

**ВОЗМОЖНЫЕ ПУТИ
ФАРМАКОЛОГИЧЕСКОЙ КОРРЕКЦИИ
ИШЕМИЧЕСКИХ ПОВРЕЖДЕНИЙ ПЕЧЕНИ
С ПОМОЩЬЮ АГОНИСТА ПЕРИФЕРИЧЕСКИХ
ИМИДАЗОЛИНОВЫХ РЕЦЕПТОРОВ С7070**

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Как при сахарном диабете, так и при метаболическом синдроме в виде коморбидного состояния развивается жировая дистрофия печени, переходящая далее в некроз печени. В статье предложены варианты фармакологической коррекции ишемии-реперфузии печени агонистами имидазолиновых рецепторов. **Материалы и методы.** Эксперимент проводился на 70 крысах обоего пола, разделённых на 7 групп (n=10): интактная группа; ложнооперированные животные (вскрытие брюшной стенки без лигирования печёночных сосудов); группа ишемии / реперфузии без коррекции препаратами; животные, подвергшиеся ишемии / реперфузии печени + метформин (50 мг/кг); животные, подвергшиеся ишемии / реперфузии печени + моксонидин (1 мкг/кг); животные, подвергшиеся ишемии / реперфузии печени + С7070 (10 мг/кг). Для оценки использовали коэффициенты, исчисляемые из уровня печеночных трансаминаз: аланинаминотрансфераза (АЛТ) и аспартатаминотрансфераза (АСТ), – а также морфометрических отношений площади некроза и глубокой ишемии печени по данным гистологического исследования. **Результаты.** Агонист периферических имидазолиновых рецепторов С7070 в значительно большей степени снижает ишемически-реперфузионные поражения печени, в сравнении с препаратами моксонидин и метформин. Гепатопротекторный эффект С7070 снимался предварительным введением блокатора периферических имидазолиновых рецепторов. Коэффициенты АЛТ/АСТ для С7070, моксонидина и метформина составили соответственно 72,8/62,13; 44,99/34,20 и 36,88/21,02. Коэффициенты морфологической гепатопротекторной активности препаратов составили:



C7070 – 82,61, моксонидин – 72,33, метформин – 38,96. **Вывод.** Агонисты имидазолиновых рецепторов достоверно и значимо снижают функциональные и морфологические проявления ишемии / реперфузии печени.

Ключевые слова: ишемия печени, реперфузия печени, сахарный диабет, C7070, моксонидин, метформин, агонисты имидазолиновых рецепторов.

POSSIBLE WAYS OF PHARMACOLOGICAL CORRECTION OF ISCHEMIC LIVER DAMAGES USING AGONIST OF PERIPHERAL IMIDAZOLINE RECEPTORS C7070

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A comorbid condition both in diabetes mellitus and in metabolic syndrome is fatty dystrophy of the liver that further progresses to hepatic necrosis. In the article variants of pharmacological correction of ischemia-reperfusion of the liver with agonists of imidazoline receptor are proposed. **Materials and Methods.** The experiment was conducted on 70 rats of both sexes divided into 7 groups (n=10): intact group; pseudo-operated animals (incision of the abdominal wall without ligation of hepatic vessels); animals subject to ischemia/reperfusion without drug correction; animals subject to ischemia/reperfusion of the liver + metformin (50 mg/kg); animals subject to ischemia/reperfusion of the liver + moxonidine (1 µg/kg); animals subject to ischemia/reperfusion of the liver+C7070 (10 mg/kg). For evaluation coefficients were used calculated from the level of hepatic transaminases: alaninaminotransferase (ALT), aspartataminotransferas (AST), – and also from morphometric ratios of the areas of necrosis and deep ischemia of the liver on the basis of histological examination. **Results.** Agonist of peripheral imidazoline receptors C7070 reduces ischemic-reperfusion damages to the liver to a significantly larger extent than moxonidine and metformin. Hepatoprotective effect of C7070 was removed by preliminary introduction of peripheral imidazoline receptor blocker. ALT/AST coefficients for C7070, moxonidine and metformin were 72.8/62.13; 44.99/34.20 and 36.88/21.02, respectively. Coefficients of morphological hepatoprotective activity of the drugs were: C7070 – 82.61, moxonidine – 72.33, metformin – 38.96. **Conclusion.** Agonists of imidazoline receptors reliably and significantly reduce functional and morphological manifestations of ischemia/reperfusion of the liver.

