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Research Article

Studies of the effect of cerebroprotective substances on the course of stress-induced behavioral depression

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Abstract

Introduction. Atrophic disturbances of neurons of the limbic structures of the brain, which lead to insufficient regulation of emotions and mood, cause depression. Substances with cerebroprotective activity have the ability to inhibit further development and even reverse atrophic damage to neurons.

Materials and methods. Using electrophysiological techniques, the cerebroprotective activity of piracetam, diacamf – (±)-cis-3-(2-benzimidazolyl)-1,2,2-trimethylcyclopentanone-carboxylic acid hydrochloride and the compound R-86, or 3,2'-spiro-pyrrolo-2-oxindole, was investigated in rat hippocampal slices. In behavioral experiments, there was studied the influence of the above substances, which had been administered for 20 days, on the most important manifestations of behavioral depression in rats caused by a five-day swim stress, such as the time of immobilization in the forced swim test and the indicator of preference for consuming sucrose solution. In addition, the influence of piracetam and diacamf was studied on the effects of the classic antidepressant imipramine.

Results and discussion. It was found that piracetam, diacamf and the compound R-86 in in vitro studies reduced the damage to the pyramidal hippocampal neurons caused by anoxia and aglycemia, the excitotoxic activity of N-methyl-D-aspartate and oxidative stress when hydrogen peroxide was applied to the slices. Cerebroprotective activity of the test substances, when they are systemically administered for 20 days, is linked with their antidepressant-like effect, which was manifested in a decrease in the immobilization time in the swim test and an increase in the sucrose solution consumption indicator. Co-administration of piracetam in rats potentiated antidepressant activity of imipramine, and diacamf showed additive synergism with the antidepressant.

Conclusion. Substances with cerebroprotective activity in their chronic administration may show an antidepressant-like effect. Those that potentiate the action of classical anidepressants can be used in conjunction with antidepressants during episodes of exacerbation of the disease. Less active cerebroprotective drugs can be recommended during remission for its prolongation.

Keywords

behavioral depression, imipramine, piracetam, diacamf, the compound R-86, antidepressant-like action, synergism.

Introduction

Administration of the most currently used antidepressants, selective serotonin reuptake inhibitors, the therapeutic effect develops in 1/3 patients after several weeks of systematic administration of the drugs; in another 1/3 of patients, the weakening of depression symptoms requires the administration of antidepressants for many

months or a year; finally, the remaining 1/3 patients do not respond to the administration of two or more first-line antidepressants (Trivedi et al. 2006). New approaches to the development of antidepressants which do not interrupt the monoamines exchange are needed.

The idea that depression is caused by the atrophy of neurons in the cortical and limbic structures of the brain that control emotions and mood is the most well accepted now. These atrophic changes are manifested in a decreased volume of pyramidal neurons, a reduced dendritic branching, a decreased number of dendritic spines and, consequently, synapses, and a decreased volume of the cortex and limbic structures (Duman and Aghajanian 2012; Savitz and Drevets 2009). The consequence of these changes, first of all, is impairment of the top-down cortical control of the activity of subcortical limbic structures, which contributes to the development of a depressive behavioral phenotype.

Since in experimental and clinical conditions the pharmacological and drug substances with cerebroprotective action can prevent or reverse atrophic damage to the brain, this study was aimed at finding out the effect of nootrope pyracetam and pharmacological substances diacamf ((±)-cis-3-(2-benzimidazolyl)-1,2,2-trimethylcyclopentanone-carboxylic acid hydrochloride) and the compound R-86 (3,2'-spiro-pyrrolo-2-oxindole) with cerebroprotective activity, which were synthesized in Kharkov National Pharmaceutical University, on the behavioral depression in rats induced by a chronic swim stress.

Materials and methods

The research was performed on white inbred rats. The cerebroprotective activity of the test substances was studied on the slices of the hippocampus, using a standard electrophysiological method. The electrophysiological studies were performed on slices of the rat dorsal hippocampus. The details of the method were given in (Abramets et al. 2011). The dorsal hippocampus was isolated from the posterior pole of the brain. The 400 μm thick slices were prepared using a Vibratome. In the hippocampal slices, using glass microelectrodes filled with 2 M NaCl solution with tip resistance of 2-5 megohms, the population (p) excitatory postsynaptic potentials (EPSP) of pyramidal neurons of the CA1 region, which had been caused by electrical stimulation of Schaffer collaterals, were recorded extracellularly. The stimulation of synaptic inputs was carried out by a bipolar nickel-chromium electrode, with rectangular current pulses of 0.1 ms duration. The NMDA component of the pEPSP of pyramidal hippocampal neurons was isolated pharmacologically. To do this, the brain slices were superfused with Krebs solution with a concentration of Mg^{2+} reduced to 0.2 mM and the addition of 10 μM of the AMPA receptor blocker – 6,7-dinitroquinoxalin-2,3-dione (DNQX), 50 μM of the non-competitive GABA receptors blocker of picrotoxin and 1 μM of the co-agonist of NMDA receptors, glycine.

