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Evaluation Of The Effectiveness Of Use Of A Complex Preparation Containing Glycine, Zinc And Curcumin As A Stress Protective Agent

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Abstract: We have developed a substance for pharmacocorrection of stress, conventionally called Kurglycin, with the ratio of components, %: zinc - 12.04, curcumin - 67.68, glycine - 13.65, water - 6.63. 14-day and 21-day oral administration of Kurglycin in the form of a 3% suspension at a dose of 5 ml/kg orally had a positive effect on the course of the stress reaction in the adrenal cortex, stabilizing the secretory activity of glucocorticoid-producing cells and reducing cortisol levels to levels close to control, in both studied groups of animals. The study of changes in the biochemical parameters of rats with low level of emotion (LLE) and high level of emotion (HLE) under the influence of Kurglycine showed a certain difference in the susceptibility of these groups both to the action of the drug.
Keywords: stress, kurglycin, zinc, curcumin, glycine

1. Introduction

Anti-stress drugs, unlike drugs that are tropic to certain functions of the body, do not exhibit an effect that is constantly localized in some organ or link of the functional-metabolic process. Their action is aimed at limiting the negative impact on the body from cause-and-effect unfavorable factors of various natures. Since the stress reaction is a general response of the entire organism, the protective effect of pharmacological agents can only be assessed at the systemic level. This requires an integrated approach and consideration of a certain range of processes that consist of key protective reactions at the cellular, subcellular and molecular levels and affect the functional state of target organs, especially those sensitive to stress.

Along with the general classification, neuropeptides (melatonin), antioxidants (Mexidol) and neuroamino acids (taurine) are described in detail as stress protectors, i.e. drugs that affect more universal stress-implementing changes that occur in the early stages of stress and ensure the progression of systemic pathology of stress genesis.

The study of the mechanisms of stress-protective action makes it possible to use for this purpose drugs that ensure the development of active forms of protection in target organs in the form of optimizing the rapid mediation of cell bioenergetics, stimulating the metabolism of nucleic acids, proteins, etc. [1,2,3,4].

Zinc is the second most abundant trace element in the human body after iron [2], equivalent to 10% of the entire human proteome, and maintains the structural integrity of many of them. Its role in regulating antioxidant stress and anti-inflammatory effects is also great. In addition, it is part of the structure of proteins, acts as a substrate, or as a regulator of enzymatic activity [3]. At the same time, the antioxidant properties of zinc are realized during DNA repair after damage, in the synthesis of biologically active molecules (for example, methionine), which is necessary for DNA methylation [4,6]. The biological essentiality of zinc is confirmed by the existence of homeostatic mechanisms regulating its absorption, distribution, cellular uptake and excretion. The total zinc content in the human body is 2–4 g with a plasma concentration of 12–16 μM [5,7,9].

To date, numerous experimental results have been obtained indicating multiple biological effects of curcumin, explaining its preventive and therapeutic properties. A bibliometric analysis performed in 2019 showed that the main contributions to these studies were made by scientists from the USA, China, India, Japan and South Korea [6,10,11,12].

Curcumin statistically significantly reduces the level of reactive oxygen species in peritoneal macrophages of rats performing fatigue work [7,8,13,15]. As shown by the assessment of antiradical properties using tests with ABTS and DPPH, the use of turmeric extract leads to a decrease in the level of prostaglandin E2 (a marker of oxidative stress) in human hepatoma HepG2 cells used in vitro to assess the induction of cytochrome P450 [8]. It was found that daily consumption of curcumin at a dose of 5-60 mg/kg during chronic stress has a long-lasting anti-stress effect, and when taken at a dose of 20-40 mg/kg, it reduces the manifestation of behavioral changes and biochemical reactions of the body caused by chronic fatigue. New studies in animal models and double-blind, placebo-controlled clinical trials have demonstrated that curcumin can be used to treat cognitive decline [9,14,15,16].

Curcumin is known to have low oral bioavailability. The bioavailability and selectivity of curcumin can be increased by using its nanostructured forms, which makes their creation and study of the possibility of therapeutic use very relevant.

