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Minireview

Cellular targets of inhalational anaesthetic- and opioid receptor agonist-induced cardioprotection

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ABSTRACT
Several anaesthetics and anaesthetic adjuvants have been shown to limit the extent of myocardial injury due to ischaemia and reperfusion, a protective phenomenon known as anaesthetic-induced cardioprotection. Inhalational anaesthetics and opioid receptor agonists are among the key players in anaesthetic-induced cardioprotection. However, the mechanisms underlying anaesthetic-induced cardioprotection are not fully understood, and as such there are currently no concrete guidelines regarding the choice of anaesthetic protocols designed to enhance cardioprotection. This mini-review provides insights into the mechanisms through which the cardioprotection due to inhalational agents and opioid receptor agonists occurs, and discusses the clinical implications thereof. The mechanisms underlying this cardioprotection are diverse and remain unresolved, but several cellular signaling cascades involve key targets such as receptors, sarcolemmal- and mitochondrial ATP-sensitive K^+ channels, the mitochondrial permeability transition pore, glycogen synthase kinase-3 beta, nitric oxide, and anti-apoptotic factors. Such factors represent potential therapeutic targets in promoting anaesthetic-induced cardioprotection.

INTRODUCTION
The potential of anaesthetic agents to provide perioperative cardioprotection has caused these drugs to assume roles that go beyond hypnosis, analgesia and muscle relaxation (De Hert et al., 2004, Murphy et al., 2006). Among anaesthetics and anaesthetic adjuvants, volatile agents and opioid receptor agonists, together, provide the greatest cardioprotection (Zaugg et al., 2014). Volatile agents such as halothane, isoflurane, and enflurane were among the first anaesthetic drugs to be shown to promote post-ischaemic myocardial functional recovery and tolerance to ischaemia (Tarnow et al., 1986, Freedman et al., 1985, Warltier et al., 1988). Subsequently, it was also recognized that anaesthetic adjuvants such as opioid receptor agonists like morphine (Schultz et al., 1996), fentanyl (Kato et al., 2000), and remifentanil (Zhang et al., 2005) exhibited substantial cardioprotective effects. Such cardioprotective effects of volatile agents and related drugs have become known as anaesthetic-induced preconditioning and postconditioning, where preconditioning provides protection before myocardial injury, whereas postconditioning occurs afterwards.

Anaesthetic-induced cardioprotection has unique characteristics that have stimulated a growing interest among anaesthesiologists. First, although cardioprotection can also be elicited by other pharmacological chemicals, anaesthetics have the distinct advantage that the beneficial effects of the drugs can be obtained even during routine perioperative use. Secondly, the cardioprotective effects occur independently of the drugs' cardio-depressant or anaesthetic actions. Finally, anaesthetic-induced protection also takes place in other major organs like the brain, kidneys, lungs, and liver. Unfortunately,

