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PERIOPERATIVE PROPHYLAXIS OF RENAL ISCHEMIA-REPERFUSION INJURY

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This paper reviews the strategies for correcting ischemia-reperfusion injury (IRI) in kidneys during surgeries and transplantation, discussed and proposed in the current literature. The pathophysiological mechanisms of IRI and a wide range of proposed methods for reducing the severity of injury are considered. The use of such techniques as the combination of ischemic, pharmacological pre- and postconditioning is still being studied. It was observed that researchers were very interested in immunological and biological (stem cell) therapeutic strategies as a potential avenue to lessen the severity of IRI.

Keywords: renal ischemia-reperfusion injury, renal IRI, antioxidants, IRI therapeutic strategies.

Ischemia-reperfusion injury (IRI) is currently a critical issue widely discussed across various fields of medicine, particularly in the context of organ transplantation and surgical or vascular interventions. Therapeutic approaches to correcting IRI vary depending on the organ affected.

This paper specifically focuses on renal IRI, which occurs during kidney surgery and transplantation, and explores potential methods to mitigate kidney injury resulting from IRI during these procedures.

The aim of this paper is to review the proposed and emerging strategies for alleviating the severity of IRI in kidney surgery and kidney transplantation (KT), as discussed in current literature.

Before delving into the methods of correction, their efficacy, and the stages at which they are applied, it is essential to first examine the mechanism of IRI in light of current research.

Mechanism of development. IRI is a form of tissue injury that occurs when blood supply is interrupted or depleted (due to blood loss or ischemia), followed by reperfusion. This process triggers the release of a variety of mediators, leading to cellular injury and, eventually, organ dysfunction. Notably, the injury caused during reperfusion is often more severe than during ischemia itself. During ischemia, tissues are deprived of metabolic reserves and oxygen, which leads to the accumulation of metabolic waste products. The absence of oxygen results in the depletion of energy reserves, such as adenosine triphosphate (ATP) and glycogen. Energy-dependent sodium-potassium (Na^+-K^+) exchangers, which help maintain an electrolyte gradient across the cell membrane, become dysfunctional due to energy depletion. As a result, the ion gradient across the cell membrane is disrupted. Sodium ions move into the cells from the extracellular space, while potassium ions shift out of the cells into the extracellular space. In response to the lack of oxygen, metabolic processes switch from aerobic to anaerobic pathways, leading to the accumulation of lactate and intracellular acidosis. This creates a vicious cycle that progressively reduces the efficiency of cellular energy production [1, 2].

Decreased intracellular pH further inhibits glycolysis, while increased intracellular sodium concentration can lead to a secondary rise in intracellular calcium levels. Calcium is also released from the mitochondria through the mitochondrial Na^+-H^+/Ca^{2+} exchanger. The activity of the sarcoplasmic reticulum Ca^{2+} pump, which helps in calcium reuptake, is suppressed, exacerbating the increase in intracellular calcium. As calcium ions accumulate inside the cell, they bind to and activate the regulatory protein calmodulin. This, in turn, activates calcium-calmodulin-dependent protein kinases, phospholipase A2, and proteases, leading to vesicle degranulation. This process releases proinflammatory chemokines and cytokines, such as interleukin-8, von Willebrand factor, and P-selectin, etc. [3].

Intracellular acidosis disrupts the hydrogen ion gradient across the mitochondrial membrane, halting ATP production. This, coupled with the increased levels of reactive oxygen species (ROS) in the mitochondria, exacerbates cellular damage. Increased intracellular calcium and elevated inorganic phosphate levels, resulting from accelerated ATP degradation [4], further influence the state of mitochondrial permeability transition pores (mPTPs). However, during the ischemic phase, low intracellular pH inhibits the opening of these mPTPs [3].

Dephosphorylation of AMP-activated protein kinase exacerbates IRI-induced acute kidney injury (AKI) by

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promoting mitochondrial dysfunction [5], accompanied by impaired mitochondrial iron homeostasis [6].

