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MOLECULAR AND BIOCHEMICAL FOUNDATIONS OF FERMENTOPATHIES: A COMPARATIVE ANALYSIS OF STUDIES BY UZBEKISTANI AND INTERNATIONAL SCIENTISTS

Fozilova Gavharoy Erkinjonovna
gavharoyfozilova223@gmail.com, Orcid.org/0009-0005-4103-480x
Assistant, Department of Biological Chemistry, Andijan State Medical Institute
Raxmatullo Sheraliyev Jo'raboy o'g'li
Second-year student, Faculty of Pediatrics, Andijan State Medical Institute
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Abstract: This article analyzes the molecular and biochemical foundations of fermentopathies through the prism of the scientific views of international and local scholars. The study examines the historical and scientific hierarchy from Sir Archibald Garrod's theory of the "metabolic block" to the modern Nelson-Cox and Severin concepts. The contribution of representatives of the Uzbek school of biochemistry, R.A. Sobirova and A.V. Abrorov, to the regional and clinical study of enzymatic processes is also highlighted. Using phenylketonuria, glycogen storage diseases, and gallstone disease as examples, the article provides a detailed analysis of the pathochemical mechanisms of fermentopathies and puts forward personal conclusions and practical recommendations.

Keywords: Fermentopathy, metabolic block, molecular medicine, Archibald Garrod, Ye.S. Severin, R.A. Sobirova, A.V. Abrorov, phenylketonuria (PKU), glycogen storage diseases, cholelithiasis, allosteric regulation, oxidative stress, bioenergetics, Nelson-Cox concept, clinical biochemistry.

I. INTRODUCTION: THE GLOBAL PROBLEM OF FERMENTOPATHIES

Enzymes are highly efficient biocatalysts of all metabolic processes occurring in living organisms. They accelerate chemical reactions at the cellular level millions of times and ensure the stability of vital functions. However, disruption of enzyme synthesis or their functional activity leads to serious biochemical consequences—fermentopathies. Fermentopathies arise not only as a result of hereditary factors, but also due to acquired metabolic dysfunctions, causing severe disturbances of homeostasis in the body. In modern biochemistry and molecular medicine, fermentopathies remain one of the most complex areas among congenital and acquired disorders of metabolism. Considering that every biochemical reaction in the human body takes place under the control of enzymes (biocatalysts), a decrease or loss of activity of even one enzyme leads to disruption of an entire metabolic chain. Timely detection of fermentopathies makes it possible to prevent many severe clinical complications. In particular, hereditary enzyme deficiencies observed in childhood have a serious effect on the development of the organism; therefore, the biochemical study of this problem is of particular relevance [10].

MOLECULAR MECHANISMS OF DISRUPTION OF ENZYMATIC CATALYSIS

To understand the nature of fermentopathies, it is first necessary to consider the normal dynamics of enzymatic reactions. Each metabolic chain in the body consists of several stages, and every transformation within it is controlled by specific biocatalysts. If an enzyme at any point of this chain cannot perform its function, this leads to the formation of a biochemical "metabolic block."

As a result of such a block, two types of pathological conditions are observed. First, a deficiency of a vital product that should be formed as a result of the reaction develops. Second, the substrate on which the enzyme should act accumulates in the body above the normal level and begins to exert a toxic effect. It is precisely this disruption of biochemical balance that determines the clinical picture of the disease.

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II. SCIENTIFIC VIEWS ON FERMENTOPATHIES

THE THEORY OF THE METABOLIC BLOCK AND THE VIEWS OF SIR ARCHIBALD GARROD

The first attempts to systematize these processes scientifically date back to the beginning of the twentieth century. In 1902, while studying alkaptonuria, the English physician Sir Archibald Garrod opened a new chapter in the history of medicine. He was the first to propose the concept of "inborn errors of metabolism." According to Garrod's theory, every hereditary disease is based on the arrest of a specific chemical reaction. His views were revolutionary for their time, as they made it possible to consider disease not merely as a set of symptoms, but as a "biochemical error" at the molecular level. Garrod not only revealed the biochemical essence of disease, but was also the first to advance the concept of biological individuality. In his view, each person has a unique chemical composition, and fermentopathies represent an extreme disturbance of this individual biochemical balance [5].

