ANHEDONIA AT EXPERIMENTAL MODELS OF CHRONIC STRESS AND ITS CORRECTION

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Abstract

Different types of chronic stress lead to neurotic and depressive disorders. Key symptoms of these disorders are anhedonia and correction of which will indicate the efficacy of proposed therapy.

The aim of the paper is to investigate the influence of amide 2-hydroxy-N-naftalen-1-il-2-(2-oxo-1,2-dihidro-indole-3-iliden) and ethyl ether 4-[2-hydroxy-2-(2-oxo-1,2-dihidro-indole-3-iliden)-acetamin]-butyric acid on anhedonia after the experimental neurosis and chronic moderate stress in rats.

Materials and methods. It was studied the influence of therapeutic and preventive administration of substances 18 and E-38 in the dosage of 12mg/kg during chronic mild stress "conflict of afferent activation" during 30 days and depression-like behavior chronic mild stress that modeled 8 weeks.

Results of investigation. Experimental neurosis caused decrease of number of comings to drinking-bowl, decrease of total number of drank sucrose and decrease of the percent of drank water with sugar in comparison with intact animals. Analogical but more significant changes were noticed during depression-like behavior. The use of amide 2-oxoindolin-3-glyoxylic acid based on neurosis counters effectively the development of

anhedonia. Substance 18 increased the number of comings to drinking-bowl with sucrose and increased the amount of the number of drank water with sucrose in comparison with control pathology without correction. The substance possibly assists in use of solution with sucrose among water and does not compromise reference-preparation such as diazepam. The administration of ethyl ether of 2-oxoindolin-3-glyoxylic acid at chronic mild stress possibly increased the number of comings to the drinking-bowl and increased the number of drank sucrose in comparison with control pathology and it was more effective than imipramine and countered anhedonia.

Conclusions. It was indicated that during 30 day experimental neurosis and 8 week depression-like behavior cause the development of anhedonia. Therapeutic use of amide 2-hydroxy-N-naftalen-1-il-2-(2-oxo-1,2-dihidro-indole-3-iliden) and ethyl ether 4-[2-hydroxy-2-(2-oxo-1,2-dihidro-indole-3-iliden)-acetamin]-butyric acid corrected effectively anhedonia after experimental neurosis and chronic mild stress in rats.

Keywords: derivatives of 2-oxoindolin, anhedonia, experimental neurosis, depression-like behavior.

Streszczenie

Różne rodzaje przewlekłego stresy prowadzą do zaburzeń neurotycznych i depresyjnych, kluczowym objawem których jest anhedonia, korekcja której świadczyć będzie o efektywności zaproponowanej terapii.

Cel pracy – zbadanie wpływu amida 2-hydroxy-N-naftalen-1-il-2-(2-oxo-1,2-dihydro-indol-3-ilidenu) (związek 18) oraz esteru etylowego 4-[2-hydroxy-2-(2-oxo-1,2-dihydro-indol-3-iliden)-acetamino]-masłowego kwasu (związek E-38) na anhedonię po eksperymentalnej neurozie i przewlekłym umiarkowanym stresie u szczurów.

Materiały i metody badania. w eksperymentach na dojrzałych płcioso szczurach linii Wistar badano wpływ profilaktyczno-leczniczego podania związków 18 i E-38 w dawce

12 mg/kg przy przewlekłej neurozi “ekonfliktu impulsów aferentnych” w ciągu 30 dób oraz stanie przypominającym depresję (przewlekły umiarkowany stres), który był modelowany przez 8 tygodni.

Wyniki badania. Eksperymentalna neuroza wywołała zmniejszenie ilości podejść do poidła, zmniejszenie łącznej ilości wypitej sacharozy oraz zmnieszyła odsetek wypitej wody z cukrem w porównaniu ze zwierzętami nienaruszonymi. Analogiczne, lecz bardziej wyraźne zmiany obserwowane były przy odtwarzaniu stanu przypominającego depresję. Stosowanie amidu 2-oxoindolin-3-dioksylowego kwasu na tle neurozy efektywnie zapobiegało rozwojowi stanu anhedonii. Związek 18 zwiększał ilość podejść do poidła z sacharozą oraz zwiększał ilość wypitej sacharozy w porównaniu z patologią kontrolną bez korekcji. Substancja prawdopodobnie sprzyjała preferowaniu spożywania właśnie sacharozy wśród wody, a pod względem aktywności nie odbiegała od preparatu referencyjnego diazepamu. Podanie eteru etylowego 2-oxoindolin-3-gioksylowego kwasu przy przewlekłym umiarkowanym stresie prawdopodobnie zwiększało ilość podejść do poidła i zwiększało ilość wypitej sacharozy w porównaniu z patologią kontrolną oraz efektywniej od imipraminu zapobiegało anhedonii.

