THE EXCHANGE OF MONOAMINES DURING THE EXPERIMENTAL NEUROSIS ON THE BACKGROUND OF USING OF AMIDE "2-HYDROXY-N-NAPHTHALEN-1-YL-2-(2-OXO-1,2-DIHYDROINDOL-3-YLIDENE)"

WYMIANA MONOAMIN W EKSPERYMENTALNYM MODELU NERWICY W TRAKCIE STOSOWANIA AMIDU - 2-HYDROKSY-N-NAFTALEN-1-YL-2-(2-OKSO-1,2-DIHYDROINDOLO-3-YLIDENU)

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ABSTRACT

Introduction: Incessant increase in the frequency and distribution of anxiety disorders stipulates searching, research and study of the mechanism of action of new substances for their correction, including the group of 2-oxoindolin-3-glyoxylic acid derivatives.

The aim: To research the effect of N-(1-naphthyl) amide-2-oxoindolin-3-glyoxylic acid on monoaminergic system of subjected to experimental neurosis of rats.

Materials and Methods: The experiments were performed on male Wistar rats, who have weight 180-220g and were researching the effect of 2-hydro-N-naphthalen-1-yl-2-(2-oxy-1,2-dihydroindol-3-ylidene)-acetamide (compound 18) at a dose (12 mg/kg), by intragastric drug injection of subjected to experimental neurosis rats, during 30 days (1 time in three days), for monoamines content (epinephrine, norepinephrine, dopamine and serotonin) in the blood, their decay products (homovanillic acid, vanillylmandelic acid and 5-oxyindolacetic acid) in the urine and the ratio of end products of the reaction to their predecessors.

Research: It was established that during the preventive-therapeutic application of N-(1-naphthyl)amide-2-oxoindolin-3-glyoxylic acid, it effectively adjusts the level of monoamines, reducing the content of adrenaline and increasing the content of noradrenaline, dopamine and 5-HT in the blood. The compound also reduces the content of products exchange of mediators (HVA,VMA and 5-OIAA) in the urine. The 2-oxoindolin derivatives reduces the ratio between HVA/dopamine, VMA/(noradrenaline + adrenaline) and 5-OIAA/5-HT, it testifies about the normalizing of enzymes activity, which are involved in the process of exchange and maintaining the constancy of monoamines. The results show that in the mechanisms of anxiolytic action of compound 18, a significant role plays the normalization of content and exchange of neurotransmitters in the organism, which caused an experimental neurosis.

Conclusion: Compound 2-hydro-N-naphthalen-1-yl-2-(2-oxo-1,2-dihydroindol-3-ylidene)-acetamide by the experimental 30-day neurosis, was reducing the expression of neurotransmitter imbalance in the blood, apparently due to correction of enzymatic synthesis links and biotransformation of monoamines.

KEY WORDS: 2-hydro-N-naphthalen-1-yl-2-(2-oxo-1,2-dihydroindol-3-ylidene)-acetamide, monoamines, experimental neurosis.

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INTRODUCTION

In recent years, the prevalence of mental disorders is increasing not only in Ukraine but also in the European Union [1]. At the same time, the frequency of these diseases have grown by more than 10%. Among mental illnesses, anxiety disorders are the most common. The basis of pharmacotherapy of these diseases make up antidepressants and also anxiolytics of the benzodiazepine series and low-dose neuroleptics with the activation effect [2]. To date, the unresolved problem remains the emergence of resistance to antidepressant therapy, decrease in efficiency, the need to increase the dose during the treatment with classic anxiolytics and other undesirable reactions with the use of antipsychotics [3].

The foregoing stipulates the development and preclinical study of new effective and safe antineurotic remedies, particularly among the recently synthesized compounds which belong to 2-oxoindolin-3-glyoxylic acid derivatives. In recent time, these substances are actively being investigated at various pathologies of the central nervous system, in particular during the acute stress [4], which can serve as a predictor of correctly chosen direction of research.

Fairly well in the scientific world are represented the particularities changes of monoamines content and their metabolites in the brain structures(hypothalamus, amygdala, frontal cortex and hippocampus) at chronic neurotization of different genesis and also in norm on the background of pharmacological drugs [5;6]. However, it presents the theoretical and practical interest of clarification of particularities changes of the level of monoamines, their ratio in the blood and metabolic products, as an integral indicators that reflect the efficacy and mechanism of protective action of the new compound in the experimental neurosis.

