INTRODUCTION

Among the various mental disorders anxiety disorders are the most common [15]. In modern conditions of social instability and socio-economic reconstruction of society anxiety becomes a chronic phenomenon. Many stressful situations can cause anxiety and it remains even after the disappearance of the traumatic situation. Throughout life, they develop in approximately 25% of the population. When referring to doctors in General medical practice the symptoms of pathological anxiety are detected in 30-40% of patients [7]. Anxiety disorders, in addition to the General (generalized) anxiety include panic, social anxiety (phobia), agoraphobia, stress, post-traumatic and obsessive-compulsive disorder. Stress response, dissociation (conversion), somatoform and other neurotic disorders, also belong to the group of anxiety disorders. They have a complex pathogenesis and are the result of acute anxiety. The high frequency of anxiety disorders, accession depressive component, an unfavorable course and prognosis of somatic diseases, explains the significant need for anxiolytic therapy in this group of patients [8; 17]. The proportion of patients remains resistant to the therapy or refuse that requires the development of new anxiolytics, notably including derivatives of 2-oxoindolyn-3-hydroxylic acid.

Psychopharmacology has been given priority of the security of treatment, focuses on the importance of matching the clinical efficacy and adverse reactions and tolerability of the drugs. Anxiolytics in the system of prevention of stress disorders takes a well-deserved place, so neuropharmacology should be directed to the normalization of stress-realizing and stress-limiting systems of the organism, and effectively adjust streammovies of conduct disorder [1]. The derived 2-oxoindole in previous studies effectively warned somatic, metabolic disturbances, and corrected excessive lipid peroxidation in acute immobilization stress and modified the emotionally-behavioral reactions of rats in the intact animals in behavioral tests [6].

AIM OF THE STUDY

It is therefore advisable to study the effect of derived 2-oxoindole-3-glioxil acid on emotional and behavioral responses subjected to stress of rats in behavioral tests of various
The effect of derived 2-oxoindole-3-naftaline acid on emotionally-behavioral reactions of animals in “open field” test under acute stress (M±m).

<table>
<thead>
<tr>
<th>Group of animals (n=10)</th>
<th>Latent period</th>
<th>Number of rising</th>
<th>Number of coming to the center</th>
<th>Number of crossing squares</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact control</td>
<td>1.2±0.4</td>
<td>19.6±2.2</td>
<td>3.9±0.3</td>
<td>99.8±9.48</td>
</tr>
<tr>
<td>Control on injection (control group)</td>
<td>1.1±0.2</td>
<td>18.5±1.8</td>
<td>4.5±0.4</td>
<td>120.1±6.96</td>
</tr>
<tr>
<td>Acute stress (control pathology)</td>
<td>2.6±0.5*</td>
<td>10.6±1.1*</td>
<td>2.8±0.3*</td>
<td>51.5±3.80*</td>
</tr>
<tr>
<td>Acute stress + compound 18</td>
<td>1.4±0.2**</td>
<td>14.1±1.0**</td>
<td>5.6±0.4**</td>
<td>107±8.0**</td>
</tr>
<tr>
<td>Acute stress + diazepam</td>
<td>1.5±0.17</td>
<td>12.5±0.99</td>
<td>8.3±0.76**</td>
<td>70.1±5.67**</td>
</tr>
</tbody>
</table>

Notes:
1. # _p<0.05 compared with intact control;
2. * _p<0.05 compared with control on injections;
3. ** _p<0.05 compared with the control pathology.

MATERIALS AND METHODS

The experiments were performed on 150 white rats-males Wistar weighing 150-200 g, grown in vivarium HEE of Ukraine “Ukrainian medical stomatological Academy” (Poltava), which is equipped in accordance with existing sanitary standards. Experiments were performed in spring from 18.00 to 20.00 hours. For the study used a derivative of 2-oxoindole (2-hydroxy-N-naftaline-1-yl-2-(2-hydroxy-1,2-dihydroindol-3-ilden)-acetamid) laboratory code 18. Substance suspendable ex tempore in water for injections, using the emulsifier “Tween-80” and was administered to animals at a dose of 12 mg per kg of body weight intraperitoneally 1 hour before the start of the playback of acute immobilization stress, which was simulated by Selye through rigid immobilization of rats on the back for three hours [2]. Animals of the control group was administered as a solvent (1 ml of water for injection with emulsifier) and subjected to the same exposure as experimental animals. As a reference drug used diazepam (“Tarchomin S. A., Poland) at a dose of 2 mg/kg.