Wniosek. Ustalono, że 30-dzienna neuroza eksperymentalna oraz 8-tygodniowy stan przypominający depresję wywołują rozwój anhedonii. Leczniczo-profilaktyczne stosowanie amida2-hydroxy-N-naftalen-1-il-2-(2-oxo-1,2-dihydro-indol-3-ilidenu) oraz esteru etylowego 4-[2-hydroxy-2-(2-oxo-1,2-dihydro-indol-3-iliden)-acetamino]-masłowego kwasu efektywnie korygowało anhedonię po neurozie eksperymentalnej i przewlekłym umiarkowanym stresie u szczurów.

Słowa kluczowe: pochodne 2-oxoindoliny, anhedonia, neuroza eksperymentalna, stan przypominający depresję

Anhedonia is a loss to get pleasure from the life and interest in different spheres of life. Risk factors of anhedonia are depression-like behaviors, and schizophrenia in relatives, influence of stress situations, hard cerebrocranial traumas, long-lasting somatic diseases, which were not treated on time and other factors. Anhedonia can be as one complex or as one of symptoms that indicates the development of psychotic pathology, for example, social anhedonia is risk factor for schizophrenia [1, 2].

There are four types of anhedonia such as social one (absent wish to communicate with relatives, to improve financial status), physical anhedonia (loss of positive conception of stimuli), sexual one (incomplete satisfaction during sex) and intellectual one (absence of desire to develop that is accompanied by pessimistic thoughts). There are such concepts as total anhedonia (all spectrum of positive emotions is increased) partial anhedonia [3].

Anhedonia is the main symptom for many mental diseases such as schizophrenia, depersonalization, depressive disorders, Parkinson's disease [4, 5]. At depressive disorders anhedonia is characterized by brief positive emotions and patients did not get pleasure from them. The main symptoms of depression for elderly people are anhedonia and bad mood. Anxiety is accompanied by sexual anhedonia [6, 7].

So, chronic stress causes anhedonia formation, which is one of the main symptoms of neurotic and depressive disorders, correction of which will indicate the efficacy of proposed therapy.

During previous investigations among new derivatives of 2-oxoindolin-3-glyoxylic acid there were established the most active substances. Anxiolytic action is definitive for amide 2-hydroxy-N-naftalen-1-il-2-(2-oxo-1,2-dihidro-indole-3-iliden) (substance 18) [8]. Ethyl ether 4-[2-hydroxy-2-(2-oxo-1,2-dihidro-indole-3-iliden)-acetamin]-butyric acid (substance E-38) defined expressed antidepressive action [9].

The aim of the paper is to investigate the influence of amide 2-hydroxy-N-naftalen-1-il-2-(2-oxo-1,2-dihidro-indole-3-iliden) and ethyl ether 4-[2-hydroxy-2-(2-oxo-1,2-dihidro-indole-3-iliden)-acetamin]-butyric acid on anhedonia after the experimental neurosis and chronic mild stress in rats.

Materials and methods. Experiments were done on mature rats of Wistar with body weight 180-230 g. Animals were taken on usual nutritional, water and during 12-hour light regimen. All investigations were done according to the Law of Ukraine «About animal's protection from heavy-handed treatment» (№3446 – IV 21.02.06), rules of European Convention about protection of vertebral animals that were used during experimental investigations and with other scientific aim [10]. Rats were used with active type of reacting in experiments. So, 2 series of experiments of 4 groups were formed, each of them contained 8 rats. Experimental investigations were done in spring.