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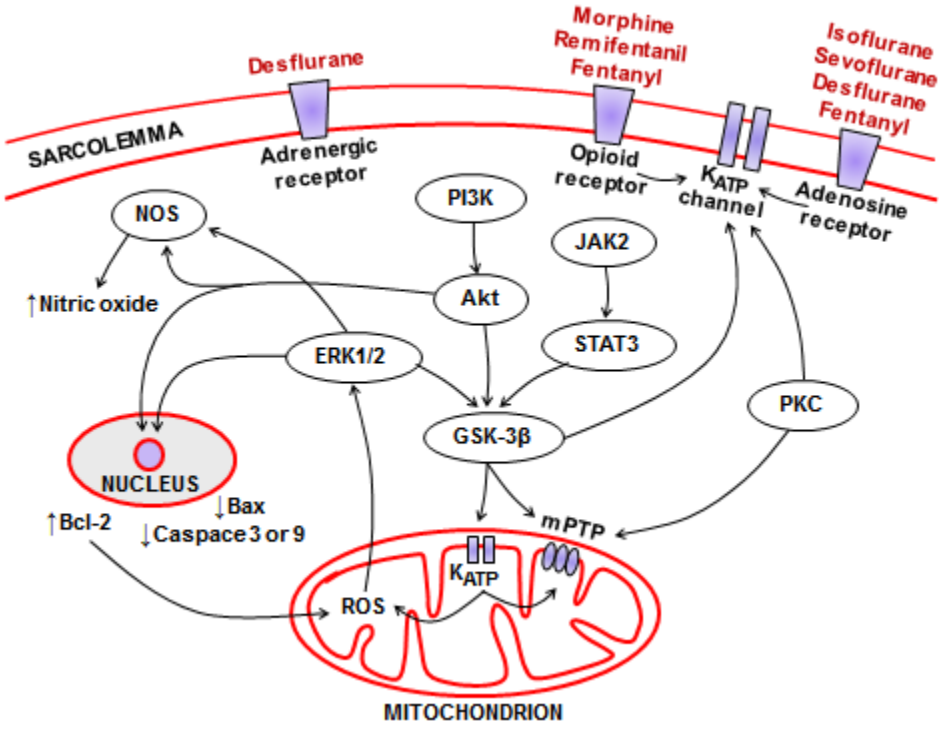

Fig. 1.
Key factors in inhalational anaesthetic and opioid cardiac pre- and postconditioning. See text for details.↑, depicts increase and ↓, depicts decrease. Abbreviations: Akt, protein kinase B; ERK, extracellular signal-regulated kinase; GSK, glycogen synthase kinase; JAK, janus kinase; K_{ATP} channel, ATP-sensitive K^+ channel; mPTP, mitochondrial permeability transition pore; NOS, nitric oxide synthase; PI3K, phosphatidylinositol-3 kinase; PKC, Ca^{2+}-dependent protein kinase; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription.

there remains a limited understanding of the mechanisms underlying anaesthetic-induced cardioprotection. This mini-review presents an overview of the key mechanisms through which inhalational anaesthetic- and opioid-induced cardioprotection take place and highlights the cellular targets involved.

Mechanisms underlying inhalational anaesthetic- and opioid-induced cardioprotection

Anaesthetic-induced cardioprotection involves several different cellular signaling molecules. Presented below, are the key players and processes that link together the apparently disparate signaling components (see Fig. 1).

Cell-surface mediators

Volatile anaesthetics are lipid soluble and are therefore able to cross cell membranes without the need for cell-surface mediators. However, specific cell-surface receptors seem to mediate the cardioprotective effects of several volatile anaesthetics and opioids. Adenosine A1 receptors mediate the preconditioning effects of volatile agents isoflurane (Roscoe et al., 2000), sevoflurane (Hu et al., 2005) and desflurane (Hanouz et al., 2002), and of the opioid fentanyl (Kato et al., 2000). The adenosine A1 receptors on both myocytes and neutrophils have been implicated in this protection (Hu et al., 2005). Preconditioning by desflurane also occurs through the binding of sarcolemmal α- and β-adrenergic receptors (Hanouz et al., 2002). For opioid drugs, the involvement of sarcolemmal opioid receptors plays a pivotal role in mediating the preconditioning- and postconditioning effects of morphine (Frassdorf et al., 2005, Schultz et al., 1996, Jang et al., 2008, Chen et al., 2008b) and remifentanil (Zhang et al., 2005, Yu et al., 2007, Wong et al., 2010), as well as the preconditioning effects of fentanyl (Gross et al., 2006). Among the opioid receptors, the kappa- and delta receptor subtypes mediate most of the cardioprotective effects. The binding of drugs to these different types of receptors leads to downstream effects by opening ATP sensitive K^+ (K_{ATP}) channels (Chen et al., 2008b, Hanouz et al., 2002, Kato et al., 2000, Schultz et al., 1996, Roscoe et al., 2000) and thereby modulating other signaling molecules discussed in this review.

