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PROTECTIVE EFFECT OF L-ARGININE ON HEPATIC ISCHEMIA REPERFUSION INJURY: AN EXPERIMENTAL STUDY

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Resume. A major problem complicating liver transplantation is the preservation injury that results from ischemia/reperfusion (I/R) injury after organ revascularization. The L-arginine-nitric oxide (NO) pathway has been recognized to play critical roles during organ injury and transplant rejection. Recent data indicates that NO synthesis has beneficial effects in several models of liver injury. The purpose of this study is to examine the role of L-arginine on preservation injury in an experimental model of rat I/R. Methods: Complete ischemia of the median and left hepatic lobes was produced by clamping the left branches of the portal vein and the hepatic artery for 45 min., than 2 h of reperfusion. Rats were pre-cotreated with L-arginine (25 mg/kg i.p.) for 3 days before, last time 10min before induced ischemia-reperfusion maneuver. Results: L-Arginine supplementation provided activation of a constitutive form of NO-synthase, thereby inducible NOS activity decreased, but remained its significantly higher than that of the control. L-Arginine influences also on the level of proinflammatory cytokines, and the content of IL-1β, IL-6 and TNF-α were decreased. Also L-Arginine decreased hepatic transaminase levels at the time of examination. Conclusions: The results show that L-arginine supplementation and NO synthesis improve hepatic injury and have a protective role in the I/R injury. The enhanced production of NO through the administration of L-arginine balanced NO-arginine system, proinflamantory cytokine profile, protect liver at I/R induced injury. The protective effect may be mediated by activation of cNOS-derived NO.

Key words: L-arginine, hepatic ischemia reperfusion.

ЗАЩИТНЫЙ ЭФФЕКТ L-АРГИНИНА НА ПЕЧЕНОЧНУЮ ИШЕМИЮ РЕПЕРФУЗИОННОГО ПОВРЕЖДЕНИЯ: ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ

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Резюме. Основная проблема осложняет трансплантацию печени травмы сохранение, что приводит к ишемии / реперфузии (I / R) травму после органной реваскуляризации.L-аргинин-оксид азота (NO) путь был признан играют важную роль в процессе повреждения органов и отторжение трансплантата. Последние данные показывают, что NO синтеза не имеет положительный эффект в нескольких моделях повреждения печени.Целью данного исследования является изучение роли L-аргинина на травмы сохранения в экспериментальной модели крыс I / R. Методы: Полный ишемия медианы и левой долей печени было произведено путем закрепления левые ветви воротной вены и печеночной артерии в течение 45 мин, чем 2 ч реперфузии. Крысам было предварительно введено L-аргинин (25 мг / кг внутрибрюшинно) в течение 3 дней прежде, последний раз 10 мин до индуцированной ишемии-реперфузии маневра. Результаты: L-аргинина, предусмотренные активацию конститутивного виде NO-синтазы, таким образом, индуцируемый активность NOS уменьшилась, но оставалась его значительно выше, чем у контрольной группы. L-аргинин влияет также на уровне провоспалительных цитокинов и содержание IL-1β, IL-6 и TNF-α были снижены. Также L-аргинин уменьшилось печеночных трансаминаз в момент обследования. Выводы: результаты показывают, что добавление L-аргинин и NO синтез улучшить повреждения печени и имеют защитную роль в травму I / R.Усиливается производство NO путем введения L-аргинина сбалансированный NO-аргинина системы, воспалительный профиль цитокинов, защитить печень вызванной травмой. Защитный эффект может быть опосредована активацией CNOS-производного NO.

Ключевые слова: L-аргинин, печеночная ишемия, реперфузия.

Inroduction. Ischemia-reperfusion (I/R) liver injury occurs when blood flow is restored after prolonged ischemia. This is a phenomenon whereby cellular damage occurs because of oxygen delivery into the liver tissue. This form of injury in the liver was recognized as a clinically important pathological disorder [1]. Liver injury caused by I/R occurs in various surgical interventions, including

hepatectomy and liver transplantation [2]. I/R injury is associated with an acute inflammatory response and microvascular dysfunction, which finally lead to irreversible cell injury [3].

