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Review Article

The Pathophysiology of Hypoxia: Unraveling the Mechanisms of Oxygen Deprivation

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Abstract

Hypoxia is a typical pathological process that develops as a result of insufficient oxygen supply to the body or its impaired utilization by cells, leading to a decrease in energy production in tissues. The study of the pathogenesis of hypoxia revealed complex interactions between various cellular and molecular mechanisms that lead to impaired functioning of organs and tissues. Understanding these mechanisms is key to developing effective strategies for the diagnosis and treatment of conditions caused by oxygen deficiency. Further study of the pathogenesis of hypoxia, including the role of specific signaling pathways and targets, opens up new opportunities for the development of therapeutic approaches. The need for in-depth study is due to the high prevalence of hypoxia in many diseases, from cardiovascular to oncological. Ultimately, a detailed understanding of the pathogenesis of hypoxia is critically important to improve patient outcomes and reduce the burden of related diseases.

Keywords: pathophysiology; hypoxia; oxygen deprivation

Introduction

Hypoxia is a typical pathological process that develops as a result of insufficient oxygen supply to the body or its impaired utilization by cells, leading to a decrease in energy production in tissues. Hypoxia is the most common pathological process. Birth, death, and most diseases are accompanied by hypoxia. A lack of oxygen and a decrease in ATP production lead to metabolic disturbances and energy-dependent processes in the body. Synonyms for hypoxia include the common terms "oxygen starvation" and "oxygen deficiency." Hypoxia is the pathogenetic basis of various pathological conditions and diseases. In any pathological process, hypoxic phenomena are present. At the end of any fatal disease, regardless of its causes, acute hypoxia occurs. [1] The body's resistance to oxygen deficiency depends on its phenotypic and genotypic characteristics, resulting in individuals with high and low individual resistance to hypoxia. Differences in sensitivity to hypoxia are revealed across a wide range of functional-metabolic parameters and are maintained at systemic, tissue, cellular, and subcellular levels. With a complete cessation of oxygen supply, signs of damage in the cerebral cortex are detected within 2.5-3 minutes. The medulla oblongata can withstand a lack of oxygen for up to 15 minutes. The ganglia of the sympathetic nervous system can continue normal activity during the first hour after hypoxic conditions occur. Striated muscles can endure reduced oxygen levels for about 2 hours. In turn, the heart muscle and most internal organs can only withstand hypoxia for 20-30 minutes.

Based on a combination of factors, such as dependence and causes of development, hypoxia can be classified into exogenous and endogenous.

Exogenous hypoxia (or hypoxic) is oxygen starvation that arisesdue to a lack of oxygen in the environment, when its partial pressure in the inhaled air decreases. Hypoxic hypoxia is observed in mountain and altitude sickness or oxygen supply accidents. Endogenous hypoxia is a lack of oxygen in the tissues that develops due to internal disorders in the body, rather than due to low oxygen content in the external environment. One of the subspecies of endogenous hypoxia is respiratory hypoxia. Respiratory hypoxia is caused by factors that lead to impaired gas exchange in the lungs and respiratory failure. Respiratory hypoxia occurs due to restriction, obstruction, asphyxia, dysregulation of the nervous system, as well as violations of ventilation-perfusion relations, diffusion of gases during "shock lung". Cardiovascular or circulatory hypoxia, depending on the etiology and area of the lesion, can be ischemic or local, as well as congestive. Ischemic hypoxia is a condition in which oxygen deficiency (hypoxia) occurs due to impaired blood supply (ischemia) to an organ or tissue, leading to oxygen starvation. [3] Unlike pure hypoxia caused by external factors, ischemia also leads to insufficient intake of nutrients and metabolic disorders. Hypoxic-ischemic encephalopathy (HIE) is common in newborns due to asphyxia during childbirth or in utero, which causes brain damage with various neurological symptoms. Congestive hypoxia is a condition in which there is sufficient oxygen in

the blood, but it does not reach the tissues in sufficient volume due to circulatory disorders. This is due to venous congestion, when blood does not flow well from the tissues, making it difficult for fresh, oxygen-rich blood to flow. [2]