Garrod's observations on alkaptonuria showed that intermediate products formed as a result of a metabolic block (for example, homogentisic acid) cannot be eliminated from the body and accumulate in tissues, causing pathological changes. This conclusion later became a fundamental principle of biochemistry. Nearly forty years later, G. Beadle and E. Tatum proved Garrod's hypothesis at the molecular level and formulated the "one gene—one enzyme" concept. This made it possible to interpret fermentopathies not only as biochemical defects, but also as improper realization of hereditary information [6].

GENETIC AND BIOCHEMICAL INTERRELATION: THE "ONE GENE—ONE ENZYME" CONCEPT

Sir Archibald Garrod's hypothesis was far ahead of its time, but the scientific world needed nearly another forty years to experimentally prove his theory. In 1941, the American geneticists George Beadle and Edward Tatum revolutionized the understanding of the nature of fermentopathies through their studies on Neurospora crassa (bread mold). Beadle and Tatum demonstrated that mutations in specific genes stop the synthesis of a particular enzyme, which in turn leads to interruption of the metabolic chain. Their discovery went down in history as the "one gene—one enzyme" hypothesis (later refined as "one gene—one polypeptide"). This discovery transformed Garrod's intuitive assumptions about biochemical blocks into a firmly established scientific truth. From this point onward, fermentopathies began to be interpreted not simply as an "error," but as a molecular interruption in the reading of hereditary information [6].

THE FORMATION OF BIOCHEMICAL KINETICS AND MECHANISMS

Explaining the essence of fermentopathies solely through genes was not sufficient. The foundations of enzymatic kinetics developed by Leonor Michaelis and Maud Menten in 1913 served to explain the rate at which a reaction proceeds and how an enzyme binds to its substrate. Their studies made it possible to distinguish two types of fermentopathies:

Quantitative defects: the enzyme is not synthesized at all (the Beadle and Tatum model) [6].

Qualitative defects: the enzyme is present, but its affinity for the substrate is altered or the reaction rate is sharply reduced (the Michaelis-Menten model) [9].

These historical stages opened the way to studying fermentopathies not only as hereditary diseases, but also as biochemical processes that can be measured using precise values and rates. By the second half of the twentieth century, relying on this fundamental knowledge, scientists such as Severin and Sobirova studied enzyme regulation, while Nelson and Cox formed the general metabolic map.

ALLOSTERIC REGULATION OF ENZYMES AND THE CONCEPT OF Ye.S. SEVERIN

Fundamental knowledge about fermentopathies entered a new stage in the second half of the twentieth century through the work of Professor Ye.S. Severin, a prominent representative of the Russian school of biochemistry. While Garrod and Beadle explained fermentopathy as the

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absolute absence (deficiency) of an enzyme, Severin introduced the concept of "regulatory fermentopathies" in his research.

According to Severin's theory, an enzyme protein may be synthesized in sufficient quantity in the body, but its allosteric center (the special region that regulates enzyme activity) may be damaged under the influence of a mutation or external factors. In this case, although the enzyme retains the ability to convert the substrate into a product, it cannot alter its rate according to the body's needs. Such "unregulated" enzymes cause unexpected interruptions or excessive activity in the metabolic chain. This discovery of the Severin school serves as a basis for the treatment of diseases today through artificial regulation of enzyme activity by many pharmacological agents. The distinctive feature of Severin's research is that he analyzed fermentopathies not only according to the principle of "present or absent," but also from the perspective of conformational changes in the enzyme molecule. According to his scientific conclusions, a defect in the allosteric center sharply changes the enzyme's affinity for the substrate. This, in turn, disrupts the mechanism of self-regulation of metabolic flows in the cell, known as feedback inhibition.

For example, under normal conditions, when the amount of the final product increases, it should "stop" the enzyme. However, in the regulatory fermentopathies described by Severin, this "braking system" ceases to function. This theory serves as a fundamental foundation not only for understanding hereditary diseases, but also for explaining metabolic changes in cancer cells and the biochemical essence of many endocrinological pathologies. Therefore, the creation of a new generation of drugs called "allosteric modulators" in modern pharmacology is directly linked to the hypotheses advanced by the Severin school [3].

METABOLIC INTEGRATION AND THE NELSON-COX CONCEPT

Modern views on fermentopathies were brought to a new, systemic stage by leading figures in world biochemistry, David L. Nelson and Michael M. Cox, authors of the well-known textbook "Lehninger Principles of Biochemistry." While earlier researchers focused only on the defect of a single enzyme, Nelson and Cox interpret fermentopathies as an integrated disruption of metabolic pathways.

