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ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Rostyslav Bubnov, MD, PhD, LLB, Senior researcher in The Interferon Department of Zabolotny Institute of Microbiology and Virology, National Academy of Sciences of Ukraine; Medical doctor in The Center of Ultrasound Diagnostics and Interventional Sonography, Clinical Hospital "Pheophania" of Administration of President of Ukraine, Kyiv 03157, Ukraine. rostbubnov@gmail.com

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

Yi-Ping Zhang, Xin-Ran Liu, Mei-Wen Yang, Shu-Long Yang, Fen-Fang Hong

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Yi-Ping Zhang, Xin-Ran Liu, Fen-Fang Hong, Experimental Center of Pathogen Biology, College of Medicine, Nanchang University, Nanchang 330006, Jiangxi Province, China

Mei-Wen Yang, Department of Surgery, Fuzhou Medical College, Nanchang University, Fuzhou 344000, Jiangxi Province, China

Shu-Long Yang, Department of Physiology, College of Medicine, Nanchang University, Nanchang 330006, Jiangxi Province, China

Shu-Long Yang, Department of Physiology, Fuzhou Medical College, Nanchang University, Fuzhou 344000, Jiangxi Province, China

Corresponding author: Fen-Fang Hong, MD, Associate Professor, Experimental Center of Pathogen Biology, College of Medicine, Nanchang University, No. 461 Bayi Road, Nanchang 330006, Jiangxi Province, China. hongfenfang@126.com

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 progression and outcome of 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) accelerates 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. Here we review the new progress in the understanding of the roles of NO during HIRI: (1) NO possesses different roles in HIRI by increasing NO bioavailability, down-regulating leukotriene C4 synthase, inhibiting the activation of the nuclear factor- κ B (NF κ B) pathway, enhancing cell autophagy, and reducing inflammatory cytokines and reactive oxygen species (ROS). And NO has both protective and deleterious effects by regulating apoptotic factors; (2) eNOS promotes NO production and suppresses its own overexpression, exerting a hepatoprotective effect reversely. Its activation is regulated by the PI3K/Akt and KLF2/AMPK pathways; and (3) iNOS derived NO mainly has deteriorating effects on HIRI, while it may have a protective function under some conditions. Their expression 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 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 progress in the understanding of the role of nitric oxide (NO) in hepatic ischemia-reperfusion injury (HIRI). NO protects HIRI by increasing NO bioavailability and cellular autophagy, down-regulating leukotriene C4 synthase, inhibiting the nuclear factor κ B (NF- κ B) 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 and Kruppel-like factor 2/adenosine monophosphate-activated protein kinase pathways. 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.

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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 ischemia, 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 by 114.0% and ended 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, very few of them are known.

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, and 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 was regarded 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 HIRI.

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 undergone 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 Ca²⁺-independent and Ca²⁺-dependent NOS in the human body. Ca²⁺-dependent NOS can be subdivided into neuronal (nNOS) and endothelial (eNOS). eNOS is an enzyme continuously expressed in vascular endothelial cells and exerts biological functions through producing NO. In contrast to eNOS, Ca²⁺-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 HIRI. 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 by 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]. 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 aims to find the role of NO during HIRI and look for candidate ways to alleviate liver damage (Table 1).

DIFFERENT ROLES OF NO DURING HIRI

Recently, studies have showed that NO has a significant role during the HIRI, which can be a positive protective function or negative deleterious function. NO was proved to reduce HIRI through various mechanisms such as increasing NO bioavailability, down-regulating leukotrienes (LTs), inhibiting liver cell apoptosis, enhancing autophagic flux, 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 *et al*[16] found that NO bioavailability was 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 ROS 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 up-regulating eNOS expression[17]. Also, simvastatin maintains NO bioavailability by preventing kruppel-like factor 2 (KLF2) down-regulation[16].

NO can down-regulate LTC4S by inhibiting the nuclear factor-kB pathway

Many studies reveal that cysteinyl leukotrienes are directly associated with hepatic IRI. Leukotriene C4 synthase (LTC4S) is one of the enzymes that are responsible for LTC4 synthesis, showing a strong relationship with the NO[18,19]. In I/R rats, the gene expression level of LTC4S is much higher. However, this is reversed by V-PYRRO/NO, which acts as an NO donor. Hong *et al*[20] also found that another NO donor, sodium nitroprusside, could down-regulate the mRNA expression of LTC4S by inhibiting nuclear factor-kappa B (NF-κB) activation in an NF-κB α inhibitor-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 factors

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. 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-κB[32]. Studies have shown that the caspase family is strongly related to hepatic cell apoptosis[33]. Zhao *et al* [21] found that steatosis-induced decline in adenosine monophosphate-activated protein kinase (AMPK)-catalyzed phosphorylation permits caspase-6 activation, leading to hepatocyte death. And Gao *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 *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 studies, mouse liver cell apoptosis can be inhibited by reducing NO content, down-regulating 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-κB pathway. And this imbalanced ratio may show a protective role in the damaged liver[30]. Jiang *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 process, which is an adaptive response to reduce the injury. Studies have found that the protective mechanism of NO during HIRI is associated with autophagic flux. Shin *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

Table 1 Roles of nitric oxide, inducible nitric oxide synthase, and endothelial nitric oxide synthase in various conditions and pharmacological protection against hepatic ischemia-reperfusion injury

