

Energy Exchange of Neurons of the Central Nervous System

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Abstract

The bioenergetic function of brain cells is maintained through continuous glucose consumption and aerobic ATP synthesis in mitochondria. At rest, the brain consumes up to 20% of the oxygen received by the human body. Under normal conditions, effective biological oxidation is the main source of energy-rich phosphate compounds necessary for the renewal of structures corresponding to the functional activity of organs and tissues. In the brain, the effects of hypoxia are most pronounced. The main energy consumer in the brain is the enzyme ATPase, which supports the electrical activity of neurons.

Keywords: Energy exchange; Neurons; Central nervous system

Introduction

The bioenergetic function of brain cells is maintained through continuous glucose consumption and aerobic ATP synthesis in mitochondria. At rest, the brain consumes up to 20% of the oxygen received by the human body. Under normal conditions, effective biological oxidation is the main source of energy-rich phosphate compounds necessary for the renewal of structures corresponding to the functional activity of organs and tissues [1-5]. In the brain, the effects of hypoxia are most pronounced. The main energy consumer in the brain is the enzyme ATPase, which supports the electrical activity of neurons. In adults, brain oxygen consumption averages 3-3.5ml / 100g /min, in children – 3.5–6ml / 100 g of tissue. Oxygen delivery is determined by the level of cerebral blood flow, which averages 50ml / 100 g/min, in the gray matter of the brain – 80ml / 100g /min, in white – 20ml / 100g /min.

The total cerebral blood flow is approximately 750ml/min and depends on the level of systemic blood pressure. At the same time, fluctuations in blood pressure within 60-160mmHg do not affect cerebral blood flow due to its autoregulation [6].

The brain's need for oxygen, compared to that of other organs, is extremely high. The main way to get energy in the brain is the aerobic breakdown of glucose. The energy needs of the brain, necessary for the normal functional activity of neurons, amount to approximately 1046J or 250cal per minute, are provided by 95% due to aerobic glycolysis. The average consumption of

glucose by the brain is 5mg/100g/min. Oxygen consumption and glucose consumption change in parallel. Glucose is the only energy substrate entering the nervous tissue, which normally can be used by its cells to form ATP. The penetration of glucose into the brain does not depend on the action of insulin, which does not penetrate the blood-brain barrier. The effect of insulin is manifested only in the peripheral nerves. Therefore, a necessary condition for the energy supply of nerve cells is a constant and continuous influx of glucose and oxygen from the bloodstream [4,5,7,8].

The strict dependence on glucose intake is due to the fact that the glycogen content in the nervous tissue is extremely low (0.1% of the brain mass) and cannot provide the brain with energy even for a short time. Since nerve cells receive energy mainly due to the aerobic oxidation of glucose, hypoglycemia is no less dangerous for the brain than hypoxia. Even with short-term hypoxia and /or hypoglycemia (with a blood glucose level of less than 2.2mmol / L), the formation of ATP in the nervous tissue is inhibited, because of which a comatose state develops rapidly, and irreversible changes occur in the brain [9].

The high rate of glucose consumption by nerve cells is ensured by the work of highly active brain hexokinase, which has 20 times more activity than the corresponding liver and muscle isozyme. With increased energy consumption, there is no possibility of accelerating the reactions of the citrate acid cycle, and therefore the high rate of aerobic glycolysis under normal conditions and the peculiarities of carbohydrate metabolism limits the compensatory

capabilities of nerve cells in hypoxia [10]. The bioelectric activity of the cortex is determined by oxygen consumption, which is the maximum in the gray matter of the cerebral cortex. The hippocampal and cerebellar neurons are the most sensitive to hypoxia [11].

A sufficient level of aerobic glycolysis is determined by the gas composition of the blood, its acid-based homeostasis, the content of hemoglobin, glucose, and the level of cerebral blood flow [4-9]. The human brain uses glucose as the only source of energy (about 75-100mg/min). With aerobic breakdown, 36 ATP molecules are formed from one glucose molecule, and with anaerobic only two together with lactic acid [12]. Brain cells need a constant supply of ATP to maintain their stability and preserve K⁺ ions inside the cell, and sodium and calcium ions outside. Since the brain is unable to accumulate energy, it requires a constant supply of oxygenated blood [13].