Speaking of hemic, blood, and hypoxia as one of the subspecies of endogenous hypoxia, we can single out anemic hypoxia, which develops due to a decrease in the number of red blood cells and/or hemoglobin with blood loss, vitamin, protein, and iron deficiency. Hemic hypoxia, which develops due to hemoglobin inactivation, is accompanied by the formation of methemoglobin, carboxyhemoglobin, sulfhemoglobin and a sharp increase or decrease in the affinity of hemoglobin to oxygen. [10] Tissue (histotoxic, cellular, cytotoxic) hypoxia develops under the action of factors that directly damage the oxygen utilization and energy production system in the cell. In this case, hypoxia occurs against the background of sufficient oxygen supply to the tissues. The mechanisms of this type of hypoxia are different. The first is the inhibition of mitochondrial ETC enzymes: CN- ions, sulfides, Na+ azide; binding of R-groups: accumulation of alkylating agents, heavy metal ions. The second is competitive inhibition: accumulation of malonate. The third is the blocking of electron transfer and the subsequent accumulation of rotenone, amytal, mixothiazole, and others. The third is a violation of the synthesis of ETC enzymes with a deficiency of vitamins: B1, B3, PP, nicotinic acid. The fourth is the disintegration of mitochondrial membranes, which is facilitated by temperature, osmotic pressure, radiation, CP, and other risk factors. Overload type - "Load hypoxia" occurs due to a mismatch between oxygen demand and delivery during heavy muscle work.[15] Thus, with excessive muscle work, skeletal muscle hypoxia, redistribution of blood flow, hypoxia of other tissues, and the development of general hypoxia occur; with cardiac overload, relative coronary insufficiency, local cardiac hypoxia, and secondary general circulatory hypoxia develop. Overload hypoxia is characterized by the formation of oxygen debt with an increase in the rate of oxygen delivery and consumption and the rate of production and excretion of carbon dioxide, venous hypoxemia, hypercapnia, and changes in the acid-base state. Substrate hypoxia develops in cases where, with normal oxygen delivery, a disturbed state of membranes and enzyme systems, a primary substrate deficiency occurs, leading to disruption of all links in biological oxidation. In most cases, such hypoxia is associated with a deficiency of glucose in cells, for example, with disorders of carbohydrate metabolism (diabetes mellitus, etc.), as well as with a deficiency of other substrates (fatty acids in the myocardium), severe starvation. After 5-8 minutes of aglycemia, that is, approximately the same period as after the cessation of O2 delivery, the death of the most sensitive neurons occurs. [5] Mixed hypoxia - hypoxia of any type, having reached a certain degree, inevitably causes dysfunction of various organs and systems involved in oxygen delivery and utilization in the body. Combinations of different types of hypoxia are observed, in particular, in shock, poisoning with chemical warfare agents, heart disease, coma and other pathological conditions. The focus of inflammation contains elements of most of the listed types of hypoxia - circulatory, hemic, tissue, and substrate. It is worth noting that any chronic hypoxia leads to the addition of tissue hypoxia.