Pretreatment	NO/ iNOS/ eNOS levels	Animals	Experimental cells	Mechanism	Liver cell necrosis and liver damage	Ref.
NMP, BMMSCs, and liver CDC	eNOS↑, iNOS↓	SPF rats	Liver tissue	Macrophage activation, ICAM-1, VCAM-1, vWF↓	↓	[5]
L-NAME and BDL	iNOS mRNA↓	Male Wistar rats	Liver tissue	TGF-β, NOx, HA↓; AMDA↑		[6]
Simvastatin and WIR	NO↑	Male Wistar rats	Primary LSEC	Nitrotyrosines, O ²⁻ ↓; Nrf2, HO-1↑	↓	[14]
Simvastatin and WIR	NO, eNOS↑	Male Wistar rats	LSEC	KLF2, p-eNOS, cGMP↑; O ²⁻ , VCAM-1↓	↓	[16]
Obestatin and HIRI	eNOS↑, iNOS↓	Adult Wistar albino male rats	Liver tissue samples	Reducing oxidative stress and inflammatory process	↓	[17]
HIRI	NO↑	Male Sprague-Dawley rats	Liver	Decrease synthesis of LTC4S, NF-κB↓	↓	[18,19]
V-PYRRO/NO and HIRI	NO↑	Male Sprague-Dawley rats	Liver	Decrease synthesis of LTC4S, NF-κB↓	↓	[20]
AMPK-caspase-6 axis and nonalcoholic steatohepatitis	-	LAKO mice	Hepatocyte	Caspases-6 activation	↓	[21]
Cd-Induced Apoptosis	NO↑ iNOS↑	Hy-Line Brown laying hen	Liver	Mitochondrial apoptotic pathway	↓	[23]
Punicalagin and cyclophosphamide	NO, iNOS↓	Sprague-Dawley male rats	Liver	Reduce cell apoptosis	↓	[25]
<i>Emblica officinalis</i> Gaertn and NAP	NO↓	Male Wistar rats	Liver	Apoptosis, autophagy, inflammation↓	↓	[28]
Tormentica acid and LPS/D-GalN	NO, iNOS↓	Male C57BL/6 mice	Liver samples	TNF-α, NF-κB↓; imbalanced Bax/Bcl-2 ratio	↓	[30]
Selenocysteine-containing 7-mer peptide	NO↓	Adult male Wistar rats	Liver tissue	Inhibit oxidant peroxynitrite, Bax↓; Bcl-2↑	↓	[34]
IPC and HIRI	NO↑	Male C57BL/6 mice	Liver tissue	p38 MAPK↑; autophagy↑	↓	[35]
Simvastatin and hepatic transplantation	NO↑	Male rats	Liver	Autophagy↑	↓	[36]
IPC	NO↑	Male Sprague-Dawley rats	Liver	Oxygen species liberation and proinflammatory cytokine↓; microcirculation↑	↓	[37]
Oxytocin and HIRI	NO↑	Adult male albino (Sprague Dawley strain)	Liver	NO bioavailability↑	↓	[38]
TELL and HIRI	eNOS↑	Male Wistar rats	Liver	Activate PI3K/Akt pathway, suppress TLR4, p-PI3K, p-Akt, Nrf2, p-NF-κB p65, p-MAPK p38, TNF-α, GSH, MyD88, HMGB-1, TBARS↑; NF-κB↓	↓	[42]
Apelin preconditioning and HIRI	eNOS↑	Male albino rats	Liver tissue	Activate PI3K/Akt pathway, suppress AT1R, counteract Ang II/AT1R system	↓	[43]
Simvastatin and WIR	eNOS↑	Male inbred Sprague Dawley rats	Liver tissue	Activate KLF2 pathway, TM, p-eNOS↑, TGF-β, TNF-α, IL-1β↓	↓	[44]
HMP and liver DCD	NO, eNOS↑	Adult male Sprague-dawley rat	Liver	KLF2↑; NF-κB p65, IL-1β, TNF-α↓	↓	[45]
TMZ and WIR	eNOS↑	Male Wistar rats	Liver tissue	p-MAPK↑; activate MAPK pathway	↓	[46]

IGL-1 and Fatty Liver Graft Cold Storage	eNOS↑	Homozygous (obese) Zucker rats	Liver	Activate MAPK pathway, ATP↑	↓	[48]
SEW2871 and WIR	eNOS↑	Male C57BL/6 mice	SECs	VE-cadherin, p-Akt↑; IFN- γ , TNF- α , IL-6, VCAM-1↓	↓	[49]
EPO and liver transplantation	eNOS↑	Female landrace pigs	Liver tissue	Activate JAK2/PI3/AKT pathway, AMPK↑; β cR2-VEGFR-2 complex	↓	[51]
HIRI	-	Female domestic (Landrace) pigs	Liver tissue	IL-6, STAT-3 and E-selectin mRNA↑	-	[52]
TDF and HIRI	eNOS, iNOS↓	Female Wistar albino rats	Liver tissue	cGMP↑, activate mitochondrial K-ATP channels, mitochondrial Ca ²⁺ ↓	↓	[53]
PTX and HIRI	eNOS, iNOS↓			cAMP↑ TNF- α , IL-1, IL-6, IL-12, TGF- β , IFN- γ , procollagen-I mRNA↓	↓	
L-NNA and HIRI	iNOS↑, eNOS, NO↓	Male Wistar rats	Liver	TNF- α , NF- κ B↑, Bcl-2↓	↑	[54]
L-Arginine/CDN and HIRI	NO, eNOS↑, iNOS↓			TNF- α , NF- κ B↓, Bcl-2↑	↓	
iNOS knockout and WIR	iNOS↓	C57BL/6 male rats	293 T cells	PUMA↓	↑	[55]
NAC and HIRI	eNOS↑, iNOS↓	Male Wistar albino rats	Liver	NOSTRIN, MDA, MPO activity↓	↓	[56]
TQ and HIRI	eNOS↑, iNOS↓			NOSTRIN, MDA, oxidative stress, nitrosative stress↓, GSH↑	↓	
LA and HIRI	iNOS mRNA↓	Male Wistar rats	Liver	NF- κ B p65, MIP-2 mRNA, GSH↓	↓	[57]
V and HIRI	NO, iNOS mRNA↓	Male Wistar rats	Lung and Liver tissue	Inhibit HIF- α /HGF/iNOS pathway	↓	[58]
Eupatilin and HIRI	iNOS↓	Male C57BL/6 mice	Embryonic liver BNL CL.2 cell	TLR2/4, p-I κ B-a↓, Bcl-2↑	↓	[59]
N-SMase inhibitor and HIRI	iNOS	Male Wistar rats	Liver tissue	Protein nitration, nitrite/nitrate levels, HNE		[60]
Ad-eNOS and small-for-size liver transplantation	NO, eNOS↑	-	Human normal liver cell line L02	TNF- α ↓, inhibit macrophage activation	↓	[61]
Ad-eNOS and HIRI	eNOS↑	Male inbred C57BL6 lean mice	Liver	ATP↓, bax, p53↑	↓	[62]