Normally, the level of cerebral blood flow on average is approximately 50-60ml / 100g/min, which with a brain weight of 1300-1400g is approximately 750-900ml/min. At the same time, oxygen consumption does not exceed 3.3-3.5ml/100g/min. However, the distribution of blood in different parts of the brain is uneven. Thus, the greatest cerebral blood flow at rest (up to 180ml/ 100g) is determined in the posterior tubercles and in the gray matter of the end sections of the visual, auditory and somatosensory analyzers. Its lowest level was registered in the white matter of the spinal cord (14ml/100g) [14]. It should be noted that only a certain part of oxygen diffuses from the blood in accordance with the needs of the brain [15].

When the AP is reduced to a critical level (9-15ml / 100g / min) morphological changes occur in the brain tissue with the formation of infarction, and when it is maintained at the level of 18-20ml / 100g /min, gross functional changes occur – the so-called “functional paralysis”, without the formation of infarction. The condition of brain tissue during perfusion is below the threshold of “functional paralysis”, but above the threshold of morphological disorders, has been called in the literature “zones of ischemic penumbra” or “penumbra” – zones of reversible changes in brain tissue. The oxidation of one glucose molecule contributes to the formation of 38 ATP molecules, which is 40% of the energy released in the cells of the oxidized substrates (the rest of the energy is dissipated as heat). The resulting ATP is used by the brain for the synthesis of proteins, lipids, and neurotransmitters (acetylcholine, serotonin, norepinephrine) – a complex of biologically active substances that ensure the normal functioning of neuronal structures, the barrier role of cell membranes and ion transport [10,16-18].

Mechanisms of Energy Transduction in Mitochondria

Mitochondria play a key role in providing energy for cellular functions, and on the other hand, they are a target, decoder and switch of intracellular signals, generator of secondary

messengers and pro-apoptotic factors [11]. Modern ideas about the mechanisms of energy transduction in the mitochondrial membrane were formed after Peter Mitchell created the chemiosmotic theory of ATP synthesis. The energy resources used by the inner mitochondrial membrane are initially directed at the transport of the conjugating proton through the membrane to an area with a higher concentration (energization of the membrane), then the proton gradient is used by the mitochondria as a driving force capable of leading to the synthesis of ATP. Isolation of mitochondrial proteins by D.E. Green and co-workers led to the formation of the idea of “complexes” of the respiratory chain [11].

Structural and Functional Organization of Mitochondria

The mitochondria have two membranes: an inner (IMM) and an outer (OMM) and, accordingly, two compartments separated from each other by an inner membrane. The outer mitochondrial membrane is permeable to small molecules and ions that move through transmembrane channels formed by a family of integral membrane proteins – porins. There is potential-sensitive anion channels (porins) OMM, which allow the exchange of metabolites between mitochondria and cytoplasm. The inner membrane is impervious to H⁺, and this extremely important property of the membrane is key for mitochondrial energy transduction. Chemicals such as ions and small molecules that cross the inner membrane have specific transporters. IMM contains integral proteins – key catalysts of oxidative phosphorylation (respiratory complexes of the electron transport chain of electron transport) and ATP synthase complex [2-5].

Components of the Mitochondrial Respiratory Chain and Respiratory Complexes

The mitochondrial respiratory chain consists of several electron carriers, representing prosthetic groups of integral proteins that function as redox pairs. There are four electron transporters, or respiratory complexes, which catalyze the process of electron transfer along the ETC. In addition to respiratory complexes, low-molecular carriers (shuttles), such as ubiquinone and cytochrome c, also participate in electron transfer. Complex I (NADH-ubiquinone oxidoreductase; NADH-dehydrogenase) consists of 42-43 different polypeptides, including FMN (flavin mononucleotide) containing a flavoprotein and 6 iron-sulfur centers. Complex I in its structure has an L-shape with two “arms”: a long “arm” consisting of a hydrophobic membrane protein located in the lipid layer of the inner mitochondrial membrane, and a short “arm” having a hydrophilic part protruding into the matrix and containing FMN and an active NADH binding center. Complex I preparations isolated according to the Hatefi procedure contain 4 moles of ubiquinone per 1 mole of FMN. Ubiquinone is a lipid-soluble benzoquinone with a long side isoprenoid chain, which is able to move by diffusion in each of the two layers of phospholipids of the inner membrane and provide shuttle electron transfer between membrane proteins [14].

Complex II (succinate dehydrogenase; succinate-ubiquinone oxidoreductase) is a membrane-bound component of the citric acid cycle (Krebs cycle), which functions as a fragment of the mitochondrial respiratory chain. The II-integral protein complex contains covalently bound FAD (flavin adenine dinucleotide) and iron-sulfur centers localized in the membrane outer domain, which catalyze electron transfer from succinate to ubiquinone and cytochrome b heme located in the hydrophobic membrane domain [19].

