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EXPERIMENTAL SUBSTANTIATION OF THE USE OF HYPOXIA-INDUCIBLE FACTOR (HIF-1A) FOR THE DEVELOPMENT OF TOXIC HEPATITIS.

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Abstract. This article provides an experimental rationale for the use of hypoxia-inducible factor (HIF-1α) for the development and course of toxic hepatitis based on heliotrin intoxication. Acute heliotrin intoxication was reproduced by a single subcutaneous administration of a sublethal dose of heliotrin to rats, prepared at the rate of 40 mg per 100 g of body weight. During the reproduction of experimental toxic hepatitis by the introduction of heliotrin, it was found that the HIF-1 content was on average 0.101667 ± 0.0022 ng / L. In blood plasma, the mean HIF-1 values were 0.2136 ± 0.0066 ng / L.

Key words: hypoxia-inducible factor; heliotrin intoxication**;** experimental toxic hepatitis; aryl hydrocarbon receptor transolator.

Relevance. Hypoxia-inducible factor (HIF) -1 is a dimeric protein complex that plays an important role in the body's response to low oxygen concentrations or hypoxia [3, 6]. HIF-1 is one of the main genes involved in the homeostatic process, which can increase vascularization in hypoxic areas such as localized ischemia and tumors [1, 4]. It is a transcription factor for dozens of target genes; HIF-1 is also important for immunological responses and is an important physiological regulator of homeostasis, vascularization, and anaerobic metabolism [2, 5, 7]. However, the pathophysiological mechanisms of the effect of HIF -1α on the development of toxic hepatitis have not yet been disclosed, which was the relevance of this study.

Purpose of the study. Determine the value of hypoxia-inducible factor (HIF-1α) on the development and course of experimental toxic hepatitis.

Materials and research methods. To achieve this goal, a model of toxic hepatitis was reproduced using the example of heliotrin intoxication.

Acute heliotrin intoxication was reproduced by a single subcutaneous administration of a sublethal dose of heliotrin to rats, prepared at the rate of 40 mg per 100 g of body weight. Toxic hepatitis was reproduced by subcutaneous administration of heliotrin (25 mg / 100 g). The material for the study is venous blood. The content of HIF-1 in the blood was determined by the enzyme immunoassay. The animals were divided into equal groups:

Group I - before reproduction of heliotrin intoxication (intact)

Group II (control) - with heliotrin intoxication,

Group III (control, comparison) - with heliotrinic intoxication after the introduction of the reference drug "Infezol 40", within 5 days, 24 hours after the last injection;

Group IV (main, experimental) - animals with heliotrin intoxication after the introduction of a new amino acid blood substitute, within 5 days, 24 hours after the last injection. Statistical processing was carried out using the Student-Fisher test, the nonparametric Mann-Winney test, the Kraskes-Wallis test

Research results. During the reproduction of experimental toxic hepatitis by the introduction of heliotrin, it was found that the HIF-1 content was on average 0.101667 ± 0.0022 ng / L. In blood plasma, the mean HIF-1 values were 0.2136 ± 0.0066 ng / L. Such indicators are explained by the effect of heliotrin on the liver and, first of all, on hepatocytes, in which mitochondria are deficient in oxygen. Thus, HIF-1 acts as an early biomarker of tissue oxygen deficiency and, since it induces angiogenesis, an upregulation of this gene in experimental animals with ischemia may promote vascular proliferation required for oxygenation. In contrast, since HIF-1 promotes the survival and

proliferation of cancer cells due to its angiogenic properties, inhibition could potentially prevent the spread of cancer. With the growing understanding of the HIF-1 pathway, inhibition and stimulation of its transcriptional activity by small molecules is now an attractive goal.

As is known, the HIF-1α subunit also contains two transactivation domains (TAD) that regulate the HIF-1 target genes. CREB-binding protein (CBP) and p300, two coactivators of HIF-1 transcription, interact with the carboxy-terminal transactivation domain (C-TAD) of HIF-1α.

Both activators are required for HIF-1 transcription and, therefore, are targets for the regulation of HIF-1 expression; inhibition of HIF-1α C-TAD interactions by hydroxylation of proline suppresses the expression of the HIF-1 gene, preventing normal transcription and translation. HIF-1β contains only one such analogous region, which is not needed for the complex function of HIF-1. Recent reports indicate that HIF-1β is identical to a previously discovered vertebrate protein, the aryl hydrocarbon receptor nuclear translocator (ARNT).

HIF-1 is the main regulator of oxygen homeostasis in cells. As a transcription factor, it influences and regulates the expression of dozens of genes involved in maintaining homeostasis when 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 accomplished through HIF-1 regulation of vascular endothelial growth factor (VEGF) transcription. VEGF is the main regulator of angiogenesis, which promotes the migration of endothelial cells towards the hypoxic area. During hypoxia, HIF-1 binds the regulatory region of the VEGF gene, inducing its transcription and initiating its expression. These endothelial cells ultimately help form new blood vessels by supplying oxygenated blood to the area.

Findings. 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 that caused by heliotrin, since by its chemical composition it belongs to pyrolizidine alkaloids, and as you know, its precursor is cadeverdine, which is oxidized to gamma-aminobutyraldehyde with the formation of non-alcohols with monobasic noncynic acids.

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