The excitotoxic effect of NMDA was studied by the method proposed in (Liu et al. 2007). For this, the slices of the hippocampus were exposed to 50 μM of NMDA in the presence of 1 μM glycine for 15 min. After that, the slices were put in the incubator, in which in the experimental group the test substances were added to the Krebs solution at concentrations equivalent to the systemically administered doses of 100 mg/kg (piracetam) or 10 mg/kg (diacamf and R-86), where they stayed for not less than 1 hour. For the electrophysiological studies, the slices were taken 1 hour after NMDA effect terminated. Anoxia and aglycemia were simulated by the method from (Tian, Baker, 2002). The slices were placed in a chamber with nitrogen atmosphere in the Krebs solution, where glucose was replaced by an equivalent amount of mannitol for 7.5 min at a temperature of 32°C. Then the slices were put into an incubator in an aerated Krebs solution containing the test substances for the experimental group. For the electrophysiological studies, the slices were taken 1 hour after the end of anoxia and aglycemia. An oxidative stress was simulated by the method from (de Almeida et al., 2008), for which the slices were exposed to H_2O_2 at a concentration of 1 mM for 30 min. After this, the slices were put into the incubator for 1 hour, after which they were used for the study. In the experimental group, the test substances were added to the Krebs solution.

Since the main function of neurons is the generation of postsynaptic and action potentials, a progressive (sometimes irreversible) decrease in the amplitudes of the pEPSP of the pyramid neurons of the CA1 region is considered to be the earliest manifestation of neuronal damage. If an amplitude decay of EPSP was less or significantly less apparent under the effect of test substances in vitro after applying damaging procedures, it is regarded as a manifestation of neuroprotective action. Each group of studies was performed on 5 to 12 sections of the hippocampus taken from 3 to 5 different rats.

The level of depressiveness in rats was assessed by recording the indicators of the swim test (Porsolt et al. 1978). The rats were placed in a plexiglass cylinder 46 cm in diameter and 45 cm in height, filled with water (temperature 23-25ºC) to a level of 30 cm from the bottom. On the first day, the duration of the swimming was 15 minutes (pre-test); 24 hours later, the rats were placed in the water for 6 minutes, and, using videorecording, the basic parameters of their behavior were recorded and stored in a separate file. The immobilization behavior was characterized by positioning the rats vertically, without any motion, with their forelegs pressed to the chest, hind legs extended, and the head above the water. The longer immobilization lasted, the higher level of depression of the animals was.

The test of sucrose preference characterizing a hedonic behavior of rats was realized by the method from (Benelli et al. 1999). For this, on day one, the rats were placed in single cages with two drinking bowls filled with 1% sucrose solution. The next day, there was water in one drinking bowl, and the solution of sucrose – in the other.

For 23 hours on the third day, the animals were subjected to food and water deprivation, and then, for 60 minutes, 2 pre-weighed drinking bowls filled with water and a solution of sucrose were returned to the cages. One hour later, the drinking bowls were weighed. In the next 2 hours of the fourth day, the animals received food and water, after which they were deprived of food and water for 21 hours. Then again, the drinking bowls were returned for 1 hour, and the percentage of preference for the consumption of sucrose solution (P) was determined by the formula:

P = the weight of consumed sucrose solution/ the weight of consumed liquid × 100.

The depressive syndrome was simulated by the method (Sun et al. 2011). For this, the rats were exposed to the swim stress every day for five days by placing the animals in water for 10 minutes after determining the initial Porsolt swim test indicators. Twenty-four hours, 10 and 20 days after the last swimming session, the immobilization time was determined. Piracetm at dose 100 mg/kg, diacamf and R-86 at a dose of 10 mg/kg was administered once a day intraperitoneally, starting from the first day after the termination of the five-day stress-inducing procedure. An equal volume of solvent (normal saline) was administered to the control animals. In the control and experimental animals, 24 hours later, as well as on the 10th and 20th days after the termination of the stress-inducing procedure, the changes in the parameters of Porsolt swim test and preferences for the consumption of sucrose solution were recorded. Each series of behavioral studies was performed in 6 to 8 rats.

