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RESEARCH OPINIONS IN ANIMAL & VETERINARY SCIENCES

Anaesthetic preconditioning and its effects on vital organs

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Abstract

Ischemia-reperfusion syndrome may be associated with many conditions that require surgical or anaesthetic intervention like organ transplantation, cardiopulmonary bypass etc. Ischemic preconditioning can act as a protective mechanism in many vital organs against the actual ischemic episodes or stressful situations. Various preconditioning determinants are cited in literature and one among them is the anaesthetic induced preconditioning (APC). This review focuses on protective effects of various anaesthetics and adjuvants on the vital organs upon anaesthetic preconditioning before the actual insult or surgical intervention. The major vital organs have been found to respond positively to APC. Anaesthetic intervention prior to surgery can precondition the vital organs, pre-empt ischemia reperfusion injury (IR) and help to minimise deleterious effects. The elucidation of the mechanism for APC may help the clinical extrapolation of the results especially during organ transplantation, trauma, shock or episodes requiring Cardiopulmonary Resuscitation (CPR).

Keywords: anaesthetic preconditioning; ischemia reperfusion injury; vital organs

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Introduction

Cellular damage after reperfusion of previously viable ischemic tissues is defined as ischemia-reperfusion injury. Preconditioning offers tolerance of critical organs to future ischemic or hypoxic insults by means of a mild exposure to the actual pathology or agents simulating such effects. Surviving a sublethal insult may result in a protective state to subsequent lethal insult (Nunes et al., 2013). This phenomenon is seen in various organs including brain where it is called cerebral preconditioning (CP) or ischemic tolerance (IT) (Tatlisumak and Durkan, 2010). The main pathophysiological aspects of cerebral ischemia and reperfusion include excitotoxic actions of glutamate, ATP, changes in ionic homeostasis and formation of free radicals (Homi et al., 2000). Attempts to ameliorate the effects of excitotoxins during reperfusion injury have been largely unsuccessful, but anaesthetics, hypothermia, sodium channel blockers and ascorbic acid are found to have some protective effect (Sanders et al., 2005). In 1986, Murry and co-workers (1986) reported that myocardial damage due to coronary artery occlusion can be ameliorated if the myocardium is exposed to sub-lethal ischemia over a period. Similarly, a transient ischemic attack can induce ischemic preconditioning in brain as well (Wegner et al., 2004). Exposing organs, such as the brain and heart, to brief periods of sub-lethal ischemia initiates ischemic tolerance via a preconditioning phenomenon (Tomai et al., 1999; Nandagopal et al., 2001). The purview of ischemia reperfusion injury extends to the veterinary medicine through many clinical conditions trans species like intussusception, mesenteric volvulus, incarceration, gastric dilation and torsion, portal venous thrombosis or post portosystemic shunt attenuation portal hypertension in dogs and cats, caecal torsion in cattle or intestinal obstruction in horses (Bretz et al., 2010). Limited work is available in literature suggesting the clinical validation of different preconditioning protocols, which protect from the ischemia-reperfusion injury in veterinary clinical conditions. However,

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reported benefits of anaesthetic preconditioning in experimental animals make it a useful technique for potential clinical application.

Pathology of ischemia reperfusion (IR) injury

Ischemia reperfusion injury causes a variety of molecular and cellular changes. The systemic inflammatory response succeeding IR injury can result in multiple organ dysfunction syndromes, leading to increased post interventional mortality. During ischemia, there may be altered membrane potential, increased cell catabolism, decreased amount of ATP, sodium potassium ATPase dysfunction, intracellular accumulation of sodium and subsequent changes in membrane potential, cellular swelling and increased activity of excitatory neurotransmitter glutamate (Farooqui et al., 1994).