Complex III (cytochrome bc₁ complex; ubiquinone-cytochrome c oxidoreductase) consists of 9-10 polypeptides, 3 of which are involved in redox reactions. These are hemes of cytochromes b₅₆₂, b₅₆₆, c₁ and (2Fe-2S). In addition, two ubisemiquinone molecules are associated with two separate domains of complex III. Cytochrome c is a peripheral protein located on the inner membrane from the intermembrane space. Cytochrome c transfers electrons from complex I to the CuA center of complex IV [20]. Complex IV (cytochrome c oxidase; cytochrome c oxidase; cytochrome c- O₂ oxidoreductase) is the final catalyst of the mitochondrial respiratory chain. Function of the complex IV consists in reducing O₂ to H₂O by transferring four electrons from the reduced cytochrome c using 2 protons from the matrix. Electronic carriers and complexes form functional ensembles ("assemblies") with characteristic protein-protein interactions that ensure efficient electron transfer. Complexes I, III and IV interact with each other to form supercomplexes characterized by a certain stoichiometric composition [14,15,21].

Electrons, successively oxidizing the components of the electron transport chain, come from electron donors – NADH or succinate to the acceptor – O₂. Complexes I, III and IV function as proton pumps that are "powered" by the free energy of conjugated redox reactions occurring in the mitochondria, while the catalyzed oxidation and H⁺ release are vector (strictly directed) and conjugate reactions. The movement of H⁺ is carried out in the direction from the matrix to the intermembrane space, due to which the matrix is charged "negatively", and the intermembrane space is "positively". The chemical free energy of the fall of the redox potential of electrons passing through respiratory complexes is used to create a proton electrochemical gradient (potential Δμ_H), expressed in units of electric potential, and called proton-driving force - Δp:

$$\Delta P \text{ (mV)} = \Delta \Psi m - (2.3RT/F) \Delta pH \text{ where?}$$

ΔΨ_m – transmembrane electrical potential of the inner mitochondrial membrane,

ΔΨ_H – pH gradient on the inner membrane.

R, T, and F – gas constant, absolute temperature, and Faraday constant, respectively.

At a temperature of 37°C Δp = ΔΨ_m - 60ΔpH.

The main contribution to the creation of Δp in most cases is made by (ΔΨ_m) which quantitatively is approximately 150–180 mV, Δp is a 200–220 mV.

Δp – the driving force of the process of phosphorylation of ADP and inhibition of electron flow in a controlled metabolic state (in the absence of ADP).

The proton potential Δμ_H consists of two components: electrical (ΔΨ_m) and chemical or osmotic (ΔpH). The biophysical basis of respiratory control is that Δp can stop the exergonic oxidation of substrates due to the establishment of an equilibrium between the free energy of the electron flow between the redox pairs of ETC and the H⁺ flow between the mitochondrial chambers. In addition, the membrane potential provides the driving force for the transfer of cations into the mitochondria, such as K⁺ and Ca²⁺ [16].

The Role of the Electrochemical Potential and F₁-ATPases of the Molecular Rotor in the Phosphorylation of ADP

In general, the process of oxidative phosphorylation critically depends on the integrity and impermeability of the inner mitochondrial membrane. The first part of the process consists in converting the chemical potential of NADH and the oxidation energy of succinic acid (succinate) into H⁺ electrochemical gradient, the second part is in the synthesis of ATP catalyzed by ATP synthase using proton gradient energy. This process is thermodynamically possible, since the released energy during electron transfer along the ETC and the driving proton force retain enough free energy, approximately 34 kJ per mole of the electron pair to lead to the resynthesis of one mole of ATP, requiring 32kJ [11].

Mitochondrial ATP synthase (complex V) is an F-type atases having two components: F₁ is a peripheral membrane protein, and F₀ is an integral protein that is an integral part of IMM. The catalytic domain F₁ is a globular community of 5 proteins – α, β, γ, δ, and ε with stoichiometry 3:3:1:1:1, where γ-, δ-, and ε-subunits form the basis of the protein ensemble [20].

To perform the function of complex V, the presence of ADP is necessary. The gradients of ADP and ATP on the inner membrane are balanced by the activity of adenine nucleotide translocase, which ensures the entry of ADP into the matrix and ATP into the cytosol. It has been experimentally established that the synthesis of one ATP molecule requires the transfer of 3–4 H⁺ to the matrix. The efficiency of phosphorylation in isolated mitochondria is defined as the ratio of ADP/O with experimental values of 2.6–2.7 for NAD-dependent substrates and 1.6–1.7 for succinate oxidation. These values are close to the theoretical ones (2.5 and 1.5, respectively), which are calculated because the amount of pumped H⁺ during electron pair transfer is 10 in the case of NADH oxidation and 6 in the case of succinate oxidation [3-7].

