the initial physiological level and the state of the conjunctiva and cornea of control non-sensitized animals (Table 3).

Thus, according to the results of the conjunctival test, of dry extract of cabbage garden does not have an allergenic effect.

Table 3

Results of studying the allergenic effect of dry extract of cabbage in the conjunctival test ($X \pm S_X$, n = 6)

Experience conditions		Ophthalmic reaction, points
Control	Control eye	0 (0-0)
	Experimental eye	0 (0-0)
Dry extract of cabbage	Control eye	0 (0-0)
	Experimental eye	0 (0-0)

Conclusions.

1. On the model of active cutaneous anaphylaxis, dry extract of cabbage does not cause the release of histamine, which indicates the absence of anaphylactic effect.

2. Under in vitro conditions in the degranulation reaction of mast cells, no changes in the degranulation index were found in comparison with the control, which indicates the absence of allergenic properties in dry extract of garden cabbage.

3. Dry extract of cabbage does not cause changes in the condition of the mucous membrane and sclera of the eye in the conjunctival test.

4. The results of the conducted studies indicate the absence of allergenic properties in dry extract of garden cabbage and allows us to recommend it as a safe gastroprotective drug.

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STUDY OF THE STRESS-PROTECTIVE EFFECT OF THE COMBINATION OF GLYCINE WITH MAGNESIUM CITRATE

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Abstract:

Stress is one of the most common diseases, which results in a number of comorbidities - coronary heart disease, intestinal disease and others. Therefore, it is important to develop new drugs that would be effective and safe for the treatment and prevention of stress. Since it is important to determine the amount of API to determine

the optimal composition and technology of drug production, the aim of the research was to study the effect of glycine, different doses of magnesium citrate and the combination of glycine with magnesium citrate on the functional state of the central nervous system. The most pronounce inhibitory effect on the locomotor activity of animals, indicative research activity and emotional reactions were observed when using a combination of glycine: magnesium citrate at a dose of 100: 350 mg, respectively.

Keywords: glycine, magnesium citrate, stress-protective effect, open field test, classical triad of stress

Introduction

Stress is a non-specific reaction of the organism that occurs under the influence of various extreme factors that threaten the disturbance of homeostasis (the state of equilibrium of the dynamic environment in which biological processes occur), and is characterized by stereotypic changes in the function of the nervous and endocrine systems. Workplace stress attributed to the 21st century main diseases by the International Health Organization and it has become the topic of a report by the International Labour Organization in 2016 [2]. As for Ukraine, 70% of Ukrainians are in a state of stress and a third of the population is in a state of severe stress [3]. This disease has an impact not only on the general condition of the body, but also on the economic indicators of society. More than $ 120 billion a year, US scientists estimate the costs associated with the impact of stress on human health. Included in this figure are the effects of stress, such as declining productivity, working hours and medical expenses for the treatment of a large number of diseases resulting from nervous overstress [2]. The effects of stress on health and comorbidities are a topic of interest for many scholars today. According to D. Sgambato et al., the frequency of emotional disorders is high in Crohn's disease and ulcerative colitis. Moreover, depression and anxiety affect the course and severity of underlying bowel disease [7]. K. Brajovic's research has confirmed the role of stress caused by acute and chronic life events in coronary heart disease (CHD) [6]. Therefore, the development of new drugs that would be effective and safe for the treatment and prevention of stress conditions is an urgent task of pharmacy and pharmacology.

We have developed sublingual tablets where, according to previous studies, glycine (G) and magnesium citrate (MC) have been selected as active pharmaceutical ingredients (API) [8]. To determine the optimal composition and production technology of a new drug, one of the most important steps is to determine the amount of API.

The aim of the study was to study the effect of glycine, different doses of magnesium citrate, and combinations of glycine with magnesium citrate on the functional state of the central nervous system by behavioural responses in the open field test and indicators of the classical triad of stress.

Materials and methods.

The study was performed on 76 white Wistar male rats, 2.0-2.5 months old and weighing 220-250 g, which were kept under standard vivarium conditions. Animals received a balanced diet and water as needed. Animal keeping and experiments were carried out in accordance with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes" (Strasbourg, 1995) [1], the "General Ethical Principles for Animal Experiments", adopted by the First National Congress on Bioethics (Kyiv, 2001) [10]. The distribution of experimental animals is shown in Tab. 1.

