PATHOGENETIC MECHANISMS OF STRESS-DIET-INDUCED HYPOXIA DEVELOPMENT IN CASE OF POOR NUTRITION (LITERATURE REVIEW)

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Abstract. *This article discusses the current understanding of the pathogenetic mechanisms of hypoxia induced by alimentary stress and poor nutrition. The concept of metabolic stress as a universal hypermetabolic response to a nutrient imbalance with activation of the hypothalamic-pituitary-adrenal system and isolation of hypoxia-induced factors is analyzed. Special attention is paid to the role of mitochondrial dysfunction, oxidative stress and aseptic inflammation in the formation of tissue hypoxia against the background of excessive consumption of fats and carbohydrates. Molecular mechanisms of interaction between nutrient imbalance and signaling pathways of adaptation to hypoxia, including HIF-dependent and independent pathways, are considered. Data on the role of PPAR receptors, endoplasmic reticulum, and adipokines in the pathogenesis of diet-induced hypoxia are presented. Clinical and experimental studies demonstrating a two-way relationship between nutrition and tissue oxygenation are discussed.*

Keywords: *stress-induced hypoxia, poor nutrition, metabolic stress, mitochondrial dysfunction, HIF-1a, oxidative stress, insulin resistance, lipotoxicity.*

Introduction.

The problem of poor nutrition has become a global pandemic in the twenty-first century. Excessive caloric intake, especially at the expense of saturated fats and simple carbohydrates, combined with a violation of the food intake regime forms a state defined in modern literature as "metabolic stress" [14]. The term "stress-diet-induced hypoxia" reflects a relatively new direction of research that considers chronic alimentary disorders as a trigger factor for the development of tissue oxygen deficiency, even in conditions of normal partial pressure of oxygen in the inhaled air [2, 25].

The concept of tissue hypoxia has traditionally been associated with respiratory disorders, cardiovascular or blood disorders. However, the experimental and clinical data accumulated over the past decade indicate the existence of an independent pathogenetic phenomenon — metabolic (cytotoxic, histotoxic, diet-induced) hypoxia. In this condition, oxygen delivery to tissues may remain within the normal range, but its utilization by cells is disrupted due to structural and functional rearrangement of metabolic pathways, mitochondrial dysfunction, and changes in signaling pathways that regulate oxygen homeostasis [5, 24].

The relevance of studying the pathogenetic mechanisms of stress-diet-induced hypoxia is due not only to the high prevalence of alimentary-dependent diseases, but also to understanding the fundamental role of oxygen imbalance in the progression of metabolic syndrome, non-alcoholic fatty liver disease, cardiovascular pathology, and type 2 diabetes mellitus. There is a perception of a vicious circle in which poor nutrition causes tissue hypoxia, and the latter, in turn, aggravates metabolic disorders [6, 11].

The aim of this work is to systematize and analyze current data on the molecular and cellular mechanisms of hypoxia induced by alimentary imbalance, with an emphasis on the interaction between nutrient signals and oxygen homeostasis systems.

Metabolic stress is a universal hypermetabolic and hypercatabolic response of the body to an imbalance in the intake of nutrients, characterized by activation of the hypothalamic-pituitary-adrenal system, increased production of stress hormones (cortisol, catecholamines), and changes in the expression of genes controlling adaptive mechanisms [14, 28]. Unlike the classical stress response

induced by trauma or infection, alimentary metabolic stress has a chronic course and is characterized by specific changes at the cellular and subcellular levels.

The key difference between metabolic stress caused by poor nutrition is its ability to induce the expression of hypoxia-induced factor (HIF-1a) under conditions of normal tissue oxygenation. Recent studies demonstrate that excess glucose, free fatty acids, and fructose can activate HIF-dependent pathways even in normoxia, forming the phenomenon of "normoxic hypoxic signaling" [2, 24].

From an evolutionary point of view, the mechanisms of response to hypoxia and nutrient deficiency are closely interrelated. Organisms have developed integrated stress response systems that allow them to survive both in conditions of oxygen starvation and lack of food. This phylogenetic similarity explains the fact that signaling pathways regulating adaptation to hypoxia (HIF pathway) and pathways controlling the metabolic response to nutrient availability (AMPK, mTOR) have many intersections [16, 26].

