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## XRONİK TOKSİK HEPATİTLİ SIÇOVULLARIN QAN SERUMUNDA İBF-1 VƏ TGF- $\beta$ SİTOKİNLƏRİNİN KONSENTRASIYASI VƏ ONLARIN LİZİNOPRİL VASİTƏSİLƏ KORREKSİYASI

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**Xülasə.** Məqalədə xronik toksik hepatit (XTH) modeli yaradılmış siçovulların qan serumunda I insulinəbənzər böyümə amilinin (İBA-1) və  $\beta$ -transformasiyaedici böyümə amilinin (TBA- $\beta$ ) konsentrasiyasını müəyyənləşdirmək və onun lizinoprillə korreksiyaedilmə imkanını araşdırmaq məqsədilə aparılmış tədqiqat işi haqqında məlumat verilmişdir. Eksperimentlər hər birində 12 baş olmaqla 5 qrupa bölünmüş 60 baş siçovul üzərində aparılmışdır. Birinci qrupda heyvanlar intakt saxlanılmış, ikinci qrup heyvanlarda 8 həftə hər gün intraqastral yolla 0,1 ml/100 q dozada CCl<sub>4</sub>-ün spirtlə kombinasiyası yeridilməklə XTH modeli yaradılmışdır. Üçüncü qrupun heyvanlarında CCl<sub>4</sub>-lə paralel olaraq 6 həftə müddətində 20 mq/kg dozada lizinopril, 4-cü qrupun heyvanlarına isə eyni müddət ərzində 30 mq/kg dozada qlutargin verilmişdir. Beşinci qrupun heyvanlarına isə CCl<sub>4</sub>-dən əlavə, həm lizinopril (20 mq/kg), həm də qlutargin (30 mq/kg) verilmişdir.

Tədqiqat nəticəsindən aydın olmuşdur ki, eksperimental XTH modeli yaradılmış siçovulların qanında İBF-1 və TBA- $\beta$  sitokinlərinin konsentrasiyası artır. Lizinoprillə qlutarginin kompleks şəkildə tətbiqi zamanı qan serumunda İBA-1 konsentrasiyası azalmışdır. Lizinopril verilmiş XTH-li heyvanların qan serumunda TBA- $\beta$ -nin konsentrasiyası preparat almayan heyvanlardakına nisbətən 2 dəfə az olmuşdur.

**Açar sözlər:** xronik toksik hepatit, I insulinəbənzər böyümə amili,  $\beta$ -transformasiyaedici böyümə amili, lizinopril

**Ключевые слова:** хронический токсичный гепатит, IGF-1, TGF- $\beta$ , лизиноприл

**Key words:** chronic toxic hepatitis, IGF-1, TGF- $\beta$ , lisinopril

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## CONCENTRATION OF IGF-1 AND TGF-B IN THE BLOOD PLASMA OF RATS WITH CHRONIC TOXIC HEPATITIS AND ITS CORRECTION WITH LISINOPRIL

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**Summary.** Materials determining the concentration of IGF-1 and TGF- $\beta$  in chronic toxic hepatitis and its therapeutic correction with lisinopril are presented in the article. Experimental studies were carried out on 60 non-linear white laboratory rats, with initial body weight of 60-80 g. The animals were divided into 5 groups - 12 rats in each group. Group 1 consisted of intact rats. Chronic toxic hepatitis was modeled in the animals of groups 2, 3, 4 and 5 by intragastric administration of CCl<sub>4</sub> Solutio oleosa in the dose of 0.1 ml/100 g of body weight twice a week in combination with 5% ethanol solution for six weeks. The rats of group 2 were administered no other agents. Along with CCl<sub>4</sub>, the animals of the remaining groups received "Lisinopril" in the dose of 20 mg/kg (group 3), "Glutargin" in the dose of 30 mg/kg (group 4), CCl<sub>4</sub> as well as "Glutargin" in the dose of 30 mg/kg and "Lisinopril" - 20 mg/kg (group 5). The study demonstrated increased serum TGF- $\beta$  and IGF-1 levels in rats receiving hepatotoxins, being indicative of chronic inflammation in the liver. Corrective combination therapy with lisinopril and glutargin promoted decrease of serum IGF-1 level in rats. The use of lisinopril in experimental CTH resulted in twofold decrease of TGF- $\beta$  content as compared to untreated animals.

