ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

CORM-3 Shows Protective Effect on Warm Hepatic Reperfusion Injuries

Khadasouski MN* and Solyanskaya EN

Grodno State Medical University, Grodno, Belarus

***Corresponding Author:** Khadasouski MN, Department of Pathophysiology, Grodno State Medical University, Grodno, Belarus.

Received: November 09, 2023**; Published:** December 21, 2023

Abstract

Reperfusion injuries of the liver are often encountered in clinical practice during transplantation, resection or trauma of the organ with temporary occlusion of the main vessels of the organ (Pringle maneuver). The purpose of the minireview is to analyze and summarize our own and literature data on the role of carbon monoxide in the development and correction of liver ischemia-reperfusion syndrome in the experiment.

Keywords: *Carbon Monoxide; Oxidative Stress; Liver; Ischemia-Reperfusion*

Introduction

Correction of hepatic reperfusion damage is an urgent problem of modern medicine. Temporary occlusion of the afferent vessels of the liver (Pringle maneuver) is used in the clinic for resections, transplantation, or traumatic injuries of the organ, when it becomes necessary to prevent severe blood loss [1]. Hepatic ischemia-reperfusion (HIR) syndrome is a complex set of pathological reactions, including microcirculation disorders, leukocyte migration, mitochondrial dysfunction, and a surge in reactive oxygen species (ROS) generation, which leads to oxidative stress and the triggering of cell death mechanisms [2]. Thus, the primary absence of transplanted liver function is observed with a frequency of 0.9 to 7.2%, which in 50% of cases leads to hospital mortality of recipients [3,4]. The use of antioxidants - ROS quenchers, such as α-tocopherol, in ischemia-reperfusion syndrome is not always effective [5]. 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. In full measure, these compounds include the class of gas transmitters of endogenously synthesized gases that can interact with both reactive oxygen species (ROS) and hemoproteins, modulating their properties and the processes of oxygen consumption by tissues [6,7]. The purpose of this work is to analyze the literature and our own data on the role of the gas transmitter CO in the mechanisms of liver protection in the ischemia-reperfusion syndrome.

The use of carbon monoxide donors for the correction of reperfusion liver damage

Carbon monoxide - CO (carbon monoxide) has long been considered an exclusively exogenous toxic substance. However, in the 1960s, it was found that CO is formed in the human body as a result of the breakdown of hemoglobin under the influence of the hemeoxygenase enzyme, which promotes the breakdown of heme into biliverdin, iron (II), and CO [8]. Until the 1990s, carbon monoxide was considered a by-product of heme breakdown in the heme oxygenase reaction, but then its neurotransmitter properties were established, which,

like nitrogen monoxide, are realized through the guanylate cyclase mechanism [9]. Given the guanylate cyclase mechanism of action of CO, its vasoactive properties were soon revealed [10], after which a period of intensive study of the role of carbon monoxide in the development of cardiovascular pathology began [11]. It has been established that CO is able to reduce platelet aggregation, activate fibrinolysis, suppress the proliferation of smooth muscle cells, fibroblasts, and T-lymphocytes, inhibit apoptosis and the synthesis of pro-inflammatory cytokines, and reduce the expression of intercellular adhesion molecules [12,13]. The authors showed the protective effect of CO in such pathologies as atherosclerosis, coronary heart disease, hypertension, ischemia-reperfusion syndrome.

It has been shown that CO donors during HIR can reduce the activity of caspases, pro-inflammatory cytokines, and the expression of intercellular adhesion molecules on endothelial cells, which can reduce the severity of reperfusion injuries [14]. At the same time, endogenous production of CO is accompanied by the formation of equimolar concentrations of free iron (II), which under conditions of oxidative stress is a powerful prooxidant factor [15]. Activation of heme oxygenase during HIR is not exclusively a cytoprotective or cytotoxic mechanism for tissues, which leaves many questions about the role of CO in this pathology [16].

