STATE OF GASTRIC MUCOSA AND SMALL INTESTINE NITRO-ERGIC SYSTEM DURING CHRONIC HELIOTRINE-INDUCED HEPATITIS

M. Kulmanova, R. Sabirova
Tashkent Medical Academy,
Farobi Str., 2, Tashkent 100100 Uzbekistan
munozat.kulmanova@mail.ru

Abstract. In chronic heliotrine-induced hepatitis (CHH), in the tissues of the mucous membrane of the ventricle and bowels an endothelial dysfunction, characterized by a decreased level of NO is formed. In CHH, eNOS activity decreases due to the action of endotoxins on the gastric mucosa tissue and bowels entering to the central bloodstream from the liver. At the same time, they initiate iNOS and formation of ONOO⁻ that leads to inhibition of eNOS. It appears as potentiating effect of endotoxins’ action produced in the liver in CHH in response to the inhibition of mucous membrane of the ventricle and bowels eNOS activity, initiation of iNOS, ONOO⁻ formation – an important cytotoxic / cytostatic compound, enhancing the proliferative and apoptotic processes, as a result, a high level of degradation and desquamation of the intestinal epithelium of the mucous membrane of the ventricle and bowels. Studied indicators of nitro-ergic system in the mucosa of the ventricle and bowels at CHH change in one direction.

Keywords: chronic hepatitis, the system of nitric oxide, mucous membrane, ventricle, bowels.

The Republic of Uzbekistan is in Central Asia wherein chronic viral hepatitis is widespread (Abdurakhmanov, 2010; Alimova and Nigmatov, 2003; Kosagovskaya and Volchkova, 2013).

Improving in their diagnosis and treatment is connected with the knowledge of cellular and molecular mechanisms of inflammation in the liver, which reveal the essence of the pathological process (Ivashkin, 1998; Mayer, 2004; Sherlok and Duli, 1999).

In the pathogenesis of hepatitis, particular importance falls on the abnormality of tissue homeostasis mucous membrane (MM) of the gastrointestinal tract, which is an important factor in favor congestion and venous stasis. All these suppose the involvement of the pathogenesis of destabilization of cellular and intracellular membranes in the mucosa of the gastrointestinal tract in patients with chronic hepatitis abnormalities of the endothelial function. An important regulator of the latter is nitric oxide (NO). Along with regulatory functions of NO, cytotoxic activity is detected, it can destroy DNA molecule, participate in the development of accelerated cell apoptosis and necrosis and permeation of cell membranes (Aguiar, Masse and Glibbs, (2005); Habib and Abi, 2011). NO molecule is synthesized in response to physiological need for NO-synthase enzyme from its metabolic precursor amino acids L-arginine, (Hirst and Robson, 2011).

Currently, NO is considered as a signal molecule of the digestive system, since it stimulates relaxation of the smooth muscles of the esophagus, ventricle, small and large bowels, gall bladder, sphincter of ampulla of the pancreaticobiliary channel (Oddi) (Glemens, 1999; Leung Tung-Ming, Tipoe, Liong et al., 2010). Under physiological conditions, the endogenous NO – one of the mediators of exocrine pancreas secretion and mucin-producing cells of the gastric mucosa and bowels, stability, nonspecific and specific mucosal protection from the action of internal and external corrosive environmental factors (Abdullaev, Kleyner and Ruzibakiev, 1985; Pshennikova, 2011). The literature provides information on the status of NOS in the mucosa of the ventricle and bowels, its role in the pathogenesis of chronic hepatitis B, which determines the importance of the problem and the need for further research.

Purpose of the work

Determining the level and activity of endothelial NO and inducible NOS (NOS and e iNOS) and peroxynitrite concentration (ONOO⁻) in the development dynamics of chronic heliotrine-induced hepatitis (CHH) in the mucous membrane of the ventricle and small intestine.
Material and methods

We used 70 albino male rats weighing 100-120 g divided into 2 groups: group 1 – animals with chronic heliotrine-induced hepatitis; 2nd group – control.

Chronic heliotrine-induced hepatitis was reproduced through oral penetration of heliotrine solution acidified with hydrochloric acid (pH 7.0) at the rate of 50 mg / kg (5 mg heliotrine100 g) weight once a week for 42 days by the method of N. Kh. Abdullayev and co-authors (Abdullaev, Kleyner and Ruzibakiev, 1985).

Mortality – 8%. The animals were slaughtered on the 60th, 90th and 120th days of the experiment.

