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Mini Review

Hemoglobin Influence on the Tissue Redox-State During Hepatic Ischemia-Reperfusion

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Abstract

Oxidative stress is an important mechanism of hepatocyte damage in ischemia-reperfusion syndrome of the liver. Hemoglobin is not only a powerful factor in maintaining homeostatic constants, such as an indicator of acidity, but is also able to participate in the regulation of prooxidant-antioxidant balance. In this article we analyzed literature and own data about participation of hemoglobin and blood oxygen-binding properties in the correction of oxidative liver damage during ischemia-reperfusion.

Keywords: *Hemoglobin; Oxidative Stress; Liver; Ischemia-Reperfusion; Nitric Monoxide*

Introduction

Oxidative stress is an important mechanism of hepatocyte damage in liver ischemia-reperfusion syndrome [1]. Reactive oxygen species (ROS) are produced by tissues during ischemia; however, after reperfusion, their generation sharply increases. Hydroxyl radical (HO*-), superoxide anion-radical (O_2^{*-}) and hydrogen hydroperoxide (H_2O_2) contribute to mitochondrial dysfunction, chemotaxis, lipid peroxidation (LPO), disintegration of proteins and cell membranes. In addition, ROS can cause damage and dysfunction of the endothelium, disrupting the processes of microcirculation in the liver after ischemia [2]. During ischemia, the breakdown of adenosine-3-phosphate (ATP) leads to the accumulation of hypoxanthine. Simultaneously, xanthine dehydrogenase is converted into xanthine oxidase, which decomposes hypoxanthine into O_2^{*-}, H_2O_2 and uric acid salt under reoxygenation conditions. Therefore, liver reperfusion inevitably leads to oxidative stress.

Hemoglobin as regulator of oxidative stress

Hemoglobin is not only a powerful factor in maintaining homeostatic blood constants, such as acidity (pH), but is also able to participate in the regulation of the prooxidant-antioxidant balance [3]. Thus, the formation of intermediate oxyferryl (Fe^{4+}=O) or peroxyferryl (Por*+–Fe^{4+}=O) hemoprotein forms with the participation of H_2O_2 leads to the antioxidant activity of hemoglobin (formula 1). However, at a high PO_2, the oxyhemoglobin bond is protonated, which can lead to the oxidation of heme to the trivalent form and the release of the peroxide radical (*OOH) (formula 2). In addition, the interaction of Por-Fe^{4+}=O with H_2O_2 can become a source of O_2^{*-} [4].

Por-Fe^{3+} + H_2O_2 → Por-Fe^{4+}=O + H_2O (1)

Fe^{2+}- -O=O + H^+ → Fe^{3+} + *OOH (2).

An important aspect of erythrocyte signaling functions is the ability of hemoglobin to interact with nitric monoxide (NO). NO can easily diffuse across the erythrocyte membrane and bind to heme, forming nitrosylhemoglobin (Hb-Fe(II)NO), or interact with SH groups, forming nitrosohemoglobin (SNO-Hb). These hemoglobin derivatives can serve as an alternative source of NO in the vascular system in case

of its deficiency [5]. SNO-Hb and Hb-Fe(II)NO are capable of influencing the hemoglobin affinity for oxygen (HOA) of the blood, and are also involved in the formation of the endogenous NO pool. Thus, as a result of the interaction of hemoglobin with NO, both the conditions for oxygen delivery to tissues and the ratio of vasoconstrictors and vasodilators may change, which may have therapeutic significance in correcting the ischemia-reperfusion syndrome. At the same time, elevated levels of NO in combination with oxidative stress can lead to the formation of peroxynitrite and have a cytotoxic effect on hepatocytes during ischemia-reperfusion [3,5]. The need to maintain a delicate balance between the damaging and protective sides of the action of NO requires a comprehensive study of the effect of NO donors on the parameters of the blood oxygen transport (BOT) function and the prooxidant-antioxidant balance during ischemia-reperfusion of the liver.