During ischemic stage, lactate is produced from the anaerobic metabolism of glucose and there is a consequent increase in H^+ concentration inside the cell (Plum, 1993). With cerebral reperfusion, the supply of oxygen and glucose will be greater than the cell capacity to use it (Dietrich, 1994). Hyperglycemia results in increased concentration of lactic acid succeeding the initial phase of ischemia and exacerbates post-ischemic injuries. During ischemia adenine nucleotide catabolism results in intracellular accumulation of hypoxanthine which is subsequently converted into toxic reactive oxygen species (ROS) upon reperfusion. Thus, electrochemical reduction of oxygen molecule occurs to form reactive oxygen species leading to oxidative stress (Lai. 1992; Abe et al., 1995). Hydroxyl radical (OH-), the potent reactive oxygen species, acts on the breakdown products of fatty acid molecules of the cell membrane. These radicals are normally neutralised by enzyme systems involving catalase, superoxide dismutase and glutathione peroxidise (Nunes et al., 2013), if available in adequate quantities.

Synergistic action of reactive oxygen species and glutamate during reperfusion leads to increased metabolism of arachidonic acid into leukotrienes through lipoxygenase pathway. Thromboxanes, prostacyclins, and prostaglandins are metabolised through the cyclooxygenase pathway (Ikeda and Long, 1990; Oh and Betz, 1991). Increased concentration of these molecules consequently leads to cytotoxic edema and damage to organelles and plasma membranes (Wahl et al., 1993). Reactive oxygen species also stimulates late leukocyte adhesion molecule and cytokine gene expression through the activation of transcription factors such as nuclear factor κB, which thereby increases leukocyte activation, chemotaxis and endothelial adherence of leukocyte after ischemia reperfusion (Collard and Gelman, 2001). Complement activation and formation of proinflammatory mediators also contribute to the pathogenesis by altering the blood flow to ischemic organs due to vascular homeostasis and increasing leukocyte-endothelial adherence.

The increased tissue vulnerability due to ischemia enhances the expression of gene products which are pro-inflammatory (leukocyte adhesion molecules, cytokines) and bioactive (endothelin, thromboxane A2) while suppressing certain protective gene products (constitutive nitric oxide synthase, thrombomodulin) and bioactive agents (prostacyclin and nitric oxide) (Collard and Gelman, 2001). Platelet endothelial cell adhesion molecule 1 facilitates leukocyte interactions with the endothelium and a series of activity occur characterised by leukocyte rolling on the endothelium, firm adherence of the leukocytes to the endothelium and endothelial transmigration of leukocytes. On reaching the extra vascular compartment, activated leukocytes release toxic reactive oxygen species, proteases and elastases, resulting in increased vascular permeability, edema and thrombosis leading to parenchymal cell death (Collard and Gelman, 2001).

The action of glutamate results in increased concentration of intracellular calcium. Excess intracellular calcium ion has a harmful effect through the activation of proteases and phospholipases. Ischemia-reperfusion injury to CNS, at its initial stages may be limited to the action of cellular proteins on membrane lipids and thus can be quickly reversed. If the changes are severe enough to impair RNA transcription or DNA alteration, there will be cellular death (Farooqui et al., 1994). In cerebral infarction, there is central necrosis wherein the peripheral changes are slow, the neurons die more slowly and mainly by apoptosis (Dirnagl et al., 1999). This process is contributed by mitochondrial cytochrome-c, activation of caspase and pro-apoptotic factors. Neurodegeneration is mainly contributed by Interleukin-1 (Nunes et al., 2013).

Molecular mechanisms for anaesthetic preconditioning and Ischemic tolerance

Ischemic tolerance can be either early or late. Early ischemic tolerance depends upon the action on the membrane receptors and can be achieved within minutes, however, late tolerance occurs in hours or days through activation of gene and subsequent synthesis of new proteins. Adenosine, hypoxia inducible factor-1α, Tumor necrosis factor- α (TNF-α), reactive oxygen species, Nitric oxide (NO) and processes involving N methyl D aspartate (NMDA) receptor activation and intracellular calcium influx have been reported in development of ischemia tolerance (Nunes et al., 2013). Opening of the chloride and potassium channels are controlled by gamma aminobutyric acid (GABA) and Glycine, which are the main inhibitory neurotransmitters. These receptors are frequent targets of the anaesthetic agents and their actions can not only reduce neuronal excitation but also offer neuroprotection by reducing excitotoxicity (Nunes et al., 2013). Alpha-2 agonists *in vivo* have been shown to attenuate neurological injuries after ganglionic blockade in rat models of incomplete cerebral ischemia (Werner et al., 1990).

