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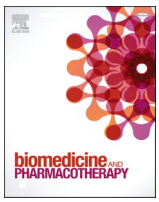

Nitric oxide in kidney transplantation

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ABSTRACT

Kidney transplantation is the treatment of choice for patients with kidney failure. Compared to dialysis therapy, it provides better quality of life and confers significant survival advantage at a relatively lower cost. However, the long-term success of this life-saving intervention is severely hampered by an inexorable clinical problem referred to as ischemia-reperfusion injury (IRI), and increases the incidence of post-transplant complications including loss of renal graft function and death of transplant recipients. Burgeoning evidence shows that nitric oxide (NO), a poisonous gas at high concentrations, and with a historic negative public image as an environmental pollutant, has emerged as a potential candidate that holds clinical promise in mitigating IRI and preventing acute and chronic graft rejection when it is added to kidney preservation solutions at low concentrations or when administered to the kidney donor prior to kidney procurement and to the recipient or to the reperfusion circuit at the start and during reperfusion after renal graft preservation. Interestingly, dysregulated or abnormal endogenous production and metabolism of NO is associated with IRI in kidney transplantation. From experimental and clinical perspectives, this review presents endogenous enzymatic production of NO as well as its exogenous sources, and then discusses protective effects of constitutive nitric oxide synthase (NOS)-derived NO against IRI in kidney transplantation via several signaling pathways. The review also highlights a few isolated studies of renal graft protection by NO produced by inducible NOS.

1. Introduction

Kidney transplantation is a renal replacement therapy that has become the treatment of choice for patients with end-stage renal disease, as it provides better quality of life and confers significant survival advantage at a much lower cost compared to dialysis therapy. However, like the transplantation of other solid organs, the long-term success of kidney transplantation is severely hampered by ischemia-reperfusion injury (IRI). Renal IRI is an inevitable clinical challenge due to temporary cessation of blood flow during renal graft procurement (warm ischemia) followed by storage in cold preservation solution (cold ischemia) and restoration of warm oxygenated blood (reperfusion) upon implantation of the renal graft. IRI increases the incidence of delayed graft function, primary non-function, and other post-transplant complications [1–3]. This has necessitated the search for novel approaches to modify the existing kidney transplantation protocol to limit IRI and its detrimental effects.

Nitric oxide (NO), formerly known as endothelium-derived relaxing factor, is the first identified member of a family of gaseous signaling molecules referred to as *"gasotransmitters"*, and has emerged as a potential candidate that holds clinical promise in mitigating IRI and protecting against acute and chronic graft rejection when it is added to kidney preservation solution or administered to the kidney donor prior to kidney procurement and to the recipient or to the reperfusion circuit at the start and during reperfusion. This is due to its therapeutic properties, which include vasodilation, antioxidant, anti-inflammatory and anti-apoptotic properties, which it shares with other members of the gasotransmitter family [4–7]. NO is a colorless and odorless free radical gas with high lipid solubility but limited water solubility, and denser than air. It is a non-flammable, poisonous and highly reactive gas, an environmental pollutant that is emitted at high concentrations into the atmosphere from fuel combustion in mobile and stationary sources [8]. However, its endogenous production at low physiological concentrations in the vascular endothelium, neural and some other cell types plays important roles in vascular homeostasis (e.g. vascular smooth muscle relaxation and regulation of arterial blood pressure), oxygen delivery,

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post-natal angiogenesis, neurotransmission, immune and sexual functions and a myriad of physiological processes. NO also has numerous vasoprotective and anti-atherosclerotic effects. Interestingly, dysregulated or abnormal endogenous production and metabolism of NO is widely associated with pathogenesis and progression of vascular dysfunction and impaired tissue perfusion, which negatively impacts kidney transplantation outcomes. For example, over-production of NO has been associated with the development of macrovascular compromise, bioenergetics failure and cytotoxicity [9–12] while reduced NO production is linked to microvascular dysfunction [13–17]. From experimental and clinical perspectives, this review presents endogenous enzymatic production of NO as well as its exogenous sources, and then discusses protective effects of constitutive nitric oxide synthase (NOS)-derived NO against IRI in kidney transplantation via several signaling pathways. The review also highlights a few isolated studies of graft protection by NO-producing iNOS.

2. Sources of nitric oxide

2.1. Production of nitric oxide in the body

As illustrated in Fig. 1 below, NO is synthesized by a group of enzymes called nitric oxide synthases (NOS), using L-arginine and molecular oxygen as substrates and reduced nicotinamide-adenine-dinucleotidephosphate (NADPH), and reduced tetrahydrobiopterin (BH4) as co-factors to produce L-citrulline, with NO as a by-product [18,19]. After its production, NO is quickly degraded to nitrate and nitrite (NOx; stable end products), and serve as noninvasive biomarkers of renal graft rejection, as they can be measured in serum and urine. The NO produced by NOS rapidly diffuses in a paracrine fashion into the adjacent smooth muscle layer, where it acts on several target proteins and enzymes to exert its physiological function through activation of soluble guanylate cyclase, an enzyme that converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) to mediate many of the biological effects of NO [20]. Three structurally distinct isoforms of NOS have been recognized in mammals and named according to tissue type in which they were first identified. These isoenzymes are neuronal NOS (nNOS or NOSI), inducible NOS (iNOS or NOSII) and endothelial NOS (eNOS or NOSIII). Interestingly, all the three NOS isoforms can be found in a variety of cell types despite their names. For example, nNOS is also found in enteric system, kidney macula densa cells, pancreatic islet cells, skeletal muscle and in the vascular smooth muscle cells besides its predominant localization in the nervous system [21,22]. Endothelial NOS is also expressed in cardiac myocytes, platelets, certain neurons in the brain, human placenta and renal tubular epithelial cells besides being predominantly found in the endothelium [22–25]. Inducible NOS is primarily found in macrophages, but its expression can be activated in any cell or tissue that receives the appropriate inducing agent [22,24]. In addition, all three isoforms bind to calmodulin, which regulates their activities. In nNOS and eNOS, which are constitutively expressed in mammalian cells, calmodulin binding is activated by increased intracellular Ca^{2+} concentration (between 200 and 400 nM), which catalyzes electron transfer reactions from NADPH during the synthesis of NO from L-arginine [26,27]. Thus, increased Ca^{2+}/calmodulin concentration increases NO production by nNOS and eNOS momentarily and in the regulation of physiological processes by NO. In iNOS, however, calmodulin binding is independent of intracellular Ca^{2+} concentration, as the binding can occur even below intracellular Ca^{2+} concentration of 40 nM [26]. This unique feature of iNOS is due to the different amino acid structure at the calmodulin-binding site compared to that in nNOS and eNOS. Hence, production of NO by iNOS lasts much longer and with much higher concentrations in cells than from nNOS and eNOS. It is important to note that iNOS is not typically expressed in resting cells, and requires induction by cytokines or microbial products such as bacterial endotoxins. Thus, iNOS is predominantly expressed in response to inflammatory stimulus but is also constitutively found in some tissues albeit at low levels [28,29]. This suggests that iNOS is a pathological isoform of NOS that contributes to pathophysiology of inflammatory conditions including graft rejection in organ transplantation. However, the balance between the beneficial and harmful effects of NO is determined by a cascade of cellular and molecular events that regulate the site and degree of NO production in response to inflammation.

