitochondria, reactive oxygen species, and mitochondrial K_{ATP} channels

Mitochondria appear to play a central role in the protective effects produced by the volatile anesthetics against ischemia and reperfusion injury. It has long been established that drugs with anesthetic properties have depressant effects on mitochondrial function [13].
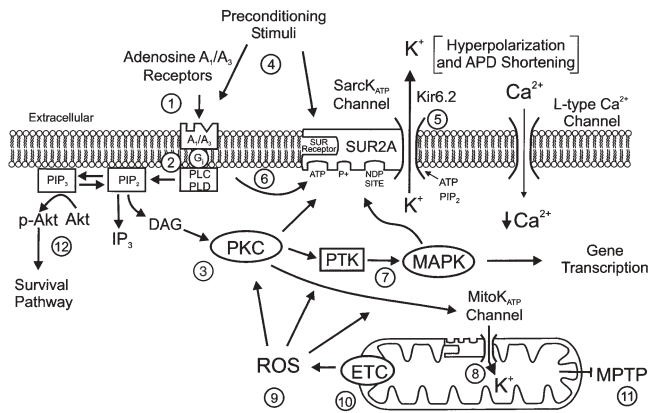
Fig. 1. Schematic diagram of some of the cellular sites and pathways thought to be involved in anesthetic-induced preconditioning (APC): *1. A_1/A_3*, adenosine receptors; *2. G_i* proteins; *3. PKC*, protein kinase C; *4.* preconditioning stimuli; *5.* direct anesthetic/K_{ATP} channel interaction; *6.* intracellular K_{ATP} channel regulators: ATP, NDP, phosphatidylinositol 4, 5-bisphosphate (*PIP_2*); *7. PTK*, protein tyrosine kinase and *MAPK*, mitogen activated protein kinase; *8.* mitochondrial redox state; *9. ROS*, reactive oxygen species; *10. ETC*, electron transport chain; *11. MPTP*, mitochondrial permeability transition pore; *12. Akt*, protein kinase B signaling and survival pathway. *Mito*, mitochondrial; *Sarc*, sarcolemmal; *APD*, action potential duration, *SUR*, sulfonylurea receptor; *PLC*, phospholipase C; *PLD*, phospholipase D; *DAG*, diacylglycerol

Studies of cardiac mitochondria exposed to halothane, isoflurane, and sevoflurane have suggested that complex I of the respiratory chain is the most common site of anesthetic action [14]. This is in agreement with findings that sevoflurane increased concentration of reduced nicotinamide-adenine dinucleotide (NADH) in isolated guinea pig hearts [15]. The slowing respiration at certain complexes of the respiratory chain may cause an electron leak and subsequently lead to the augmented generation of ROS. Indeed, similar to ischemic preconditioning, there is compelling evidence for a role of ROS in the phenomenon of APC. Radical scavengers administered to rabbits in vivo during treatment with isoflurane abrogated the protection of APC against ischemia and reperfusion [16,17]. In a study on isolated guinea pig hearts, preconditioning with sevoflurane caused an immediate and reversible increase in fluorescence of the ROS indicator dihydroethidium, as determined spectrophotometrically in real-time measurements [18]. Complex III of the respiratory chain might also be a source of ROS during APC. The complex III inhibitor myxothiazol, but not the complex I inhibitor diphenyleneiodonium, abolished ROS generation and prevented the isoflurane-induced myocardial infarct size reduction [19]. Taken together, these findings indicate that ROS generation during APC is a critical trigger for cellular protection. It is important to