Chronic toxic hepatitis (CTH) is manifested by fibrous changes in liver tissue - pathological condition characterized by excessive collagen development due to formation of new fibrils. Despite certain etiological and clinical differences, in most chronic fibrous disorders there is a persistent stimulus that facilitates production of growth factor, proteolytic enzymes and fibrogenic cytokines, which promote the accumulation of connective tissue elements with subsequent reorganization and destruction of organ's architectonics [1, 2].

Cytokine link of the immune system is of vital importance in pathogenesis of CTH, its mediators regulating the activity of hepatocyte apoptosis and necrosis, inflammation and fibrosis of liver tissue. However, the role of certain cytokines in those processes, in case of CTH in particular, requires further investigation [3].

Because of that, recently researchers have been focused on the study of action of several profibrogenic cytokines, insulin-like growth factor-1 (IGF-1) and transforming growth factor- $\beta$  (TGF- $\beta$ ) in particular, on cells and systems of the body [4].

Increase of IGF-1 concentration in toxic liver injury, it being synthesized by Kupffer's cells and stellate Ito's cells in the process of fibrogenesis, is indicative of importance of this factor in the development of liver fibrosis (LF) [5, 6]. Modern studies demonstrate IGF-1 to play an essential role in apoptosis regulation. According to the results of recent experimental studies, IGF-1 was found to enhance stellate cell (SC) apoptosis, and at the same time – proliferation of myofibroblasts (activated by SC) playing a key role in development and progression of liver cirrhosis (LC) [7-9].

Pleiotropic cytokine-TGF- $\beta$  is known to be the major component in hepatocyte growth system, fibrosis formation and apoptosis control [10, 11]. In studies of A.A. Mahmoud et al. direct relationship between blood TGF- $\beta$  level and the severity of fibrosis [12] was found, and S. Wahl et al. demonstrated correlation between blood TGF- $\beta$  level and the severity of liver damage, determined by Knodell method [13].

The importance of inhibiting renin-angiotensin-aldosterone system (RAAS) as a factor influencing the pathogenesis of CTH and LC and slow-

ing the rate of LF progression, has been demonstrated in recent studies; and this finding seems to become a promising strategy in treatment of such condition [14, 15]. Given that local RAAS is involved in regulation of fibrogenesis in the liver, it is lisinopril, not subjected to hepatic metabolism, that can become the drug of choice in patients with liver pathology [16].

**Aim** – to study the role of IGF-1 and TGF- $\beta$  under conditions of experimentally modeled chronic toxic hepatitis and its therapeutic correction with lisinopril.

**Research material and methods.** 60 non-linear laboratory rats aged 1.5 months weighting 60-80 grams were used in experimental study. The duration of the experiment was six weeks. All the animals were divided into five equal groups (12 rats in each group). Group 1 consisted of intact rats. Chronic toxic hepatitis was modeled in the animals of groups 2, 3, 4 and 5 by intragastric administration of CCl<sub>4</sub> Solutio oleosa in the dose of 0.1 ml/100 g of body weight and 5% ethanol solution twice a week [17]. The rats of group 2 were administered no other agents. Along with hepatotoxins, the animals of the remaining groups received angiotensin-converting enzyme inhibitor (ACE inhibitor) "Lisinopril" ("Astrapharm", Ukraine) in the dose of 20 mg/kg/day (group 3), intragastric "Glutargin" (0.75g, LLC "Zdorovya") in therapeutic and prophylactic dose [18] of 30 mg/kg/day (group 4), intragastric 20% CCl<sub>4</sub> Solutio oleosa in the dose of 0.1 ml/100 g of body weight twice a week in combination with 5% ethanol solution, as well as "Glutargin" (0.75g, LLC "Zdorovya") in the dose of 30 mg/kg and "Lisinopril" in the dose of 20 mg/kg (20 mg, LLC "Astrapharm") (group 5). On completion of the experiment, the animals were withdrawn under thiopental narcosis in euthanasia conditions by decapitation, and collection of blood for biochemistry was done.

The content of TGF- $\beta$  and IGF-1 was determined by enzyme immunoassays using the following kits: "Rat TGF beta 1 Platinum ELISA" (eBioscience, Austria) for TGF- $\beta$ , "m/r IGF-1-ELISA (IGFBP-blocked)" (Mediagnost, Germany) for IGF-1, as directed by producer company.

The protocol of examination of patients and conditions of research was approved by the Committee on Bioethics by Vinnytsia National Pirogov Memorial Medical University (protocol number 8 dated September 5, 2018).