Emotionally-behavioral reactions of animals after stressing effects were assessed in open field test. To analyze the behavior uses the following physiological indicators: the latent period of the first move (sec.) the number of exits to the center, ambulace (horizontal activity), the number of columns (vertical activity), indicators of autonomic balance: the number of acts of grooming and acts of defecation by the number of fecal boluses and latent period of the first moving and reduce the number of boluses in 1.9 times in comparison with intact animals (p<0.001) (fig. 1).

RESULTS AND DISCUSSION

After 1 h after injection of the solvent with an emulsifier in the control group significant changes of investigated parameters were noted in comparison with the values of intact animals (table. 1).

After playing the acute immobilization stress in rats was observed the changes of emotional-behavioral reactions. First of all suppressed research activity, as evidenced by the increase in the latent period of the first moving 2.3 times compared to control (p<0.01) and a decrease in the number of outputs in the center of the “open field” in 1.6 times in comparison with indicators of intact animals, which were injected solvent (p<0.01). Under the influence of acute stress has varied indicators of motor activity, as indicated by the reduction of 2.3 times the number of crossed squares (p<0.001) and 1.9 times the number of the standing in comparison with the control group rats (p<0.002). In experimental pathology experimental animals, along with the violation of exploratory parameters were varied vegetative reactions, as indicated by the decrease in the number of washings 1.9 times compared to control (p<0.0001) and an increase in the number of boluses in 1.9 times in comparison with intact animals (p<0.001) (fig. 1).

Thus, after playback of acute immobilization stress decreased the activity of rats in open field test, as indicated by the increase in the latent period of the first moving and reduce the number of outputs in the centre and evidence of the violation of the processes of adaptation to new conditions of stay and the presence of feelings of anxiety and discomfort. Also raised aversives because of experimental anxiety has a heterogeneous character and is a companion to emotional stress [5].
research activity in the form of reducing the number of ambulance and vertical standing. The revealed changes indicate the inhibition of interest and interest in the environment. Against this background, a significant decrease in the number of acts of grooming and inversely proportional to the change in the number bolus balls are the important patterns of violations of the emotional sphere of animals, there is a sense of anxiety that accompanies exposure to stressing factor [9]. The change of emotional-behavioral reactions, obviously, testifies to the disturbing nature of stress-induced behavior disorders. These mental disorders can be regarded as a consequence of hyperproduction of hypothalamic corticis, which is considered as a mediator of stress from anxiety, and central activation of sympa-tho-adrenal system, which is always observed in the effects on the body emergency factors [14].

Application of the substance 18 is reliably warned of stress change of the latent period of the first moving compared to the stress without correction. After prophylactic administration of a derivative of 2-oxoindole-3-glyoxylic acid number of outputs in a center increased 2 times as compared to that under acute stress without pharmacoproteomic (p<0.01) (table. 1). Motor activity was characterized by the increase in the number of crossed squares in 2.6 times (p<0.001) and increase in the number of the standing 1.6 times (p<0.05) in comparison with stress without correction. Use of a compound with the laboratory code 18 warned stress violations of motor activity of rats. A quantitative index of ambulance grew 2.1 times (p<0.001), significantly increased the number of vertical standing compared with the control pathology (p<0.001) (figure). In conditions of acute stress diazepam increased the number of exits in the center of the open field 3 times in comparison with stress without correction (p<0.001). The reference drug significantly increased the number peresta squares and reduced the number bolus balls compared with the control pathology without correction (table. 1; figure).