The pathogenesis of liver damage during transplantation, as an example of I/R, is very complex and occurs in two stages; the initial injury is caused by ischemia but aggravated further by reperfusion of the organ. I/R injury in the liver involves an early acute phase, associated with the generation of free radicals and nitric oxide (NO), and with T-lymphocyte and Kupffer cell activation, followed by a subacute phase, characterized by neutrophil infiltration leading to continued oxidant, cytokine, and chemokine production [4,5].

Since the discovery of nitric oxide (NO) about 30 years ago, the field of NO research has been rapidly expanding and new aspects of NO activity continue to emerge. L-Arginine is the substrate constitutive and inducible NOS and arginase for the production of NO and urea, respectively [6]. In mammals, α-amino acid arginine is classified as a semiessential or conditionally essential amino acid, depending on the developmental stage and health status of the individual. The L-form is one of the 20 most common natural amino acids [7]. Nitric oxide (NO) – a potent vasodilator, that diffuses freely across cell membranes and acts intracellularly by the activation of guanylate cyclase. NO is an inducer of vasodilatation at the level of the sinusoid as well as at presinusoidal sites [8]. In addition to its vasodilatory effect, NO reacts with superoxide to form the potent oxidant peroxynitrite [9]. NO inducer of vasodilatation at the site of sinusoid as well as at presinusoidal sites[10,11], which causes vasodilatation in Kupffer cells. NO also reacts with superoxide to form the potent oxidant peroxynitrite [12]. Inducible nitric oxide synthase (iNOS) from hepatocytes activates Kupffer cells to produce nitric oxide (NO). We, as some other scientists, hypothesized that the modulation of vasodilatation by NO could explain the protective effects of liver from I/R induced injury [13].

The effect of L-arginine therapy on hepatic ischemia has not yet been completely elucidated. Therefore, it was decided to investigate the role of nitric oxide donor L-arginine in I/R-induced injury, and the present study was designed to ascertain whether differences in the production of NO by hepatocytes cells could explain the differences in liver state found in I/R injury. Further pathological changes in the different experimental and sham-operated control groups were correlated with histopathology study.

Materials and methods: L-arginine were procured from Sigma; Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) Kits were procured from “Filisit-Diagnisric”; TNF-α, IL-1β, IL-6, eNOS, and iNOS ELISA Kits were procured “Uscn limited inc”.

Animal model. Male white rats (Ternopil state medical university vivarium, Ukraine) 8-10 week old, weight 300-350 g, were used in these experiments. All animals were fasted 12 h before experimentation and allowed water ad libitum. All animal received care in compliance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, revised 1985). The studies performed were carried out according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the local animal committee.

Induction of ischemic and reperfusion injury. The hepatic ischemia-reperfusion (I/R) protocols were performed as described in a previous study by Oleshchuk, 2012 [14]. There was no mortality with this model. After the induction of anesthesia (thiopentale sodium 20 mg/kg i.p.), the liver of each rat was exposed through a midline laparotomy. Complete ischemia of the median and left hepatic lobes was produced by clamping the left branches of the portal vein and the hepatic artery for 45 min. The right hepatic lobe was perfused to prevent intestinal congestion. After the period of ischemia, the ligatures around the left branches of the portal vein and hepatic artery were removed. To accurately evaluate the blood flow of the median and left hepatic lobes after ischemia, the right branches of the portal vein and the hepatic artery were ligated to prevent shunting to the right lobe after reperfusion and perfused for 2 h. The wound was closed with 3.0 silk suture. Sham-operated animals were similarly prepared except that no ligature was placed to obstruct the blood flow to the left and median hepatic lobes. Instead, the blood flow to the right lobe of the liver was occluded. In all groups rats were sacrificed after 1-h ischemia followed by 3-h reperfusion. A total of 18 white rats were equally divided into three groups (n=6 each group). Group I (sham-operated control group) and Group II (ischemia and reperfusion group) were given 0.9% saline (1 mL/kg, i.p.) for 3 days. Group III was pre-cotreated with L-arginine (25 mg/kg i.p.) for 3 days before, last time 10min before induced ischemia-reperfusion maneuver.

