ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2017 April 14; 23(14): 2453-2634

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, Digital Object Identifier, and Directory of Open Access Journals. The 2015 edition of Journal Citation Reports® released by Thomson Reuters (ISI) cites the 2015 impact factor for *WJG* as 2.787 (5-year impact factor: 2.848), ranking *WJG* as 38 among 78 journals in gastroenterology and hepatology (quartile in category Q2).

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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PUBLICATION DATE
April 14, 2017

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World J Gastroenterol 2017 April 14; 23(14): 2505-2510

DOI: 10.3748/wjg.v23.i14.2505

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

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

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Supported by National Natural Science Foundation of China, No. 81260504, No. 81660151 and No. 81660751; Science Foundation of Science Commission of Jiangxi Province, China, No. 20161BBG70067; School Teaching Reform Fund of Nanchang University, No. NCUJGLX - 14-1-111.

Conflict-of-interest statement: There is no conflict of interest associated with any of the authors in this manuscript.

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Manuscript source: Unsolicited manuscript

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Received: December 6, 2016
Peer-review started: December 8, 2016
First decision: December 30, 2016
Revised: January 11, 2017
Accepted: February 16, 2017
Article in press: February 16, 2017
Published online: April 14, 2017

Abstract

Hepatic ischemia reperfusion injury (HIRI) is a clinical condition which may lead to cellular injury and organ dysfunction. The role of nitric oxide (NO) in HIRI is complicated and inconclusive. NO produced by endothelial nitric oxide synthase (eNOS) activation plays a protective role during early HIRI. But eNOS overexpression and the resulting excessive NO bioavailability can aggravate liver injury. NO induced by inducible nitric oxide synthase (iNOS) may have either a protective or a deleterious effect during the early phase of HIRI, but it may protect the liver during late HIRI. Here, we reviewed the latest findings on the role of NO during HIRI: (1) NO exerts a protective effect against HIRI by increasing NO bioavailability, downregulating p53 gene expression, decreasing inflammatory chemokines, reducing ROS *via* inhibiting the mitochondrial respiratory chain, activating sGC-GTP-cGMP signal pathway to reduce liver cell apoptosis, and regulating hepatic immune functions; (2) eNOS protects against HIRI by increasing NO levels, several eNOS/NO signal pathways (such as Akt-eNOS/NO, AMPK-eNOS/NO and HIF-1α-eNOS/NO) participating in the anti-HIRI process, and inhibiting over-expression of eNOS also protects against HIRI; and (3) the inhibition of iNOS prevents HIRI. Thus, the adverse effects of NO should be avoided, but its positive effect in the clinical treatment of diseases associated with HIRI should be recognized.

Key words: Liver; Hepatic ischemia reperfusion injury; Nitric oxide; Nitric oxide synthase

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Core tip: The latest findings on the role of nitric oxide (NO) during hepatic ischemia reperfusion injury (HIRI) include: NO exerts a protective effect against HIRI by increasing NO bioavailability, downregulating p53 gene expression, decreasing inflammatory chemokines, reducing ROS by inhibiting the mitochondrial respiratory chain, activating sGC-GTP-cGMP signal pathway to reduce liver cell apoptosis, and regulating hepatic immune functions; eNOS protects against HIRI by increasing NO levels, several eNOS/NO signal pathways (such as Akt-eNOS/NO, AMPK-eNOS/NO and HIF-1α-eNOS/NO) participating in the anti-HIRI process; inhibiting over-expression of eNOS also protects against HIRI; and finally, the inhibition of iNOS prevented HIRI.

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(14): 2505-2510 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i14/2505.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i14.2505

INTRODUCTION

Hepatic ischemia reperfusion injury (HIRI) is a clinical condition which may lead to cellular injury and organ dysfunction, mediated mainly through the production of reactive oxygen species and inflammatory cytokines[1]. Deterioration of hepatic homeostasis, as observed in IR, cold preservation and transplantation, septic organ failure, and hepatic resection-induced hyperperfusion, are associated with high rates of morbidity and mortality. It is well known that HIRI involves several mechanisms, which include pH imbalance, Ca^{2+} overload, mitochondrial damage induced by oxygen free radicals, endothelin (ET)/nitric oxide (NO) ratio imbalance, liver microcirculation dysfunction, activation of Kupffer cells and neutrophils, and the impact of various cytokines. During IR, there are interactions among liver cells, Kupffer cells, neutrophils, hepatic sinusoidal endothelial cells, and fat-storing cells. Platelets and alexin are also involved[2]. These activated cells release a large quantity of proinflammatory cytokine and lipid inflammatory factor, which can lead to inflammatory reaction and cell apoptosis.