Modulation of ATP-sensitive K^+ (K_{ATP}) channels and other ion channels

The activation of K_{ATP} channels contributes to cardiac protection, and has been proposed to be one of the main

common effector mechanisms for volatile agents and opioid receptor agonists (Patel et al., 2002). Activation of sarcolemmal K_{ATP} channels hyperpolarizes cells, thereby preventing the excitation and contraction of ischaemic myocytes. In the mitochondrion, the K^+ inflow through K_{ATP} channels slightly depolarizes the organelle and decreases the electrical driving force for mitochondrial Ca^{2+} overload. The stimulation of Ca^{2+}-dependent protein kinase (PKC)-mediated pathways appears to be an important pre-step in the activation of K_{ATP} channels by agents such as isoflurane (Kawano et al., 2008) and fentanyl (Zaugg et al., 2002). The preconditioning effects of isoflurane are mediated by the opening of both sarcolemmal- (Kersten et al., 1997, Tonkovic-Capin et al., 2002, Kawano et al., 2008), and mitochondrial (Tonkovic-Capin et al., 2002) K_{ATP} channels. Downstream, the isoflurane-induced activation of mitochondrial K_{ATP} channels leads to the production of protective amounts of reactive oxygen species (ROS) (Tanaka et al., 2003), and to the inhibition of the mitochondrial permeability transition pore (mPTP) (Krolikowski et al., 2005), described below. Sevoflurane and desflurane also induce both preconditioning and postconditioning through pathways involving K_{ATP} channels (Lemoine et al., 2008, Hanouz et al., 2002, Obal et al., 2005, Mathur et al., 1999). For opioids, sarcolemmal K_{ATP} channels mediate the pre-conditioning effects of morphine (Schultz et al., 1996) and fentanyl (Kato et al., 2000), whereas mitochondrial K_{ATP} channels mediate fentanyl preconditioning (Zaugg et al., 2002) and morphine postconditioning (Chen et al., 2008b).

Besides K_{ATP} channels, other ion channels can also mediate anaesthetic-induced cardioprotection. Morphine preconditioning activates mitochondrial Ca^{2+}-sensitive K^+ channels (Frassdorf et al., 2010), whereas sevoflurane protects ventricular myocytes against Ca^{2+} paradox-induced Ca^{2+} overload through blocking transient receptor potential canonical (TRPC) channels (Kojima et al., 2011). This TRPC channel effect on Ca^{2+} is consistent with the known cardioprotective action of halothane that is attributed to the reduction in intracellular Ca^{2+} (Lochner et al., 1994).

Glycogen synthase kinase-3 beta (GSK-3β) inhibition and the regulation of associated signaling molecules

The inhibition of glycogen synthase kinase-3 beta (GSK-3β) through its phosphorylation is an important intracellular step mediating the effects of several upstream pathways such as the phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt)-, the janus kinase (JAK)/signal transducer and activator of transcription (STAT)-, or the extracellular signal-regulated kinase (ERK)-dependent pathways. The inhibition of GSK-3β underlies the preconditioning effects of morphine and fentanyl (Gross et al., 2007a, Gross et al., 2006) as well as the postconditioning effects of morphine (Gross et al., 2007b) and sevoflurane (Li et al., 2008). The GSK-3β inhibitory effects of opioids are mediated by pathways involving JAK2 regulation of Akt and STAT3 (Gross et al., 2007a, Gross et al., 2006) as well as ERK1-dependent signaling (Gross et al., 2007a). The postconditioning effects of sevoflurane are mediated by the inhibition of GSK-3β via the PI3K/Akt pathway (Li et al., 2008). Although desflurane-induced preconditioning also involves Akt and ERK1/2 (Lemoine et al., 2008), any possible link with GSK-3β inhibition has not yet been identified.