Normally, activation of these pathways is adaptive and is aimed at cell survival under stress. However, in chronic alimentary imbalance, pathological constitutive activation or, on the contrary, suppression of these signaling cascades occurs, which leads to a breakdown in adaptation and the formation of a vicious circle of metabolic disorders. A high-fat diet, as studies on Drosophila melanogaster show, changes the body's tolerance to hypoxic effects, and the nature of these changes depends on the type of hypoxia (intermittent or permanent) [7].

Chronic alimentary stress is accompanied by persistent activation of the hypothalamic-pituitary-adrenal system. An increase in cortisol levels in obesity and metabolic syndrome has a twofold meaning. On the one hand, cortisol helps to mobilize energy resources by stimulating gluconeogenesis and lipolysis. On the other hand, chronic hypercortisolemia induces insulin resistance, promotes visceral obesity, and suppresses antioxidant protection [28].

It is important to note that the activation of the hypothalamic-pituitary-adrenal axis during poor nutrition is closely related to the production of neuropeptide S and catecholamines, which, in turn, modulate the activity of HIF-1a and the expression of genes controlling glycolysis and the tricarboxylic acid cycle [8]. Thus, a neuroendocrine-metabolic complex is formed that provides integration of stress and hypoxic responses.

Hypoxia-induced factor (HIF-1) is a heterodimeric transcription factor consisting of a constitutively expressed β-subunit and an O2-sensitive α-subunit. Under normoxic conditionsнормоксии, HIF-1a undergoes hydroxylation with prolyl hydroxylases (PH.D.), which ensures its recognition by ubiquitin ligase VHL and subsequent degradation in proteasomes. In hypoxia, hydroxylation is inhibited, HIF-1a is stabilized, translocated to the nucleus, and activates transcription of target genes, including angiogenesis factors (VEGF), glucose transporters (GLUT1, GLUT2), glycolytic enzymes, and erythropoiesis regulators (erythropoietin) [24].

The phenomenon of "pseudohypoxia" consists in the activation of HIF-dependent pathways under the conditions of normal tissue oxygenation under the influence of metabolic factors. Madan E. Research et al. (2025) demonstrated that mice with a diet-induced metabolic syndrome (high-fat or high-fructose diet) show activation of the hypoxic response in aortic tissues in the complete absence of systemic hypoxemia [13].

The mechanisms of pseudohypoxia are diverse and include:

1. **Accumulation of Krebs cycle metabolites**, such as succinate and fumarate, which inhibit the activity of prolyl hydroxylases, competing with 2-oxoglutarate [5].
2. **Formation of reactive oxygen species (ROS)** in mitochondria, which stabilize HIF-1a through inhibition of Fe2+ - dependent prolyl hydroxylases [26].
3. **Activation of NF-kB and other proinflammatory pathways**that enhance HIF-1a transcription [22].

Excessive fructose intake plays a special role in the induction of pseudohypoxia. Fructose metabolism in the liver is characterized by a high rate of phosphorylation by fructokinase without

reverse inhibition, which leads to rapid depletion of ATP and accumulation of AMP. AMP is further metabolized to uric acid and other products that can induce oxidative stress and stabilize HIF-1a. In addition, fructose stimulates de novo lipogenesis, which leads to the accumulation of triglycerides and the development стеатозаof liver steatosis [12, 29].

Lipid peroxidation products, such as 4-hydroxynonenal and малоновый malondialdehyde, can also modify prolyl hydroxylases, reducing their activity and promoting the accumulation of HIF-1a. This creates an additional link between oxidative stress, lipotoxicity, and hypoxic signaling [10].

Mitochondria are not only the main consumers of oxygen, but also key organelles that determine the sensitivity of the cell to hypoxia. Poor nutrition, especially excessive fat intake, leads to structural and functional rearrangement of mitochondria. Fernandes J. L. et al. (2023) showed that a high-fat diet reduces mitochondrial density and the antioxidant potential of hepatocytes, while chronic intermittent hypoxia reduces the activity of oxidative phosphorylation complexes (OXPHOS) [5].

Mitochondrial dysfunction in diet-induced metabolic syndrome is characterized by:

- Decreased activity of complex I and complex IV of the respiratory chain;
- Violation of the integrity of the inner mitochondrial membrane;
- Leakage of cytochrome C into the cytosol;
- Reduced levels of mitochondrial biogenesis factors (TFAM, PGC1a) [28].

