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Review

Cardioprotection by volatile anesthetics

Martin W. Bienengraeber[a], Dorothee Weihrauch[a], Judy R. Kersten[a], Paul S. Pagel[a,b,c], David C. Warltier[a,b,c,*]

[a]*Departments of Anesthesiology, Pharmacology and Toxicology, and Medicine, (Division of Cardiovascular Diseases), Medical College of Wisconsin, 8701 Watertown Plank Road,, Milwaukee, Wisconsin 53226, USA*
[b]*Clement J. Zablocki Veterans Affairs Medical Center, 5000 West National Avenue, Milwaukee, Wisconsin 53295, USA*
[c]*Department of Biomedical Engineering, Marquette University, P O Box 1881, Milwaukee, Wisconsin 53201, USA*

Abstract

Preconditioning describes a very powerful endogenous mechanism by which the heart may be protected against ischemia and reperfusion injury. Transient administration of a volatile anesthetic before a prolonged ischemic episode reduces myocardial infarct size to a degree comparable to that observed during ischemic preconditioning. Many components of the signal transduction pathways responsible for cardioprotection are shared by anesthetic and ischemic preconditioning. Exposure to volatile anesthetics generates small "triggering" quantities of reactive oxygen species (ROS) by directly interacting with the mitochondrial electron transport chain or indirectly through a signaling cascade in which G-protein-coupled receptors, protein kinases, and mitochondrial ATP-sensitive potassium (K_{ATP}) channels play important roles. Several clinical studies also suggest that preconditioning by volatile anesthetics exerts beneficial effects in patients undergoing cardiac surgery. This review summarizes some of the recent major developments in the understanding of cardioprotection by volatile anesthetics.

Keywords: Cardioprotection; Myocardial ischemia; Ischemia and reperfusion; Preconditioning; Anesthetics

Contents

* Corresponding author. Medical College of Wisconsin, MEB-M4280, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226, USA. Tel.: +1 414 456 5735; fax: +1 414 456 6507.

E-mail addresses: mbieneng@mcw.edu (M.W. Bienengraeber), dorothee@mcw.edu (D. Weihrauch), jkersten@mcw.edu (J.R. Kersten), pspagel@mcw.edu (P.S. Pagel), warltier@mcw.edu (D.C. Warltier).

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1. Introduction

The observation that volatile anesthetics, including halothane, isoflurane, enflurane, sevoflurane, and desflurane protect myocardium from ischemic damage has been known for two decades, and intense research has been conducted in recent years to determine the mechanisms responsible for these beneficial effects (Davis et al., 1983; Warltier et al., 1988; Marijic et al., 1990). Administration of enflurane during demand-induced ischemia produced by a critical coronary artery stenosis decreased lactate production independent of alterations in subendocardial blood flow (van Ackern et al., 1985). These results suggested that myocardial metabolism may be improved by administration of a volatile anesthetic during an ischemic episode. A subsequent investigation found that halothane protects against ischemia in hearts arrested with cardioplegia (Preckel et al., 1999). Volatile anesthetics were also shown to improve the functional recovery of isolated hearts subjected to global ischemia and reperfusion (Cope et al., 1997; Coetzee et al., 1993). These data provided further support for the hypothesis that volatile agents exert cardioprotective effects independent of their actions on systemic or coronary hemodynamics.

Acute or delayed pharmacologic preconditioning by volatile anesthetics (termed "anesthetic-induced preconditioning," APC) describes the phenomenon by which exposure to a volatile anesthetic attenuates cardiac ischemia/reperfusion injury with early or late memory periods, respectively. In the laboratory setting, APC was first described by Kersten et al. (1997a). Barbiturate anesthetized dogs received a 30 min exposure to 1.0 minimum alveolar concentration (MAC) isoflurane, which then was discontinued for 30 min before a prolonged coronary artery occlusion and reperfusion. This exposure to isoflurane produced a marked reduction in myocardial infarct size as compared to control conditions without isoflurane. The magnitude of protection produced by APC was similar to that observed during ischemic preconditioning (IPC). Isoflurane-induced cardioprotection was also observed in rabbits by another research group (Cason et al., 1997). Several excellent reviews of APC and its clinical ramifications have been recently published (Tanaka et al., 2004a; Stowe and Kevin, 2004; Kwok and Aizawa, 2004; Zaugg et al., 2003a,b). In this review we will summarize several of the emerging concepts regarding the signaling pathways that mediate APC and will also present new observations that suggest that APC has potentially very important clinical implications.

2. Reactive oxygen species

Compelling experimental evidence indicates that reactive oxygen species (ROS) play a central role in APC. ROS scavengers administered to rabbits in vivo during pretreatment with isoflurane abrogated the protective effects of APC against ischemia and reperfusion injury (Mullenheim et al., 2002; Tanaka et al., 2002). In an elegant study conducted in isolated guinea pig hearts, dihydroethidium was used to spectrophotometrically observe ROS generation with a fiberoptic probe placed against the left ventricular wall (Kevin et al., 2003). Administration of sevoflurane caused an immediate and reversible increase in ethidium fluorescence consistent with production of a small quantity of triggering ROS. Volatile anesthetics are small. Hydrophobic molecules that readily pass through cell membranes and are known to depress mitochondrial respiration at several oxidative phosphorylation complexes (Hall et al., 1973). This attenuation of respiration may cause a leak of electrons from the inner mitochondrial matrix and augment ROS generation. Hanley et al. (2002a) investigated the effects of volatile anesthetics on electron transport in submitochondrial particles. Isoflurane and sevoflurane inhibited NADH/ubiquinone oxidoreductase activity, suggesting that complex I was a likely target of volatile anesthetics. In contrast, succinate oxidation was unaffected, indicating that these volatile agents did not affect complexes II and IV. These observations were supported by the results of another study demonstrating that administration of sevoflurane increases NADH concentration in isolated guinea pig hearts (Riess et al., 2002a). Interestingly, sevoflurane-induced attenuation of complex I respiration in isolated guinea pig mitochondria was abolished by free radical scavengers (Riess et al., 2004). These latter data suggested that volatile anesthetic-induced ROS formation may contribute to a positive feedback mechanism by also attenuating complex I activity that serves to further amplify ROS signaling for triggering APC. Results from experiments conducted in our laboratory implicated complex III of the respiratory chain as a potential source of ROS during APC. The complex III inhibitor myxothiazol, but not the complex I inhibitor diphenyleneiodonium, abolished isoflurane-induced reductions in generation of ROS and myocardial infarct size (Ludwig et al., 2004a). Taken together, these data indicate that ROS generation from the mitochondrial electron transport chain is a critical trigger for cellular protection during APC.

In contrast to small quantities of ROS required to initiate APC, large amounts of ROS play a major role in the pathophysiology of reperfusion injury. Volatile anesthetics have also been shown to produce cardioprotection by attenuating the adverse consequences of this burst of ROS upon reperfusion. For example, the protective effect of APC is associated with a pronounced reduction in ROS formation during ischemia and reperfusion (Kevin et al., 2003). Elevated ROS production during reperfusion enhances Ca^{2+} influx into mitochondria, an action that opens the mitochondrial permeability transition pore and contributes to apoptotic cell death. Desflurane improved the resistance of the transition pore to Ca^{2+}-induced opening after ischemia and reperfusion (Piriou et al., 2004). These data