NO is an unstable carbon-centered radical with a short half-life. There are two sources in organisms: one is non-enzymstigenese derived from the degradation or transformation of inorganic nitrogen chemicals in the body and food; and the other one is enzymstigenese, in which NO is produced in a redox reaction between L-arginine and oxygen molecules by NO synthase (NOS) catalyzation. There are three types of NOS: endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase (nNOS), and inducible nitric oxide synthase (iNOS). Endothelial nitric oxide synthase exists mainly in vascular endothelial cells while iNOS exists mainly in the cytoplasm of some inflammatory cells, such as white blood cells associated with diseases characterized by inflammation, tumors, and degeneration. NOS not only appears in soluble cytoplasm but also in some subcellular organelles. NO is produced mainly by eNOS catalysis, and also by the upregulation of iNOS expressions during acute hepatic ischemia[3]. It has been reported that iNOS is induced to produce large amounts of NO by lipopolysaccharide, interleukin-1 (IL-1), and tumor necrosis factor (TNF), which play a role in the pathophysiological process of some diseases and in many inflammation and immune reactions[4]. iNOS-derived NO may have either a protective or a deleterious effect during the early phase of IR injury, but it plays a protective role in the late phase of HIRI[5] (Table 1).

PROTECTIVE EFFECT OF NO DURING HIRI

NO was proved to reduce HIRI through various mechanisms[6,7], such as inhibiting liver cell apoptosis, slowing the infiltration of macrophages, eliminating superoxide anion produced by neutrophils, protecting the liver sinus structure and maintaining liver microcirculation blood flow, accelerating the liver tissue oxygenation, stabilizing ATP levels, decreasing oxidative stress injury, preventing the reduction of glutathione and the increase of endothelin side effects, and inhibiting platelet aggregation.

Increase of NO bioavailability involved in its protective effect in HIRI

In addition to NO donors, an increase in NO bioavailability can also protect the liver from HIRI. Human serum albumin (HSA) is a non-glycosylated protein, by which a series of recombinants, and mannosylated-HSA mutants (Man-rHSAs) are prepared; their triple mutant (TM-rHSA) can be selectively delivered to the liver *via* a mannose receptor on non-parenchymal liver cells, which can effectively deliver NO to the liver and have a significant inhibitory effect against HIRI[8].

NO downregulates the expression of the p53 gene and decreases inflammatory chemokines

During IR, NO donors may decrease p53 gene expression and the levels of IL-1 and TNF-α as well as inhibit cell apoptosis to protect the heart, liver, lungs, and kidneys from IR injury. Elevated NO levels can inhibit p53 gene expression and decrease the production of proinflammatory cytokines and chemokines, such as intercellular adhesion molecule (ICAM), TNF-α, IL-1, MIP-1, and MIP-2. In particular, lower levels of ICAM,