These processes are now collectively referred to as the ischemic sterile tissue injury theory, which suggests that ischemia leads to the release of endogenous molecules known as damage-associated molecular patterns (DAMPs), such as ATP, calcium, uric acid, and DNA. The cells of the innate immune system recognize these molecular signals, triggering a cascade of events. This includes the release of cytokines that promote chemotaxis, the labeling of damaged cells for clearance (opsonization), and direct cell killing. Such disorders activate the complement system, which, in turn, triggers chemotaxis and facilitates cell death through the formation of the terminal complement complex (C5b-9) [7].

IRI triggers a series of local and systemic pathophysiological mechanisms that ultimately result in cell death through necrosis, apoptosis, and autophagy. Necrosis is an uncontrolled process associated with inflammation [8], whereas apoptosis is a regulated, programmed form of cell death that occurs without inflammation. Apoptosis, as a programmed cell death process, is driven by intracellular changes following reperfusion. These changes include increased ATP production and calcium binding in mitochondria via Na^{+}-Ca^{2+} exchangers when intracellular pH returns to normal. ROS, generated during ischemia and reperfusion, play a critical role in the opening of mPTPs. During the ischemic phase, mPTPs remain closed due to low intracellular pH. However, when acidosis is corrected during reperfusion, mPTP opening occurs, leading to cell death by mitoptosis [9, 10]. The opening of mPTPs increases mitochondrial outer membrane permeability and facilitates the release of pro-apoptotic proteins like cytochrome c. Evidence suggests that BNIP3-mediated mitophagy plays a vital role in mitochondrial quality control and cell survival during IRI [11]. The loss of cytochrome c from the mitochondrial membrane triggers a cycle of reduced aerobic respiration, increased ROS production, and consequently, amplified apoptotic activity.

Mitochondria contain several antioxidants, such as Mn-superoxide dismutase (Mn-SOD), glutathione, glutathione peroxidase, thioredoxin-2, and glutaredoxin, which neutralize ROS and aid in cellular repair. However, these antioxidant systems become significantly overexpressed during ischemia and reperfusion. Additionally, mitochondrial ROS production stimulates the secretion of extracellular vesicles by epithelial cells, containing RNA, lipids, and proteins, suggesting their involvement in the pathogenesis of the process [12]. Spatial transcriptome sequencing has revealed mechanisms that drive tissue infiltration by immune cells [13].

At the same time, ischemic injury to endothelial cells reduces the production of nitric oxide (NO), endothelium-dependent hyperpolarizing factor, and prostacyclin, thereby increasing the risk of microthrombosis. The oxygen free radicals generated during reperfusion can further damage the vascular endothelium. For instance, superoxide radicals react directly with NO, which results in the loss of NO's physiological activity and the formation of peroxynitrite, a highly cytotoxic free radical [14].

We report the identification of 8-oxoguanine DNA glycosylase (OGG1) as a key mediator of hypoxia- and reoxygenation-induced apoptosis *in vitro*, as well as renal tissue injury in a renal ischemia-reperfusion injury (IRI) model. OGG1 is recognized for its role in the excision repair of damaged nuclear and mitochondrial DNA during IRI. These findings suggest that OGG1 may represent a novel clinical target with therapeutic potential [15, 16].

The N6-methyladenosine (m6A) mRNA methylase METTL14 has been shown to exacerbate renal IRI by suppressing Yes-associated protein 1 (YAP1). The discovery of the METTL14–YAP1 pathway offers a new perspective on the molecular mechanisms underlying IRI and paves the way for the development of innovative therapeutic strategies and molecular targets [17].

In addition to the mechanisms already discussed in the pathogenesis of IRI, recent studies have reported the expression of transient receptor potential melastatin 7 (TRPM7) in renal IRI, a finding previously documented only in IRI of other organs [18]. This novel evidence expands the potential role of TRPM7 in mediating renal injury during ischemia-reperfusion. Furthermore, various signaling pathways influencing gene regulation, including those involving microRNAs (miRNAs), have been explored. Several miRNAs have been identified as either upregulated or downregulated during IRI, suggesting their potential utility as biomarkers for early detection of IRI or as future therapeutic targets in clinical practice [19].