THE AIM

To research the effect of 2-hydroxy-N-naphthalen-1-yl--2-(2-oxy-1,2-dihydroindol-3-ylidene)-acetamide (compound 18) on monoaminergic system of subjected to the experimental neurosis of rats.

MATERIALS AND METHODS

The experiments were performed on 32 albino pubescent male Wistar rats, weighing 180-220g that have been bred in the vivarium of the higher state educational institution of Ukraine «Ukrainian Medical Stomatological Academy» (Poltava city), which is equipped in accordance with existing sanitary standards. In the experiments were using rats with the active type of response, which were selected by preliminary tests.

The chronic neurosis were modeling by "conflict of afferent impulses" whose task was in the action of stressors: the light from the light bulb 300 W, sound stimulus of 60 dB intensity, electrical current of threshold value through the floor [7]. Neurotic disorders were reproduced within 30 days, at the same time, these rats were exposed to stressors 120 min. continuously, every day.

This research was required a use of 2-hydroxy-N-naphthalen-1-yl-2-(2-oxy-1,2-dihydroindol-3-ylidene)-acetamide. The substance was suspended ex tempore in saline solution, using an emulsifier «Твін-80» (LAUROPAN, Italy) and was injected inside to rodents at a dosage of 12 mg/kg, 1 hour prior to the impact of stressors and every 3 days during the all period of neurotization. As a comparator product was used "Diazepam" (2 mg/kg) («Tarchomin S.A.», Poland), it was injected analogically to compound that is tested.

After 1 hour after the last action of stressors, the rodents were inferred from experiment with the help of thiopental anesthesia (50 mg/kg). For these experiments was used a blood plasma, in which were determined the level of adrenaline, noradrenaline and dopamine and the blood serum in which was determined the level of serotonin. The content of monoamines was researched by the ELISA using a set of firms («TriCat TM ELISA» IBL International GmbH, Germany) and («Serotonin EIA» Demeditec Diagnostics GmbH, Germany). During the last days of experiment, it was conducted a sampling of the urine, in which were determined the contents of monoamine metabolites: Homovanillic acid (HVA) («HVA TM ELISA» Labor Diagnostika Nord GmbH, Germany) - a metabolite of dopamine, Vanillylmandelic acid (VMA) (a metabolite of norepinephrine) («VMA TM ELISA» Labor Diagnostika Nord GmbH, Germany) – a metabolite of serotonin, and also 5-oxyindolacetic acid (5-OIAA) («5-HIAA TM ELISA» Labor Diagnostika Nord GmbH, Germany) – a metabolite of serotonin.

In order to assess the state of enzyme systems of catecholamines exchange, it was counted the ratio of the reaction products to their predecessors: HVA/DA, NA/DA, A/NA/VMA/ (NA+A) and 5-OIAA/5-HT

The processing of the results was carried out by software Microsoft Statistica 6.0 (StatSoft, Inc., USA) using the Student's t-test.

RESULTS AND DISCUSSION

The modeling of the experimental neurosis in the blood serum caused an increase of level of adrenaline in 1.6 times in comparison with the intact animals ($p<0,001$). The development of control pathology was accompanied by the likely content decrease of noradrenaline and dopamine in the blood serum. Under these conditions, it was a decrease in the level of serotonin in 1.7 times compared with the intact animals ($p<0,01$) (table. I).

During the experimental neurosis along with changes in the content of monoamines in the blood serum, was an increase of the level of their metabolic products in the urine, it was indicating on the elevated level of HVA in the 1.6 times like that in the intact animals ($p<0,001$) (table. II). The development of neurosis was accompanied by the likely concentration raise of VMA, and also by the concentration increase of 5-OIAA in the urine in the 1.9 times in comparison with a control group of rats ($p<0,001$).

For the overall assessment of the state of enzyme systems of catecholamines exchange, it was counted the ratio of the end products of metabolism to the initial reaction products. Comparing the neurosis group with an intact group it was established, that the state of the dopaminergic system was characterized by the enhancing of HVA/dopamine of 167% which indicates an increased dopamine deamination by monoamine oxidase.