L-NAME: Nomega-nitro-L-arginine methyl ester; BDL: Bile duct ligation; WIR: Warm ischemia and reperfusion; LSEC: Rat liver sinusoidal endothelial cells; KLF2: Kruppel-like factor 2; VCAM-1: Vascular cell adhesion molecule-1; HIRI: Hepatic ischemia reperfusion injury; NF- κ B: nuclear factor-kappaB; LTC4S: Leukotriene C4 synthase; AMPK: Adenosine monophosphate activated protein kinase; NAP:N-nitrosodiethylamine; LPS: Lipopolysaccharide; D-GalN: D-galactosamine; TNF- α : Tumor necrosis factor- α ; Bax: BCL2-Associated X; Bcl-2: B-cell lymphoma-2; MAPK: Mitogen-activated protein kinase; IPC: Ischemic preconditioning; TM: Thrombomodulin; PI3K: Phosphoinositide 3-kinase; TLR4: Toll like receptor-4; Nrf2: Nuclear erythroid-related factor 2; MyD88: Myeloid differentiation primary-response protein 88; TBARS: Thiobarbituric acid reactive substances; AT1R: Angiotensin type 1 receptor; VE-cadherin: Vascular endothelial cadherin; JAK: Janus activated kinase 2; DCD: Donated after circulatory death; HMP: Hypothermic machine perfusion; TMZ: Trimetazidine; IGL-1: Institut georges lopez-1; SECs: Sinusoidal endothelial cells; EPO: Erythropoietin; TDF: Tadalafil; PTX: Pentoxifylline; SPF: Pathogen-free; BMSCs: Bone marrow mesenchymal stem cells; NMP: Normothermic machine perfusion; L-NNA: Nomega-nitro-L-arginine; CDN: Cardamonin; PUMA: p53 up-regulated modulator of apoptosis; HIF- α : Hypoxia inducible factor 1 α ; HGF: Hepatocyte growth factor; MIP-2: Macrophage inflammatory protein-2; LA: Alpha-lipoic acid; V: Vildagliptin; MPO: Myeloperoxidase, MDA: Malondialdehyde; NAC: N-acetylcysteine; TQ: Thymoquinone; Ad-eNOS: Adenovirus-eNOS; N-SMase: Neutral sphingomyelinase; HNE: 4-hydroxynonenal; VEGFR: Vascular endothelial growth factor receptor; ICAM-1: Intracellular cell adhesion molecule-1; β cR: Common β receptor; NOSTRIN: Nitric oxide synthase trafficking.

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 ROS generation occurred, 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 *et al*[38] proved this by adding Nomega-nitro-L-arginine methyl ester (L-NAME) in IRI model rats treated with oxytocin. In this group, not only did 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 produces 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, and inhibiting platelet activation and aggregation. It has been confessed that eNOS shows a hepatoprotective effect in HIRI by improving the production of NO (Figure 1).

There are two main regulation pathways for eNOS activation, one dependent on intracellular concentration of Ca²⁺ and the other independent. The increasing intracellular Ca²⁺ level can enhance the affinity of calmodulin binding to eNOS and activate enzymes to produce NO[39]. For the Ca²⁺-independent regulation pathway, phosphorylation of the Ser1177 residue or dephosphorylation of the Thr495 residue activates it to produce NO[40].

Calcium-dependent 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 Ca²⁺[41]. Besides, anaerobic glycolysis induces an increase in H⁺, which activates intracellular proteases to increase cellular permeability. Furthermore, Na⁺/Ca²⁺ exchange is activated due to a high concentration of H⁺, leading to a further influx of Ca²⁺. Consequently, eNOS is activated due to the increase of intracellular concentration to produce NO, carrying anti-HIRI activities at the initial stage.