The involvement of AMP-activated protein kinase (AMPK) in renal IRI has been demonstrated, with several potential mechanisms proposed for its protective effects [20]. The renin-angiotensin system has also been implicated in the development and progression of IRI [21].

The measures employed to manage IRI in KT differ significantly from those used in non-transplant kidney surgeries. In transplantation, the first substantial injury to the allograft often occurs while the organ is still in the donor. Notably, the development of ROS-mediated oxidative stress following brain death (BD) is well-documented in both experimental models and clinical observations involving deceased donors. BD is believed to contribute to the maturation of immunostimulatory dendritic cells, which act as potential sources of DAMPs. These DAMPs activate the innate immune system of the deceased donor, particularly following severe trauma, leading to acute systemic autoimmune syndrome.

DAMPs released from injured graft cells further stimulate the recipient's innate immune response, triggering the secretion of pro-inflammatory cytokines such as tumor necrosis factor (TNF), type I interferons, interleukin (IL)-1, IL-6, and various chemokines. Neutrophils play a pivotal role in mediating microvascular occlusion and local tissue destruction during IRI [7].

Consequently, regulated forms of cell death such as necroptosis, pyroptosis, and ferroptosis have been reported in numerous models of post-ischemic reperfusion injury, including those within transplantation contexts. Among these, necroptosis and ferroptosis have garnered particular attention in the field of organ transplantation due to their emerging relevance in mediating graft injury [2, 22, 23]. Recent findings suggest that ferroptosis may represent an first stage of IRI, preceding the subsequent development of inflammatory responses and necrotic cell death [24].

Following donor organ transplantation, reperfusion-induced oxidative stress results in the release of DAMPs, which in turn reignite the innate immune response, creating a booster effect. Mitoglitazone has demonstrated a protective effect against renal IRI by inhibiting ferroptosis through its action on mitoNEET-regulated ferroptosis, also considered as a promising target for therapeutic intervention [25].

A variety of donor resuscitation and graft perfusion strategies have been explored to mitigate the effects of IRI in transplantation. In humans, prevention of IRI remains a major area of investigation, focusing on donor conditioning, modification of preservation solutions, graft reperfusion techniques, and optimization of recipient-targeted interventions [26]. One promising area of research includes the use of pharmacological additives, such as hydrogen sulfide (H_2S), in renal preservation solutions, as well as the modulation of preservation temperatures to improve graft viability and enhance recipient survival rates [27].

To prevent the excessive accumulation of oxygen-derived free radicals during organ storage and reperfusion, several pharmacological strategies have been proposed. These include the incorporation of xanthine oxidase inhibitors like allopurinol into preservation solutions, along with antioxidant agents such as reduced glutathione, mannitol, superoxide dismutase, desferrioxamine, and 21-aminosteroids [28]. Preconditioning of kidney grafts with H_2S is thought to mitigate IRI.

As previously discussed, intracellular calcium (Ca^{2+}) overload is a critical factor in the pathogenesis of IRI. Several strategies have been proposed to mitigate Ca^{2+} accumulation during reperfusion, including reducing extracellular Ca^{2+} levels in preservation solutions, supplementation with magnesium (Mg^{2+}) – which competes with Ca^{2+} for binding sites on exchangers and pumps – and pharmacological inhibition of Ca^{2+} influx. The latter involves the use of Ca^{2+} channel blockers and Na^+/H^+ exchanger inhibitors. However, some experimental studies have reported limited efficacy of verapamil in reducing renal IRI [29].

GM-CSF-induced MCP-1/CCR2 signaling has been implicated in sustaining cross-reactivity between injured tubular epithelial cells, infiltrating immune cells, and myofibroblasts, which promotes chronic inflammation and progressive interstitial fibrosis in the later stages of IRI [30].

