

Gasotransmitters against Hepatic Reperfusion Injury

Khodosovsky MN*

Grodno State Medical University, Grodno, Belarus

*Corresponding Author: Khodosovsky MN, Grodno State Medical University, Grodno, Belarus.

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Abstract

Hepatic reperfusion injury occur in clinical practice during liver transplantation, resection or trauma, when vascular clamping should be used. The review is aimed to analyze the literature and our own data about the role of gasotransmitters like NO and H₂S in the liver protection during ischemia-reperfusion syndrome.

Keywords: Liver; Ischemia-Reperfusion; Gasotransmitters; Blood Oxygen Transport; Prooxidant-Antioxidant Balance

Introduction

The development of hepatic ischemia-reperfusion (HIR) disorders is an urgent problem of modern medicine. Temporary occlusion of the great vessels of the liver is used in a number of clinical situations associated with resection, transplantation or traumatic organ damage [1]. The restoration of blood flow after liver ischemia is accompanied by an increased generation of reactive oxygen species (ROS), which leads to oxidative stress and initiates a cascade of pathophysiological reactions, including activation of Kupffer cells, endothelial dysfunction, microcirculation disturbances, white blood cell migration to the liver parenchyma, damage to mitochondria, and triggering of cellular death mechanisms [2]. The use of antioxidants - "scavengers" of ROS, such as α -tocopherol, in case of ischemia-reperfusion syndrome is not always effective [3].

Correction of reperfusion damage to the liver requires a complex effect on many signaling mechanisms responsible for the transport and use of oxygen after ischemia. The class of gas transmitters (NO, H₂S, etc.) that can interact with both ROS and hemoproteins, modulating their properties and processes of oxygen consumption by tissues can be fully attributed to such compounds [4-6]. The goal of this work is to analyze the literature and our own data on the role of NO and H₂S gas transmitters in the mechanisms of modern methods of protecting the liver with its ischemia-reperfusion syndrome.

The effect of NO donors on the development of reperfusion injury in the liver

The results of our studies showed that NO donors (nitroglycerin and sodium nitroprusside) have a powerful protective effect in ischemia-reperfusion of the liver (IRP) [7,8]. This is expressed in a decrease in the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) of mixed venous blood both under the influence of nitroglycerin and with the introduction of sodium nitroprusside. This effect was accompanied by a modulating effect of NO donors on the oxygen-binding properties of blood, which led to a decrease in real hemoglobin half-saturation index (p50real) by 11.9% (p < 0.05) under the influence of nitroglycerin, and standard hemoglobin half-saturation index by 19.3% (p < 0.001) under the influence of sodium nitroprusside in the reperfusion period. An increase in the hemoglobin oxygen affinity (HOA) in the blood and a decrease in the oxygen flow in the tissue during reperfusion under the influence of

nitroglycerin and sodium nitroprusside contributed to a decrease in the level of diene conjugates (DCs), malondialdehyde and Schiff bases in the liver, indicating a decrease in the activity of free radical lipid peroxidation processes (LPO). At the same time, in the liver under the influence of NO donors, at the end of reperfusion, the level of α -tocopherol, retinol, and catalase activity normalizes.

It has been shown that the protective effect of nitroglycerin is observed under conditions of ischemia-reperfusion of the heart [9]. The protective effect of NO donors in case of IRP can be substantiated by an improvement in microcirculation conditions and a decrease in the synthesis of intercellular adhesion molecules [10]. However, the improvement of microcirculation processes leads to an increase in the flow of O_2 into tissues with its potential involvement in free radical processes during reperfusion [11]. An important aspect in this situation is the state of oxygen-binding properties of blood, which can significantly affect the return of O_2 in the tissue [12]. According to our data, it has been established that both nitroglycerin and sodium nitroprusside increase blood HOA during HIR and thereby optimize the supply of O_2 to tissues in the reperfusion period. This combination of effects: improving microcirculation and shifting the oxyhemoglobin dissociation curve (ODC) to the left, helps to reduce ROS generation in liver cells during reperfusion, which affects the activity of LPO processes and the improvement of antioxidant defense parameters, as well as the integrity of hepatocyte cell membranes (judging by the activity of ALT and AST).

