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Preconditioning, postconditioning, and remote conditioning in solid organ transplantation: basic mechanisms and translational applications

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Abstract

Ischemia and reperfusion (I/Rp) injury is inherent to solid organ transplantation and can result in primary nonfunction or delayed function of grafts, which is associated with a significant morbidity and mortality posttransplantation. It is also a major obstacle for the use of marginal grafts to increase the donor pool, as these grafts are prone to a higher degree of I/Rp injury. Pre-, post-, and remote conditioning are protective strategies against I/Rp injury, which can be applied in the transplant setting. These strategies hold the potential to reduce graft injury and to safely expand the donor pool. However, despite convincing experimental data, the protective effects of the "conditioning" protocols remain unclear, and only few have translated to clinical practice. This review summarizes pre-, post-, and remote conditioning strategies in clinical use in solid organ transplantation and discusses an overview of the mechanistic pathways involved in each strategy.

Solid organ transplantation can result in prolonged deprivation of tissue oxygen and activation of the anaerobic pathway. The restoration of oxygen delivery during reperfusion leads to organ injury [1-4]. This phenomenon is known as ischemia and reperfusion (I/Rp) injury. Liver resection, trauma, hypovolemic shock, and cardiac bypass surgery are other clinical situations leading to prolonged ischemia and are associated with reperfusion injury. Ischemia and reperfusion injury produces a series of molecular and cellular changes such as activation of inflammatory cascades, oxidative damage, energy depletion, and pH and ion imbalances that culminate ultimately in deterioration of cell function leading to cell death, which severity is directly related to the intensity of the injury [1,3,5-7].

Strategies to attenuate I/Rp injury are important in transplantation and surgery. Despite the development of multiple protective strategies against I/Rp injury in experimental models, only few have demonstrated efficacy in human studies and made the transition to the clinical practice. Preconditioning by either ischemic preconditioning (IP) or pharmacologic pre-, post-, and remote conditioning are among the protective strategies currently used in human transplantation [8-13].

Transplantation surgery offers the perfect clinical opportunity for all types of protective strategies, as the beginning and end of the ischemic insult are exactly defined, and they can be applied during each of the 3 different stages of organ transplantation, that is, (1) during organ procurement in the donors, (2) after organ procurement during cold static preservation, and (3) or at the time of transplantation in the recipients. These strategies will be discussed in this review.

1. Organ preconditioning

Organ procurement and storage in the cold preservation solution requires a scheduled transient ischemic period that offers an ideal opportunity for preconditioning strategies. Evidence for the application of organ preconditioning has been provided in animal models of mice and rat liver [14,15] and kidney transplantation [16] and has subsequently been tested at least in some organs such as the liver in several human randomized, controlled trials.

2. Ischemic preconditioning

In 1986, Muray et al [17] reported the observation that the size of a myocardial infract resulting from a 40-minute ischemia of the coronary artery can be reduced by 70% if the myocardium is subjected to 4 times occlusion of the

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coronary artery for 5 minutes alternated with 5-minute periods of reperfusion immediately before the infarct. This protective effect was lost if the myocardium was rendered ischemic for 3 hours, emphasizing the need for early reperfusion, irrespective of the circumstances. This powerful cardioprotective strategy termed *IP* appears to be intrinsic defense mechanisms to an acute ischemic stress. Further studies subsequently demonstrated that the ability to undergo preconditioning is almost ubiquitous in tissues and is highly conserved across species from mice [15], rats [18], dogs [19], and humans [10]. In recent years, the IP effect has been reproduced in a variety of other organs including the kidney [20], liver [15], small intestine [21], and brain [22].

The underlying mechanistic pathways of IP are complex in nature and include trigger factors, mediators, and effectors (Fig. 1). Studies in the myocardium identified 2 windows of protection that can be distinguished in IP: an early protective effect named classical IP that is transient, disappearing beyond 4 hours after procedure, and a delayed phase of resistance known as second window of protection also referred as delayed or late IP that appears 12 to 24 hours later and lasts up to 2 to 3 days [23]. Although classic IP and second window of protection share common underlying mechanisms, including triggers, transduction mechanisms, and effectors, downstream effects differ between the 2 phases.