The statistical analysis of the obtained digital results was carried out using parametric and nonparametric methods of the STATISTICA 5.5 statistical software package (belongs to VNMU named after Pirogov, license No. AXXR910A374605FA) using parametric and nonparametric methods.

The normal distribution of features for each of the obtained variation series, standard errors, and deviations of the mean for each feature were estimated.

The significance of differences in values between independent quantitative variables with a normal distribution was determined using the Student's test, in other

cases – by the Mann-Whitney U test.

**Research results and discussion.** The study found that plasma levels of TGF- $\beta$ 1 in rats with CCl<sub>4</sub> induced CTH, were increased by 13.5% compared with animals of the intact group ( $p < 0,05$ ), which confirms its pathogenic role in this pathology as a cytokine with anti-inflammatory and strong antifibrotic properties. The findings overlap with experimental work published by Farouk K. El-Baz et al. in 2019, which investigated TGF- $\beta$ 1 levels in 40 rats with thiochetamide-induced hepatic fibrosis. The average level of TGF- $\beta$ 1 in the study group was two times higher than that in the control group: ( $34,33 \pm 0,70$  and  $65,07 \pm ,.80$ ) pg/l respectively [19].

We used L-arginine L-glutamate as well studied, local cytoprotective agent with pronounced antihypoxic and membranostatic effects to compare the antifibrotic effect of lisinopril. Therapeutic administration of L-arginine L-glutamate showed a decrease of the TGF- $\beta$ 1 level by 36,7% ( $p < 0,05$ ) compared to the untreated group of animals, which confirms the therapeutic effect of that drug in CTH. Comparable results were obtained by Krylova O.A. (2016) who studied the dynamics of immune response and inflammatory mediators by the treatment of patients with chronic pancreatitis. The serum TGF- $\beta$ 1 concentrations statistically significantly decreased in patients with L-arginine L-glutamate (from  $39,34 \pm 8,05$  to  $22,12 \pm 3,37$ ) pg/l [20].

A comparative analysis of our experimental studies' results showed that Lisinopril treatment reduced the serum TGF- $\beta$ 1 levels by 54,11% ( $p < 0,05$ ) compared to untreated animals. Our results are consistent with previous

reports on the effects of the ACE inhibitors on the serum TGF- $\beta$ 1 dynamics published by Qing-Qing Fang et al. in 2018 [21].

The TGF- $\beta$ 1 level was reduced by 21% in the group of hepatotoxins animals with lisinopril and glutargin administration compared to animals with CTH that did not receive drug correction ( $p < 0,05$ ) (table).

The analysis of recent studies on the IGF-1 dynamics in liver diseases is mixed. Hitoshi Nishizawa et al. (2016) indicates a decrease in serum IGF-1 levels in patients with chronic diffuse liver diseases [22]. At the same time, Stefano J. et al. describes an increase in the concentration of IGF-1 in the blood of patients with acute viral hepatitis, as a result of an increase in the number of IGF-1 receptors in the liver tissue [23].

During our research with the introduction of hepatotoxins, an increase in the IGF-1 content in the blood serum by 2,7% was found compared with intact animals.

Therapeutic administration of glutargin showed decreasing of the IGF-1 level by 7,6% (from  $318,40 \pm 25,86$  to  $335,74 \pm 19,38$  pg/l,  $p < 0,05$ ); with the administration of lisinopril - by 2, 6% (from  $335,90 \pm 32,26$  to  $335,74 \pm 19,38$  pg/l,  $p < 0,05$ ), while the most significant decrease in the concentration of this anti-inflammatory cytokine occurred with the simultaneous administration of both drugs, which was 10,5% (from  $308,53 \pm 18,98$  to  $335,74 \pm 19,38$  pg/l,  $p < 0,01$ ).