The eIF5A hypusination inhibitor GC7 (N1-guanyl-1,7-diaminoheptane) has been shown to protect against ischemic injury. GC7 treatment has been shown to attenuate BD-induced renal injury, preserve mitochondrial homeostasis, and enhance antioxidant defenses, thereby improving post-transplant outcomes [31, 32].

The addition of sigma-1 receptor (S1R) agonists to preservation solutions improves graft function and minimizes structural damage, ultimately leading to enhanced long-term transplant outcomes. By reducing ischemic injury during cold storage, S1R agonists can potentially increase the pool of viable donor organs available for transplantation [33]. Quantitative assessment of ischemic tubular lesions in donor kidney biopsies – in kidneys retrieved after cardiac death – serves as a valuable predictive tool for post-transplant kidney function and is considered a reliable metric for evaluating graft quality [34].

These findings underscore the critical importance of a comprehensive understanding of IRI pathophysiology and the development of effective strategies for mitigating or reversing its effects in clinical practice. However, it is important to acknowledge that, while significant advances have been made in elucidating the mechanisms underlying IRI, the therapeutic approaches for its correction remain relatively underdeveloped [35].

Currently, IRImitigation strategies are broadly categorized into pharmacological and non-pharmacological approaches. The non-pharmacological methods include ischemic preconditioning (IPC) and ischemic postconditioning (IPostC).

IPC involves subjecting the target organ to brief, controlled periods of ischemia followed by reperfusion prior to a more prolonged ischemic stroke. This technique has been shown in both clinical and experimental studies to effectively reduce tissue damage, particularly in organs such as the liver [36]. While the exact protective mechanisms of IPC are still not fully understood, it is thought to slow ATP depletion, enhance autophagy, and preserve mitochondrial function during ischemic stress. In addition, IPC enhances autophagy and reduces cellular damage and mitochondrial dysfunction during injury. The so-called preischemic renal artery washout, proposed in experimental rat models, suggests that flushing

the renal artery before ischemia may reduce the burden of circulating leukocytes [37].

IPostC, on the other hand, entails a series of brief, intermittent reperfusion periods, each separated by short occlusion phases, followed by continuous reperfusion. Its beneficial effects have been demonstrated in experimental models [38] and further validated in clinical trials, particularly in cardiac patients [39]. The pathophysiological rationale for IPostC was described as early as 1989 by Russian researcher Marianna Bilenko, who found that perfusion of kidneys with blood twice depleted of oxygen and enriched with antioxidants can significantly reduce the severity of reperfusion injury [40]. Unlike donor preconditioning, which is not always feasible, graft postconditioning offers a more practical and adaptable intervention. It can be tailored to the specific risk factors associated with the donor organ and is particularly valuable in complex cases involving prolonged ischemia [41]. IPostC can also be included in complex non-transplant cases requiring prolonged periods of ischemia.

Non-pharmacological strategies also encompass the use of specially designed electric fields, which have demonstrated efficacy in delaying ATP depletion during ischemia and preserving Na^+/K^+-ATPase activity. This technique has been shown to reduce renal injury by approximately 45%, as evidenced by plasma creatinine levels of 1.17 ± 0.04 mg/dL in treated groups versus 1.97 ± 0.06 mg/dL in controls. Allograft function improved by over 50% compared to untreated counterparts [42].

Promising results have also been reported with pharmacological preconditioning and postconditioning using metformin, particularly in *ex vivo* models of normothermic machine perfusion involving rat and pig kidneys. These studies indicate that metformin exhibits renoprotective properties, potentially reducing the extent of IRI when administered prior to transplantation [43].

Contemporary pharmacological strategies to mitigate IRI are remarkably diverse. While early approaches predominantly relied on antihypoxants, the current landscape has expanded to include immunological, enzymatic, and biological interventions. However, much of the supporting evidence remains experimental or indirect, particularly concerning the effectiveness of pharmacological organ protection during procurement, preservation, and the early postoperative phase [35].

A number of medications have the ability to limit or completely inhibit ROS formation. These include urea, ceruloplasmin, nicotinic acid, mannitol, trimetazidine dihydrochloride (Trimetazidine), sodium polyhydroxyphenylene thiosulfonate (Hypoxene), and melatonin.