In our experiments, the use of a carbon monoxide donor-tricarbonylchloro(glycinate)ruthenium(II) (CORM-3) in rats contributed to a decrease in ALT activity by 45.3% ($p < 0.01$) and AST by 45.2% ($p < 0.001$), as well as an increase in blood hemoglobin oxygen affinity (HOA) in mixed venous blood at the end of reperfusion [17]. Thus, at the 120th minute of liver reperfusion, the p50real index of mixed venous blood decreased by 14.2% ($p < 0.05$) in relation to animals without CORM-3. At the same time, in rats treated with a CO donor, an improvement in the parameters of the prooxidant-antioxidant state was observed: a decrease in the level of conjugated dienes (CD) by 55.3% ($p < 0.001$), Schiff bases (SB) by 58.9% ($p < 0.001$), an increase in the content of α-tocopherol by 9.0% ($p < 0.01$), 20.1% retinol ($p < 0.001$) in blood at the end of reperfusion. The total content of nitrate/nitrite in the blood of animals treated with CORM-3 did not differ from the control, which indicates an improvement in the NO-synthase function of the endothelium. It is possible that the use of a CO donor during ischemia-reperfusion leads to the stabilization of mitochondrial membranes and a decrease in cell death by apoptosis mechanisms [18]. It was shown in [19] that the use of small doses of CORM-3 (from 1 to 20 μmol) significantly increases the efficiency of tissue respiration and reduces the production of H_2O_2 by mitochondrial complex II. These results are consistent with the data obtained in our study on changes in the activity of succinate dehydrogenase and dihydronicotinamide adenine dinucleotide dehydrogenase in the liver at the end of the reperfusion period, which indicates an improvement in electron transport in the mitochondrial respiratory chain and activation of the tricarboxylic acid cycle under the influence of small doses of CO. On the other hand, carbon monoxide can reduce the expression of pro-inflammatory cytokines (TNF-α, IL-1, etc.), which reduces leukocyte migration and the degree of oxidative stress in the liver during reperfusion [20]. Direct antioxidant effects of carbon monoxide cannot be ruled out when using CORM-3 in experimental animals [21].

The role of carbon monoxide in the mechanisms of liver protection by hypoxic preconditioning

An increase in tissue resistance to hypoxia is an important mechanism for protecting organs from oxidative stress during ischemia and subsequent reperfusion. In experiments on animals that were previously subjected to general hypoxia of the body (hypoxic preconditioning - HP), the researchers obtained a protective effect, expressed in a decrease in the activity of transaminases and blood cytokines, a decrease in the activity of LPO processes and morphological disorders during HIR [22,23]. It is known that changes in the oxygen-binding properties of blood play an important role in the body's adaptation to hypoxia [24]. Since the issue of the effect of HP on the oxygen-binding properties of blood during HIR was not studied by the authors, we studied the effect of this method on the state of the mechanisms of oxygen transport in the blood and oxidative damage to the liver in rabbits. It has been established that HP in rabbits contributes to an increase in blood glucose levels, improves the parameters of the acid-base balance and prevents the development of oxidative stress, which corrects the functional state of the liver during ischemia-reperfusion [25].

It was found that HP in rabbits led to less metabolic disorders in the liver, possibly due to a greater conjugation of oxidative phosphorylation processes, i.e. an increase in the efficiency of tissue respiration reduces electron leakage and the intensity of oxidative stress during reperfusion [26]. In addition, HP promotes an increase in the expression of transcription factors such as HIF-1α, c-Fos, NF-κB, etc. which leads to the activation of genes that produce pro-adaptive proteins, in particular, peptide antioxidants, anti-apoptotic proteins of the bcl-2 family, families of stress-proteins HSP, erythropoietin, and others involved in the processes of cell survival under damaging effects [27]. An increase in blood HOA with a simultaneous decrease in pO_2 in it during liver reperfusion may be one of the mechanisms preventing the degradation of HIF-1α and the induction of many protective effects during ischemia-reperfusion, such as anti-inflammatory, antiapoptotic, antioxidant, and metabolic [28]. It is known that the interaction of CO with hemoglobin leads to the formation of carboxyhemoglobin and an increase in blood glucose levels. Since HP led to an increase in blood glucose levels, we studied the role of this gas transmitter in the mechanism of the protective effect of hypoxic preconditioning.