Mitochondrial dysfunction under alimentary stress is accompanied by a decrease in the efficiency of oxidative phosphorylation and a compensatory switch of cellular metabolism to anaerobic glycolysis-a phenomenon known as aerobic glycolysis or the Warburg effect. Despite the fact that glycolysis allows maintaining ATP production in conditions of mitochondrial insufficiency, it is less effective per glucose molecule and leads to the accumulation of lactate, which aggravates metabolic acidosis [24].

It is important to note that activation of HIF-1a in pseudohypoxia promotes transcriptional activation of glycolytic enzyme genes and suppression of pyruvate dehydrogenase activity through activation of pyruvate dehydrogenase kinase, which additionally inhibits pyruvate entry into the tricarboxylic acid cycle and increases the metabolic shift towards glycolysis [11].

Long-term consumption of a high-fat diet is accompanied by changes in the expression of uncoupling proteins (UCP). Cole M. A. et al. (2016) demonstrated that mice fed a high-fat diet increased UCP3 expression in cardiomyocytes, which reduced the efficiency of oxidative phosphorylation and increased heat production. This change is probably adaptive in nature, aimed at limiting ROS production, but in conditions of hypoxic stress, respiratory dissociation further exacerbates the energy deficit [9].

Succinate (succinic acid) occupies a special place in the pathogenesis of diet-induced hypoxia, acting not only as an intermediate of the Krebs cycle, but also as a signal molecule. In mitochondrial dysfunction and stress, succinate accumulates in the mitochondrial matrix and enters the cytoplasm and extracellular space. The accumulated succinate inhibits prolylhydroxylases, stabilizing HIF-1a and triggering a pseudohypoxic cascade. In addition, succinate activates its SUCNR1 receptor (GPR91), which mediates proinflammatory and profibrotic effects [5, 13].

In clinical practice, this justifies the use of succinate-containing drugs to activate urgent adaptive mechanisms, however, with chronic hyperproduction of succinate, its effects become pathological [14].

Poor nutrition is accompanied by excessive production of reactive oxygen species from several sources. First, the overload of mitochondria with substrates (fatty acids, glucose) leads to an increase in the mitochondrial membrane potential and an increase in ROS production in complexes I and III of the respiratory chain. Secondly, activation of NADPH oxidases, especially NOX4, in endothelial cells and adipocytes significantly contributes to oxidative stress [30]. Third, peroxisomal fatty acid oxidation and xanthine oxidase activity in hyperuricemia additionally generate ROS.

Studies conducted in rats have shown that a high-fat diet reduces the overall antioxidant capacity of tissues, including the activity of superoxide dismutase (SOD-1) and the content of reduced glutathione, which disrupts the balance between ROS production and utilization [5].

Mitochondrial DNA (mtDNA), lacking protective histones and located in close proximity to the respiratory chain, is particularly vulnerable to oxidative damage. Accumulation of mtDNA mutations under chronic oxidative stress leads to disruption of the synthesis of subunits of respiratory complexes encoded by the mitochondrial genome, which aggravates mitochondrial dysfunction [26].

In addition, ROS directly inactivate iron-sulfur clusters of respiratory chain and Krebs cycle enzymes (aconitase, complexes I and II), and also oxidize thiol groups of antioxidant enzymes, reducing their activity. Studies by Fernandes J. L. have demonstrated that both chronic intermittent hypoxia and a high-fat diet cause changes in тиолахcysteine-related thiols, which reflects a violation of redox regulation [5].

Proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), play a key role in potentiating hypoxic damage. In obesity and metabolic syndrome, there is a chronic, sluggish inflammation of adipose tissue, liver, and vascular wall associated with macrophage infiltration and adipocyte dysfunction [1, 25].

The role of interleukin-4 (IL-4) and asymmetric dimethylarginine (ADMA) deserves special attention. Madan E. We found that in metabolic syndrome, increased levels of IL-4 and ADMA in the aorta correlate with the induction of mitochondrial dysfunction and hypoxic response. Previously, these molecules were associated with hypoxia in lung tissue, but their role in vascular dysfunction in metabolic syndrome demonstrates the systemic nature of disorders [13].