Peripheral blood and tissue procurement. Blood sampling for determination of liver enzymes. Blood samples were obtained from the right ventricle via left anterior thoracotomy at the time of sacrifice. Blood was collected in a sterile syringe without anticoagulant and centrifuged at 2000 g to separate the serum. The serum samples were stored at −20°C until use for AST and ALT assays.

Blood sampling for cytokine and NOS determination. Serum was removed from blood samples by clotting for 2 hours on ice; serum was centrifuged at 2,500×g (4ºC), filtered, aliguoted, and frozen at −20°C until assayed for TNF-α, IL-1β, IL-6, eNOS, and iNOS.

Small liver samples were collected from each rat, than frozen immediately and stored in liquid nitrogen until used for eNOS, and iNOS assays.

Determination of liver enzymes function. Determination of AST and ALT in plasma was performed by Raytman-Frenkel method, using a standard Kits "Filisit-diagnostic", Ukraine according to the manufacture's instruction. The activity of AST and ALT in serum were expressed in mmol / (L × h).

Cytokine assays. For detection of TNF-α in plasma, a specific rat Enzyme-linked Immunosorbent Assay Kit E90133Ra Uscn Life science inc. For rat interleukin 1 beta (IL-1β) detection in plasma, Enzyme-linked Immunosorbent Assay Kit E90563Ra Uscn Life science inc. For detection of rat interleukin 6 (IL-6) in plasma, a specific Enzyme-linked Immunosorbent Assay Kit E90079Ra Uscn Life science inc.

NOS assays. Determination of eNOS activity and was performed by ELISA method using «Enzyme-linked Immunosorbent Assay Kit for Rat Nitric Oxide Synthase 3, Endothelial (NOS3)», Uscn, Life Science Inc, E90868Ra.

Determination of iNOS activity and was performed by ELISA method using «Enzyme-linked Immunosorbent Assay Kit for Rat Nitric Oxide Synthase 2, Inducible (NOS2)», Uscn, Life Science Inc, E90837Ra.

eNOS and iNOS expression was investigated in blood plasma and liver tissue. Blood was collected using EDTA as an anticoagulant. Samples were centrifuged for 15 min at 1000 g/min at t 2-8ºC within 30 min after collection. Determination was carried out immediately or frozen at t- 20º C.

The procedure liver cells lysis was performed as follows:

1. Preparing liver homogenates on isotonic NaCl at a ratio of 1:10.
2. Liver cells were centrifuged 5 min at 300 g, the supernatant was then removed.
3. Cells were washed twice with isotonic NaCl, after each wash was centrifuged at 300g 5 min.
4. By adding normal liver tissue lysis buffer PBS (1 ml of buffer at 1×10^6 liver cells). It was centrifuged 5 min at 300g.
5. The supernatant was collected. Determination of enzyme activity was carried out immediately or frozen at t- 20º C.

Determination of eNOS and iNOS concentration were performed by ELISA method and according to the he manufacture's instruction.

eNOS and iNOS activity in serum expressed as U/ml, hepatocytes expressed as U/g.

Histopathology study. A portion of the tissue from ischemic liver lobe was fixed in 10 % neutral-buffered formalin solution for 5 days, embedded in paraffin, and sectioned. The sections were stained with hematoxylin and eosin.

Statistical analysis. Statistical analyses were performed by OriginPro Program. All data are expressed as mean±standart devitation. Differences between experimental groups were analyzed with an unpaired 2-tailed Student *t* test. All differences were considered statistically significant at a $p<0.05$.

Results. The results indicate that after 45 min ischemia followed by 2 h reperfusion the activity of ALT in the blood increased from (0,44 ± 0,10) in the sham control group to (2,35 ± 0,09) in animals with an I/R that is 5.3 times, increased AST activity in accordance with (1,63 ± 0,12) h to (4,27 ± 0,37), ie 2.6 times. The described dynamics indicates that under simulated experimental injury process cytolysis of hepatocytes is evolving (table 1).