Keywords: *hepatic ischemia, hepatic reperfusion, diabetes mellitus, C7070, moxonidine, metformin, imidazoline receptor agonists.*

Ischemia is both a triggering point and a stage of pathogenesis of many pathologic conditions [1]. Both in diabetes mellitus and in metabolic syndrome fatty dystrophy of the liver develops as a comorbid condition that further progresses to hepatic necrosis [2]. The drugs used in treatment for the metabolic syndrome and diabetes mellitus do not produce a sufficient protective effect on the damaged liver. In this context of doubtless interest is a study of a possibility of using biguanides for additional pharmacological correction of standard therapy [3].

Thus, a study of pleiotropic hepatoprotective properties of agonist of peripheral imidazoline receptors C7070 seems interesting from the point of view of its practical application in medicine.

Materials and Methods

Hepatotropic anti-ischemic activity was studied using the method described by D.A. Lopatin [4]. The experiment was conducted on 70 rats of both sexes divided into 7 groups: intact group; pseudo-operated animals (incision of the abdominal wall without ligation of hepatic vessels); animals with modeled ischemia/reperfusion not given any medicinal treatment; animals with modeled ischemia/reperfusion given treatment with Metformin (50 mg/kg); animals with modeled ischemia/reperfusion given treatment with Moxonidine (1 µg/kg); animals with modeled ischemia/reperfusion given treatment with C7070 preparation (10 mg/kg); animals with modeled ischemia/reperfusion given treatment

with C7070 preparation (10 mg/kg) with simultaneous introduction of peripheral imidazoline receptor antagonist BU224 (BU224 hydrochloride solid, Sigma-Aldrich, Switzerland).

All selected doses corresponded to minimal therapeutic doses of the drugs recalculated for rats using common formulas. Dose of C7070 was selected on the basis of the minimal therapeutic dose of the closest analog – Diacamph (Ukraine).

Before modeling, the animals were introduced the drugs in single dose and saline per os. The animals were narcotized by intraperitoneal introduction of chloral hydrate solution in the dose of 300 mg/kg. A narcotized animal was made the midline laparotomy along the white line. Using a blunt method, the major hepatic ligament was isolated that carries vessels supplying blood to the liver. This ligament was clamped with an atraugrip for 15 minutes. After that the contents of the abdominal cavity were placed back, and the surgical wound was sutured layer-by-layer.

Within 3 days the animals were introduced the studied drugs and saline per os. In 3 days after the experiment the animals were subject to euthanasia through overdose of inhalation diethyl ether narcosis after which blood was taken from the heart for biochemical examination, and the liver was isolated for morphological analysis. No mortality of animals was noted in experiments.

Function of the liver was evaluated by biochemical markers of hepatocyte damage –

AST and ALT in blood taken from the heart of experimental animals immediately before euthanasia (after 3 days of the experiment) [5]. Biochemical parameters were evaluated on the biochemical analyzer Olympus AU 640. The parameters were determined using sets of Olympus reagents: «AST/GOT (ASPARTATE AMINOTRANSFERASE)», «ALT/GPT (ALANINE AMINOTRANSFERASE)».

For evaluation of structural changes histological sections of the liver of experimental animals were obtained with their subsequent morphological analysis [6].

Morphological evaluation of structural changes was carried out on the base of Regional Pathanatomical Bureau of Healthcare Committee of Kursk Region according to the internal standards. The preparations were stained with a standard mixture of hematoxylin and eosin with subsequent digital microscopy and planimetric calculation of the detected areas using Adobe Photoshop CC computer software (2015.2).

Statistical analysis of the obtained data was carried out using pair-wise Student-test (for parametric set) and Mann-Whitney U-test (for nonparametric set). The mean (M) and error of the mean (m) were preliminarily calculated. All calculations were carried out using Statistica 10.0 software. All differences obtained from comparison of parameters of different groups of animals as well as all changes were considered statistically reliable at $p < 0.05$.