Calcium-independent eNOS activation

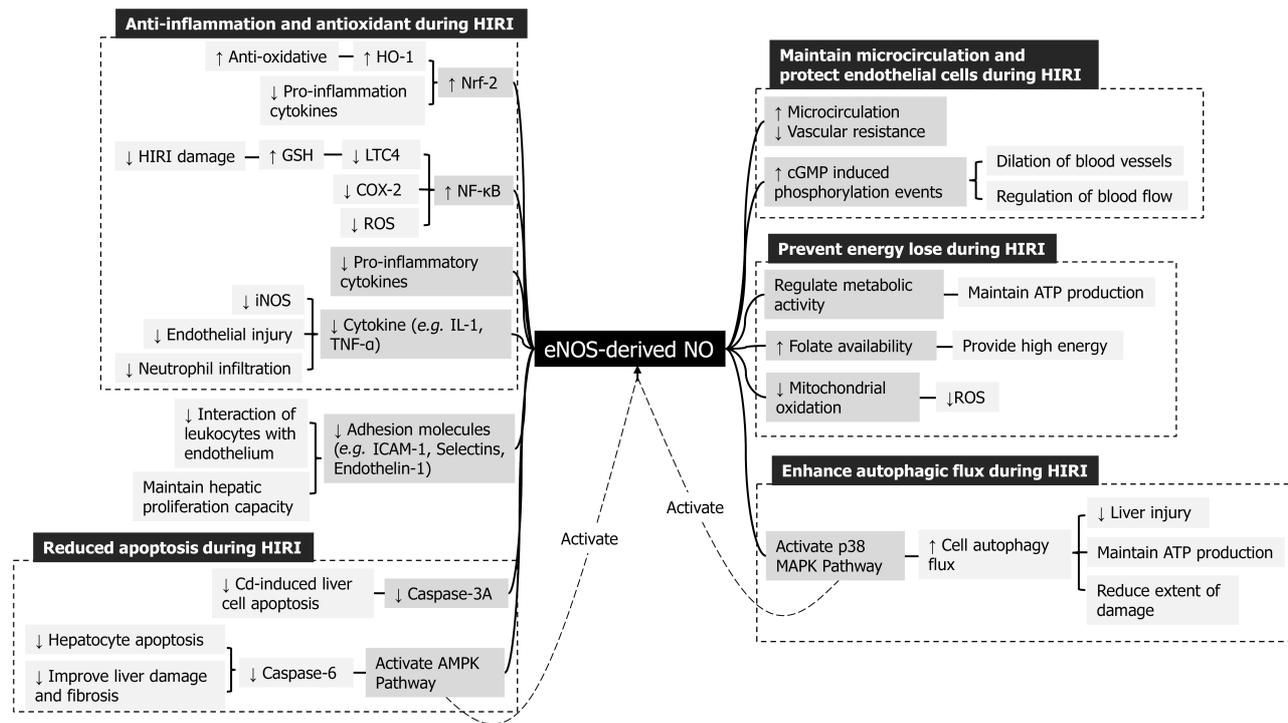
Phosphoinositide 3-kinase/Akt pathway induced eNOS activation: The phosphoinositide 3-kinase (PI3K)/Akt signaling pathway is a cell survival pathway that regulates cell proliferation and apoptosis, as well as an endogenous negative feedback regulator that functions in anti-inflammation and anti-apoptosis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

PI3K can activate Akt to act on the phosphorylation of eNOS. It has been proven that telluric acid has a hepatoprotective effect by elevating the 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- κ B and activates nuclear erythroid-related factor-2, reducing pro-inflammation cytokine 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 HIRI[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 KLF2 in endothelial cells. Also, this reduction is accompanied by a decrease in phosphorylated eNOS (p-eNOS), one of the KLF2 targets. And the IR damage can be mitigated by pretreatment with simvastatin through a KLF2-dependent mechanism, upregulating the mRNA expression of *KLF2* and *eNOS* as well as the protein expression of KLF2 and p-eNOS[16,44]. Hu *et al*[45] also demonstrated that hypothermic machine perfusion inhibited NF- κ B 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 for 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 *et al*[46] reported that repeated administration of trimetazidine protected against WIR injury by decreasing liver damage and oxidative stress. The underlying mechanism involves 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, and improving vascular resistance and function during IR[47,48].

Other pathways: SEW2871, a selective sphingosine-1-phosphate receptor 1 (S1PR1) agonist, can restore



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Figure 1 Hepatoprotective effects of endothelial nitric oxide synthase-derived nitric oxide during hepatic ischemia-reperfusion injury and underlying mechanisms. Nrf2: Nuclear erythroid-related factor; HO-1: Heme oxygenase-1; IL-1: Interleukin-1; TNF- α : Tumor necrosis factor- α ; NF- κ B: Nuclear factor- κ -gene binding; LTC4: Leukotriene C4; GSH: Glutathione; COX-2: Cyclooxygenase 2; ROS: Reactive oxygen species; ICAM-1: Intracellular cell adhesion molecule-1; AMPK: Adenosine monophosphate activated protein kinase; MAPK: Mitogen-activated protein kinase; iNOS: Inducible nitric oxide synthase.

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 preconditioning (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, 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 *et al*[51] showed that low-dose erythropoietin (EPO) treatment significantly increased hepatic NO bioavailability by up-regulating eNOS expression. EPO-mediated eNOS phosphorylation is promoted by EPOR-mediated activation of the Janus kinase 2/PI3K/Akt pathway and common β receptor (β cR)-dependent activation of AMPK. In addition to this, activation of the β cR2-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 aggravates HIRI

Hide *et al*[14] found a surge of NO in WIR 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 and 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- κ B, 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 *et al*[55] found 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.

REGULATING INOS AND ENOS EXPRESSION TO PROTECT HIRI

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

Iwasaki *et al*[6] demonstrated that L-NAME, an 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 mediated by the inhibitory effects of iNOS. It also prevented the increase of asymmetric dimethylarginine, which is an exogenous inhibitor of eNOS, to protect against IRI at the early stage.

Bone marrow mesenchymal stem cell (BMMSC) 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 combined use 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 with N-acetylcysteine or thymoquinone can up-regulate eNOS along with NO production and down-regulate iNOS and NOSTRIN expression to attenuate HIRI injury, showing the protective effect of increasing eNOS and NO levels and inhibiting iNOS expression against IRI in rat liver[56].

Inhibiting 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- κ B, 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 expression and NO 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 receptor 2/NF- κ B 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 nitrication and nitrite/nitrate levels in WIR[60].

Inhibiting 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 endothelial damage during the progression 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 studies demonstrating the beneficial effects of NO-releasing compounds and some drugs that promote NO release in ameliorating hepatic IRI, the results of trials and evaluations 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 both be ways 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 down-regulate LTC4S by inhibiting the NFκB 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 promotes the production of NO in response to stimuli, thus exacerbating 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 underlying mechanisms are urgently needed to be clarified.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Yi-Ping Zhang 0000-0003-4425-2165; Xin-Ran Liu 0000-0002-6050-2497; Mei-Wen Yang 0000-0002-8322-6181; Shu-Long Yang 0000-0002-1407-6255; Fen-Fang Hong 0000-0001-6440-1311.