The downstream effects of GSK-3β phosphorylation include the inhibition of mPTP opening and the activation of K_{ATP} channels. The mPTP on the mitochondrial inner membrane is normally in a closed state and ensures the relative mitochondrial impermeability, thereby creating a membrane potential and optimum organelle volume suitable for energy production. During ischaemia, the mPTP tends to remain closed due to the effects of lactic acidosis, but at the commencement of reperfusion, the pathological amounts of ROS, the mitochondrial Ca^{2+} overload, and the correction of acidosis lead to the opening of the mPTP. The leakage of osmotically-active molecules into the organelle through the pore causes mitochondrial swelling and uncoupling of the respiratory chain that are associated with further ATP depletion and the release of pro-apoptotic proteins like cytochrome *c*. Isoflurane preconditioning and postconditioning effects are mediated by the inhibition of the mPTP through the inhibition of GSK-3β (Pagel et al., 2006, Feng et al., 2005), and the activation of PKCε (Pravdic et al., 2009). The inhibition of mPTP opening is also involved in sevoflurane postconditioning (He et al., 2008, Yao et al., 2010), but whether GSK-3β plays a role remains unclear. The other downstream effect of GSK-3β inhibition is the opening of both sarcolemmal- and mitochondrial K_{ATP} channels such as that which occurs in morphine-induced postconditioning (Gross et al., 2007b).

Nitric oxide production

Nitric oxide (NO) is a trigger and mediator of anaesthetic-induced cardioprotection. It is a downstream factor of signaling pathways such as those involving PI3K/Akt and mediates the protective effects of cGMP/protein kinase G. In isoflurane preconditioning, an initial small release of NO triggers nuclear factor-κB to induce the upregulation of the inducible NO synthase (iNOS), which enhances further production of NO (Chen et al., 2008a). Consistent with an essential role for NO in cardioprotection, isoflurane preconditioning is absent in a mouse knockout model deficient of caveolin-3 (Tsutsumi et al., 2010), a

scaffolding protein that is known to interact with both endothelial NO synthase (eNOS) and the eNOS regulator Hsp90 (Garcia-Cardena et al., 1996). The isoflurane-induced eNOS activity is also dependent on the co-localization of eNOS with Hsp90 and on the presence of the other eNOS regulator tetrahydrobioprotein (Amour et al., 2010). Isoflurane postconditioning also occurs through PI3K/Akt-dependent NO production, and is linked to eNOS-dependent production of NO via the activation of ERK1/2 and ribosomal protein p70s6K signaling pathways (Krolikowski et al., 2006). Among opioids, the morphine postconditioning effects, involving the inhibition of mPTP, are mediated by NO via cGMP/protein kinase G pathway (Jang et al., 2008).

Prevention of apoptosis

Preconditioning with isoflurane, sevoflurane and remifentanil, as well as postconditioning with sevoflurane have all been associated with decreases in apoptotic factors. Isoflurane preconditioning promotes cell survival by decreasing the expression of the pro-apoptotic factor Bax and by increasing anti-apoptotic factors Bcl-2 and Bad via the PI3K/Akt pathway (Raphael et al., 2005, Raphael et al., 2006). Sevoflurane decreases cell death due to apoptosis through ROS-dependent activation of nuclear transcription factor-κB and through increased expression of Bcl-2 (Lu et al., 2009). The remifentanil preconditioning via ERK1/2-dependent pathways is associated with increased expression of Bcl-2, and with decreased expression of pro-apoptotic factors Bax and cytochrome *c* (Kim et al., 2010). Postconditioning with sevoflurane decreases infarct size via PI3K- and ERK1/2-dependent inhibition of caspase 3 and 9 activity (Inamura et al., 2010).