Table 1

Distribution of experimental animals depending on the dosage of the test compounds

Group of animals	API dose	
	Glycine	Magnesium citrate
1 Intact control	-	-
2 Control pathology	-	-
3	100 mg	-
4	-	200 mg
5	-	250 mg
6	-	350 mg
7	100 mg	200 mg
8	100 mg	250 mg
9	100 mg	350 mg

The test compounds were administered sublingually using a special device: the tablet was placed in a gauze bag with laces, which were fixed to the lower incisors and tied to the ears of rats. Given the presence of a small amount of saliva in rats and a decrease in its formation under conditions of activation of the sympatho-adrenal system, 1 drop of NaCl saline was applied to the tablet 1 min before fixing the package, which facilitated its rapid absorption. The exposure time was 15 min to allow oral absorption of the drug during this time. Animals in this period were placed in special small cage boxes to restrict the movement of rats [4]. The small cages were made of plastic with a diameter of 5 × 10 cm, a height of 5 cm and had sections with cutouts for the head and tail of the animal. The posterior

section was movable, allowing changing the pencil area depending on the size of the rat. In the group of animals with control pathology, the gauze packet was moistened with saline NaCl in the mouth similar to the experimental animals, but without the tablet. After that, all the animals were kept in the cages for 6 hours [5]. The slaughter was performed under thiopental anaesthesia (100 mg / kg of body weight intraperitoneal).

The effect of substances on the central nervous system (CNS) was studied by the "open field" test, which reveals the behaviour of animals in emotional and stressful situations [9]. The camera for this test is a rectangular arena (100 × 70 cm) with walls 50 cm high, whose field is divided into 10 × 10 cm squares and illuminated by a 100 W lamp. The front of the chamber is transparent. Observations were made through it part. The evaluation criteria were horizontal motor activity (line crossings), vertical motor activity (rearing), number of washes (grooming) and centre square entries within 5 min of observation [9].

After animals' autopsy, the stress-competent organs were removed: thymus, adrenal glands and stomach. Organs were released from excess connective and adipose tissue. Determination of mass ratio (MR) of the thymus and adrenal glands, were done on electronic scales series AD manufactured by "AXIS" (Poland), which meets the requirements of GOST 24104-88. The mass coefficient of the organ was calculated by the formula:

MR = organ weight (g) / body weight (g) × 100.

To determine ulcer formation, the stomach was sectioned longitudinally along a small curvature, washed with running water, and examined the mucosa using a magnifier (x8). The relief of the mucous membrane, the presence of ulcers, hemorrhage were determined. The severity of ulcerative lesions was evaluated in the presence of 1-5 ulcers – with scale 1-5 points. The frequency of gastric lesions was determined by the number of rats that had ulcerations in the gastric mucosa to the total number of animals in the group, the multiplicity of lesions by the number of gastric ulcers in all rats to the number of animals in the group [9].

Statistical analysis of the results was carried out by the method of variational statistics. The significance of the difference between the indicators was evaluated using the Student's parametric t-test and the non-parametric Mann-Whitney method using standard Statistica for Windows 8. The differences were considered significant in the case of $p < 0.05$.

Results and discussion

The results of the study are shown in Tab. 2.

Table 2

Results of a study of the effects of glycine, magnesium citrate and their combination on behavioural responses by Mann-Whitney (M±m)