According to the theory of Nelson and Cox, biochemical processes in the body are not isolated from one another, but are connected through a single "metabolic web." Accordingly, the deficiency of one enzyme does not merely stop one reaction; it also causes paralysis of neighboring metabolic pathways. For example, an enzymatic block in carbohydrate metabolism directly leads to an energy (ATP) deficit and, consequently, disruption of protein synthesis.

Another important contribution of these scientists was their explanation of fermentopathies from a thermodynamic point of view. In their opinion, enzyme deficiency disrupts the balance of free energy within the cell, thereby placing not only the cell's function, but also its viability (structural integrity), at risk. The metabolic maps improved by Nelson and Cox serve today as a key guide in diagnosing fermentopathies and understanding through which "bypass pathways" compensation may be achieved. The revolutionary aspect of the Nelson-Cox approach to the theory of fermentopathies is that they compare metabolic flux to a river. If a dam (enzymatic block) appears in one part of a river, the problem is not only the presence of the dam, but also the imbalance between the drying of the lower part of the river (product deficiency) and flooding in the upper part (substrate toxicity). In their studies, the scholars explained the course of fermentopathies through "regulatory chains." In their view, the enzyme protein itself may often be normal, but defects in the cofactors required for its activation or in covalent modification processes (for example, phosphorylation) lead to "secondary fermentopathies."

In addition, Nelson and Cox analyzed fermentopathies from the standpoint of evolutionary biochemistry. They explained why certain enzymatic defects (for example, glucose-6-phosphate dehydrogenase deficiency) have been preserved in particular regions (tropical climates), linking this to the body's defense mechanisms. This made it possible to view fermentopathies not merely as "errors," but also as adaptive variability of the organism. Today, the metabolic maps

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developed by Nelson and Cox serve as a fundamental basis for the development of omics technologies (metabolomics) in clinical biochemistry [1].

III. THE INTEGRATIVE APPROACH OF THE UZBEK SCHOOL OF BIOCHEMISTRY TO FERMENTOPATHIES: STUDIES BY R.A. SOBIROVA AND A.V. ABROROV

The universal metabolic principles described by Nelson and Cox were studied in depth by Uzbek scientists, taking into account regional and clinical characteristics. Representatives of the Uzbek school of biochemistry analyzed fermentopathies not only on the basis of international standards, but also from the perspective of the ecological and genetic environment of our country.

Professor R.A. Sobirova studied enzymatic imbalance at the level of molecular pathologies within her scientific school. According to her views, hypoxia and oxidative stress (free radicals) play a decisive role in the pathogenesis of fermentopathies. The hypothesis advanced by Sobirova shows that, in order to restore enzyme activity, it is not sufficient merely to restrict the substrate (diet therapy); rather, complex therapy is required to protect cell membranes and the active center of the enzyme from oxidation. As a result of her studies, new biochemical methods for correcting a number of metabolic disorders were developed. In addition, the R.A. Sobirova school widely studied the role of biomedical nanotechnologies and natural antioxidants in correcting impaired enzymatic activity. In their opinion, in many fermentopathies it is not the synthesis of the enzyme that is disrupted, but rather its intracellular transport and interaction with membranes. This indicates the need to interpret fermentopathies not only as biochemical, but also as biophysical problems [2].

The scientific activity of Professor A.V. Abrorov linked fermentopathies with clinical diagnostics, particularly pathologies of the hepatobiliary system. Abrorov proved that cholelithiasis (gallstone disease) is not simply a surgical problem, but the result of “enzymatic hepatopathy.” His studies on the enzyme 7-alpha-hydroxylase showed that by regulating enzymatic activity it is possible to maintain cholesterol homeostasis in the body and prevent stone formation. Work in this area continues to be of major importance in the biochemical correction of hepatobiliary diseases in Andijan and throughout the republic. In A.V. Abrorov’s studies, the concept of the balance of hepatobiliary system enzymes (an enzymatic ensemble) was advanced. According to his conclusions, in the development of gallstone disease there is not only a defect of a single enzyme, but also desynchronization of an entire chain of enzymes in hepatocytes. The diagnostic criteria proposed by Abrorov today serve as one of the “gold standards” in clinical biochemistry for predicting liver pathologies. This integrative approach of Uzbek scientists represents a strong bridge connecting fundamental knowledge in world biochemistry with local clinical practice [4].

