PharmacologyOnLine
Archives • 2021 • vol.3 • 1004-1009

(Mg, Co) BIS (CITRATO) GERMANATES ANTIDEPRESSIVE PROPERTIES

[1]Shemonayeva, K. F.; [1]Matiushkina, M. V.; [1]Vastyanov, R. S.; [1]Nikogosian, L. R.;
[1]Antonenko, P. B.; [2]Badiuk, N. S.*
[1]Odessa National Medical University, Odessa, Ukraine
[2]Odessa International Medical University, Odessa, Ukraine

*corresponding author *badiuk_ns@ukr.net

Abstract

The antidepressant properties of magnesium bis(citrate)germanate (hermacyte) and cobalt bis(citrate)germanate (hercocyte) were studied.

The research studies were carried out with male Wistar rats during the Porsolt test (so-called "forced swimming test"). The compounds were administered at the doses of 1/80, 1/110 and 1/135 LD_{50}, and the results were compared with the control group and with the reference drug Melipramin.

Analysis of the results revealed that cobalt bis(citrate)germanate (hercocyte) showed statistically significant indicators of reducing the duration of immobilization of the rats (by 5.3 times compared with the control animals and by 1.7 times compared with the reference drug Melipramin), significantly increased the number of jumps (by 4.1 times compared with the control animals and by 1.6 times in comparison with the reference drug

Melipramin) and the total time of active swimming (by 1.7 times compared with the control group and by 1.2 times in comparison with Melipramin). In this experimental modeling of the depressive state, cobalt bis(citrate)germanate (hercocyte) has significant antidepressant properties at the dose of 1/135 LD_{50} to a greater extent than germacyte and even exceeds the indicators of the reference drug, so it is a promising compound for further research study.

Keywords: *cobalt, magnesium, germanium, citric acid, antidepressant properties*

Introduction

In modern medical practice, pathology of the emotional sphere, especially anxiety and depression, becomes especially important [12]. According to the data of WHO, nowadays approximately 110 million people in the world (3-6% of the population) have certain manifestations of such disorders [12]. Moreover, the prevalence and detection of the depressive disorders tends to increase, and there is a variety of forms and manifestations of the depressive states, a combination of emotional depression and low mood with anxiety, cognitive impairment [1, 5]. During a mass examination at the industrial enterprises, various depressive disorders were detected in 26% of people, and among those patients who accessed to the professionals in general practice – 68% [9]. Depression causes a development of the somatic diseases, worsens the course of the disease and the prognosis of life expectancy. Approximately 2/3 of the patients, diagnosed with depression, are prone to suicide attempts and 10-15% of them commit suicide [5]. It must be also noted that the prevalence of the depressions among children and teenagers has increased in recent decades, and nowadays they are being diagnosed at an earlier age. There is a clear link between the increase in the number of depressions among children and teenagers and the increase in the number of suicides [5, 7].

Thus, the growing urgency of the problem of depressions is due to their prevalence, the significant impact of the disease on quality of life and social functioning, as well as the highest level (among the mental disorders) of the suicides caused by them [5].

Together with the development of the psychopharmacology in the 1950s, many antidepressants and drugs with antidepressant properties appeared in the doctor's arsenal. However, unfortunately, all this does not solve completely the problem of treating depressive moods, and the successful pharmacotherapy of depressions remains a difficult task for a doctor. This fact is due to a number of subjective and objective reasons. Firstly, any depression is a complex of phenomena that require psychopharmacological, psychotherapeutic and somatic treatment, which depends on a correct diagnosis of the patient's condition. Secondly, an abundance of the antidepressants, their various side effects, which are due to different mechanisms of action, and hence, the differential personalized psychotropic impact on the central nervous system, complicate the treatment of a depression of a particular patient. Therefore, a significant number of patients, treated with modern antidepressants, do not achieve the desired clinical effect [3, 13]. And this results in the relevance of a search for the new medicinal substances with antidepressant properties.