The current paradigm suggests that IP recruits signaling pathways comprising cell surface receptors to several autocoids such as adenosine, bradykinin, endothelin, and opioids [24]. Binding of these substances to their cell surface receptors (G-protein–coupled receptors) activates several signal transduction cascades that include 1,2-diacylglycerol [25], protein kinase C (PKC) [26], mitogen-activated protein kinase (MAPK) [27], heat shock factor 1, and nuclear factor κ B [28]. Activation of nuclear transcription results in production of protective mediators, such as heat shock proteins (heat shock protein 27, heat shock protein 70) [29], inducible nitric oxide synthase (iNOS), antioxidants (superoxide dismutase [SOD]) [30], and inhibitors of apoptosis [31,32]. Activation of these mediators results in the opening of the adenosine triphosphate (ATP)–dependent mitochondrial

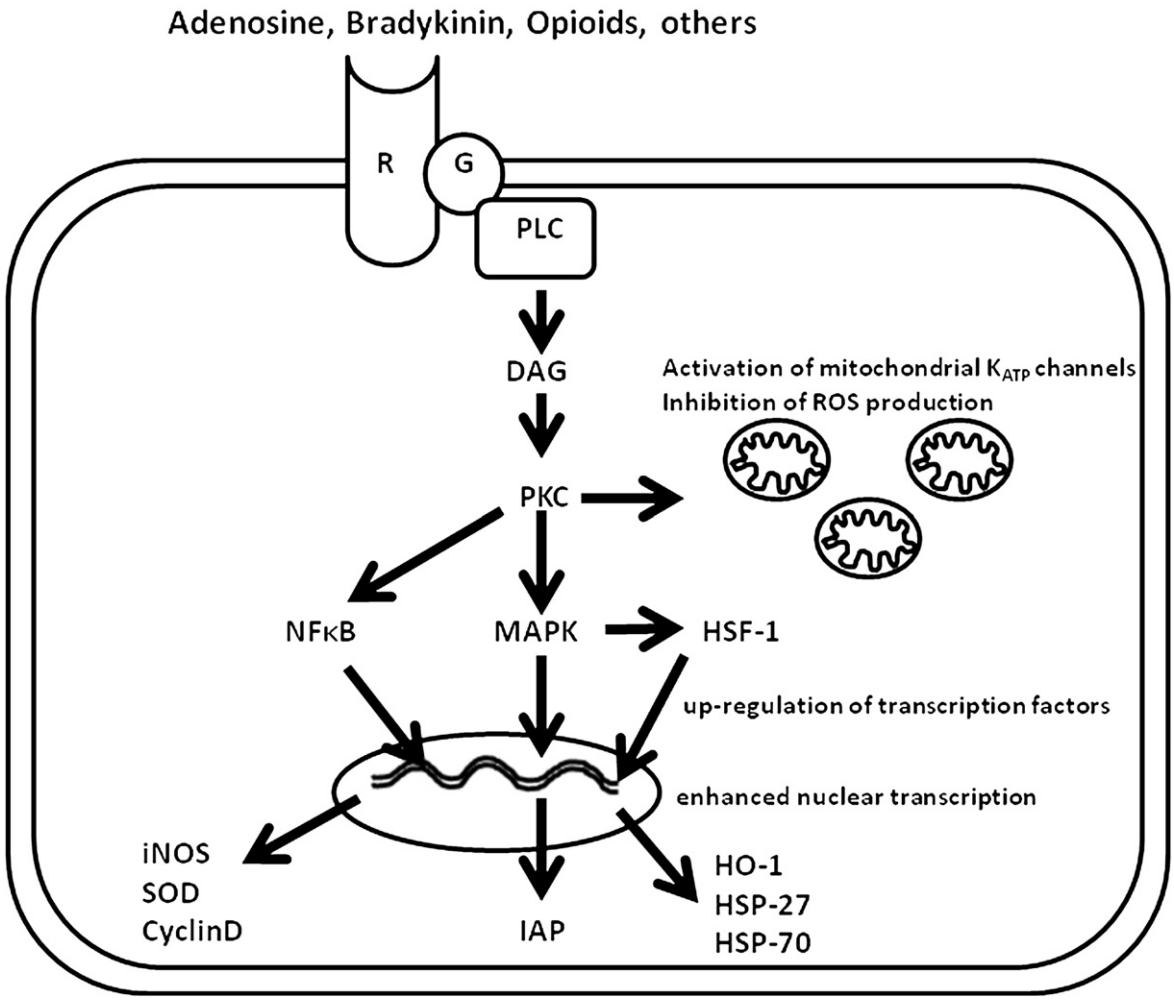

Fig. 1. Mechanisms of IP. Adenosine, bradykinin, opioids, or other mediators bind to the G-protein–coupled cell surface receptor. This induces a diacylglycerol-mediated activation of PKC, MAPK, heat shock factor 1, and NFκB. This increases the nuclear transcription of protective mediators, such as heat shock proteins 27 and 70, iNOS, SOD, and inhibitors of apoptosis.

potassium channel [33] and reduction of reactive oxygen species [34]. Alternative protective mechanisms of IP might exist that are independent of signal transduction pathways, such as anti-inflammatory mechanisms.