The research results were analyzed using the conventional methods of variation statistics and licensed Medstat software. For each series, the mean and standard error of the mean were determined. The significance of the differences in the compared values was assessed using paired Student t-test.

Results and discussion

First of all, the test substances were assessed in regard of their capacity to improve the functional status of the brain, which manifests in the the ability to reduce brain damage caused by excitotoxic action of N-methyl-D-aspartate, anoxia, glucose deprivation and oxidative stress. The rat dorsal hippocampus was chosen as an object of action, as it is a highly organized brain structure, extremely vulnerable to damaging effects.

With a single exposure, the test substances showed a moderate neuroprotective activity. However, when the test substances were systemically (intraperitoneally) administered to the animals for at least 10 days, this activity increased significantly.

As seen in Fig. 1, due to the impact of anoxia and aglycemia on hippocampal slices, the amplitude of the pEPSP of pyramid neurons of the CA1 region in the control slices decreased from 2.7 mV to 0.35 mV, i.e. almost by an order of magnitude. At the same time, in the slices of the hippocampus of rats which had been treated by piracetam at a dose of 100 mg/kg systematically for 10 days, anoxia and aglycemia reduced the amplitude of the pEPSP only three times (Fig. 1). Consequently, piracetam protects hippocampal tissue from the damaging effects of anoxia and aglycemia. Similarly, piracetam and other test pharmacological substances reduce the damage to pyramidal neurons manifested by a decrease in the amplitudes of pEPSP and caused by anoxia and aglicemia, excitotoxic action of NMDA and oxidative stress. The range of cerebroprotective activity of the test substances is presented in Table 1.

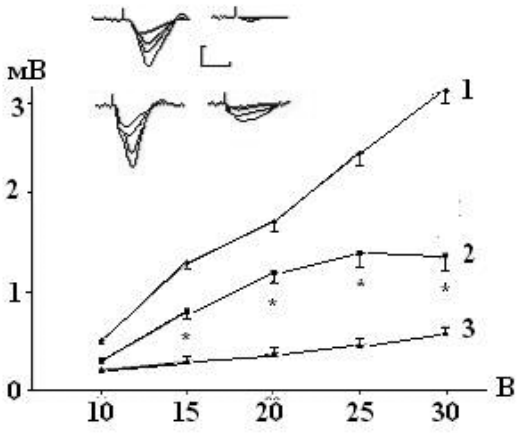

Figure 1. The effect of the systemic administration of piracetam at a dose of 100 mg/kg for 10 days on the damage of pyramidal neurons caused by anoxia and aglycemia. *Note:* **1** – amplitude of pEPSP of the pyramid neurons in the control slices; **2** – amplitude of EPSP of the pyramid neurons in brain sections of rats that were administered piracetam; **3** – amplitude of EPSP of the pyramid neurons 1 hour after termination of anoxia and aglycemia in brain slices of rats, which were administered solvent. At top left, there are samples of pEPSP averaged over 10 realizations and obtained in individual experiments on individual slices of the hippocampus of the control (top row) and experimental rats (bottom row) before (left) and after (right) exposure to anoxia/aglycemia. Calibration: 1 mV, 10 ms. * – differences are significant at $p<0.05$.

So piracetam showed its maximum protective activity against the damage to neurons caused by oxidative stress and minimally weakens glutamate excitotoxicity. Diacamf markedly and nearly equally reduced disturbances of the vital activity of neurons caused by anoxia and oxidative stress, but did not have anti-excitotoxic action. The compound R-86 weakened excitotoxic damage to neurons in the most pronounced way, and moderately counteracted the negative effect of the anoxia and oxidative stress on neurons. Finally, the classical antidepressant imipramine only 20 days after systemic administration to rats showed the attenuation of the neuronal damage caused by anoxia, aglycemia and exposure to hydrogen peroxide (Table 1).

Table 1. The relative activity of drugs used in the study according to their effect on the test electrophysiological parameters 10 days after their systemic administration to rats

Options	Study substances			
Decrease of the studied parameters	Piracetam	Diacamf	Compound R-86	Imipramine
Glutamate exitotoxicity	1.15 ± 0.07	1.00 ± 0.10	1.40 ± 0.09	1.33 ± 0.09
Oxidative stress	3.00 ± 0.18	3.00 ± 0.21	1.87 ± 0.13	–
Anoxic damages	2.14 ± 0.15	3.09 ± 0.24	2.39 ± 0.16	1.76 ± 014

Note: Value = 1.0 –absence of the effect; the value > 1.0 indicates how many times the studied parameter has decreased.