Recently, a number of the coordination compounds of germanium have been synthesized, which include magnesium, cobalt and citric acid. Along with low toxicity, these compounds have a unique spectrum of neurotropic activity (tranquilizing, anti-aggressive, nootropic) [8]. That stipulated the feasibility of studying those biologically active substances (BAS) for their antidepressant action.

The aim of the present study is to search for the new effective antidepressants in a number of bimetallic coordination compounds of germanium with citric acid.

Materials and methods

The investigations were carried out on 62 male Wistar rats weighing 200-220 g, which were kept on a standard diet of the Odessa National Medical University's medico-biological; clinic ('vivarium'). The Porsolt test (so-called "forced swimming test") was used as an experimental model [10]. During the test, there was assessed the time when the animal, attempting actively to find a way out of an unpleasant situation (immersion in water and inability to leave the installation), went to immobility, "hanging", which the researchers associate with a despair or so-called "state of loss of hope by the animal – hopelessness" [4]. This test is valid for the depressive state evaluation [6]. In addition, there were evaluated the attempts to resist actively the influence of the aversive factors, which were registered by the number of jumps and the duration of active swimming [2].

The studied BAS – magnesium bis(citrate)germanate (hermacyte) and cobalt

bis(citrate)germanate (hercocyte) – were injected to the rats once intraperitoneally (i.p.) with three doses – 1/80, 1/110 and 1/135 LD_{50} respectively: hermacyte – 23,0; 28,0; 38,0 mg/kg, hercocyte – 2,25; 1,70; 1,50 mg/kg. The antidepressant Melipramin at a dose of 15,0 mg/kg (Egis Pharmaceuticals, Hungary) was injected i.p. as a reference drug. The isotonic solution of sodium chloride (Darnitsa, Ukraine) was administered to the control animals in the equivalent volume.

The data obtained were calculated statistically using the parametric ANOVA criterion, which was accompanied as a correspondence by the Newman-Keuls test [11]. The minimum statistical probability was determined at $p<0.05$.

Experimental studies were conducted in accordance with the rules established by the Directive of the European Parliament and the Council (2010/63 / EU), by the order of the Ministry of Education and Science, Youth and Sports of Ukraine No. 249 of March 1, 2012 "On Approval of the Procedure for conducting scientific experiments, experiments on animals by scientific institutions " and methodical recommendations.

Results

The analysis of the obtained data revealed that BAS showed the antidepressant properties, most pronounced at a dose of 1/135 LD_{50} (table).

Thus, when hermacyte was administered at the indicated dose, the duration of immobilization of the rats was decreasing by 3.8 times compared with the intact animals (70,21±5,61) versus (18,22±1,87) s and by 1.2 times in comparison with the reference drug Melipramin (22,02±2,36) s ($p<0,05$). Hercocyte was decreasing that indicator by 5,3 times compared with the control (13,33±2,38) and by 1,7 times in comparison with Melipramin ($p<0,05$). Hermacyte at a dose of 1/110 LD_{50} was decreasing the indicator by 1,9 times (36,89±2,76) s compared with the control animals, but was increasing it by 1,7 times ($p<0,05$) in comparison with Melipramin (table). Whereas the introduction of hercocyte at the same dose led to a decrease by 2,7 times (26,22±3,01) s, but increased it by 1,2 times ($p<0,05$) compared with Melipramin.

While administering hermacyte at a dose of 1/80 LD_{50}, the indicator of immobilization of the rats even slightly increased compared with the control and by 3,4 times in comparison with Melipramin ($p<0,05$). The introduction of hercocyte at the specified dose led to the opposite effect, as evidenced by the increase of the indicator concerning the duration of immobilization of the rats by 1,1 times than that one of the control, and by 3.6 times compared with Melipramin ($p<0,05$) (table).

