Disturbance of Biosynthesis of Membrane Phospholipids in Acute Alcohol Intoxication and Possible Mechanisms of Regulation

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Key words
Acute alcohol intoxication; molixan; glycerokinase; glycerophosphate dehydrogenase; glycerophosphate; biosynthesis of phospholipids

The activity of enzymatic systems of phosphatidogenesis and lipid-lipid ratios in biomembranes can reflect the ability of the cell to react to changes occurring in tissues and organs in pathological conditions and in dynamics of therapy [1-3]. At the same time, it is known that, the treatment of acute severe intoxication with ethanol remains ineffective and is a frequent cause of death.

It has been established, that the preventive use of molixan in case of intoxication, caused by the introduction of ethanol at the dose of 1.5 LD50 (12 g/Kg) significantly reduced the severity of poisoning, decreased the number of animals that were in terminal coma 4.9 times, increased the survival rate of rats by 66% [4].

Considering, that the biosynthesis of phosphatide-glycerides begins with a glycerocyanase reaction catalyzing the formation of L-α glycerophosphate (L-α-GF), we considered it interesting to follow the patterns in the variation in L-α-GF and the activity of glycerokinase (GC).

Simultaneously followed the patterns in the changes in the activity of mitochondrial and cytoplasmic glycerophosphate dehydrogenases (L-α-GFD), catalyzing respectively the oxidation reaction of (L-α-GF), (direct reaction) with the formation of dihydroxyacetone phosphate (DOAP) and reduction of DOAF to (L-α-GF), (reversible reaction). This would help to identify the nature of the limiting mechanisms for the formation of L-α-GF, in norm and in case of acute alcohol intoxication, as well as to identify possible mechanisms for the regulation and correction of disturbed metabolic processes.

Materials and Methods
The studies were performed on 34 white outbred male Wistar rats weighing 200-220 g. A day before the introduction of ethanol, the animals were not fed. Ethanol

Abstract
A study of the mechanisms of the action of molixan in acute ethanol intoxication at a dose of 1.5 LD50 indicates its positive effect on the processes of biosynthesis of membrane phospholipids. The obtained data are solid evidence of the high efficiency of molixan in the regulation of the activity of enzymes of phosphatidogenesis-glycerol kinases and glycerol-3-phosphate dehydrogenases, as well as the level of glycerophosphate in acute alcohol intoxication, which indicates the prospective use of the given preparation in practical medicine.

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was administered intraperitoneally in the form of 40% aqueous solution at a dose of 12 g/Kg body weight; per two times with a 15 minute interval.

Molixan was administered intraperitoneally at a dose of 30 mg/kg body weight. Rats were divided into 2 experimental groups of 12 animals in each group. The liver was isolated and treated in the cold. Used mitochondria and sub mitochondrial fluid (microsomal fraction) of the homogenate obtained after centrifugation of the latter at 17000 g.

The activity of glycerol kinase, L-α-GFD, (catalyzing the direct reaction) and the content was determined micro spectrophotometrically by the Kennedy method; activity of the (L-α-GFD), (catalyzing the reversible reaction) activity was determined using DOAF as the substrate of the enzyme [2]. The latter was obtained by enzymatic cleavage of fructosodiphosphate. The obtained data were expressed in μmoles per 1 g fresh tissue.

Statistical data processing was performed taking into account differences and reliability of Student’s criterion.

Table 1: Activity of glycerokinase and L-α-GFD in membrane structures of rat hepatocytes in acute ethanol poisoning and after application of molixan (μmol per 1 g of fresh tissue)

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Control n=10</th>
<th>Alcohol intoxication n=12</th>
<th>After applying molixan n=12</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerokinase</td>
<td>1.20.01</td>
<td>0.230.02</td>
<td>0.8 0.02</td>
<td>P1&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2&lt;0.001</td>
</tr>
<tr>
<td>L-α-GFD (direct reaction)</td>
<td>6.7 0.15</td>
<td>3.1 0.12</td>
<td>5.80.09</td>
<td>P1&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2&lt;0.001</td>
</tr>
<tr>
<td>L-α-GFD (reverse reaction)</td>
<td>7.2 0.20</td>
<td>2.4 0.07</td>
<td>6.50.17</td>
<td>P1&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2&lt;0.001</td>
</tr>
</tbody>
</table>

Note: P1 - comparison of experience data with control
P2 - comparison of data after application of molixan with experimental data

Results and discussion

The results of the observations (Tables 1, 2) indicate a notable, statistically significant decrease in the liver hepatocyte membrane structures of the activity of the studied enzyme systems and lipid metabolites (GF) in acute severe alcohol intoxication. In the liver, the activity of GK is significantly inhibited (by 80%). Herewith, it is noted a sharp, statistically significant suppression of GDF activity in the oxidation of GF in DOAF (p<0.001).

When studying the reverse reaction of DOAF to L-α-GFD, a more pronounced (66%) decreased activity of GDF in the DOAF reduction reaction in the GF was identified. As follows, from table 2, after double intraperitoneal injection of ethanol in the liver tissue, the level of L-α-GF is decreased by 45%.

When studying the efficacy of molixane in acute ethanol intoxication, a simultaneous increase in the activity of all the enzyme systems studied before the level of control values. It is noteworthy, that under these conditions a statistically significant (p<0.001) increase in the activity of GDF in the direct reaction and almost complete normalization of the activity of the studied enzyme in the reaction of the reduction of DOAF in the GF (p<0.001), was observed.

It should be emphasized that the increase in the level of L-α-GF, is less pronounced. This can partially explain the elevated blood level of unesterified fatty acids.

Activation of both glycerokinase and glycolytic pathways for the formation of L-α-GF in acute severe ethanol poisoning against the background of the use of molixan indicates the regulating effect of the latter on the processes of biosynthesis of membrane phosphatides-glycerides.

Considering that molixan is a hepatoprotective agent with an immunostimulating effect and regulates thiol-disulphide metabolism, as well as inhibits the cytolysis of functionally active hepatocytes, induces apoptosis, it can be assumed that the preparation is also a regulator of the initial stages of the biosynthesis of phosphatides-glycerides [4, 5]. It is possible that a significant decrease in the content of the L-α-GF basic metabolite of lipogenesis...
in the liver under the influence of molixan in acute severe ethanol poisoning can be considered as a consequence of changes in L-α-GF–acyltransferase [6].

The obtained data are convincing proof of the high efficiency of molixan in the regulation of the activity of glycerokinase, glycerophosphate dehydrogenase and the level of glycerophosphate in acute alcohol intoxication, which indicates the prospects of using this drug in practical medicine.

References


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<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-α-GF</td>
<td>2.40.05</td>
<td>1.40.07</td>
<td>1.90.04</td>
<td>P₁ &lt;0.01, P₂ &lt;0.05</td>
</tr>
</tbody>
</table>

Table 2: The level of L-α-GF, in the membrane structures of rat hepatocytes in acute ethanol poisoning and after the application of molixan