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Activity Of Monooxygenase And Nitrergic Systems In Liver Microsomes Under The Action Of Drug Metabolism Inhibitors In Animals With Acute Toxic Hepatitis And Cirrhosis Of The Liver

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Abstract: In studies on white mongrel male rats weighing 180-250 g., it has been established that under the action of the inhibitor of the monooxygenase system, cimetidine, the inhibition of the rate of monooxygenase reactions is characterized by an increase in NOS activity due to both its constitutive (eNOS) and unconstitutive (iNOS), with a simultaneous increase in the content of NO and ONO2- in microsomes.

Cimetidine at a dose of 10 mg/kg in animals with hypertension contributed to an even more pronounced inhibition of the activity of liver monooxygenase system (MOS) enzymes. Against the background of advanced liver pathology caused by CCl4, cimetidine aggravated the process of inhibition of eNOS enzyme activity, and even more so, induced iNOS activity, expression of NO and ONO2- content.

Keywords: Pathophysiology, liver pathologies, NO – system with monooxygenase, cytochrome P-450, Endhoytelial (eNOS), neuronal (nNOS), inducible (iNOS).

Introduction: Monooxygenase system (MOS) inhibitors are widely used in clinical practice in the treatment of many liver diseases [5,9,11]. At the same time, it remains unclear by what mechanisms their toxic effect develops [1, 10, 11]. A range of researchers associate the development of the toxic effect of MOS inhibitors through the mechanisms of induction of reactive oxygen species (ROS) and, above all, the effect on the activity of the nitrergic system (NOS) [2,3]. The nitrergic system as an intra- and intercellular transmitter can also change its activity under the influence of specific (selective, non-selective inhibitors and inducers), as well as under favorable and unfavorable conditions of the internal and external environment [4,7,8]. The effect of MOS inhibitors on the activity of the nitrergic system is not fully elucidated, which determines the urgency of the problem [2,6].

In this connection, the objective of our research was to study the activity of MOS and NOS in their comparative aspect in liver microsomes in animals with acute toxic hepatitis (AH) and cirrhosis of the liver under the action of the drug metabolism inhibitor - cimetidine.

METHODS

Studies were conducted on 63 white mongrel male rats that had a body weight of 180-250 g. Animals were divided into series and groups (7-8 individuals each), depending on the experimental conditions. Control for all groups – intact animals (8 individuals in each group).

The first series consisted of groups of animals that were intragastrically injected with 1% aqueous solution of cimetidine at doses of 10, 25, 75 and 100 mg/kg for 6 days. The animals of the second series were divided into 3 groups: animals with acute toxic CCl4 hepatitis (fatty degeneration); group 2 – animals with acute toxic CCl4 hepatitis, which were injected Cimetidine in an effective dose of 10 mg / kg intragastrically for 6 consecutive days; control group 3.

The liver was perfused through the inferior vena cava with a cooled (0±4 ° C) 50 mM Tris HCl buffer, pH 7.4, containing 0.05 M KCl and 0.25 M sucrose. After washing the liver from blood, it was crushed and

homogenized in the same solution (1: 3). Microsomes were precipitated from the postmitochondrial fraction obtained by centrifugation on VAC-602 (Germany) after 20 min of unscrewing at 12.000 g at 105 thousand g. g for 60 minutes. All procedures were performed in a KKhS-12 refrigerator (Russia) at 0±4 ° C. In microsomes resuspended in 100 mM Tris-NSl buffer, pH 7.4, the activity of the monooxygenase system was evaluated by the content of cytochromes P-450, P-420, andB5 using the classical method of T. Omura and R. Sato (1964), and the activity of NADPH c-reductase (NADPH-cit.with-ed.) by C. H. Williams, H. Kamin (1961), benzo(a)pyren hydroxylases (BaPH) - according to C..H..Yang, L..P..Kicha (1978), aniline hydroxylase (AG) according to A. I. Archakov et al. (1975), amidopyrine N-demethylase (N-AP) according to A. Bast, J. Nordhosck (1981), glucose-6-phosphatase (G-6-Phase) by N. S. Gnosh, N. C. Kar (1983).