The administration of hermacyte at a dose of 1/135 LD_{50} led to an increase in the number of jumps of the rats (indicating an attempt of the active resistance) by 3,1 times (15,56±0,84) compared with the indicators of the control (4,95±0,52) ($p<0,05$) and by 1.2 times in comparison with the reference drug (13,04±0,69) ($p<0,05$). Under the influence of hercocyte injected at the same dose, the number of jumps increased slightly – by 4,1 times (20,34±0,67) more than those of the control animals and by 1.6 times more than in comparison with the administration of Melipramin ($p<0,05$).

Under an influence of the introduction of hermacyte 1/110 LD_{50}, the mentioned indicator was increasing by 2,5 times (8,22±0,70) ($p<0,05$) compared with the control, however, it was at the level of the reference drug. Hermacyte at a dose of 1/80 LD_{50} increased the number of jumps slightly (3,64±0,72) ($p<0,05$) compared with the control animals. And in comparison with Melipramin, the number of jumps was decreasing by 3,6 times ($p<0,05$) (table).

Under the influence of the studied BAS, the total time of active swimming was changing also. The administration of hermacyte at a dose of 1/135 LD_{50} led to an increase by 1,5 times (229,22±8,66) versus (152,50±13,91) s ($p<0,05$) compared with the control and by 1,1 times (215,05±9,03) s in comparison with Melipramin ($p<0,05$). Hercocyte at the same dose was causing an increase of the total time of active swimming by 1,7 times (136,48±12,65) s ($p<0,05$) compared with the control and by 1,2 times more than Melipramin ($p<0,05$). After the administration of hermacyte at a dose of 1/110 LD_{50}, the total time of active swimming of the rats increased slightly, only by 1,2 times (176,34±3,82) s ($p<0,05$) compared with the control and decreased by 1,2 times in comparison with the introduction of Melipramin ($p<0,05$) (table).

The administration of hercocyte at a dose of 1/110 LD_{50} led to an increase of the indicator by 1,4 times (212,25±8,37) s ($p<0,05$) compared with the control

animals and was at the level of the indicator after the introduction of Melipramin (p<0,05).

The administration of hermacyte at a dose of 1/80 LD_{50} led to a slight decrease of the indicator compared with the control (136,48 ±12,65) s (p<0,05) and by 1,6 times less in comparison with Melipramin (p<0,05). The injection of hercocyte at a dose of 1/80 LD_{50} resulted in a decrease of the total active swimming time by 1.2 times (122,35±10,01) s in comparison with the control animals and by 1.8 times compared with Melipramin (p<0,05) (table).

Thus, both BAS revealed the antidepressant effect at a dose of 1/135 LD_{50}, however, hercocyte showed more pronounced antidepressant properties, as there were obtained statistically significant indicators of reducing the duration of immobilization of the rats. The results of the research studies testify to a reduction of the behavioral depression, which is manifested by immobilization of the animals in an aversive environment, presence of active resistance to the aversive factors, which are estimated by the number of jumps and by the duration of active swimming.

Conclusions

1. Cobalt bis(citrate)germanate (hercocyte) showed statistically significant indicators of reducing the duration of immobilization of the rats (by 5,3 times compared with the control animals and by 1,7 times in comparison with the reference drug Melipramin), it was increasing significantly the number of jumps (by 4,1 times compared with the control animals and by 1,6 times in comparison with the reference drug) and the total time of active swimming (by 1,7 times compared with the control and by 1,2 times in comparison with Melipramin).

2. In this experimental modeling of the depressive state, cobalt bis(citrate)germanate (hercocyte) has pronounced the antidepressant properties at a dose of 1/135 LD_{50} to a greater extent than germacyte and even exceeds the indicators of the reference drug, therefore, it is a promising compound for a further research study.

Acknowledgments

The authors declsre that there are no conflicts of interest.