There is also a class of drugs known as scavengers – also referred to as free radical traps or interceptors. Their antioxidant mechanism involves neutralizing lipid radicals, lipoperoxide radicals, and lipid hydroperoxides, thereby interrupting the lipid peroxidation (LP) chain reaction. Examples include tocopherols, oxypyridine derivatives such as ethylmethylhydroxypyridine succinate (Mexidol) and methyl ethylpyridinol (Emoxipin), ionol, flavonoids, glutathione, acetylcysteine, methionine, as well as derivatives of succinic, fumaric, and other organic acids, ubiquinones, selenites, retinols, and carotenoids.

Recombinant preparations used by Russian authors that either inactivate ROS directly or the enhance endogenous biosynthesis of LP inhibitors have also been developed [44].

Vitamins have been used for decades as a means to reduce IRI, and research into their mechanisms and therapeutic potential continues to generate interest. These vitamins are generally classified into two types: water-soluble (hydrophilic), such as ascorbic acid (vitamin C), and fat-soluble (hydrophobic), such as beta-carotene and alpha-tocopherol (vitamin E). Hydrophilic antioxidants primarily interact with oxidants in blood plasma and the cytosol of cells, while hydrophobic antioxidants function predominantly to protect cellular membranes from lipid peroxidation [45]. Curcumin, which has pronounced antioxidant and anti-inflammatory properties, has been shown to have a positive effect [46].

Melatonin, a potent antioxidant synthesized by the pineal gland, also plays a significant role in combating oxidative stress and inflammation [47]. It not only scavenges reactive oxygen species and reactive nitrogen species (RNS) but also enhances the activity of key antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR), contributing to membrane stabilization [36]. Due to its endogenous origin and low toxicity profile, melatonin is typically well tolerated [48, 49]. Emerging evidence supports its therapeutic potential, including studies that highlight the efficacy of melatonin alone [49], as well as in combination with mesenchymal stem cells and their exosomes, in reducing renal IRI in experimental rat models [48].

The prognosis of IRI can be improved by targeting the expression of endogenous cytokines. One such pharmacological agent is sevoflurane, a third-generation halogenated inhalational anesthetic known for its influence on the duration of neuromuscular blockade induced by non-depolarizing muscle relaxants. In experimental studies, pre-treatment with sevoflurane significantly reduced concentrations of TNF-alpha, IL-8 and IL-6 [50]. Sevoflurane has been reported to protect rat kidneys from IRI by reducing the expression of transient receptor potential melastatin 7 (TRPM7) [15].

Anesthetics help limit the elevation of extracellular glutamate levels and inhibit the overactivation of excitatory glutamatergic receptors, both of which are associated with increased oxidative stress in ischemic

tissues. In particular, ketamine has been reported to exert beneficial effects in rat models [51].

The use of medical gases in oxidative stress therapy represents an emerging therapeutic approach. These gases can be administered directly to patients via inhalation using a nasal cannula, face mask, or ventilator. IRI has been treated with several therapeutic gases, including hydrogen (H_2), hydrogen sulfide (H_2S), nitric oxide (NO), and carbon monoxide (CO). The therapeutic effects of H_2S have been demonstrated in rodent models of IRI, and it has been shown that H_2S can induce reversible hypothermia and an anabiosis-like state. The antioxidant effects of H_2S may be attributed to its interaction with cytochrome c oxidase and its influence on mitochondrial function. H_2S may modulate gene expression through pathways involving nuclear factor-kappa B (NF-κB) and extracellular signal-regulated kinase (ERK) [52].

In a rat model, evodiamine administration significantly reduced renal injury resulting from IRI, owing to its potent antioxidant, anti-inflammatory, and anti-apoptotic properties [53].