2.2. Exogenous sources of nitric oxide

As dysregulated or abnormal production and metabolism of endogenous NO is widely associated with pathogenesis and progression of vascular dysfunction and impaired tissue perfusion [12,15,17], and the fact that the classic form of inhalation of NO gas is hampered by rapid scavenging and inactivation by hemoglobin after diffusion into the blood (i.e. short half-life) and thereby limiting its vasodilatory effect largely to the lungs, there are organic and inorganic compounds from other exogenous sources that function as NO donor molecules by producing NO through mechanisms that are independent of NOS [30,31]. These NO donor molecules represent a useful pharmacological tool to transport and control the release of NO systemically to mimic endogenous NO synthesis, and have been used clinically for several decades. These compounds include nitroprusside and nitroglycerin (glyceryl trinitrate), which are widely used in vascular medicine [32]. Under ischemic condition, NO donor molecules stimulate microcirculatory relaxation and inhibit inflammatory pathways. This property makes NO a suitable candidate drug for patients undergoing organ transplantation. Other NO donors are isosorbide dinitrate, isosorbide mononitrate, isoamyl nitrate, nicorandil, S-nitrosothiols, inorganic nitroso compounds, sydnonimines, NONOates, and hybrid NO donors such as nitroaspirin and S-nitro-NSAIDs [30,33,34].

3. Nitric oxide in kidney transplantation

There is currently a global shortage of donor kidneys due to the increasing number of dialysis patients on the transplant waiting list compared to the number of transplantable kidneys available. This has led to increasing use of suboptimal renal grafts from high-risk donors such extended criteria donors, donors-after-brain-death (DBD) and donors-after-cardiac-death (DCD), previously called non-heart-beating

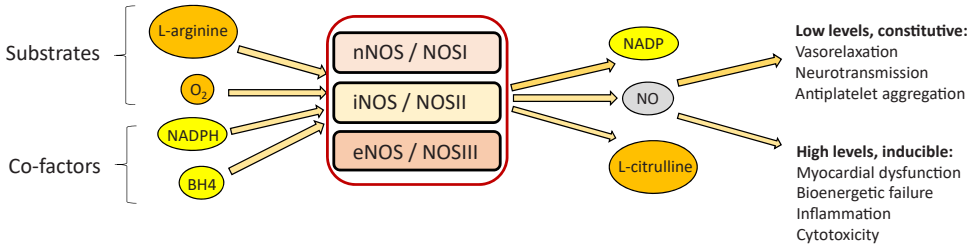

Fig. 1. Enzymatic production of endogenous NO. NO is synthesized by a group of enzymes called nitric oxide synthases (nNOS, iNOS and eNOS) using L-arginine and molecular oxygen as substrates and reduced nicotinamide-adenine-dinucleotide phosphate (NADPH), and reduced tetrahydrobiopterin (BH4) as co-factors.

donors. However, kidneys from these sources have greater ischemic damage prior to reperfusion and show reduced viability after transplantation. Nonetheless, they represent an inevitable option to expand the donor pool to meet the increasing global shortage and demand for donor kidneys. The current clinically approved method of donor kidney preservation for transplantation is static cold storage (SCS) in University of Wisconsin (UW) solution or histidine-tryptophan-ketoglutarate (HTK) solution on ice at 4 °C with the aim of mitigating IRI by slowing cellular activity and reducing production of toxic metabolites prior to transplantation [35–38]. However, SCS also contributes to IRI of the renal graft with increased rates of acute tissue necrosis, decreased graft survival, and delayed graft function [35,39–41]. The patholphysiology of IRI involves complex and multifactorial mechanisms including deleption of adenosine triphosphate (ATP), opening of mitochondrial permeability transition pores (MPTP; an indicator of mitochondrial dysfunction) during ischemia and subsequent realease of calcium into the the cytoplams, and thereby activating Ca^{2+}-dependent cytosolic phospholipases and lipases and resulting cell swealling. In addition, MPTP opening results in mitochondrial release of pro-apoptotic factors such as cytochrome c, endonuclease G and apoptosis-inducing factor into the cytoplasm and nucleus, which activate caspase cascade and other downstream events that lead to apoptosis in a caspase-dependent and caspase-independent manner [35,42,43]. Restoration of warm oxygenated blood during reperfusion of the ischemic graft also activates additional pathological pathways including over-production of reactive oxygen species (ROS; a destructive mediator of cell and tissue injury) mainly from the mitochondria as well as system release of pro-inflammatory mediators such as cytokines, chemokines, adhesion molecules, which compromises cell permeability and culminates in cell death [35,42,43]. While limiting warm and cold ischemic time is currently the only approach to minimize IRI, there is a growing interest in experimentally exploring novel pharmacological strategies involving endogenous nitric oxide and its donor compounds against IRI, which could aid the necessity of increasing the quality of renal graft preservation and perhaps safely extend the cold ischemic time with minimal or no injury.

3.1. Endogenously produced nitric oxide in kidney transplantation

As mentioned in subsection 2.1 above, iNOS is a pathological isotype of NOS that contributes to pathophysiology of inflammatory conditions. Therefore, inhibition of iNOS has been reported to protect renal grafts. In a rat model of kidney allotransplantation, Barakat et al. [44] observed markedly decreased serum creatinine and blood urea nitrogen (BUN) and minimal renal tubular damage in transplant recipient rats following administration of 300 mg/kg L-arginine (precursor of NO) to donor rats before renal graft procurement and transplantation. Although the authors did not explore potential mechanisms underlying renal graft protection by L-arginine, other studies reported that inhibition of NO/cGMP signaling pathway abolished renal graft-protecting effect of L-arginine [45], suggesting that the graft protecting-effect of L-arginine is dependent on NO/cGMP mechanism, a pathway that mediates vasodilation and other biological effects (Fig. 2). The involvement of NOS in renal allograft protection was confirmed by the same research group when they reported that administration of constitutive NOS inhibitors resulted in renal allograft dysfunction in transplant recipient rats [44]. In another study, L-arginine also reduced proteinuria and glomerulosclerosis and improved the function and survival of renal allografts in acute phase of kidney transplantation in rats [46]. Similarly, pharmacological inhibition of constitutive NOS with n-omega-nitro-L-arginine methyl ester (L-NAME) and NG-monomethyl-L-arginine (L-NMMA) in a rat model of renal allograft rejection produced a severe graft damage by aggravating alloimmune response evidenced by vascular leukostasis, vasculitis, and T-cell and monocyte infiltration of the tubulointerstitium under cyclosporine A therapy [47]. In a dog model of renal autotransplantation in which renal grafts were cold-stored in UW solution for 24 h, renal production of NO was significantly higher following reperfusion, which correlated with reduced levels of serum creatinine, nitrogenous free radicals while NO inhibition abrogated these benefits, contributing to death of the transplant recipient dogs after post-transplant day 7 [48]. Also, as iNOS expression is well-known to be upregulated in acute and chronic rejection in renal allografts in concert with influx of macrophages and other immune cells [49,50], its blockage with the specific inhibitors, iminoethyl-lysine and 7-butylhexahydro-1H-azepin-2-imine in transplant recipient rats under cyclosporine A therapy improved