2.1. Ischemic preconditioning in the donor

2.1.1. Liver

Liver transplantation is, to date, the only curative treatment of acute and chronic liver disease. Because of remarkable improvement in the peri- and postoperative management of patients, liver transplantation has gained tremendous success over the last 3 decades leading to a persistent gap between the number of patients awaiting a liver transplant and the number of available grafts. Consequently, the use of extended criteria donor (ECD) organs, previously called marginal organs, has enhanced interest. The ECD organs include older donors, steatotic livers, livers with prolonged cold ischemic time, or donation after cardiac death (DCD). These grafts are prone to severe injury during retrieval of organs and transplantation surgery and, subsequently, to a higher risk of postoperative complications including primary nonfunction of the graft and poor outcome [35-37]. Efficient treatment of I/Rp injury may help to sustain the use of the ECD organs and safely expand the donor pool. Indeed, animal studies have often focused on the impact of preconditioning protocols in ECD livers such as fatty livers [38] and livers from older animals [3].

2.1.1.1. Animal studies. Several preclinical studies in mouse and rat models of warm or cold ischemia have reported decreased liver injury and improved survival in animals treated with 5 to 10 minutes of ischemia followed by 10 to 15 minutes of reperfusion before either warm or cold ischemia [39-41]. Similarly, it has been shown in a rat model that IP improves graft survival after cold organ storage and orthotopic liver transplantation [42].

2.1.1.2. Human studies. The beneficial effect of IP in patients undergoing liver resection was initially reported by Clavien et al [43,44] and has been subsequently reproduced by others [10,45]. Ischemic preconditioning demonstrated a stronger protective effect in patients with liver steatosis but was not effective in patients older than 60 years [44]. Since these reports, several randomized, controlled trials have evaluated the efficacy of IP in liver transplantation [9,11-13,46,47]. Most of these studies were performed in cadaveric donors with different types of protocols and controversial results.

Koneru et al [11] were the first group to study the clinical efficacy of IP in deceased donors in 2005. The authors compared donor IP in 34 patients receiving a cadaveric liver transplant with 28 controls undergoing a liver transplant without IP. There were no significant differences in the quality of the liver graft between the 2 groups. Overall, 36% of the allografts in the control group and 26% in the IP group had evidence of macrosteatosis on baseline biopsies. The mean cold ischemic time were identical between the 2 groups (~400 minutes). The selected IP protocol consisted of 5 minutes of ischemia and 5 minutes of reperfusion only, which is shorter than the protocol used in most experimental and human studies (10/10 minutes). This study did not show any reduction in the severity of reperfusion injury as assessed by biochemical and histologic parameters of liver grafts.

Azoulay et al [9] investigated the efficacy of IP on the outcome of the liver transplantation in terms of graft injury and function. All the grafts were procured from a donor without cardiac arrest or severe hemodynamic instability. About 15% of the grafts had evidences of steatosis (defined as macrovesicular steatosis in >20% of hepatocytes) in both groups. Using an IP protocol of 10 minutes of ischemia and 10 minutes of reperfusion, the authors demonstrated a reduction of liver injury by IP as assessed by lower serum aminotransferases levels. Intriguingly, IP was also the only variable significantly associated with early graft dysfunction. However, the early graft dysfunction had no impact on patient and graft survival. The authors concluded that IP did neither improve nor compromise the outcome of the graft posttransplantation.

Two more randomized, controlled trials in 2006 demonstrated a partial effect of IP of cadaveric liver donors with decreased hepatocellular necrosis and shorter intensive care unit stay compared with the control group. Of note, in the study by Cescon et al [13], despite a lower degree of hepatocellular necrosis in the IP group, total serum bilirubin levels, prothrombin activity, and infiltrating neutrophil in the liver biopsies were not different between the IP and control groups. Furthermore, the incidence of graft nonfunction was similar between the IP and the control groups. Importantly, no benefit was observed in graft and patient survival, suggesting that IP had no clinical benefit in cadaveric liver transplantation.

