The Relationship between Serum IGF-1 and Hydroxyproline Levels in the Rats with Chronic Toxic Hepatitis

N.A.Rykalo, Y.M.Beregovenko

Vinnytsia National Pirogov Memorial Medical University

(Pirogov str. 56, Vinnytsia, Ukraine, 21018)

Key words: chronic toxic hepatitis, rats, IGF-1, lizinopril

Urgency of the research. Pathogenic action of toxic factors is proved to result in liver dysfunction, having the negative impact on the level of insulin-like growth factor-1 (IGF-1) in blood, but information about the mechanisms of this influence on hepatocytes is limited and controversial [4]. It is well known that hepatocytes begin to secrete IGF-1 during the inflammatory reaction, thus inhibiting the inflammatory response by decreased macrophagal infiltration and IGF-1 level, decreasing oxidative stress as well as inhibiting apoptosis of parenchymal cells and endothelial cells [6]. Increase of IGF-1 concentration in toxic liver injury, it being synthesized by Kupffer's cells and stellate Ito's cells, is indicative of importance of this factor in the process of liver fibrosis development [1, 9, 12, 15]. Release of IGF-1 is stimulated by somatotropic hormone. Anti-inflammatory and hepatoprotective properties of IGF-1 have been proved by a number of investigations presented in the literature. The studies demonstrated IGF-1 to play an important role in apoptosis inhibition [8]. It is known that at liver cirrhosis the intensity of the processes of synthesis and decay of collagen reflects fractions of hydroxyproline (HP) [2, 3, 5]. According to the literature, the maximum collagen synthesis occurs when chronic toxic hepatitis (CTH) is active, as evidenced by an increase in the serum content of peptide-bound hydroxyproline (PHP), which characterizes collagen formation [13]. In these patients there is and probable increase of free hydroxyproline (FHP), which reflects the processes of synthesis and destruction of immature collagen on the background of decreasing elastase activity. For this reason, the problems of mechanisms of regulatory factors triggering the processes of reparative regeneration after toxic hepatocyte damage in CTH are still urgent.

Objective: to study the content of profibrogenic cytokine IGF-1 in rats under conditions of experimentally modeled chronic toxic hepatitis and drug correction with lizinopril.

Materials 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 20% CCl_4 Solutio oleosa in the dose of 0.1 ml/100 g of body weight and 5% ethanol solution twice a week [7]. 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) “Lizinopril” (“Astrapharm”, Ukrain) in the dose of 20 mg/kg/day (group 3), intragastric “Glutargin” (0.75g, LLC "Zdorovya") in therapeutic and prophylactic dose of 30 mg/kg/day (group 4**)** [14], intragastric 20% CCl_4 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 “Lizinopril” 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 blood was centrifuged for 15 minutes at the speed of 3000 rotations per minute on the laboratory centrifuge OPn-3 with separation of plasma for further biochemical examination. The content of profibrogenic cytokines IGF-1 and TGF-β1 [11] was determined by enzyme immunoassays. Serum FHP, PHP and total hydroxyproline (THP) were determined as well [10].

Results and discussion. After the administration of hepatotoxins, serum IGF content increased by 2.7% in experimental animals as compared to the intact rats (344.74±16.72 versus 335±19.38 pcg/l, $p>0.05$). After therapeutic prophylactic administration of glutargin, serum IGF content decreased by 7.6% (318.40±25.86 versus 335±19.38 pcg/l, $p<0.05$), in lizinopril administration – by 2.6 % (335.90±32.26 versus 335±19.38 pcg/l, $p>0.05$), while the most significant decrease

of this anti-inflammatory cytokine concentration occurred in simultaneous administration of both drugs - by 10.5 % (308.53±18.98 versus 335±19.38 pcg/l, $p<0.01$).

Strong direct correlation relationship between IGF and PHP concentration (0.78, $p<0.05$) was found in the animals who received corrective combination treatment with lizinopril and glutargin, indicated by significant decrease of PHP level together with the decrease of IGF concentration. Besides, significant increase of FHP and PHP concentrations was found in the rats with CTH. The use of lizinopril as monotherapy of experimental CTH, as well as its combination with glutargin, significantly decreased the content of PHP, an important factor of fibrosis formation in the liver [10].

Table 1. Correlation relationship between IGF-1 level and hydroxyproline fractions in studied groups (plasma).

IGF-1		
Intact (Group 1)		
FHP	PHP	THP
-0.58	-0.23	-0.73

IGF-1		
CCl4 (Group 2)		
FHP	PHP	THP
-0.55	-0.19	-0.26

IGF-1		
CCl4+Lizinopril (Group 3)		
FHP	PHP	THP
0.58	0.49	0.55

IGF-1		
CCl4+Glutargin (Group 4)		
FHP	PHP	THP
0.86	-0.47	0.40

IGF-1
CCl4+Lizinopril+Glutargin (Group 5)

FHP	PHP	THP
-0.77	0.78	0.59

Conclusions:

1. The use of lizinopril in experimental CTH resulted in normalization of serum IGF-1 level, which is likely to have favorable prognosis in chronic liver pathology.
2. Strong direct correlation relationship between IGF and PHP concentrations was found in the animals who received combination therapy with lizinopril and glutargin for correction, confirmed by significant decrease of PHP on the background of IGF concentration decrease.

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Vinnytsia National Pirogov Memorial Medical University

Abstract. The values of profibrogenic cytokine IGF-1 content in the rats under conditions of experimentally modeled chronic toxic hepatitis and drug correction with lizinopril are presented in the article. Experimental studies were carried out on 60 non-linear white laboratory immature rats, with an initial body weight of 50-70 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 20% CCl_4 Solutio oleosa in the dose of 0.1 ml/100 g of body weight and 5% ethanol solution twice a week [7]. 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) “Lizinopril” (“Astrapharm”, Ukrain) in the dose of 20 mg/kg/day (group 3), intragastric “Glutargin” (0.75g, LLC "Zdorovya") in therapeutic and prophylactic dose of 30 mg/kg/day (group 4**)** [14], intragastric 20% CCl_4 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 “Lizinopril” in the dose of 20 mg/kg (20 mg, LLC “Astrapharm”) (group 5). The use of lizinopril in experimental CTH resulted in normalization of serum IGF-1 level, which is likely to have favorable prognosis in chronic liver pathology. Besides, strong direct correlation relationship between IGF and PHP concentration was found in the animals who received corrective combination therapy with lizinopril and glutargin, indicated by significant decrease of PHP on the background of IGF concentration decrease.

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