Research findings showed that plasma TGF- $\beta$ 1 levels in rats with CCl<sub>4</sub>-induced CTH were increased by 13,5% compared with animals of the intact group ( $p < 0,05$ ), confirms

**Table.** The content of TGF- $\beta$  and IGF-1 in the blood plasma of rats with CTH and drug correction (M  $\pm$  m)

| Groups of animals            | Values                           |                                      |
|------------------------------|----------------------------------|--------------------------------------|
|                              | IGF-1 (pg/l)                     | TGF- $\beta$ 1 (pg/l)                |
| Intact rats                  | $335,74 \pm 19,38^{\gamma}$      | $55,31 \pm 9,89^{\alpha\beta}$       |
| CTH                          | $344,74 \pm 16,72^{\beta\gamma}$ | $62,77 \pm 2,87^{\alpha\beta\gamma}$ |
| CTH + lisinopril             | $335,90 \pm 32,26$               | $28,80 \pm 9,29^{* \# \beta \gamma}$ |
| CTH + glutargin              | $318,40 \pm 25,86^{\#}$          | $39,69 \pm 6,16^{* \# \alpha}$       |
| CTH + lisinopril + glutargin | $308,53 \pm 18,98^{* \#}$        | $49,59 \pm 10,30^{* \alpha}$         |

**Note:** \* –  $p < 0,05$  compared with intact animals; # –  $p < 0,05$  with CTH animals;  $\alpha$  –  $p < 0,05$  with a group of CTH rats treated with lisinopril;  $\beta$  –  $p < 0,05$  with a group of CTH rats treated with glutargin;  $\gamma$  –  $p < 0,05$  compared with CTH rats, which were administered lisinopril and glutargin.

its pathogenetic role in this pathology as a cy-

tokine with anti-inflammatory and strong antifibrotic properties. Therapeutic administration

of L-arginine L-glutamate showed decreasing of the TGF- $\beta$ 1 level by 36,7% ( $p < 0,05$ ) compared with untreated animals, indicating a certain therapeutic effect of this drug in CTH.

The drug correction with Lisinopril was the most effective, according to the results of our experimental studies, since the plasma TGF- $\beta$ 1 levels decreased by 54,11% ( $p < 0,05$ ) in comparison with untreated animals.

The TGF- $\beta$ 1 level was reduced by 21% in the group of hepatotoxins animals with lisinopril and glutargin administration compared to animals with CTH that did

### Conclusions

1. In our research, with the administration

of hepatotoxins to animals, an increase in the plasma levels of TGF- $\beta$  and IGF-1, cytokines with profibrogenic and anti-inflammatory effects, was shown compared with intact animals, which indicates signs of chronic inflammation in the liver;

2. Therapeutic correction of CTH with combination of lisinopril and glutargin resulted in decrease of serum IGF-1 level in rats;

3. TGF- $\beta$  decrease appeared to be the most significant in therapeutic correction of CTH with lisinopril, while it was less evident when using glutargin or combination of those drugs not receive drug correction ( $p < 0,05$ ).

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**Рыкало Н.А., Олейник Ю.М., Семенчук С.А., Иваница А.О.**

## **КОНЦЕНТРАЦИЯ IGF - 1 И TGF - $\beta$ В КРОВИ ПРИ ХРОНИЧЕСКОМ ТОКСИЧНОМ ГЕПАТИТЕ У КРЫС И ЕГО КОРРЕКЦИИ ЛИЗИНОПРИЛОМ**

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**Резюме.** В статье представлены материалы по определению концентрации IGF-1 и TGF- $\beta$  при хроническом токсичном гепатите и его медикаментозной коррекции лизиноприлом. Экспериментальные исследования проведены на 60 нелинейных белых лабораторных крысах с исходной массой тела 60-80 г. Животные были разделены на 5 групп по 12 крыс в каждой. Группа 1 - интактные крысы. Хронический токсический гепатит моделировали у животных 2-й, 3-й, 4-й и 5-й групп путем внутрижелудочного введения маличного раствора CCl<sub>4</sub> в дозе 0,1 мл / 100 г массы тела два раза в неделю в сочетании с 5% раствором этанола в течение шести недель. Крысам 2-й группы никаких других препаратов не вводили. Помимо CCl<sub>4</sub>, животные остальных групп получали «Лизиноприл» в дозе 20 мг / кг (группа 3), «Глутаргин» в дозе 30 мг/кг (группа 4), CCl<sub>4</sub>, а также «Глутаргин». в дозе 30 мг/кг и «Лизиноприл» - 20 мг/кг (группа 5). Исследование демонстрирует повышенные уровни TGF- $\beta$  и IGF-1 в сыворотке крови у крыс, получавших гепатотоксины, что указывает на хроническое воспаление в печени. Корректирующая комбинированная терапия лизиноприлом и глутаргином способствовала снижению уровня сывороточного IGF-1 у крыс. Использование лизиноприла в экспериментальной ХТГ приводило к двукратному снижению содержания TGF- $\beta$  по сравнению с нелеченными животными.

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