The use of aminoacid additives in antistress neuroprotective diets

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Abstract. Throughout life, the human body is constantly exposed to stressful factors. The influence of stress reduces the overall state of the body (especially the immune system), reproductive capabilities, performance, memory, and leads to premature aging. Especially affected are people whose professional activities are associated with unfavorable factors (daily duties, psychoemotional overstrains, physical exertion, violation of the diet), which leads to early professional burnout. Therefore, it is necessary to search for substances that increase the body’s resistance to stress and the possibility of using them for preventive purposes. This article presents the results aimed at studying the antistress properties of the N-phenylacetyl-L-prolylglycine compound. The substance was synthesized in the Research Institute of Pharmacology of the Russian Academy of Medical Sciences. The study was conducted on rats with a high level of anxiety of two ages (3 months old, 1.5 years old), since they are the most sensitive to stress influence. For the selection of animals, the following physiological tests were used: the "Porsolt swimming test", the "open field" test. A 30-minute swim at a water temperature of 28-30°C was used as a stress factor. The neuroprotective properties of the aminoacid additive were determined by indicators of peroxidation and activation of the antioxidant system. The content of malondialdehyde and superoxide dismutase, the activity of ceruloplasmin and catalase, the concentration of extra-erythrocyte hemoglobin, the total peroxidase activity was evaluated. The aminoacid additive (N-phenylacetyl-L-prolylglycine) was found to develop neuroprotective properties. In all animals, the use of an aminoacid additive reduces the intensity of the processes of lipid peroxidation and activates the antioxidant systems. However, in young rats the changes in indicators were significantly positive. The results of this study may be the basis for the use of aminoacid additives as functional ingredients with neuroprotective properties in the production of food in the food industry.

1. Relevance of the study
The life of a modern person is constantly connected with a stress state. In addition to psychoemotional and environmental stress, lifestyle, low motor activity, violation of the daily routine, obesity and bad habits play a great role [1]. This leads to a violation of homeostasis in the human body and the development or chronization of diseases and pathological conditions.
Stress causes pathophysiological changes in the brain which are reflected in behavioral and cognitive disorders [2]. In people who are under stress, the protective properties of the immune system are reduced, which leads to an increase in the incidence of disease [3]. The influence of stress on the cardiovascular system can lead to the development of myocardial infarction and death [4]. Stress reduces appetite and affects the normal functioning of the gastrointestinal tract negatively [5]. It can activate or change the activity of the organs of the endocrine system [6]. At the same time, each person has an individual reaction to stress [7].

The human body is under the influence of stress at all stages of life. The combined effects of occupational stress and life-long accumulated stress lead to early occupational burnout, premature aging and increased mortality [8, 9].

During stress, as well as during aging, the processes of oxidative stress are activated. The ability of a cell to resist oxidative stress is determined by the balance between the formation of reactive oxygen species and the activation of the antioxidant system. Violation of balance between these systems leads to abnormalities in cellular homeostasis, development of diseases and induction of premature aging.

It is necessary to prevent stressful conditions. One of the most convenient and common ways is to use antistress diets based on the introduction of functional food into the diet. These can be products containing probiotic and prebiotic components [10, 11] or natural components of animal and plant origin [12, 13]. There are very few studies that consider aminoacid complexes as ingredients of functional products. The closer the chemical composition of the compounds is to the natural ones, the more effective their use is [14].

Therefore, we suggest using an aminoacid compound as a functional component of food products for stress prevention. Regulatory peptides regulate physiological processes at all levels, from functioning of individual cells to complex behavioral manifestations [15], and also affect the processes of premature aging [16]. An aminoacid additive consisting of glycine and proline was used in our study.

Glycine plays a crucial role in the cytoprotection, immune response, growth, development, metabolism and survival of human beings and a number of mammals [17]. Under stress, it reduces the accumulation of lipid peroxidation products, the content of Schiff bases of diene conjugates, activates endogenous antioxidant systems (superoxide dismutase, catalase and ceruloplasmin) and has antithrombotic and anti-inflammatory effects in models of acute nonimmune and chronic immune inflammation [18]. It was found that the use of glycine additives in food in order to correct glutathione deficiency reduces oxidative stress significantly [19]. However, the mechanism of this process has not been clarified yet [20]. The maximum daily dose of glycine for an adult should not exceed 15 g [21].

Proline is also of great interest for use as a functional component of food products. It is established that it is involved in the regulation of biochemical and physiological processes of cells. Proline plays a major role in protein biosynthesis and cell growth, osmoregulation [22], redox signaling [23], protein responses and protein stability [24], cellular bioenergetics [25] and stress resistance [26].