Preconditioning is dependent upon the activation of Protein kinase C (PTK) and adenosine triphosphate sensitive potassium channels (KATP channel) opening within mitochondrial membranes (Speechly-Dick et al, 1995). Stimulation of the adenosine A1 and A3 receptors can also mimic anaesthetic preconditioning (Carr et al., 1997). The expression of immediate early genes (IEGs) is also implicated in conditions of ischemic tolerance in brain (Kapinaya et al., 2000). Immunohistochemically, various anaesthetic agents has shown an increase in c-fos protein expression in supra-spinal neurons of rats (Takayama et al., 1994). However, it will be early to attribute preconditioning and tolerance to ischemic injury to IEGs since it requires Meta analysis of the experimental data before drawing any conclusion.

Reactive oxygen and nitrogen species are increased following an ischemic event and lead to lipid peroxidation and cell membrane damage (Watanabe et al., 1990; Piantadosi and Zhang, 1996; Forman et al., 1998). Evidence exists implicating the glutamate receptor-Nitric oxide synthase-NOS soluble guanylyl cyclase system as an important mediator in both physiological and pathological processes of ischemia-reperfusion injury (Fedele and Raiteri, 1999). Interactions between NO and $GABA_A$ receptors suggest the possibility that NO may directly modulate GABAergic transmission (Robello et al., 1996; Fedele and Raiteri, 1999; Wall, 2003; Pepicelli et al., 2004). The brain and heart share a common signal transduction pathway in the activation of KATP channels following ischemic preconditioning (Heurteaux et al., 1995; Perez-Pinzon and Born, 1999). The functional significance of these mitochondrial KATP channels within the brain have shown to be critical in conferring neuroprotection following Mid Cerebral Artery occlusion (MCAo) in the rat (Shimizu et al., 2002). The preconditioning effects of isoflurane and halothane have shown to induce ischemic tolerance in the brain against transient MCAo (Kapinya et al., 2002). Xiong and co-workers (2003) also demonstrated that administration of glibenclamide (5 mg/kg IP), a KATP channel blocker, given prior to each isoflurane exposure abolished the tolerance afforded by isoflurane, demonstrating that isoflurane protection is mediated via the activation of KATP channels. The importance of KATP channel opening has also been elaborated following anoxia-induced preconditioning to neocortical and hippocampal neurons in rat brain slices (Garcia de Arriba et al., 1999; Perez-Pinzon and Born, 1999).

Anaesthetic preconditioning of the CNS

Animal models of focal ischemia, both *in vivo* and *in vitro* have elaborated on the neuroprotection offered by anaesthetics (Harada et al., 1999; Kimbro et al., 2000; Kudo et al., 2001). Neuoprotection is not correlated with anaesthetic efficacy and moreover the use of anaesthetics to induce neuroprotection depends on factors like its potency, route, methods of administration, side effects and patient tolerability (Nunes et al., 2013). For volatile and injectable general anaesthetics the GABAergic sites are considered to be the main receptors. The modulation of these inhibitory neurotransmitter sites can reduce both excitability and excitotoxicity. Isoflurane has been proved to be a superior neuroprotective agent in combination with nitrous oxide and fentanyl (Homi et al., 2003) and its protective effects can be attributed to the reduced cerebral metabolic rate (Meckensen et al., 2000). Isoflurane reduced neurological deficit in about 20% of the sample in a canine model of cardiac arrest at anaesthetic doses in contrast to pentobarbital, which was effective only at a CNS suppression dose (Blank et al., 2000). Desflurane also showed neuroprotective properties equivalent to those of isoflurane in an animal model of incomplete cerebral ischemia, and both agents proved to be superior to fentanyl and nitrous oxide based anesthesia (Engelhard et al., 1999). Bickler et al. (2003) showed that the neuroprotective effect of isoflurane was dependent on GABA receptors with the use of bicuculline, another GABA receptor antagonist. Volatile anaesthetics can also protect against glutamate excitotoxicity and promote its uptake which cannot be obtained with pentobarbital, an intravenous agent that also exerts neuroprotective effect (Miyazaki et al., 1997). It was found that isoflurane at MAC 2 was more potent against severe ischemia in rats than metohexital. The depression effect of cerebral metabolic rate was similar for both; however, metohexital at anaesthetic doses had no neuroprotective effects during complete ischemia when compared to isoflurane (Baughman et al., 1990).