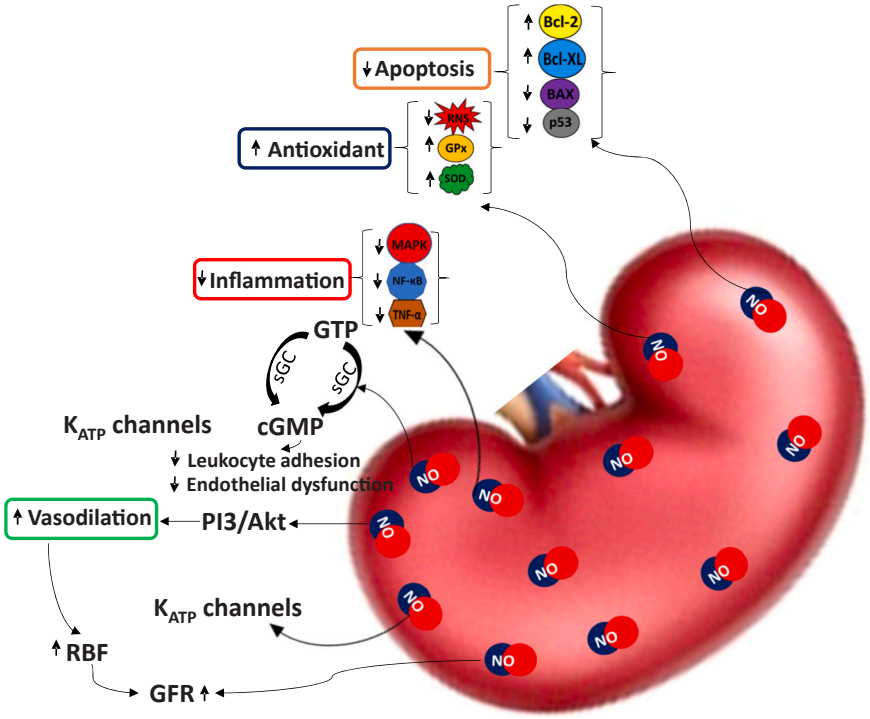

Fig. 2. Renal allograft protection mediated by NO. Endogenous production of NO or its exogenous supplementation mediates renal graft protection by inhibiting inflammatory and pro-apoptotic pathways while simultaneously activating antioxidant and vasodilatory pathways. BAX; Bcl-2-associated X protein, BCL; B-cell lymphoma, cGMP; cyclic guanosine monophosphate, GPx; glutathione peroxidase, GTP; guanosine triphosphate, K_{ATP}; potassium-sensitive adenosine triphosphate channel, MAPK; mitogen-activated protein kinase, NF-κB; nuclear factor-kappaB, NO; nitric oxide, sGC; soluble guanylate cyclase, and SOD; superoxide dismutase.

renal hemodynamics, reduced renal vascular resistance and restored glomerular filtration rate (GFR) along with reduced tubulointerstitial injury compared to cyclosporine A-treated control rats that did not receive iNOS inhibitors [49,51]. Furthermore, renal proximal tubules isolated from iNOS knockout mice were resistant to hypoxic injury (in vitro version of ischemic injury in in vivo models) in comparison with wildtype control tubules, while tubules from constitutive NOS succumbed to hypoxic injury [52]. These pieces of laboratory evidence suggest that NO production by iNOS contributes to pathophysiology of renal allografts and that pharmacological or genetic inhibition of iNOS may be protective against IRI in transplantation. In contrast, iNOS deficiency in kidney donors resulted in significantly advanced allograft failure in a mouse model of kidney allotransplantation [53]. This was evidenced by decreased recipient survival by over 4-folds along due to more severe renal tubular injury and marked decrease in renal function compared to wildtype allografts [53]. In a separate eperiment by the same authors, upregulation of iNOS expression in renal tubular epithelial cells was associated with a stronger resistance to apoptosis mediated by allogeneic lymphocytes [53]. This suggests that renal production of NO by iNOS can also contribute to renal allograft protection. However, further investigations are needed to support this report.

Beyond the boundaries of these promising preclinical findings, a clinical study involving 18 patients who underwent DCD kidney transplantation revealed increased iNOS expression in acute renal graft rejection [54] while increased eNOS expression during early reperfusion in 25 children who underwent living related-donor kidney transplantation was associated with enhanced recovery from renal ischemia and prolonged graft survival [55]. In another clinical study, L-arginine administration increased renal blood flow (RBF) and GFR with a decline in renal vascular resistance in kidney transplant recipients [56] and also improved renal function in a randomized, double-blind study in which 54 kidney transplant recipients received grafts that were subjected to a short period of cold storage and from young donors [46]. Taken together, NO produced by iNOS participates in renal graft injury while NO produced by constitutive NOS protects renal grafts.

3.2. Nitric oxide donors in kidney transplantation

A substantial body of experimental evidence has established protective effects of NO donors in kidney transplantation and their importance in vascular homeostasis. In an *ex vivo* porcine model of DCD kidney transplantation to determine the effects of NO on renal function, 18 h of cold storage of the renal graft in Marshall's solution at 4ºC followed by 3 h of reperfusion at 37ºC with addition of sodium nitroprusside (NO donor) to the reperfusion circuit at a rate of 1.5 mg/h resulted in significantly increased RBF, improved renal oxygen consumption, creatinine clearance, fractional excretion of sodium compared to control grafts without sodium nitroprusside supplementation [57]. This result supports that of a previous *ex vivo* porcine model DCD of kidney transplantation by another research group in which sodium nitroprusside delivered at a rate of 25 mL/h for 5 min before and during the first hour of reperfusion markedly improved RBF and reduced serum creatinine level following 2 h of warm preservation at 39ºC and 16 h of cold storage at 4ºC [58]. In both studies, the improvement in RBF observed in the NO-supplemented renal grafts implies vasodilation induced by NO, which could be via mechanisms such as PI3/Akt and sGC/PKG signaling pathways and opening of adenosine triphosphate-sensitive potassium (K_{ATP}) channels as was reported in a rat model of renal ischemia-reperfusion injury [59,60] (Fig. 2). In addition, the graft-protecting property of NO is partly due to its ability to suppress the signaling pathways of mitogen activated protein kinases (MAPK; a major inflammatory mediator) as well as free radical formation and apoptosis [61–63] (Fig. 2).