The significant increase in ALT and AST activities that occurred in the I/R group was significantly suppressed by pre co-administration of 25 mg/kg L-arginine (Table 1).

Table 1.

Effect of L-arginine in activities of ALT and AST in the liver of sham and experimental groups of rat

Data	Sham (group 1)	I/R injury (group 2)	L-arginine +I/R (group 3)
ALT	0,44±0,10	2,35±0,09 p<0,001	1,10±0,09 p<0,005 p_1<0,001
AST	1,63±0,12	4,27±0,37 p<0,001	2,83±0,20 p<0,01 p_1<0,05

Results are expressed as mean±SD (n=6); Significantly different p – from sharm, p_1 – from I/R injury group; activity of ALT and AST expressed in mmol/(l×h)

Thus, the enzyme activity of cytolysis were significantly lower ALT (at 53.2%), AST (at 33.6 %). So, it was found that the prophylactic 3 days L-arginine administration animals with IP improved function of the liver.

The results of the ELISA studies showed significantly increased levels of proinflammatory cytokines in the blood serum. Thus, the concentration of IL-1β, IL-6 and TNF-α increased respectively 8.8, 3.2 and 6.6 times in comparison with the group 1 of animals (Figure 1).

In analyzing the impact of NO precursor L-arginine in the level of proinflammatory cytokines we found that the content of IL-1β, IL-6 and TNF-α decreased by 38.9, 29.0, 33.9 % respectively.

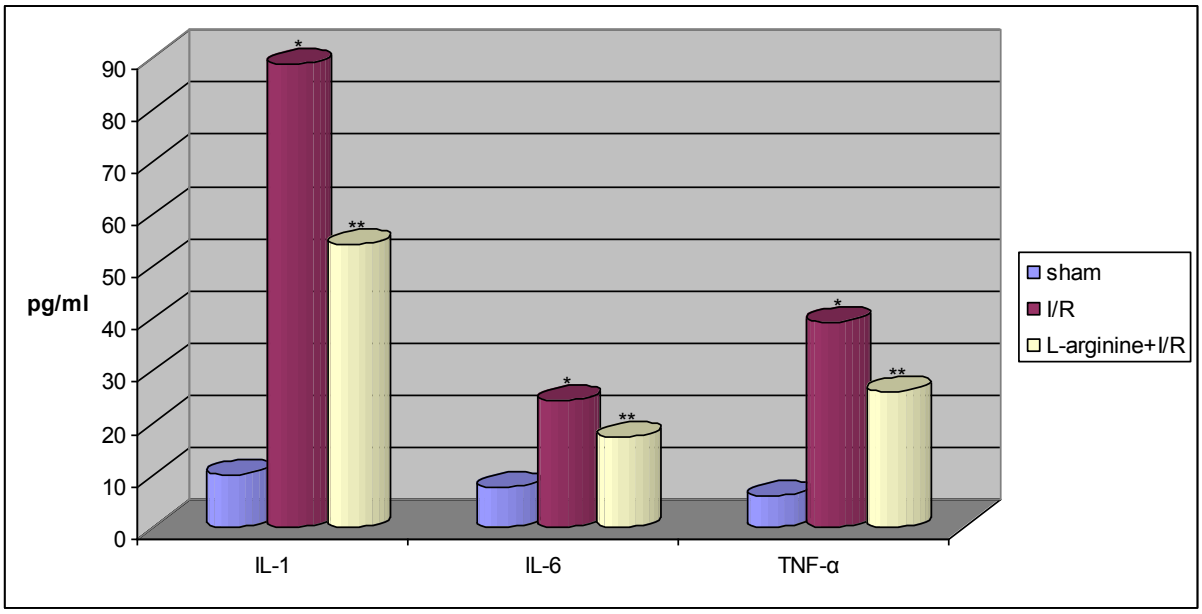

Figure 1: The content of proinflammatory cytokines in the serum of experimental animals: * – significantly different from sham-operated group, ** – from I/R injury group.

