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New progress in roles of nitric oxide during hepatic ischemia reperfusion injury

Zhang YP *et al*. Nitric oxide action on HIRI

Abstract

Hepatic ischemia-reperfusion injury (HIRI) is a major clinical cause of morbidity and mortality in liver surgery and transplantation. Many studies have found that nitric oxide (NO) plays an important role in the HIRI and its increase or decrease can affect the progress and outcome of the HIRI. However, the role of NO in HIRI is controversial and complicated. NO derived by endothelial NO synthase (eNOS) shows a protective role in HIRI, while excessive NO derived by inducible NO synthase (iNOS) accelerate inflammation and increases oxidative stress, further aggravating HIRI. Nevertheless, the overexpression of eNOS may exacerbate HIRI and iNOS-derived NO in some cases reduces HIRI damage. Here we reviewed the new progress in roles of nitric oxide during HIRI: (1) NO possesses different roles in HIRI by increasing NO bioavailability, downregulates leukotriene C4 synthase, inhibiting the nuclear factor-κB (NF-κB) activation pathway, enhancing cell autophagy and reducing inflammatory cytokines and reactive oxygen species (ROS). And NO has both protective and deleterious function by regulating apoptotic factors; (2) eNOS promotes NO production and suppresses its own overexpression, exerting a hepatoprotective effect reversely. Its activation is involved by PI3K/Akt pathway, KLF2 and AMPK pathway to regulate its activities. (3) iNOS derived NO mainly has deteriorated effects on HIRI, while it may have a protective function under some conditions. Their expressions should reach a

balance to reduce the adverse side and make NO protective in the treatment of HIRI. Thus, it can be inferred that NO modulating drugs may be a new direction in the treatment of HIRI or may be used as an adjunct to mitigate the harm caused by HIRI for the purpose of protecting the liver.

Key Words: Hepatic ischemia-reperfusion injury; Nitric oxide; Endothelial nitric oxide synthase; Inducible nitric oxide synthase

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Core Tip: This review focuses on the new developments in the role of nitric oxide (NO) in hepatic ischemia-reperfusion injury (HIRI). NO protect HIRI through increasing NO bioavailability and cellular autophagy, down-regulating leukotriene C4 synthase, inhibiting nuclear factor κB (NF-κB) pathway, and reducing inflammatory cytokines and reactive oxygen species. While by regulating apoptotic factors, it has dual effects. eNOS exerts hepatoprotective effects by promoting NO production through the involvement of the phosphoinositide 3-kinase/Akt pathway, Kruppel-like factor 2 and adenosine monophosphate-activated protein kinase pathway. The function of eNOS overexpression remains controversial. iNOS-derived NO mainly deteriorates HIRI, but it may reduce damage under certain conditions. The balance of eNOS and iNOS is important for the HIRI protection.

INTRODUCTION

Hepatic ischemia-reperfusion injury (HIRI) is a major complication often seen in liver surgery and organ transplantation. It manifests as cellular damage during the ischemic phase and worsens during reperfusion. Depending on the different conditions of ischemic, HIRI can be divided into warm ischemia-reperfusion (WIR) injury and cold

ischemia-reperfusion injury (IRI), which have similar pathophysiology but different clinical injury sites[1].

With a high incidence of cases, liver cancer has increased 114.0% and ends up with 1007800 cases in 2016[2]. Many liver cancer patients are supposed to be treated by liver transplantation or hepatectomy, where HIRI occurs during the operation[3]. Although HIRI is receiving increasing attention to improve the success rate of surgery and improve prognosis, we still know very few of them.

The pathophysiological process of hepatic IRI involves the interaction of many different cell types and numerous signaling pathways such as anaerobic metabolism, acidosis, oxidative stress, intracellular calcium overload. Among the interactions, the imbalance in the ratio of endothelin (ET) to nitric oxide (NO) is one of the mechanisms involved in HIRI. Normally, their function is to regulate blood flow to the hepatic sinusoids. In contrast, in the first few hours after reperfusion, as ET rises, plasma expression of NO decreases, leading to an increase in the ET/NO ratio and the possible appearance of HIRI[4,5].