Mitochondrial Sequestration of Ca²⁺

The addition of Ca²⁺ ions to isolated mitochondria, even in the presence of ATP, leads to their energy-dependent capture

(sequestration) by mitochondria upon termination of ATP synthesis. The mitochondria absorb Ca^{2+} in exchange for H^+ in a process driven by an ATP or membrane potential that drives a $\text{Ca}^{2+}/\text{H}^+$ pump with a stoichiometry of 1:1. Mitochondria can accumulate a large amount of Ca^{2+} with simultaneous absorption of Pi. Ca^{2+} can be deposited in the matrix in the form of hydroxyapatite, which does not lead to a significant change in the concentration of its dissolved fraction. Another route of Ca^{2+} entry into the mitochondria is functionally related to the opening of Ca^{2+} -mediated pores of high permeability. Intramitochondrial Ca^{2+} is an allosteric activator of some matrix dehydrogenases, such as NADH –isocitrate dehydrogenase, pyruvate dehydrogenase, α -ketoglutarate dehydrogenase, and a cofactor of mitochondrial NO synthase (mtNOS) [6-9].

The direct source of energy that the cell uses to produce work is the energy contained in the structure of adenosine triphosphate (ATP). This is a very valuable evolutionary acquisition: energy extracted from an external source is stored in the form of “high-energy bonds” between phosphate groups. ATP easily sends its phosphate groups to other molecules, being an indispensable intermediary for the transfer of chemical energy. Due to the peculiarities of its structure, this compound is rich in energy and the breaking of bonds between its phosphate groups can occur in such a way that the released energy is used to produce work. Energy storage in the form of ATP occurs because of oxidative phosphorylation, which is a metabolic pathway for the oxidation of nutrients. The dichotomous pathway of aerobic glucose breakdown provides the cell with 38 ATP molecules because of three stages. The first – glycolysis – takes place in the cytosol, the rest in the mitochondria. The formation of ATP is associated with the dehydrogenation of the substrate and the oxidation of hydrogen (formation of H_2O) with the participation of NAD- and FAD-dependent dehydrogenases, ubiquinone dehydrogenase, cytochromes, and cytochrome oxidase.

The energy for ATP synthesis comes from substrates containing high-energy electrons during their dehydrogenation in the Krebs cycle implemented in the cytosol. During oxidative phosphorylation, electrons are transferred from donor compounds to acceptor compounds during redox reactions [12-15].

NADH and FADN2 molecules transfer electrons to the respiratory chain localized in the inner mitochondrial membrane. The complex of respiratory chain enzymes is located between the outer and inner membranes [8]. NAD-dependent dehydrogenases contain NAD and NADP as coenzymes. The pyridine ring of nicotinamide can attach hydrogen electrons and protons from various substrates, serving as the main collector of the energy of oxidized substances and the main source of electrons with high energy potential for the tissue respiration chain. Flavin dehydrogenases contain FAD or FMN as coenzymes. These coenzymes are formed in the human body from vitamin B2. Flavin coenzymes are strongly associated with apoenzymes. The isoalloxazine conjugated cyclic system serves as the working

part of FAD and FMN. Most FAD-dependent dehydrogenases are soluble proteins localized in the mitochondrial matrix that serve as electron acceptors from many substrates [5].

The cytochrome system contains cytochromes and cytochrome oxidase, which contain an iron-porphyrin prosthetic group. Among the oxidases, iron-containing enzymes and carriers belonging to the cytochrome system play an important role. Being included in a certain sequence in the process of electron transfer, transferring them from flavoproteins to molecular oxygen, when electrons are transferred by cytochromes, reversible oxidation and reduction of iron occurs, because of which, when an electron is given or acquired, their valence changes. In the respiratory chain, the direction of electron transport is determined by the value of the redox potential of cytochromes. Only cytochrome oxidase, which has the greatest affinity for oxygen, is capable of transferring electrons directly to oxygen. Cytochrome oxidase inhibitors are CO, cyanide, and aside [16-18].

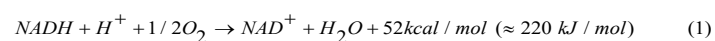
Oxidative Phosphorylation of ADP

Oxidative phosphorylation requires the energy of electron movement in the respiratory chain. Since electrons tend to move from electronegative systems to electropositive ones, their transport along the electron transport chain (ETC) to oxygen is accompanied by a decrease in free energy [5].