However, the effects of NO during HIR are not limited by modulation of the microcirculation and blood HAO. It has been shown that the use of sodium nitroprusside in HIR in rats leads to inhibition of the nuclear factor Kappa B (NF- κ B), followed by a decrease in the expression of the inducible isoform of NO synthase (iNOS) and leukotriene-C4 synthase, while increasing the activity of endothelial NO synthase (eNOS) [13]. In addition, it was found that NO interferes with mitochondrial damage and edema during HIR, reducing the death toll by hepatocyte necrosis and also reduces the level of tumor necrosis factor alpha (TNF- α) and Fas-ligand-dependent apoptosis [14]. It was revealed that under the influence of NO donors in mitochondria, the conjugation of oxidation and phosphorylation processes increases, ROS generation and free radical damage to these organelles decrease, and the level of adenosine triphosphate (ATP) in tissues during HIR increases [10]. Some data indicate an inhibition of autophagy processes in case of HIR using NO [14]. The presence of NO during reperfusion promotes the accumulation of the factor induced by hypoxia-1 α (HIF-1 α) and the activation of various cytoprotective genes, including hemoxygenase-1 (HO-1) [15].

At the same time, the interaction of NO with ROS generated during reperfusion can lead to the formation of new toxic free radical forms of nitrogen (for example, peroxynitrite), which will increase oxidative stress [6]. It has been shown that with IRP, the effect of iNOS is synergistic for a number of proinflammatory cytokines - TNF- α and interleukin-1 (IL-1), which contribute to the aggravation of reperfusion damage to the liver [16]. In this regard, the ability of NO donors to inhibit the expression of iNOS seems to be very important for HIR [13]. Thus, the use of NO donors (nitroglycerin and sodium nitroprusside) during the early phase of reperfusion has a complex cytoprotective effect in case of HIR.

The influence of hydrogen sulfide donor on the hepatic reperfusion injury

In our experiments, it was found that when using sodium hydrosulfide, an H_2S donor during HIR modulation in rats, an improvement in the parameters of blood oxygen transport, HOA, prooxidant-antioxidant balance and also a number of morphofunctional liver parameters was revealed [17]. It was shown that the use of a hydrogen sulfide donor leads to a decrease in blood activity of ALT and AST at the end of liver reperfusion. At the 120th minute of the reperfusion period, under the influence of NaHS, the p50real index in mixed venous blood decreased, the level of CDs, malondialdehyde, Schiff bases decreased in the liver in relation to animals that were not infused with a hydrogen sulfide donor during HIR. An increase in blood HAO in rats treated with NaHS could be due to an increase in hemoglobin sulfhydrogenation [18].

The shift of ODC to the left under the influence of a hydrogen sulfide donor during liver reperfusion can have a positive effect on the prooxidant-antioxidant state due to an increase in the conjugation of oxidative phosphorylation in mitochondria and a decrease in their generation of ROS. Administration of NaHS to rats was shown to preserve the membrane potential of mitochondria, increase ATP production by them and decrease cytochrome c output from mitochondria to the cytoplasm, as well as restore the function of cerebral cortical neurons in modeling ischemia-reperfusion by short-term 6-minute cardiac arrest [19]. In our experiments, the management of NaHS in HIR contributed to the partial restoration of the activity of succinate dehydrogenase in the liver at the end of reperfusion, which is consistent with the above-described effect of the hydrogen sulfide donor on mitochondrial function. The restoration of acid phosphatase activity in rats treated with NaHS may indicate an improvement in autophagy processes. A decrease in the generation of ROS by mitochondria and an improvement in the mechanisms of intracellular protection contribute to an increase in the level of reduced glutathione, as well as normalization of the content of α -tocopherol and retinol in the liver of rats treated with NaHS during HIR. It was found that the introduction of C57BL6/J mice of a hydrogen sulfide donor - sodium sulfide (Na_2S) 5 minutes before the start of liver reperfusion helps to increase the ratio of reduced and oxidized forms of glutathione, decrease lipoperoxide radicals, increase the expression of thioredoxin, heat shock protein (Hsp90) and apoptosis regulators (bcl-2), which indicates its antioxidant and antiapoptotic effects [20].

It has been established that H_2S has a direct antioxidant effect, comparable to the effects of classical antioxidants - cysteine and glutathione [21]. Thus, in the hypoxanthine/xanthine oxidase system, a dose-dependent suppression of superoxide anion generation occurs at H_2S concentrations from 10^{-9} to 10^{-4} mol [22]. At the same time, hydrogen sulfide quenches free radicals as a chemical reducing agent. In addition, hydrogen sulfide can increase the glutamate-dependent transport of cysteine into the cell and increase the level of reduced glutathione, which is also a mechanism of antioxidant protection of mitochondria and the cell as a whole against ROS [23].