While the result by Yates et al. [57] is promising, they also observed accumulation of nitrogenous free radicals later in reperfusion, which impaired RBF. This corroborates a previous finding in a rat model of ischemic preconditioning in kidney allotransplantation to determine the most suitable preconditioning schedule. In that study, prolonged reperfusion after administration of spermine NONOate (NO donor) in donor rats at 5 minutes before induction of warm ischemia followed by cold storage in Euro-Collins solution at 4ºC abrogated preconditioning-induced allograft protection, with increased renal content of reactive nitrogen species (RNS; a destructive tissue mediator) while allograft protection was observed during early reperfusion and associated with reduced renal RNS [64]. Clinically, this suggests that although NO administration to the organ donor prior to graft procurement or addition to the reperfusion circuit improves renal allograft function, caution should be taken to prevent potential detrimental effects associated with accumulation of nitrogenous compounds in the renal allograft. In a rat model of kidney transplantation to assess the effect of newly developed NO donors (LA-803, LA807 and LA810), 24 hours of cold storage of renal allografts in Euro-Collins solution followed by supplementation with 1.8 μmol/kg these NO donors at 30 minutes prior to 4 hours of reperfusion as well as administration of the NO donors in recipient rats significantly reduced tissue and plasma levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin-1beta (IL-1β) and neutrophil infiltration, and superoxide anions while increasing the level of IL-10 (an anti-inflammatory mediator) [65]. Overall, administration of NO donors to organ donors prior to transplantation or to transplant recipients or its addition during reperfusion improves renal allograft function and survival via mechanisms which include PI3/Akt, sGC/PKG signaling pathways, K_{ATP} channel opening, antioxidant, anti-inflammatory, anti-apoptotic and other potentially unidentified mechanisms.

4. Spatiotemporal pattern of nitric oxide release kinetics and biological effect

The biological effects of NO such as vasodilation can be attributed to the spatiotemporal patterns of its production and degradation. For example, the response of blood vessels to NO was determined by the spatial location of NO synthesis in which large vasodilation events were followed by post-stimulus vasoconstrictions due to increased NO degradation by high levels of free hemoglobin in the plasma under pathological conditions such as hypoxia or hyperoxia [66]. Using magnetic resonance imaging and computational fluid dynamics modeling, Qian and colleagues [67] also observed uneven distribution of NO on the endothelial surface in human atherosclerotic carotid artery, with higher volume-weighted average NO concentrations in areas with atherosclerotic plaques compared to plaque-free regions. This report indicates that atherosclerotic plague or its components contribute in determining space-averaged NO concentration on the endothelial surface in arteries. These two results are in agreement with a previous study in which intracellular near-infrared fluorescent nanosensor probe revealed spatiotemporal NO signaling gradients in pathologies as well as in physiological functions [68]. Collectively, these studies suggest that vascular dynamics may be due to averaged local concentrations of NO.

5. Other gasotransmitters in kidney transplantation

Besides NO, other members of the gasotransmitter family such as carbon monoxide (CO) and hydrogen sulfide (H_2S) have also been reported to be beneficial in experimental kidney transplantation. Although historically regarded solely as a poisonous gas, CO is the second identified member of the gasotransmitter family, with therapeutic potential at low physiological concentrations. Using a rat model of orthotopic kidney transplantation, SCS of renal allografts in UW solution at 4 °C for 24 hours followed by implantation in CO-treated recipients (250 ppm) markedly downregulated the expression of pro-inflammatory genes including HO-1 and iNOS genes, reduced serum creatinine level and macrophage sequestration in renal allografts relative to air-exposed

control recipients [69]. Compared to air-exposed control group, CO also significantly reduced tubular necrosis score, interstitial hemorrhage and edema in renal allografts in CO-treated recipients, along with preserved glomerular vasculature and improved RBF, and thereby contributing to prolonged recipient survival [69]. This implies that CO affords renal allograft protection against transplantation-IRI via several mechanisms that include HO-1/CO/NO signaling pathway. The same salutary effect, including reduction in the occurrence of delayed graft function, was observed in other animal models of kidney transplantation in which CO was either added to preservation solution during SCS of renal grafts or administered to donor animals prior to donor kidney procurement [70–73]. In place of gaseous CO, other researchers also used CO-releasing molecules and reported the same therapeutic benefits after experimental kidney transplantation [74–76].

Just like NO and CO, renal graft protection has also been reported following administration of H_2S. H_2S is the third established member of the gasotransmitter family after NO and CO, and has been used in the form of donor compounds (e.g. sodium thiosulfate, sodium hydrosulfide, GYY4137 and AP39) in a various animal models of human diseases including kidney transplantation. In a recent rat model of syngeneic orthotopic kidney transplantation, for example, supplementation of UW solution with 150 μM of sodium thiosulfate (STS) during 24 h of SCS of renal isografts at 4°C, improved acute tubular necrosis scores and graft function, with significantly decreased serum creatinine level that was comparable to sham-operated rats, and culminated in prolonged recipient survival compared to control group without STS treatment [77]. Similarly, addition of 200 nM of AP39 to UW solution during 4 hours of SCS at 4 and 21°C significantly improved renal graft outcomes compared to untreated control grafts in a porcine model of *ex vivo* kidney preservation and reperfusion [78,79]. This was evidenced by significantly higher urine production, tissue oxygenation, perfusate pO_2 levels, as well as reduced proteinuria and apoptotic injury in comparison with control grafts [78,79]. Other H_2S donors such as sodium hydrosulfide and GYY4137 produced the same outcomes by preventing ROS-induced oxidative stress, downregulating the expression of pro-apoptotic genes (e.g. BID) while upregulating anti-apoptotic gene (e.g. ERK-1) expression in experimental models of kidney transplantation [80–82]. In the same animal models of kidney transplantation, these H_2S donors also inhibited inflammatory pathways by reducing neutrophil and macrophage infiltration in renal grafts and downregulating renal expressions of IFN-γ and intercellular adhesion molecule-1, and increased RBF along with decreased renal resistive index through vasodilation [80–82]. It is important to note that among these H_2S donor compounds, STS is the only one which is clinically viable, and is currently used to treat calciphylaxis in patients with end-stage renal disease, cisplatin-induced toxicity in cancer patients and as an antidote for acute cyanide poisoning [83–85]. Collectively, H_2S shows the same renal graft protection after kidney transplantation as was shown using NO and CO. Remarkably, while other H_2S donors are not clinically viable, the finding that STS offers the same renal graft protection as non-clinically viable H_2S donors in experimental kidney transplantation is a promising outcome, and suggests its future use in clinical transplantation, with the potential of becoming an inexpensive and non-toxic pharmacological approach to modify conventional renal graft preservation technique, which could be extended to preservation of other transplantable solid organs. However further experimental studies including the use of large animal models (e.g. pigs) are required to validate this first preclinical result.