note that, in contrast to the requirement that minute amounts of ROS must be generated to initiate APC, the protection conferred by APC also involves a decrease in the detrimental large bursts of ROS that occur during ischemia and on reperfusion [18]. Elevated ROS production on reperfusion, together with increased mitochondrial Ca^{2+}, may cause opening of the mitochondrial permeability transition pore, leading to both apoptotic and necrotic cell death. To this end, desflurane was found to improve the resistance of the mitochondrial permeability transition pore to calcium-induced opening after ischemia and reperfusion [20], and isoflurane attenuated the apoptosis induced by hypoxia and reperfusion under both in vitro [21] and in vivo [22] conditions. The suppression of ROS formation observed during treatment with anesthetics is thought to trigger a tyrosine kinase cascade and a protein kinase C cascade, thus mediating a memory effect that lasts beyond withdrawal of the anesthetic, affecting the mitochondrial (mito) and sarcolemmal (sarc) K_{ATP} channel function [23–25]. While the identity of the sarcK_{ATP} channel is well established (see below) the molecular structure and even the existence of the mitoK_{ATP} channel are still under debate. Pertaining to the molecular structure of these channels, suggestions range from the well-known subunits of the sarcK_{ATP} channel [26] to a multiprotein complex comprised of succinate dehydrogenase, mitochondrial ATP-binding cassette protein 1, adenine nucleotide translocator (ANT), ATP synthase, and inorganic phosphate carrier [27]. Evidence for the importance of mitoK_{ATP} channels in cardiac preconditioning has been primarily based on pharmacological studies that utilized putative mitoK_{ATP} channel activators and inhibitors such as diazoxide and 5-hydroxydecanoate (5-HD). However, the lack of specificity of mitoK_{ATP} openers and blockers should not be ignored, based on the evidence that the channel openers, diazoxide and pinacidil, can also target components of the respiratory chain [28], and the blocker 5-HD exhibits complex metabolic effects on fatty acid oxidation [29]. In rabbit [30] and rat [31] in vivo models, 5-HD abolishes pharmacological preconditioning by isoflurane. In a cellular model of ischemia, Zaugg et al. [24] demonstrated that isoflurane and sevoflurane mediated cardiomyocyte protection by potentiating diazoxide-activated mitoK_{ATP} channels. This indirect effect was abolished by 5-HD, implying that the mitoK_{ATP} channels are responsible for the cytoprotection conferred by volatile anesthetics. Opening of the mitoK_{ATP} channels can be assessed indirectly by monitoring the native auto-fluorescence of mitochondrial flavoprotein, because it has been suggested that the mitochondrial redox state reflects the activity of the mitoK_{ATP} channel [32]. Yet it is unclear how the increase in flavoprotein fluorescence that corresponds to the increased rate of

mitochondrial oxidation agrees with the aforementioned increase in NADH observed during preconditioning. This could possibly be explained by differences in the energetic state of cardiomyocytes in different experimental models. In contrast to the intravenous anesthetics, the volatile anesthetics isoflurane and sevoflurane both increased flavoprotein fluorescence in intact guinea pig and rat cardiomyocytes [33–35], as well as in isolated rat hearts [36]. In fact, the latter study suggested that the activation of mitoK_{ATP} channels was essential both for preconditioning triggering and for mediating the cardioprotection conferred by isoflurane. This dual action of the mitoK_{ATP} channel was confirmed in a recent in vitro study on isolated adult rat cardiomyocytes, using the mitoK_{ATP} channel inhibitor 5-HD [37]. More specific evidence for the direct action of volatile anesthetics on the mitoK_{ATP} channel was obtained using inner mitochondrial membranes reconstituted in lipid bilayers [38]. In that study, the mitoK_{ATP} channels were identified and characterized based on their electrophysiological properties, sensitivity to activation by diazoxide, and inhibition by 5-HD. In that model, isoflurane was demonstrated to increase the open probability of mitoK_{ATP} channels and decrease channel sensitivity to ATP [38].