Results and Discussion

Modeling of 15-min ischemia of the liver followed by reperfusion led to 5-fold increase in the levels of ALT and AST on the 3^d day of the experiment (Tab. 1). The param-

eters of the pseudo-operated animals did not show any reliable differences from those of intact animals. At the same time, morphometric measurements of the areas of ischemic and necrotic zones were 0.387 ± 0.014 and $0.207 \pm 0.021 \text{ mm}^2$, respectively (Tab. 2).

Application of the studied preparations shows a statistically significant reduction of the level of enzymes in blood of experimental animals. Of all used preparations, the highest activity was seen in C7070 (10 mg/kg), with levels of ALT and AST 143.27 ± 16.931 and 395.85 ± 33.311 , respectively (Table 1). In parallel with this, C7070 significantly and reliably reduced the areas of ischemic lesion and of necrosis to 0.058 ± 0.029 and 0.046 ± 0.013 , respectively. Moxonidine and metformin also reduced biochemical markers and morphometric parameters, but to a lesser extent than C7070 (Tab. 1-2).

For convenience of evaluation it is reasonable to compare the extent of reduction of the level of hepatic transaminases in different groups of animals using a simple mathematical formula:

$$K_{ALT} = 100 - \frac{ALT(\text{exp})}{ALT(\text{contr})} * 100\%,$$

where ALT (exp) is ALT level in blood of animals of experimental groups, ALT (contr) is ALT level in blood of animals of control group.

The same formula is applicable to study the level of AST:

$$K_{AST} = 100 - \frac{AST(\text{exp})}{AST(\text{contr})} * 100\%,$$

where AST (exp) is AST level in blood of animals of experimental groups, AST (contr) is AST level in blood of animals of the control group.

Table 1

***Influence of Agonists of Imidazoline Receptors on Level
of Hepatic Transaminases (ALT, AST) in Modeling
of Ischemia/Reperfusion of Liver
(M±m, n=10)***

Group of Animals	ALT (Un/ml)	AST (Un/ml)
Intact	102.89±8.82	284.14±19.36
Pseudo-operated	110.27±21.96*	289.80±16.29*
Ischemia/reperfusion (I/R)	526.90±17.97**	1045.16±80.02**
I/R+C7070 (10 mg/kg)	143.27±16.93 ¹	395.85±33.31 ¹
I/R+moxonidine (1µg/kg)	289.86±15.27 ¹	687.71±28.37 ¹
I/R+metformin (50 mg/kg)	332.56±22.05 ¹	825.49±22.46 ¹
I/R+C7070 (10 mg/kg)+BU224 (10 mg/kg)	300.45±19.44 ¹	798.59±21.34 ¹

Note: *p>0.05 in comparison with the group of intact animals;

**p<0.05 in comparison with the group of pseudo-operated animals;

¹p<0.05 in comparison with Ischemia/Reperfusion group

Table 2

Influence of Agonists of Imidazoline Receptors on Area of Ischemic Damage Zone of Liver and Area of Necrotic Zone of Hepatic Tissue in Modeling of Ischemia/Reperfusion of Liver (M±m, n=10)

Group of Animals	Area of Ischemic Damage Zone, mm ²	Area of Necrotic Zone, mm ²
Intact	-	-
Pseudo-operated	-	-
Ischemia/reperfusion (I/R)	0.387±0.014	0.207±0.021
I/R+C7070 (10 mg/kg)	0.058±0.029*	0.046±0.013*
I/R+moxonidine (1 µg/kg)	0.090±0.025*	0.075±0.015*
I/R+metformin (50 mg/kg)	0.238±0.052*	0.125±0.020*
I/R+C7070 (10 mg/kg) +BU224 (10 mg/kg)	0.159±0.031*	0.104±0.008*

Note: *- p<0.05 in comparison with the group Ischemia/Reperfusion

Using the given formula, we obtained of the drugs (Tab. 3).
the following data about functional protection

Table 3

***Hepatoprotective Activity of C7070, Moxonidine and Metformin
in Modeling of Ischemia/Reperfusion of Liver according to Data
of Biochemical Examination
(M±m; n=10)***

Coefficient of Hepatoprotective Activity, Unit	C7070 (10 mg/kg)	Moxonidine (1 µg/kg)	Metformin (50 mg/kg)
K _{ALT}	72.81±1.71*	44.99±1.23	36.88±1.02
K _{AST}	62.13±1.34*	34.20±1.21	21.02±1.49

Note: * – p<0.05 in comparison with coefficients obtained in treatment with moxonidine and metformin

It follows from the given data that agonist of peripheral imidazoline receptors (IR₂) C7070 possesses the highest anti-ischemic activity among the drugs studied within the frames of the given work.