It has been established that inhibition of hemoxigenase-1 (HO-1) in rabbits reduces the protective effect of HP during HIR [29]. Thus, when rabbits with HP were given the HO-1 inhibitor zinc protoporphyrin-9 (ZnPP) before HIR, the p50 value of hepatic venous blood increased by 24.6% at the end of reperfusion ($p < 0.01$), and an increase in the content of CD by 145.5 was observed in the liver. % ($p < 0.001$), SB - by 142.9% ($p < 0.001$), decrease in the concentration of α-tocopherol - by 14.5% ($p < 0.01$) and retinol - by 18.5% ($p < 0.001$), in relation to animals with HP only. The results obtained are consistent with the data of [22], which showed a decrease in the protective effect of HP during HIR under conditions of inhibition of HO-1 with ZnPP. The decrease in blood HOA revealed in our experiments during liver reperfusion under conditions of HO-1 inhibition in rats with HP to a certain extent explains the increase in oxidative damage and is consistent with a significant violation of the redox state of mitochondria in this pathology [30]. It has been shown that an increase in the permeability of mitochondrial membranes under the influence of oxidative stress during HIR leads to the death of hepatocytes by necrosis or apoptosis [31]. It is known that ischemia/hypoxia is the main condition preventing the degradation of HIF-1α, which triggers many protective mechanisms during ischemia-reperfusion [32]. Obviously, a decrease in blood HOA and an increase in the O_2 flux in the tissues contributed to the acceleration of HIF-1α hydroxylation in the reperfusion period. The latter could neutralize HIF-1α protection pathways independent of HO-1, which led to reperfusion damage to the liver in experimental animals. It is known that the ability of HO-1 to stabilize the work of mitochondria and prevent inflammation and apoptosis during HIR can be realized due to the antioxidant effects of both CO and biliverdin [33]. In order to eliminate the antioxidant effects of bilirubin or biliverdin during HP-induced activation of HO-1, CO donor infusion (CORM-3) was performed against the background of HO-1 inhibition.

In our studies, it was found that in animals treated with ZnPP and CORM-3, the previously established protective effect of HP was restored during HIR [29]. Thus, the p50 index of hepatic venous blood decreased by 18.0% at the end of reperfusion ($p < 0.05$), a decrease in CD content was observed in the liver by 60.2% ($p < 0.001$), SB - by 56.3% ($p < 0.001$), and increase in the concentration of α-tocopherol - by 16.4% ($p < 0.01$) and retinol - by 19.6% ($p < 0.05$), in relation to animals without CORM-3. An increase HOA may be a factor of limitation of LPO and oxidative damage (judging by the change in CD and SB), as well as one of the mechanisms preventing the ubiquitinization of HIF-1α, which activity can cause the induction of such protective anti-inflammatory, anti-apoptotic and antioxidant effects during HIR.

It has been shown that HIF-1α is able to improve the function of hepatocyte mitochondria and reduce ROS production during HIR [34]. It is also known that CO is a powerful cell protector in cardiovascular diseases, sepsis and shock, organ transplantation, and acute lesions of the lungs, kidneys, and liver [21]. CO in small doses can exhibit antioxidant activity by activating the genes of antioxidant enzymes [35]. Analysis of data on the role of CO in the correction of reperfusion liver injuries revealed their similar protective effects in HIR.

It is known that CO in ischemia-reperfusion syndrome can reduce the expression of IL-1, intercellular adhesion molecules, iNOS, and cyclooxygenase-2 [33]. CO has been shown to increase the production of heat shock proteins (Hsp70), Nrf2 expression, and superoxide

dismutase activity in acute kidney injury [36]. Taking into account the obtained data, we can conclude that in order to achieve possible antioxidant effects of CORM-3, it is preferable to use its exogenous donors, which are classified as promising therapeutic agents for pathology accompanied by oxidative stress, rather than using endogenous HO-1 inducers, risking aggravating the condition with prooxidant effects. free iron [37]. The involvement of CO in the modulation of autophagy mechanisms in HIR cannot be ruled out [33].