Earlier works indicating that general anaesthetics offer tolerance against cerebral ischemia induced due to brief periods of carotid artery occlusion (Wells et al., 1963) and that pentobarbital can offer tolerance to cerebral hypoxia (Goldstein et al., 1966) have evoked curiosity on anaesthetic preconditioning. Evidences for neuronal protection by preconditioning with halothane, fentanyl, nitrous oxide and lidocaine on spinal cord injury in a rat model have been cited (Cole et al., 1989). Triggering of both early and late phases of ischemic tolerance by volatile anaesthetics like isofluorane and halothane has been demonstrated (Kapinya et al., 2002; Zeng and Zuo, 2003). Volatile aesthetics like halothane, isoflurane, sevoflurane and desflurane all have shown significant protection against focal cerebral ischemia and improved neurological outcome (Werner et al., 1995; Engelhard et al., 1999). Sevoflurane is also able to afford significant protection against hypoxia-induced injury *in vitro* in a dose-dependent manner (Kehl et al., 2004) which was shown to involve the activation of KATP channels. In a global model of cerebral ischemia induced by cardiac arrest, short exposure to sevoflurane has been shown to produce early neuroprotection when assessed at 7-day post-insult (Payne et al., 2005). Repetitive

exposure to sevoflurane on 4 consecutive days provided delayed (24 h) preconditioning against ischemic injury.

Following unilateral common carotid artery ligation induced cerebral ischemia, both propofol and sevoflurane extended significant protection via inhibition of Bax-mediated apoptosis (Engelhard et al., 2004). Caspase-dependent activation of apoptosis can occur via either intrinsic (mitochondrial-mediated) or extrinsic (death receptor-mediated) pathways. The intrinsic pathway is initiated following the binding of the pro-apoptotic protein Bax to the permeabilization-related protein, adenine nucleotide translocator which is located within the mitochondrial membrane and permits the release of cytochrome C (Cao et al., 2001). This increase in Bax can be counterbalanced by the anti-apoptotic protein Bcl-2 by forming heterodimers with the Bax protein (Oltvai et al., 1993). This is how the anti apoptotic effects of anaesthetics work. Since apoptosis mediated neurodegenerative damage has been shown to play a critical role in a number of degenerative pathologies (Northington et al., 2005), the compounds or agents with both anti-apoptotic and anti-excitotoxic effects would prove of some benefit in offering neuroprotection (Clarkson, 2007).

Barbiturates also offer neuroprotection but with little effects on the rate of cerebral metabolism (Nunes et al., 2013). The variable dose rates of thiopental have shown difference in EEG suppression in dose dependent manner and therefore reduce cerebral metabolism with no apparent effect in the reduction of infarct volume (Schmid-Elsaesser et al., 1999). Propofol was found to be neuroprotective in *in vivo* models of focal (Koch et al., 1992) and global (Yamaguchi et al., 1999) cerebral ischemia. This anaesthetic-induced neuroprotection is most likely due to its antioxidant effects via the activation of its phenolic hydroxyl group. The use of propofol also resulted in up-regulation of Bcl-2 and mdm-2 expression and down regulation of Bax expression after brain ischemia in rats, thereby showing an anti-apoptotic action of this drug (Englehard et al., 2004).