For complete evaluation of anti-ischemic activity of the drugs, evaluation of only aminotranferases is insufficient.

For evaluation of hepatoprotective activity of the drugs a coefficient was calculated that characterizes the extent of protection of hepatic tissue from damages induced by ischemia and the subsequent reperfusion of the liver. This coefficient takes into account both zones of ischemic lesion, and zones of necrosis.

The coefficient was calculated from the formula:

$$K = 100\% - \left(\frac{Mi(\text{prep}) + Mn(\text{prep})}{Mi(\text{contr}) + Mn(\text{contr})} * 100\% \right)$$

where Mi(pre) is the average area of ischemic lesions of liver in rats of experimental groups, Mn(pre) is the average area of necrosis of liver in rats of experimental groups, Mi(contr) is the average area of ischemic lesions of liver in rats of control group, Mn(contr) is the average area of necrosis of liver in rats of control group.

Thus, we obtain data of anti-ischemic hepatoprotective activity of the studied preparations (Tab. 4).

Table 4

***Hepatoprotective Activity of C7070, Moxonidine and Metformin
in Modeling of Ischemia/Reperfusion of Liver according to Data
of Morphometric Examinations
(M±m; n=10)***

№	Group of Animals	Coefficient of Hepatoprotective Activity, units.
1.	I/R+C7070 (10 mg/kg)	82.61±3.22*
2.	I/R+moxonidine (1µg/kg)	72.33±1.04
3.	I/R+metformin (50 mg/kg)	38.96±5.69

Note: * – p<0.05 in comparison with pp. 2 and 3.

Thus, among all preparations studied within the frames of the given work, agonist of peripheral imidazoline receptors C7070 possesses the highest hepatoprotective activity in ischemia/reperfusion of the liver.

The obtained data can be explained by differences in mechanisms of actions of the drugs. The main component of the mechanism of metformin is reduction in production of glucose by the liver which, according to the data of numerous research, correlates with reduction in glycemia. Metformin plays a role in improvement of peripheral effects of insulin, in reduction of gluconeogenesis and oxidation of free fatty acids in the liver, in increase in the activity of anaerobic pathway of glucose metabolism with production of lactate, and in suppression of lipolysis. A number of studies conducted *in vivo*

and *in vitro* showed activating influence of metformin on cellular enzyme AMP-kinase that plays a role in transmission of glucose across cell membrane with the help of GLUT4 and in oxidation of free fatty acids. The improvement of glycemic profile in treatment with this drug is probably as well associated with similar cellular aspects of its mechanism of action. Besides, dimethyl biguanide demonstrated an ability to reduce hardness of cell membranes which is commonly observed in patients with diabetes mellitus and may contribute to its complications [7].

Metformin activates AMP-activated protein kinase (AMPK) – a hepatic enzyme that plays an important role in insulin signaling, as well as in the total energetic balance of the body, and in metabolism of glucose and fats, including that occurring in the liver. Activation

of AMPK is required for inhibitory effect of metformin on hepatic gluconeogenesis [8].

Summarizing the above, it may be said that anti-ischemic action of metformin is based on accumulation of energetic resources of hepatocytes and retardation of consumption of the currently existing resources of nutrients.

Moxonidine being an agonist of central imidazoline receptors (IP₁) participates in redistribution of hepatic blood flow through opening of collaterals originating from *a. gastrica sinistra* that remained free from compression. Besides, the additional activity may be due to central influence of moxonidine on the opening of hepatic vessels at the moment of reperfusion of the liver. A certain influence of moxonidine on peripheral imidazoline receptors should not be excluded either [9].