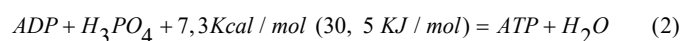
When comparing the values of the electrochemical potentials of electron carriers, a decrease in free energy occurs at each stage of the ETC, and the energy of the electrons is released in portions. There are 3 sections in the respiratory chain in which electron transfer is accompanied by a relatively large decrease in free energy. These steps can provide energy for the synthesis of ATP, since the amount of free energy released is approximately equal to the energy required for the synthesis of ATP from ADP and phosphate. It has been experimentally confirmed that the process of electron transfer by ETC and the synthesis of ATP are energetically coupled [4].

The first process is the transfer of electrons from the reduced coenzymes NADH and FADH2 through the ETC to oxygen exergonic.

For example:



The second process – phosphorylation of ADP, or synthesis of ATP, is endergonic:



Synthesis of ATP from ADP and H_3PO_4 due to the energy of electron transfer by ETC, it is called oxidative phosphorylation.

Proton Gradient and Electrochemical Potential

The transfer of electrons along the respiratory chain from NADH to oxygen is accompanied by the pumping of protons from the mitochondrial matrix through the inner membrane into the

intermembrane space. This work consumes part of the energy of the electrons transported by the ETC. Protons transferred from the matrix to the intermembrane space cannot return to the matrix due to the impenetrability of the inner membrane for protons. Thus, a proton gradient is created in which the concentration of protons in the intermembrane space is greater and the pH is lower than in the matrix. Each proton carries a positive charge, because of which there is a potential difference on both sides of the membrane: a negative charge on the inside and a positive charge on the outside. Together, the electrical and concentration gradients make up the electrochemical potential $\Delta\mu H^+$ – energy source for ATP synthesis. Since the most active transport of protons into the intermembrane space is necessary for the formation of $\Delta\mu H^+$, occurs at the sites of the ETC corresponding to the location of complexes I, III and IV, these sites are called the points of conjugation of respiration and phosphorylation [3]. The mechanism of proton transport through the mitochondrial membrane at the interface points is not clear enough. It is known that KoQ plays an important role in this process. The mechanism of proton transfer with the participation of KoQ has been studied in the most detail at the level of complex III, [10]. KoQ transfers electrons from complex I to complex III and protons from the matrix to the intermembrane space, performing a kind of cyclic transformation called Q-cycles. The electron donor for complex III is reduced ubiquinone (QH₂), and the acceptor is cytochrome c. Cytochrome c is located on the outside of the inner membrane of the mitochondria; there is also the active center of cytochrome c, from which electrons are transferred to cytochrome c.

Energy of the proton potential (electrochemical potential $\Delta\mu H^+$) it is used for the synthesis of ATP if protons return to the matrix through the ion channels of ATP synthase [14]. The reduced ubiquinone (QH₂) interacts with Fe³⁺ of heme b₁ and, restoring it, releases a proton into the aqueous phase, turning into semiquinone (HQ•). The electron from heme b₁ is transferred to Fe³⁺ of heme b₂. HQ• gives the second electron to the FeS center located closer to the outer surface of the membrane; in this case, the second proton is in the intermembrane space; the electron is transferred to cytochrome b₁, and then to cytochrome c. The oxidized Q diffuses to the inner side of the membrane, where it receives an electron from heme b₂ and a proton from the matrix, turning into HQ•. receives an electron from complex I and a proton from the matrix; QH₂, is formed in the membrane, and the whole process is repeated from the beginning [10-15].

There is a stationary Q/QH₂ pool in the membrane, from which each QH₂ molecule in one cycle ensures the transfer of protons from the matrix to the intermembrane space and electrons, which eventually enter oxygen. The work performed when pumping protons consumes part of the free energy, which is released during the transfer of electrons along the gradient of the redox potential. The energy of the electrochemical potential ($\Delta\mu H^+$) is used for the synthesis of ATP if protons return to the matrix through the ion channels of ATP synthase [9].

Structure of ATP Synthase and Synthesis of ATP

ATP synthase (H⁺-ATPase) is an integral protein of the inner membrane of mitochondria. It is near the electron transport chain. ATP synthase consists of 2 protein complexes, designated as F₀ and F₁. The hydrophobic complex F₀ is immersed in the membrane. It serves as a base that fixes ATP synthase in the membrane. The F₀ complex consists of several subunits forming a channel through which protons are transferred to the matrix [8].