Glycine regulates metabolism and provides protective inhibition processes in the central nervous system, reduces irritability and nervous tension, and increases mental performance. It blocks the release of adrenaline and norepinephrine (the main stress hormones), cleanses the body of toxins and free radicals that destroy brain tissue cells. In showed that glycine prevents D-galactosidase-induced c-Jun N-terminal kinase (JNK) enzyme activation, neuroapoptosis, neuroinflammation, synaptic dysfunction and memory impairment in exposed mice D-galactosidase. It has been shown that the administration of glycine prevents stress-induced inhibition of proliferation and differentiation of erythroid cells during the anxiety stage of stress.

Glycine is a non-essential amino acid and in healthy people with a nutritious diet enters the body in sufficient quantities. Glycine deficiency in the blood is observed in some diseases. A decrease in glycine concentrations is also characteristic of many diseases associated with severe inflammatory processes, and may be caused by epigenetic changes that disrupt its biosynthesis. Glycine helps normalize metabolism in the liver and reduce blood cholesterol levels, reduces lipid peroxidation and microvascular damage.

Analysis of the literature allows us to characterize the anti-stress mechanism of glycine. Glycine-induced activation of central inhibitory mechanisms is due not only to the direct effect of glycine, but also to its effect on other stress-limiting mechanisms: GABAergic, dopaminergic and prolactin. Thus, glycine limits the excitation of centers that determine the stress response. As a result, the release of releasing factors that release ACTH is inhibited, the excitation of adrenergic centers is reduced, which prevents the rise in the level of catecholamines and glucocorticoids [17,18,19].

Replenishing the combined deficiency of glycine and zinc is an important element in the correction of post-stress CNS dysfunction. In the work shown that the amino acid glycine, along with gamma-aminobutyric acid (GABA), is a key neurotransmitter that regulates the processes of physiological inhibition in the central nervous system by increasing transmembrane conductance in specific ligand-dependent chloride channels. The introduction of zinc ions can potentiate the opening of these receptors by increasing their affinity for glycine, resulting in increased inhibition processes in CNS neurons.

The use of Zn^{2+} together with glycine will allow the formation of chelated forms of zinc, the undeniable advantages of which include maximum bioavailability even in conditions where the absorption of components is impaired (lack of interaction with food, other minerals and hydrochloric acid of the stomach, absence of adverse reactions) [20].

Based on the above, we have developed a complex agent (substance) for the pharmacocorrection of stress, conventionally called Kurglycin, having the structural formula I with the following ratio of components, %:

Zinc - 12.04,
curcumin – 67.68,
glycine – 13.65,
water –6.63.

(I)

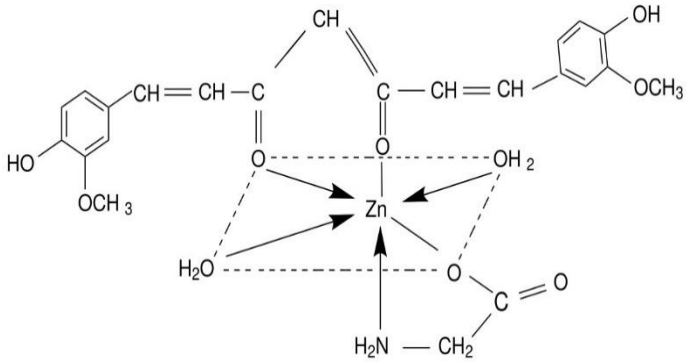

Fig 1:

The components of the substance contribute to the pharmacocorrection of stress, exhibiting stress-protective, antioxidant, cytoprotective and hepatoprotective effects, which have been repeatedly described in the literature [21].

2. Purpose of the research

The purpose of the study is to study the individual metabolic characteristics of neuromotor function disorders under experimental stress and to search for ways of their pharmacocorrection.

3. Materials and Methods

The objects of the study are laboratory animals, as well as a substance containing glycine, zinc and curcumin, conventionally called Kurglycin.