Changes in the levels of reactive oxygen species (ROS)

ROS generated from the mitochondria during oxidative stress can be either toxic or protective, probably depending on factors such as the amount produced, the type of feedback to the mitochondria, or the nature of interactions between ROS and nitric oxide. Preconditioning with both isoflurane and sevoflurane can increase ROS production, and this increase has been implicated in cardioprotection (Tanaka et al., 2002, Tanaka et al., 2003, Mullenheim et al., 2002, Shiomi et al., 2014). Furthermore, isoflurane decreases oxidative stress-induced lipid peroxidation and maintains the integrity of the mitochondrial respiratory chain (Lotz et al., 2015). In contrast to these effects, isoflurane-induced production of ROS promotes Ca^{2+} overload during ischaemia (Dworschak et al., 2004) and in some studies isoflurane-induced preconditioning decreased ROS production (Tanaka et al., 2002, Sedlic et al., 2010). Thus, for isoflurane, the exact role of ROS remains unclear.

Other factors

Apart from the above-mentioned key players and processes, other factors such as translocation of proteins within cell membranes, activation of enzymes and regulatory proteins and protection of the endothelial glycocalyx also contribute to anaesthetic-induced cardioprotection. Isoflurane preconditioning requires the translocation of the proteins caveolin-3 and glucose transporter (GLUT)-4 to the membrane caveolae (Tsutsumi et al., 2010). It also induces PKCε-mediated phosphorylation of mitochondrial aldehyde dehydrogenase (ALDH)-2, which metabolises toxic aldehydes (Lang et al., 2013), as well as the adenosine monophosphate protein kinase (AMPK)- and PKCε-mediated increase of the cytokine macrophage migration inhibitory factor (MIF) (Goetzenich et al., 2014). The enzyme cyclooxygenase 2 also plays a role in isoflurane-induced preconditioning (Alcindor et al., 2004), but its involvement in mediating the actions of other agents is still not known. The preconditioning and postconditioning effects of sevoflurane are proposed to protect the endothelial glycocalyx from degradation by minimizing endothelial cell adhesion (Chappell et al., 2011) and by decreasing the activity of lysosomal proteases (Annecke et al., 2010).

Clinical implications

The evaluation of the impact of the use of specific anaesthetic protective protocols in clinical practice has inherent limitations, given the nature of anaesthesiology as a polypharmacy practice and the medical- or surgery-related confounding factors. As a result, there are currently no clear recommendations regarding the choices of anaesthetic protocols. In patients undergoing cardiac surgery, isoflurane and morphine have been shown to be protective in preconditioning protocols (Belhomme et al., 1999, Murphy et al., 2006). In another group of similar patients, sevoflurane and desflurane were associated with shorter intensive care unit (ICU) and hospital stays compared to propofol and midazolam, but there were no differences in the incidences of post-operative complications (De Hert et al., 2004). In contrast, in other patients undergoing coronary artery surgery, the choice of anaesthetic regimen did not change the incidence of complications or the duration of stay in the ICU (Tuman et al., 1989). In addition, volatile agents themselves can diminish the collateral cardioprotection that occurs through the preconditioning in other organs (Zhou et al., 2013). Similarly, although the intravenous anaesthetic agent propofol itself is cardioprotective (He et al., 2008, Mathur et al., 1999), it also inhibits desflurane-induced preconditioning in rabbit hearts

(Smul et al., 2011). Therefore, besides the lack of clarity concerning the precise nature of anaesthetic-induced cardioprotection in clinical practice, there is also a potential for interference from co-administered anaesthetics (Zaugg et al., 2014).

CONCLUSIONS

The potential benefits of anaesthetic-induced cardioprotection present an opportunity to design anaesthetic protocols that maximise perioperative myocardial survival. The mechanisms underlying inhalational anaesthetic- and opioid receptor agonist-induced cardioprotection are diverse and a lot still remains unknown, but most of the cellular signaling cascades involved converge onto key targets such as K_{ATP} channels, mPTP, GSK-3β, NO and ROS. There are also other molecules involved whose exact roles and connections to mainstream pathways still require further clarifications in future studies. A better understanding of the mechanisms underlying anaesthetic-induced cardioprotection is needed to facilitate the formulation of concrete clinical guidelines that take advantage of the drugs' protective characteristics.

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