The use of α2-agonist agents reduced neurological blockade after ganglionic injury with hexamethonium in an *in -vivo* model of incomplete cerebral ischemia in rats (Werner, et al., 1990). This neuroprotective effect was partially reversed by intravenous administration of norepinephrine and epinephrine. Administration of dexmedetomidine before ischemia significantly reduced the levels of plasma catecholamines and decreased neurological co-morbidities at functional and pathophysiological parameters (Hoffman et al., 1991). Furthermore, Maier et al. (1993) reported neuroprotective effects of dexmedetomidine in a model of transient focal ischemia in rabbits.

Ketamine, nitrous oxide, and xenon have anaesthetic action by antagonizing N methyl D aspartate (NMDA) glutamate receptors. The proposed key-role of NMDA receptor in neurotoxicity led to numerous investigations on these anaesthetics' potential to induce neuronal survival after injury. Ketamine at very high doses is necessary to achieve its ischemia protection ability (Lees, 1995). High-dose ketamine has neuroprotective effects on cortical ischemia *in vivo* (Lees et al., 1995; Proescholdt et al., 2001). Ketamine was similar to remifentanil when compared to the neuroprotective efficacy in open-heart surgery in combination with propofol in a randomized controlled trial (Nagels et al., 2004). A factor that could reduce the neuroprotective effect of ketamine is the increased emboli movement due to its vasodilatory effect. Nitrous oxide has the neuroprotective and neurotoxic characteristics of an NMDA antagonist (Todorovik et al., 1998). However, it has been identified that the neuroprotection induced by nitrous oxide combined with an opioid is less potent than that induced by inhaled anaesthetics. Co-administration of isoflurane synergistically increased xenon neuroprotection *in vitro* which is of great clinical importance, as xenon by itself is not sufficiently potent to induce anaesthesia (MAC value 63-71%). Xenon attenuated neuronal damage induced by N-methyl- D-aspartate (NMDA) administration in rats (Wilhem et al., 2002). Homi et al. (2003) reported neuroprotective effect of xenon in a model of focal ischemia with 70% xenon administration during ischemia induced by cerebral artery occlusion in rats. They reported a significant reduction in total infarct size, cortical and subcortical in xenon group compared to nitrous oxide and provided superior neurocognitive protection (Homi et al., 2003).

Anaesthetic preconditioning in myocardial Ischemia

Reactive oxygen species (ROS) are central to cardiac ischemic and reperfusion injury. Myocardial dysfunction post ischemia reperfusion is characterised by myocardial stunning, a transient contractile dysfunction which are reversible through mechanical circulatory and inotropic support. The mechanism facilitating this is characterised by decreased post perfusion ATP resynthesis, ROS mediated cytotoxic injury, coronary microvascular spasm or plugging, and abnormal calcium metabolism. Reperfusion arrhythmias can occur as a result of rapid and sudden alterations in the ion concentrations within the ischemic regions upon reperfusion in patients undergoing thrombolytic therapy (Collard and Gelman, 2001).Multiple laboratory studies and clinical trials have evaluated large number of potential scavengers of ROS to protect the heart from the effects of ischemia and reperfusion. Several IV anaesthetic drugs act as ROS scavengers. Volatile anaesthetics have been demonstrated to generate small quantities of ROS in the heart, because of inhibitory effects on cardiac mitochondria. These ROS although injurious in large quantities, can have a protective effect within the heart. Thus through anaesthetic preconditioning, a lasting protection of

myocardium is elicited by brief exposure to a volatile anaesthetic. Free radicals are now known to act as second messengers in the preconditioning cell-signalling pathway. Volatile anaesthetic drugs have been shown to enhance generation of free radicals in cardiac cells, probably by causing uncoupling of the mitochondrial electron transport chain (Kevin et al., 2005).