The composition of F₀ includes polypeptide chains that form a channel that penetrates the membrane through. Through this channel, protons return to the matrix from the intermembrane space; protein F₁ protrudes into the matrix from the inside of the membrane and contains 9 subunits, 6 of which form 3 pairs of α and β ("head") covering the core part, which consists of 3 subunits γ , δ and ϵ . γ and ϵ are mobile and form a rod rotating inside a fixed head and connected to the F₀ complex. In the active centers formed by pairs of α and β subunits, ADP, inorganic phosphate (Pi) and ATP bind. The catalytic cycle of ATP synthesis includes 3 phases, each of which takes place alternately in 3 active centers:

- 1 – binding of ADP and H₃PO₄.
- 2 – formation of the phosphoanhydride bond of ATP.
- 3 – formation of the final product.

Each time protons are transferred through the F₀ channel to the matrix, all 3 active centers catalyze the next phase of the cycle. The energy of the electrochemical potential is spent on turning the rod, as a result of which the conformation of α - and β -subunits changes cyclically, and ATP synthesis occurs.

The F₁ complex protrudes into the mitochondrial matrix. It consists of 9 subunits (3 α , 3 β , γ , ϵ , δ). The α and β subunits are stacked in pairs, forming a "head"; between the α - and β -subunits there are 3 active centers in which ATP synthesis occurs; the γ -, ϵ -, δ -subunits bind the F₁ complex to the F₀. An increase in the concentration of protons in the intermembrane space activates ATP synthase. The electrochemical potential $\Delta\mu H^+$ causes protons to move through the ATP synthase channel into the matrix. In parallel, under the action of $\Delta\mu H^+$, conformational changes occur in the pairs of α , β -subunits of the F₁ protein, because of which ATP is formed from ADP and inorganic phosphate. The electrochemical potential generated at each of the 3 interface points in the ETC is used to synthesize one ATP molecule [7].

Coefficient of Oxidative Phosphorylation

The oxidation of the NADH molecule in the ETC is accompanied by the formation of 3 ATP molecules; electrons from FAD-dependent dehydrogenases enter the ETC at KoQ, bypassing the first interface point, so only 2 ATP molecules are formed. The ratio of the amount of phosphoric acid (P) used for phosphorylation of ADP to the oxygen atom (O) absorbed during respiration is called the coefficient of oxidative phosphorylation and is designated

P/O. Therefore, for NADH P/O = 3, for succinate P/O = 2. These values reflect the theoretical maximum of ATP synthesis, in fact, this value is less [20].

The P/O coefficient shows the number of inorganic phosphate (Pi), molecules that have passed into the organic state (ATP) per each oxygen atom absorbed. In fact, it is equal to the number of ATP molecules that are formed during the transportation of 2 electrons along the respiratory chain per oxygen atom [19].

Respiratory control ratio is a direct effect of the electrochemical gradient on the speed of movement of electrons along the respiratory chain (i.e., on the amount of respiration). In turn, the magnitude of the gradient directly depends on the ratio of ATP / ADP, the quantitative sum of which in the cell is almost constant ([ATP] + [ADP] = const) [11,16-18,22].

Oxidation of substrates and phosphorylation of ADP in mitochondria are closely related. The rate of use of ATP regulates the rate of electron flow in the ETC. If ATP is not used and its concentration in cells increases, then the flow of electrons to oxygen stops. On the other hand, the consumption of ATP and its conversion into ADP increases the oxidation of substrates and the absorption of oxygen. The dependence of the mitochondrial respiration intensity on the concentration of ADP is called respiratory control ratio. The mechanism of respiratory control ratio is characterized by high accuracy and is important, since because of its action, the rate of ATP synthesis corresponds to the energy needs of the cell. There are no reserves of ATP in the cell. The relative concentrations of ATP / ADP in tissues vary within narrow limits, while the energy consumption of the cell, i.e., the frequency of revolutions of the ATP and ADP cycle, can vary tenfold [11].

Transport of ATP and ADP Through Mitochondrial Membranes

In most eukaryotic cells, the synthesis of the main amount of ATP occurs inside the mitochondria, and the main consumers of ATP are located outside it. On the other hand, a sufficient concentration of ADP should be maintained in the mitochondrial matrix. These charged molecules cannot independently pass through the lipid layer of the membranes. The inner membrane is impervious to charged and hydrophilic substances, but it contains a certain number of transporters that selectively transfer such molecules from the cytosol to the matrix and from the matrix to the cytosol [23].

