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PATHOPHYSIOLOGICAL RATIONALE FOR THE USE OF A NEW AMINO ACID MIXTURE FOR LIVER DAMAGE

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SUMMARY.

Objective: determination of the pathophysiological validity of the use of the new amino acid mixture for damage to the liver.Materials methods. Acute heliotrin intoxication is reproduced by single administration of rats subcutaneous sub-lethal doses of heliotrin, prepared at the rate of 40 mg per 100 g of body weight. Toxic hepatitis is reproduced by subcutaneous administration of heliotrin. Results. During the reproduction of experimental toxic hepatitis by introducing heliotrin, it was found that the HIF-1 content was on average 0.101667 ± 0.0022 ng /l. In blood plasma, the average HIF-1 was 0.2136 ± 0.0066 ng / L. Such indicators are explained by the effect of heliotrin on the liver and, above all, on hepatocytes, in which mitochondria are experiencing an oxygen deficiency. Thus, HIF-1 acts as an early biomarker of oxygen tissue deficiency and since it causes angiogenesis, the strengthening of this gene in experimental animals with ischemia can contribute to the proliferation of vessels necessary for oxygenation. Conclusions: The developed aminoacid mixture in terms of the effectiveness of the impact on the development and course of experimental toxic hepatitis surpasses traditional methods of treatment, which is proved by the study.

Keywords: heliotrin intoxication; inflammation biomarkers; amino acid mixture; Infesol experimental animals.

RELEVANCE

At the same time, more than 180 hepatotoxic drugs have been identified, of which 6 groups seriously injure the liver. At the same time, 50% of drugs are hepatotoxic, especially in women this effect is more pronounced. Medicines cause hepatocellular damage, even liver necrosis, which is clinically manifested mainly by jaundice, fever, and increased liver enzymes [10]. Many pathogenetic aspects of pathogenetic disorders in chronic liver diseases remain unexplored [1-4]. One of the most common causes of chronic hepatitis and liver cirrhosis is infection with hepatitis B and C [5-9].

The problem of creating new, modern, effective means of metabolic correction of homeostasis in critical conditions continues to be relevant, the solution of which, in many respects, determines the course and outcome of treatment of serious diseases of various etiologies. Modern ideas about the metabolic response in critical conditions, an understanding of the mechanisms of violations of all types of metabolism, the formation of hypercatabolism, hypermetabolism and the development of tissue metabolism disorders determines the need for the use of substances, capable of influencing metabolic homeostasis and the cell-based energy-forming system [20].

The best means of influencing metabolic homeostasis are mixtures of pure amino acids compiled according to certain recipes, since protein synthesis occurs only from free amino acids. Nitrogen preparations used for parenteral nutrition contain all essential amino acids in sufficient quantities, the so-called replaceable nitrogen (glycin and others) [15-18]. Currently, there are a number of drugs widely used by medicine, balanced in content of irreplaceable and replaceable amino acids, – Infezol 40, Infesol 100 («Berlin-Hemi», Germany), Aminoplasm E – 5%, 1% («B. Brown», Germany), Aminosol – 600, 800, KE («Hemopharm», Yugoslavia). Recently, much attention has been paid to bioenergy antioxidant complexes capable of restoring metabolism in cells, and influencing the vital activity of the body as a whole [11-13]. This will allow doctors to correctly apply amino acid solutions and correctly build a parenteral nutrition program. The high cost of such foreign drugs limits their widespread use in medicine [14, 19]. In this regard, the development of domestic, more advanced metabolic means of correction of homeostasis is of great importance for domestic medicine.

A blood substitute containing amino acids and an antioxidant complex with a wide range of actions capable of protein synthesis, mobilization of energy and plastic resources was developed at the Research Institute of Hematology and Blood Transfusion of MH RU, optimization of the activities of physiological systems, acceleration of recovery processes in severe diseases of various etiologies associated with protein and energy metabolism disorders.

The purpose of the study. Determination of the pathophysiological validity of the use of the new amino acid mixture for damage to the liver.

MATERIALS AND RESEARCH METHODS

To achieve this goal, a model of toxic hepatitis was reproduced using heliotrin intoxication as an example.

Acute heliotrin intoxication is reproduced by single administration of rats subcutaneous sub-lethal doses of heliotrin, prepared at the rate of 40 mg per 100 g of body weight. Toxic hepatitis is reproduced by subcutaneous administration of heliotrin(25 mg / 100 g). The material for the study is venous blood. The indicators of protein balance are studied: total blood serum protein, albumin and globulin and biological materials (ALT, AST, bilirubin and alpha amylase by biochemical analysis using the HUMAN test systems (Germany) on the semi-automatic biochemical analysis of BA88A (Mindray, China). Protein fractions will be determined by the turbidimetric method according to the generally accepted methodology. The blood content of HIF-1 was determined by the immuno-farm method. Animals were divided into equal groups:

I group – before the reproduction of heliotrin intoxication (intact)

II group (control) – with heliotrin intoxication,

III group (control, comparisons) – with heliotrin intoxication after the introduction of the comparison drug « Infezol 40 », within 5 days after the last introduction;