Amide 2-hydroxy-N-naftalen-1-il-2-(2-oxo-1,2-dihidro-indole-3-iliden) substance 18 was used for the experiment. And ethyl ether 4-[2-hydroxy-2-(2-oxo-1,2-dihidro-indole-3-iliden)-acetamin]-butyric acid (substance E-38) was also used. Substances which are investigated were suspended ex tempore in physiological solution, emulsifier «Tvin-80» (LAUROPAN, Italy) was used and it was administered in the dosage of 12 mg/kg intraorally before 1 hour to the start of stressors influence and each 3 hours during all period of neurotization.

Chronic neurosis was modeled by «conflict of afferent activation», that had such action: light from electric lamp 300 W, sound activator 60 dB and electrical current of threshold through floor [11]. Neurotic disorders were indicated during 30 days, thus way rats were done stress actions during 120 хв. without breaks every day.

Chronic mild stress during 8 weeks was used for modeling depression-like behavior in rats. Stress influence was done daily, with use of typical stressors, that change: the change of

cycle day/night (in the afternoon is darkly, in the night is lightly); deprivation (disposal from water or food during 24 hours); decline of cage on 45^0 degrees during the day; light in dark period of the day (light is twenty-four hours); sounds of invaders were during 8 hours; empty cage with water of 0,3-0,5 sm during 24 hours [12, 13].

Amide 2-hydroxy-N-naftalen-1-il-2-(2-oxo-1,2-dihidro-indole-3-iliden) (substance 18) was used for neurosis correction. Ethyl ether 4-[2-hydroxy-2-(2-oxo-1,2-dihidro-indole-3-iliden)-acetamin]-butyric acid (substance E-38) was administered based on chronic mild stress. Substances that are investigated were suspended ex tempore in physiological solution and emulsifier «Tvin-80» (LAUROPAN, Italy) was used and it was administered intraorally in the dosage of 12 mg/kg before1 hour to the start of stressors influence and each 3 days during 4 weeks during experimental neurosis and 8 weeks during chronic mild stress. Drugs forms of preparations of imipramine («Egis Pharmaceuticals PLC», Hungary) in the dosage of 25 mg/kg, diazepam 2 mg/kg («Tarchomin Pharmaceutical Works S.A.», Poland) were used to get homogenous suspension for intravenous use and substances were previously suspended using «Tvin-80» (LAUROPAN, Italy).

Scoring of received results was done based on programmes Microsoft Statistika 6.0 з with the use of t Student criterion.

Results. One of key indices that display the development of neuroticism in animals, and also the efficacy of proposed correction is the test evaluation of sucrose intake. It was indicated that neurosis caused decrease of number of comings to drinking-bowl in 1,9 times ($p<0,001$) and decrease of total number of drank sucrose in 2,2 times in comparison with intact animals ($p<0,001$) (Table 1). It has been seen possible decrease of the percent of drank water with sugar in comparison with control group (Fig. 1).

After 4 weeks of neurosis of diazepam administration increased the number of comings to drinking-bowl in 1,4 ($p<0,02$), it also possible increased the number of drank

sucrose and the percentage of used sugar to general number of liquid in comparison with experimental pathology (Table 1, Fig. 1).

Preventive and therapeutic intake of amide of 2-oxoindolin-3-glyoxylic acid of substance 18 after 4 weeks of neurosis modeling counters anhedonia that developed in rats. The influence of substance was characterized by increase of comings to drinking-bowl with sucrose in 1,4 ($p<0,02$) and increase of number of drank sucrose in 1,3 ($p<0,02$) in comparison with control pathology without correction (Table 1). During this period substance possibly assists in sucrose solution intake among water (Fig. 1).

So, experimental neurosis was accompanied by the development of typical emotional and behavioral disorders (decrease of quantative and qualitative indices of sucrose intake). Preventive and therapeutic use of amide of 2-oxoindolin-3-glyoxylic acid corrected effectively the development of indicated disorders and did not compromise diazepam.

Next series of experiments modeled depression-like behavior that caused chronic moderate stress. In 8 weeks after this pathology it was observed decrease of the number of comings to drinking-bowl in 3,8 ($p<0,001$) and decrease of the number of drank sucrose in 4,3 times in comparison with intact animals ($p<0,001$) (Table 2). So, the percent of sucrose intake among general number of liquid decreased in 1,6 times in comparison with control group of rats ($p<0,001$) (Fig. 2).