Finally, a recent meta-analysis of all randomized clinical trials analyzed 270 cadaveric liver transplants randomized to IP or no preconditioning during donor liver retrieval. The study found no difference in mortality, initial poor function, primary graft nonfunction, retransplantation rate, intensive care unit stay, and length of hospitalization [48].

The impact of IP on the outcome of living donor liver transplantation was recently investigated in a randomized, controlled trial by Andreani et al [49]. In this study, 44 adult right lobe living donors were randomized to receive IP or no preconditioning. The authors did not find any significant difference in the severity of ischemic injury, primary graft nonfunction, rate of acute cellular rejection, morbidity, and mortality between the 2 groups. Of note, because of the mandated requirement to wait for cardiopulmonary cessation before organ retrieval, IP has not been tested in DCD donors.

In summary, the current data do not support a benefit of IP in human liver transplantation despite favorable results from numerous experimental studies. It is clear that further studies of IP in donor livers require a modification of the preconditioning protocol in humans. Perhaps careful selection of the grafts that are more prone to ischemic injury (fatty grafts or older grafts) or a better recipient selection should be considered to translate the protective effect from the

animal studies into clinical practice and to justify further pursuing clinical studies with IP.

2.1.2. Kidney

Acute tubular necrosis and renal dysfunction [50,51] are well-known complications of I/Rp in the setting of kidney transplantation. Depending on the severity of reperfusion injury, 20% to 40% of deceased donor kidney transplant recipients develops acute tubular necrosis and requires temporary dialysis support in the first week after transplantation, a condition termed as *delayed graft function*. A recent meta-analysis of observational studies shows that delayed graft function, at least in kidneys from donors after brain death, is independently associated with a 40% increased risk of chronic graft failure [52].

Ischemia and reperfusion injury is also particularly deleterious in the setting of kidneys procured from non–heart-beating donors. In contrast to donation after brain death, kidneys from non–heart-beating donors have warm ischemic injury from circulatory arrest until cold static preservation. As a result, most of these kidneys experience delayed graft function. Furthermore, up to 15% to 25% of these kidneys will not show functional recovery, a condition called primary nonfunction requiring retransplantation [53].

Modulation of I/Rp injury–induced acute kidney injury holds the potential to reduce the incidence of early graft dysfunction and may help to sustain and expand the donor pool.

2.1.2.1. Animal studies. Torras et al [16] were the first group to describe a 1-cycle schedule of 15 minutes of warm ischemia and 10 minutes of reperfusion in the kidney as the most suitable schedule for IP. This protocol allowed protection from warm ischemia through a local production of nitric oxide. During the last decade, several reports have corroborated the efficacy of IP in kidneys both in early and late preconditioning windows, implicating conventional mediators such as nitric oxide, superoxide dismutase, or iNOS [54,55]. Subsequently, 2 other studies failed to identify any benefit of IP on renal dysfunction or morphological damage in models of porcine and dog kidney transplantation [56,57].

In terms of protection against cold ischemic injury, 2 experimental studies showed evidences that IP improved renal function and preserved morphological structures of kidneys transplanted after 5- and 24-hour storage in cold preservation solution [16,58].

Despite experimental studies demonstrating a decrease in renal allograft injury and improvement of allograft function, no clinical studies have, so far, evaluated the role of IP in human renal transplantation.

2.2. Pharmacologic preconditioning in liver and kidney transplantation

The concept of *pharmacologic preconditioning* is based on mimicking the protective mechanisms and biologic effects induced by IP. In human liver surgery, a total of 14 randomized, controlled trials evaluating antioxidants, anti-inflammatory drugs, vasodilators, and glucose infusion have evaluated the potential benefit of this concept with promising results. However, in liver transplantation setting, only few studies have assessed the efficacy of pharmacologic preconditioning of the donors in recipients outcome. In a recent randomized, controlled trials, Kotsch et al [59] have shown that pretreatment of donors with 100 mg of methylprednisolone at the time of organ retrieval improved significantly the severity of I/Rp injury post liver transplantation and lowered the incidence of acute cellular rejection in the treated group. The protective effect seems through reduction of brain death–associated inflammation as measured by lower levels of proinflammatory cytokines and down-regulation of adhesion molecules.