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REFERENCES

- Ikeda T, Yanaga K, Kishikawa K, Kakizoe S, Shimada M, Sugimachi K. Ischemic injury in liver transplantation: difference in injury sites between warm and cold ischemia in rats. *Hepatology* 1992; 16: 454-461 [PMID: 1639355 DOI: 10.1002/hep.1840160226]
- Liu Z, Jiang Y, Yuan H, Fang Q, Cai N, Suo C, Jin L, Zhang T, Chen X. The trends in incidence of primary liver cancer caused by specific etiologies: Results from the Global Burden of Disease Study 2016 and implications for liver cancer prevention. *J Hepatol* 2019; 70: 674-683 [PMID: 30543829 DOI: 10.1016/j.jhep.2018.12.001]

- 3 **Phillips L**, Toledo AH, Lopez-Neblina F, Anaya-Prado R, Toledo-Pereyra LH. Nitric oxide mechanism of protection in ischemia and reperfusion injury. *J Invest Surg* 2009; **22**: 46-55 [PMID: 19191157 DOI: 10.1080/08941930802709470]
- 4 **Rampes S**, Ma D. Hepatic ischemia-reperfusion injury in liver transplant setting: mechanisms and protective strategies. *J Biomed Res* 2019; **33**: 221-234 [PMID: 32383437 DOI: 10.7555/JBR.32.20180087]
- 5 **Yang L**, Cao H, Sun D, Hou B, Lin L, Shen ZY, Song HL. Bone marrow mesenchymal stem cells combine with normothermic machine perfusion to improve rat donor liver quality-the important role of hepatic microcirculation in donation after circulatory death. *Cell Tissue Res* 2020; **381**: 239-254 [PMID: 32347385 DOI: 10.1007/s00441-020-03202-z]
- 6 **Iwasaki J**, Afify M, Bleilevens C, Klinge U, Weiskirchen R, Steitz J, Vogt M, Yagi S, Nagai K, Uemoto S, Tolba RH. The Impact of a Nitric Oxide Synthase Inhibitor (L-NAME) on Ischemia-Reperfusion Injury of Cholestatic Livers by Pringle Maneuver and Liver Resection after Bile Duct Ligation in Rats. *Int J Mol Sci* 2019; **20** [PMID: 31035686 DOI: 10.3390/ijms20092114]
- 7 **Donnarumma E**, Ali MJ, Rushing AM, Scarborough AL, Bradley JM, Organ CL, Islam KN, Polhemus DJ, Evangelista S, Cirino G, Jenkins JS, Patel RA, Lefer DJ, Goodchild TT. Zofenopril Protects Against Myocardial Ischemia-Reperfusion Injury by Increasing Nitric Oxide and Hydrogen Sulfide Bioavailability. *J Am Heart Assoc* 2016; **5** [PMID: 27381758 DOI: 10.1161/JAHA.116.003531]
- 8 **Kim JS**, Ohshima S, Padiaditakis P, Lemasters JJ. Nitric oxide protects rat hepatocytes against reperfusion injury mediated by the mitochondrial permeability transition. *Hepatology* 2004; **39**: 1533-1543 [PMID: 15185294 DOI: 10.1002/hep.20197]
- 9 **Hara Y**, Teramoto K, Kumashiro Y, Sato E, Nakamura N, Takatsu S, Kawamura T, Arai S. Beneficial effect of tetrahydrobiopterin on the survival of rats exposed to hepatic ischemia-reperfusion injury. *Transplant Proc* 2005; **37**: 442-444 [PMID: 15808670 DOI: 10.1016/j.transproceed.2004.12.051]
- 10 **Hibbs JB Jr**, Taintor RR, Vavrin Z, Rachlin EM. Nitric oxide: a cytotoxic activated macrophage effector molecule. *Biochem Biophys Res Commun* 1988; **157**: 87-94 [PMID: 3196352 DOI: 10.1016/s0006-291x(88)80015-9]
- 11 **Zhang YQ**, Ding N, Zeng YF, Xiang YY, Yang MW, Hong FF, Yang SL. New progress in roles of nitric oxide during hepatic ischemia reperfusion injury. *World J Gastroenterol* 2017; **23**: 2505-2510 [PMID: 28465634 DOI: 10.3748/wjg.v23.i14.2505]
- 12 **Crane BR**, Arvai AS, Ghosh DK, Wu C, Getzoff ED, Stuehr DJ, Tainer JA. Structure of nitric oxide synthase oxygenase dimer with pterin and substrate. *Science* 1998; **279**: 2121-2126 [PMID: 9516116 DOI: 10.1126/science.279.5359.2121]
- 13 **Förstermann U**, Sessa WC. Nitric oxide synthases: regulation and function. *Eur Heart J* 2012; **33**: 829-837, 837a [PMID: 21890489 DOI: 10.1093/eurheartj/ehr304]