Analyzing the state of the biosynthesis of noradrenaline during the neurotic state, it should be noted that there have been observing a slight increase by 19% of the interrelation of noradrenaline/dopamine on the background of reducing the level of dopamine, it indicates on the comparable changes in activity of dopamine hydroxylase-β which is involved in the synthesis of noradrenaline from dopamine. The next interrelation is adrenaline/noradrenaline that reflects the activity of phenylethylamine-N-methyltransferase, – it indicates in favor of increasing the amount of adrenaline in the experimental pathology at 119%. The state of conversion of noradrenaline to adrenaline and then to VMA, was analyzed according to the interrelation of VMA/(noradrenaline + adrenaline) that reflects the activity of monoamine oxidase (MAO) and catechol-O-methyltransferase. This ratio increased by 93% compared with that in the intact animals and this indicates a significant increase of the end product of metabolism of these monoamines and their accelerated circulation. Under these conditions the ratio between 5-OIAA/5-HT increased by 207%. It shows that quite significant changes in metabolism of monoamines are been observed in the serotonergic neurotransmitter link and are accompanied by the excessive destruction of 5-HT in the experimental neurosis.

Was detected changes of levels of monoamines and the state of enzyme systems of their metabolism reflect in general disorders of neurotransmitter processes, occurring in the central nervous system under conditions of the neurotic state that were described by other authors [8;9].

It is known that the level of adrenaline is associated with the nature of emotional reaction, and the level of

Table. I The influence of 2-hydroxy-N-naphthalen-1-yl-2-(2-oxy-1,2-dihydroindol-3-ylidene)-acetamide on the level of monoamines during the experimental neurosis in rats (n=8, M±m)

Group of animals	Adrenalin, blood plasma, pg/ml	Noradrenaline, blood plasma, pg/ml	Dopamine, blood plasma, pg/ml	Serotonin, serum, ng/ml
1. Intact + (control group)	47,9+3,64	92,4+6,36	36,2+3,40	862+88,3
2. The experimental neurosis (control pathology)	75,4+4,85 <0,001	66,1+4,63 <0,01	21,8+1,52 <0,01	519+37,5 <0,01
3. The experimental neurosis + diazepam, 2 mg/kg	63,3+3,81 <0,1	69,3+4,52 -	34,2+2,27 <0,001	1119+88,8 <0,001
4. The experimental neurosis + compound 18, 12 mg/kg	54,5+3,58 <0,01	89,1+4,41 <0,01	30,5+2,87 <0,02	1047+123 <0,002

Notes: * – p<0,05 compared with the control group;
** – p<0,05 compared with the control pathology;
n – the number of animals in the group.

Table. II The influence of 2-hydroxy-N-naphthalen-1-yl-2-(2-oxy-1,2-dihydroindol-3-ylidene)-acetamide on the activity of enzymes exchange of monoamines in the experimental neurosis in rats (n=8, M±m)

Group of animals	Homovanillic acid, urine, pg/ml	Vanillylmandelic acid, urine, mkg/ml	5-Oxyindolacetic acid, mkg/ml
1. Intact (control group)	1,29+0,088	3,92+0,39	10,4+0,81
2. The experimental neurosis (control pathology)	2,03+0,120 <0,001	7,63+0,46 <0,001	19,3+1,39 <0,001
3. The experimental neurosis + diazepam, 2 mg/kg	1,49+0,122 <0,01	5,77+0,47 <0,02	13,5+0,811 <0,01
4. The experimental neurosis + compound 18, 12 mg/kg	1,43+0,068 <0,001	5,87+0,39 <0,02	12,9+1,12 <0,01

Notes: * – p<0,05 compared with the control group;
** – p<0,05 compared with the control pathology;
n – the number of animals in the group.