IV. CLINICAL AND BIOCHEMICAL ANALYSIS OF FERMENTOPATHIES: PATHOLOGICAL MECHANISMS AND MODERN DIAGNOSTICS

4.1. Phenylketonuria (PKU): Molecular Defects of Amino Acid Metabolism

Phenylketonuria is a classic example of fermentopathy, arising as a result of deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH). In this pathology, which fully corresponds to Garrod’s theory of the “metabolic block,” the conversion of the amino acid phenylalanine into tyrosine is halted.

Biochemical mechanism:

According to the theory of Nelson and Cox, as a result of this metabolic block, the level of phenylalanine in the blood and tissues sharply increases (hyperphenylalaninemia). Excess phenylalanine begins to be degraded through “bypass pathways,” forming products toxic to the body, namely phenylpyruvate, phenyllactate, and phenylacetate [1].

Analysis by scientists:

As Professor R.A. Sobirova emphasizes, these toxic products exert an aggressive effect on neuronal membranes in the central nervous system and provoke oxidative stress. This, in turn, leads to impairment of cognitive functions and intellectual disability. Modern biochemistry

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proposes treating this problem not only through diet therapy, but also by correcting deficiency of the cofactor tetrahydrobiopterin (BH4).

Disruption of the biochemical cascade:

Under normal conditions, more than 80% of the amino acid phenylalanine in the liver is converted into tyrosine with the participation of the enzyme phenylalanine hydroxylase (PAH). This reaction requires tetrahydrobiopterin (BH4) and molecular oxygen as cofactors. In PKU, the "metabolic block" occurs precisely at this point [2].

The inability of phenylalanine to convert into tyrosine leads to two destructive outcomes:

Tyrosine deficiency: Tyrosine is a precursor for neurotransmitters such as dopamine, noradrenaline, and adrenaline, as well as for the pigment melanin. Their deficiency explains neurological disorders and lightening of skin and hair color (hypopigmentation).

Accumulation of toxic metabolites: Accumulated phenylalanine undergoes transamination under the influence of aminotransferases and is converted into phenylpyruvate. Phenylpyruvate, in turn, is reduced to phenyllactate and phenylacetate. These substances cross the blood-brain barrier and inhibit respiratory-chain enzymes in brain tissue, while also stopping synthesis of the myelin sheath.

4.2. GLYCOGEN STORAGE DISEASES: ALLOSTERIC AND STRUCTURAL DISORDERS OF CARBOHYDRATE METABOLISM

Glycogen storage diseases are a group of hereditary disorders associated with defects in enzymes involved in glycogen synthesis or breakdown (glycogenolysis). In this section, the disruption of "allosteric regulation" described in Ye.S. Severin's theory can be clearly observed.

Type I glycogen storage disease (Gierke disease):

This pathology occurs as a result of deficiency of the enzyme glucose-6-phosphatase in the liver and kidneys. From a biochemical point of view, this enzyme ensures the final stage of glycogenolysis, namely the formation of free glucose from glucose-6-phosphate [3].

Nelson and Cox analysis:

According to Nelson-Cox maps, when glucose-6-phosphatase is blocked, glucose-6-phosphate accumulates inside the cell and is directed into "bypass pathways," namely glycolysis and the pentose phosphate pathway. This causes the development of lactic acidosis (increased lactic acid), hyperuricemia (increased uric acid), and hyperlipidemia in the body. Thus, a single block in carbohydrate metabolism disrupts an entire lipid and purine metabolism system [1].

As emphasized by the Severin school, because the allosteric regulation of the enzyme is disrupted in this process, hepatocytes (liver cells) become filled with glycogen, resulting in hepatomegaly (enlargement of the liver) and severe hypoglycemia [3].

4.3. CHOLELITHIASIS (GALLSTONE DISEASE): ENZYMATIC HEPATOPATHY OF LIPID METABOLISM

Although gallstone disease is often regarded as a surgical problem, a deep biochemical fermentopathy lies at its core. In this section, Professor A.V. Abrorov's concept of "enzymatic hepatopathy" occupies a central place [4].