NOS condition in the supernatant homogenates of ventricle mucosa and intestine were evaluated in the concentration of NOx major stable metabolite of nitrate and nitrite (NO$_2^-$ and NO$_3^-$) on P.P.Golikov method (Golikov, Nikolaeva, Gavrilenko et al., 2000) as well as the activity of NO-synthases (NOS): endothelial (eNOS) – on V. V. Sumbaev, I. M. Yasinskaya (Sumbaev and Yasinskaya, 2003) and inducible (iNOS) – on A. S. Komarin, R. K. Azimov (Komarin and Azimov, 2005). Peroxynitrite level (ONO$_2^-$) was determined by the method A. S. Komarin, R. K. Azimov (Starodubseva, 2011).

Experiments were carried out in accordance with international standards adopted when dealing with experimental animals.

The study results are processed with software programs Statistica 6, Biostat. Data are presented as arithmetic means (M) and standard deviation (m). For comparison, samples were used Student's t-test. The level of significance was considered significant at P <0.05.

Results and discussion

In observation of the dynamics in the gastric mucosa and intestine in rats, we observed reduction of the oxide (see Table), the most expressed on the 120th day of the experiment – respectively 1.3 and 1.5 times, compared to the control.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>The control group</th>
<th>CHH, day</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO, mmol / l</td>
<td></td>
<td>60-</td>
</tr>
<tr>
<td>in the ventricle</td>
<td>2,3±0,1</td>
<td>2,1±0,05</td>
</tr>
<tr>
<td>in bowel</td>
<td>10,6±0,47</td>
<td>9,2±0,27</td>
</tr>
<tr>
<td>eNOS, mcM / min / liter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in bowel</td>
<td>6,2±0,29</td>
<td>5,8±0,17</td>
</tr>
<tr>
<td>in bowel</td>
<td>9,3±0,44</td>
<td>8,3±0,30</td>
</tr>
<tr>
<td>iNOS, mcM / min / liter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in the ventricle</td>
<td>0,10±0,005</td>
<td>0,11±0,005</td>
</tr>
<tr>
<td>in bowel</td>
<td>0,15±0,006</td>
<td>0,17±0,011</td>
</tr>
<tr>
<td>ONO$_2^-$, mcM / liter:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in the ventricle</td>
<td>0,04±0,002</td>
<td>0,05±0,007</td>
</tr>
<tr>
<td>in bowel</td>
<td>0,13±0,006</td>
<td>0,14±0,010</td>
</tr>
</tbody>
</table>

Note. * – P <0.05 compared to control.

Reducing the concentration of NO, presumably was due to a decrease in tissues of ventricle CO and bowels eNOS activity. As seen from the table, the activity of eNOS in gastric mucosa as well as bowel in 90th and 120th days of experiment significantly reduced respectively by 21%, 29% and 28%, 32.3%. One reason for the low activity of eNOS in the mucosa of the ventricle and bowels at CHH, apparently, is the expression of ONO$_2^-$ as a result of initiation iNOS activity.

INOS activity induced is most expressed on the 120th day of experiment, compared with the rate control in the mucosa of the ventricle and bowels, respectively 90 and increased to 106.6%. Upon activation of iNOS, high concentration of NO is formed, and at pathological conditions, cells react with oxygen, superoxide (O$_2^-$) with formation of ONO$_2^-$ (Komarin and Azimov, 2005).
In our studies, the content of \( \text{ONO}_2 \) on 90th and 120th days of the experiment, respectively, increased by 2.5; 3.75 and 1.77; 2.15 times.

Consequently, at CHH, there is an expressed endothelial dysfunction in the tissues of the gastric mucosa and intestine, which is a characteristic feature of reducing NO level. At CHH, eNOS activity decreases due to the action of endotoxins to gastric mucosa tissue, and bowels, entering to the central bloodstream from the liver. They initiate iNOS and formation of \( \text{ONO}_2^- \) that leads to inhibition of eNOS. In our experiments, it appears as potentiating effect of endotoxins’ action produced in the liver in CHH in response to the inhibition of mucous membrane of the ventricle and bowels eNOS activity, initiation of iNOS, \( \text{ONO}_2^- \) formation – an important cytotoxic / cytostatic compound, enhancing the proliferative and apoptotic processes (Shibata, Nagata and Kovayaghi, 2011), as a result, a high level of degradation and desquamation of the intestinal epithelium of the mucous membrane of the ventricle and bowels.

**Conclusion**

The results showed that at the mechanism of endogenous intoxication, high epithelial proliferation in the mucosa of the ventricle and bowels, the processes of endothelial dysfunction play main role. The dynamics of the studied parameters of nitro-ergic system in the mucous membrane of the ventricle and bowels have unidirectionality in chronic heliotrine-induced hepatitis.

**References**


---