Group of animals / Indicators	1 Intact control n = 10	2 Control pathology n = 9	3 G100 n = 6	4 MC200 n = 5	5 MC250 n = 8	6 MC350 n = 6	7 G100+MC 200 n = 7	8 G100+MC 250 n = 10	9 G100+MC350 n = 10
Locomotor activity (line crossings)	80.6 ±4.91	138.0 ±7.82 $p_{1-2}<0.05$	28.8 ±5.93 $p_{1-3}<0.05$ $p_{2-3}<0.05$	77.2 ±8.54 $p_{2-4}<0.05$ $p_{3-4}<0.05$	48.2 ±11.72 $p_{2-5}<0.05$	57.8 ±11.56 $p_{2-6}<0.05$	84.7 ±15.37 $p_{2-7}<0.05$	92.9 ±7.40 $p_{2-8}<0.05$ $p_{3-8}<0.05$ $p_{5-8}<0.05$	56.6 ±9.43 $p_{2-9}<0.05$ $p_{3-9}<0.05$ $p_{8-9}<0.05$
Orienteering research activity: - rearing	14.80 ±2.15	23.67 ±2.60 $p_{1-2}<0.05$	3.17 ±1.3 $p_{1-3}<0.05$ $p_{2-3}<0.05$	12.0 ±2.31 $p_{2-4}<0.05$ $p_{3-4}<0.05$	7.75 ±1.88 $p_{1-5}<0.05$ $p_{2-5}<0.05$	5.33 ±1.42 $p_{1-6}<0.05$ $p_{2-6}<0.05$ $p_{4-6}<0.05$	9.57 ±2.52 $p_{2-7}<0.05$ $p_{3-7}<0.05$	15.30 ±2.37 $p_{2-8}<0.05$ $p_{3-8}<0.05$ $p_{6-8}<0.05$	9.56 ±2.20 $p_{2-9}<0.05$ $p_{3-9}<0.05$
- centre square entries	0.40 ±0.38	1.44 ±0.26 $p_{1-2}<0.05$	0.33 ±0.30 $p_{2-3}<0.05$	0.60 ±0.21	0.50 ±0.25	0.67 ±0.30	1.50 ±0.27 $p_{1-7}<0.05$	1.20 ±0.37	0.89 ±0.20 $p_{1-9}<0.05$
Emotional reaction (grooming)	2.90 ±0.71	4.33 ±0.38	2.17 ±0.49 $p_{2-3}<0.05$	4.60 ±0.96	2.62 ±0.46 $p_{2-5}<0.05$	3.33 ±0.65	4.57 ±0.90	3.90 ±0.79	2.89 ±0.37 $p_{2-9}<0.05$

Note:

1. G – glycine;

2. MC – magnesium citrate;

3. n – the number of animals in the group;

As can be seen from the data in Table 2, the animals in the control group, compared with the intact rats, significantly (p <0.05) increased motor activity, oriented research response, which was evaluated by the number of rearings and centre square entries. There were no statistically significant changes in the emotionality of animals in terms of grooming acts.

Under the influence of glycine at a dose of 100 mg, the degree of motor activity of animals (the number of

crossed lines decreased by 79,1%), the oriented research activity (the number of rearings decreased by 86,6%, centre square entries by - 77.0%) and emotionality of animals (the number of grooming acts decreased by 50.0%) significantly slowed down relative to the control pathology (p <0,05). Such results are likely due to the physicochemical properties and features of the pharmacokinetics of glycine tablets.

The use of magnesium citrate at a dose of 200 mg significantly (p <0.05) reduced the locomotor activity of animals compared to the control by 44.0% and oriented research activity by reducing the rearings by 49.3%. At that dose magnesium citrate had no statistically significant effect on emotional responses.

Magnesium citrate at a dose of 250 mg showed inhibitory effect on all studied indicators of behavioural and emotional reactions of animals compared with control pathology. The motor activity of rats was inhibited (the number of line crossings decreased by 65.0%), the orienting-research activity (the number of rearings decreased by 67.2%), emotional reactions (the number of grooming acts decreased by 39.5%).

Similar to the effect of magnesium citrate at 200 mg and 250 mg doses, was the influence of magnesium citrate at a dose of 350 mg, as the degree of motor activity (the number of line crossings decreased by 58.1%) and the oriented research activity (the number of rearings decreased by 77.5%). However, the emotional responses to the grooming indicator did not differ significantly from animals with control pathology.

Therefore, comparing the effects of different doses of magnesium citrate on the behavioural and emotional responses of animals in the “open field” test, it can be noted that magnesium citrate at a dose of 250 mg is greater than magnesium citrate at a dose of 200 mg, inhibits locomotor and oriented research activity and reduces emotional reactions to control pathology. Magnesium citrate at a dose of 350 mg was found to have the greatest inhibitory effect on orientation activity, which was observed with respect to intact animals, a group of rats’ wit control pathology, and animals receiving magnesium citrate at a dose of 200 mg.

In the study of the combination of the preparation of glycine at a dose of 100 mg with magnesium citrate at a dose of 200 mg was found a inhibition of motor activity (the number of crossed lines decreased by 38,6%) and oriented research activity in terms of rearings (which decreased by 59.6%) against the background of no statistically significant changes in the number of exits to the centre of the field and grooming. All changes were significant (p <0,05) relative to the control pathology group.