IV group (main, experienced) – animals with heliotrin intoxication after the introduction of a new amino acid blood substitute, within 5 days after the last introduction. Statistical processing was carried out using the Stüdent-Ficher criterion, the non-parametric criterion of Mann-Winnie, the Crasquez-Wallis criterion

RESEARCH RESULTS

During the reproduction of experimental toxic hepatitis by introducing heliotrin, it was found that the HIF-1 content was on average 0.101667 ± 0.0022 ng / L. In blood plasma, the average HIF-1 was 0.2136 ± 0.0066 ng / L. Such indicators are explained by the effect of heliotrin on the liver and, above all, on hepatocytes, in which mitochondria are experiencing an oxygen deficiency. Thus, HIF-1 acts as an early biomarker of oxygen tissue deficiency and since it causes angiogenesis, the strengthening of this gene in experimental animals with ischemia can contribute to the proliferation of vessels necessary for oxygenation. On the contrary, since HIF-1 promotes the survival and proliferation of cancer cells due to its angiogenic properties, inhibition can potentially prevent the spread of cancer. With a growing understanding of the HIF-1 path, inhibiting and stimulating its transcription activity with small molecules is now an attractive target.

As you know, the HIF-1α subunit also contains two transactivation domains (TAD) that regulate the HIF-1 target genes. CREB-binding protein (CBP) and p300, two HIF-1 transcription coactivators, interact with the carbon dioxide transactivation domain (C-TAD) HIF-1α.

Both activators are necessary for transcription of HIF-1 and, therefore, are targets for regulating the expression HIF-1; inhibition of HIF-1α C-TAD interactions by hydroxylating the strait inhibits the expression of the HIF-1 gene, preventing normal transcription and broadcast. HIF-1ß contains only one such similar area that is not needed for the complex function HIF-1. Recent reports show that HIF-1ß is identical to the previously discovered vertebral protein, the nuclear anil hydrocarbon receptor translocator(ARNT).

HIF-1 is the main regulator of oxygen homeostasis in cells. As a transcription factor, it affects and regulates the expression of dozens of genes involved in maintaining homeostasis when the oxygen concentration changes. One of the important functions of HIF-1 is to promote angiogenesis; HIF-1 directs the migration of mature endothelial cells into a hypoxic environment. This is done through HIF-1 regulation of transcription of the vascular endothelium growth factor (VEGF). VEGF is the main regulator of angiogenesis, which contributes to the migration of endothelial cells towards the hypoxic region. During hypoxia, HIF-1 binds the regulatory area of the VEGF gene, inducing its transcription and initiating its expression. Such endothelial cells ultimately help shape new blood vessels, supplying this area with oxygen-saturated blood.

During the reproduction of experimental toxic hepatitis by introducing heliotrin, it was found that the ALT content was on average 25.93 ± 2.91 Eid / L, and the AST content was at 22.23 ± 1.95 Eid / L. The number de Rits was at 1.17 ± 0.16. Direct bilirubin was at the level of 3.90 ± 0.44 mmol / l, indirect bilirubin – 8.10 ± 0.8 mmol / l. The total bilirubin was 12.01 ± 1.16 mmol / l. Moreover, OSH (the odds ratio) was 0.93219976. DI (confidence interval) 95% was 0.88765239. χ 2 = 0.9633286 (Wilconson's criterion). The Manna-Winnie criterion (the U) criterion was 0.87219981 at $p < 0.05$. These indicators indicate that protein balance indicators are directly dependent on oxygen deficiency caused by heliotrin.

However, the ALT level – is an unreliable marker of the pathological process in the liver. This is primarily due to the peculiarity of the laboratory method, when it is determined not the actual

level of the enzyme, but its catalytic activity, the rate of the catalytic reaction. Thus, the amount of enzyme is determined indirectly.

The results indicate that as a result of treatment, the overall bilirubin in group IV has reliably improved. The dynamics of ALT was positive in the IV group, which received the developed amino acid mixture, there was no reliable positive dynamics of ALT and AST indicators in the III group that received Infezol.

In general, we can say that in the case of toxic hepatitis with a 2-fold or more increase in ALT activity, intravenous Infezolome therapy with a simple removal of the damaging factor is not effective enough. In addition, the restoration of the detoxification function of the liver to the end of the course of treatment, which was observed in the studied group that received the developed amino acid mixture, can be interpreted as the most important indicator of the effectiveness of therapy, which speaks in favor of metabolic therapy.. Of interest is the use of the recommended amino acid mixture, which was clearly positive for all — values, a decrease in cytolysis and cholestasis and an increase in the detoxification function of the liver.

CONCLUSIONS

Summarizing the above, hypoxia-inducible factor 1 (HIF-1α) is an important pathogenetic link in the development of oxygen deficiency and its deficiency at an early stage can serve as an important diagnostic biomarker of toxic hepatitis, including those caused by heliotrin, since in chemical composition it belongs to pyrolyzedin alkaloids, and as you know, its predecessor is cadeverdin, which is oxidized to gamma-aminomaslic aldehyde with the formation of non-inine alcohols with single-core non-cinic acids. The developed amino acid mixture in terms of the effectiveness of the impact on the development and course of experimental toxic hepatitis surpasses the traditional methods of treatment
(Infezol), which is proved by the study.

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