Many pieces of evidence show that NO plays an important role in ischemia-reperfusion (I/R)[6,7]. However, as a vasodilator, the role of NO has been controversially discussed by scientists[8,9]. In past studies, NO is treated as a negative factor because of its cytotoxic effect[10]. Nevertheless, a recent study indicated that NO can induce either a positive or negative effect during the early phase of HIRI and have a protective effect during late HIRI[11]. Therefore, it is important to further explore the protective mechanism of NO in hepatic IRI.

NO is a small molecule free radical that can easily penetrate cell membranes. It is also an important effector and messenger molecule of biological information, which has been made many extensive types of research in the past few years. There are two sources of NO in the human body—enzymatic production and non-enzymatic production. Non-enzymatic production mainly comes from chemical degradation and inorganic nitrogen transformation on the body surface or ingested. For enzymatic production, NO is oxidized from L-arginine by NO synthase (NOS)[12].

There are Ca^{2+}-independent and Ca^{2+}-dependent NOS in the human body. Ca^{2+}-dependent NOS can be subdivided into neuronal (nNOS) and endothelial (eNOS). eNOS is an enzyme continuously expressed in vascular endothelial cells and takes biological functions through producing NO. In contrast to eNOS, Ca^{2+}-independent inducible NOS (iNOS) is activated by some exterior factors including viruses, bacteria, pro-inflammatory interferon, and cytokines[13]. iNOS produces a large amount of NO in hepatocytes, cholangiocytes and Kupffer cells (KCs), helping macrophages to mount an immune response[14].

eNOS and iNOS are believed to take actions in hepatic IRI. While depending on different isoforms of NOS, NO has a dual effect on hepatocellular functions during IR. eNOS-derived NO is hepatoprotective of ischemia following IRI through improving hepatic microcirculation and counteracting the deteriorate functions of reactive oxygen species (ROS) [4]. However, an augmented level of iNOS activation upon reperfusion will produce excessive NO, resulting in endothelial dysfunction and aggravating liver damage in HIRI[14]. Although it has been reported that iNOS-derived NO may have a positive or negative function in HIRI depending on the different conditions[15].

This review is trying to find the role of NO during hepatic IRI and look for candidate ways to alleviate the liver damage (Table 1).

DIFFERENT ROLES OF NO DURING HIRI

Recently studies showed that NO has a significant role during the HIRI which can be a positive protective function or can be a negative deleterious function. NO was proved to reduce HIRI through various mechanisms such as increasing NO bioavailability, downregulating leukotrienes (LTs), inhibiting liver cell apoptosis, enhancing autophagic, maintaining liver microcirculation blood flow, stabilizing ATP levels and reducing oxidative stress injury. Whereas NO can also regulate some apoptotic signal pathways to accelerate the apoptosis of hepatic tissue.

Increase of NO bioavailability involved in its protective effect in HIRI

Hide D *et al*[16] found that NO bioavailability reduced during reperfusion by detecting the levels of cyclic guanosine monophosphate, a second messenger of NO. They concluded that the decreased NO bioavailability can be explained by the reduction of eNOS activity leading to less synthesis of NO and increased NO clearance by reacting with reactive oxygen species and forming peroxynitrite, which may later react with cell components such as proteins, lipids and DNA further damaging the cell. Therefore, increasing NO bioavailability can protect the liver from further damage during HIRI. It is reported that obestatin enhances NO bioavailability by upregulating eNOS expression[17]. Also, Simvastatin maintains NO bioavailability by preventing KLF2 down-regulation[16].

NO can downregulate LT C4 synthase by inhibiting the nuclear factor-κB activation pathway

Many studies reveal that cysteinyl leukotrienes are directly associated with hepatic IRI. Leukotrienes C4 synthase (LTC4S) is one of the LTC4 synthesis enzymes showing a strong relationship with the NO in recent studies[18,19]. In I/R rats, the gene expression level of LTC4S is much higher. While this is reversed by V-PYRRO/NO, which acts as an NO donor. Hong FF *et al*[20] also found that another NO donor, sodium nitroprusside, could downregulate the mRNA expression of LTC4S through inhibiting nuclear factor-kappa B (NF-κB) activation in an inhibitor of NF-κB α-independent manner by detecting the protein levels of NF-κB p65 and p50 in the nuclear extracts using western blot.