The use of tablets with a combination of glycine at a dose of 100 mg and magnesium citrate at a dose of 250 mg indicates a decrease, compared with the control pathology (respectively p <0,05), locomotor activity (the number of line crossings by 32.7%) and orientation research activity (the number of rearings decreased by 64.6%). There were no significant changes in the number of centre square entries and the emotional reactions of the animals. However, it is worth noting that all the studied parameters, which characterize the horizontal and vertical motor activity and emotional state, were almost the same as in animals of intact control. The correction effect of glycine (100 mg) in combination with magnesium citrate at a dose of 250 mg is also indicated by significant (p <0.05) changes in locomotor and orientation research activity compared to the action of glycine at a dose of 100 mg and magnesium citrate at doses of 250 mg and 350 mg.

The greatest inhibitory effect on the animal's condition compared to the control pathology manifested the combination of glycine at a dose of 100 mg with magnesium citrate at a dose of 350 mg. Significantly (p <0.05) decreased horizontal motor activity (number of line crossings decreased by 59.0%), orientation research activity (number of rearings decreased by 59.6%) and there was trend (p <0.2) to reduce the number of centre square entries. In contrast to the effect of the combination of glycine (100 mg) with magnesium citrate at doses of 200 mg and 250 mg, there was a significant (p <0.05) decrease in emotional response (by 32.2%). It should be noted that the combination of glycine (100 mg) with the maximum dose of magnesium citrate outweighed the inhibitory effect of the combination of glycine 100 mg and magnesium citrate 250 mg on locomotor activity (p <0.05).

Therefore, to determine the most effective combination of API between the composition of 100 mg of glycine with 250 mg of magnesium citrate and the composition of 100 mg of glycine with 350 mg of magnesium citrate was carried out an additional experiment on the classic triad of stress. As you know, stress reaction can be accompanied by morphological changes in a number of organs and tissues. First of all, it refers to the appearance of ulcers in the gastric mucosa, the development of thymus involution and the increase in the relative mass of the adrenal glands. The results of the effect of the tested compounds on the indicators of the mass ratios of the thymus and adrenal glands in conditions of immobilization stress are shown in Tab. 3.

Table 3

The results of the influence of the studied compounds on the indicators of the mass ratios of the thymus and adrenal glands in conditions of immobilization stress (M ± m)

Organs / Group of animals	Thymus (mg/g)	Adrenal glands (mg/g)
Intact control n=10	0.0828 ± 0.00258	0.0173 ± 0.00068
Control pathology (stress) n=10	0.0477 ± 0.00360 p<0.001	0.0155 ± 0.00152 p<0.5
Stress + G 100 mg +MC 250 mg n=13	0.0700 ± 0.00280 p_1<0.001	0.0219 ± 0.00059 p_1<0.25
Stress + G 100 mg + MC 350 mg n=13	0.0611 ± 0.00330 p_1<0.02	0.0251 ± 0.00167 p_1>0.5
Stress + MC 250 mg n=10	0.0597 ± 0.00362 p_1<0.05	0.0150 ± 0.00098 p_1>0.5
Stress + MC 350 mg n=10	0.0626 ± 0.00527 p_1<0.05	0.0136 ± 0.00120 p_1<0.5
Stress + G 100 mg n=10	0.0662 ± 0.00469 p_1<0.001	0.0123 ± 0.00162 p_1<0.25

Note:
1. G – glycine;
2. MC – magnesium citrate;
3. n – the number of animals in the group;
4. Differences are reliable (p <0.05 between intact animal groups and control pathology; p1<0.05 between control pathology and correction of compounds).

Against the background of immobilization stress, a significant decrease in the thymus mass factor (p (0.001) was observed in rats, with no significant changes in the adrenal mass factor. Therapeutic and prophylactic use of both individual test compounds and their combinations prevented to a varying degree of the thymus stressful involution. The most pronounced protective effect had the combination of compounds of glycine 100 mg with magnesium citrate 250 mg and glycine 100 mg, under the action of which the thymus mass ratio was 1.47 times and 1.39 times bigger, respectively (p<0.001), relative to the index of animals control pathology.

The adrenal mass factor under the influence of the used compounds did not show any significant changes. However, the combination of glycine 100 mg with magnesium citrate 250 mg and individual glycine 100 mg showed a tendency (p<0.25, respectively) to decrease this indicator relative to the indicators of animals that were exposed to stressors and did not receive drugs.