In our experiments, it was shown that the administration of NaHS to rats with HIR reduces venous congestion in the liver, judging by the width of the hepatic sinusoids, which confirms the ability of hydrogen sulfide to improve microcirculation in the liver [17]. It is important to note that in our experiments to study the effects of NaHS in HIR, the total content of nitrate/nitrite in the blood remained below the control, which indicates a NO-independent mechanism of the vasoactive effect of hydrogen sulfide in IRP. It is possible that the vasoactive effect of H_2S is mediated by the endothelial hyperpolarizing factor (EDHF) [24], which explains the absence of an increase in the total nitrate/nitrite content during RTI. It is interesting to note that a number of studies claim that EDHF is H_2S produced by endothelial cystathionine- γ -lyase, the activity of which decreases with oxidative stress [25]. Indeed, after HIR in rats, along with the development of disturbances in the prooxidant - antioxidant balance, we found a decrease in plasma H_2S level in relation to the control, which may be a consequence of oxidative damage to the endothelium, while NaHS infusion helps to restore the hydrogen sulfide content and the prooxidant - antioxidant state [17].

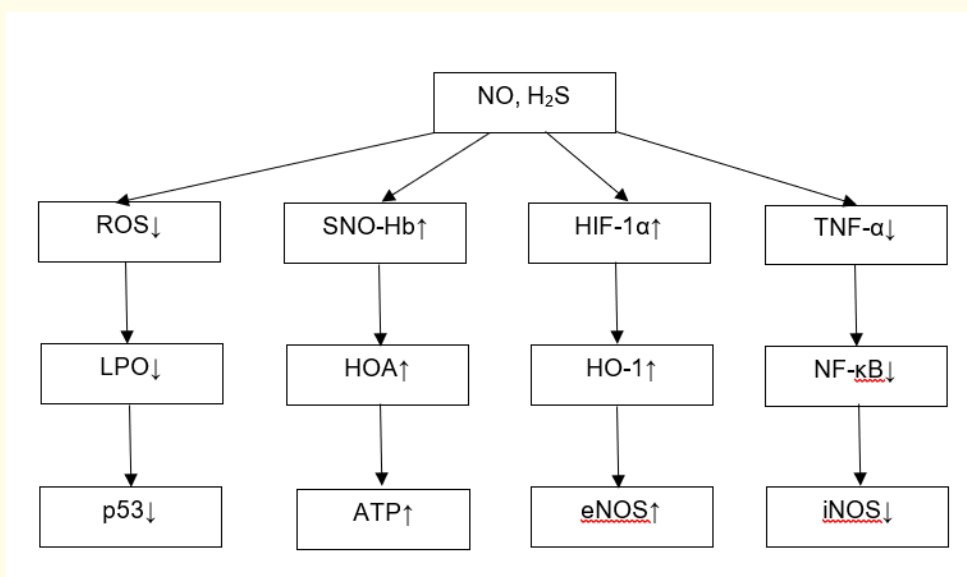


Figure : Possible mechanisms of the protective effect of NO and H2S in ischemia-reperfusion of the liver, where SNO-Hb: S-nitrosogemoglobin; HIF-1 α : Hypoxic Inducible Factor 1 α ; TNF- α : Tumor Necrosis Factor- α ; HO-1: Hemoxygenase-1; NF- κ B: Nuclear Factor- κ B; p53: Transcription Factor p53; eNOS: Endothelial Isoform of NO Synthase; iNOS: Inducible Isoform of NO Synthase.

Conclusion

Thus, the data obtained by us indicate that violations of the blood oxygen transport parameters of the blood occurring during the modeling of the HIR syndrome in experimental animals, a decrease in the HOA, a lack of NO synthase function, a shift in the prooxidant-antioxidant state towards radical formation and the development of oxidative stress, an increase in blood transaminase activity in the reperfusion period, are adjusted by the use of donors of nitrogen monoxide and hydrogen sulfide (Figure). Gasotransmitters exhibit many similar protective mechanisms for ischemia-reperfusion syndrome associated with post-translational modification of proteins. The ability of NO and H₂S to have an additive protective effect in ischemia-reperfusion of the liver due to nitrosylation and sulfhydrogenation looks quite predictable. These data are important for understanding the essence of the processes and pathogenetic foundations of post-ischemic disorders in the liver, as well as the role of gas transmitters in the development of ischemia-reperfusion syndrome. The revealed new properties and protective mechanisms of such compounds as nitroglycerin, sodium nitroprusside, sodium hydrosulfide can be the theoretical basis for the development of new methods for the correction of hepatic reperfusion damage.