In kidney transplantation, most pharmacologic strategies have only been tested in animal models, and no human studies are currently available. Among these strategies, erythropoietin (EPO) preconditioning has recently shown intriguing results in the brain, heart, kidney, and other tissues. Erythropoietin mediates preconditioning by limiting the destructive potential of tumor necrosis factor α and other proinflammatory cytokines. As local production of EPO is generally suppressed after injury, administration of exogenous EPO has been proved to be a successful therapeutic approach in preclinical and clinical studies [60]. Pretreatment by EPO provided significant protection in attenuating renal I/Rp injury in an experimental model of rat kidney transplantation.

Glutamine pretreatment of donors has shown protective effects on renal graft function in a model of rat kidney transplantation with severe preservation reperfusion injury. The beneficial effects of this strategy seems through cytoprotection conferred by enhancing endogenous heat shock protein expression [61].

Other drugs such as sildenafil (a phosphodiesterase-5 inhibitor) have been tested in an experimental model of kidney graft autotransplantation in minipigs. The model included 45 minutes of warm ischemia induced by vascular clamping, nephrectomy, and 60 minutes of isolated hypothermic pump perfusion [62]. Although the results showed some improvement of renal vasculature flow and resistance recorded up to 60 minutes after autotransplantation, the long-term protective effects of this drug in terms of acute kidney injury remains unclear.

3. Postconditioning

One of the major limitations of IP is related to the timing of the procedure as it has to be instituted before the initiation of ischemic injury that, in clinical practice, is not always feasible. Attempts to overcome this limitation have prompted the development of a new concept called “ischemic postconditioning” (IPoCo), which is performed at the onset of reperfusion. Zhao et al [63] reported in 2003 the application of postconditioning to limit lethal reperfusion injury in an experimental model of acute myocardial infarct. Ischemic postconditioning focuses exclusively on events

occurring during reperfusion, identifying the early phase of reperfusion as a key therapeutic window. The protocol includes brief repetitive cycles of ischemia with intermittent reperfusion after prolonged ischemia. Ischemic postconditioning has been evaluated in preclinical studies in the heart, brain, liver, and kidney.

The current mechanistic paradigm for IPoCo involves the activation of signal transduction cascades by autacoid triggers; these triggers accumulate extracellularly in response to the postconditioning stimulus and act on cell surface receptors (Fig. 3). Several extracellular factors produced endogenously are known to play an essential role in IPoCo (adenosine, bradykinin, opioid peptides, and reactive oxygen species). Other additional autacoids could also play a role because their exogenous administration at reperfusion mimics the effect of IPoCo. These include natriuretic peptides (atrial natriuretic peptide and brain natriuretic peptide), peptide growth factors (insulin-like factor-1 and fibroblast growth factor -2), and tumor necrosis factor α. After binding to cell surface receptors, these autacoids promote the activation of kinase signaling pathways including the activation of PI3K/Akt and p42/p44 ERKs known as RISK pathway [64,65]. Up-regulation of this kinase cascade subsequently results in inhibition of the mitochondrial transition pores and activation of the ATP-dependent potassium channels. Similar to IP, all aspects of the signaling pathway of IPoCo can be subject to pharmacologic manipulation and development of pharmacologic postconditioning strategies.

3.1. Liver and kidney IPoCo

Studies in animal models have suggested a protective effect of IPoCo, but disappointingly, only few studies have examined the role of IPoCo in humans. In liver, IPoCo has shown to reduce hepatocyte apoptosis and reduce hepatic I/Rp injury in a rat model of I/Rp injury [59]. The IPoCo protocol used in this study included 60 minutes of ischemia followed by 4 cycles of 2 minutes of reperfusion before 95 minutes of reperfusion [66]. Similarly, in a rat model of orthotopic liver transplantation, Wang et al [67] found that liver function parameters of grafts treated with IPoCo (2 cycles of 30 seconds of ischemia followed by 30 seconds of reperfusion at the onset of reperfusion) are significantly improved compared with the untreated control group. This improvement is further associated with higher levels of antioxidants in animals treated with IPoCo. More recently, Zeng et al [68] have reported a protective effect of IPoCo against I/Rp. In this rat model of liver transplantation, the grafts were subjected to 24 hours of cold static preservation. The IPoCo group was treated with 6 cycles of 60 seconds ischemia and 60 seconds of reperfusion at the onset of reperfusion and compared with an untreated control group. Livers exposed to IPoCo had significantly decreased liver injury (lower serum transaminases and improved histology) compared with the untreated groups [68]. The authors found that the protective effect is likely through up-regulation of hemeoxygenase 1. Comparative studies with both IP and IPoCo in animal models of either warm ischemia alone or