NO can regulate some apoptotic signal transduction pathways and factor

NO has a significant role in regulating some apoptotic signal transduction pathways which can be potentially activated to induce or inhibit the hepatic cell apoptosis process caused by HIRI during the hepatic operation or other hepatic diseases prognosis. The signal pathways or apoptosis-related genes including caspases[21-25], Bcl-2 gene family[26-

[30], mitogen-activated protein kinase (MAPK)[31] and NF-kB[32]. Studies have shown that the caspase family is strongly related to hepatic cell apoptosis[33]. Peng Zhao found that steatosis-induced decline in adenosine monophosphate-activated protein kinase (AMPK)-catalyzed phosphorylation permits caspase-6 activation, leading to hepatocyte death[21]. And Gao D *et al*[22] indicated that caspase-3A is involved in cadmium (Cd)-induced cell apoptosis in common carp which showed 71.8% sequence similarity and 59.3% sequence identity to human caspase-3. Zhang R *et al*[23] found that Cd treatment increased the level of iNOS and NO. The overexpression of NO leads to chicken hepatic cell apoptosis by inducing the mitochondrial apoptotic pathway. In two other experiments, mice liver cell apoptosis can be inhibited by reducing NO content, downregulating Bax protein expression and increasing Bcl-2 protein expression[24,25]. Besides, an imbalanced Bax/Bcl-2 ratio is caused by decreasing levels of NO and iNOS and increasing Bcl-2 expression through the NF-kB pathway. And this imbalanced ratio may show a protective role in the damaged liver[30]. Jiang Q *et al*[34] also found that 7-mer peptide can increase the level of Bcl-2 and decrease the level of Bax expression to reduce apoptosis and protect against IRI.

NO protects against I/R-induced liver injury by enhancing autophagic flux.

NO has an important role in protecting against I/R-induced liver injury by enhancing autophagic flux. During severe environments such as IRI, the cell will undergo an autophagic system which is an adaptive response to reduce the injury. Studies have found that the protective mechanism of NO during HIRI is associated with autophagic. Shin JK *et al*[35] demonstrated that NO could enhance light chain-3 Lipidation and autophagosome-lysosome fusion during hepatic I/R. Also, eNOS-induced NO enhances autophagy *via* p38 MAPK activation during liver I/R. Simvastatin, which is used to protect the donor liver, can activate autophagy and increase NO release during hepatic transplantation. This also indicates the possible connection between NO and autophagy[36].

NO decreases inflammatory cytokines and reduces ROS by inhibiting the mitochondrial respiratory chain

During reperfusion, the surge of inflammatory factors, cytokine liberation, neutrophil infiltration and radical oxygen species generation happened which led to hepatic injury. An increased level of NO can reduce cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-1 which stimulate infiltration and endothelial injury. Also, continuous NO production can reduce ROS and proinflammatory cytokine generation as well as neutrophil infiltration[37]. Inversely, NO deficiency can induce TNF-α expression as a result of ROS surging. Ragy MM *et al*[38] proved this by adding Nomega-nitro-L-arginine methyl ester (L-NAME) in rats subjected to the IRI rat model which treated with oxytocin. In this group, not only the parameter damage increase but also the inflammatory factor such as TNF-α level increased compared with the control group.

ROLE OF ENOS IN HIRI

Activated eNOS produce NO to protect HIRI

eNOS performs various biological functions by promoting the production of NO, which is important for maintaining vascular tone and cardiovascular hemostasis, inhibiting platelet activation and aggregation. It has confessed that eNOS shows a hepatoprotective effect in HIRI through improving the production of NO (Figure 1).

There are two main regulation pathways for eNOS activation, one dependent on intracellular concentration of Ca^{2+} and the other independent. The increasing intracellular Ca^{2+} level can enhance the affinity of calmodulin binding to eNOS and activate enzymes to produce NO[39]. For the Ca^{2+}-independent regulation pathway, phosphorylation of the Ser1177 residue or dephosphorylation of the Thr495 residue activates it to produce NO[40].