Nitrooxygenase activity was determined by the content of stable metabolites of nitrites and nitratesNO-NO2- and NO3- - according to the method of P. P. Golikov et al. (2000), endothelial NOS (eNOS) activity according to V. V. Sumbaeva, I. M. Yasinskaya (2000), inducibleNOS (iNOS) and peroxynitrite (ONO2-) concentrations according to M. Yu. Ravaeva, E. N. Chuyan(2011), the content and activity of monooxygenase and oxidoreductases of the nitrooxygenase system were recorded on a computerized two-beamlaser. UV-2100 spectrophotometer (Ltd, China). The content and activity of oxidoreductases were calculated in microsomes per milligram of protein in 1 ml (mg / ml), which was determined by the method of O. N. Lowry et al. (1951).

The obtained results were subjected to statistical processing using the application software package Excel, Statistic for Windows V.6, 0. The distribution of samples was carried out on the basis of the Student's criterion (t) with the calculation of the error probability (P). The relationship between the indicators was determined using Pearson correlation analysis (r). The data were considered reliable at $p<0.05$.

RESULTS AND DISCUSSION

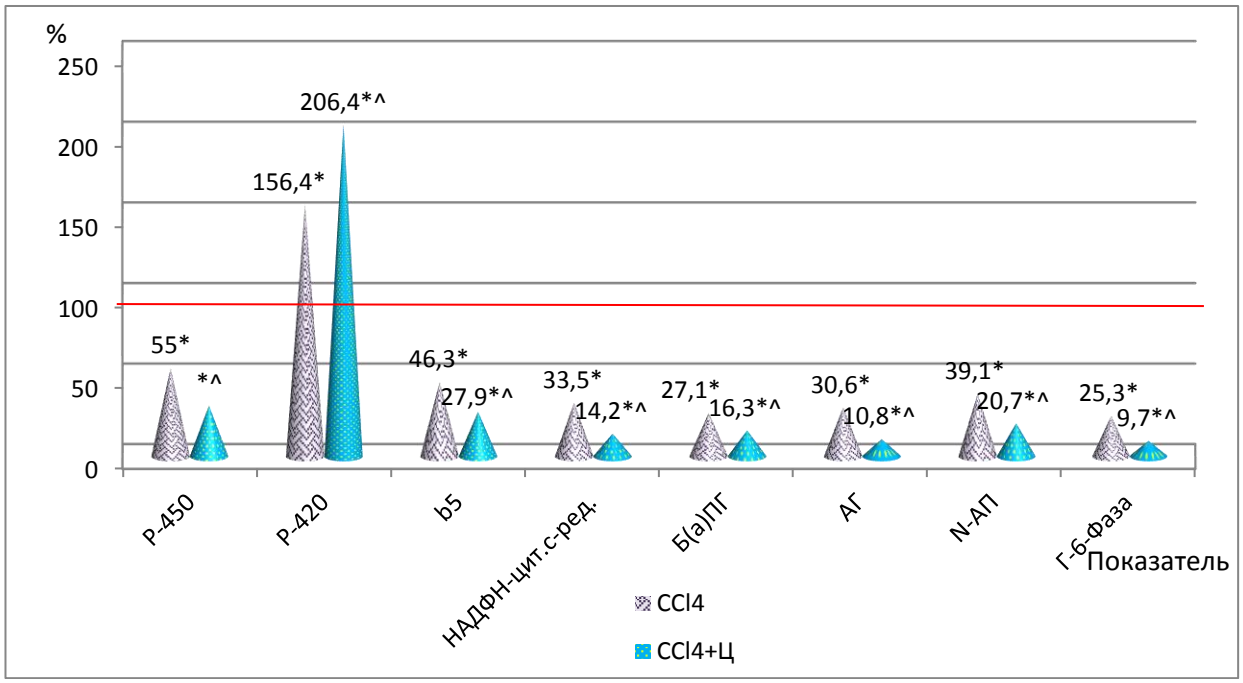
When cimetidine was administered to intact animals, as its dose increased from 10 to 100 mg/kg, there was a gradual dose-dependent inhibition of the main indicators of liver MOS-cytochromesP-450,bb5, and enzyme activity B(a)PG,N-Ap, AG. NADPH cit.with-ed.. enzymes and G-6-Phase at doses of 10 and 25 mg/kg remained practically within the control values, and decreased at doses of 75-100 mg/kg (Table 1).