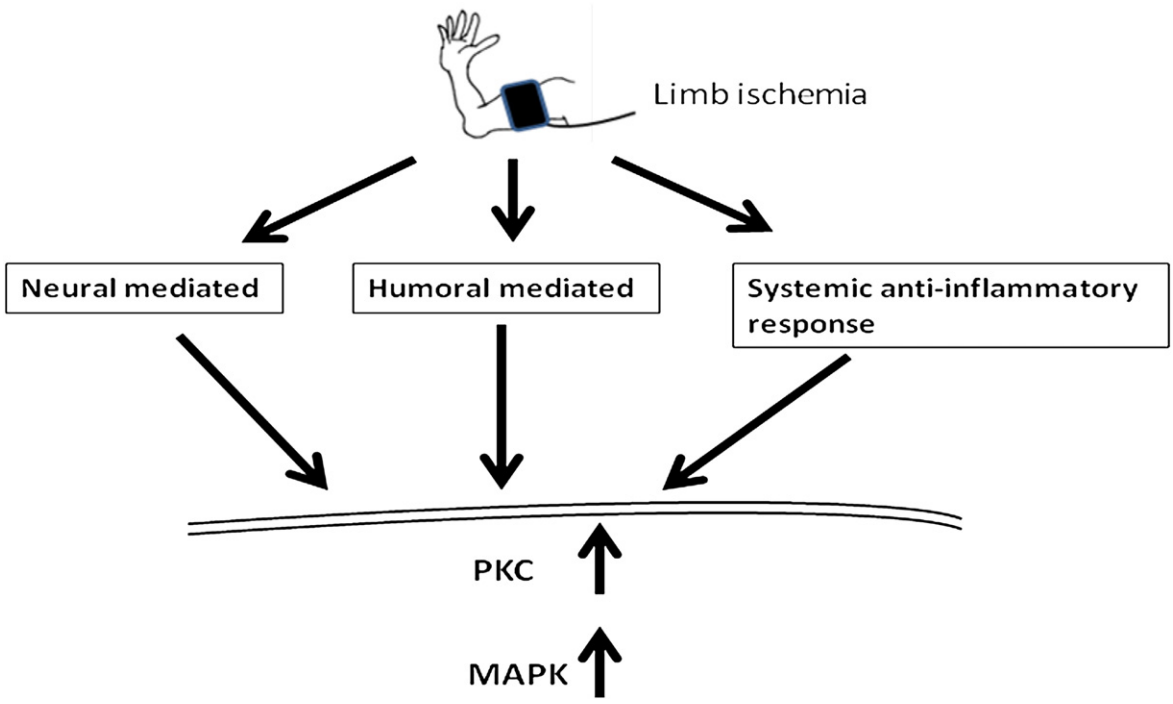

Fig. 2. Remote preconditioning is induced by limb ischemia. The factors transmitting the protective effect remain unclear. Three possible mechanisms have been proposed involving a neuronal signal transmission, a release of humoral mediators, or the induction of a systemic anti-inflammatory response, which might involve multiple factors. The protective pathways in the recipient organ are similar to ischemic preconditioning and involve activation of PKC and MAPK.