Bibliography

1. Zhang Y, *et al.* "Hepatic Ischemic Preconditioning Alleviates Ischemia-Reperfusion Injury by Decreasing TIM4 Expression". *International Journal of Biological Sciences* 14.10 (2018): 1186-1195.
2. Guan LY, *et al.* "Mechanisms of hepatic ischemia-reperfusion injury and protective effects of nitric oxide". *World Journal of Gastrointestinal Surgery* 6.7 (2014): 122-128.
3. Hu XX, *et al.* "The Cardioprotective Effect of Vitamin E (Alpha-Tocopherol) Is Strongly Related to Age and Gender in Mice". *PLoS One* 10.9 (2015): e0137405.
4. Olson KR. "Hydrogen sulfide as an oxygen sensor". *Antioxidants and Redox Signaling* 22.5 (2015): 377-397.
5. Kolluru GK, *et al.* "Gasotransmitter Heterocellular Signaling". *Antioxidants and Redox Signaling* 26.16 (2017): 936-960.
6. Reiniers MJ, *et al.* "Reactive oxygen and nitrogen species in steatotic hepatocytes: a molecular perspective on the pathophysiology of ischemia-reperfusion injury in the fatty liver". *Antioxidants and Redox Signaling* 21.7 (2014): 1119-1142.
7. Khodosovskii MN and Zinchuk VV. "Effect of nitroglycerine on some parameters of the prooxidant-antioxidant balance and functional state of the liver during ischemia/reperfusion". *Bulletin of Experimental Biology and Medicine* 142.6 (2006): 675-678.
8. Khodosovskii MN. "Effect of sodium nitroprusside on the prooxidant-antioxidant system of the rabbit liver under ischemia-reperfusion". *Proceedings of the National Academy of Sciences of Belarus: Medicine series* 5.3 (2008): 23-27.
9. Bibli SI, *et al.* "Nitroglycerin limits infarct size through S-nitrosation of Cyclophilin D: A novel mechanism for an old drug". *Cardiovascular Research* (2018).
10. Abu-Amara M, *et al.* "The nitric oxide pathway - evidence and mechanisms for protection against liver ischaemia reperfusion injury". *Liver International* 32.4 (2012): 531-543.
11. Diamond JM, *et al.* "The relationship between plasma lipid peroxidation products and primary graft dysfunction after lung transplantation is modified by donor smoking and reperfusion hyperoxia". *The Journal of Heart and Lung Transplantation* 35.4 (2016): 500-507.
12. Malte H and Lykkeboe G. "The Bohr/Haldane effect: a model-based uncovering of the full extent of its impact on O₂ delivery to and CO₂ removal from tissues". *Journal of Applied Physiology* 125.3 (2018): 916-922.

13. Yang SL, et al. "Sodium nitroprusside regulates mRNA expressions of LTC₄ synthesis enzymes in hepatic ischemia/reperfusion injury rats via NF-kappaB signaling pathway". *Pharmacology* 80.1 (2007): 11-20.
14. Go KL, et al. "Mitochondrial Dysfunction and Autophagy in Hepatic Ischemia/Reperfusion Injury". *BioMed Research International* (2015): 183469.
15. Zaouali MA, et al. "Hypoxia inducible factor-1alpha accumulation in steatotic liver preservation: role of nitric oxide". *World Journal of Gastroenterology* 16.28 (2010): 3499-3509.
16. Zhang YQ, et al. "New progress in roles of nitric oxide during hepatic ischemia reperfusion injury". *World Journal of Gastroenterology* 23.14 (2017): 2505-2510.
17. Khodosovskii MN. "Uchastie gazotransmitterov v korrektsii reperfuzionnykh povrezhdenii pecheni". Grodno: GrSMU (2017). 212.
18. Kimura H. "Physiological Roles of Hydrogen Sulfide and Polysulfides". *The Handbook of Experimental Pharmacology* 230 (2015): 61-81.
19. Pan H, et al. "Protective and biogenesis effects of sodium hydrosulfide on brain mitochondria after cardiac arrest and resuscitation". *European Journal of Pharmacology* 741 (2014): 74-82.
20. Jha S, et al. "Hydrogen sulfide attenuates hepatic ischemia-reperfusion injury: role of antioxidant and antiapoptotic signaling". *The American Journal of Physiology - Heart and Circulatory Physiology* 295.2 (2008): H801-H806.
21. Li Q and Lancaster JRJr. "Chemical foundations of hydrogen sulfide biology". *Nitric Oxide* 35 (2013): 21-34.
22. Al-Magableh MR, et al. "Hydrogen sulfide protects endothelial nitric oxide function under conditions of acute oxidative stress *In vitro*". *Naunyn-Schmiedeberg's Archives of Pharmacology* 387.1 (2014): 67-74.
23. Kimura Y, et al. "Hydrogen sulfide increases glutathione production and suppresses oxidative stress in mitochondria". *Antioxidants and Redox Signaling* 12.1 (2010): 1-13.
24. Wang M, et al. "Involvement of Hydrogen Sulfide in Endothelium-Derived Relaxing Factor-Mediated Responses in Rat Cerebral Arteries". *The Journal of Vascular Research* 53.3-4 (2016): 172-185.
25. Cheng Z, et al. "Hyperhomocysteinemia potentiates diabetes-impaired EDHF-induced vascular relaxation: Role of insufficient hydrogen sulfide". *Redox Biology* 16 (2018): 215-225.

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