ORIGINAL

Isoflurane-induced postconditioning via mitochondrial calcium-activated potassium channels

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Abstract : Purpose : Activation of the mitochondrial calcium-activated potassium (mK_{Ca}) channel reportedly confers resistance to myocardial ischemic stress. However, the role of the mK_{Ca} channel in postconditioning induced by volatile anesthetic remains unclear. Methods : Male Japanese white rabbits underwent coronary artery occlusion for 30 min followed by reperfusion for 3 h. Volatile anesthetic, isoflurane, was administered at 3 min prior to reperfusion for 5 min. Rabbits were injected with the mK_{Ca} channel blocker, iberiotoxin, or the mK_{Ca} channel opener, NS1619, at 8 min prior to reperfusion. Myocardial infarct size and the area at risk (AAR) were measured at the end of the experiment. Results : Isoflurane significantly reduced infarct size (23.0±9.8% of the AAR, $P<0.05$) compared with the control (44.0±9.1%). Iberiotoxin abolished the cardioprotective impact of isoflurane (43.0±11.6%), while iberiotoxin alone exerted no effect on infarct size (45.0±9.5%). NS1619 and isoflurane/NS1619 both significantly reduced infarct size (21.0±10.3% and 19.0±8.8%, respectively, $P<0.05$ vs control group), but isoflurane/NS1619 showed no additional benefits compared with isoflurane alone. Conclusion : These results indicate that activation of the mK_{Ca} channel contribute isoflurane-induced postconditioning. J. Med. Invest. 63 : 80-84, February, 2016

Keywords **:** *Mitochondrial calcium-activated potassium channel, Anesthetic-induced postconditioning, Isoflurane*

INTRODUCTION

Volatile anesthetics, such as isoflurane, sevoflurane and desflurane, have cardioprotective effects and reduce myocardial infarct size after ischemia/reperfusion injury (1). This phenomenon is termed anesthetic-induced preconditioning when the volatile compounds are administered before ischemia (1, 2), and anesthetic-induced postconditioning when they are administered in the early minutes of reperfusion (3). A large number of studies have investigated the cardioprotective mechanisms of volatile anesthetic-induced preconditioning and postconditioning, and current evidence indicates that these processes may share some of the same signaling pathway(s) and/or signaling components (4-6).

The mitochondrial calcium-activated potassium (mK_{Ca}) channel is also involved in conferring resistance to ischemic stress (7-11). Notably, morphine-induced postconditioning is mediated by activation (opening) of the mK_{Ca} channel (11), which similarly regulates desflurane-induced preconditioning (12). These studies indicate that the cardioprotective effects of certain drugs are associated with the activation/opening of the mK_{Ca} channel. However, few reports are available regarding this subject, and the role of the mK_{Ca} channel in postconditioning induced by volatile anesthetics. Therefore, we evaluated the connection between mK_{Ca} channel activation and isoflurane-induced postconditioning.

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METHODS

Approvals

All experimental procedures and protocols in the present study were approved by the Animal Investigation Committee of Tokushima University (3-8-15 Kuramoto Tokushima 770-8503, Japan). The experiments were conducted according to the animal use guidelines of the American Physiologic Society (Bethesda, MD) (13).

Surgery

Japanese white rabbits (male, 13 weeks old at experimental onset, 2.5-3.0 kg) were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Additional doses of pentobarbital were administered as necessary, such that the pedal and palpebral reflexes were absent throughout the experiment. After the rabbits became unresponsive, they were subjected to a tracheostomy procedure and tracheal cannulation. The animals were then ventilated with positive pressure by using 100% oxygen. The respiratory rate and tidal volume were adjusted so as to maintain arterial blood gas tension and acid-base status within a normal physiologic range (pH 7.35-7.45, $PaCO_2$ (partial pressure of arterial CO_2) 25-40 mmHg) throughout the experiment.

Heparin-filled catheters were inserted into the right carotid artery and the left jugular vein for the measurement of arterial blood pressure and fluid or drug concentration, respectively. Lactated Ringer's solution was continuously infused (15 $ml \cdot kg^{-1} \cdot h^{-1}$) as a maintenance fluid throughout the experiment. A heating blanket was used to maintain body temperature at 38.5°C. A left thoracotomy was performed at the fourth intercostal space. After identification of a prominent branch of the left anterior descending coronary artery (LAD), the rabbits were anticoagulated with heparin (500 U i.v.), and a monofilament ligature was placed around the branch at a position approximately half way between the base of the branch and the apex to produce coronary artery occlusion and reperfusion. The rabbits were then observed for epicardial cyanosis and an

epicardial hyperemic response to accurately verify coronary artery occlusion and reperfusion, respectively. Hemodynamic data were continuously recorded on a polygraph throughout the experimental period.