The subject of the study is the physiological and biochemical parameters of laboratory animals.

We used generally accepted methods of experimental pharmacology and biochemistry: immobilization stress, open field, forced swimming, rotarod, running wheel, enzyme immunoassay, etc.

4. Results and Discussion

I. The influence of Kurglycin on the biochemical parameters of experimental animals under stress, taking into account their individual typological parameters

Chronic emotional stress in rats, stimulating the hypothalamic-pituitary-adrenal system, causes an increase in the level of glucose, triglycerides (TG), cholesterol, β-lipoproteins, a decrease in the activity of lactate dehydrogenase, alanine aminotransferase in the blood plasma. Along with this, the secretion of catecholamines increases, resulting in increased mobilization of adipose tissue with the formation of free fatty acids (FFA) entering the blood. If the body does not need to utilize FFA, they are converted into TG and can be encapsulated in sebaceous gland cysts. FFA metabolism occurs in the cytochrome P450 system. Psycho-emotional stress in rats (aggressive-conflict situation) leads to an increase in the amount of extracellular DNA in the blood plasma with a sharp increase in its concentration against the background of cerebral ischemia, and in the cerebral cortex - to a pronounced increase in the content of biogenic amines - dopamine and serotonin.

Currently, there are individual indications of individuality and fairly wide variability in stress-induced fluctuations in neuroimmune parameters, in particular, the concentration of cytokines and the functional properties of their receptors. These changes largely depend on the genetic (sex, genomic indicators), hormonal and other characteristics of mammals. In addition, observations in humans have shown that the level of stress reactivity, as well as indicators of learning and intellectual abilities in general, correlate with the concentration of blood cytokines - IL-6, IFN-γ, TNF-α and IL-10.

Stress loads of varying intensity lead to specific changes in the perceptual and emotional components of nociception in rats, the direction of which depends on the initial characteristics of the animals' behavior and the period of research. Fluctuations in the level of cytokines in the blood at different stages after a single long-term immobilization and in the dynamics of repeated stressors are more pronounced in passive animals compared to active individuals. The number of correlations between indicators of nociceptive sensitivity and the cytokine

profile of the blood after an acute stress load is greater in behaviorally active rats, and during chronic stress, in passive rats.

Thus, based on the provisions substantiated in the literature on the influence of individual typological parameters of animals on the course of the stress reaction, we studied the effect of Kurglycin on the biochemical parameters of rats under normal conditions and under stress.

In our experiments, after immobilization stress in rats of both groups, the level of cortisol increased by an average of 10% compared to the control. Tables 7 and 8 show the effect of Kurglycin on the biochemical parameters of rats under stress.

14-day and 21-day oral administration of Kurglycin in the form of a 3% suspension at a dose of 5 ml/kg orally had a positive effect on the course of the stress reaction in the adrenal cortex, stabilizing the secretory activity of glucocorticoid-producing cells and reducing cortisol levels to levels close to control (Table 1), in both groups.

Table 1: Effect of Kurglycin on cortisol levels in experimental animals under immobilization stress (N= 10, p)

Groups	**Cortisol level, pmol/l**	
	After 14 days of administration of the composition	**After 21 days of administration of the composition**
HLE	61.896±0.620	60.463±0.895
LLE	63.710±0.398	61.250±0.529

*HLE - high level of emotionality, LLE - low level of emotionality

The study of changes in the biochemical parameters of rats with LLE and VUE under the influence of Kurglycine showed a certain difference in the susceptibility of these groups both to the action of the drug and to the action of glycine taken as a control.

As can be seen from Table 8, after 14- and 21-day administration of Kurglycin at a dose of 5 ml/kg orally and glycine for pharmacocorrection of stress in animals of the LLE group, a process of gradual restoration of the functional activity of the liver is observed, as evidenced by the restoration of pre-stress ALT levels in the blood of stressed animals, AST, alkaline phosphatase, LDH, glucose and cholesterol reduction. In animals with HLE, the administration of Kurglycine and glycine had virtually no effect on the level of ALT reduced during stress, but led to an increase in the reduced levels of AST, LDH, glucose, and a decrease in the level of alkaline phosphatase and cholesterol.