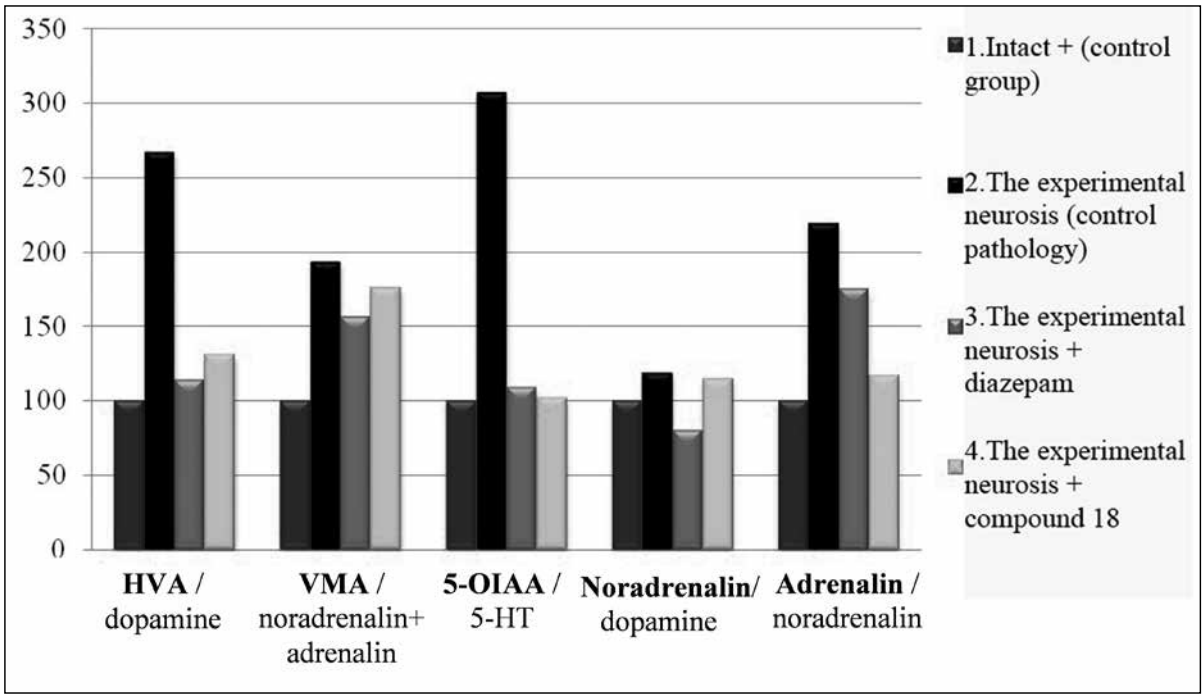

Fig. 1. The influence of 2-hydroxy-N-naphthalen-1-yl-2-(2-oxy-1,2-dihydroindol-3-ylidene)-acetamide on the state of exchange of monoamine during the experimental neurosis (percentage).

noradrenaline is connected with the type of activity [8]. In the vast majority of neurotic states, it is detected the reduction level of dopamine which indicates on the exhaustion of sympathoadrenal system. Our observations have set the following fact: the level of adrenaline is decreased and the level of noradrenaline is increased which indicates the development of neurotic state in the animals where the sense of fear and anxiety is prevailed. Such a picture of changes in the animals in clinical settings is correspond to neurosis of obsessional states, among the key symptoms of which prevail the sadness and melancholy [10].

The neurotic status is accompanied by disorders of monoaminergic system, in the form of acceleration of the catabolism of neurotransmitters and changes of their interrelation, particularly in the brain structures which are responsible for status of anxiety [11]. At presence of panic disorders, it is marked an excessive activation of adrenergic neurons, increase the level of this neurotransmitters in the blood serum and myocardium [12]. At presence of anxiety disorders, are also present a lack of serotonergic and noradrenergic activity [13]. Herewith, an insufficient number of noradrenaline and 5-HT leads to increase the level of glucocorticoids which trigger a cascade of disorders most enzyme systems of the body [14]. Obviously the excess of glucocorticoids activates tryptophan pyrolysis that stimulate the metabolism of tryptophan by kynurenine pathway and thus, reduces the level of tryptophan from which 5-HT is synthesized [15]. At the same time, an increased cortisol secretion elevates the activity of tyrosine transaminase enzyme, which can lead to reduction of amount of tyrosine fraction, that goes to the biosynthesis of catecholamines and reduces their content, including noradrenaline [16]. Herewith, the activity of MAO may continue to rise under the influence of high level of corticosterone. MAO deaminates serotonin and noradrenaline with the different speed and during the pathological condition, the speed of deamination of monoamines changes, which can disrupt their concentration and balance in tissues [15]. The changes described in previous studies and confirmed by our results.

Preventive and therapeutic use of diazepam significantly increase the level of dopamine and 5-HT in the blood serum in comparison with the experimental neurosis. Such changes in the content of monoamines occurred along with a decrease in the urine of HVA in 1.4 times ($p<0,01$) and authentic decrease in the number of other metabolites: VMA and 5-OIAA compared with the control pathology without correction (table. II).

Researching the influence of classical anxiolytic on the ratio of monoamine metabolism products with their predecessors was found that the interrelation between HVA/dopamine decreased by 153% compared with neurosis that indicates on inhibition of dopamine deamination by the monoamine oxidase enzyme (figure). The interrelation between VMA/(noradrenaline + adrenaline) characterizes the metabolism of noradrenaline to adrenaline and then to VMA under the action of monoamine oxidase and catechol-O-methyltransferase into diazepam declines by 37%, but did not reach the level of the intact animals. By analyzing the ratio between 5-OIAA/5-HT, it should be noted that the classical anxiolytic normalized turnover of 5-HT. The biosynthesis of noradrenaline on the background of using diazepam, was accompanied by a decrease in

ratio of noradrenaline/dopamine of 39% in comparison with the control pathology that obviously indicates on reducing the activity of dopamine-β-hydroxylase which catalyzes the synthesis of noradrenaline from dopamine. Herewith, the interrelation between adrenaline/noradrenaline decreased by 44%,it shows rather high activity of phenylethylamine-N-methyltransferase and to some extent the ability of diazepam affect the synthesis of adrenaline under conditions of experimental neurosis.