Postconditioning

The experimental design is shown in Figure 1. All rabbits were randomly assigned to one of six experimental groups, as described below. Baselines of systemic hemodynamic data were recorded in each group for 30 min after instrumentation was complete. Each rabbit underwent 30 min of LAD occlusion as described above, followed by 180 min of reperfusion.

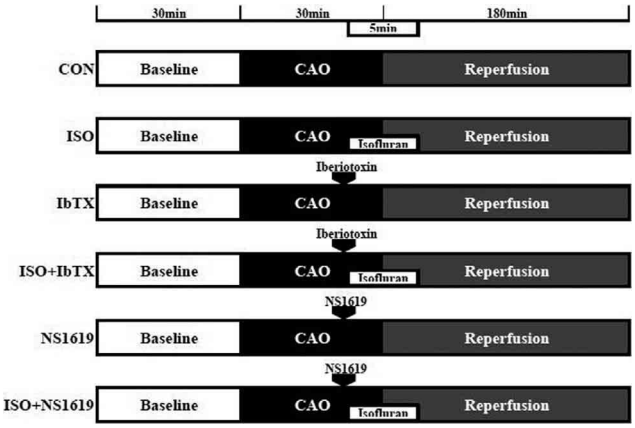

Figure 1. Schematic diagram of the experimental protocol
CAO = left anterior descending coronary artery occlusion.
CON = control ; ISO = isoflurane ; IbTX = iberiotoxin.

Group 1 rabbits (control, CON) received no treatment during or after LAD occlusion. Group 2 rabbits (ISO) received 1.0 minimum alveolar concentration (MAC) isoflurane (2.1%) for 5 min, administered at 3 min prior to reperfusion. Group 3 rabbits (iberiotoxin, IbTX) received the mK_{Ca} channel blocker, iberiotoxin (10 μg/kg), via intravenous injection at 8 min prior to reperfusion. Group 4 rabbits (ISO+IbTX) received iberiotoxin (10 μg/kg) via intravenous injection at 8 min prior to reperfusion plus 1.0 MAC isoflurane for 5 min, administered at 3 min prior to reperfusion. Group 5 rabbits (NS1619) received the mK_{Ca} channel opener, NS 1619 (200 μg/kg), via intravenous injection at 8 min prior to reperfusion. Group 6 rabbits (ISO+NS1619) received NS1619 (200 μg/kg) via intravenous injection at 8 min prior to reperfusion plus 1.0 MAC isoflurane for 5 min, administered at 3 min prior to reperfusion.

The expiration for each rabbit was sampled at the tip of the tracheal tube, and the concentration of end-tidal isofiurane was measured with an infrared anesthetic analyzer.

Determination of cardiac parameters

The size of the myocardial infarct, the area at risk for infarction (AAR) and the weight of the left ventricle (LV) were measured at the end of the experiment by dual staining technique. The myocardial infarct size and the AAR were determined as follows. After the LAD was again occluded, 10% methylene blue dye (3 ml) was intravenously injected into the animals to stain the non-ischemic area blue. The heart was removed under deep anesthesia immediately after the eyes of rabbits stained blue. Because the AAR did not stain blue, this at-risk area could readily be identified and separated from the surrounding normal areas of the heart, which did stain blue. The separated AAR was then incubated at 37°C for 30 min in 1% 2,3,5-triphenyltetrazolium chloride in 0.1 M phosphate buffer (adjusted to a pH of 7.4). After overnight storage in 10% formaldehyde, the non-infarcted myocardium stained red in the presence of dehydrogenase enzymes, on the other hand the infarcted myocardium within the AAR remained unstained because it lacks the activity of enzymes. The infarcted and non-infarcted portions of the AAR were carefully separated into small pieces and weighed, and the myocardial infarct size was expressed as a percentage of the total AAR (infarcted plus non-infarcted myocardium). Rabbits with intractable ventricular fibbits with and those with an AAR of less than 15% of the LV mass were excluded from subsequent analysis.