Table 2: Changes in biochemical parameters of rats with low and high levels of emotionality under the influence of Kurglycin (N=10, p)

Index (M+m)	**Groups**			
	LLE			
	After 14 days of Kurglycin administration	**After 21 days of Kurglycin administration**	**After 14 days of glycine administration**	**After 21 days of glycine administration**
ALT, Units/l	74.85±10.20	73.92±5.86	77.74±2.24	76.162±2.08
AST, Units/l	219.31±42.05	204.59±43.83	233.73±2.90	207.4±10.14
Alkaline phosphatase, U/l	366.86±75.45	383.18±100.96	387.11±5.58	391.64±14.57
Lactate dehydrogenase, U/l	599.20±81.18	523.87±60.09	672.14±11.02	525.868±14.34
Glucose, mm/l	6.53±0.69	6.19±0.69	5.15±0.32	5.466±0.16
Total cholesterol, mm/l	1.10±0.07	0.80±0.09	1.10±0.05	0.984±0.04
Total protein, g/l	75.03±1.76	68.33±3.42	84.16±2.12	70.12±1.73

Creatinine, mm/l	51.81±2.09	47.79±2.88	53.34±1.15	49.762±1.17
	HLE			
ALT, Units/l	65.72±6.89	65.72±6.89	69.16±5.37	54.04±6.67
AST, Units/l	189.06±16.84	189.06±16.84	207.38±5.20	176.61±25.09
Alkaline phosphatase, U/l	252.26±43.20	252.26±43.20	301.14±13.36	289.12±48.38
Lactate dehydrogenase, U/l	517.80±79.96	517.80±79.96	624.91±5.15	443.73±57.53
Glucose, mm/l	6.39±0.23	6.39±0.23	5.874±0.13	7.05±0.30
Total cholesterol, mm/l	0.79±0.13	0.79±0.13	0.93±0.03	0.72±0.04
Total protein, g/l	80.63±2.98	80.63±2.98	83.68±2.51	73.74±3.07
Creatinine, mm/l	50.59±2.10	50.59±2.10	52.20±1.80	51.38±1.37

Thus, judging by the changes in biochemical parameters, under the influence of Kurglycine and glycine taken as a control, the processes of recovery from stress occur more intensely in stressed animals with a high level of emotionality.

The influence of emotionality and stress resistance of experimental animals to stress-protective agents is also noted in the literature. Thus, when studying the effect of selective opioid receptor agonists on morphological disorders in the liver in rats that had undergone 6-hour immobilization stress, it was found that all the studied opioids had a stress-protective effect, which was manifested by a decrease in the total volume of sinusoids and an increase in regenerative processes in the liver parenchyma, both in the group of stress-resistant and stress-unresistant animals. In stress-resistant rats, a decrease in the specific volume of dystrophically altered cytoplasm was also noted upon administration of peptides.

There is evidence in the literature that glycine is very effective in optimizing the activity of g-glutamyl transpeptidase, alkaline phosphatase, aspartic transaminase, tissue fatty acid composition and alanine transaminase. Moreover, glycine can optimize or change lipid levels during, for example, chronic alcohol intake, maintaining membrane integrity. The functional role of glycine and alanine in stimulating the expression of genes encoding the synthesis of stress proteins and in protecting cells against stress damage has been shown.

Zinc is an essential trace mineral used as a supplement in the treatment of many diseases. Fourteen days of zinc administration prevents lipid peroxidation in normal albino rats.

The work shows that zinc sulfate has a beneficial effect on biochemical and hematological parameters in diabetic and healthy animals.