There is an ATP/ADP antiporter protein in the membrane that transports these metabolites across the membrane. The ADP molecule enters the mitochondrial matrix only if the ATP molecule exits the matrix. The driving force of such an exchange is the membrane potential of electron transfer along the ETC. Calculations show that about a quarter of the free energy of the proton potential is spent on the transport of ATP and ADP. Other

transporters can also use the energy of the electrochemical gradient. This is how inorganic phosphate, necessary for the synthesis of ATP, is transferred into the mitochondria. The proton potential, not the ATP energy, also serves as a direct source of free energy for the transport of Ca^{2+} into the matrix [21]. The flows of various substances (ATP, ADP, H_3PO_4 , Ca^{2+}) pass through specific transporters, while the energy of the electrochemical potential of the membrane is consumed [14].

Conjugation of Respiration and Phosphorylation

According to Mitchell's chemiosmotic theory, there is no direct connection of respiratory chain enzymes with phosphorylation enzymes in mating membranes. The conjugation of respiration and phosphorylation is carried out through the membrane. When protons are transferred through the membrane, it passes into an energized state with the appearance of proton concentration gradients and an electric potential difference across the membrane. At the same time, forces arise that seek to return protons to the matrix. Under the influence of these forces, protons pass through the channel of enzyme F₀ from the outer region to enzyme F₁ located on the inner side of the membrane. The proton transfer energy is used by this enzyme to synthesize the ATP molecule in the matrix. The electrons go along the respiratory chain, part of the energy from these movements is spent for pumping protons into the intermembrane space, because of which the enzymes F₀ and F₁ convert the kinetic energy of the moving proton into macrouid energy with phosphorylation of ADP [13].

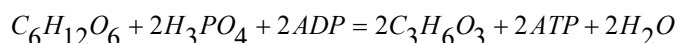
Separation of Respiration and Phosphorylation

Some chemicals (protonophores) can transfer protons or other ions (ionophores) from the intermembrane space through the membrane into the matrix, bypassing the proton channels of ATP synthase. As a result, the electrochemical potential disappears, and ATP synthesis stops. This phenomenon is called the disconnection of respiration and phosphorylation. As a result of separation, the amount of ATP decreases, and ADP increases. In this case, the rate of oxidation of NADH and FADH₂ increases, the amount of oxygen absorbed also increases, but energy is released in the form of heat, and the P/O coefficient decreases sharply. As a rule, the disconnectors are lipophilic substances that easily pass through the lipid layer of the membrane. One such substance is 2,4-dinitrophenol, which easily passes from an ionized form to a non-ionized one by attaching a proton in the intermembrane space and transferring it to the matrix [11].

The protonated form of 2,4-dinitrophenol transports protons through the inner membrane of mitochondria and prevents the formation of a proton gradient. Some medications can also be examples of disconnectors, for example, the anticoagulant dicoumarol or metabolites that are formed in the body, bilirubin (a product of heme catabolism), thyroxine (a thyroid hormone). All these substances exhibit a disconnecting effect only at their high concentration [6].

Anaerobic Breakdown of Glucose (anaerobic glycolysis)

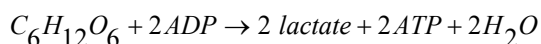
The process of splitting glucose, which proceeds without oxygen and ends with the formation of lactate from pyruvic acid, is called anaerobic glycolysis [16]. This process does not depend on the work of the mitochondrial respiratory chain. ATP is formed due to substrate phosphorylation reactions. Summary equation of the anaerobic glycolysis process:



Glycolysis is a sequence of enzymatic reactions that lead to the conversion of glucose into pyruvate with the simultaneous formation of ATP [1].

The Sequence of Reactions Before the Formation of Pyruvate (anaerobic glycolysis)

With a lack of oxygen, pyruvate is reduced to lactate:



During anaerobic glycolysis, all 10 reactions identical to aerobic glycolysis occur in the cytosol. Only the 11th reaction, where pyruvate is reduced by cytosolic NADH, is specific for anaerobic glycolysis [2-6]. The reduction of pyruvate to lactate, providing NAD⁺ regeneration, is catalyzed by lactate dehydrogenase. This reaction ensures the regeneration of NAD⁺ from NADH without the participation of the mitochondrial respiratory chain in situations associated with insufficient oxygen supply to cells. The role of the hydrogen acceptor from NADH (like oxygen in the respiratory chain) is performed by pyruvate. Lactate is excreted into the blood and disposed of, turning into glucose in the liver, or when oxygen is available, it turns into pyruvate, which enters the general pathway of catabolism, oxidizing to CO₂ and H₂O.