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

Pretreatment	NO/iNOS/eNOS levels	Animals	Experimental cells	Mechanism	Liver cell necrosis and liver damage	Ref.
L-arginine and HIRI	NO↑	Male Sprague-Dawley rats	Hepatocytes	O2-↓, NO2-/NO3- concentration↑	↓	[6]
L-NAME and HIRI	NO↓	Male Sprague-Dawley rats	Liver cells	NO2-/NO3- concentration↓	↑	[7]
Human serum albumin↑	NO↑	Rats underwent HIRI	Liver parenchyma	Man-rHSAs↑	↓	[8]
SNAP and HIRI	NO↑	-	Vein endothelial cells	ICAM, TNF-α, NF-κB, p38, ERK, JNK, p53, caspase-3↓	↓	[9,10]
Nitrite and hypoxia/reoxygenation	NO↑	Trachemys Acripta elegans	Various cell types	Cytochrome oxidase, oxygen radical↓	↓	[13]
L-arginine and HIRI	NO↑	-	Liver cells	sGC, cGMP, PKG, PI3K, V-ATPase ↑, intracellular Na+, H+↓	↓	[5]
L-arginine and HIRI	NO↑	Rats	Liver cells	TNF-α, IL-1β↓	↓	[14,15]
HIRI	eNOS,NO↑	-	Bovine aortic endothelial cells and COS-7cells	Intracellular Na+, H+, PKC, Ca2+↑	↓	[16,17]
rHuEPO and HIRI	NO↑	Adult male Sprague-Dawley rats	Liver cells	PI3K/Akt/eNOS pathway	↓	[18]
Institut Georges Lopez-1 and HIRI	eNOS↑	Adult male SD rats	Liver cells	Akt,AMPK↑	↓	[19]
Adiponectin and HIRI	eNOS↑	Adult male Wistar rats	Hepatocytes	AMPK/eNOS pathway	↓	[20]
Heparin cofactor Ⅱ and ischemia	eNOS↑	Male heterozygote HC Ⅱ-deficient mice and male littermate WT mice	Vascular endothelial cell	AMPK/eNOS signaling pathway	↓	[21]
Trimetazidine, IGL-1, and HIRI	eNOS,NO↑	Isolated perfused rats liver model	Steatotic and non-steatotic livers cells	HIF-1α, heme-oxygenase-1↑	↓	[22]
Knockdown of AK139328 and HIRI	eNOS↑	Mice	Liver cells	p-eNOS, p-Akt, PGSK-3 ↑,macrophage infiltration, NF-κB↓	↓	[23]
Ad-eNOS and HIRI	eNOS↑	Male inbred C57BL/6 lean mice	Liver cells	ATP↓, bax↑	↑	[24]
Riboflavin and HIRI	eNOS,iNOS,NO↓	Mice	Liver	GSH↑	↓	[25]
Rosmarinic acid and HIRI	eNOS,iNOS,NO↓	Rats	Liver	eNOS excessive expression↓ NF-κB activity, TNF-α and IL-1β gene expression↓	↓	[26]
Alpha lipoic acid and HIRI	iNOS,NO↓	Male Wistar strain rats	Hepatocytes	iNOS mRNA stability↓	↓	[31]

-: No data; Man-rHSAs: Mannosylated-HSA mutants; HIRI: Hepatic ischemia reperfusion injury; IGL-1: Institut georges lopez-1; SNAP: S-nitroso-N-acetylpenicillamine; ICAM: Intercellular adhesion molecule; Akt: Protein kinase B; AMPK: Adenosine monophosphate-activated protein kinase; TNF-α: Tumor necrosis factor-α; NF-κB: Nuclear factor-κ-gene binding; ERK: Extracellular regulated protein kinase; JNK: c-Jun N-terminal kinase; PI3K: Phosphoinositide 3-kinase; V-ATPase: Vacuolar H^+-ATPase; rHuEPO: Recombinant human erythropoietin; HIF-1α: Hypoxia inducible factor 1α; PGSK-3: Phosphorylated glycogen synthase kinase 3; eNOS: Endothelial nitric oxide synthase; iNOS: Inducible nitric oxide synthase.

MIP-1, and MIP-2 are accompanied by less neutrophil infiltration[9,10]. The application of ICAM-1 monoclonal antibody 1A29F is likely to provide a more effective treatment for primary grafted liver dysfunction[11]. NO can also reduce the level of TNF-α to inhibit NF-κB. Decreased NF-κB can inhibit MAPKs, including p38, ERK, and JNK. A reduced p38 level can lead to the inhibition of caspase-3 and gene p53 expression. Thus, the downregulation of p53, ERK and JNK results in reduction of cell inflammation[9].

NO reduces ROS by inhibiting the mitochondrial respiratory chain

Using transgenic knockout rats, Datta studied the molecular mechanism of HIRI. It was found that the initial liver injury is initiated by reactive oxygen species, which cause direct cellular injury and also activate a cascade of molecular mediators, leading to microvascular changes, increased apoptosis, and acute inflammatory changes with increased hepatocyte necrosis. However, during the period of reperfusion, some adaptive changes occur in order to reduce HIRI[12]. Exogenously administered NO donors can inhibit the oxidation of mitochondrial cytochrome and reduce ROS production. Excessive ROS is generated in liver cells after its hypoxia/reoxygenation, which causes protein oxidation and lipid peroxidation. Hence, NO reduces ROS production by inhibiting

mitochondrial respiratory chain complexes[13].