- 14 **Hide D**, Warren A, Fernández-Iglesias A, Maeso-Díaz R, Peralta C, Le Couteur DG, Bosch J, Cogger VC, Gracia-Sancho J. Ischemia/Reperfusion Injury in the Aged Liver: The Importance of the Sinusoidal Endothelium in Developing Therapeutic Strategies for the Elderly. *J Gerontol A Biol Sci Med Sci* 2020; **75**: 268-277 [PMID: 30649272 DOI: 10.1093/gerona/glz012]
- 15 **Abu-Amara M**, Yang SY, Seifalian A, Davidson B, Fuller B. The nitric oxide pathway--evidence and mechanisms for protection against liver ischaemia reperfusion injury. *Liver Int* 2012; **32**: 531-543 [PMID: 22316165 DOI: 10.1111/j.1478-3231.2012.02755.x]
- 16 **Hide D**, Ortega-Ribera M, Garcia-Pagan JC, Peralta C, Bosch J, Gracia-Sancho J. Effects of warm ischemia and reperfusion on the liver microcirculatory phenotype of rats: underlying mechanisms and pharmacological therapy. *Sci Rep* 2016; **6**: 22107 [PMID: 26905693 DOI: 10.1038/srep22107]
- 17 **El-Gohary OA**. Obestatin improves hepatic injury induced by ischemia/reperfusion in rats: Role of nitric oxide. *Gen Physiol Biophys* 2017; **36**: 109-115 [PMID: 27901469 DOI: 10.4149/gpb_2016030]
- 18 **Cavaliere B**, Perrelli MG, Aragno M, Ramadori P, Poli G, Cutrin JC. Ischaemic preconditioning modulates the activity of Kupffer cells during *in vivo* reperfusion injury of rat liver. *Cell Biochem Funct* 2003; **21**: 299-305 [PMID: 14624466 DOI: 10.1002/cbf.1028]
- 19 **Matuschak GM**, Henry KA, Johanns CA, Lechner AJ. Liver-lung interactions following Escherichia coli bacteremic sepsis and secondary hepatic ischemia/reperfusion injury. *Am J Respir Crit Care Med* 2001; **163**: 1002-1009 [PMID: 11282780 DOI: 10.1164/ajrccm.163.4.2003020]
- 20 **Hong FF**, Wang YF, Liu H, Yang MW, Yang SL. V-PYRRO/NO downregulates mRNA expression levels of leukotriene C4 synthase during hepatic ischemia reperfusion injury in rats *via* inhibition of the nuclear factor- κ B activation pathway. *Biomed Rep* 2016; **4**: 112-116 [PMID: 26870346 DOI: 10.3892/br.2015.533]
- 21 **Zhao P**, Sun X, Chagga C, Liao Z, In Wong K, He F, Singh S, Loomba R, Karin M, Witztum JL, Sattiel AR. An AMPK-caspase-6 axis controls liver damage in nonalcoholic steatohepatitis. *Science* 2020; **367**: 652-660 [PMID: 32029622 DOI: 10.1126/science.aay0542]
- 22 **Gao D**, Xu Z, Qiao P, Liu S, Zhang L, He P, Zhang X, Wang Y, Min W. Cadmium induces liver cell apoptosis through caspase-3A activation in purple red common carp (*Cyprinus carpio*). *PLoS One* 2013; **8**: e83423 [PMID: 24349509 DOI: 10.1371/journal.pone.0083423]
- 23 **Zhang R**, Yi R, Bi Y, Xing L, Bao J, Li J. The Effect of Selenium on the Cd-Induced Apoptosis *via* NO-Mediated Mitochondrial Apoptosis Pathway in Chicken Liver. *Biol Trace Elem Res* 2017; **178**: 310-319 [PMID: 28062951 DOI: 10.1007/s12011-016-0925-7]
- 24 **Abdel Moneim AE**. Indigofera oblongifolia Prevents Lead Acetate-Induced Hepatotoxicity, Oxidative Stress, Fibrosis and Apoptosis in Rats. *PLoS One* 2016; **11**: e0158965 [PMID: 27391413 DOI: 10.1371/journal.pone.0158965]
- 25 **Foad AA**, Qutub HO, Al-Melhim WN. Punicalagin alleviates hepatotoxicity in rats challenged with cyclophosphamide. *Environ Toxicol Pharmacol* 2016; **45**: 158-162 [PMID: 27310207 DOI: 10.1016/j.etap.2016.05.031]
- 26 **Zhao J**, Liu T, Ma L, Yan M, Zhao Y, Gu Z, Huang Y. Protective effect of acteoside on immunological liver injury induced by Bacillus Calmette-Guerin plus lipopolysaccharide. *Planta Med* 2009; **75**: 1463-1469 [PMID: 19548187 DOI: 10.1055/s-0029-1185796]
- 27 **Yang T**, Wu J, Wang C, Liu Q, Ma X, Peng J, Kaku T, Liu K. Protective effect of JBP485 on concanavalin A-induced liver injury in mice. *J Pharm Pharmacol* 2009; **61**: 767-774 [PMID: 19505367 DOI: 10.1211/jpp.61.06.0009]