Compound 18 was reduced latent period of the first moving and increased the number of exits to the center “open field”. So it warned the disturbed processes of adaptation to stress and reduced anxiety, which is especially enhanced under conditions of novelty under which the experimental animal is. The derived 2-oxoindole normalized reduced stress horizontal and vertical motor activity and decreased response defection of rats. Therefore, it can be argued that the existing anxiety activity in compounds that are investigated, i.e. the ability to prevent excessive stimulation of the nervous system and optimize behavioral responses under stress.

From the above it can be stated that the substance 18 in the “open field” test prevents the development of anxiety behaviour changes stressing genesis and activity is not inferior to the reference drug diazepam.

In the next series of experiments studied the effect of compound 18 on emotional and behavioral responses of animals in the test "elevated cruciform maze" . It is established that the introduction of solvent and emulsifier (tween-80) in the control group did not significantly affect physiological parameters of rats in this experimental test (table II).

Under conditions of acute immobilization stress decreased the number of outputs in open sleeves of the labyrinth by 2.4 times (p<0.001) compared to control (table II). Also significantly decreased the time spent and the number looking at the open sleeves compared to control injection. Stresemann contributed to the decrease in the number of looking down 1.8 times (p<0.001) and increased the number of bolus balls in 1.3 times in comparison with control group animals (p<0.01).

Thus, in the test “elevated cruciform maze” acute stress increased the phenomenon of anxiety, which was manifested by a reduction of interest in the open space in the form of reducing the amount of looking and of the sleeve and re-
Reducing the time spent in the open sleeve and risk assessment (reduction of looking down) and increased emotionality evidenced by the increase in the number of boluses.

Prophylactic use of a compound 18 significantly prevented decrease in the number of outputs in open sleeves of the maze and reduced the number of boluses in 2.2 times compared with that in acute stress (p<0.001) (table II). Introduction of diazepam before stressmania rats significantly increased the number of outputs in open sleeves elevated cross maze and the time spent in it in comparison with the control pathology (table II). Also, the drug increased the number of looking into a clear sleeve 1.3 times (p<0.01) and increased the number looking down 1.5 times (p<0.01) compared to the stress without correction (p<0.02). Against this background, the classic tranquilizer, reduced the number of boluses in 4.9 times compared with the control pathology.

Along with the study anxiety action of compound 18 under the stress of soft to medium aversives tests used a conflict situation, a variant of Vogel.

In conditions of acute stress significantly increased the time latency of the first approach and the number of approaches to the drinker as compared with the control group animals (table III). Anticonflict the effect of derived 2-oxoindole and classic anxiety of diazepam on the background of acute immobilization stress has undergone changes (table III). Compound 18 did not significantly affect on latent period approach to the drinker, however, increased the number of approaches to the drinking bottle 1.7 times (p<0.001) in comparison with stress without correction. Diazepam stronger warned stress-induced changes in behavior in the test of “conflict behaviour”, as evidenced by a reduction of latent period to approach drinkers in 1.4 times (p<0.001) and increased the number of approaches to the drinking bottle 3.4 times (p<0.001) compared with that in the control pathology (table III).

As you can see that anticonflict the action of connection 18 after an acute stress persisted, but was less pronounced than in the diazepam.

Therefore, under the influence of acute immobilization stress in classical tests, behavioral tests, attenuated the anxiolytic effects of compounds 18 and diazepam, which is typical for the vast majority of benzodiazepine anxiety and drugs of different structure [3; 4].

Thus stress causes changes anxiety activity of compound 18 and diazepam in behavioral tests. Their effects depend on the degree aversives test. The effectiveness of compound 18 in the “open field” test was at the level of a reference drug, in a test of “elevated cruciform maze” decreased a little, and in the test of “conflict behaviour” there was a further decrease in the efficiency of the substance that is investigated. Thus was less effective and diazepam.