The pyruvate dehydrogenase complex (PDC) complex consists of three types of catalytic protomers forming three enzymes:

E1 – pyruvate decarboxylase,

E2 – dihydrolipoyl transacetylase,

E3 – dihydrolipoyl dehydrogenase.

Each enzyme contains a different number of protomers. The protomers of each of the three enzymes contain coenzymes strongly bound to proteins. Coenzymes NAD⁺, HS-KoA are included in the complex only at the time of reactions and are released at the end of the process as part of the final products – Acetyl-CoA, NADH and H⁺.

17. Oxidative Decarboxylation of Pyruvic acid Includes Five Stages:

1. Pyruvate combines with thiamine pyrophosphate (TPP) in the composition of E1 and undergoes hydroxylation.

2. Dihydrolipoyl transacetylase catalyzes the transfer of a hydrogen atom and an acetyl group from TPP to an oxidized form of lipolysis groups to form an acetyl thioether of lipoic acid.

3. At this stage, CoA interacts with the acetyl derivative E2, resulting in the formation of acetyl-CoA and a fully reduced lipoic residue, prosthetic group E2.

4. Dihydrolipoyl dehydrogenase (E3) catalyzes the transfer of hydrogen atoms from reduced lipoic groups to FAD, the prosthetic group of the enzyme E3.

5. The reduced FADH₂ transfers hydrogen to NAD⁺ with the formation of NADH. PDC supplies electrons to the respiratory chain together with NADH and provides synthesis of 3mol of ATP per 1mol of pyruvate by oxidative phosphorylation. An increase in the concentration of NAD⁺ stimulates oxidative decarboxylation of pyruvate, an increase in the concentration of ATP and NADH reduces the speed of this process [14].

Hydrogen atoms released in redox reactions are delivered to the ETC with the participation of NAD- and FAD-dependent dehydrogenases, resulting in the synthesis of water and oxidative phosphorylation of ADP. The bond between carbon atoms in acetyl-CoA is resistant to oxidation [13].

The citric acid cycle includes the following sequence of reactions:

1. Formation of citrate from oxaloacetate. Enzyme: citrate synthase.

2. Conversion of citrate to isocitrate. Enzyme: aconitase.

3. Oxidative decarboxylation of isocitrate. α-ketoglutarate is formed. Enzyme: isocitrate dehydrogenase, (two forms: one with coenzyme NAD⁺, the second – NADP⁺).

4. Oxidative decarboxylation of α-ketoglutarate. Succinyl-CoA is formed. Enzyme: α-ketoglutarate dehydrogenase complex.

5. Conversion of succinyl-CoA to succinate. Enzyme: succinyl-CoA synthetase.

6. Dehydrogenation of succinate. Fumarate is formed. Enzyme: succinate dehydrogenase.

7. Formation of malate from fumarate. Enzyme: fumarase.

8. Dehydration of malate. Oxaloacetate is formed. Enzyme: malate dehydrogenase.

For each acetyl residue included in the citrate cycle, 12 ATP molecules are formed (due to oxidative phosphorylation of 3 ATP from three NAD, 2 ATP – one FAD and the last due to substrate phosphorylation). The reduced coenzymes (3 NADH molecules and one FADH₂ molecule) give electrons to oxygen [12]. Glucose is used as the main fuel in the brain. The sources of carbohydrates of the body are carbohydrates of food – mainly starch and glycogen, as well as sucrose and lactose. In addition, glucose can be formed in the body from amino acids, as well as from glycerin, which is part of fat. The main sources of glucose in the body are food, the breakdown of the reserve glycogen polysaccharide, the synthesis of glucose from non-carbohydrate precursors (mainly from

glycogenic amino acids) – gluconeogenesis [13].

Anaerobic breakdown of glucose is energetically ineffective. Aerobic breakdown is the main pathway of glucose catabolism in humans and other aerobic organisms [11]. Substrate phosphorylation is associated with the transfer of macrourid phosphate or the energy of the macrourid bond of a substance (substrate) to ADP. Such substances include metabolites of glycolysis (1,3-diphosphoglyceric acid, phosphoenolpyruvate), citric acid cycle (succinyl-CoA) and phosphocreatine. The hydrolysis energy of their macrourid bond is higher than 7,3kcal/mol in ATP, and the role of these substances is reduced to using this energy to phosphorylate the ADP molecule to ATP [3]. The data presented in the article can serve as a fundamental basis for further study of the brain in normal and pathological conditions with further extrapolation of the obtained data to humans.

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