FREE AMINO ACIDS AND THEIR DERIVATIVES IN ONCOLOGY

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Abstract

The purpose of this work is a theoretical and practical justification for the creation of effective compositions of highly purified free amino acids and specialized mini-aminosols for metabolic therapy of malignant growth.

On the basis of the experimental data we suggest that the differences discovered in certain amino acids concentrations in blood plasma, red blood cells, and tumors are criteria in early diagnostics of primary cancerous growth as well as in estimation of the efficacy of specific cancer treatments. Clinical studies on biological fluids and tumors of patients with cancer of the mammary gland, lungs, prostate, ovaries, bladder or digestive tract showed significant changes in physiological concentrations of amino acids which either directly or indirectly regulate processes of antitumor response, oncogenesis, immunogenesis and apoptosis were shown. Our strategy of application of amino acids as medicinal preparations includes a targeted effect on the functional and metabolic relationships which are changed in specific pathology through the effect on the regulatory mechanisms of intermediate metabolic reactions, limiting stages of metabolic flows, utilization of energy substrates and transport systems restricting the processes of amino acids pool formation. The creation methodology of pathogenetic compositions of amino acids and their derivatives on the basis of their physiological concentration for practical application of their regulatory effects in oncology was discussed.

Key words: Free amino acids, regulatory effects, oncology.

Introduction

Tumor, the formation of amino acid imbalances and metabolic processes in the background of malignant growth: the levels and nature of the interaction.

The appearance of a malignant neoplasm is accompanied by changes in the intermediate metabolism, which manifest themselves at the level of the whole organism, individual organs, tissues, cells and enzymatic reactions. These changes are determined primarily by the properties of the tumor as a structure consisting of relatively poorly differentiated cells, characterized by unregulated growth, metastasis and necrosis [1-11].

Active tumor growth against the background of the relative reduction of individual chemical reactions (in particular, low enzyme activity and the rate of enzymatic amino acid metabolism) and the lack of perfect regulatory mechanisms

to maintain the metabolic balance in malignant cells leads to a competitive relationship between the tumor and the host organism in metabolism and energy.

These relationships are manifested in the ability of tumor cells to use the plastic material of the tumor carrier for the generation of energy and their own growth. Thereby, a high activity of metabolic processes is ensured in the tumor, in particular, accompanied by the formation of a significant amount of energy. Thus, the substrate provision of tumor cells becomes the limiting factor of their growth.This is particularly pronounced in cases where compounds that are absolutely or relatively essential (for example, some amino acids, essential lipids) for a macroorganism are used as an energy or plastic material. In addition, as is well known, a significant amount of cofactors of key enzymatic reactions (vitamins, microelements) are also irreplaceable nutrient factors to varying degrees.

The degree of indispensability of the above compounds against the background of malignant growth, thus, increases, inducing the formation of their functional deficiency both in the body of the tumor carrier and in the tumor itself.

Obviously, with their additional exogenous intake, the elimination of this deficiency will be determined by the activity of the transport systems of such compounds into host cells or tumors. Therefore, for example, anorexia at the level of the microorganism, on the one hand, and the ability of the tumor to actively "capture" endogenous compounds and nutrients, on the other hand, should be considered adaptive responses that provide in these conditions the principle of maximum survival of each system.

Such a kind of "metabolic competition" of a tumor and a macroorganism significantly limits the possibilities of metabolic correction and treatment of cancer patients in cases where it is associated with the need to introduce additional quantities of biologically active compounds of natural origin.

The next most important element that determines the tumor-tumor carrier relationship at the biochemical level is the phase growth of the tumor, in particular, periods of massive necrosis of cancer cells, accompanied by the appearance in the host fluids and tissues of significant amounts of a wide range of non-oxidized products and highly active prooxidants that induce a redox potential and metabolic imbalance in normal cells.