The severity of depressive behavior was assessed by increasing the immobilization time in the Porsolt swim test and by reducing the preference for consumption of sucrose solution in comparison with water, which correspondingly reflect the motivational and hedonic components of animal behavior. The fact that a five-day swim stress causes behavioral depression is indicated by an increase in the time of immobilization of rats in the forced swim test to 70.2±3.6 sec versus 45.5±2.6 sec ($p< 0.05$) in the control group. In addition, under the same conditions, the value of the preference for the consumption of sucrose solution decreased ($p<0.05$) from 83.6±3.4% to 65.4±5.5% (Table 2). Currently, it is established that the depressive phenotype of behavior caused by chronic stress is due to inhibition of the vital activity of neurons of the brain limbic structures, which is manifested in a decrease in the size of neurons and dendritic branching, a decrease in the density of dendritic spines and synaptic contacts (Silva-Gometz et al. 2003; Radley et al. 2004).

TChronic administration of the classic tricyclic antidepressant imipramine at a dose of 20 mg/kg for 20 days reversed the behavior disorders caused by chronic swim stress. Indeed, the immobilization time of the rats in the forced swim test decreased from 70.2±3.6 sec to 24.5±2.6 sec and its value became less than that of the intact control. In addition, the value of preference for the consumption of sucrose solution increased to 85.3±4.7% versus 65.4 ± 5.5% in animals to which the solvent had been injected (Table 2).

Similar to the action of imipramine, chronic administration of the test substances was accompanied by a decrease in the levels of helplessness and anhedonia caused by chronic swim stress. Thus, piracetam, diacamf and the compound R-86 reduced the immobilization time of rats in the forced swim test to 47.4±9.4 s, 41.6±3.9 sec and 50.6±3.3 sec respectively versus 70.2±3.6 sec in the control animals (Table 2). On the other hand, piracetam, diacamf and the compound R-86 increased the preference of the consumption of sucrose solution up to 85.6±5.7% and 84.5±4.2 % and 76.7±2.9 % respectively versus 65.4±5.5 % of the rats which had received the solvent (Table 2). Consequently, the used drugs have the antidepressant-like action, but are not antidepressants like imipramine. Their difference from antidepressants is that with one dose delivery to the animals, they do not affect the time of immobilization in the forced swim test, while imipramine reduces the time of immobilization even under these conditions.

The plausible reasons for the development of neuroatrophic damage to the limbic structures (excluding amygdala), when exposed to chronic stress, may be a disruption of the expression of brain neurotrophins, primarily BDNF; impaired glutamate clearance and its accumulation in the extracellular space and excitotoxic damage to neurons; damage to the mitochondria leading to the reduction of the synthesis of high-energy compounds and oppression of biosynthetic processes, and to an increase in the production of free radicals, trigge-

Table 2. Influence of the test substances on the immobilization time in the forced swim test and on the consumption of sucrose solution by the animals in the sucrose preference test in the control conditions and against the background of the behavioral depression caused by chronic swim stress

Experimental conditions	Immobilization time in the forced swimming test (s)	% of the preferences of the consumption of sucrose solution
Intact control	45.5 ± 2.6	83.6 ± 3.4
20 days after stress termination, administration of the solvent	70.2 ± 3.6*	65.4 ± 5.5*
20 days after stress termination, administration of piracetam	47.4 ± 9.4#	85.6 ± 5.7#
20 days after stress termination, administration of diacamf	41.6 ± 3.9#	84.5 ± 4.2#
20 days after stress termination, administration of the compound R-86	50.6 ± 3.3#	76.7 ± 2.9#
20 days after stress termination, administration of imipramine	24.5 ± 2.6#	85.3 ± 4.7#

Note: * – differences are significant in comparison with the control at $p< 0.05$; # – differences are significant in comparison with the damaging effects of the swimming stress at $p< 0.05$ after 20 days of administration of the study drugs.

ring lipid peroxidation reactions; and, finally, the development of inflammation (Autry et al. 2009; Niciu et al. 2014; Shalbuyeva et al. 2006; Haroon et al. 2017). According to Table 1, the test substances have the ability to attenuate the atrophic damage to neurons caused by glutamate excitotoxicity, high-energy compounds deficiency with a lack of oxygen, as well as lipid peroxidation. It is obvious that with a one dose delivery these drugs can not change the neurochemical processes in the brain limbic structures that determine the development of a depressive behavioral phenotype. However, with chronic administration, substances with cerebroprotective activity prevent further progress of pathochemical processes and, due an increased biosynthesis of proteins, nucleic acids and phospholipids, are likely to reverse the already formed atrophic damage to neurons.