Agonist of peripheral imidazoline receptors (IR₂) C7070 realizes its hepatoprotective effect by mechanisms analogous to those occurring in ischemization of a skin graft. It is evident that its influence on preservation of mitochondria is realized through ATPase channels present in the outer and inner membranes of mitochondria. Retardation and block of the avalanche flow of iron ions, in its turn, reduces oxidative stress with all its manifestations in reperfusion of the liver [10].

Activation of imidazoline receptors leads to enhanced synthesis of arachidonic acid and to inhibition of Na⁺/H⁺ ionic channels. There are grounds to think that imidazoline receptors belong to the family of neurocytokine receptors [11]. Activation of central I₁-receptors decreases arterial pressure and the heart rate. All these are results of the influence on the peripheral sympathetic nervous system through its central inhibition.

Throughout the period of existence of a new generation of imidazoline receptors numerous preclinical and clinical studies of effectiveness of these pharmaceutical drugs were conducted.

Thus, for example, it has been demonstrated that intravenous application of moxonidine increased diuresis, excretion of sodium and potassium in rats. This effect was completely blocked by a selective antagonist of imidazoline receptors efaroxan and was weakened by α -adrenoreceptor blocker yohimbine [12].

The central I₁-receptors of hypothalamic region are involved into regulation of the level of glycemia that was shown in the experiment with selective agonist of I₁-receptors agmatine that causes reduction in the blood glucose level. A similar effect is seen in moxonidine. Besides, imidazoline receptors are supposedly located in the pancreas, and their activation leads to increase in insulin secretion [13].

Application of moxonidine in rats of *Zucker* line (obesity model) reduced the level of hypothalamic neuropeptide Y which may be one of mechanisms that can explain reduction in body mass in treatment with this drug [14].

It should be noted that not all the mentioned effects can be attributed to activation of central I₁-receptors. It is likely that some of them are nevertheless mediated by α_2 -adrenoreceptors. Besides, a certain contribution is made by peripheral effect of drugs.

On the contrary, representatives of Kharkov pharmacological school paid attention to an ability of agonists of peripheral imidazoline receptors to produce influence on blood glucose level [15]. According to their research, preparations of this group are not inferior to metformin in the hypoglycemic effect, but have much less

side effects. Besides, unlike metformin, agonists of peripheral imidazoline receptors do not cause hypoproteinemia and hyperlactacidemia.

Besides other localizations, imidazoline receptors are also found on the membranes of adipocytes – fat tissue cells. Stimulation of these receptors leads to enhancement of lipid metabolism.

In treatment of patients with arterial hypertension with moxonidine (0.4 mg/day) within 8 weeks, a reliable decrease in the arterial pressure was noted, while the levels of total lipids, of oxidized low density lipoproteins and the ratio of different subtypes of low density lipoproteins did not show any reliable changes [16].

All the above evidences the advantage of application of agonists of peripheral imidazoline receptors (IR₂) as medical drugs reducing structural and functional damages to the liver in its ischemia/reperfusion.

Conclusions

1. Agonist of II type imidazoline receptors C7070 in the dose of 10 mg/kg 4.5 times prevents increase in the levels of ALT and AST and 2.5 times reduces the areas of ischemic lesions and necrosis in modeling of

15-minute ischemia of the liver. Hepatoprotective effect of C7070 was 50% reduced by antagonist of peripheral imidazoline receptors BU224 (10 mg/kg).

2. Moxonidine possesses a less pronounced hepatoprotective effect and reduces areas of ischemic lesion and of necrosis 3.9-4.5 times. According to the data of laboratory studies, coefficients of hepatoprotective activity of moxonidine for ALT and AST were 44.99 and 36.88, respectively. Coefficient of histologic histoprotective activity of moxonidine is 72.33.

3. According to morphometric coefficients, metformin decreases areas of ischemic lesions and necrosis by one third and recovers the levels of ALT and AST after preceding ischemia/reperfusion of the liver only by 50%. Coefficients of hepatoprotective activity of metformin for ALT and AST were 34.20 и 21.02, respectively. Coefficient of histological hepato-protective activity of metformin was 38.96.

4. In terms of hepatoprotective activity the studied preparations were inferior to C7070 (72.81/62.13/82.61 ALT/AST/ histology, respectively).

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