At the end of 8 week of chronic moderate stress modeling reference-preparation imipramine did not change the number of comings to drinking-bowl, the number of drank sucrose per one coming, the general number of drank sucrose and the correlation of used sucrose solution to general number of drank liquid in comparison with control pathology (Table 2, Fig. 2).

Preventive and therapeutic intake of ethyl ether of 2-oxoindolin-3-glyoxylic acid of substance E-38 during chronic mild stress increased the number of comings to drinking-bowl

in 2,4 times in comparison with indices of control pathology ($p<0,001$) and in 1,7 times in comparison with imipramine ($p<0,001$) (Table 2). Based on this substance the number of drank sucrose increased in 1,9 according to analogical index at chronic mild stress ($p<0,01$) and in 1,5 times in comparison with administration of reference-preparation ($p<0,05$). It has been indicated possible predominance of sucrose intake (Fig. 2).

Depressive condition that was associated with the development of typical emotional and behavioral disorders for anhedonia: decrease of quantative and qualitative indices of sucrose intake. Preventive and therapeutic intake of ethyl ether of 2-oxoindolin-3-glyoxylic acid corrected effectively the development of indicated disorders. Substance E-38 did not compromise imipramine and supported indices of experimental animals of control group, and in the test of predominance of sucrose intake increased reference-preparation. Analogical antianhedonic properties manifested other antidepressants [14, 15, 16].

Comparing the development of anhedonia it should be indicated that during depression-like behavior it was more expressed than during experimental neurosis. During chronic mild stress in rats the number of comings to drinking-bowl was less in 2,0 times in comparison with neurotic disorders ($p<0,001$). Also depression-like behavior was accompanied by possible decrease percents of sucrose intake in comparison with neurosis (Fig. 3).

It is known that anhedonia during chronic emotional and painful syndrome and chronic stress was accompanied by decreased level of corticosterone in blood. During chronic emotional and painful stress increase of corticosterone in hypocamp and neocortex was indicated, but such increase was not observed during chronic depression-like behavior [17]. It can indicate common mechanisms of anhedonia during experimental neurosis and depression-like behavior. But during depression this symptom is more expressed and it indicates про neurally mediated disorders and other neurally mediated disorders of hormonal systems.

Also inhibition of dopamine D_1- and D_2-receptors causes anhedonia and increase of sensitivity of postsynaptic dopamine receptors and antidepressants use such as imipramine restores such disorders [18]. It should be indicated that stress influence causes desensitization of inhibitive serotonin $5HT_{1A}$-receptors in dorsal nucleus of raphe and increases serotonin output (5-HT). But agonists of postsynaptic 5-HT_{1A}-receptors counter the development of anhedonia and correct intake of sugar solution [19]. That's why anhedonia was caused by 5-HT-receptors.

Based on depression-like behavior taste changes are manifested individually and can depend on concrete situation. But, positive influence on sucrose intake and predominance of sucrose should be considered as the basis of substances efficacy during the treatment of anxious and depressive disorders. Analysis of anhedonia and its correction detect mechanisms of positive action of the substance that are caused by agonistic influence on 5-HT_{1A}-receptors and decrease of 5-HT release and activity of serotonin neurons that are proved by results of received investigations [8, 9].

So, 30 day experimental neurosis and 8 week chronic mild stress (depression-like behavior) cause the development of anhedonia. Therapeutic and preventive use of amide 2-hydroxy-N-naftalen-1-il-2-(2-oxo-1,2-dihidro-indole-3-iliden) and ethyl ether 4-[2-hydroxy-2-(2-oxo-1,2-dihidro-indole-3-iliden)-acetamin]-butyric acid corrected effectively the development of anhedonia after experimental neurosis and chronic mild stress in rats.

In further experiments it should be planned to investigate monoaminergic mechanisms of positive action of derivatives of 2-oxoindolin-3-glyoxylic acid during chronic stress in rats.

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for pharmacological correction of adaptive processes during homeostasis disorders of different etiology» (№ of state registration is 0111U004879, term of implementation is 2011-2015. Research adviser is Doctor of Medical Sciences, Prof. V.M. Bobyriov).

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