II. The influence of Kurglycin on the physiological parameters of experimental animals under stress, taking into account their individual typological parameters

In addition to the teratogenic and pathological effects of zinc deficiency, such as skin lesions, anorexia, growth retardation, delayed wound healing, altered immune function, impaired night vision, and altered acuity of taste and smell, characteristic behavioral changes have been observed in animal and human models in patients suffering from zinc deficiency. Zinc deficiency is associated with many neurodegenerative and neuropsychological disorders.

The literature shows the effect of zinc compounds on motor activity and behavioral parameters of laboratory animals. Testing of animals using the forced swimming method showed a statistically significant difference in the time of immobilization of animals receiving the lowest (10 mg/kg) and maximum (30 mg/kg) doses of zinc compared to the control group. On the first day of testing behavioral indicators, a tendency was noted to increase the motor activity of animals at the lowest dose of zinc (10 mg/kg), and on the next day a decrease in activity was detected at the highest dose (30 mg/kg).

The zinc deficiency leads to a decrease in the motor activity of animals. Moreover, the concentration of corticosterone in the blood serum of mice after 2, 4 and 10 weeks of zinc deprivation in the forced swimming test increased by 11, 97 and 225%, respectively.

In our experiments in the forced swimming test in animals with VUE, the time of forced swimming until fatigue after 14 days of taking Kurglycin at a dose of 5 ml/kg orally increases by 25%, and after 21 days – by 45% compared to the control. In animals with LLE, taking Kurglycin for 14 days is 35%, and after 21 days it is 60%.

Thus, in animals with LLE, Kurglycin on the 21st day of administration causes the greatest increase in endurance in the forced swimming test (Table 3).

Table 3: Indicators of swimming time before fatigue in rats with HLE and LLE in the forced swimming test (N= 6, p)

Groups	Index (M+m), min.	
	After 14 days of Kurglycin administration	After 21 days of Kurglycin administration
HLE	25,0±0,57	29,0±0,57
LLE	21,0±0,57	25,0±0,79

In the rotarod test, rats with LLE after stress showed a longer retention time on the rotarod compared to LLE. After 14 and 21 days of taking Kurglycin at a dose of 5 ml/kg orally, rats with HLE showed better retention results on the rotarod (Table 10).

Thus, our data show that non-stress-resistant animals (LLE) are more sensitive to Kurglycin therapy than stress-resistant animals (LLE).

Table 4: Indicators of retention time on rotarod in rats with HLE and LLE (N= 6, p)

Groups	Fall latency time (M+m), sec.	
	After 14 days of Kurglycin administration	After 21 days of Kurglycin administration
HLE	34.0±0.66	33.0±0.77
LLE	46.6±0.69	46.5±1.02

The obtained data on the influence of individual typological parameters on sensitivity to pharmacotherapy with stress-protective drugs are directly or indirectly confirmed by the literature. Thus, zinc supplementation to female rats throughout pregnancy improved the motor activity of female pups (21.60%). For the rotarod test, there was a significant ($P < 0.05$) decrease in mean fall time in (54.30%) male and (65.93%) female pups compared to control puppies. However, zinc supplementation significantly increased the mean time of decline in puppies of both sexes.

Curcumin has been reported to improve or prevent movement disorders in Parkinson's disease (PD); however, its low bioavailability is the biggest barrier to its use. A new oil solution of curcumin showed a better protective effect against movement disorders caused by the neurotoxin MPTP.

The mechanisms of the stress-protective effect of the combination of glycine and zinc are explained. It has been shown that glycine, along with gamma-aminobutyric acid (GABA), is a key neurotransmitter that regulates the processes of physiological inhibition in the central nervous system (CNS) by increasing transmembrane conductance in specific heteropentameric ligand-gated chloride channels. The introduction of zinc ions can potentiate the opening of these receptors by increasing their affinity for glycine, resulting in increased inhibition processes in CNS neurons. Replenishing the combined deficiency of glycine and zinc is an important element in the correction of post-stress CNS dysfunction.