To challenge the adverse effects of ischemia reperfusion injury on myocardium through manipulation of the mechanism leading to it has been a subject of study for long. Surgical measures to achieve early arterial blood flow and strategies to enhance ischemic tolerance are practiced in clinical setting. However, ischemia-reperfusion of the heart routinely occurs in a variety of clinical situations, such as during transplantations, vascular surgery or coronary artery bypass grafting or without any surgical interventions like as a transient myocardial ischemia during a stressful anaesthetic induction. There is increasing evidence that anaesthetic agents can interact with the underlying pathological mechanisms of ischemia-reperfusion injury and protect the myocardium by a preconditioning mechanism ((Weber et al., 2005).

During off-pump coronary artery bypass surgery, the heart is subjected to ischemia and reperfusion. The volatile anaesthetics were hypothesised to function as ischemic preconditioning (IPC) agents in preserving myocardial function during off-pump cardiac surgery. The effects of enflurane on its calcium inhibition and anti-oxidative properties were compared with mechanical IPC in preserving myocardial cellular markers. Coronary occlusion during off-pump coronary artery bypass surgery resulted in increased production of ischemia-related metabolic products. The application of volatile anaesthesia appears to reduce the free-radical production, metabolic deficit, and physiologic changes (Drenger et al., 2008).

Anaesthetic preconditioning (APC) is known to protect the heart against necrosis and contractile dysfunction. Kevin and Novalija (2008) examined the occurrence of arrhythmias, their mean duration, and the magnitude-squared coherence (MSC) of spectral components that provide a quantitative measure of rhythm organization at multiple sites in the heart, expressed as a function of time and observed delayed onset and decreased duration of arrhythmias on reperfusion in isoflurane-treated hearts. Isoflurane-treated hearts exhibited moderate-to-high levels of MSC during reperfusion compared to control with reduced incidence of arrhythmia after global and regional ischemia.

Anaesthetic preconditioning may contribute to the cardioprotective effects of sevoflurane in patients having coronary artery bypass surgery. Investigation on two different sevoflurane administration protocols showed to induce preconditioning in patients having coronary artery bypass. All patients received a total intravenous anesthesia with sufentanil (0.3 μg/kg/h) and propofol as target controlled infusion (2.5 μg/mL). Two periods of sevoflurane preconditioning significantly reduced cellular damage compared with controls and sevoflurane-induced preconditioning was reported to depend on the preconditioning protocol used (Frabdorf et al., 2009).

After ischemia–reperfusion, cardioprotection was assessed with sevoflurane and bupivacaine from infarct size and recovery of ventricular function, and phosphorylation levels of glycogen synthase kinase 3β (GSK3β) and 5'AMP activated protein kinase (AMPK). Sevoflurane-induced cardioprotection was not affected by bupivacaine in the non-cardiotoxic range. Both the anaesthetics reduced infarct size, though they activated different signalling kinases, indicating the existence of different cardioprotective intracellular signalling cascades (Bouwman et al., 2010).

The mechanism of volatile anaesthetic-induced preconditioning (APC) is thought to be mediated by nitric oxide (Smul et al., 2010). Nitric oxide synthases (NOSs) mediate the first window of anaesthetic-induced preconditioning (APC). It has been hypothesised that endothelial NOS (eNOS) mediate the first window and inducible NOS (iNOS) mediate the second window of APC (Redel at al., 2013). In a study in mice a 45-minute coronary artery occlusion (CAO) and a 180-minute reperfusion revealed that Endothelial NOS and iNOS work independently to mediate the first and second windows of APC, respectively. Desflurane significantly reduced the infarct size after ischemic injury when administered 30 min., hours, 2 hours, 24 hours, 48 hours and 72 hours before CAO. Desflurane induced a first (30 min.-2 hours) and second window of preconditioning (24-72 hours) in the rabbit model of acute myocardial infarction and the second window of APC was mediated by nitric oxide (Smul et al., 2010)

Desflurane-induced preconditioning markedly reduced infarct size but the effect was blocked by propofol, whereas ischemic preconditioning itself was not blocked by propofol. The results suggested an important interference between propofol and anaesthetic-induced preconditioning and might explain some contradictory findings in studies in humans (Smul et al., 2011).