Calcium-depended eNOS activation

At the early stage of HIRI, the ischemia will lead to a shortage of oxygen and nutrients, which can decrease ATP availability. Without energy, ATP-dependent ion channels or transporters cannot work. The incompetence of the Na^+/K^+ pump leads to depolarization of the cell membrane, resulting in the influx of Ca^{2+}. Besides, anaerobic glycolysis induces an increase in H^+, which activates intracellular proteases to increase cellular permeability. Furthermore, Na^+/Ca^{2+} exchange is activated due to a high concentration of H^+, leading to a further influx of Ca^{2+}[41]. Consequently, eNOS is activated due to the increase of intracellular concentration to produce NO, carrying the anti-HIRI activities at the initial stage.

Calcium-independent eNOS activation

Phosphoinositide 3-kinase/Akt pathway induced eNOS activation: Phosphoinositide 3-kinase (PI3K)/Akt signaling pathway is a cell survival pathway that regulates cell proliferation and apoptosis, as well as an endogenous negative feedback regulator that functions in anti-inflammation and anti-apoptosis effects in IR.

The PI3K can activate Akt to act on the phosphorylation of eNOS. It has been proven that telluric acid has a hepatoprotective effect with an elevation expression of eNOS, which is accompanied with elevated expression of p-PI3K and p-Akt proteins. Besides, the activation of PI3K/Akt also inhibits NF-κB and activates nuclear erythroid-related factor-2, reducing pro-inflammation cytokines expression and inducing anti-oxidative effects[42]. Moreover, through the PI3K/Akt pathway, apelin preconditioning can increase the expression of eNOS and counteract the pathological effects of the angiotensin II/angiotensin II type 1 receptor system in hepatic IRI[43]. Thus, the activation of the PI3K/Akt pathway leads to the phosphorylation of eNOS and continuous catalysation of NO production, which is essential to counteract HIRI.

KLF2 induced eNOS activation: There may exist other ways of influencing the eNOS activity during IR. It has been proven that WIR injury can decrease the expression of Kruppel-like factor 2 (KLF2) in endothelial cells. Also, this reduction is accompanied by

a decrease in phosphorylated eNOS (p-eNOS), one of the KLF2 target genes. And the IR damage can be mitigated by pretreatment with Simvastatin through a KLF2-dependent mechanism, upregulating the mRNA of KLF2 and eNOS as well as the proteins of KLF2 and p-eNOS[16,44]. Hu X *et al*[45] also demonstrated that hypothermic machine perfusion inhibited NF-κB signaling and activated eNOS/NO signaling through KLF2 expression, thereby alleviating the inflammatory response and oxidative stress injury. It has demonstrated that KLF2 activators can be candidate therapeutic agents of HIRI.

AMPK induced eNOS activation: AMPK plays a key role in the regulation of cellular energy homeostasis. The activation of this kinase is a response to the stimulus. Mahfoudh Boussaid A *et al*[46] reported that repeated administration of trimetazidine protected against WIR injury by decreasing liver damage and oxidative stress. The underlying mechanism is involved by the activation of the AMPK/eNOS signaling pathway. In addition, similar mechanisms have been identified in the protective effect of Institut Georges Lopez 1 solution on cold-stored fatty liver grafts. The effect is mainly exerted through the activation of the AMPK pathway, which targets eNOS to produce NO, offsetting aggravated microcirculatory changes, improving vascular resistance and function during IR[47,48].

Other pathways: SEW2871, a selective sphingosine-1-phosphate receptor 1 (S1PR1) agonist, can restore the expression of eNOS and vascular endothelial (VE) cadherin in sinusoidal endothelial cells during HIRI *in vivo* and does not influence the expression of p-Akt. Thus, there may be a regulation pathway between S1PR1 and eNOS[49]. And the expression of VE-cadherin is important for vascular integrity, which is the basis for eNOS expression[49].

Moreover, ischemia precondition (IPC) can protect HIRI through p38 MAPK activation, which induces eNOS-derived NO expression to enhance cell autophagy in HIRI[35]. However, pretreatment with 3,7-dimethyl-1-propargylxanthine, which is an adenosine A2 receptor (A2AR) antagonist, can repeal the protective effect induced by

IPC. Therefore, it can be inferred that there may be a relationship between the A2AR and eNOS[50].