Statistical analysis

All data are expressed as means±standard deviation (SD). Statistical power analysis revealed a group size of n=6 to detect a difference in infarct size of 25% with sufficient power of 0.8 at an α level of 0.05. Seven or eight rabbits were included in each group. Statistical analyses were conducted using PASW software (version 18.0, SPSS Inc., Chicago, IL). Statistical comparisons of data between groups were performed with one-way analysis of variance (ANOVA) followed by the post-hoc Tukey-Kramer test. Statistical comparisons of data among groups were performed with two-way ANOVA followed by the post-hoc Tukey-Kramer test. A value of $P < 0.05$ was considered significant.

RESULTS

Fifty-three rabbits were instrumented to obtain 44 successful experimental data sets (CON, IbTX, NS1619, ISO+NS1619, n=7 ; ISO, ISO+IbTX, n=8). Three rabbits (two CON, one ISO+IbTX) were excluded from the study because the LV AAR was < 15% of the LV mass. Six rabbits (one CON, one ISO, one IbTX and three ISO+IbTX) were excluded because of intractable ventricular fibrillation.

Hemodynamics

Table 1 summarizes the results of the systemic hemodynamics analysis. At 3 h after LAD occlusion, the heart rates (HRs) in the ISO+IbTX, NS1619 and ISO+NS1619 groups were significantly lower than in the control (CON) group ($P < 0.05$). Furthermore, the mean arterial blood pressure (MABP) was significantly higher in the IbTX group than in the CON group ($P < 0.05$). However, no clear differences in the rate pressure product (RPP) were observed between the groups during the experimental period. In addition, the arterial blood gas tension and the acid-base status were successfully maintained within the normal range in all rabbits throughout the experiment.

Myocardial infarct size

Body weight, LV weight and the ratio of AAR to total LV mass (AAR/LV, %) were similar between groups (Table 2). Administration of 1.0 MAC isoflurane for 5 min during reperfusion (from 3 min prior to reperfusion until 2 min after reperfusion) significantly reduced the myocardial infarct size in ISO group rabbits compared with the control (CON) group (23.0±9.8% vs. 44.0±9.1% of the LV AAR, $P < 0.05$) (Figure 2). Administration of iberiotoxin alone at 8 min prior to reperfusion had no effect on infarct size (45.0±9.5%) relative to the control. However, the use of iberiotoxin at 5 min prior to isoflurane (8 min prior to reperfusion) eliminated the cardioprotective effect of the anesthetic, resulting in an infarct size of 43.0± 11.6%. On the other hand, administration of NS1619 at 8 min prior to reperfusion significantly reduced the infarct size (21.0±10.3%, $P < 0.05$), as did the combination of NS1619 and isoflurane (19.0±

Table 1. Hemodynamics

	Baseline	15 min LADO	Reperfusion 2 min	Reperfusion 1 h	Reperfusion 2 h	Reperfusion 3 h
HR, min^{-1}						
CON	265 (17)	247 (22)	250 (22)	249 (18)	237 (25)	249 (23)
ISO	265 (34)	252 (29)	252 (19)	246 (21)	254 (21)	253 (23)
IbTX	267 (18)	261 (26)	255 (15)	244 (11)*	234 (16)*	232 (12)*
ISO+IbTX	248 (36)	250 (22)	253 (22)	235 (16)	234 (14)	218 (9)*†
NS1619	273 (19)	262 (28)*	246 (14)*	235 (23)*	206 (12)*	213 (18)*†
ISO+NS1619	246 (21)	245 (19)	251 (28)	240 (16)	211 (24)*	210 (24)*†
MABP, mmHg						
CON	76 (14)	65 (10)*	60 (9)*	72 (12)	74 (12)	73 (15)
ISO	69 (10)	56 (5)*	45 (14)*	58 (8)	66 (12)	68 (12)
IbTX	82 (18)	82 (18)	83 (19)†	91 (13)	92 (25)	104 (18)*†
ISO+IbTX	75 (12)	68 (8)	65 (10)	75 (14)	80 (10)	78 (12)
NS1619	69 (9)	66 (11)	55 (8)*	63 (10)	67 (12)	69 (14)
ISO+NS1619	74 (11)	68 (12)	53 (19)*	67 (18)	66 (13)	68 (13)
RPP, min^{-1}·mmHg·10^3						
CON	24 (3.4)	19 (3.1)*	18 (3.2)*	21 (3.5)	20 (3.2)*	22 (4.1)
ISO	21 (4.0)	17 (2.3)*	14 (4.5)*	17 (2.4)*	20 (3.5)	20 (4.9)
IbTX	23 (6.3)	22 (5.2)	23 (5.4)	23 (3.2)	23 (4.5)	26 (4.9)
ISO+IbTX	22 (4.5)	20 (3.3)	22 (3.3)	22 (4.5)	22 (3.2)	20 (2.5)
NS1619	25 (3.4)	22 (3.2)	19 (2.6)*	20 (3.8)*	18 (3.7)*	19 (4.0)*
ISO+NS1619	22 (3.5)	20 (2.9)	18 (4.6)*	22 (2.8)	19 (3.6)	19 (3.4)