The obtained results confirm that the impact of extraordinary factors on the body suppressed the functional ability of the GABA-benzodiazepine receptor complex, and reduced volume of distribution of GABA receptors in the prefrontal cortex and other parts of the brain that regulate behavior of animals and in particular the development of anxiety [16]. During stress endogenous ligands endosan usemodule with benzodiazepine plot of the GABA receptor and disrupt binding to it exogenous ligands and diminish the signs of anxiety actions in anxiety, in particular diazepam. However, the continued effectiveness of diazepam after stress indicates a greater affinity of the drug to receptors at conservan with endogenous ligands [4]. Discovered saving anxiety actions derived 2-oxoindole in acute stress, apparently due to the original mechanism of action, which, obviously, is to indirectly stimulate GABA-benzodiazepine receptor complex by increasing the affinity of endogenous GABA to the corresponding receptor and/or indirectly stimulate GABA receptors via other neurotransmitter systems, particularly serotonergic. Since the interrelation of these systems, particularly under pathological conditions [11].

**Table II.** The effect of derived 2-oxoindole on levels of anxiety of animals in the test “elevated cross maze” after acute immobilization stress.

<table>
<thead>
<tr>
<th>Group of animals (n=10)</th>
<th>The number of outputs in open sleeves</th>
<th>The time spent in the open sleeve, sec</th>
<th>Number of looking into the open sleeve</th>
<th>Number of looking down</th>
<th>Number of boluses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact control</td>
<td>3.70±0.50</td>
<td>29.3±3.11</td>
<td>4.0±0.44</td>
<td>7.1±0.44</td>
<td>5.43±0.24</td>
</tr>
<tr>
<td>Control on injection (control group)</td>
<td>3.9±0.23</td>
<td>26.1±2.28</td>
<td>3.9±0.31</td>
<td>7.4±0.45</td>
<td>5.30±0.20</td>
</tr>
<tr>
<td>Acute stress (control pathology)</td>
<td>1.6±0.16</td>
<td>21.1±1.30</td>
<td>1.7±0.21</td>
<td>4.2±0.33</td>
<td>6.8±0.47</td>
</tr>
<tr>
<td>Acute stress + compound 18</td>
<td>2.71±0.21</td>
<td>24.7±1.96</td>
<td>1.8±0.25</td>
<td>4.80±0.39</td>
<td>3.1±0.31</td>
</tr>
<tr>
<td>Compound 18</td>
<td>5.70±0.37**</td>
<td>69.7±4.72**</td>
<td>3.90±0.31**</td>
<td>8.20±0.44**</td>
<td>2.80±0.29**</td>
</tr>
<tr>
<td>Acute stress + diazepam</td>
<td>2.9±0.28</td>
<td>28.7±2.08</td>
<td>2.5±0.17</td>
<td>5.6±0.40</td>
<td>1.4±0.16</td>
</tr>
<tr>
<td>Intact+diazepam</td>
<td>6.0±0.44**</td>
<td>54.1±3.51**</td>
<td>4.6±0.31**</td>
<td>7.56±0.44**</td>
<td>2.2±0.13**</td>
</tr>
</tbody>
</table>

**Notes:**
1. # – p<0.05 compared with intact control;
2. * – p<0.05 compared with control on injections;
3. ** – p<0.05 compared with the control pathology.
CONCLUSIONS

Peculiarities of anxiety actions derived 2-oxoindole after the impact of extraordinary factors on the body involve the use of 2-hydroxy-N-naftaline-1-yl-2-(2-hydroxy-1,2-dihydro-indol-3-iliden)-acetamid when postsecretory disorders of various etiologies, complicated by anxiety.

It is planned to detect receptor and biochemical anxyolitic mechanisms of action of 2-oksoindoline in further research.

The work is a piece of research topic of the chair of Experimental and Clinical Pharmacology of SHEI of Ukraine “Ukrainian Medical stomatological Academy” t. Poltava “Search tools from a number of 2-oksoindole, 3-oksypirydyne derivates and other biologically active substances for pharmacological correction of adaptive processes in disorders of homeostasis of different ethiology” (№ state registration 0111U004879, deadline 2011-2015. supervisor - MD, professor Bobyrov VM).

REFERENCES


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