The vascular wall is also involved in the pathological process. Endothelial dysfunction with a combination of alimentary imbalance and hypoxia is systemic in nature and creates the basis for the development of atherosclerosis and arterial hypertension. It is important to note that even short-term intermittent hypoxia can induce disorders of endothelium-dependent vasodilation, and obesity significantly enhances this effect [30].

Inflammation and oxidative stress lead to endothelial dysfunction — a key factor in impaired tissue perfusion. Zhang Y. et al. (2017) showed that mice on a high-fat diet in combination with chronic intermittent hypoxia develop a pronounced violation of endothelium-dependent vasodilation. Molecular mechanisms include:

- Reduced expression and activity of endothelialNO synthase (eNOS);
- Increased expression of NADPH oxidase 4 (NOX4);
- Increased production of pro-inflammatory cytokines TNF-α and IL-1β;
- Reduced expression of PPAR-γ in the vascular wall [30].

Restoration of endothelial function with the use of the PPAR-γ agonist pioglitazone confirms the key role of this transcription factor in the pathogenesis of vascular disorders in the combination of alimentary imbalance and hypoxia [9].

Peroxisomal proliferator-activated receptor α (PPARa) is a key regulator of fatty acid metabolism and adaptation to starvation. Under conditions of hypoxia, there is a physiological decrease in PPARa expression in the heart, which is accompanied by a decrease in fatty acid oxidation and an increase in glucose utilization, a metabolic shift that is adaptive for the survival of cardiomyocytes in conditions of oxygen deficiency [9].

However, a high-fat diet prevents this adaptive reduction of PPARa. Cole M. A. et al. demonstrated that in mice treated with a high-fat diet, PPARa expression in the heart remains high even under hypoxia, which prevents the metabolic switch to glycolysis and leads to the preservation of high levels of fatty acid oxidation. Since fatty acid oxidation requires more oxygen per unit of ATP produced than glucose, this metabolic pattern under conditions of limited oxygen delivery leads to energy deficiency and reduced myocardial contractile function [3].

PPARy, on the other hand, plays a predominantly protective role in the vascular wall, exerting an antioxidant and anti-inflammatory effect. In obesity induced by a high-fat diet, a decrease in PPARy expression in vascular tissue is observed, which creates a predisposition to endothelial damage under additional стрессорныхstressors, including intermittent hypoxia [30].

Research by Zhang Y. It is demonstrated that a decrease in vascular PPARy in obesity leads to excessive activation of pro-inflammatory and pro-oxidant pathways in response to hypoxia, which is manifested by an increase in NOX4 expression, an increase in superoxide production, and a decrease in the bioavailability of nitric oxide. The use of PPARy agonists completely prevents these disorders, which indicates a potential therapeutic target [9, 30].

The relationship between HIF and PPAR signaling pathways is complex and often reciprocal. On the one hand, HIF-1a suppresses the expression of PPARa and PPARy, promoting a metabolic switch from fatty acid oxidation to glycolysis. On the other hand, PPARy activation may limit the HIF-dependent response through modulation of inflammation and oxidative stress. In case of poor nutrition, this delicate balance is disturbed: adaptive suppression of PPARa is blocked by excess fat in the diet, and protective PPARy is reduced, which creates conditions for uncontrolled activation of pro-inflammatory and pro-oxidant pathways [9, 30].

Adipose tissue in obesity is characterized by relative hypoxia due to the discrepancy between the rapid growth of adipocytes and the rate of angiogenesis. Emerging hypoxic zones in adipose tissue activate HIF-1a, which leads to changes in adipokine secretion: increased production of leptin, resistin, and proinflammatory cytokines, while reducing adiponectin secretion [1, 25].

Adipose tissue hypoxia also contributes to fibrosis and macrophage infiltration, which supports chronic inflammation and systemic insulin resistance. АдипоцитыUnder hypoxic conditions, adipocytes switch to glycolytic metabolism with increased production of lactate, which can further modulate lipolysis and secretory activity via the GPR81 receptor [28].

The liver plays a central role in the pathogenesis of diet-induced hypoxia. Excessive intake of fats and carbohydrates leads to the development of non-alcoholic fatty liver disease (NAFLD), which is associated with tissue hypoxia even in the absence of respiratory failure. Research by Yuan F. fructose consumption induces endoplasmic stress (ERS) in hepatocytes, which гепатоцитаxis manifested by an increase in the marker proteins GRP78, CHOP, and caspase-12, which leads to apoptosis and steatosis [29].