The question of how the opening of mitoK_{ATP} channels leads to cardioprotection remains controversial, and several mechanisms have been suggested. Holmuhamedov et al. [39] proposed that opening of the mitoK_{ATP} channel prevented fatal mitochondrial Ca^{2+} overload by inducing mitochondrial depolarization. Indeed, APC attenuates cytoplasmic [40] and mitochondrial [35,41] Ca^{2+} loading, it has been demonstrated that this effect is antagonized by 5-HD [35,41]. In contrast, other investigators did not observe significant changes in the mitochondrial membrane potential when mitoK_{ATP} channel openers were used in effective concentrations, and suggested that mitoK_{ATP} channels play a role in the regulation of matrix volume and pH [42,43]. A recent study by Tanaka et al. [44] has provided evidence that the isoflurane-induced opening of the mitoK_{ATP} channel leads to the generation of ROS, which trigger APC. These findings were based on the observation that 5-HD prevented the increase in dihydroethidium fluorescence when given before, but not after, the administration of isoflurane. However, controversy exists regarding the temporal relation between the opening of the mitoK_{ATP} channel and ROS production. In isolated guinea pig hearts, 5-HD did not prevent the sevoflurane-induced increase in ROS fluorescence, but it did abolish the protection of the heart conferred by preconditioning [18]. Thus, while it is evident that mitochondria play a crucial role in the phenomenon of anesthetic preconditioning, the exact role of the mitoK_{ATP} channel will require further clarification.

Sarcolemmal K_{ATP} channels

The sarcolemmal ATP-sensitive potassium channel (sarcK_{ATP} channel) was discovered more than 20 years ago by Noma [45] in the heart, and was subsequently described in pancreatic β-cells, skeletal muscle, vascular and nonvascular smooth muscle, brain, and peripheral neurons. The K_{ATP} channels are gated by intracellular nucleotides, whereby intracellular ATP closes the channel, but intracellular Mg-ADP enhances channel activity. These channels, therefore, are sensors of the cellular metabolic state and couple the metabolism with the electrical activity of the cell [45]. Although expressed at a very high density in the plasma membrane of cardiomyocytes, sarcK_{ATP} channels remain predominantly closed under normal physiological conditions when the levels of intracellular ATP are high. Thus, under normal conditions, they do not contribute to the resting membrane potential of myocardial cells, and their exact physiological role is still unclear [46]. However, the sarcK_{ATP} channels open during metabolic stress, such as ischemia or hypoxia, and their opening results in K^+ efflux and membrane hyperpolarization that stabilizes the membrane potential near the K^+ equilibrium potential, and leads to the closing of L-type calcium channels and shortening of the action potential [45,47]. The protective effects of sarcK_{ATP} channel opening have been attributed to these profound effects on cell excitability that help to maintain cellular homeostasis during stress, most likely through decreasing potentially detrimental intracellular Ca^{2+} loading [48,49].

The cardiac sarcK_{ATP} channels are hetero-octameric complexes of two protein subunits, the pore-forming inward rectifying Kir6.2 channel and the regulatory sulfonylurea receptor SUR2A [50,51]. The binding of intracellular ATP to sites on each Kir6.2 subunit promotes channel closure, and this effect is counteracted by intracellular phosphatidylinositol-4,5-bisphosphate (PIP$_2$). In addition, binding of Mg-ATP and Mg-ADP at the nucleotide binding domains of SUR2A opposes the inhibitory effects of Kir6.2-bound ATP and enhances channel opening [52]. Pharmacological modulators of the K_{ATP} channel—the openers: pinacidil, cromakalim, and nicorandil; and the blockers: glibenclamide and HMR-1098—exert their actions through binding to defined sites on the SUR2A subunit.

Although the exact physiological role of the cardiac sarcK_{ATP} channel is not completely elucidated, evidence is accumulating that these channels play an important role in myocardial protection from metabolic stress, ischemia/reperfusion injury, and cardiac arrhythmias, and in myocardial preconditioning. The role of sarcK_{ATP} channels in cardioprotection has been extensively studied using pharmacological and genetic approaches, including the disruption of K_{ATP} channel subunits. The

lack of functional K_{ATP} channels in Kir6.2 knockout mice is associated with reduced tolerance to stress and exercise, and increased mortality due to augmented myocardial Ca^{2+} loading [53–55]. Only recently, mutations within the sarcK_{ATP} channel were related to cardiac disease in humans. Two mutations that alter the metabolic gating of the K_{ATP} channel were identified within a gene encoding for SUR2A in patients suffering from severe idiopathic dilated cardiomyopathy [56].