References

1. Bekeneva L.V. Depressive disorders in the psychiatric practice. *Bulletin of the North-Eastern Federal University named after M.K. Amosov. Series "Medical Sciences".* 2017; 4 (09): 17-22 [In Russian].
2. Garibova T.L., Kraineva V.A., Voronina T.A. Animal models of depression. *Pharmacokinetics and Pharmacodynamics*. 2017; 3: 14-19. [In Russian].
3. Golovacheva V.A., Parfyonov V.A. Depression in neurological practice: prevalence, diagnosis, treatment standards and new options for pharmacotherapy. *Medical Council.* 2015; 5: 55-60 [In Russian].
4. Khabriev R.U. Guidelines for experimental (preclinical) studies of new pharmacological substances. Moscow, 2005: 832 p. [In Russian].
5. Korostiy V.I., Kozhina A.M., Zelennskaya E.A., Khmain S.H. Use of Epileptal in the complex treatment of the depressive disorder of those patients who has a high risk of suicide. *International Journal of Neurology*. 2014; 5 (67): 66-71 [In Russian].
5. Kovaleva M.A., Makarova M.N., Makarov V.G., Goryacheva M.A. Application of the test "forced swimming" in preclinical studies. *International Veterinary Bulletin*. 2015; 4: 90-95 [In Russian].
6. Martsenkovsky I.A., Kaptiltseva A.V. Severe depressive episode of teenagers: in search of a balance between psychopharmacotherapy and psychotherapy. *Neuronews. Psychoneurology and Neuropsychiatry*. 2014; 6 (61): 182-190 [In Russian].
7. Matyushkina M.V. Pharmacological activity of the new coordination compounds of metals with citric acid. Thesis, PhD (Pharmacy): 14.03.05. Kharkiv, 2018. 24 p [In Ukrainian].
8. Mikhailov B.V. A problem of depressions in the general somatic practice. *International Medical Journal*. 2003; 9 (3): 22-27[In Russian].
9. Mironova A.N., Bunyatyan N.D., Vasilieva A.N. Guidelines for Preclinical Trials of Medicinal Products. Part 1. / M .: Grifi i K, 2012: 944 p [In Ukrainian].
10. Nasledov A.D. Professional statistical data analysis. SPb : Piter, 2011: 400 p [In Russian].
11. News release of WHO. "Depression: let's talk". Geneva. March 30, 2017. [Electronic resource]

Access mode: https://www.who.int/ru/news-room/detail/30-03-2017--depression-let-s-talk-says-who-as-depression-tops-list-of-causes-of-ill-health

12. Wang S-M., Han C., Lee S-J., Jun T-Y., Patkar A.A., Masand P.S., Pae C-U. Second Generation Antipsychotics in the Treatment of Major Depressive Disorder: An Update. *Chonnam Med. J.* 2016; 52 (3): 159-172.

Table. The influence of the investigated (Mg, Co) bis (citrato) germinates on Porsol test indexes

N	Investigated BAS, (mg/kg)	Porsol test indexes (M±m)		
		Duration of immobilization (s)	Number of jumps	Active swimming duration, (s)
	Control (NaCl 0,9%)	70,21±5,61	4,95±0,52	152,50±13,91
	Melipramin (15.0)	22,02±2,36*	13,04±0,69*	215,05±9,03*
	Hermacyte (23.0)	18,22±1,87*	15,56±0,84*	229,22±8,66* #
	Hermacyte (28.0)	36,89±2,76* #	8,22±0,70* #	176,34±3,82* #
	Hermacyte (38.0)	74,77±4.64* #	3,64±0.72* #	136,48±12,65* #
	Hercocyte (1.5)	13,33±2.38* #	20,34±0.67* #	252,44±9,22* #
	Hercocyte (1.7)	26,22±3,01* #	12,44±0,58*	212,25±8,37*
	Hercocyte (2.25)	80,21±1,98* #	5,22±0,69 #	122,35±10,01* #

Note:
* – p<0,05 - the significant differences of the investigated indexes compared with the same data in control group;
# – p<0,05 - the significant differences of the investigated indexes compared with the same data in animals which were injected with Melipramin (ANOVA+Newman-Keuls test).