Alkaline phosphatase (ALP) has also emerged as a potential therapeutic agent for attenuating IRI. A double-blind, randomized, placebo-controlled, single-center pilot study investigated the safety and feasibility of peri-procedural ALP administration in living donor KT. Participants in the treatment group received 1000 IU of bRESCAP (bovine RESCue Alkaline Phosphatase, test substance name: bovine intestinal alkaline phosphatase, bIAP; EC 3.1.3.1). The study concluded that bRESCAP administration was safe, feasible, and may help reduce IRI-induced renal inflammation. Notably, this was the first trial to assess the use of bRESCAP in the context of KT, and further studies are currently planned to explore its therapeutic potential [55].

Inhibition of pyruvate dehydrogenase kinase-4 (PDK4) has been demonstrated to improve kidney IRI outcomes by reducing succinate accumulation during ischemia and preserving mitochondrial function during reperfusion [56]. Downregulation of G protein-coupled receptor kinase 4 (GRK4) has been shown to exert a protective effect against kidney IRI [57].

The NFAT inhibitor 11R-VIVIT has been shown to reduce renal fibrosis in mice after IRI. As a peptide inhibitor of nuclear factor of activated T-cells (NFAT), 11R-VIVIT was found to exert a renoprotective effect during a transition to chronic kidney disease after IRI. The study's findings support the hypothesis that NFAT2 inhibition may represent a promising new therapeutic strategy to prevent post-IRI kidney fibrosis [58].

In another mouse study, researchers identified a fucosylated ligand associated with ischemic injury that plays a role in initiating complement activation and AKI. The findings suggest that administration of supraphysiological levels of L-fucose in the renal cortex may exert therapeutic effects, likely through altering the cell-binding properties of collectin-11 (CL-11). These preliminary results warrant further investigation [59].

Propofol has been reported to confer a protective effect against IRI, although its precise mechanism of action remains unclear [60].

The polyoxylate-based copolymer APP-103, which incorporates vanillyl alcohol (VA) into its hydrophobic polymer backbone, has demonstrated high sensitivity and specificity to hydrogen peroxide (H_2O_2). In experimental models, APP-103 was shown to be safe and effective in improving renal function after IRI and enhancing survival following KT [61].

Prostacyclin (PGI_2), a product of prostacyclin synthase (PGIS), has also been identified as a renoprotective agent in IRI-induced AKI cases. The PGIS/PGI_2 axis presents a promising therapeutic target in AKI [62]. Another promising compound is N-(p-Amylcinnamoyl) anthranilic acid, an inhibitor of phospholipase A_2 and a potential melastatin-2 receptor blocker, which has shown protective effects against renal IRI [63].

Semaglutide, a GLP-1 receptor agonist, was found to exert renoprotective effects through modulation of inflammatory and oxidative pathways, particularly via the PI3K/AKT signaling pathway [64].

Disulfiram has demonstrated efficacy in ameliorating IRI-induced AKI by inhibiting the caspase-11–GSDMD pathway. Interestingly, disulfiram selectively blocked this pathway without significantly affecting classical pyroptosis markers such as NLRP3 and ASC, suggesting its targeted action on caspase-11-mediated pyroptosis [65].

Inhibition of NADPH oxidase 1 (NOX1) has also shown protective effects in the context of kidney IRI [66].

Cholecalciferol (vitamin D_3), a clinically available compound, has been reported to protect kidney function in IRI by reducing ROS production, inhibiting NF-κB activation, and suppressing GSDMD-mediated pyroptosis [67].

Gold-platinum nanoparticles (AuPt NPs) – consisting of a gold core and a loosely branched platinum shell – have been proposed as a novel therapeutic strategy for renal IRI) [68]. Mitoglitazone improves kidney IRI by inhibiting ferroptosis [25, 69]. Modulation of NF-κB signaling via exosomal delivery is being explored as a potential therapeutic approach for AKI resulting from IRI [70].

There is also growing evidence suggesting sex hormones influence the susceptibility to renal IRI. Female sex hormones, particularly estradiol, appear to confer protective effects, while male hormones may exacerbate ischemia-induced renal injury [71]. Experimental studies in rats have shown that estradiol administration significantly reduces renal injury and improves outcomes following IRI [72, 73].

