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Review Article

Carbon Monoxide Participation in Hepatic Ischemia-Reperfusion Syndrome

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Abstract

Hepatic reperfusion syndrome is frequent clinical complication of liver transplantation, resection or trauma, when afferent vascular clamping is used. The review is aimed to analyze the literature and our own data about the role of carbon monoxide in the liver protection during ischemia-reperfusion syndrome. A PubMed search was conducted using the MeSH database, "Carbon monoxide", "Liver" AND "ischemia-reperfusion" were the combined MeSH headings; e-LIBRARY was also searched using the same terms. 52 relevant studies were found. The pathophysiology and protective mechanisms of carbon monoxide during hepatic ischemia-reperfusion are discussed.

Keywords: *Carbon Monoxide; Liver; Ischemia-Reperfusion; Blood Oxygen Transport; Pro-Antioxidant Balance*

Abbreviations

CO: Carbon Monoxide; CORM-3: Carbon Monoxide-Releasing Molecule-3; HbCO: Carboxyhemoglobin; HIF-1α: Hypoxic Inducible Factor 1α; HIR: Hepatic Ischemia-Reperfusion; HO-1: Hemoxygenase-1; HOA: Hemoglobin Oxygen Affinity; HP: Hypoxic Preconditioning; TNF-α: Tumor Necrosis Factor-α; IL-1: Interleukin-1; ZnPP: Zinc Protoporphyrin-9

Introduction

The search for new approaches to the correction of liver reperfusion injuries is an urgent problem of modern medicine. Temporary occlusion of the afferent vessels of the liver is used in the clinic for resections, transplantation, or traumatic organ injuries [1]. Hepatic ischemia-reperfusion (HIR) syndrome is a complex set of pathological reactions, including microcirculation disorders, leukocyte migration, mitochondrial dysfunction, and a surge in the generation of reactive oxygen species, which leads to oxidative stress and the triggering of cell death mechanisms [2]. Thus, early dysfunction of the hepatic transplant, the main mechanism of which is considered to be reperfusion injury, is a frequent complication of this operation and according to a number of authors, amounts to 9.6 to 31.9% of cases [3,4]. None of the existing approaches provide guaranteed protection against postischemic disorders [5]. Correction of reperfusion injuries of the liver requires a complex effect on many signaling mechanisms responsible for the transport and use of oxygen after ischemia. The purpose of this work is to analyze the literature and our own data on the role of the CO in the mechanisms of liver protection during ischemia-reperfusion syndrome.

Involvement of carbon monoxide in the regulation of pro-antioxidant balance during hepatic ischemia-reperfusion

Carbon monoxide (CO) is formed in the human body as a result of the breakdown of hemoglobin under the influence of the enzyme hemoxygenase-1 (HO-1), which promotes the breakdown of heme into biliverdin, iron (II) and CO [6]. Until the 90s, carbon monoxide was considered a byproduct of the hemoxygenase reaction, but then its neurotransmitter properties were established, which are realized,

as in nitrogen monoxide, through the guanylate cyclase mechanism [7]. Taking into account the guanylate cyclase mechanism of CO action, its vasoactive properties were soon revealed [8], after which a period of intensive study of the role of carbon monoxide in the development of cardiovascular pathology began [9]. It was found that CO is able to reduce platelet aggregation, activate fibrinolysis, suppress the proliferation of smooth muscle cells, fibroblasts and T-lymphocytes, inhibit apoptosis and synthesis of pro-inflammatory cytokines, reduce the expression of intercellular adhesion molecules [10,11].

It was revealed that CO donors in HIR can reduce the activity of caspases, proinflammatory cytokines and the expression of intercellular adhesion molecules on endothelial cells, which can reduce the severity of reperfusion injuries [12]. 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 [13]. Activation of HO-1 during HIR is not an exclusively cytoprotective or cytotoxic mechanism for tissues, which leaves many questions about the role of CO in this pathology [14]. In our experiments, the use of the donor carbon monoxide-tricarbonylchloro(glycinate)ruthenium(II) (CORM-3) in rats contributed to a decrease in ALT activity by 45.3% ($p < 0.01$) and AST activity 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 [15]. Thus, at the 120th minute of liver reperfusion, the $p50_{real}$ index of mixed venous blood decreased by 14.2% ($p < 0.05$) in relation to animals without CORM-3. At the same time, the rats receiving the CO donor showed an improvement in the parameters of the prooxidant-antioxidant state: a decrease in the level of conjugated dienes by 55.3% ($p < 0.001$), Schiff bases by 58.9% ($p < 0.001$), an increase in the content of α-tocopherol by 9.0% ($p < 0.01$), retinol by 20.1% ($p < 0.001$) in the blood at the end of reperfusion. The total content of nitrate/nitrites in the blood in animals treated with CORM-3 did not differ from the basal level, which indicates an improvement in the NO-synthase function of the endothelium.

It is possible that the use of a CO donor in ischemia-reperfusion leads to stabilization of mitochondrial membranes and a decrease in cell death by the mechanisms of apoptosis [16]. It was shown in [17] that the use of small doses of CORM-3 (from 1 to 20 μmol) significantly increases the efficiency of tissue respiration and helps to reduce the production of H_2O_2 by complex II of mitochondria. These results are consistent with the data obtained in our study on changes in the activity of succinate dehydrogenase and NADH-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 Krebs cycle under the influence of small doses of CO. On the other hand, carbon monoxide can reduce the expression of proinflammatory cytokines (TNF-α, IL-1, etc.), leukocyte migration and the degree of oxidative stress in the liver during reperfusion [18]. Direct antioxidant effects of carbon monoxide cannot be ruled out when using CORM-3 in experimental animals [19].