Data are given as means (SD).
LADO=left anterior descending coronary artery occlusion ; HR=heart rate ; MABP=mean arterial blood pressure ; RPP=rate pressure product.
CON=control ; ISO=isoflurane ; IbTX=iberiotoxin.
*Significantly different from baseline ($P< 0.05$).
† Significantly different from the respective value in control experiments ($P< 0.05$).

Table 2. Area at risk

	Body weight, kg	LV, g	AAR/LV, %
CON	2.66 (.22)	3.33 (.35)	39.4 (9.4)
ISO	2.59 (.24)	3.35 (.41)	41.0 (12.1)
IbTX	2.59 (.10)	3.35 (.16)	44.9 (12.2)
ISO+IbTX	2.51 (.13)	3.24 (.36)	42.1 (12.2)
NS1619	2.45 (.13)	2.84 (.18)	42.6 (6.6)
ISO+NS1619	2.51 (.13)	3.08 (.39)	40.4 (10.6)

Data are given as means (SD).
AAR=area at risk ; LV=left ventricle.
CON=control ; ISO=isoflurane ; IbTX=iberiotoxin.

8.8%, $P< 0.05$). Nonetheless, the NS1619/isoflurane combination was no more efficacious than either agent alone (Figure 2).

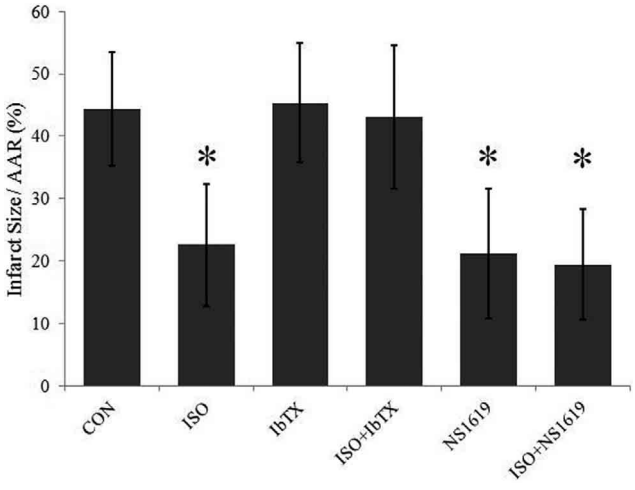

Figure 2. Myocardial infarct size expressed as a percentage of the area at risk (AAR)
CON=control ; ISO=isoflurane ; IbTX=iberiotoxin.
Data are given as means±SD.
*Significantly different from control ($P< 0.05$).

DISCUSSION

The current study set out to determine whether activation of the mK_{Ca} channel was related to isoflurane-induced postconditioning. Like isoflurane, the administration of NS1619, an mK_{Ca} channel opener, decreased myocardial infarct size after ischemia/reperfusion injury. These data support the hypothesis that the activation/opening of the mK_{Ca} channel contributes to the reduction of myocardial damage after ischemia reperfusion.

The administration of 1.0 MAC isoflurane during the early phase of reperfusion significantly decreased myocardial infarct size, reflecting the cardioprotective actions of isoflurane-induced postconditioning. However, this effect was overturned by the mK_{Ca} channel blocker, iberiotoxin, indicating that the activation of the mK_{Ca} channel critically participates in the cardioprotection exerted by isoflurane-induced postconditioning against ischemia/reperfusion injury. Therefore, the present investigation implies that the opening of the mK_{Ca} channel may be involved in a general mechanism of volatile anesthetic-induced postconditioning.