As indicated above, the sarcK_{ATP} channel appears to play an important role in the phenomenon of cardiac preconditioning, including APC. The cardioprotective effects of ischemic preconditioning were initially attributed to the opening of sarcK_{ATP} channels [57], because preconditioning could have been mimicked with K_{ATP} channel openers and prevented by K_{ATP} channel blockers. Although initially the protective effects of sarcK_{ATP} channel opening were attributed to a shortening of the action potential, later studies have demonstrated that the cardioprotective effects of K_{ATP} channel opening are independent of action potential shortening [58,59]. Following a more recent discovery of mitoK_{ATP} channels in the inner mitochondrial membrane [60] and the development of selective mito- and sarcK_{ATP} channel blockers, experimental evidence has suggested that mitoK_{ATP} channels, rather than sarcK_{ATP} channels, play an essential role in cardioprotection [61,62]. HMR-1098, a specific inhibitor of the sarcK_{ATP} channel, has often failed to abolish the protection conferred by ischemic and pharmacological preconditioning, while cardioprotection was elicited by the mitoK_{ATP} channel opener diazoxide [62,63]. These findings have led to a widespread opinion that the cardioprotective effects of preconditioning are dependent on the opening of the mitoK_{ATP} channel. However, the results of more recent studies suggest that the potential involvement of sarcK_{ATP} channels in cardioprotection should not be ignored [49,64,65].

The first studies that suggested the possibility of APC demonstrated that treatment with isoflurane improved the contractile recovery of stunned myocardium [2] and that inhibition of the K_{ATP} channel by glibenclamide completely abolished the protection conferred by isoflurane in an in vivo canine model [66]. Subsequently, a role of K_{ATP} channels in APC has been demonstrated in several other species, using different experimental models [17]. The majority of studies pointed to the mitoK_{ATP} channel as the main contributor to myocardial protection, while finding no apparent involvement of the sarcK_{ATP} channels [24,67–69]. However, a few studies have demonstrated that sarcK_{ATP} channels play an important role in APC [30,70,37]. A recent study that utilized the isolated rat cardiomyocyte model revealed that sarcK_{ATP} channels were essential contributors to

APC, acting as an effector [37]. Pronounced differences in results from studies that have investigated the role of sarcK_{ATP} channels in APC may be attributed to differences in the experimental models (acutely isolated cardiomyocytes, atrial trabeculae, Langendorff perfused isolated hearts, in vivo preparation) and differences in the type of insult on the myocardium (ischemia and reperfusion in vivo, simulated ischemia without reperfusion, hypoxia, oxidative stress, metabolic inhibition). Moreover, the measured endpoints of cardiac injury differ substantially as well (cell death or infarcted area versus functional parameters such as developed force of contraction). Finally, there are differences in the timing and duration of application of pharmacological inhibitors (application during preconditioning stimulus versus application during stress period). In the study by Marinovic et al. [37], the timing of HMR-1098, but not 5-HD application, was found to be crucial. When HMR-1098 was applied only during the preconditioning stimulus (isoflurane exposure), cytoprotection was still present, but when HMR-1098 was applied during stress only, the cytoprotective effect of isoflurane was abolished. Therefore, when evaluating the results of studies that test the role of sarcK_{ATP} channels in preconditioning, the timing of application of the channel blockers is an important factor to be considered.

Nearly all studies investigating the role of K_{ATP} channels in APC have demonstrated that channel blockade abolishes the protective effects of preconditioning. However, inhibition of K_{ATP} channels in the absence of preconditioning did not affect the baseline damage caused by various stresses. This suggests that preconditioning by anoxia, ischemia, anesthetics, or other stimuli specifically influences the function of K_{ATP} channels. That preconditioning alters the function of sarcK_{ATP} channels has indeed been demonstrated in a number of studies. Zhu et al. [71] showed that anoxic preconditioning of isolated guinea pig cardiomyocytes shortened the latency of sarcK_{ATP} channel opening during metabolic inhibition and enhanced the K_{ATP} channel current, and these effects were mediated by PKC. In another more recent study, Budas et al. [72] demonstrated that hypoxic preconditioning of single beating cardiomyocytes enhanced the opening of sarcK_{ATP} channels during subsequent prolonged hypoxia compared to control nonpreconditioned myocytes.