Diabetes mellitus mitigated remifentanil induced cardioprotection against ischemia–reperfusion, which might be associated with reduced recovery of the activities of proteins involved in anti-apoptotic pathways including extracellular signal-related kinases (ERK1/2) and the abnormal expression of sarcoplasmic reticulum genes as a result of ischemia–reperfusion in rat hearts (Soo Kim et al., 2010).

Combined isoflurane/xenon anesthesia reduced infarct size after CAO in similar lines as the protection offered by isoflurane alone. However, ischemic preconditioning was more effective with the use of the combination than the anaesthetics used alone (Baumert et al., 2009).

Opioids, including remifentanil, have been demonstrated to confer cardiac protection against ischemia-reperfusion injury in animals. A study evaluated whether remifentanil preconditioning is protective in first-time elective on-pump coronary artery bypass surgery patients receiving a standardized fentanyl (25 μg/kg in total) and propofol anaesthetic (Wong et al., 2010). The addition of remifentanil to the anaesthesia regimen reduced the degree of myocardial damage. This incremental benefit may be attributable either to remifentanil itself or to an overall increased opioid dose, the latter may be necessary to trigger cardiac protection.

Dexmedetomidine (DEX) is a highly selective α2-agonist used for sedation and analgesia in daily anaesthetic practice. DEX was associated with reduced infarct size in ischemia/reperfusion injury in regional ischemia in a rat model but found to have no effect on the incidence of arrhythmias (Kocoglu et al., 2008). Ibacache et al. (2012) showed that dexmedetomidine administration activates cardiac survival kinases *in vivo* and *ex vivo* and induces cardioprotection against regional ischemia-reperfusion injury. Dexmedetomidine preconditioning and peri-insult administration produced cardioprotection against regional ischemia-reperfusion injury mediated by the activation of pro-survival kinases after cardiac α2-adrenergic receptor stimulation (Ibacache et al., 2012).

Anaesthetic preconditioning of liver

Hepatic inflow occlusion during the liver surgery may result in a transient ischemia period followed by reperfusion which can initiate liver injury leading to postoperative liver dysfunction. Propofol is one of the main intravenous drugs used in TIVA during surgical procedures and for the sedation of patients; it undergoes rapid and extensive metabolism mainly in the liver and kidneys. Propofol is not known to have a negative impact on hepatic and renal functions as long as hepatic and renal blood flows are intact (Cammu et al., 2007) and it can present antioxidant and anti-inflammatory properties (Peters et al., 2001; Vasileiou et al., 2001). Propofol presents its anti-inflammatory effects in liver through inhibiting iNOS over expression. The antioxidant properties of propofol can be partially attributed to its scavenging effect on peroxynitrite (Brasil et al., 2006). Tao et al. (2010) proposed that volatile anaesthetics might be more beneficial than propofol for postoperative liver function in cirrhotic patients undergoing hepatectomy .

Preconditioning with propofol in hepatic I-R inhibits the apoptosis of hepatocytes as evidenced by decreased terminal deoxynucleotidyl transferase dUTP nick end labelling–positive cells. Moreover, propofol suppressed the mitochondrial GSK-3β and hence limiting the opening of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and preventing the mitochondrial swell and membrane potential loss. Propofol protects liver from I-R injury by sustaining the mitochondrial function, through the modulation of MPTP and Glycogen synthase kinase 3 beta (GSK-3β) (Zhao et al., 2013).

Remifentanil preconditioning to protect ischemia-reperfusion injury to liver was reported by Zhao et al. (2013). The massive degenerative death of liver cells due to I-R and enhanced cell apoptosis was ameliorated by remifentanil preconditioning, thereby reducing mitochondrial swelling and loss of membrane potential. I-R-induced increases in tumor necrosis factor α , nuclear factor κB p65 and intercellular adhesion molecule 1levels in liver tissues was prevented by remifentanil preconditioning and also inhibited the loss in superoxide dismutase and rise in malondialdehyde levels in liver tissues going through I/R injury.