Participation of carbon monoxide in protective effect of hypoxic preconditioning during liver ischemia-reperfusion

Increasing tissue resistance to hypoxia is an important mechanism for protecting organs from oxidative stress during ischemia and subsequent reperfusion. In experiments on rabbits, which were previously subjected to general hypoxia of the body (hypoxic preconditioning - HP), it was found that HP promotes an increase in blood HOA, improves the parameters of acid-base balance and prevents the development of oxidative stress, corrects the functional state of the liver during ischemia-reperfusion [20]. It was revealed that HP in rabbits led to less metabolic disturbances in the liver, possibly due to a greater conjugation of oxidative phosphorylation processes, i.e. increasing the efficiency of tissue respiration reduces electron leakage and the intensity of oxidative stress during reperfusion [21]. An increase in blood HOA with a simultaneous decrease in pO_2 during liver reperfusion may be one of the mechanisms of preventing the degradation of hypoxia inducible factor-1α (HIF-1α) and the induction of many protective effects during ischemia-reperfusion, such as anti-inflammatory, anti-apoptotic, antioxidant, and metabolic influences [22].

It is known that the interaction of CO with hemoglobin leads to the formation of carboxyhemoglobin and an increase HOA in the blood. Since HP led to an increase in blood HOA, we studied the role of this gas transmitter in the mechanism of the protective effect of hypoxic preconditioning. It was found that the inhibition of HO-1 in rabbits reduces the protective effect of HP on HIR [23]. Thus, when rabbits with HP were administered the HO-1 inhibitor zinc protoporphyrin-9 (ZnPP) before HIR, the p50 index of hepatic venous blood increased

at the end of reperfusion by 24.6% ($p < 0.01$); in the liver we found increasing conjugated dienes content by 145.5% ($p < 0.001$), Schiff bases level - by 142.9% ($p < 0.001$) and decreasing in the concentration of α-tocopherol - by 14.5% ($p < 0.01$) and retinol - by 18.5% ($p < 0,01$), in relation to animals with HP without ZnPP.

The decrease in blood HOA detected in our experiments in rabbits with HP and HO-1 inhibition during HIR can explain the intensification of oxidative stress and is consistent with a significant violation of the mitochondrial redox state in this pathology [24]. 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 [25]. It is known that ischemia/hypoxia is the main condition preventing the degradation of HIF-1α, which triggers many defense mechanisms during ischemia-reperfusion [22]. It is obvious that a decrease in blood HOA and an increase in the O_2 flux in the tissue promoted the acceleration of HIF-1α hydroxylation in the reperfusion period. The latter could neutralize the pathways of HIF-1α protection independent of HO-1, which led to reperfusion damage to the liver in experimental animals.

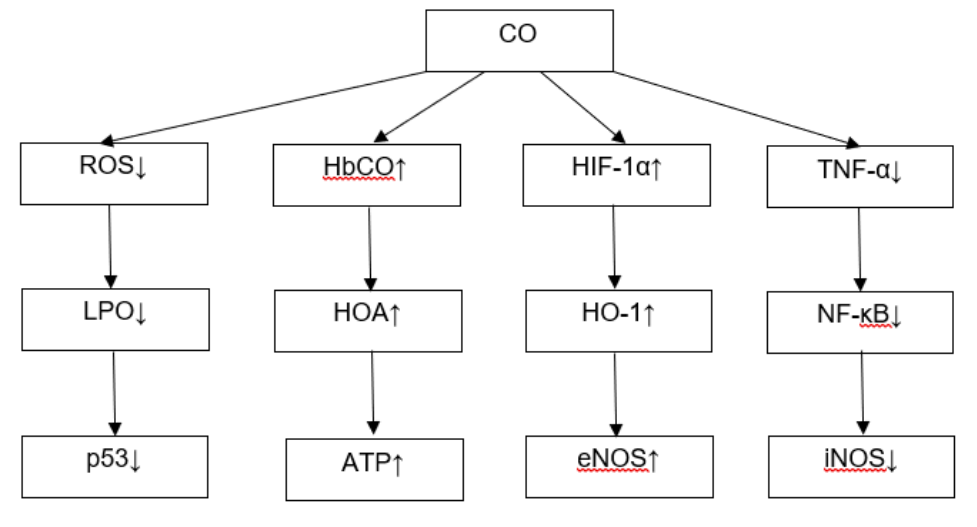

Figure: *Possible mechanisms of the protective effect carbon monoxide (CO) in ischemia-reperfusion of the liver, where HbCO: Carboxyhemoglobin; HIF-1α: Hypoxic Inducible Factor 1α, TNF-α: Tumor Necrosis Factor-α; HO-1: Hemoxygenase-1; NF-κB: Nuclear Factor-κB; p53: Transcription Factor p53; eNOS: Endothelial Isoform of NO Synthase; iNOS: Inducible Isoform of NO Synthase.*

Conclusion

Thus, our data indicate that the disturbances in blood oxygen transport parameters, a decrease in HOA, an insufficiency of the NO-synthase function, a shift in the prooxidant-antioxidant state towards radical formation and the development of oxidative stress, an increase in the activity of reperfusion period, corrected by the use of a carbon monoxide donor (CORM-3). Gasotransmitter CO has many mechanisms of protective effect in ischemia-reperfusion syndrome associated with antioxidant, anti-inflammatory and anti-apoptotic effects (Figure). 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 CO can serve as a theoretical basis for the development of new approaches to the correction of liver reperfusion injuries. Future studies should answer for the question about clinical safety of carbon monoxide compounds and possibilities to activate the endogenous mechanisms of the production of this gasotransmitter during hepatic ischemia-reperfusion syndrome.

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