Effects of NO donors on hemoglobin and tissue redox state

It has been established that modeling of liver ischemia-reperfusion in rabbits leads to a significant deterioration in BOT, the prooxidant-antioxidant state, and an increase in the level of biochemical markers of hepatocyte damage (ALT and AST), while the introduction of nitroglycerin significantly improved the studied parameters [6]. It is interesting to note that at the end of the reperfusion period in the hepatic and mixed venous blood, the p50real index in rabbits increased relative to the initial levels by 29.9% ($p < 0.001$) and 29.4% ($p < 0.001$), respectively, indicating a decrease in Blood SGC. These changes in BOT at the 120th minute of reperfusion were accompanied by an increase in the level of conjugated dienes (CD), malondialdehyde (MDA) and Schiff bases (SB) in liver tissues by 120.2% ($p < 0.001$), 101.1% ($p < 0.001$) and 212.0% ($p < 0.001$), respectively, reflecting the activation of free radical LPO processes.

The administration of nitroglycerin to rabbits at a dose of 1.5 μg/kg 5 min before the start of the reperfusion period in the liver led to a decrease in the p50 index at the end of reperfusion in the hepatic and mixed venous blood decreased by 15.6% ($p < 0.01$) and 11.9% ($p < 0.05$) compared to animals that did not receive nitroglycerin, respectively. An increase in HOA the end of reperfusion in animals treated with nitroglycerin was accompanied by a decrease in CD, MDA and SB in the liver in relation to rabbits in which liver ischemia-reperfusion was modeled without the drug, by 44.6% ($p < 0.001$), 42.0% ($p < 0.01$) and 64.1% ($p < 0.001$), respectively. In addition, the administration of nitroglycerin to rabbits reduced the activity of ALT and AST in mixed venous blood at the end of reperfusion by 42.0% ($p < 0.001$) and 27.1% ($p < 0.05$), respectively, in relation to animals without the drug.

Similar results were obtained using sodium nitroprusside at a dose of 10 μmol/kg in rabbits with liver ischemia-reperfusion. The introduction of this drug to experimental animals led to a decrease in p50, the activity of ALT, AST in the blood and lipid peroxidation products in the blood and liver, as well as an improvement in the parameters of the antioxidant defense (α-tocopherol, catalase activity) of the organ at the end of the reperfusion period. In animals treated with NO donors, the total content of nitrate/nitrite increased in the blood during ischemia-reperfusion of the liver. Perhaps, along with the known effects of NO during liver reperfusion, such as a decrease in the expression of the p53 gene and pro-inflammatory cytokines - intelukin-1, tumor necrosis factor-α [7], nitric oxide is involved in the modification of the oxygen-binding properties of hemoglobin by combining with its SH-groups and forming SNO-Hb, which increases blood glucose levels in experiments with nitroglycerin and sodium nitroprusside.

Since an increasing of HOA in blood usually leads to a decrease in oxygen delivery to tissues, modification of hemoglobin in SNO-Hb is able to regulate the redox state of tissues, which apparently results in a decrease in oxidative stress during reperfusion. This assumption is consistent with the fact of the protective effect of inhibition of oxidation processes in the respiratory chain of mitochondria with the help of NO donors, which reduces the production of ROS during liver reperfusion [2]. In addition, in the blood circulation system, most of the NO passes into erythrocytes, diffusing even against the concentration gradient [8]. Due to the reversibility of the SNO-Hb formation reaction, the latter can act as NO donor in tissues, improving microcirculation processes and the balance between vasoconstrictors and vasodilators after ischemia [9].

Conclusion

The change in the oxygen-binding properties of hemoglobin when using NO donors is an important mechanism for regulating the redox state of tissues in modeling the ischemia-reperfusion syndrome of the liver, which improves the parameters of the prooxidant-antioxidant balance and biochemical markers of hepatocyte damage (ALT and AST) in this pathology.

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