While relatively little information is available concerning the

drug-related actions of the mK_{Ca} channel, the mitochondrial permeability transition pore (mPTP) is widely regarded as an important end-factor in the cardioprotective mechanism of anesthetic-induced preconditioning and postconditioning (2, 14, 15). Inhibition of mPTP opening at the final step of selective signaling pathways achieves cardioprotection against ischemia/reperfusion injury (16, 17). Many complex processes, including mitochondrial Ca^{2+} overloading (2, 18), the generation of reactive oxygen species (ROS) (19-21), the activation of AKT/phosphoinositol 3-kinase (PI3-K)/glycogen synthase kinase 3 beta (GSK-3β) signaling cascades (15, 22), and molecular events involving endothelial nitric oxide synthase (eNOS) (23) are all related to the blockade of mPTP opening. For example, mitochondrial potassium channels can impede the opening of mPTP by controlling mitochondrial Ca^{2+} overloading (24-26). Although the mitochondrial ATP-sensitive potassium (mK_{ATP}) channel was initially thought to contribute to the inhibition of mitochondrial permeability transition (14), consensus regarding the association between the mK_{ATP} channel and mPTP has not been reached (24). On the other hand, the mK_{Ca} channel has become the subject of increasing focus (7, 8, 12, 27), and ample evidence suggests that the mK_{Ca} channel is associated with the obstruction of mPTP opening (9, 28-30).

The activation of the mK_{Ca} channel with consequent inactivation of mPTP is implicated in the mechanism of volatile anesthetic-induced cardioprotection. Redel and colleagues reported that PKA-mediated activation of the mK_{Ca} channel by desflurane contributes to the beneficial effects of desflurane-induced preconditioning (12). The results of our present study demonstrate that isoflurane can evoke postconditioning *in vivo* through mK_{Ca} channel activation.

However, we did not investigate the effects of PKA that modulates mK_{Ca} channel activity on isoflurane-induced postconditioning. PKA is an essential regulator in β-adrenergic receptor stimulation (4), and its activation facilitates preconditioning-induced cardioprotective effects by opening the mK_{Ca} channel (31, 32). Interestingly, PKA activation has the opposite effect in the signal transduction pathways underlying postconditioning. Lange *et al.* showed that the administration of the PKA blocker, H-89, in early reperfusion decreased myocardial infarct size after ischemia/reperfusion, perhaps by suppressing signals downstream of the β receptor (4). Thus, the relationship between the mK_{Ca} channel and PKA on isoflurane-induced postconditioning is a subject of future study.

Another possible limitation is that we did not investigate the relationship between the mK_{Ca} channel and mPTP in the current study. Inhibition of mPTP opening is known to contribute to isoflurane-induced postconditioning (14, 15, 33, 34). Nonetheless, the connection between the mK_{Ca} channel and mPTP opening in isoflurane-induced postconditioning is unclear in the current study.

Additionally, we used NS1619 and iberiotoxin, a selective activator and blocker of the mK_{Ca} channel, respectively (35-39), to investigate the relationship between isoflurane-induced postconditioning and the mK_{Ca} channel. NS1619 and iberiotoxin have been used in previous studies concerning preconditioning and postconditioning in the heart (11, 12, 30). However, we did not directly verify whether or not the mK_{Ca} channel was, in fact, open or closed in the presence of NS1619 and iberiotoxin. In addition, although NS1619 does not influence the mK_{ATP} channel (9), an effect of NS1619 and iberiotoxin on other ion channels cannot be excluded.

In conclusion, the current study demonstrated that the mK_{Ca} channel participated in isoflurane-induced postconditioning. Our observations support the hypothesis that the mK_{Ca} channel plays an important role in postconditioning stimulated by volatile anesthetics. However, further study is necessary to clarify the associated signaling cascades upstream and downstream of the mK_{Ca} channel.

AUTHOR'S CONTRIBUTIONS

Michiko Kinoshita designed the study and collected the data, analyzed the data, and wrote the manuscript. Yasuo M Tsutsumi and Katsuya Tanaka helped to design the study and collected the data. Kohei Fukuta and Asuka Kasai helped to collect the data and analyze the data.

All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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