Conclusion

Thus, our data indicate that disturbances in blood oxygen transport parameters, a decrease in blood HOA, a deficiency in NO-synthase function, a shift in the prooxidant-antioxidant state towards radical formation and oxidative stress. Increase in the activity of blood transaminases in reperfusion period are corrected by the use of a carbon monoxide donor. This gasotransmitter has many protective mechanisms in ischemia-reperfusion syndrome associated with antioxidant, anti-inflammatory and anti-apoptotic effects. We also found that the protective effect of hypoxic preconditioning is largely mediated by the induction of endogenous CO synthesis. The revealed new properties and mechanisms of the protective effect of CORM-3 can serve as a theoretical basis for the development of new methods for correcting reperfusion liver 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. Rummo OO. "7 years of liver transplantation in the Republic of Belarus". *Russian Journal of Transplantology and Artificial Organs* 17.2 (2015): 100-104.
4. Bolondi G., *et al*. "Predictive factors of short-term outcome after liver transplantation". *World Journal of Gastroenterology* 22.26 (2016): 5936-5949.
5. 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.
6. Olson KR. "Hydrogen sulfide as an oxygen sensor". *Antioxidants and Redox Signaling* 22.5 (2015): 377-397.
7. Kolluru GK., *et al*. "Gasotransmitter heterocellular signaling". *Antioxidants and Redox Signaling* 26.16 (2017): 936-960.
8. Coburn RF., *et al*. "Endogenous carbon monoxide production in man". *Journal of Clinical Investigation* 42.7 (1963): 1172-1178.
9. Dawson TM and Snyder SH. "Gases as biological messengers: nitric oxide and carbon monoxide in the brain". *Journal of Neuroscience* 14.9 (1994): 5147-5159.
10. Suematsu M., *et al*. "Carbon monoxide: an endogenous modulator of sinusoidal tone in the perfused rat liver". *Journal of Clinical Investigation* 96.5 (1995): 2431-2437.
11. Otterbein LE., *et al*. "Heme oxygenase-1 and carbon monoxide in the heart: the balancing act between danger signaling and pro-survival". *Circulation Research* 118.12 (2016): 1940-1959.
12. Olas B. "Carbon monoxide is not always a poison gas for human organism: Physiological and pharmacological features of CO". *Chemico-Biological Interactions* 222 (2014): 37-43.

13. Ayer A., *et al*. "Heme oxygenases in cardiovascular health and disease". *Physiological Reviews* 96.4 (2016): 1449-1508.

14. Wei Y., *et al*. "Carbon monoxide-releasing molecule-2 (CORM-2) attenuates acute hepatic ischemia reperfusion injury in rats". *BMC Gastroenterology* 10 (2010): 42.

15. Niu X., *et al*. "Iron-induced oxidative rat liver injury after non-heart-beating warm ischemia is mediated by tumor necrosis factor α and prevented by deferoxamine". *Liver Transplantation* 20.8 (2014): 904-911.

16. Bauer M and Bauer I. "Heme oxygenase-1: redox regulation and role in the hepatic response to oxidative stress". *Antioxidants and Redox Signaling* 4.5 (2002): 749-758.

17. Khodosovsky MN. "Involvement of gasotransmitters in the correction of liver reperfusion injury". Grodno: GrSMU (2017): 212.

18. Sener A., *et al*. "Carbon monoxide releasing molecules inhibit cell death resulting from renal transplantation related stress". *Journal of Urology* 190.2 (2013): 772-778.

19. Lo Iacono L., *et al*. "A carbon monoxide-releasing molecule (CORM-3) uncouples mitochondrial respiration and modulates the production of reactive oxygen species". *Free Radical Biology and Medicine* 50.11 (2011): 1556-1564.