- 28 **Chen KH**, Lin BR, Chien CT, Ho CH. *Emblica officinalis* Gaertn. attenuates N-nitrosodiethylamine-induced apoptosis, autophagy, and inflammation in rat livers. *J Med Food* 2011; **14**: 746-755 [PMID: 21761987 DOI: 10.1089/jmf.2010.1459]
- 29 **Tsuchihashi S**, Kaldas F, Chida N, Sudo Y, Tamura K, Zhai Y, Qiao B, Busuttill RW, Kupiec-Weglinski JW. FK330, a novel inducible nitric oxide synthase inhibitor, prevents ischemia and reperfusion injury in rat liver transplantation. *Am J Transplant* 2006; **6**: 2013-2022 [PMID: 16796718 DOI: 10.1111/j.1600-6143.2006.01435.x]
- 30 **Lin X**, Zhang S, Huang R, Tan S, Liang S, Wu X, Zhuo L, Huang Q. Protective effect of tormentic acid from *Potentilla chinensis* against lipopolysaccharide/D-galactosamine induced fulminant hepatic failure in mice. *Int Immunopharmacol* 2014; **19**: 365-372 [PMID: 24560903 DOI: 10.1016/j.intimp.2014.02.009]
- 31 **Zhao Y**, Zhou P, Liu B, Bambakidis T, Mazitschek R, Alam HB, Li Y. Protective effect of suberoylanilide hydroxamic acid against lipopolysaccharide-induced liver damage in rodents. *J Surg Res* 2015; **194**: 544-550 [PMID: 25479907 DOI: 10.1016/j.jss.2014.10.056]
- 32 **Yang BY**, Zhang XY, Guan SW, Hua ZC. Protective Effect of Procyanidin B2 against CC14-Induced Acute Liver Injury in Mice. *Molecules* 2015; **20**: 12250-12265 [PMID: 26151119 DOI: 10.3390/molecules200712250]
- 33 **Sherif IO**, Al-Shaalan NH. Vildagliptin Attenuates Hepatic Ischemia/Reperfusion Injury via the TLR4/NF- κ B Signaling Pathway. *Oxid Med Cell Longev* 2018; **2018**: 3509091 [PMID: 30405876 DOI: 10.1155/2018/3509091]
- 34 **Jiang Q**, Pan Y, Cheng Y, Li H. Protection of rat liver against hepatic ischemia-reperfusion injury by a novel selenocysteine-containing 7-mer peptide. *Mol Med Rep* 2016; **14**: 2007-2015 [PMID: 27431272 DOI: 10.3892/mmr.2016.5464]
- 35 **Shin JK**, Kang JW, Lee SM. Enhanced nitric oxide-mediated autophagy contributes to the hepatoprotective effects of ischemic preconditioning during ischemia and reperfusion. *Nitric Oxide* 2016; **58**: 10-19 [PMID: 27246638 DOI: 10.1016/j.niox.2016.05.007]
- 36 **Gracia-Sancho J**, García-Calderó H, Hide D, Marrone G, Guixé-Muntet S, Peralta C, García-Pagán JC, Abraldes JG, Bosch J. Simvastatin maintains function and viability of steatotic rat livers procured for transplantation. *J Hepatol* 2013; **58**: 1140-1146 [PMID: 23428876 DOI: 10.1016/j.jhep.2013.02.005]
- 37 **Rodríguez-Reynoso S**, Leal-Cortés C, Portilla-de Buen E, López-De la Torre SP. Ischemic Preconditioning Preserves Liver Energy Charge and Function on Hepatic Ischemia/Reperfusion Injury in Rats. *Arch Med Res* 2018; **49**: 373-380 [PMID: 30554858 DOI: 10.1016/j.arcmed.2018.11.004]
- 38 **Ragy MM**, Aziz NM. Prevention of renal ischemia/perfusion-induced renal and hepatic injury in adult male Albino rats by oxytocin: role of nitric oxide. *J Basic Clin Physiol Pharmacol* 2017; **28**: 615-621 [PMID: 28742516 DOI: 10.1515/jbcpp-2016-0197]
- 39 **Michel JB**, Feron O, Sacks D, Michel T. Reciprocal regulation of endothelial nitric-oxide synthase by Ca²⁺-calmodulin and caveolin. *J Biol Chem* 1997; **272**: 15583-15586 [PMID: 9188442 DOI: 10.1074/jbc.272.25.15583]
- 40 **Fleming I**, Busse R. Molecular mechanisms involved in the regulation of the endothelial nitric oxide synthase. *Am J Physiol Regul Integr Comp Physiol* 2003; **284**: R1-12 [PMID: 12482742 DOI: 10.1152/ajpregu.00323.2002]
- 41 **Nakazato PCG**, Victorino JP, Fina CF, Mendes KDS, Gomes MCJ, Evora PRB, D'Albuquerque LAC, Castro-E-Silva O. Liver ischemia and reperfusion injury. Pathophysiology and new horizons in preconditioning and therapy. *Acta Cir Bras* 2018; **33**: 723-735 [PMID: 30208134 DOI: 10.1590/s0102-86502018008000008]
- 42 **Rabie MA**, Zaki HF, Sayed HM. Telluric acid ameliorates hepatic ischemia reperfusion-induced injury in rats: Involvement of TLR4, Nrf2, and PI3K/Akt signaling pathways. *Biochem Pharmacol* 2019; **168**: 404-411 [PMID: 31386827 DOI: 10.1016/j.bcp.2019.08.001]
- 43 **Sabry MM**, Ramadan NM, Al Dreny BA, Rashed LA, Abo El Enein A. Protective effect of apelin preconditioning in a rat model of hepatic ischemia reperfusion injury; possible interaction between the apelin/APJ system, Ang II/AT1R system and eNOS. *United European Gastroenterol J* 2019; **7**: 689-698 [PMID: 31210947 DOI: 10.1177/2050640619826847]
- 44 **Liu Z**, Lai CH, Zhang X, Luo J, Huang X, Qi X, Wang W, Zhong Z, Xiaoli F, Li L, Xiong Y, Senninger N, Wang Y, Ye Q, Ye S. Simvastatin ameliorates total liver ischemia/reperfusion injury via KLF2-mediated mechanism in rats. *Clin Res Hepatol Gastroenterol* 2019; **43**: 171-178 [PMID: 30274910 DOI: 10.1016/j.clinre.2018.08.014]
- 45 **Hu X**, Wang W, Zeng C, He W, Zhong Z, Liu Z, Wang Y, Ye Q. Appropriate timing for hypothermic machine perfusion to preserve livers donated after circulatory death. *Mol Med Rep* 2020; **22**: 2003-2011 [PMID: 32582977 DOI: 10.3892/mmr.2020.11257]
- 46 **Mahfoudh Boussaid A**, Selmi R, Bejaoui M, Hadj Ayed K, Zaouali MA, Ben Abdennebi H. Effectiveness of a single vs repeated administration of trimetazidine in the protection against warm ischemia/reperfusion injury of rat liver. *Turk J Med Sci* 2016; **46**: 1258-1264 [PMID: 27513433 DOI: 10.3906/sag-1505-102]
- 47 **Panissello Rosello A**, Teixeira da Silva R, Castro C, G Bardallo R, Calvo M, Folch-Puy E, Carbonell T, Palmeira C, Roselló Catafau J, Adam R. Polyethylene Glycol 35 as a Perfusate Additive for Mitochondrial and Glycocalyx Protection in HOPE Liver Preservation. *Int J Mol Sci* 2020; **21** [PMID: 32784882 DOI: 10.3390/ijms21165703]
- 48 **Panissello-Roselló A**, Verde E, Amine Zaouali M, Flores M, Alva N, Lopez A, Folch-Puy E, Carbonell T, Hotter G, Adam R, Roselló-Catafau J. The Relevance of the UPS in Fatty Liver Graft Preservation: A New Approach for IGL-1 and HTK Solutions. *Int J Mol Sci* 2017; **18** [PMID: 29088097 DOI: 10.3390/ijms18112287]
- 49 **Ito T**, Kuriyama N, Kato H, Matsuda A, Mizuno S, Usui M, Sakurai H, Isaji S. Sinusoidal protection by sphingosine-1-phosphate receptor 1 agonist in liver ischemia-reperfusion injury. *J Surg Res* 2018; **222**: 139-152 [PMID: 29273365 DOI: 10.1016/j.jss.2017.09.048]
- 50 **Robertson FP**, Fuller BJ, Davidson BR. An Evaluation of Ischaemic Preconditioning as a Method of Reducing Ischaemia Reperfusion Injury in Liver Surgery and Transplantation. *J Clin Med* 2017; **6** [PMID: 28708111 DOI: 10.3390/jcm6070069]
- 51 **Kebschull L**, Theilmann LFC, Mohr A, Uennigmann W, Stoeppler S, Heitplatz B, Spiegel HU, Bahde R, Palmes DM, Becker F. EPOR₂/ β CR₂-independent effects of low-dose epoetin- α in porcine liver transplantation. *Biosci Rep* 2017; **37** [PMID: 29127105 DOI: 10.1042/BSR20171007]
- 52 **Athanasopoulos P**, Mastoraki A, Papalois A, Nastos C, Kondi-Pafiti A, Kostopanagiotou G, Smyrniotis V, Arkadopoulos N. Expression of Inflammatory and Regenerative Genes in a Model of Liver Ischemia/Reperfusion and Partial