Table 1. Activity of monooxygenases in liver microsomes of intact rats exposed to cimetidine, M±m

Groups	Monooxygenase system							
	cytochrome, nmol / mg			NADPH-cit. c-ed., nmol / min / mg	B(a)PG nmol / min / mg	AG, nmol / min / mg	N-AP, nmol / min/mg	G-6-Phase, nmol P neorg. / min / mg
	P-450, nmol / mg	P-420, nmol / mg	b5, nmol / mg					
Cimetidine 10	0.81±0.025*	0,084±0,003*	0,57±0,013*	107,3±3,650	2,49±0,08*	0,71±0,020*	4,03±0,117*	78,6±2,201*
25	0,69±0,027*	0,101±0,002*	0,48±0,011*	105,1±3,473*	2,06±0,06*	0,63±0,016*	3,20±0,106*	77,3±2,423*
75	0,52±0,014*	0,117±0,004*	0,41±0,012*	87,3±2,532*	1,74±0,04*	0,52±0,014*	2,81±0,095*	60,9±1,775*
100	0,43±0,011*	0,156±0,008*	0,34±0,009*	68,1±2,247*	1,33±0,03*	0,371±0,008*	1,77±0.052*	37.3±1.417*
Reference	0,97±0,031	0,036±0,001	0,63±0,026	106,9±3,955	2,86±0,09	0,88±0,023	4,85±0,151	79,8±3,056

* - $p<0.05$ compared to the control.

Against the background of the advanced liver pathology caused by CCl4, Cimetidine at a dose of 10 mg/kg (less toxic dose) contributed to an even more pronounced inhibition of the activity of liver MOX enzymes (Fig. 1).



1. Activity of liver MOS enzymes under the action of cimetidine in animals withCCl4 AH

* - P<0.05 compared to the control (100%)

- P<0.05 compared to the outcome (AH)

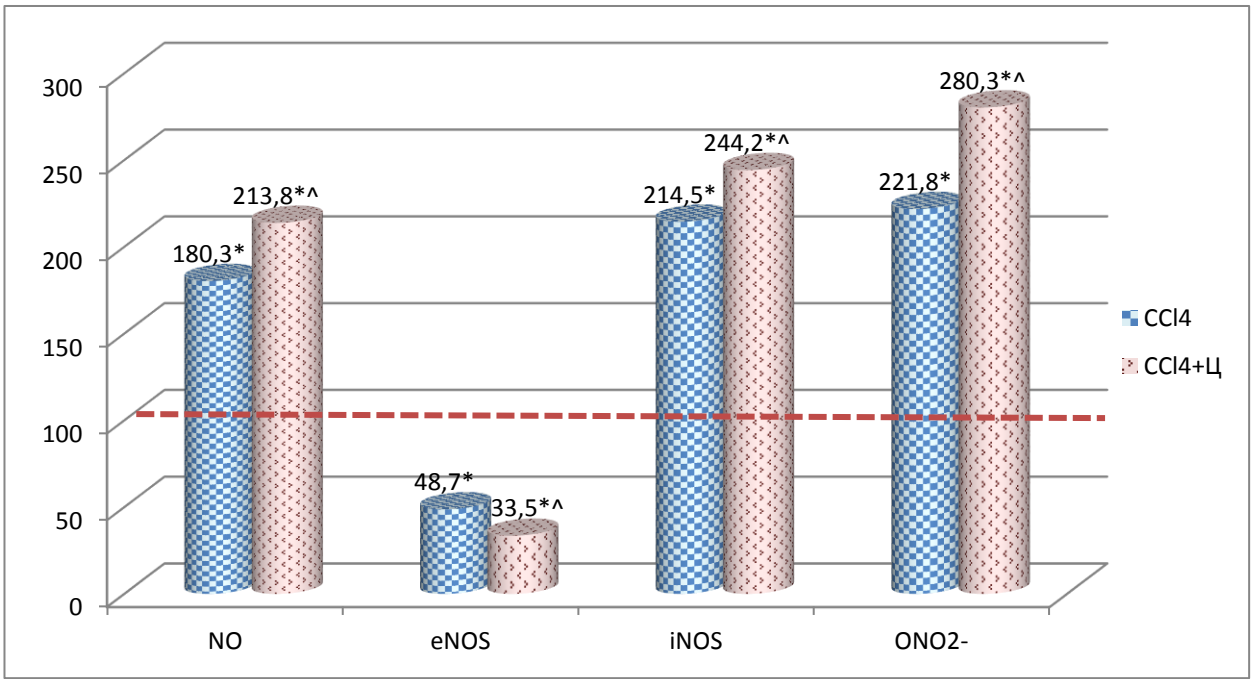
When studying the effect of cimetidine on the activity of the nitrergic system, it was found that its effect is determined by the initial state of the functional activity of the NOsystem. When using cimetidine at doses of 10 and 25 mg/kg, the level of NO and ENOS (constitutive) activity in liver microsomes in intact animals increased. At the same time, the expression of iNOS andONO22- increased. At doses of 75 and 100 mg / kg, while maintaining a high level of NO and eNOS activity (at the level of drug action at a dose of 10-25 mg / kg), iNOS activity and ONO2 content increased2-dynamically (Table 2).