20. Kaizu T., *et al*. "Protection of transplant-induced hepatic ischemia/reperfusion injury with carbon monoxide via MEK/ERK1/2 pathway downregulation". *American Journal of Physiology. Gastrointestinal and Liver Physiology* 294.1 (2008): G236-G244.

21. Bauer I and Pannen BH. "Bench-to-bedside review: Carbon monoxide--from mitochondrial poisoning to therapeutic use". *Critical Care* 13.4 (2009): 220.

22. Lai IR., *et al*. "The protective role of heme oxygenase-1 on the liver after hypoxic preconditioning in rats". *Transplantation* 77.7 (2004): 1004-1008.

23. Choukèr A., *et al*. "*In vivo* hypoxic preconditioning protects from warm liver ischemia-reperfusion injury through the adenosine A2B receptor". *Transplantation* 94.9 (2012): 894-902.

24. Simonson TS., *et al*. "Increased blood-oxygen binding affinity in Tibetan and Han Chinese residents at 4200 m". *Experimental Physiology* 99.12 (2014): 1624-1635.

25. Khodosovsky MN. "Effects of hypoxic preconditioning on the mechanisms of oxygen transport and oxidative damage during hepatic ischemia-reperfusion syndrome in rabbits". *International Journal of Physiology and Pathophysiology* 8.2 (2017): 165-175.

26. Hummitzsch L., *et al*. "Culture media from hypoxia conditioned endothelial cells protect human intestinal cells from hypoxia/reoxygenation injury". *Experimental Cell Research* 322.1 (2014): 62-70.

27. Samoilov MO., *et al*. "Signal molecular and hormonal mechanisms of formation of the hypoxic preconditioning protective effect". *Patologicheskaia Fiziologiia I Eksperimental'naia Terapiia* 56.3 (2012): 3-10.

28. Akhtar MZ., *et al*. "The role of hypoxia-inducible factors in organ donation and transplantation: the current perspective and future opportunities". *American Journal of Transplantation* 14.7 (2014): 1481-1487.

29. Khodosovsky MN. "Contribution of carbon monoxide to correction of hepatic reperfusion damages by means of hypoxic preconditioning method". *Journal of the Grodno State Medical University* 15.3 (2017): 324-328.

30. Go KL., *et al*. "Mitochondrial dysfunction and autophagy in hepatic ischemia/reperfusion injury". *BioMed Research International* (2015): 183469.

31. Kim JS., *et al*. "Mitochondrial permeability transition in rat hepatocytes after anoxia/reoxygenation: role of Ca^{2+}-dependent mitochondrial formation of reactive oxygen species". *American Journal of Physiology. Gastrointestinal and Liver Physiology* 302.7 (2012): G723-G731.

32. Schneider M., *et al*. "Loss or silencing of the PHD1 prolyl hydroxylase protects livers of mice against ischemia/reperfusion injury". *Gastroenterology* 138.3 (2010): 1143-1154.

33. Liu B and Qian JM. "Cytoprotective role of heme oxygenase-1 in liver ischemia reperfusion injury". *International Journal of Clinical and Experimental Medicine* 8.11 (2015): 19867-19873.

34. Zhong Z., *et al*. "Activation of the oxygen-sensing signal cascade prevents mitochondrial injury after mouse liver ischemia-reperfusion". *American Journal of Physiology. Gastrointestinal and Liver Physiology* 295.4 (2008): G823-G832.

35. Kim HJ., *et al*. "CO/HO-1 Induces NQO-1 Expression via Nrf2 Activation". *Immune Network* 11.6 (2011): 376-382.

36. Bolisetty S., *et al*. "Heme oxygenase 1 as a therapeutic target in acute kidney injury". *American Journal of Kidney Diseases* 69.4 (2017): 531-545.

37. Cebová M., *et al*. "Cardiovascular effects of gasotransmitter donors". *Physiological Research* 65.3 (2016): S291-S307.

Volume 11 Issue 1 January 2024