Indicators of the state of the gastric mucosa against the background of the stress and its correction are shown in Tab. 4.

Table 4

The results of the effects of the test compounds on the gastric mucosa (M ± m)

Indicators / Group of animals	UFF	Multiplicity	Severity (points)	Area of ulcers (mm^2)	Haemorrhage (number)
Intact control n=10	0/0	0	0	0	0
Control pathology (stress) n=10	9/10	2.7±0.40 p<0.001	2.7±0.40 p<0.001	6.9±1.36 p<0.001	1.7±0.56 p<0.001
Stress + G 100 mg +MC 250 mg n=13	2/13	0.15±0.10 p_1<0.001	0.15±0.10 p_1<0.001	0.38±0.25 p_1<0.001	0.46±0.20 P_1<0.1
Stress + G 100 mg + MC 350 mg n=13	2/13	0.15±0.10 p_1<0.001	0.15±0.10 p_1<0.001	0.46±0.30 p_1<0.001	0.61±0.25 p_1<0.25
Stress + MC 250 mg n=10	5/10	1.2±0.39 p_1<0.02	1.2±0.39 p_1<0.02	3.6±1.42 p_1<0.25	1.2±0.44 P_1<0.5
Stress + MC 350 mg n=10	5/10	1.3±045 p_1<0.05	1.3±0.45 p_1<0.05	3.8±1.62 p_1<0.25	0.8±0.23 p_1<0.25
Stress + G 100 mg n=10	2/10	0.5±0.38 p_1<0.001	0.5±0.38 p_1<0.001	2.1±1.47 p_1<0.05	0.8±024 p_1<0.25

Note:
1. G – glycine;
2. MC – magnesium citrate;
3. n – the number of animals in the group;
4. UFF – ulcer formation frequency;
5. Differences are reliable (p <0.05 between intact animal groups and control pathology; p_1<0.05 between control pathology and test groups).

As shown in Tab. 4, the development of stress was accompanied by the formation of ulcers in the gastric mucosa in 90% of animals (group of control pathology); the multiplicity of lesions of the gastric mucosa in these animals was 2.7 points, the average area of ulcerative lesions - 6.9 mm^2, the number of haemorrhage - 1.7.

The use of test compounds and their combinations to a different extent prevented damage to the gastric mucosa. The lowest incidence of ulcerative lesions was observed in the groups of animals that received combinations of compounds of glycine 100 mg with magnesium citrate 250 mg, glycine 100 mg with magnesium citrate 350 mg and glycine 100 mg (15%, 15% and 20%, respectively). This was accompanied by a significant decrease in the number, severity and area of ulcers in the gastric mucosa and a tendency to decrease haemorrhages numbers by 3.68, 2.76 and 2.12 times, respectively.

Compounds of magnesium citrate 250 mg and magnesium citrate 350 mg equally in 50% of the animals in the respective group reduced the incidence of ulcers in the gastric mucosa and more than 2 times reduced the multiplicity and severity of gastric ulcer ($p<0.02$, $p<0.05$, respectively) relative to control pathology. The area of ulcerative lesions and haemorrhages in the gastric mucosa did not differ from that of stressed animals that did not receive the test compounds. Thus, all compounds revealed a reliable protective effect on gastric ulcer and prevented the stress involution of the thymus.

Conclusions

1. It was found that against the background of acute stress, sublingual administration of 100 mg glycine tablets probably ($p <0.05$) slowed down all studied parameters: locomotor activity, orientation research activity and emotional reactions.
2. According to the parameters of behavioural reactions under the influence of magnesium citrate tablets at doses of 200 mg, 250 mg and 350 mg. the greatest sedative effect was found by magnesium citrate at a dose of 250 mg.
3. The greatest inhibitory effect on locomotor activity of animals, orienting research activity and emotional reactions was observed when using the combination of glycine + magnesium citrate at a dose of 100 and 350 mg, respectively.
4. According to the results of the screening study of the stress-protective effect of the combination of glycine with magnesium citrate, and of individual components according to the indicators of the functional state of the CNS (behavioral reactions in the "open field" test) and the classical triad of stress, it can be argued that the combination of glycine 100 mg with magnesium citrate 250 mg by area of ulcers in the gastric mucosa, the amount of haemorrhage, thymus and adrenal mass ratios showed the highest curative and prophylactic effect in comparison among the studied combinations.

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