Interestingly, chronic intermittent hypoxia (a model of sleep apnea) has a twofold effect on the liver. On the one hand, it aggravates lipid infiltration and inflammation in obese animals, and on the other hand, it can have a protective effect in certain regimens, suppressing endoplasmic stress and improving metabolic parameters [29]. These data indicate the importance of taking into account the parameters of hypoxic exposure and baseline metabolic status.

The myocardium is highly aerobic tissue that is extremely sensitive to oxygen supply disorders. With a combination of a high-fat diet and hypoxia, a complex of pathological changes develops in the heart:

- Violation of metabolic flexibility while maintaining a high level of fatty acid oxidation;
- Decrease in the concentration of ATP and creatinephosphate;
- Reduction of the emission fraction;
- Increased expression of UCP3, which uncouples oxidation and phosphorylation [3, 9].

Kidney tissue is also affected by diet-induced hypoxia. Interstitial fibrosis and tubulointerstitial damage in obesity are associated with chronic hypoxia of the tubular epithelium. Impaired erythropoietin production by interstitial fibroblasts can lead to renal anemia, which in turn exacerbates tissue hypoxia [4].

On the other hand, the activation of HIF-2a in the kidneys may be protective, promoting adaptation to hypoxia through increased erythropoiesis and angiogenesis. However, chronic

activation of hypoxic signaling under conditions of metabolic stress contributes to the progression of nephrosclerosis and chronic kidney disease [16].

The tricarboxylic acid cycle performs not only an energy, but also an anabolic function, providing intermediates for the synthesis of amino acids, heme and other compounds. The Krebs cycle intermediate pool is maintained through anaplerotic reactions (replenishment of substrates) and cataplerotic reactions (removal of excess).

Maltseva L. A. and co-authors emphasize the importance of anaplerotic therapy in the clinic of critical conditions, including the use of alternative substrates for the Krebs cycle and respiratory chain. Under conditions of metabolic stress, anaplerotic support is aimed at increasing ATP production and can be performed by replenishing the pool of substrates (pyruvate, aspartate, glutamine) or by removing the products of cataplerotic reactions from tissues [14].

In diet-induced hypoxia, the balance between anaplerosis and cataplerosis is disturbed. Excess acetyl-CoAproduced by beta-oxidation of fatty acids condenses with oxaloacetateto form citrate. If the activity of the Krebs cycle is reduced (due to mitochondrial dysfunction or lack of oxygen), citrate is released into the cytoplasm and used for the synthesis of fatty acids and cholesterol, exacerbating steatosis [10].

In conditions of hypoxia and limited glucose availability, ketone bodies can serve as an alternative energy substrate. Miron N. and Tirosh O. (2019) showed that fortifying the diet with cholesterol prevents hypoxic hypoglycemia in mice by inducing a ketogenic shift in metabolism. This effect is mediated by activation of the iNOS/AMPK axis, suppression of gluconeogenesis and glycogenolysis, while increasing the production of ketone bodies in the liver [17].

Ketogenesis can be considered as an adaptive mechanism that provides energy supply to the brain and heart during hypoxia. However, in patients with obesity and metabolic syndrome, this mechanism may be disrupted due to insulin resistance, fatty liver disease, and mitochondrial dysfunction [28].

The concept of anaplerotic therapy involves the use of energy substrates that do not require insulin stimulation to enter cells. Fructose in small doses (less than 60 g / day) can be such a substrate, but excessive fructose intake (more than 100 g/day) is associated with a deterioration in metabolic parameters [12, 29].

Fat emulsions, including среднецепочечныеmedium-chain triglycerides (MCTs) and emulsions enriched with omega-3 fatty acids, are also used in critical nutritional support. Of particular interest is triheptanoin — an anaplerotic substrate that increases the survival rate of patients in critical conditions [14].

Glutamine plays a special role as a nitrogen and carbon skeleton donor, supporting the pool of Krebs cycle intermediates and glutathione synthesis. Under metabolic stress, the need for glutamine increases, and its exogenous administration may be pathogenetically justified [14].