According to the criterion of prevalence, general or generalized hypoxia is distinguished. It includes exogenous, respiratory and circulatory hypoxia, which were mentioned earlier. It is also possible to distinguish local hypoxia, which includes such pathological conditions as ischemia, venous hyperemia and local stasis. In clinical practice, the following types of oxygen deficiency are usually distinguished by the rate of development. The first type is lightning hypoxia. Lightning hypoxia is an acute form of oxygen starvation that develops in seconds or tens of seconds, which leads to a serious condition, loss of consciousness and can cause death. [14] It occurs due to the immediate impact of factors that disrupt the supply or assimilation of oxygen, such as aircraft depressurization, severe injuries or failure of vital organs. The second type is acute hypoxia. Acute hypoxia is a sharp, rapid decrease in oxygen levels in tissues or organs that occurs within a few tens of minutes or hours and requires emergency intervention to prevent irreversible damage. [4] The condition can be caused by serious pathologies or external factors and is manifested by disorders in the functioning of vital organs, especially the central nervous system. The third type is subacute hypoxia. Subacute hypoxia is a form of oxygen deficiency that develops over several hours or days, unlike acute (minutes) or chronic (months) hypoxia. [6] It is characterized by a gradual decrease in oxygen supply to tissues and organs, which can lead to serious disorders of their functioning, including damage to the heart, lungs and brain. [8] The fourth type is chronic hypoxia. Chronic hypoxia is a long–term condition in which body tissues experience oxygen deficiency for months or years, which leads to a gradual disruption of cellular metabolism and organ functions. [8] Unlike acute hypoxia, it does not have pronounced symptoms in the initial stages, but it can cause shortness of breath, cyanosis of the fingers, and even irreversible damage to organs, especially the brain. To study such a problem as hypoxia, it is necessary to fully understand the pathogenesis of this disease. [11] Hypoxia has two stages of development: compensation and decompensation. Initially, due to compensatory and adaptive reactions, normal tissue respiration and energy formation are maintained. When the adaptive mechanisms are depleted, the decompensation stage develops, or oxygen starvation proper. Maintaining a normal oxygen level in the blood can be considered as a chain of mutually dependent processes. From the result of one process, the next one arises, which, in turn, gives rise to a ladder sequence of biochemical processes occurring at the cellular level. If one link in the chain of reactions falls out or is replaced by another, a pathological condition occurs by a pathological process. Using the example of hypoxia, we can note that the main link in the pathogenesis of this pathological condition is a violation of oxidative phosphorylation in mitochondria. Thus, we can draw a parallel between the disruption of oxidative phosphorylation in mitochondria and the disruption of ATP formation, as well as the subsequent energy deficiency and disruption of energy-dependent processes. Violations of energy-dependent processes can include a violation of contractility and, as a result, a malfunction of contractible structures, contracture. Energy deficiency disrupts the synthesis of proteins, lipids, and nucleic acids. Also, cells in the human body are faced with a violation of active transport. A large amount of water enters the cell, which can lead to hyperhydration of the cell. [7] The cell also receives an increased content of calcium ions. With an increase in the level of calcium in the cytoplasm, Ca2+-dependent enzymes are activated, which can lead to the destruction of cell membranes and fragmentation of chromatin in the nucleus.

The next link in the pathogenesis will be the activation of glycolysis and the subsequent accumulation of lactic acid, activation of the Krebs Cycle, which leads to acidosis. [9] Acidosis causes a blockade of glycolysis, the only way to produce ATP without oxygen, increased permeability of the plasma membrane, activation of lysosomal enzymes in the cytoplasm, followed by cell autolysis. [12] In conditions of hypoxia, the body activates protective and adaptive reactions. Emergency adaptation reactions include changes in behavior, respiration, cardiovascular system, blood, organs, tissues, and moderate stress. Long-term adaptation includes a decrease in basal metabolism, hypertrophy of the myocardium and respiratory system, an increase in the amount of hemoglobin and erythrocytes in the blood, in the density of capillaries in tissues, in the number of mitochondria in the cell and an increase in the conjugation of oxidation and phosphorylation processes, an increase in the resistance of the nervous system to hypoxia. Long-term adaptation to hypoxia is based on the regulation of transcription of various genes. The main mediator of this response is HIF - hypoxia inducible factor. As mentioned earlier, hypoxia can lead to various changes in the body, both at the biochemical and at the general organizational level. It is worth noting the metabolic disorder that characterizes hypoxia at the molecular level. Typical manifestations of metabolic disorders include impaired carbohydrate metabolism: decreased aerobic oxidation of pyruvate, decreased ATP, creatine phosphate, activation of anaerobic glycolysis, glycogenolysis, and the development of acidosis. Lipid metabolism disorders: increased

lipolysis, ketonemia, ketoacidosis, hyperlipemia. Violation of nucleoprotein metabolism: inhibition of protein synthesis, negative nitrogen balance, ammonemia, decreased rate of DNA replication, RNA transcription. [13]

In conclusion, the study of the pathogenesis of hypoxia revealed complex interactions between various cellular and molecular mechanisms that lead to impaired functioning of organs and tissues. Understanding these mechanisms is key to developing effective strategies for the diagnosis and treatment of conditions caused by oxygen deficiency. Further study of the pathogenesis of hypoxia, including the role of specific signaling pathways and targets, opens up new opportunities for the development of therapeutic approaches. The need for in-depth study is due to the high prevalence of hypoxia in many diseases, from cardiovascular to oncological. Ultimately, a detailed understanding of the pathogenesis of hypoxia is critically important to improve patient outcomes and reduce the burden of related diseases.

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