- Hepatectomy. *J Invest Surg* 2016; **29**: 67-73 [PMID: 26375364 DOI: 10.3109/08941939.2015.1060280]
- 53 **Bektas S**, Karakaya K, Can M, Bahadir B, Guven B, Erdogan N, Ozdamar SO. The effects of tadalafil and pentoxifylline on apoptosis and nitric oxide synthase in liver ischemia/reperfusion injury. *Kaohsiung J Med Sci* 2016; **32**: 339-347 [PMID: 27450022 DOI: 10.1016/j.kjms.2016.05.005]
- 54 **Atef Y**, El-Fayoumi HM, Abdel-Mottaleb Y, Mahmoud MF. Effect of cardamonin on hepatic ischemia reperfusion induced in rats: Role of nitric oxide. *Eur J Pharmacol* 2017; **815**: 446-453 [PMID: 28966130 DOI: 10.1016/j.ejphar.2017.09.037]
- 55 **Du Q**, Luo J, Yang MQ, Liu Q, Heres C, Yan YH, Stolz D, Geller DA. iNOS/NO is required for IRF1 activation in response to liver ischemia-reperfusion in mice. *Mol Med* 2020; **26**: 56 [PMID: 32517688 DOI: 10.1186/s10020-020-00182-2]
- 56 **Ren Y**, Wang LH, Deng FS, Li JS, Jiang L. Protective effect and mechanism of alpha-lipoic acid on partial hepatic ischemia-reperfusion injury in adult male rats. *Physiol Res* 2019; **68**: 739-745 [PMID: 31424256 DOI: 10.33549/physiolres.934095]
- 57 **Sherif IO**, Al-Shaalan NH. Alleviation of remote lung injury following liver ischemia/reperfusion: Possible protective role of vildagliptin. *Int Immunopharmacol* 2021; **91**: 107305 [PMID: 33388732 DOI: 10.1016/j.intimp.2020.107305]
- 58 **Lee HM**, Jang HJ, Kim SS, Kim HJ, Lee SY, Oh MY, Kwan HC, Jang DS, Eom DW. Protective Effect of Eupatilin Pretreatment Against Hepatic Ischemia-Reperfusion Injury in Mice. *Transplant Proc* 2016; **48**: 1226-1233 [PMID: 27320593 DOI: 10.1016/j.transproceed.2016.01.024]
- 59 **Unal B**, Ozcan F, Tuzcu H, Kirac E, Elpek GO, Aslan M. Inhibition of neutral sphingomyelinase decreases elevated levels of nitrate and oxidative stress markers in liver ischemia-reperfusion injury. *Redox Rep* 2017; **22**: 147-159 [PMID: 27077455 DOI: 10.1080/13510002.2016.1162431]
- 60 **Abd-Elbaset M**, Arafa EA, El Sherbiny GA, Abdel-Bakky MS, Elgendy AN. Thymoquinone mitigate ischemia-reperfusion-induced liver injury in rats: a pivotal role of nitric oxide signaling pathway. *Naunyn Schmiedebergs Arch Pharmacol* 2017; **390**: 69-76 [PMID: 27717985 DOI: 10.1007/s00210-016-1306-7]
- 61 **Zhang B**, Liu QH, Zhou CJ, Hu MZ, Qian HX. Protective effect of eNOS overexpression against ischemia/reperfusion injury in small-for-size liver transplantation. *Exp Ther Med* 2016; **12**: 3181-3188 [PMID: 27882135 DOI: 10.3892/etm.2016.3762]
- 62 **Palanisamy AP**, Cheng G, Sutter AG, Liu J, Lewin DN, Chao J, Chavin K. Adenovirus-mediated eNOS expression augments liver injury after ischemia/reperfusion in mice. *PLoS One* 2014; **9**: e93304 [PMID: 24667691 DOI: 10.1371/journal.pone.0093304]



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