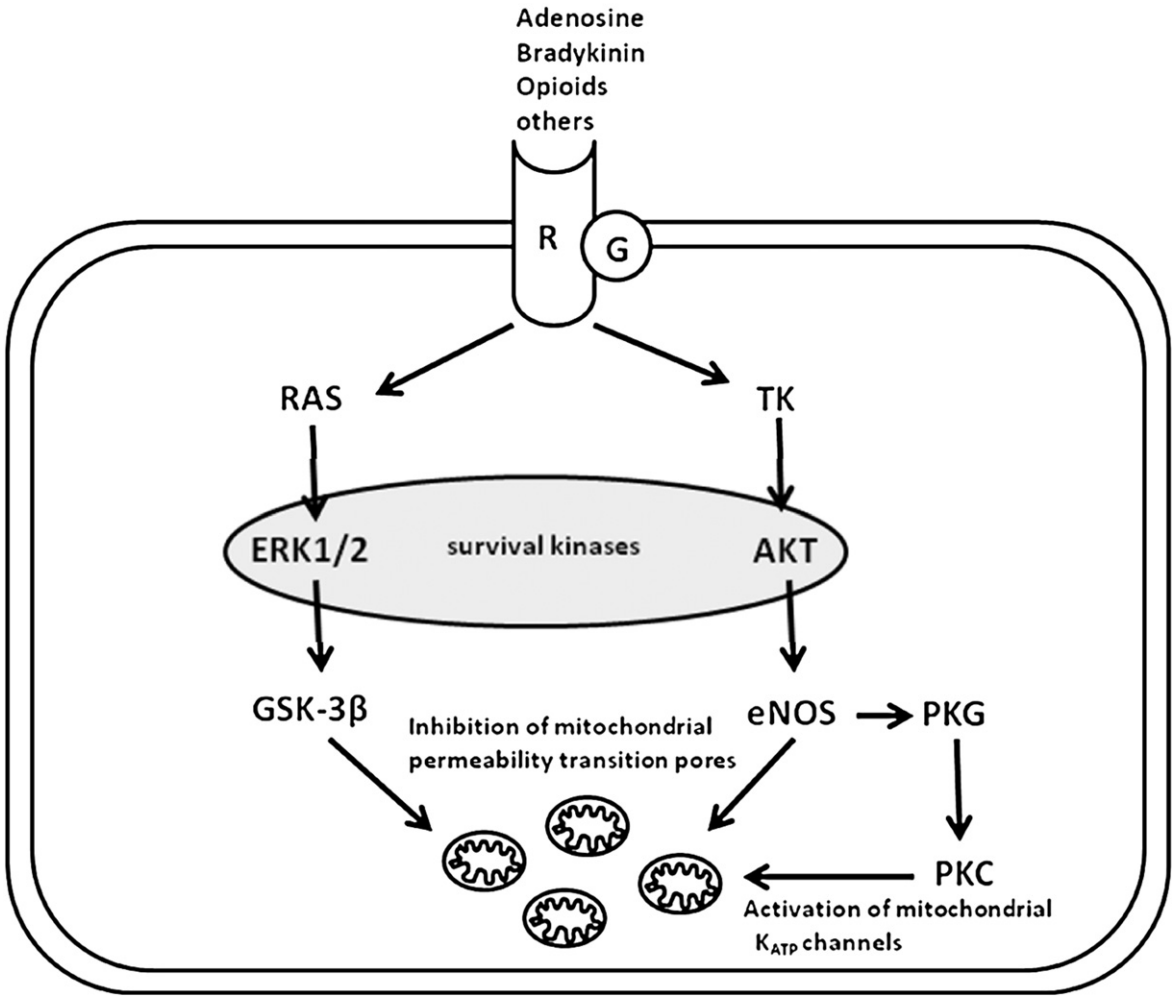

Fig. 3. Mechanisms of IPoCo. Mediators, such as Adenosine, bradykinin, or opiods bind to the G-protein coupled cell surface receptor. This results in the activation of intracellular kinases including tyrosine kinase, Akt, and ERK1/2. This cascade has also been labeled as the RISK pathway. The production of eNOS and PKC activates mitochondrial ATP-dependent potassium channels and inhibits the mitochondrial permeability transition pore. TK indicates tyrosine kinase.

combined cold and warm ischemia have shown equal protection in terms of liver injury between both protective strategies [69]. No animal studies had yet evaluated the role of IPoCo in a model of DCD liver transplantation. Liver IPoCo represents an alternative and effective approach to attenuate I/Rp in liver surgery. Despite the experimental data, no clinical study has yet evaluated the role of this protective strategy in human liver transplantation.

Similarly to the liver, in kidney transplantation, only few experimental studies have demonstrated evidences for IPoCo in the setting of delayed graft function. Szwarc et al [70] reported an improvement of renal function at day 2 post kidney transplantation with 30 minutes of warm ischemia in the IPoCo (3 cycles of 30 seconds of I/Rp)–treated group compared with the controls. Here, again, to our knowledge, no clinical studies are yet available to test the efficacy of IPoCo in kidney transplantation. Clearly, the available experimental data are not strong enough to allow the translation of this technique to human liver and kidney transplantation.

3.2. Liver and kidney pharmacologic postconditioning

Postconditioning can also been induced by using various pharmacologic agents, termed as *IPoCo mimetics*. Hausenloy et al [64] have evaluated the protective effect of postconditioning using edaravone, a free-radical scavenger in a rat model of I/Rp injury. Rats were subjected to 45-minute ischemia followed by 24-hour reperfusion. Edaravone was administered during the last 3 minutes of ischemia before reperfusion. They showed that edaravone postconditioning significantly decreased serum creatinine and blood urea nitrogen concentration and ameliorated histologic damage of renal tissue compared with the untreated control group. Wang et al [71] investigated the impact of inhalation anesthetics like isoflurane on renal protection in a model of rat I/Rp. Isoflurane inhaled at the onset of reperfusion potentiates the renal protective effect of IPoCo through a nitric oxide-dependent mechanism [72]. Sevoflurane, another volatile anesthetic can activate the mitochondrial K_{ATP} channels in the rat after reperfusion that has been associated

with the cardioprotection of preconditioning and postconditioning [73]. Experimental studies especially in cardiac postconditioing suggested that the same signaling components recruited in IPoCo appear to be implicated in pharmacologic postconditioning. Pharmacologic preconditioning with sevoflurane is currently evaluated in a phase III randomized, controlled clinical trial in patients undergoing kidney transplantation.