Volatile anesthetics that produce preconditioning have been shown to also modulate the function of the cardiac sarcK_{ATP} channel. The first patch-clamp study of the effects of volatile anesthetics on the sarcK_{ATP} channel demonstrated that isoflurane directly inhibited the activity of single K_{ATP} channels and decreased the channel sensitivity to inhibition by intracellular ATP [73]. Subsequently, the direct effects of isoflurane on the sarcK_{ATP} channel were shown to be pH-dependent [74].

Under excised patch configuration, in inside-out membrane patches from guinea pig ventricular myocytes and at intracellular pH 7.4, isoflurane either had no effect or tended to decrease channel activity. However, at moderately acidic intracellular pH 6.8, as occurs during early ischemia, isoflurane enhanced the activity of single sarcK_{ATP} channels by increasing the channel open-state probability and decreasing channel sensitivity to inhibition by intracellular ATP [74]. This direct pH-dependent interaction of isoflurane with the sarcK_{ATP} channel was found to be mediated by the nucleotide binding domains (NBD) of SUR2A, specifically, the NBD1 domain [75]. In addition to direct interaction between isoflurane and the K_{ATP} channel, a whole-cell patch-clamp study by Kwok et al. [76] has demonstrated that isoflurane may also indirectly modulate the sarcK_{ATP} channel. Although unable to open the channel, isoflurane markedly increased the K_{ATP} current pre-activated by either the metabolic inhibitor 2,4-dinitrophenol or the K_{ATP} channel opener, pinacidil [76]. However, isoflurane-induced facilitation of the sarcK_{ATP} channel was evident only in the intact cells, under whole-cell patch clamp or in the cell-attached mode, but not under cell-free conditions, in the inside-out membrane patches [77]. Subsequently, intracellular mediators of isoflurane actions on the sarcK_{ATP} channel were identified. Some of them include PTK [23], PKC [78–80], adenosine [81], ROS [82] (Fig. 1) and phosphatidylinositol-3 kinase (PI3K) [81]. In addition to these acute and immediate effects, isoflurane was shown to produce a long-lasting effect on the sarcK_{ATP} channel that corresponds to the early memory phase of APC. A whole-cell patch-clamp study by Marinovic et al. [80] demonstrated that the transient exposure of isolated cardiomyocytes to isoflurane sensitized the sarcK_{ATP} channel to opening, and the effect persisted even after withdrawal of the anesthetic. This effect was independent of the mode of anesthetic application, and continued after in vivo rat exposure to isoflurane (in vivo APC) and for several hours following APC with isoflurane [83]. The same study demonstrated that, during the memory phase, following in vivo APC, channel sensitivity to inhibition by ATP was markedly attenuated, suggesting that these channels would be more likely to open at higher intracellular levels of ATP [83]. Furthermore, there is evidence that, in isolated rat ventricular cardiomyocytes, PKC-δ, a classical PKC isoform, is the most likely candidate mediator of the memory phase of APC induced by isoflurane [80]. Thus, isoflurane appears to have dual action on the cardiac sarcK_{ATP} channel: a direct one that is more pronounced at moderately acidic intracellular pH as it occurs during early ischemia, and an indirect one that is mediated by PKC.

Conclusion

Intense research efforts have brought about new findings regarding the roles of cardiac mitochondria, ROS, and the mitoK_{ATP} and sarcK_{ATP} channels in the myocardial protection conferred by volatile anesthetics. Data from experimental animal studies support the concept of the leading role of cardiac mitochondria and the importance of the mitoK_{ATP} channel as a trigger and an effector of APC, while the sarcK_{ATP} channel appears to be an effector of APC. Although some of the controversies regarding the respective roles of mito- and sarc-K_{ATP} channels have been clarified, further investigations are required to find answers to these questions. Last but not least, it remains to be determined whether the findings from experimental animal work would be applicable in the clinical situation to patients with cardiovascular disease and whether patients at high risk for ischemia and infarction would benefit from anesthetic preconditioning.

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