6. Conclusion

Nitric oxide synthase appears to have biphasic actions in biological systems, playing beneficial and detrimental roles in renal grafts as seen in its anti-inflammatory and pro-inflammatory responses. Several studies have established that pharmacological and genetic inhibition of iNOS and production of constitutive NOS-derived NO protect renal grafts against IRI and acute and chronic graft rejection. Also, administration of the NO precursor, L-arginine, or NO donors to the organ donor prior to transplantation and/or to the organ recipient before or after transplantation or addition to the cold preservation solution and reperfusion circuit improves renal graft quality and increases graft function and survival via several molecular mechanisms such NO/sGC/cGMP signaling pathways, PI3/Akt, K_{ATP} channel opening, antioxidant, anti-inflammatory and anti-apoptotic pathways. While the results of these studies are promising, a few studies have also reported divergent results in which upregulated iNOS expression correlated with graft protection while constitutive NOS such as eNOS produced detrimental effect. However, these contradictory findings should be considered in individual cases. Overall, it is apparent that NO derived from constitutive NOS exhibits renal graft-protecting effect while NO produced by iNOS plays a significant detrimental role in renal IRI and graft rejection after transplantation.

CRediT authorship contribution statement

Conceptualization: GJD; Literature search and collection: GJD Manuscript writing: GJD; Manuscript review and editing: GJD; Figure preparation: GJD.

Declaration of Competing Interest

None.

References

[1] I. Lobb, M. Davison, D. Carter, W. Liu, A. Haig, L. Gunaratnam, A. Sener, Hydrogen sulfide treatment mitigates renal allograft ischemia-reperfusion injury during cold storage and improves early transplant kidney function and survival following allogeneic renal transplantation, J. Urol. 194 (6) (2015) 1806–1815.
[2] S. Juriasingani, A. Jackson, M.Y. Zhang, A. Ruthirakanthan, G.J. Dugbartey, E. Sogutdelen, M. Levine, M. Mandurah, M. Whiteman, P. Luke, A. Sener, Evaluating the effects of subnormothermic perfusion with AP39 in a novel blood-free model of ex vivo kidney preservation and reperfusion, Int. J. Mol. Sci. 22 (13) (2021) 7180.
[3] M.Y. Zhang, G.J. Dugbartey, S. Juriasingani, M. Akbari, W. Liu, A. Haig, P. McLeod, J. Arp, A. Sener, Sodium thiosulfate-supplemented UW solution protects renal grafts against prolonged cold ischemia-reperfusion injury in a murine model of syngeneic kidney transplantation, Biomed. Pharm. 145 (2022), 112435.
[4] I.H. Vos, J.A. Joles, T.J. Rabelink, The role of nitric oxide in renal transplantation, Semin Nephrol. 24 (4) (2004) 379–388.
[5] G.J. Dugbartey, S. Juriasingani, M.Y. Zhang, A. Sener, H_2S donor molecules against cold ischemia-reperfusion injury in preclinical models of solid organ transplantation, Pharm. Res. 172 (2021), 105842.
[6] G.J. Dugbartey, K.K. Alornyo, P.P.W. Luke, A. Sener, Application of carbon monoxide in kidney and heart transplantation: a novel pharmacological strategy for a broader use of suboptimal renal and cardiac grafts, Pharm. Res. 173 (2021), 105883.
[7] G.J. Dugbartey, Carbon monoxide as an emerging pharmacological tool to improve lung and liver transplantation protocols, Biochem. Pharm. 193 (2021), 114752.
[8] J.M. Fukuto, Chemistry of nitric oxide: biologically relevant aspects, Adv. Pharm. 34 (1995) 1–15.
[9] D. Brealey, M. Brand, I. Hargreaves, S. Heales, J. Land, R. Smolenski, N. Davies, C. Cooper, M. Singer, Association between mitochondrial dysfunction and severity and outcome of septic shock, Lancet 360 (2002) 219–223.
[10] A. Cauwels, Nitric oxide in shock, Kidney Int 72 (2007) 557–565.
[11] A. Dyson, N.S. Bryan, B.O. Fernandez, M.F. Garcia-Saura, F. Saijo, N. Mongardon, J. Rodriguez, M. Singer, M. Feelisch, An integrated approach to assessing nitroso-redox balance in systemic inflammation, Free Radic. Biol. Med. 51 (2011) 1137–1145.
[12] E. Antonucci, E. Fiaccadori, K. Donadello, F.S. Taccone, F. Franchi, S. Scolletta, Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment, J. Crit. Care 29 (2014) 500–511.
[13] G.J. Hodges, S. Nawaz, G.A. Tew, Evidence that reduced nitric oxide signal contributes to cutaneous microvascular dysfunction in peripheral arterial disease, Clin. Hemorheol. Micro 59 (1) (2015) 83–95.
[14] C. Franssen, S. Chen, A. Unger, H.I. Korkmaz, G.W. De Keulenaer, C. Tschöpe, A. F. Leite-Moreira, R. Musters, H.W. Niessen, W.A. Linke, W.J. Paulus, N. Hamdani, Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction, JACC Heart Fail 4 (4) (2016) 312–324.
[15] Z. Melik, P. Zaletel, T. Virtic, K. Cankar, L-arginine as dietary supplement for improving microvascular function, Clin. Hemorheol. Micro 65 (3) (2017) 205–217.
[16] U. Pohl, D. Lamontagne, Impaired tissue perfusion after inhibition of endothelium-derived nitric oxide, Basic Res Cardiol. 86 (Suppl 2) (1991) 97–105.