Table 2.

eNOS and iNOS content in liver and blood of sham and experimental groups

Goups	blood		liver	
	eNOS U/ml	iNOS ng/ml	eNOS од./мл (1 ml- 1×10^6 cells)	iNOS нг/мл (1 ml - 1×10^6 cells)
Sham	3,18±0,17	24,95±0,97	7,95±0,60	2,68±0,16
I/R	2,60±0,14 p<0,05	71,22±4,01 p<0,001	4,86±0,24 p<0,001	4,22±0,16 p<0,001
L–arginine +I/R	3,50±0,24 p>0,1 p_1<0,05	53,54±1,74 p<0,001 p_1<0,001	6,98±0,17 p>0,1 p_1<0,001	3,41±0,14 p<0,05 p_1<0,001

Results are expressed as mean±SD (n=6); Significantly different p – from sharm, p_1 – from I/R injury group

Cytokines are potent inducers of iNOS, whose content in the liver increased in 57.6 % and in the serum – in 185.0 %. Unlike this, the concentration of eNOS in the liver was reduced by 38.5 % and in the blood by 18.2 % compared with the group 1 (table 2).

We observed one-way influence of the substance on the contents of NO-synthase, both in blood and in the liver. Enzyme immunoassay results showed that the use of L-arginine in I/P leads to increased eNOS content in hepatocytes (43.5 %) and the reduction of iNOS (19.2 %) (table 2).

At blood was observed a similar pattern. Inducible NO-synthase was reduced by 24.8 % with the introduction of L-arginine, but remained higher than 2.1 times, compared with sham group of animals. Endothelial isoform of the enzyme increased by 34.5 % compared to its index in group 1.

Summarizing the above, we can say that prophylactic co-administration of NO precursor L-arginine before I/P is provided activation of a constitutive form of NO-synthase, thereby inducible

NOS activity decreased, but remained its significantly higher than that of the control.

Discussion. One of the criteria for liver assessment in I/R experimental modelling is to determine the activity in serum indicators cytolysis of cells - enzymes ALT and AST. This study shows significant activation in the I/R indicated enzymes, which is consistent with the results of other researchers [15]. This and previous our study indicate that the prophylactic L-arginine administration animals with IP has hepatoprotective effect by inhibition of cytolisis [16].

It is an established fact that reactive oxygen species and cytokines are potent inducers iNOS [16]. In this I/R study level of IL-1β, IL-6 and TNF-α in I/R significantly increase, expression of liver iNOS increased, eNOS level decreased. Our analysis of the research results of other scholars showed that the most pronounced hyperproduction of iNOS-dependent NO occurs only after 4-6 hours after onset of reperfusion, due to time-consuming transcription and synthesis of the enzyme [17]. Therefore, in the early periods of reperfusion there is lack of synthesis of NO, which may be due to inhibition of eNOS [17]. Previously, we have found that 2 hours of reperfusion levels of end products of nitric oxide metabolism of nitrate does not change significantly in the blood decreased in the liver, and conversely decreased blood nitrite levels [16]. This ratio NO_2^- and NO_3^- in the body can be explained by the activation of nitrate and nitrate reductase cycle ($NO_3^-\rightarrow NO_2^-\rightarrow NO^-$) under pathophysiological NO failure at I/R. These data can be estimated as a reduction total NO metabolites both in blood and liver, which is confirmed by other researchers that demonstrate the lack of NO at I/R [18]. We suggest that NO deficiency is due not only to inhibition of eNOS, but due to uncoupled of iNOS [20], which is caused by high levels of ADMA at I/R [19], and decrease of NO bioavailability in the early reperfusion period [21].

I/R is characterized by changes in microcirculation, hypoxia, cytolysis and oxidative stress in the liver [22]. NO donators and precursors may improve microcirculation, suppress hypoxia, cytolysis and oxidative stress.