NO activates sGC-GTP-cGMP signaling pathway to reduce liver cell apoptosis

NO derived from blood vessels can activate soluble guanylyl cyclase (sGC), catalyzing guanosine triphosphate (GTP) to produce cyclic 3′, 5′ guanosine monophosphate (cGMP). The protection of cGMP-dependent protein kinase (PKG) activated by cGMP results in the activation of PI3K and the phosphorylation of p38 MAPK, leading to the activation of vacuolar H^+-ATPases (V-ATPases), which lead to the extrusion of $[H^+]$ ($[H^+]i$) from the cytosol of hepatocytes into the extracellular environment, thereby resulting in inhibition of the H^+-driven Na^+/H^+ exchanger (NHE) and Na^+/HCO_3^- cotransporter (NHCT), with a consequent reduction in $[Na^+]$ ($[Na^+]i$) and protection from hepatocyte death[5]. Diao *et al*[11] observed that NO plays an important protective role in organ preservation by supplementing sufficient NO donors to enhance the NO/cGMP pathway.

NO regulates hepatic immune function

NO is also an important effector molecule that is involved in immune regulation and host innate and acquired immunity. NO inhibits proinflammatory cytokines, including TNF-α, IL-1β, IL-1α, and IL-12, which may induce the inflammatory cascade during HIRI. In addition, NO can decrease the number of T helper 1 (Th1) cells and promote the proliferation of Th2 cells, regulate leukocyte adhesion, and induce the generation of T regulatory (Treg) cells[14,15].

It has also been reported that excessive NO may paradoxically damage liver tissue by forming nitrogen peroxide, indicating that the dose of exogenous NO donors is vital to HIRI therapy.

ENOS CONTRIBUTES TO PROTECTIVE FUNCTIONS AGAINST HIRI

ENOS activation increases NO levels

Intracellular Ca^{2+} levels are the key factors that activate eNOS. During HIRI, Na^+/Ca^{2+} exchange protein on the cell membrane is activated directly or indirectly by the high concentration of Na^+, H^+, and PKC, leading to an increase in intracellular Ca^{2+}. Furthermore, with the liver cell membrane structure damaged, Ca^{2+} transports into the cellular membrane increased, and the endoplasmic reticulum and sarcoplasmic reticulum are also destroyed, which inhibits the function of the calcium pump to elevate the intracellular Ca^{2+} concentration. Meanwhile, stored intracellular Ca^{2+} is released. All these may lead to a higher intracellular Ca^{2+} concentration, which activates eNOS to produce more NO[16,17]. The basic low-dose NO catalyzed by eNOS could mitigate the hepatic microcirculation pressure caused by reperfusion.

ENOS/NO SIGNALING PATHWAYS PARTICIPATE IN ANTI-HIRI ACTIVITY

Akt-eNOS/NO pathway

PI3K is a heterodimer composed of the catalytic subunit p10 and regulatory subunit p85, and is also a lipid second messenger. PI3K can phosphorylate the serine/threonine of its downstream signal kinase Akt, which may further phosphorylate eNOS to promote an increase in endogenous NO generation. The protective effect of rHuEPO in IR injury is mediated *via* the activation of the PI3K/AKT/eNOS signaling pathway, at least in part, by increasing p-AKT and p-eNOS, which leads to the maintenance of an elevated level of NO[18]. It has been reported that IGL-1 solution results in better liver preservation and protection against HIRI by activating Akt and AMPK, which are concomitant with increased eNOS expression and nitrite/nitrate levels[19].

AMPK-eNOS/NO pathway

Zhang C reported that adiponectin (APN) can protect the liver from HIRI by reducing the inflammatory reaction and hepatocyte apoptosis, the process that likely involves the AMPK/eNOS pathway[20]. In addition, heparin cofactors II (HCII) potentiates hepatic vascular endothelial cell activity and the promotion of angiogenesis *via* an AMPK/eNOS signaling pathway to decrease vascular injury[21].

HIF-1α-eNOS/NO pathway

Adding trimetazidine, an anti-ischemia drug, to IGL-1 induces NO and eNOS activation. In normoxic reperfusion, the presence of NO favors hypoxia-inducible factor-1α (HIF-1α) accumulation, and also promotes the activation of other cytoprotective genes to reduce HIRI, such as heme-oxygenase-1. In addition, NO could reduce HIRI *via* the HIF-1α/NO pathway[22].