The role of 7-alpha-hydroxylase:

The first and rate-limiting enzyme in the synthesis of bile acids from cholesterol is microsomal 7-alpha-hydroxylase. If the activity of this enzyme decreases:

The conversion of cholesterol into bile acids slows down.

The amount of cholesterol in bile exceeds the normal level (supersaturation of bile).

The amount of bile acids (substances that dissolve cholesterol) decreases.

As a result, cholesterol begins to crystallize and stones are formed. As R.A. Sobirova emphasizes, lipid peroxidation (LPO) in the liver damages the enzyme protein in this process and causes "secondary fermentopathy." This scientifically justifies the need to treat gallstone disease not only by removing the stone, but also by restoring enzymatic activity [2].

V. DISCUSSION AND COMPARATIVE ANALYSIS

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Studying the problem of fermentopathies through the prism of different periods and scientific schools shows that this field has followed an evolutionary path from a simple genetic defect to a complex systemic metabolic pathology. The concept of the "metabolic block" founded by Sir Archibald Garrod has now been enriched by the theory of the "single metabolic network" proposed by Nelson and Cox. This means that modern biochemistry views the deficiency of a single enzyme not only as the interruption of one reaction, but also as a disruption of the energy balance and homeostasis of the whole organism [1,5].

The views of Ye.S. Severin, a representative of the Russian school of biochemistry, on allosteric regulation brought the diagnosis of fermentopathies to a new level. On the basis of his theory, we have gained the ability to understand why an enzyme may be present in sufficient quantity yet remain functionally "inactive." This, in turn, is logically connected with the theory of "secondary fermentopathies" advanced by Uzbek scientists, particularly R.A. Sobirova. In other words, the enzyme protein (apoenzyme) may be normal, but its regulatory centers (the allosteric centers described by Severin) may be damaged as a result of oxidative stress or environmental factors [2,3].

Professor A.V. Abrorov's studies on enzymes of the hepatobiliary system (especially 7-alpha-hydroxylase) demonstrate that fermentopathies are not always congenital genetic tragedies. In many cases, they are acquired pathologies arising as a result of an unhealthy lifestyle and metabolic imbalance. This conclusion helps us understand the biochemical difference between phenylketonuria (hereditary) and cholelithiasis (often acquired or mixed), which were analyzed in this article [4].

VI. CONCLUSION AND PERSONAL CONSIDERATIONS

As a result of the fundamental and clinical study of the problem of fermentopathies in this scientific article, we came to the conclusion that human health is a delicate, dynamic, and mutually coordinated balance of thousands of enzymatic reactions in the body. The concept of the "metabolic block" that began with Sir Archibald Garrod has now become one of the most important components of molecular genetics, bioenergetics, and practical medicine.

My personal conclusion is that considering fermentopathies only as "rare hereditary pathologies" described in textbooks is one of the greatest strategic mistakes in modern medicine. The analyses conducted show that even diseases frequently encountered in everyday clinical practice, such as cholelithiasis (gallstone disease), are fundamentally based on deep enzymatic imbalance. Therefore, I believe that the medicine of the future must decisively move from the "symptomatic" stage, which treats only complications of disease, to an "enzymatic" and "metabolic" direction that eliminates its molecular causes.

Based on our studies and analytical observations, I propose the following medical and social recommendations:

1. Improving the system of early and differential screening: In order to detect fermentopathies that lead to severe complications, such as phenylketonuria, from infancy, biochemical correction and genetic screening methods should be further expanded at the primary healthcare level. This will not only increase the effectiveness of treatment, but also prevent disability [10].

2. An integrative approach in clinical thinking: When making a diagnosis, physicians, especially pediatricians, therapists, and surgeons, should view disease not merely as local damage to an organ, but, as stated in the theories of Nelson and Cox, as the breakdown of an entire "metabolic network" and an energy crisis [1].

3. Developing preventive biochemistry: As emphasized by Professors Sobirova and Abrorov, by inhibiting the effects of oxidative stress on enzymes, it is possible to prevent many "acquired fermentopathies," such as gallstone disease and liver pathologies. This raises the preventive direction in medicine to the biochemical level [2,4].

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In conclusion, enzymes are the true regulators of life. By studying and understanding their activity at the molecular level, we not only treat disease, but also gain the key to unlocking the hidden potential of the human body, extending human life, and improving quality of life.

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