Correction of resistance to antidepressants in patients with depression is quite a difficult task. In most cases, a combination therapy is recommended, with the addition of either another antidepressant ("double therapy") or a drug from a different group (not an antidepressant) to enhance the effect of the main antidepressant – enhanced therapy, augmentation (Bykov et al. 2013). In this regard, an attempt was made to find out the nature of the impact of the substances (piracetam and pharmacological substances diacamf and compound R-86) with cerebroprotective activity on the antidepressant effects of imipramine in the simulation of behavioral depression.

Imipramine, which was chronically administered to rats at a dose of 20 mg/kg, reduced ($p<0.05$) the time of immobilization of rats in the swim test, as an indicator of helplessness, from 83.4±3.0 to 40.2±1.8 sec. In addition, the antidepressant weakened anhedonia, as evidenced by an increased indicator of the preference for the consumption of sucrose solution from 66.6±2.1% to 85.5±3.4% (Table 3). At the same time, the chronic administration of impramine at a dose of 5 mg/kg (1/4 of the previously used dose) did not affect the manifestations of stress-induced behavioral depression, such as helplessness and anhedony (Table 3).

Table 3. Influence of chronic 20-day administration of imipramine and combinations of partial doses of imipramine and substances with cerebroprotective activity on indicators of behavioral depression caused by swim stress

Study substanses	The time of immobilization (s)	% of the preference of the consumption of sucrose solution
The solvent	83.4 ± 3.0	66.6 ± 2.1
Impramine 20 mg/kg	40.2 ± 1.8*	85.5 ± 3.4*
Impramine 5 mg/kg	74.4 ± 3.6	63.6 ± 2.7
Impramine 5 mg/kg + Piracetam 50 mg/kg	36.6 ± 2.4#	88.2 ± 3.4#
Impramine 5 mg/kg + Diacamf 5 mg/kg	63.2 ± 2.4#	78.5 ± 3.4#

Note: * – values significantly ($p < 0.05$) differ from the control; # – values significantly ($P < 0.05$) differ from the imipramine activity indicators administered at a dose of 5 mg/kg.

However, when imipramine at a "non-effective" dose of 5 mg/kg was chronically administered along with piracetam at a dose of 50 mg/kg, at which, when administered independently, piracetam reduced the time of immobilization to 58.6±2.7 s, the time of immobilization decreased ($p<0.05$) to 36.6±2.4 sec versus 74.4±3.6 when only imipramine was administered at a dose of 5 mg/kg (Table 3). In chronic co-administration of imipramine and piracetam at doses of 5 and 50 mg/kg, respectively, the preference for the consumption of sucrose solution increased from 66.6±2.1% in rats, to which the solvent had been administered, to 88.2±3.6% ($p<0.05$; Table 3). At the same time, these values were 63.6±2.7% with only imipramine being administered, and 71.6±2.9% with only piracetam being administered. Therefore, the administration of ¼ dose of imipramine and ½ dose of piracetam produces the same effect as the administration of the full dose of the antidepressant, i.e. piracetam potentiates the antidepressant effect of imipramine.

The different results were obtained when imipramine was administered with diacamf at a dose of 5 mg/kg. The time of immobilization of the rats in this case was reduced to 63.2±2.4 sec versus 74.4±3.6 sec in the rats to which only imipramine had been administered (Table 3). Chronic administration of only diacamf at a dose of 5 mg/kg reduced the time of immobilization of the rats to 68.6±2.7 sec. With regard to the preference for the consumption of sucrose solution, the combined administration of imipramine and diacamf at a dose of 5 mg/kg to rats with stress-induced behavioral depression increased this indicator to 78.5±3.4% versus 63.6±2.7 % in the rats to which only imipramine had been administered at a dose of 5 mg/kg (Table 3). Diacamf, when chronically administered alone at the same dose, increased the preference for the consumption of sucrose solution to a level of 70.8±2.6%. Therefore, unlike piracetam, co-administration of partial doses of imipramine and diacamf gives a smaller effect than a full dose of the antidepressant, i.e. the effects of the two substances are summed (additive synergism).

On the basis of these results, it is possible to use together nootrope piracetam and antidepressants to enhance the action of the latter when treating patients with depression during the exacerbation of the disease. As for diacamf and similar substances, they are better to be used chronically during a remission of the disease in order to prolong the remission period and delay the onset of the next depressive episode.

Conclusion

Substances with cerebroprotective activity, when chronically administered, can exhibit an antidepressant-like activity. Those that potentiate the action of classical antidepressants can be co-administered with antidepressants during episodes of exacerbation of the disease. Less active cerebroprotective drugs can be recommended during remission for its prolongation.

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