The cell has a complex system of sensors that assess the availability of oxygen and nutrients. Key integrators are:

- **AMPK** (AMP-activated protein kinase) is an energy status sensor activated when the AMP/ATP ratio increases [17].
- **mTOR** (rapamycin target) is a sensor of amino acid and energy availability that regulates growth and proliferation [26].
- **HIF**-oxygen status sensor [24].
- **Sirtuins** are NAD+ - dependent deacetylasesthat link redox status with metabolic regulation [16].

With poor nutrition, all these pathways are involved in the pathological process. An excess of nutrients activates mTOR, suppresses AMPK and, through the accumulation of metabolites, stabilizes HIF even in normoxia. Dysregulation of these pathways creates a vicious circle in which metabolic disorders exacerbate tissue hypoxia, and hypoxia, in turn, increases the metabolic imbalance [11, 24].

The relationship between hypoxia and dietary patterns is bi-directional. On the one hand, as discussed in detail above, poor nutrition induces a state of pseudohypoxia and tissue hypoxia. On the other hand, hypoxia (for example, in case of sleep apnea or being in the highlands) significantly modulates eating behavior and metabolic responses to diet [6, 20].

Studies on Drosophila show that the interaction between hypoxia and a high-fat diet can be both damaging and compensatory, depending on the nature of hypoxic exposure. Intermittent hypoxia, in contrast to permanent hypoxia, partially restored the flies ' tolerance to cold stress, which indicates a complex nature of interactions [7].

In mammals, chronic intermittent hypoxia (a model of sleep apnea) induces insulin resistance and dysmetabolism independently of obesity. At the same time, additional exposure to a high-fat diet does not always exacerbate these disorders, which may indicate saturation of pathogenetic pathways and convergence of mechanisms [5, 15].

Eating disorders are closely associated with dysregulation of circadian rhythms, which is important for the development of metabolic syndrome and hypoxic conditions. Circadian genes (Clock, Bmal1, Per, Cry) regulate not only sleep and wake cycles, but also metabolic pathways, including insulin sensitivity, glucose tolerance, and the activity of antioxidant enzymes [19, 23].

Intermittent hypoxia, which is characteristic of sleep apnea, itself disrupts circadian regulation, which creates an additional level of complexity in the pathogenesis of diet-induced hypoxia. Nocturnal meals, typical of the modern lifestyle, exacerbate the mismatch between central and peripheral oscillators, contributing to metabolic dysregulation [19].

The main body of information about the mechanisms of diet-induced hypoxia was obtained in experimental studies on animals. The most common models are:

1. **Mice on a high-fat diet (60% of calories come from fat)** - classic model of obesity and insulin resistance. In such animals, there is a decrease in the activity of mitochondrial complexes, oxidative stress, HIF-1a activation in various tissues, and endothelial dysfunction [5, 30].
2. **High-fructose diet models** - allow us to study the specific effects of fructose, including the induction of endoplasmic stress and aliver steatosis. Adding fructose to drinking water (10%) for 6 weeks has been shown to induce metabolic syndrome in rats with elevated blood pressure, triglycerides, and insulin [12, 29].
3. **Models of chronic intermittent hypoxia**-reproduce the conditions of sleep apnea by cyclically reducing O2 to 5%, followed by reoxygenation. Such models allow us to study the interaction between hypoxic stress and diet [5, 21].
4. **Drosophila melanogaster models** provide unique opportunities for genetic analysis of the interaction between diet and hypoxia due to the conservativeness of key signaling pathways [7].
5. **Isolated mitochondrial and cell culture models**are used to study the direct effects of nutrients and hypoxia on mitochondrial respiration and ROS production [26].

Clinical studies confirm the association between dietary patterns, obesity, and signs of tissue hypoxia. Patients with obesity and metabolic syndrome have the following symptoms:

- Increased levels of HIF-1a in adipocytes and peripheral blood mononuclear cells [2];
- Reduction of the partial pressure of oxygen in subcutaneous adipose tissue (measured using polarographic electrodes) [25];
- Increased expression of HIF target genes (VEGF, GLUT1) in adipose tissue [1];
- Markers of mitochondrial dysfunction in skeletal muscles and liver [28];
- Microcirculation disorders and endothelium-dependent vasodilation [4].