Our previous studies have shown that the application of L-arginine at I/R causes activation of nitric oxide synthesis [16]. Increased concentrations of NO stable metabolites nitrite and nitrate anion in both blood and liver is consistent with our previous and other scientists data [16, 23, 24].

We observed one-way impact on the content of NO-synthase isoform in blood and in the liver. The level of endothelial forms increased and inducible – declined.

Increase in expression of endothelial nitric oxide synthase in like circumstances recorded also Rivera–Chavez F. A. et al., 2001 [25]. Therefore, we can assume that the increase of nitric oxide synthesis in the introduction of its precursors is due to activation of constitutive forms NOS.

The mechanism of the protective influence of precursor of nitric oxide synthesis in their care administration, according to H. V. Markov,1996 [26], can be explained by the accumulation of endogenous NO in the cells in a relatively stable depot, which, if necessary, serves as an additional source of endogenous nitric oxide. The mechanism of the protective action of depot NO related on NO-synthase inhibition on the principle of negative feedback, or from disposing of excess active nitric oxide. Perhaps this protective mechanism can prevent the overproduction of NO and its related cytotoxicity [27]. In addition, studies of P. Chattopadhyay, 2010 showed that the protective effect of arginine on functional status and ultrastructure of liver in I/R connected with NO-dependent reduction the Bcl-2 protein family expression and thus inhibit the development of necrosis and apoptosis of hepatocytes [24].

In conclusion, the enhanced production of NO through the administration of L-arginine balanced NO-arginine system, proinflamantory cytokine profile, protect hepatobiliary system in liver I/R induced injury. The protective effect may be mediated by activation of cNOS-derived NO.

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REPERFUSION JAROHATLANISH NATIJASIDA JIGAR ISHEMIYASIDA L-ARGININNING HIMOYA TA'SIRI: EKSPERIMENTAL TADQIQOT

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Rezyume. Bir yo'l organ zarar va naql rad muhim rol o'ynaydi, deb organ revaskulyarizatsii.L-arginin-nitrat oksidi so'ng ishemiya / reperfüzyon (I / R) jarohat olib keladi murakkablashtiruvchi jigar transplant saqlash jarohati asosiy muammo (NO) e'tirof etildi. Ekranga tomonidan ishlab chiqarilgan edi jigar Full ishemiya vosita va chap lobları: Oxirgi ma'lumotlar NO sintez bu o'rganish I / R. usullari eksperimental irillagan modelida jarohati saqlash bo'yicha L-arginin rolini tadqiq qilish uchun bo'ladi zarar pecheni.Tselyu bir necha modellari hech ijobiy ta'sirga ega ekanligini ko'rsatadi 45 daqiqa, reperfüzyon kamida 2 soat davomida Portal ven va jigar arteriyasi chap filiali. Rats ishemiyasi reperfüzyon ogohlantirgandan manevra oldin oxirgi 10 daqiqa oldin 3 kun L-arginin (25 mg / kg i.p.) oldindan qilingan. Natijalar: L-arginin, NO-sintazın bir asoschilari aktivlashtirishni taqdim, shunday indüklenebilir NOS faoliyat kamaydi, ammo bu nazorat guruhiga nisbatan sezilarli darajada yuqori bo'lib qoldi. L-arginin yallig'lanish tsitokinlari va mazmuni IL-1β darajasini ta'sir, IL-6 va TNF-α pasaytirildi. Bundan tashqari, L-arginin so'rov o'tkazilgan paytda jigar transaminazalari kamaydi. Xulosa: natijalar L-arginin qo'shilishi va NO sintez jigar zarar yaxshilash va L-arginin Arginine NO-muvozanatli tizimini, yallig'lanish sitokin tatbiq tomonidan I / R.Usilivaetsya NO ishlab chiqarish shikast himoya, bir o'rni bor, travma oqibatida jigar himoya ekanligini ko'rsatadi. Himoya ta'siri faollashtirish CNOS olingan hech vositachilik mumkin.

Kalit so'zlar: L-arginin, jigar ishemiyasi, reperfusiya.