Multipotent adult progenitor cells (MAPC®) have potent immunomodulatory properties that may mitigate IRI [74]. This is the first reported series in which cell therapy was successfully delivered directly to human donor kidneys as an isolated *ex vivo* perfusion platform. Kidneys treated with MAPC cells exhibited improved clinically relevant outcomes, along with reduced tissue injury and lower levels of pro-inflammatory biomarkers. These effects may be mediated through alterations in circulating cytokines or secretion of soluble anti-inflammatory mediators. This approach could represent a paradigm shift in transplant medicine, offering a novel opportunity to treat donor organs directly prior to transplantation in order to minimize IRI [75].

Of particular interest is recent work exploring advanced technologies such as 3D renal organoids and kidney-on-a-chip platforms. The review provides information for creating models to study acute renal conditions associated with IRI [76, 77].

In addition, a study identified two distinct IRI clusters based on differentially expressed necroptosis-related genes (DE-NRGs). The researchers developed predictive models for delayed graft function (DGF) and graft survival, providing a framework for early prevention and personalized management of postoperative complications in KT recipients [78].

Russian researchers have also made significant strides in investigating potential solutions to IRI. In recent years, Netrebenkoet et al. have presented several studies examining the effects of various substances on the severity of kidney IRI. Notably, infliximab has shown experimental effectiveness in kidney IRI models, demonstrating a positive impact on IRI severity [79–81]. Similarly, a combination of a peptide mimicking the alpha helix of erythropoietin beta has been found to exert a beneficial effect in kidney IRI [81–83].

Carbamylated darbepoetin [84] and arginase II [85] have been demonstrated in experiments to be effective in preventing kidney IRI. Acyzol, based on zinc bisvinylimidazole diacetate, has been proposed for use as post-ischemic pharmacological conditioning. In preclinical studies, Acyzol showed positive effects when administered starting from the first day after surgery [86].

Goncharov et al. developed a genetically engineered construct encoding the PSH enzyme. In a mouse model, administration of a chimeric recombinant protein (PSH antioxidant enzyme) 15 minutes prior to ischemia was shown to reduce the severity of kidney IRI, offering a form of pharmacological ischemic preconditioning (IPC) [87, 88]. Additionally, Goncharov's team proposed the recombinant protein TAT-Prx2, a modified human peroxiredoxin 2, for intravenous administration to mitigate complications associated with kidney IRI. This protein was shown to enhance cellular resistance to IRI in experimental models [89]. Further research also demonstrated its efficacy in liver IRI [90].

Of significant scientific and practical interest are the works of Russian authors focused on understanding the mechanisms and developing preventive strategies for IRI in various organs. A substantial body of work by Konstantin Popov has provided in-depth and comprehensive analyses of the mechanisms underlying liver IRI and various treatment methods [91–100]. Other studies have also explored approaches to liver IRI treatment, contributing to a growing body of research in this area [101–105].

Several studies by Russian researchers have addressed the challenges posed by myocardial IRI [106–113]. While a detailed review of these studies is beyond the scope of the current discussion, their inclusion highlights the broad scientific interest in IRI-related research.

Furthermore, the development of the biobank model offers promising potential for large-scale studies, aiding in the prediction and prevention of IRI across various organ systems [114].

Based on the analysis of a broad spectrum of studies addressing the treatment of IRI, it is evident that there is currently an active, multidirectional, and pathophysiologically grounded effort to identify effective strategies for mitigating kidney injury associated with IRI. Continued development and refinement of approaches – such as combined ischemic preconditioning and postconditioning, alongside pharmacological and mechanical pre- and post-ischemic interventions – reflect this dynamic field of investigation.

Several of the pharmacological agents presented, including those with novel structures, mechanisms of action, and methods of synthesis, offer considerable promise and highlight important avenues for future research. The search for optimal solutions will persist until a standardized, situation-specific protocol for ischemic conditioning is established.

The authors declare no conflict of interest.

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