The described trends in cancer diseases are especially pronounced in the metabolism of amino acids. Our particular interest in studying the patterns of formation of a free amino acid pool is justified by the fact that malignant growth:

1. Against the background of anorexia, causes quantitative insufficiency of essential and relatively essential amino acids in the body – simultaneously, as a result of the activation of the degradation processes of endogenous proteins and amino acids, inducing a negative nitrogen balance;
2. Violates the processes of absorption and transport of free amino acids;
3. Shifting the redox potential of cells disrupts the relationship between anabolic and catabolic reactions in the exchange of amino acids;
4. The toxic effect of the decay products of the tumor is blocked by amino acids directly interacting with them (cystine, lysine) or their derivatives (glutathione), which leads to a deficiency of these compounds;

5. Changes the ratio and activity of metabolic processes associated with intermediate metabolism of amino acids (glycolysis, gluconeogenesis), as well as the processes of formation and energy consumption;
6. In addition, as mentioned above, amino acids and their derivatives are natural regulators of the activity of the processes of proliferation, differentiation and apoptosis of malignant cells [1-11].

Amino acids and their derivatives are mostly universal natural regulators and endogenous modifiers of biological reactions. However, numerous biological properties of these compounds as drugs have been used for correction of deficiencies or realization of pharmacological and immediate metabolic effects, disregarding any regulatory action. Amino acid profile indices that allow early detection of diseases, which would provide time for intervention before irreversible damage occurs, are being created. Thus, amino acid profiles represent biomarkers for diseases or deviations from a normal state of health. Our array technology will play an important role in metabolomics in biomarker discovery, clinical medicine, including cancer, as well as at other stages of drug discovery and development (for example, target discovery, mechanism of action, or predicting toxicity) [1-7].

Changes in the amino acid pool in liquids and tissues of patients specifically characterize the development of cancer. Correction of the intermediate metabolic changes in cancer can be reached by the use of certain amino acids or their combinations [8-10].

To understand the metabolic processes and vital functions of the regulatory effect of amino acids which manifests itself under natural or near concentrations of these compounds in body fluids and tissues, it is obvious that the effective use of L-amino acids or their derivatives for metabolic correction and directional changes in metabolism under pathological or extreme conditions is limited by insufficient accumulation of information about the key mechanisms of regulatory effects of the compounds tested at concentrations comparable to their physiological (endogenous) levels [1-3,7,10-13].

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At present, there are the following main lines in exploitation of the biochemical (metabolic) properties of amino acids and their derivatives in clinical practice:

- Use of amino acids or multicomponent mixtures of amino acids (mainly, essential elements combined with vitamins and trace elements) for replacement therapy or deficiency of essential nutrients and proteins.
- Use of drugs containing individual amino acids or their compositions, designed on the basis of their additive functional and metabolic action, which "exploits" pharmacological activity (the effects of activation of redox processes, reactions of energy metabolism and neutralization of xenobiotics compounds) of this class [4-6,9].

However, the use of certain levels of L-amino acids, or their compositions or their deficiency, implements direct pharmacological effects that practically ignore their regulatory effects on metabolic processes and key metabolic reactions.

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Materials and methods

The results and our concept are based on research into the formation of free amino acids found in the biological liquids and tissues of about 1500 patients with cancer of the mammary gland, lungs, prostate, ovaries, bladder or digestive tract.

Our development methodology is based on:

- Studies on physiological concentrations of free amino acids, their derivatives, precursors and metabolites, as well as biochemical marker parameters in healthy donors and patients with various pathologies.
- Creation of a unified database for the parameters investigated, construction of an empirical mathematical model consisting of pathogenic markers of specific pathology and amino acid profiles.
- Specialized development of new formulations of the compositions of infusion solutions of amino acids and their derivatives [4].

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Results and discussion

Numerous results determining amino acids and their derivatives in human body fluids and tissues [3] allowed systematization of the accumulated data and identified the areas for exploitation of their metabolic effects, primarily in laboratory diagnostics, and application in clinical practice as drugs [4].

In view of the fact that free amino acids are represented by a wide range of related chemical structures and metabolic transformations of compounds that are formed in the body fluids and tissues, the findings obtained proved that quantification of the amino acid pool contributes to the diagnosis of various diseases, including hepatobiliary pathology, cardiovascular and immune systems, oncological cases, cerebrovascular pathology, as well as alcoholism and diabetes [1,2,4,9-11]. It turned out that the vast majority of the diagnostic values of the group had alterations in the levels of functionally and metabolically related amino acids and their derivatives while no specific changes, as such, were observed in the concentrations of individual compounds of this class.