Special attention should be paid to studies of patients with obstructive sleep apnea, in whom the combination of obesity and intermittent hypoxia creates the maximum risk of cardiovascular complications. These patients have the most pronounced activation of pro-inflammatory and pro-oxidant pathways, as well as the most severe endothelial dysfunction [6, 11, 22].

The basis for the prevention and treatment of diet-induced hypoxia is the normalization of the nature of nutrition. However, in some cases, especially with already formed metabolic disorders, specialized nutritional support is required.

The concept of anaplerotic therapy involves:

- Early use of glucose solutions with intensive insulin therapy for hyperglycemia (target glucose level <10 mmol / l);
- Metabolic preconditioning with restriction of food intake before interventions;
- Use of energy substrates that do not require insulin (fructose in moderate doses);
- The purpose of balanced amino acid mixtures (1.3-1.5 g/kg / day of protein) with the addition of glutamine;
- Application of fat emulsions with omega-3 fatty acids;
- Use of Krebs cycle intermediates (succinate-containing preparations);
- Ensuring adequate intake of thiamine to maintain the activity of key enzymes [14].

Identification of key molecular mechanisms of diet-induced hypoxia allows us to identify potential pharmacological targets:

1. **ProlylHydroxylase** - modulation of PH.D. activity can regulate the stability of HIF-1a. PH.D. inhibitors (roxadustate, vadadustate) are used to treat anemia, but their effects in the metabolic syndrome need to be studied [24].
2. **PPAR receptors** - agonists of PPARy (thiazolidinediones) improve endothelial function and reduce oxidative stress in obesity [9, 30]. PPARa agonists (fibrates) modulate lipid metabolism and can improve metabolic flexibility [3].
3. **Mitochondrial-directed antioxidant** drugs that accumulate in mitochondria (MitoQ, SkQ1) can reduce ROS production and improve the function of the respiratory chain [26].
4. **Anti-inflammatory agents** — inhibitors of proinflammatory cytokines (anti-TNF-α, anti-IL-1β) can reduce systemic inflammation and improve insulin sensitivity [22].
5. **Sirtuin activators**such as resveratrol and other SIRT1 activators can restore mitochondrial function and improve metabolic parameters [16].

In addition to the qualitative composition of the diet, the diet is important. Interval fasting andtime - restricted feedingsynchronize food intake with circadian rhythms and can improve metabolic parameters regardless of the caloric content of the diet [19, 23].

Physical activity remains the most effective non-drug method for improving mitochondrial function and insulin sensitivity. Aerobic training increases mitochondrial biogenesis, increases the activity of oxidative enzymes, and improves tissue oxygenation [27].

Given the heterogeneity of metabolic disorders, a personalized approach to the correction of diet-induced hypoxia is necessary. Genetic polymorphisms, microbiome features, initial metabolic status, and concomitant diseases should be considered when choosing a therapeutic strategy [8, 18].

Conclusion.

Stress-induced hypoxia is a complex multifactorial phenomenon that occurs with chronic poor nutrition and is characterized by the development of tissue oxygen deficiency with preserved systemic oxygenation. Pathogenetic mechanisms include activation of HIF-dependent pathways under conditions of normoxia (pseudohypoxia), mitochondrial dysfunction with impaired oxidative phosphorylation, oxidative stress, chronic inflammation, dysregulation of PPARsignaling, and endothelial dysfunction.

The key role in the development of diet-induced hypoxia is played by:

- Excessive consumption of saturated fat, which blocks adaptive metabolic switching;
- High doses of fructose that induce endoplasmic stress and steatosis;
- An imbalance between the intake of nutrients and the ability of mitochondria to oxidize them;
- Chronic activation of pro-inflammatory and pro-oxidant pathways;
- Reduced expression of protective factors (PPARy, antioxidant enzymes).

The relationship between nutrition and hypoxia is bi-directional, which creates a vicious circle underlying the progression of metabolic syndrome, non-alcoholic fatty liver disease, cardiovascular pathology, and other alimentary-dependent diseases. Understanding these mechanisms opens up new perspectives for therapeutic interventions, including anaplerotic support, PPAR receptor modulation, mitochondrial-directed antioxidant therapy, and dietary adjustment.

Further research should focus on studying the tissue-specific features of diet-induced hypoxia, identifying biomarkers for early diagnosis, and developing personalized approaches to the correction of metabolic disorders, taking into account the individual characteristics of the patient.

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