4. Remote IP

Remote IP (RIPC) is a novel protective strategy introduced by Przyklenk et al [74] in the early 1990s. The authors showed that a brief circumflex occlusion could reduce subsequent infarction size induced by the subsequent occlusion of the left anterior descending artery, a process termed *intraorgan preconditioning*. Subsequently, Yarlagadda et al [52] demonstrated that 4 cycles of 5 minutes of ischemia followed by 5 minutes of reperfusion of the hind limb protected against myocardial infarction in pigs undergoing 40-minute occlusion of the left anterior descending coronary artery. There are now results showing that, in animals, transient ischemia of a wide range of tissues induces a systemic multiorgan protection against subsequent extended I/Rp injury [54,75,76].

It has been suggested that some of the underlying mechanistic pathways activated in RIPC may be similar to those recruited in the setting of local preconditioning [77,78]. However, recent results suggest that there are important mechanistic differences between local and remote preconditioning (Fig. 2) [79]. The exact nature of signal transduction from remote tissue to target organ remains to be fully elucidated. Three theories have been postulated, and it is important to appreciate that these pathways may interact with each other (Fig. 3). Early results have proposed that substances released from the preconditioned organ such as adenosine, bradykinin, opioids, or *calcitonin* gene–related peptide stimulated local afferent nerves pathways, which then relay to efferent nerve pathway ending on the myocardium to confer cardioprotection [80-82]. The efferent signal has not been well characterized, but local release of adenosine might be important for mediation of cardioprotection.

An alternative hypothesis is that circulating effectors released from the preconditioning organ are carried in the blood stream to the heart where they manifest their protective effect. This theory is based on evidences that blood taken from a rabbit that had been subjected to simultaneous IPC of both the heart and kidney could reduce myocardial infract size when transfused into an untreated rabbit [83]. Finally, a multifactor anti-inflammatory effect of remote conditioning has been proposed. Clearly, further studies are needed to clarify the underlying mechanisms of RIPC.

Early experimental studies using this procedure in the setting of I/Rp injury have had promising results in reduction of injury in the heart, liver, lung, and kidney [84]. In the setting of transplantation, RIPC of the recipients have demonstrated reduction of myocardial ischemic injury in an experimental model of heart and lung transplantation [85,86].

In human, the first clinical application of this strategy was in children undergoing corrective cardiac surgery for congenital heart failure [87]. This randomized, controlled trial demonstrated the myocardial protective effect using a protocol of four 3-minute cycles of lower limb I/Rp on common femoral artery. Similarly, RIPC also demonstrated significant reduction of myocardial injury in patients undergoing coronary artery bypass graft surgery [88]. Currently, a phase III clinical trial is assessing the protective effect of this strategy in short- and long-term outcome of the recipients of the liver, kidney, and pancreas transplantation [82].

5. Conclusion

During the last decade, we have gained tremendous insight into the mechanisms of pre-, post-, and remote conditioning of solid organs. These novel techniques have been successfully investigated in experimental models with proven protective effect against I/Rp injury. Despite promising results in experimental settings, the translation of the pre-, post-, and remote conditioning to the clinical setting of organ transplantation has not been successful yet, and studies, in particular, in liver transplantation failed to show any relevant benefit. This might be related to the difference between animal models and the human setting of transplantation. For example, inflammation induced by brain death could modify the preconditioning cascade. In addition, in contrast to well-defined animal models, clinical transplantation involves multiple donor and recipient factors that impact on the severity of reperfusion injury. Furthermore, these strategies have, most probably, a true clinical benefit in ECD grafts that are more prone to I/Rp injury such as grafts from older donors or fatty livers. Because standard grafts can sustain some degree of reperfusion injury without major alteration in the graft function, it is conceivable that further studies should focus on assessing the role of these strategies in marginal organs.

The authors report no conflicts of interest.

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