The study of Kebschull L *et al*[51] showed low-dose erythropoietin (EPO) treatment significantly increased hepatic NO bioavailability by upregulating eNOS expression. EPO-mediated eNOS phosphorylation is promoted by EPOR-mediated activation of the Janus kinase 2/PI3K/Akt pathway and common β receptor (βcR)-dependent activation of AMPK. In addition to this, activation of the βcR2-vascular endothelial growth factor receptor-2 complex is also involved in the regulation, but its downstream signaling is currently unclear.

ROLE OF INOS IN HIRI

As mentioned above, iNOS-derived NO may have different functions in HIRI[15]. Although in most cases iNOS is considered to be harmful to the HIRI, it does not affect or even protects the HIRI in some conditions. In a study of models with liver ischemia and partial liver resection, iNOS mRNA expression was not found to be significantly altered compared to the sham group. While during 6 to 8 h after hepatectomy, iNOS expression and NO production were promoted by cytokines, thereby improving liver microcirculation and preventing cell apoptosis[52]. The protective effect of iNOS has only been demonstrated in a few specific experiments and lacks widespread validation. Due to differences in experimental subjects, measurement criteria and experimental time constraints, iNOS-derived NO exhibits a more complex and unclear role than eNOS.

iNOS aggravate HIRI

Hide D *et al*[14] found a surge increase of NO in warm IR damage in aged livers, which was mainly induced by iNOS production. The surge of NO derived from iNOS can increase the expression of reactive nitrogen species (RNS) and inflammatory cytokines, resulting in cytotoxic damage in hepatocytes. Besides, the damage from iNOS is also confirmed in other studies. As intrahepatic macrophages, KCs are activated in early IRI,

producing excessive amounts of iNOS-derived NO, leading to massive production of pro-inflammatory factors, cytokines and ROS, which are key links to impaired microcirculation in the liver and deteriorate HIRI[5,53].

At the late phase of HIRI, the function of iNOS will be at a prominent stage. Excess NO derived from iNOS has cytotoxic effects that induce inflammation and excessive oxidation, and performs many deleterious functions in HIRI. Increased iNOS expression is associated with increased TNF-α and NF-κB, which leads to increased expression of pro-inflammatory genes, inflammatory mediators and regulatory enzymes[54]. They are both important to trigger inflammation reactions and may have deleterious effects on IRI. Besides, in studying the role of iNOS/NO in the interferon regulatory factor-1 (IRF1) signaling pathway of primary human hepatocytes, Du Q *et al*[55] performed the existence of a positive-feedback loop between iNOS and IRF1. The IRF1 and p53 can upregulate the p53 up-regulated modulator of apoptosis (PUMA), which is a modulator of apoptosis, resulting in hepatocyte death and further damage to hepatic IRI.

REGULATE INOS AND ENOS EXPRESSION TO PROTECT HIRI

The extent and intensity of eNOS and iNOS in HIRI are both higher than that of normal, while excess NO will produce peroxynitrite to aggravate IR damage. These scores can be reduced by using high doses of tadalafil and pentoxifylline to mitigate the deterioration of nitrosative stress and endothelial cell injury[53].

Iwasaki J *et al*[6] demonstrated that L-NAME, a NOS inhibitor, attenuated liver damage in IRI of Cholestatic Livers by inhibiting the NO production. Comparing the expression of iNOS and eNOS with L-NAME treatment, they found that this kind of protection was mainly involved by the inhibitory effects of iNOS. It also prevented the increase of Asymmetric dimethylarginine, which is an exogenous inhibitor of eNOS, to protects against IRI at the early stage.

Bone marrow mesenchymal stem cells (BMMSCs) transplantation can regulate NOS synthesis by increasing eNOS expression as well as inhibiting iNOS expression and excessive NO production to protect HIRI and reduce hepatocyte apoptosis. Its regulations are closely related to the inhibition of NOS-induced macrophage activation, the suppression of large amounts of iNOS and NO synthesized by macrophages, and the amelioration of endothelial damage. And the combination uses of BMMSCs and normothermic machine perfusion can increase the balance of ET/NO ratio[5].