Therefore, the development and production of functional products containing aminoacid additives with neuroprotective properties may become a new priority in the food industry.

2. Methods and materials

60 white laboratory rats (males) were used for the study. They were kept in a vivarium at room temperature (22-25 C) without restricting access to water and food. Performing the experiment, we followed the principles of animal experiments and the main regulations of the Helsinki Declaration. The experiment was carried out according to the European Convention for the Protection of Vertebrates Used for Experiments or for Other Scientific Purposes (Strasbourg, March 18, 1986) and the Order of the Ministry of Health of the Russian Federation No. 267 from 19.06.2003. The number of experimental animals corresponded to the minimum one according to the method of statistical processing of the obtained data.

The study used the rats that were the most sensitive to the influence of external factors. They were selected by physiological tests - the "Porsolt swimming test" [27] and the "open field" test [28]. The purpose of the "Porsolt swimming test" was to evaluate the behavior of the animal in the water. To do
this, a container with a diameter of 50 cm and a depth of 40 cm was used and filled with water for more than 70%. The rats that showed chaotic movements leading to rapid fatigue or passive movements with numbness [27] were selected. The "open field" test was performed in a rectangular chamber (40x50x50 cm). On the floor of the cell, the squares of 10x10 cm were marked. The stress factor was a 50 W lamp located at a height of 150 cm above the center of the cell. The animal was placed in a cell and its behavior was observed for 9 minutes during 5 days. The rats with very high or low motor activity (vertical, horizontal), continuous fading, continuous grooming, high level of defecation were selected [28].

From the selected animals, 2 groups were formed, based on age. The first group included males that were 3 months old (weight - 100-130 g); the second group included males that were 1.5 years old (weight - 350-480 g). Intact rats of the same age were used as controls.

In the experiment, an aminoacid additive -N-phenylacetyl-L-prolylglycine, synthesized in the Research Institute of Pharmacology of the Russian Academy of Medical Sciences in Moscow, was used. The aminoacid additive was given to rats per os with the usual vivar feed ration, at a dose of 5 mg/kg, once.

Swimming is a strong stress factor for rats, so a forced 30-minute swim was performed at a water temperature of 28-30°C [27].

The intensity of free radical oxidation processes was determined by the colorimetric method on a photoelectric concentration colorimeter KFC 2-MP (ZOMF, Russia). The level of malondialdehyde in rat brain homogenate was measured at λ=535 nm, against the reagent control, in which distilled water was added instead of the substrate [29]. The activity of the antioxidant system was assessed by the level of superoxide dismutase in brain homogenate and erythrocyte lysate [30]. The content of ceruloplasmin in blood plasma was measured at λ= 535 nm [31]. The concentration of extra-erythrocyte hemoglobin was assessed in blood plasma using a standard test kit manufactured by Klini Test-Hem (λ = 540 nm) (Russia) [32]. The total peroxidase activity was measured in blood plasma (λ=600 nm) [33]. Catalase activity was determined in plasma, erythrocyte lysate and brain homogenate at λ=410 nm [34].

Statistical data processing was carried out in the environment of integrated statistical software packages "Statistica 10". The arithmetic mean of the series M and the mean square deviation m were calculated. The nonparametric Mann-Whitney U-test was used to assess the differences between the compared groups. The differences were considered significant at p<0.05.

3. Results of the study
The neuroprotective properties of the aminoacid additive were determined by the activation of the LPO and antioxidant system processes. After the first day of introduction of the aminoacid additive into the food, the concentration of malondialdehyde in the brain homogenate did not change in rats, regardless of age. The stress factor (30-minute swimming) caused a significant increase in malondialdehyde in 1.5-year-old animals by 29%; in 3-month-old animals, the indicator did not show a significant change. The results obtained after adding an aminoacid additive in order to reduce stress had age-related differences. In adult rats, the concentration of malondialdehyde corresponded to the state of stress. In young rats its level decreased significantly by 30% (table 1).