The results testify that diazepam contributed to the restoration of monoamine metabolism which was manifested by reliable reduction in end products of metabolism and normalization of the activity of monoamine oxidase. Herewith, the greatest activity diazepam has shown on the stages of preservation of sustainable level of dopamine and the amount of exchange of 5-HT. The previous studies have been established a similar direction process of the exchange of monoamines in brain tissues of animals during the prolonged injection of diazepam [17].

Preventive and therapeutic use of compound 18 decreased the level of adrenaline and increased the level of noradrenaline in the blood serum an average of 1.4 times compared with the experimental neurosis ($p<0,01$) (table. I). As well, this substance was likely raised the dopamine level in the blood serum and the level of serotonin in 2.0 times in comparison with the control pathology without correction ($p<0.002$). During analyzing the content of the end products of metabolism, it was established that 2-oxoindolin amide was likely reduced amount of HVA that excretes from the body (table. II). Compound 18 also reduced the urinary content of VMA in 1.3 times ($p<0.02$) and reduced the amount of 5-OIAA in 1.5 times compared with the control pathology without correction ($p<0,01$).

Under the influence of 2-oxoindolin the ratio between HVA/dopamine was decreasing that shows the normalization of monoamine oxidase activity and in the future it will increase the level of dopamine (figure). Under these conditions, the reduced excretion of HVA on the background of increasing the amount of dopamine clearly indicates, that the substance adjusts the level of the neurotransmitter mainly due to inhibition of his destruction. By using compound 18 the value of the ratio between VMA/(noradrenaline + adrenaline) slightly decreased, that on the background of the previous indicator shows the ability of substance to modify the activity of catechol-O-methyltransferase. The derivative of 2-oxoindolin-3-glyoxylic acid effectively corrected the ratio between 5-OIAA/5-HT that shows the normalization of enzymes activity, which are involved in the metabolism and maintaining a sustainable level of 5-HT. On the background of using 2-oxoindolin derivative, the ratio between noradrenaline/dopamine did not change significantly, but recovered the further metabolism of monoamines. This is evidenced the ratio reduction between adrenaline/noradrenaline of 102% in comparison with the experimental neurosis without correction.

CONCLUSIONS

The results indicate that N-(1-naphthyl)amide-2-oxo-indolin-3-glyoxylic acid effectively adjusts the level of monoamines, reducing the content of adrenaline and increasing the content of noradrenaline, dopamine and 5-HT in the blood, also this compound reduces the content of metabolic products of mediators (HVA,VMA,5-OIAA) in the urine and positively affect the value of the ratio of the reaction products to their predecessors. This may be due to inhibition of MAO as it shown in previous studies with the use of monoamine precursors of L-dioxyfenilalanin and 5-oxytryptofane [18;19]. These assumptions are confirmed the ability of other indole derivatives, both synthetic compounds and alkaloids, to inhibit the activity of MAO [20;21]. It should be noted that 2-hydroxy-N-naphthalen--1-yl-2-(2-oxo-1,2-dihydroindol-3-ylidene)-acetamide during the injection to the intact animals in the above described mode, is not likely effect the level of monoamines and the ratio of noradrenaline to dopamine in the blood [22]. However, 2-oxoindolin-ester during the depressed condition, expressively reduced the displays of neurotransmitter imbalances in the blood which caused the experimental neurosis [23].

In further studies is been planned to examine the other compounds from the group of 2- oxoindolin-3-glyoxylic acid, the availability of other neuropsychotropic properties and to find out their mechanisms.

This work is a piece of research topic of the department of Experimental and Clinical Pharmacology of the higher state educational institution of Ukraine «Ukrainian Medical Stomatological Academy», Poltava «The search of facilities among 2-oxoindol, 3-oxo-pyridine derivatives and other biologically active substances for pharmacological correction of adaptive processes by disorders of homeostasis of different etiology» (№ state registration 0111U004879, deadline 2011-2015, supervisor -MD, professor Bobyryov V.M.)

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