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Research Article

# Role of Kupfer Cells in the Endothelium-Dependent Mechanisms of Liver Reperfusion Injury

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## Abstract

The prooxidant-antioxidant balance during liver ischemia-reperfusion in rats was investigated after administration of a Kupffer cell blocker - gadolinium (III) chloride - and/or NO synthase inhibitor - L-NAME. It was detected, that Kupffer cells potentiate endothelial dysfunction by activating free radical processes and disrupt the production of nitrogen monoxide during liver ischemia-reperfusion.

***Keywords:*** *Kupffer Cells; Nitrogen Monoxide (NO); Hepatic Ischemia-Reperfusion (HIR)*

## Introduction

Hepatic ischemia-reperfusion (HIR) is common in surgical practice, especially in organ transplantation. Available data on the role of Kupffer cells in the development of endothelial dysfunction in HIR are contradictory. It has been established that activation of these cells during ischemia-reperfusion can increase liver damage, potentiating the inflammatory process and microcirculatory disorders [3]. At the same time, a number of studies have shown that Kupffer cells can have a protective effect during liver reperfusion [2,5]. The role of nitrogen monoxide (NO) in the development of liver reperfusion injury remains controversial. NO, as a free radical molecule, can contribute to the development of oxidative and nitrosative stress in ischemia-reperfusion syndrome [4]. The use of NO synthase inhibitors has been shown to reduce the severity of liver reperfusion injuries [1]. At the same time, there is evidence of a negative effect of NO synthesis inhibitors in liver ischemia-reperfusion (IRI), while the administration of L-arginine, a substrate for endogenous NO synthesis, contributed to the correction of this pathology [6].

### Purpose of Investigation

To study changes in the prooxidant-antioxidant balance during liver ischemia-reperfusion in rats, under conditions of administration of a Kupffer cell blocker - gadolinium (III) chloride - and an NO synthase inhibitor.

## Materials and Methods

The experiments were performed on white adult male rats weighing 280 - 340g. Liver ischemia was induced using the Pringle maneuver for 30 minutes. The reperfusion period lasted 2 hours. At the end of the study, liver tissue was collected to study the parameters of the prooxidant-antioxidant balance. The animals were divided into groups: group 1 (n = 10) - control; in group 2 (n = 10) HIR was modeled; in

the 3rd (n = 6) group, Nω-nitro-L-arginine methyl ester (L-NAME, Sigma, i.p., 10 mg/kg) was administered 20 minutes before ischemia; in group 4 (n = 6) - gadolinium chloride (GdCl3, Sigma, i.p., 10 mg/kg) was administered 48 hours and 24 hours before HIR; in group 5 (n = 6) - experiments were carried out as in group 4, but L-NAME (Sigma, i.p., 10 mg/kg) was also administered 20 minutes before liver ischemia. The following indicators of the prooxidant-antioxidant state were studied: the concentration of conjugated dienes (CD), malondialdehyde (MDA) and catalase activity. Statistical processing of the obtained data was carried out using Student's t-test or U-test, depending on the normality of the sample distribution. Differences were considered significant at $p < 0.05$.

## Results and Discussion

It was found that the administration of L-NAME (group 3) during ischemia-reperfusion in rats did not lead to an improvement or deterioration in the parameters of the prooxidant-antioxidant balance of the liver or blood transaminases (Table 1). It was shown that the level of LPO products -CD and MDA in the liver at the end of reperfusion in animals treated with GdCl3 (group 4) decreases relative to the group with HIR by 47.2% ($p < 0.001$) and 24.7% ($p < 0.01$), respectively. An increase in liver catalase activity at the end of reperfusion under the influence of gadolinium chloride was observed in relation to animals of the 2nd group by 100.6% ($p < 0.001$).

| Parmeter | Control (1st group) | HIR (2nd group) | HIR + L-NAME (3rd group) | HIR + $GdCl_3$ (4th group) | HIR + $GdCl_3$ + L-NAME (5th group) |
|---|---|---|---|---|---|
| n | 10 | 10 | 6 | 6 | 6 |
| Conjugated dienes, $\Delta E_{233}$/g | 8,52 ± 0,74 | 46,62 ± 2,65* | 42,0 ± 3,34* | 24,6 ± 2,28*# | 42,1 ± 2,78*$ |
| Malondialdehyde, mkM/g | 24,94 ± 1,59 | 39,42 ± 2,1* | 38,57 ± 3,39* | 29,7 ± 2,4*# | 40,6 ± 2,44*$ |

***Table 1:*** *Lipid peroxidation products during liver ischemia-reperfusion in rats, under conditions of administration of gadolinium (III) chloride and an NO synthase inhibitor (M ± m).*

*Note: * - significant difference in relation to the control, # - in relation to the 2nd (HIR) group, $ - in relation to the 4th group ($).*

At the same time, the activity of liver catalase at the end of the experiments in rats of the 4th group remained lower in relation to the control by 18.0% ($p < 0.05$). It was found that the use of an NO synthase inhibitor along with the administration of gadolinium chloride (group 5) led to a significant deterioration in the parameters of the prooxidant-antioxidant balance in the liver during HIR. Thus, the level of LPO products - CD and MDA in the liver at the end of reperfusion in animals receiving GdCl3 with L-NAME increased relative to group 5 by 70.9% ($p < 0.001$) and 36.7% ($p < 0,01$), respectively. The use of gadolinium (III) chloride during HIR in rats helps to improve the parameters of the prooxidant-antioxidant balance of the liver during the reperfusion period, while the administration of L-NAME neutralizes its protective effect.

## Conclusion

Thus, Kupffer cells potentiate endothelial dysfunction by activating free radical processes and disrupt the production of nitrogen monoxide during liver ischemia-reperfusion.

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