Table 2. NOS activity in liver microsomes of intact rats exposed to cimetidine, M±m

Groups	Nitrergic system			
	NO, mmol / mg	eNOS, mmol / min / mg	iNOS, mmol / min/mg	ONO_2^-, mmol/mg
Cimetidine 10	7,62±0,223*	20,83±0,558*	0,12±0,003*	0,089±0,002*
25	8,80±0,343*	24,77±0,781*	0,15±0,003*	0,093±0,002*
75	11,59±0,374*	22,90±0,842*	0,21±0,006*	0,105±0,003*
100	16,15±0,531*	25,61±0,721*	0,26±0,006*	0,119±0,003*
Control	panel 5,52±0,164	17,42±0,627	0,10±0,002	0,080±0,0016

* - p<0.05 compared to the control.

At the same time, in animals with AH, cimetidine aggravated the process of inhibition of ENOS enzyme activity, and to an even greater extent, induced iNOS activity, expression of NO and ONO22- content (Fig.2).



2. Markers of NO-system activity in liver microsomes under the action of cimetidine (C) in animals with CCl4 AH.

* - P<0.05 compared to the control (100%)

- P<0.05 compared to the outcome (AH)

When monooxygenase inhibitors are prescribed, the increased activity of NO and eNOS is undoubtedly due to the need to provide microsomal enzymes with oxygen. However, arginine, as a substrate for the activation of cytochrome P-450, is more likely to be consumed for the activation of both eNOS and iNOS. At the same time, the oversaturation of cells with NO and iNOS may further inhibit the reactions of cytochrome P-450 enzymes. An increase in iNOS activity as a consequence of NO overexpression at high concentrations of cimetidine (75, 100 mg/kg) occurs against the background of inhibition of the activity of microsomal NADPH-cit enzymes. c-red and G-6 Phases are the main limiting factors of cytochrome P-450 functioning.

Therefore, the classical inhibitor of drug metabolism cimetidine inhibits the activity of liver MOS, and the activity of the nitrergic system is determined by the functional state of the NO system. In animals with AH, cimetidine inhibits eNOS to an even greater extent eNOS and initiates the expression of NO, iNOS, and ONO22-.

CONCLUSION

The drug metabolism inhibitor cimetidine dose-dependently inhibits the activity of MOS, increases the level of nitric oxide and peroxynitrite due to the activation of both eNOSand iNOS. The effective dose of cimetidine is 10 mg / kg.

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