Metabolically related amino acids and their derivatives had the nature of amino acid profiles of the body fluids and tissues of animals and humans when compared with the use of a multivariate analysis and mathematical modeling. At the same time, it was convincingly demonstrated that removal or correction of intermediate metabolic changes can be achieved using individual amino acids and their derivatives, or a combination of them as universal natural bioregulators – compounds that at physiological concentrations have a direct effect on the mechanisms of cellular metabolism [5,6,12].

By now, there is some evidence for the importance of not only amino acids as building blocks for protein synthesis, but also regulators of gene expression at the level of mRNA translation by an mTOR-dependent mechanism, signaling molecules and biological response modifiers, as well as precursors of a wide range of bioregulators, which play a key role in the integration of major metabolic fluxes [10-15].

Based on the positions of metabolomics, the free amino acid pool in biological fluids and tissues is regarded as a single information unit which is a kind of "chemical projection" of the genome; the proteome realized through this approach not only develops ideas about the pool of amino acids as a dynamic system-generated supply of them from outside, but also due to endogenous synthesis, transport, degradation and excretion, allows the identification of "key points" in the intermediate metabolic equilibrium shift that may reflect ratios at the individual levels of endogenous amino acids and related species (metabolically- related) compounds [4].

We were the first to demonstrate that endogenous levels of free amino acids in fluids and tissues are the most important integral indicators and regulators of metabolism.

This enables us to prove the use of individual amino acids or their combinations for guided correction of metabolism under specific human diseases, and significantly expands the area of practical application of these compounds as blood substitutes. The regulatory effects of amino acids contribute

to understanding their influence on biochemical processes and vital functions which is manifested at natural (endogenous) or close to natural concentrations of these compounds. The regulatory effect observed after administration of amino acids can be achieved by using either individual amino acids, or a combination of their small sets. The structure of these compositions in specific ratios may include almost any amino acids, their structural analogs, or derivatives with a known mechanism of action.

The trend developed is notable since it allows assessment of the pool of amino acids in biological fluids and tissues as a single information unit and while analyzing it, it makes possible to estimate the segments which disturb the metabolic balance (changes in the metabolic flow ratio and their balance shifts).

Our methodology proposed for development of new formulations of multicomponent infusion solutions based on amino acids and related compounds for the correction of metabolic imbalance occurring in various diseases relies on the application of research results to the regularities of formation of the amino acid pool in biological fluids and tissues under various pathological conditions. The composition and amount of highly purified amino acids in these infusion solutions should be determined primarily by their physiological (regulatory) concentrations, which distinguishes them from traditionally used amino acid solutions for parenteral nutrition, where the content of their components is calculated from the daily requirements of the human body for them without due consideration for the regulatory actions of the compounds administered.

In oncological practice, individual amino acids or their compositions should be applied according to their physiological concentrations and changes in the structure of the amino acid pool in patients. Amino acids with anti-carcinogenic effects may be leucine, tryptophane, and taurine.

Conclusion

Changes in the amino acid pool of liquids and their fund tissues of patients specifically characterize a cancer illness. To a large extent, they arise as a result of metabolic competition for common substrates for the plastic needs of the body cells and tumors. Correction of intermediate metabolic changes at a cancer can be reached by the use of separate amino acids or their combination.

The methodology of development of new constituents of multicomponent infusion solutions offered by us on the basis of amino acids and their related connections is intended for correction of the metabolic imbalance arising in various diseases and is based on application of the results on research regularities of formation of the amino acid pool in biological liquids and tissues of individuals under most various pathological states.

In oncological practice, certain amino acids or their compositions should be applied according to their physiological concentrations and changes in the structure of amino acids pools in patients. As a result of numerous experimental and clinical studies, we proved that diagnostically significant in oncology and as an "anticarcinogenic" are such amino acids as leucine, tryptophan, and taurine.

The new methodology of developing minicomponent amino acid infusion solutions offered by us intended for correction of the metabolic imbalance arising in the case of various localization and stages of malignant growth is based on the results of research into the regularities of formation of amino-acid pools in biological liquids and tissues.

The ratios of the individual components and their amount in such mixtures should comply with their physiological (endogenous) concentrations in normal blood plasma and tissues.

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