[17] A.A.M. Marques, C.H.F. da Silva, P. de Souza, C.L.B. de Almeida, V. Cechinel-Filho, E.L.B. Lourenço, A. Gasparotto Junior, Nitric oxide and Ca 2+-activated high-conductance K+ channels mediate nothofagin-induced endothelium-dependent vasodilation in the perfused rat kidney, Chem. Biol. Inter. 327 (2020), 109182.
[18] B.R. Crane, A.S. Arvai, D.K. Ghosh, C. Wu, E.D. Getzoff, D.J. Stuehr, J.A. Tainer, Structure of nitric oxide synthase oxygenase dimer with pterin and substrate, Science 279 (1998) 2121–2126.
[19] W.K. Alderton, C.E. Cooper, R.G. Knowles, Nitric oxide synthases: structure, function and inhibition, Biochem. J. 357 (2001) 593–615.
[20] F. Murad, Cyclic guanosine monophosphate as a mediator of vasodilation, J. Clin. Invest. 78 (1986) 1–5.
[21] M. Nakane, H.H. Schmidt, J.S. Pallock, U. Forstermann, F. Murad, Cloned human brain nitric oxide synthase is highly expressed in skeletal muscle, FEBS Lett. 316 (1993) 175–180.
[22] U. Forstermann, E.I. Closs, J.S. Pollock, M. Nakane, P. Schwarz, I. Gath, H. Kleinert, Nitric oxide synthase isozymes. Characterization, purification, molecular cloning, and functions, Hypertension 23 (1994) 1121–1131.
[23] K.Y. Xu, D.L. Huso, T.M. Dawson, D.S. Bredt, L.C. Becker, Nitric oxide synthase in cardiac sarcoplasmic reticulum, Proc. Natl. Acad. Sci. 96 (1999) 657–662.
[24] U. Forstermann, Regulation of nitric oxide synthase expression and activity, in: B. Mayer (Ed.), Handbook of Experimental Pharmacology – Nitric Oxide, Springer, Berlin, 2000, pp. 71–91.
[25] M.E. Ward, M. Toporsian, J.A. Scott, H. Teoh, V. Govindaraju, A. Quan, A. D. Wener, G. Wang, S.C. Bevan, D.C. Newton, P.A. Marsden, Hypoxia induces a functionally significant and translationally efficient neuronal NO synthase mRNA variant, J. Clin. Invest. 115 (2005) 3128–3139.
[26] H.J. Cho, Q.W. Xie, J. Calaycay, R.A. Mumford, K.M. Swiderek, T.D. Lee, C. Nathan, Calmodulin is a subunit of nitric oxide synthase from macrophages, J. Exp. Med. 176 (1992) 599–604.
[27] B. Hemmens, B. Mayer, Enzymology of nitric oxide synthases, Methods Mol. Biol. 100 (1998) 1–32.
[28] E. Bonmann, C. Suschek, M. Spranger, V. Kolb-Bachofen, The dominant role of exogenous or endogenous interleukin-1 beta on expression and activity of inducible nitric oxide synthase in rat microvascular brain endothelial cells, Neurosci. Lett. 230 (2) (1997) 109–112.
[29] H. Fujisawa, S. Nakagawa, Y. Ohkubo, M. Matsui, S. Yamaguchi, M. Kawamura, K. Hatanaka, Y. Kawakubo, Y. Hiramoto, H. Kobayashi, Y. Harada, Local and systemic expression of inducible nitric oxide synthase in comparison with that of cyclooxygenase-2 in rat carrageenin-induced pleurisy, Nitric Oxide 12 (2) (2005) 80–88.
[30] L.J. Ignarro, C. Napoli, J. Loscalzo, Nitric oxide donors and cardiovascular agents modulating the bioactivity of nitric oxide: an overview, Circ. Res. 90 (1) (2002) 21–28.
[31] P.G. Wang, M. Xian, X. Tang, X. Wu, Z. Wen, T. Cai, A.J. Janczuk, Nitric oxide donors: chemical activities and biological applications, Chem. Rev. 102 (4) (2002) 1091–1134.
[32] S.M. Ranadive, A.R. Eugene, G. Dillon, W.T. Nicholson, M.J. Joyner, Comparison of the vasodilatory effects of sodium nitroprusside and nitroglycerin, J. Appl. Physiol. 123 (2017) 402–406.
[33] M.R. Willmot, P.M. Bath, The potential of nitric oxide therapeutics in stroke, Expert Opin. Invest. Drugs 12 (3) (2003) 455–470.
[34] B.R. Buca, L. Mititelu-Tarţau, R.V. Lupuşoru, G.E. Popa, C. Rezuş, C.E. Lupuşoru, New nitric oxide donors with therapeutic potential, Rev. Med. Chir. Soc. Med. Nat. Iasi 120 (4) (2016) 942–946.
[35] A.K. Salahudeen, H. Huang, M. Joshi, N.A. Moore, J.K. Jenkins, Involvement of the mitochondrial pathway in cold storage and rewarming-associated apoptosis of human renal proximal tubular cells, Am. J. Transpl. 3 (3) (2003) 273–280.
[36] G. Opelz, B. Döhler, Multicenter analysis of kidney preservation, Transplantation 83 (3) (2007) 247–253.
[37] P.J. Morris. Kidney Transplantation, Principles and Practice. S.l, 6th ed., Elsevier, Saunders, 2008, p. 126e127.
[38] M. Bond, M. Pitt, J. Akoh, T. Moxham, M. Hoyle, R. Anderson, The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model, Health Technol. Assess. 13 (38) (2009) iii-156.
[39] D. Dragun, U. Hoff, J.K. Park, et al., Prolonged cold preservation augments vascular injury independent of renal transplant immunogenicity and function, Kidney Int. 60 (3) (2001) 1173–1181.
[40] I. Quiroga, P. McShane, D.D. Koo, et al., Major effects of delayed graft function and cold ischaemia time on renal allograft survival, Nephrol. Dial. Transpl. 21 (6) (2006) 1689–1696.
[41] L.K. Kayler, J. Magliocca, I. Zendejas, T.R. Srinivas, J.D. Schold, Impact of cold ischemia time on graft survival among ECD transplant recipients: a paired kidney analysis, Am. J. Transpl. 11 (12) (2011) 2647–2656.
[42] M.P. Castaneda, A. Swiatecka-Urban, M.M. Mitsnefes, D. Feuerstein, F.J. Kaskel, V. Tellis, P. Devarajan, Activation of mitochondrial apoptotic pathways in human renal allografts after ischemiareperfusion injury, Transplantation 76 (1) (2003) 50–54.
[43] D.R. Green, G. Kroemer, The pathophysiology of mitochondrial cell death, Science 305 (5684) (2004) 626–629.
[44] N. Barakat, A.A. Hussein, M. Abdel-Maboud, M.A. El-Shair, A. Mostafa, H. Abol-Enein, Ischaemia-reperfusion injury in renal transplantation: the role of nitric oxide in an experimental rat model, BJU Int. 106 (8) (2010) 1230–1236.
[45] X.Z. Zhang, G. Ardissino, L. Ghio, A.S. Tirelli, V. Daccò, D. Colombo, E. Pace, S. Testa, A. Claris-Appiani, l-arginine supplementation in young renal allograft recipients with chronic transplant dysfunction, Clin. Nephrol. 55 (6) (2001) 453–459.
[46] L. Schramm, M. La, E. Heidbreder, M. Hecker, J.S. Beckman, K. Lopau, J. Zimmermann, J. Rendl, C. Reiners, S. Winderl, C. Wanner, H.H. Schmidt, L-arginine deficiency and supplementation in experimental acute renal failure and in human kidney transplantation, Kidney Int. 61 (4) (2002) 1423–1432.