5. Conclusion

Anti-stress drugs, unlike drugs that are tropic to certain functions of the body, do not exhibit an effect that is constantly localized in some organ or link of the functional-metabolic process. Their action is aimed at limiting the negative impact on the body from cause-and-effect unfavorable factors of various natures. Since the stress reaction is a general response of the entire organism, the protective effect of pharmacological agents can only be assessed at the systemic level.

Replenishing the combined deficiency of glycine and zinc is an important element in the correction of post-stress CNS dysfunction. It has been shown that the amino acid glycine, along with gamma-aminobutyric acid (GABA), is a key neurotransmitter that regulates the processes of physiological inhibition in the central nervous system by increasing transmembrane conductance in specific ligand-dependent chloride channels. The

introduction of zinc ions can potentiate the opening of these receptors by increasing their affinity for glycine, resulting in increased inhibition processes in CNS neurons. The use of Zn^{2+} together with glycine allows the formation of chelated forms of zinc, the undeniable advantages of which include maximum bioavailability even in conditions where the absorption of components is impaired.

Curcumin is a plant-derived antioxidant. It was found that daily consumption of curcumin at a dose of 5–60 mg/kg during chronic stress has a long-lasting anti-stress effect, and when taken at a dose of 20–40 mg/kg, it reduces the manifestation of behavioral changes and biochemical reactions of the body caused by chronic fatigue. New research in animal models and double-blind, placebo-controlled clinical trials have demonstrated that curcumin can be used to treat cognitive decline.

Based on the above, based on these three components, we have developed a substance for pharmacocorrection of stress, conventionally called Kurglycin, with the ratio of components, %: zinc - 12.04, curcumin - 67.68, glycine - 13.65, water - 6.63. 14-day and 21-day oral administration of Kurglycin in the form of a 3% suspension at a dose of 5 ml/kg orally had a positive effect on the course of the stress reaction in the adrenal cortex, stabilizing the secretory activity of glucocorticoid-producing cells and reducing cortisol levels to levels close to control, in both studied groups of animals. The study of changes in the biochemical parameters of rats with LLE and HLE under the influence of Kurglycine showed a certain difference in the susceptibility of these groups both to the action of the drug and to the action of glycine taken as a control.

After 14- and 21-day administration of Kurglycine and glycine for pharmacocorrection of stress in animals of the LLE group, a process of gradual restoration of the functional activity of the liver is observed, as evidenced by the restoration in the blood of stressed animals of pre-stress levels of ALT, AST, alkaline phosphatase, LDH, glucose and a decrease in cholesterol levels. In animals with HLE, the administration of Kurglycine and glycine had virtually no effect on the level of ALT reduced during stress, but led to an increase in the reduced levels of AST, LDH, glucose, and a decrease in the level of alkaline phosphatase and cholesterol. Thus, judging by the changes in biochemical parameters, under the influence of Kurglycine and glycine taken as a control, the processes of recovery from stress occur more intensely in stressed animals with a high level of emotionality. There is evidence in the literature that glycine is very effective in optimizing the activity of g-glutamyl transpeptidase, alkaline phosphatase, aspartic transaminase, tissue fatty acid composition and alanine transaminase. Moreover, glycine can optimize or alter lipid levels during, for example, chronic alcohol intake, maintaining membrane integrity.

In our experiments in the forced swimming test in animals with HLE, the time of forced swimming until fatigue after 14 days of taking Kurglycin at a dose of 5 ml/kg orally increases by 25%, and after 21 days – by 45% compared to the control. In animals with LLE, taking Kurglycin for 14 days is 35%, and after 21 days it is 60%. Thus, in animals with LLE, Kurglycin on the 21st day of administration causes the greatest increase in endurance in the forced swimming test.

In the rotarod test, rats with LLE after stress showed a longer retention time on the rotarod compared to HLE. After 14 and 21 days of taking Kurglycin at a dose of 5 ml/kg orally, rats with LLE showed better retention results on the rotarod (Table 10).

Thus, our data show that Kurglycin can be used for pharmacocorrection of post-stress disorders, and non-stress-resistant animals (HLE) are more sensitive to Kurglycin therapy than stress-resistant animals (LLE).

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