Other new pathways

Deregulated long noncoding RNA (LncRNAs) AK139328 is involved in HIRI. In the IR liver, the knockdown of AK139328 increases survival-signaling proteins including phosphorylated Akt (pAkt), glycogen synthase kinase 3 (pGSK3), and endothelial nitric oxide synthase (peNOS). Furthermore, the knockdown of AK139328 also reduces macrophage infiltration and inhibits NF-κB activity and inflammatory cytokine expression[23]. This could provide some new options for the diagnosis and treatment of liver diseases, such as surgery or transplantation.

Inhibition of eNOS overexpression to protect HIRI

The most current evidence supports the idea that the overexpression of eNOS is detrimental in the setting of hepatic IR[24]. Sanches SC found that during HIRI, the riboflavin infusion partially recovered hepatic GSH reserves and decreased eNOS/iNOS and NO levels in

the liver, and that riboflavin could have antioxidant and anti-inflammatory effects in the ischemic liver, protecting hepatocytes against IR injury[25].

Rosmarinic acid, which is a kind of water-soluble phenolic acid compound and a natural antioxidant, has many biological functions, such as antibacterial, antiviral, and anti-inflammatory effects, prevention of high calcium concentrations in the cell, and regulation of immune function. Also, it could inhibit eNOS overexpression in the liver, decrease eNOS/iNOS and NO levels in the liver, attenuate NF-κB activation, downregulate TNF-α and IL-1β gene expression, and exert anti-inflammatory and antioxidant effects in the ischemic liver, thereby protecting hepatocytes against IRI[26].

ROLE OF INOS IN HIRI

During sudden hepatic ischemic stress, upregulated iNOS in the liver produces a large quantity of NO as a response. However, up-regulating the expressions of iNOS gene and protein requires time[7].

iNOS aggravates HIRI

Some evidence suggests that eNOS can lead to "dysfunction" during oxidative stress, so production of a large amount of NO against IRI appears to be necessary for the expression of iNOS[27,28]. Hu *et al*[29] discovered that while the expression of iNOS mRNA peaked 3 h after hepatic reperfusion, the highest protein level appeared after 6 h. After 4 h of reperfusion, the increased iNOS mRNA transcription did not result in increased NO production, and this lack of increase may be linked to different degrees of tissue damage[30].

Inhibition of iNOS prevented liver from HIRI

Alpha lipoic acid (α-LA) has been shown to alleviate HIRI in rats. The underlying mechanism may be that α-LA inhibits the expression of the iNOS gene antisense-transcript, which is involved in iNOS mRNA stability. Therefore, there may be useful therapeutic effects associated with the suppression of iNOS induction involved in liver injury[31].

IL-1β and TNF-α are important proinflammatory cytokines[14]. The upregulation of IL-1β receptors accelerates the iNOS transcription process, but the mechanism involved in its downstream signaling pathway is unknown[32]. Blocking IL-1 receptors may be a way to alleviate HIRI. Although it is uncertain whether the reduction of IL-1 receptors is related to iNOS transcription, it does show that iNOS is involved in the process[33].

CONCLUSION

NO plays a complicated role during HIRI. NO can inhibit the expression of p53 gene and the aggregation of proinflammatory cytokines and chemokines, reduce ROS by inhibiting the mitochondrial respiratory chain, participate in hepatic immune modulation, inhibit the inflammatory cascade, and exhibit anti-inflammatory properties. In addition, as the first messenger, NO activated the NO/cGMP pathway to inhibit $[Na^+]i$ from entering the cells, thereby helping to maintain hepatic cell integrity. Conversely, excessive NO in serum can aggravate liver injury. Elevating NO levels appropriately, such as by applying exogenous NO donors or increasing NO availability in the liver, may be a good way to prevent and treat HIRI. There are two ways to activate eNOS which can promote an increase in endogenous NO generation to protect liver tissue from HIRI. One is elevating Ca^{2+} levels in cells or phosphorylating the active site of eNOS gene, and the other is knocking out gene AK139328. Both can protect the liver from HIRI. But excessive NO levels derived from eNOS are detrimental to the liver. iNOS has a synergistic effect with some inflammatory mediators, which cause cellular swelling and apoptosis. Excessive NO derived from iNOS plays a protective role in the late period of HIRI. Thus, adverse effects of NO should be avoided, and its positive effects in the clinical treatment of diseases associated with HIRI should be recognized.

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P- Reviewer: Neri V **S- Editor**: Ma YJ **L- Editor**: Ma JY
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ISSN 1007-9327

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