Dexmedetomidine markedly reduced the oxidative stress in plasma, liver, and in multiple remote organs induced by hepatic I-R injury, and ameliorated the histologically evident damage in the liver. Biochemical analyses of the samples revealed that total oxidase activity (TOA) and oxidative index (OSI) values were significantly lower, while total antioxidant capacity (TAC), paraoxonase (PON-1) values increased with dexmedetomidine treatment. In addition, dexmedetomidine ameliorated hepatic histopathological changes inducing IR, but there were no significant histological changes in the remote organs (Tüfek et al., 2013).

Anaesthetic preconditioning in kidney

Perioperative renal dysfunction is associated with a high mortality. Isoflurane preconditioning was proved to protect against renal ischemic reperfusion injury by hypoxia inducible factor 1α up regulation (Zhang et al., 2011). There was significant increase in survival rate and expression of hypoxia induced factor-1α (HIF-1α) and erythropoietin while apoptosis, renal tubule score, blood plasma urea and creatinine were decreased by isoflurane preconditioning. Preconditioning effect of isoflurane and remifentanil in renal ischemia-reperfusion injury was studied and it was observed that ischemic preconditioning showed no protective effect in the isoflurane group (IP). When isoflurane was administered with remifentanil (RP), there was a beneficial effect on the kidney, which was evident in flow cytometry and serum creatinine values (Vianna et al., 2009) which are quite contradictory results when compared to the observation of Zhang et al. (2011).

Anaesthetic Preconditioning of Intestine

Ischemia-reperfusion injury of the gastrointestinal tract is associated with various pathological conditions and surgical interventions like strangulated bowel, vascular surgery and hemorrhagic shock. I-R leads to breakdown of the intestinal barrier function leading to impaired motility and absorption, increased intestinal permeability which leads to bacterial translocation into

the portal and systemic circulation. Systemic inflammatory response syndrome succeeds the pathological changes which ultimately results in Multiple Organ Dysfuction (Collard and Gelman, 2001).

The effects of NMDA receptor antagonists over intestinal ischemia/reperfusion injury were investigated. Ketamine's protective effects over ischemia/reperfusion do not appear to be NMDA mediated, but it could be playing a role in protecting the intestine against ischemia-induced functional changes (Cámara-Lemarroy et al., 2009).

Dexmedetomidine treatment was found to have biochemical and histopathological benefits in preventing I-R-related cellular damage of intestinal and renal tissues as evident in an experimental mesenteric ischemia model. The use of dexmedetomidine for anesthesia during the mesenteric ischemia procedure may attenuate I-R injury in intestinal and renal tissues (Kiliç et al., 2012)

Differential protective effects of pre-treatment with isoflurane or sevoflurane on lung inflammation in a rat model of cecal ligation and puncture (CLP) induced sepsis was studied and it was found that both sevoflurane and isoflurane attenuated inflammatory response, lipid peroxidation and oxidative stress. Sevoflurane was more effective in modulating sepsis induced inflammatory response at the chosen concentration in sepsis model (Bedirli et al., 2012). Ischemic reperfusion injury of the small intestine in a rat model was found to get ameliorated by preconditioning with an ultra short acting opioid remifentanil and thereby curbed the post perfusion injury and systemic inflammatory syndrome (Cho et al., 2013). The preconditioning effects were characterised by amelioration of the mucosal injury, a reduction in the oxidative stress locally and inflammation systemically as revealed by decreased concentrations of gut tissue malodialdehyde (MDA) and plasma interleukin IL-6.

Conclusions

Anaesthetics aided protection against ischemia reperfusion injury to vital organs of the body is a topic of current interest among the scientific community. Several molecular mechanisms leading to anaesthetic preconditioning effects have been elucidated by many researchers and some more are still being investigated. Future strategies to translate the positive effects of APC in clinical application depend on acquiring and refreshing knowledge of the genetic, molecular and pharmacological kinetic-dynamic mechanisms underlying and their possible variation trans-species.

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