Besides, the eNOS traffic inducer (NOSTRIN) can significantly inhibit NO release by decreasing the enzymatic activity of eNOS. Pretreatment of N-acetylcysteine or thymoquinone can upregulate eNOS along with NO production and downregulate iNOS and NOSTRIN expressions to attenuate HIRI injury, showing the protective effect of increasing eNOS and NO levels and inhibiting iNOS expression against IRI in rat liver[56].

Inhibit iNOS to protect HIRI

After reperfusion, the expression of inflammatory factors such as macrophage inflammatory protein-2 and iNOS increase with the activation of NF-κB, leading to a series of inflammation reactions. Alpha-lipoic acid can reduce the formation of excess NO during reperfusion by decreasing the expression of iNOS mRNA and reduce cellular damage from NO-forming NOS superoxide and peroxide anions[57]. Beyond that, in a study of vildagliptin function in lung injury after hepatic IRI, significant inhibition of iNOS mRNA and NO expression was observed by the involvement of the hypoxia-inducible factor (HIF)-α/hepatocyte growth factor/iNOS pathway. The evaluated HIF-α can increase iNOS expression in various models. Therefore, targeting HIF-α expression can reduce tissue damage[58]. Furthermore, hepatic IR-induced iNOS protein expression can be diminished by eupatilin, which also suppresses the toll-like receptors 2/NF-κB pathway to ameliorate inflammation response[59]. In addition, neural-sphingomyelinase (N-SMase) can produce ceramide, which is a mediator of

iNOS expression. Inhibition of N-SMase leads to a decrease in iNOS levels, along with a decrease in protein nitrification and nitrite/nitrate levels in WIR[60].

Inhibit overexpression of and eNOS

Some studies have demonstrated the hepatoprotective effect of genetic eNOS overexpression in small-for-size liver transplantation and illustrated the importance of promoting eNOS expression for hepatoprotection[61]. However, there is insufficient evidence for a protective effect of eNOS overexpression, and evidence that eNOS overexpression is detrimental to HIRI[62]. The dual effect of eNOS in HIRI remains controversial.

The fact is that the expression of eNOS will be deteriorated by oxidative stress and endothelium damage during the progress of ischemia, while the function of iNOS will be stimulated by oxidative stress during reperfusion and aggravate the liver injury. The imbalance of eNOS and iNOS can also aggravate IRI.

THERAPEUTIC PERSPECTIVES

NOS drugs as well as drugs for the regulation of NOS enzymes may be the way forward for liver protection. However, more in-depth studies are still needed. Not only do drugs need to be stable, but they also need to avoid the harm that NO and NOS can cause to reduce side effects. Besides, despite a number of experimental articles demonstrating the beneficial effects of NO-releasing compounds and some drugs that promote NO release on ameliorating hepatic IRI, the results of their trial and evaluation in the clinical setting are still lacking. Perhaps more randomised controlled clinical trials should be strengthened in the future to obtain more therapeutic results.

In a nutshell, increasing or decreasing NO availability in the hepatic tissue may be both a way to prevent and treat HIRI and identifying ways to balance the expression of eNOS and iNOS is important to protect IR and can be a promising direction for clinical research.

CONCLUSION

In general, NO along with eNOS and iNOS can play complex roles in HIRI. NO can downregulate LTC4S by inhibiting the NF-κB activation pathway, inhibit apoptotic related genes such as Bax and Bcl-2, enhance autophagic flux, decrease inflammatory cytokines and reduce ROS by inhibiting the mitochondrial respiratory chain. Furthermore, NO induced by different NOS results in a duality of action in HIRI. NO derived by eNOS prefers to protect endothelial cells and attenuate liver injury in HIRI. However, iNOS overexpresses NO in response to stimuli, exacerbates liver damage. But their role is not set in stone. Overexpression of eNOS also worsens HIRI, whereas iNOS has also been reported to have a protective effect against HIRI. Actually, these views remain controversial, and the underline mechanisms is urgently needed.

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