The activation of the antioxidant system under extreme conditions was measured by the level of ceruloplasmin in the blood plasma. An increase in its concentration in blood plasma leads to an increase in antioxidant activity since it interacts with the precursor of the superoxide-anion radical (hydrated electron) [35]. The oxidase activity of ceruloplasmin increased significantly after the introduction of an aminoacid additive into the food. In 1.5-year-olds it increased by 34%, and in 3-month-olds – by 22%. After 30 minutes of swimming, the concentration of ceruloplasmin increased significantly, regardless of age. In 3-month-old rats, the content of ceruloplasmin increased by 30%, in 1.5-year-old rats - by 37%. The use of an aminoacid additive under stress resulted in a moderate increase in the level of ceruloplasmin by 24% in young animals and in a more significant increase in adult animals (+40%) (table 1).
Table 1. Effect of an aminoacid additive on the concentration of malondialdehyde (nmol/g tissue in 20 minutes) in the brain homogenate and the ceruloplasmin in the blood plasma (mkmol/ml) of rats (M±m, n=10, p – significance of differences compared to the control).

| Conditions                  | 3- month-old rats | 1,5 -year-olds rats |
|-----------------------------|-------------------|---------------------|
|                             | malondialdehyde   | ceruloplasmin       | malondialdehyde   | ceruloplasmin       |
| Control                     | 26.92 ± 0.45      | 2.47 ± 0.67         | 27.11 ± 0.21      | 2.51 ± 0.15         |
| Aminoacid additive 1 day    | 27.73 ± 2.15      | 3.34 ± 0.09         | 32.26 ± 2.09      | 3.36 ± 0.07         |
| Stress (30-minute forced swimming) | +3%               | +22%                | +19%              | +34%                |
| Aminoacid additive + forced swimming | p>0.1             | p<0.05              | p+0.1             | p+0.05              |
|                             | 31.77 ± 0.39      | 3.21 ± 0.29         | 34.97 ± 1.03      | 3.44 ± 0.23         |
|                             | +18%              | +30%                | +29%              | +37%                |
|                             | p>0.05            | p<0.05              | p<0.05            | p<0.05              |
|                             | 18.74 ± 0.78      | 3.06 ± 0.18         | 35.14 ± 0.49      | 3.51 ± 0.58         |
|                             | -30%              | +24%                | +30%              | +40%                |
|                             | p<0.05            | p<0.05              | p<0.05            | p<0.05              |

The content of extra-erythrocyte hemoglobin after the use of an aminoacid additive exceeded the values of the control group in blood plasma significantly only in 3-month-old rats (+36%) in a day. Under stress, the level of extra-erythrocyte hemoglobin increased equally, regardless of age, by 35% in young animals and by 36% in adult animals. Under stress with the addition of an aminoacid additive, the concentration of extra-erythrocyte hemoglobin increased significantly only in 1.5-year-old rats by 39%, which indicates a violation of the stability of red blood cell membranes (table 2).

The use of an aminoacid additive does not affect the total peroxidase activity in blood plasma significantly. The use of 30-minute swimming as a stress model led to a significant increase in total peroxidase activity. The level of the indicator in 3-month-old rats increased by 79%, and in 1.5-year-old rats - by 103%. Aminoacid additive under stress conditions affected the manifestation of total peroxidase activity in young animals significantly. It dropped to -45%. In adult animals, a less intense effect was observed. The total peroxidase activity of this group decreased only by 17% (table 2).

Table 2. Effect of an aminoacid additive on the content of extra-erythrocyte hemoglobin (mg%) and the total peroxidase activity (conventional units/ml) in blood plasma of rats (M±m, n=10, p – significance of differences compared to the control).

| Conditions                  | 3- month-old rats | 1,5 -year-olds rats |
|-----------------------------|-------------------|---------------------|
|                             | extra-erythrocyte hemoglobin | total peroxidase activity | extra-erythrocyte hemoglobin | total peroxidase activity |
| Control                     | 21.25 ± 0.19      | 10.27 ± 0.17        | 17.93 ± 0.38         | 11.25 ± 0.21         |
| Aminoacid additive 1 day    | 28.90 ± 0.89      | 9.55 ± 0.72         | 19.90 ± 0.43         | 9.34 ± 1.48         |
| Stress (30-minute forced swimming) | +36%              | -7%                 | +11%                | -17%                |
|                             | p<0.05            | p>0.1               | p+0.1               | p+0.1               |
|                             | 28.69 ± 0.75      | 18.38 ± 1.44        | 24.43 ± 0.57         | 22.84 ± 1.79        |
|                             | +35%              | +79%                | +36%                | +103%               |
|                             | p<0.05            | p<0.05              | p<0.05              | p<0.05              |
|                             | 25.24 ± 1.12      | 14.89 ± 0.67        | 24.92 ± 0.63         | 20.93 ± 0.94        |
|                             | +19%              | +45%                | +39%                | +86%                |
|                             | p<0.05            | p<0.05              | p<0.05              | p<0.05              |