[47] T. Stojanovic, H.J. Gröne, R.K. Gieseler, B. Klanke, R. Schlemminger, D. Tsikas, E. F. Gröne, Enhanced renal allograft rejection by inhibitors of nitric oxide synthase: a nonimmunologic influence on alloreactivity, Lab Invest. 74 (2) (1996) 496–512.
[48] D. Casanova, M. Correas, J.L. Moran, E. Salas, J.A. Amado, M.T. Garcia Unzueta, J. R. Berrazueta, Nitric oxide in cold and warm ischemia reperfusion renal transplantation, Transpl. Proc. 34 (1) (2002) 45–46.
[49] I.H. Vos, J.A. Joles, M. Schurink, G. Weckbecker, T. Stojanovic, T.J. Rabelink, H. J. Gröne, Inhibition of inducible nitric oxide synthase improves graft function and reduces tubulointerstitial injury in renal allograft rejection, Eur. J. Pharm. 391 (1–2) (2000) 31–38.
[50] F. Ziai, H. Nagano, M. Kusaka, A.J. Coito, J.L. Troy, K.C. Nadeau, H.G. Rennke, N. L. Tilney, B.M. Brenner, H.S. MacKenzie, Renal allograft protection with losartan in Fisher→Lewis rats: hemodynamics, macrophages, and cytokines, Kidney Int. 57 (6) (2000) 2618–2625.
[51] W.M. Moore, R.K. Webber, G.M. Jerome, F.S. Tjoeng, T.P. Misko, M.G. Currie, L-N6-(1-iminoethyl)lysine: a selective inhibitor of inducible nitric oxide synthase, J. Med. Chem. 37 (23) (1994) 3886–3888.
[52] H. Ling, P.E. Gengaro, C.L. Edelstein, P.Y. Martin, A. Wangsiripaisan, R. Nemenoff, R.W. Schrier, Effect of hypoxia on proximal tubules isolated from nitric oxide synthase knockout mice, Kidney Int. 53 (6) (1998) 1642–1646.
[53] C. Du, J. Jiang, Q. Guan, H. Diao, Z. Yin, S. Wang, R. Zhong, A.M. Jevnikar, NOS2 (iNOS) deficiency in kidney donor accelerates allograft loss in a murine model, Am. J. Transpl. 7 (1) (2007) 17–26.
[54] E.W. Albrecht, H. van Goor, A.T. Tiebosch, H. Moshage, A.M. Tegzess, C. A. Stegeman, Nitric oxide production and nitric oxide synthase expression in acute human renal allograft rejection, Transplantation 70 (11) (2000) 1610–1616.
[55] T. Ishimura, M. Fujisawa, S. Isotani, K. Iijima, N. Yoshikawa, S. Kamidono, Endothelial nitric oxide synthase expression in ischemia-reperfusion injury after living related-donor renal transplantation, Transpl. Int. 15 (12) (2002) 635–640.
[56] R.S. Gaston, S.D. Schlessinger, P.W. Sanders, C.V. Barker, J.J. Curtis, D. G. Warnock, Cyclosporine inhibits the renal response to L-arginine in human kidney transplant recipients, J. Am. Soc. Nephrol. 5 (7) (1995) 1426–1433.
[57] P.J. Yates, S.A. Hosgood, M.L. Nicholson, A biphasic response to nitric oxide donation in an ex vivo model of donation after cardiac death renal transplantation, J. Surg. Res. 175 (2) (2012) 316–321.
[58] S.A. Hosgood, A. Bagul, M. Kaushik, J. Rimoldi, R.S. Gadepalli, M.L. Nicholson, Application of nitric oxide and carbon monoxide in a model of renal preservation, Br. J. Surg. 95 (8) (2008) 1060–1067.
[59] S. Shimizu, M. Saito, Y. Kinoshita, F. Ohmasa, F. Dimitriadis, K. Shomori, A. Hayashi, K. Satoh, Nicorandil ameliorates ischaemia-reperfusion injury in the rat kidney, Br. J. Pharm. 163 (2) (2011) 272–282.
[60] L. Li, X. Wang, L. Zheng, J. Li, M. Xu, R. Rong, T. Zhu, Y. Jia, Downregulation of endothelin A receptor (EtaR) ameliorates renal ischemia reperfusion injury by increasing nitric oxide production, Life Sci. 228 (2019) 295–304.
[61] K. Dobashi, I. Singh, J.K. Orak, K. Asayama, A.K. Singh, Combination therapy of N-acetylcysteine, sodium nitroprusside and phosphoramidon attenuates ischemia-reperfusion injury in rat kidney, Mol. Cell Biochem. 240 (1–2) (2002) 9–17.
[62] A. Mehta, C.P. Sekhon, S. Giri, J.K. Orak, A.K. Singh, Attenuation of ischemia/reperfusion induced MAP kinases by N-acetyl cysteine, sodium nitroprusside and phosphoramidon, Mol. Cell Biochem. 240 (1–2) (2002) 19–29.
[63] H. Ko, J.S. Kim, J.H. Shin, K.H. Jeong, H.J. Ahn, Efficacy of nitric oxide-releasing nanofibers in reducing renal ischemia-reperfusion injury in a rat model, Ann. Transpl. 27 (2022), e934800.
[64] J. Torras, I. Herrero-Fresneda, N. Lloberas, M. Riera, J. Ma Cruzado, J. Ma Grinyó, Promising effects of ischemic preconditioning in renal transplantation, Kidney Int. 61 (6) (2002) 2218–2227.
[65] F.J. García-Criado, P. Rodriguez-Barca, M.B. García-Cenador, J.V. Rivas-Elena, M. T. Grande, J.F. Lopez-Marcos, M. Mourelle, J.M. López-Novoa, Protective effect of new nitrosothiols on the early inflammatory response to kidney ischemia/reperfusion and transplantation in rats, J. Interferon Cytokine Res. 29 (8) (2009) 441–450.
[66] W.D. Haselden, R.T. Kedarasetti, P.J. Drew, Spatial and temporal patterns of nitric oxide diffusion and degradation drive emergent cerebrovascular dynamics, PloS Comput. Biol. 16 (7) (2020), e1008069.
[67] S. Qian, T. Ma, N. Zhang, X. Liu, P. Zhao, X. Li, D. Chen, L. Hu, L. Chang, L. Xu, X. Deng, Y. Fan, Spatiotemporal transfer of nitric oxide in patient-specific atherosclerotic carotid artery bifurcations with MRI and computational fluid dynamics modeling, Comput. Biol. Med. 125 (2020), 104015.
[68] Z.W. Ulissi, F. Sen, X. Gong, S. Sen, N. Iverson, A.A. Boghossian, L.C. Godoy, G. N. Wogan, D. Mukhopadhyay, M.S. Strano, Spatiotemporal intracellular nitric oxide signaling captured using internalized, near-infrared fluorescent carbon nanotube nanosensors, Nano Lett. 14 (8) (2014) 4887–4894.
[69] J.S. Neto, A. Nakao, K. Kimizuka, A.J. Romanosky, D.B. Stolz, T. Uchiyama, M. A. Nalesnik, L.E. Otterbein, N. Murase, Protection of transplant-induced renal ischemia-reperfusion injury with carbon monoxide, Am. J. Physiol. Ren. Physiol. 287 (5) (2004) F979–F989.
[70] K.S. Ozaki, J. Yoshida, S. Ueki, G.L. Pettigrew, N. Ghonem, R.M. Sico, L.Y. Lee, R. Shapiro, F.G. Lakkis, A. Pacheco-Silva, N. Murase, Carbon monoxide inhibits apoptosis during cold storage and protects kidney grafts donated after cardiac death, Transpl. Int. 25 (1) (2012) 107–117.