The activity of superoxide dismutase when using an aminoacid additive in the food increased in a day, especially in the group of 1.5-year-old rats. In them, the activity of superoxide dismutase increased in the brain by 47%, and in the erythrocyte hemolysate - by 61%. The influence of stress (30 minutes of swimming) increased the activity of superoxide dismutase in young rats by 56% in blood hemolysate...
and by 31% in brain homogenate. In adult rats, the activity of superoxide dismutase increased by 23%, and in erythrocyte hemolysate - by 73%. The addition of an aminoacid additive to the food under stress conditions affected the increase in the activity of the enzyme. In the erythrocyte hemolysate of 3-month-old animals it increased by 59%, and in the homogenate – by 98%. The same tendency was observed in 1.5 year-old animals (table 3).

Table 3. Effect of an aminoacid additive on the activity of superoxide dismutase in the brain and in the erythrocyte hemolysate of rats (conventional units/g protein/10 min, (M±m, n=10, p – significance of differences compared to the control).

| Conditions | 3- month-old rats | 1.5 -year-olds rats |
|------------|-------------------|---------------------|
|            | brain             | hemolysate          | brain             | hemolysate          |
| Control    | 10.39 ± 0.99      | 17.73 ± 0.94        | 6.48 ± 0.41       | 16.77 ± 0.76        |
| Aminoacid additive | 13.19 ± 0.23      | 21.98 ± 0.52        | 9.53 ± 0.35       | 27.00 ± 0.97        |
| 1 day Stress | +27%              | +24%                | +47%              | +61%                |
| (30-minute forced swimming) | p<0.05            | p<0.05              | p<0.05            | p<0.05              |
| Aminoacid additive | 16.47 ± 0.68      | 35.13 ± 0.52        | 10.28 ± 0.41      | 34.69 ± 0.62        |
| +59%       | +56%              | +23%                | +73%              |
| + forced swimming | p<0.05            | p<0.05              | p<0.05            | p<0.05              |

The obtained results confirm the opinions of other authors that with "physiological" aging, the intensity of redox reactions decreases, as evidenced by a decrease in the level of maximum oxygen consumption and a decrease in the activity of enzyme systems that ensure the use of oxygen by tissues, as well as a decrease in the intensity of lipid peroxidation [36, 37].

In a day after the introduction of the aminoacid additive into the food, a significant decrease in catalase activity was observed in 3-month-old rats in blood plasma by -39% and brain homogenate by-34%, and in erythrocyte hemolysate increased by + 61% (table 4). In 1.5-year-old rats, there were no significant changes in the brain plasma and homogenate. In the erythrocyte hemolysate, the level of catalase increased by +44% (table 5). Under stress, the catalase content increased significantly regardless of age, but the highest rates were observed in 1.5-year-old rats. The use of an aminoacid additive in food under stress led to a significant increase in the level of catalase in brain homogenate (98%) and erythrocyte hemolysate (104%) (tables 4,5).

Thus, the obtained data show that the use of an aminoacid additive in food under the influence of stress in 3-month-old animals prevents the accumulation of malondialdehyde, the concentration of extra-erythrocytic hemoglobin in the blood plasma corresponds to the values of the control group, and the total peroxidase activity is significantly increased (tables 1,2). In 1.5 year-old animals, these indicators exceed the control values significantly (tables 1,2). The increased content of superoxide dismutase, ceruloplasmin and catalase in both groups of animals reflects the activation of the antioxidant system (tables 1,3,4,5). These results match the data obtained earlier on the greatest effectiveness of the use of an aminoacid additive for young animals [38].

Table 4. Effect of an aminoacid additive on the activity catalase in blood plasma, brain homogenate and erythrocyte hemolysate of 3- month-old rats (conventional units/ml, M ± m, n=10, p – significance of differences compared to the control).

| Conditions | plasma | brain | hemolysate |
|------------|--------|-------|------------|
| Control    | 1.15± 0.03 | 2.49±0.11 | 11.38±0.21 |
| Aminoacid additive | 0.70 ± 0.03 | 1.64 ±0.09 | 18.32 ± 0.21 |
| 1 day      | -39%   | -34%  | +61%       |
4. Conclusion
The use of an an aminoacid additive under the influence of stress reduces the intensity of free radical oxidation processes and increases the activity of antioxidant defense enzymes in various organs and tissues of the body. It was found that the use of an aminoacid additive for young animals was the most effective.

The obtained data can become the basis for the use of aminoacid additives as functional ingredients that reduce stress-inducing effects in the production of functional products in the food industry.

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