[71] A. Nakao, J.S. Neto, S. Kanno, D.B. Stolz, K. Kimizuka, F. Liu, F.H. Bach, T. R. Billiar, A.M. Choi, L.E. Otterbein, N. Murase, Protection against ischemia/reperfusion injury in cardiac and renal transplantation with carbon monoxide, biliverdin and both, Am. J. Transpl. 5 (2) (2005) 282–291.
[72] D.W. Hanto, T. Maki, M.H. Yoon, E. Csizmadia, B.Y. Chin, D. Gallo, B. Konduru, K. Kuramitsu, N.R. Smith, A. Berssenbrugge, C. Attanasio, M. Thomas, B. Wegiel, L. E. Otterbein, Intraoperative administration of inhaled carbon monoxide reduces delayed graft function in kidney allografts in Swine, Am. J. Transpl. 10 (11) (2010) 2421–2430.
[73] J. Yoshida, K.S. Ozaki, M.A. Nalesnik, S. Ueki, M. Castillo-Rama, G. Faleo, M. Ezzelarab, A. Nakao, B. Ekser, G.J. Echeverri, M.A. Ross, D.B. Stolz, N. Murase, Ex vivo application of carbon monoxide in UW solution prevents transplant-induced renal ischemia/reperfusion injury in pigs, Am. J. Transpl. 10 (4) (2010) 763–772.
[74] Y. Caumartin, J. Stephen, J.P. Deng, D. Lian, Z. Lan, W. Liu, B. Garcia, A. M. Jevnikar, H. Wang, G. Cepinskas, P.P. Luke, Carbon monoxide-releasing molecules protect against ischemia-reperfusion injury during kidney transplantation, Kidney Int. 79 (10) (2011) 1080–1089.
[75] A. Sener, K.C. Tran, J.P. Deng, B. Garcia, Z. Lan, W. Liu, T. Sun, J. Arp, M. Salna, P. Acott, G. Cepinskas, A.M. Jevnikar, P.P. Luke, Carbon monoxide releasing molecules inhibit cell death resulting from renal transplantation related stress, J. Urol. 190 (2) (2013) 772–778.
[76] R.N. Bhattacharjee, M. Richard-Mohamed, Q. Sun, A. Haig, G. Aboalsamh, P. Barrett, R. Mayer, I. Alhasan, K. Pineda-Solis, L. Jiang, H. Alharbi, M. Saha, E. Patterson, A. Sener, G. Cepinskas, A.M. Jevnikar, P.P.W. Luke, CORM-401 reduces ischemia reperfusion injury in an ex vivo renal porcine model of the donation after circulatory death, Transplantation 102 (7) (2018) 1066–1074.
[77] M.Y. Zhang, G.J. Dugbartey, S. Juriasingani, M. Akbari, W. Liu, A. Haig, P. McLeod, J. Arp, A. Sener, Biomed. Pharm. 145 (2022), 112435.
[78] S. Juriasingani, A. Jackson, M.Y. Zhang, A. Ruthirakanthan, G.J. Dugbartey, E. Sogutdelen, M. Levine, M. Mandurah, M. Whiteman, P. Luke, A. Sener, Evaluating the effects of subnormothermic perfusion with AP39 in a novel blood-free model of ex vivo kidney preservation and reperfusion, Int. J. Mol. Sci. 22 (13) (2021) 7180.
[79] G.J. Dugbartey, S. Juriasingani, M. Richard-Mohammed, et al., Static cold storage with mitochondria-targeted hydrogen sulfide donor improves renal graft function in an ex vivo porcine model of controlled donation-after-cardiac-death kidney transplantation, Int. J. Mol. Sci. 24 (2023) 14017.
[80] Hosgood, Nicholson, Hydrogen sulphide ameliorates ischaemia-reperfusion injury in an experimental model of non-heart-beating donor kidney transplantation, Br. J. Surg. 97 (2) (2010) 202–209.
[81] I. Lobb, J. Jiang, D. Lian, W. Liu, A. Haig, M.N. Saha, R. Torregrossa, M.E. Wood, M. Whiteman, A. Sener, Hydrogen sulfide protects renal grafts against prolonged cold ischemia-reperfusion injury via specific mitochondrial actions, Am. J. Transplant. 17 (2) (2017) 341–352.
[82] I. Lobb, M. Davison, D. Carter, W. Liu, A. Haig, L. Gunaratnam, A. Sener, Hydrogen sulfide treatment mitigates renal allograft ischemia-reperfusion injury during cold storage and improves early transplant kidney function and survival following allogeneic renal transplantation, J. Urol. 194 (6) (2015) 1806–1815.
[83] R. Burnie, S. Smail, M.M. Javaid, Calciphylaxis and sodium thiosulfate: a glimmer of hope in desperate situation, J. Ren. Care 39 (2013) 71–76.
[84] V.S. Bebarta, M. Brittain, A. Chan, et al., Sodium nitrite and sodium thiosulfate are effective against acute cyanide poisoning when administered by intramuscular injection, Ann. Emerg. Med. 69 (6) (2017) 718–725.e4.
[85] R.Y. Tsang, T. Al-Fayea, H.J. Au, Cisplatin overdose: toxicities and management, Drug Saf. 32 (12) (2009) 1109–1122.