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Elizaveta I Bon *

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Review Article

Regulation of Mitochondrial Respiration by Adenosine Diphosphate and Adenosine Triphosphate

Dremza I.K., Maksimovich N.Ye., Bon E.I *, Vishnevskaya E.I., Moroz E. V.

Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus

***Corresponding Author:** Elizaveta I Bon, Candidate of biological science, Assistant professor of pathophysiology department named D. A. Maslakov, Grodno State Medical University; Grodno State Medical University, 80 Gorky St,230009, Grodno, Belarus.

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Abstract

Very often, we present metabolic cycles schematically, i.e. we limit ourselves only to listing precursors, intermediates and end products of metabolism. Meanwhile, it is now well known that poly-enzyme systems have the ability to self-regulate, which is the result of the specific organization of the sequence of reactions, the specific properties of individual enzymes of the system, as well as the action of feedback mechanisms and other types of inhibition. In this report, we will consider the dynamics of electron transfer in mitochondria and its regulation by ADP and ATP

Keywords: regulation; mitochondrial respiration; adenosine diphosphate; adenosine triphosphate

Introduction

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It goes without saying that the intensity of respiration should depend on the concentration of Krebs cycle substrates and oxygen [3]. However, it is now firmly established that the intensity of mitochondrial respiration also depends on the concentration of reacting substances — ADP and Ph — and the product of conjugated oxidative phosphorylation in the respiratory chain — ATP [4]. The role of ADP to maximize respiration intensity in intact mitochondria was first studied by Lardy and his collaborators, who made the important assumption that the concentration of ADP regulates the intensity of respiration inside the cell. This provision was then analyzed in detail by Chance and his staff and extrapolated to the regulatory effect of ATP and Fn.

Chance and Williams analyzed the general conditions affecting the respiration rate of intact mitochondria and the mechanisms of oxidation-reduction of components of the respiratory chain [5]. They identified 5 states of mitochondrial respiration. State 1 is characterized by the absence of a substrate and ADP, state 2 is characterized by the presence of one of the substrates. State 3 is characterized by the presence of all necessary components, so that the limiting factor is the respiratory chain itself - this is the state of "active" phosphorylating respiration. State 4 is characterized by a deficiency of only ADP - this is the so-called controlled state, or a state of rest, or a state of ADP deficiency. State 5 is characterized by the absence of oxygen only.

They also show the degree of oxidation — reduction of individual carriers in each of the respiratory conditions. If respiration is limited by the substrate, and all other components are present in excess, then the carriers are in the most oxidized state. The aerobic stationary state (state 3) is characterized by an intermediate degree of reduction with a gradual increase in the degree of oxidation of the carriers in the direction from pyridine nucleotides to oxygen. An even higher degree of carrier recovery is observed in a controlled state (state 4), and the maximum degree of recovery of respiratory chain carriers is characteristic of state 5. Thus, the intensity of respiration and the degree of oxidation — reduction of vectors in a stationary state are extremely finely balanced and are a function of the concentration of substrates for respiration, ADP and oxygen [6].

However, as we will see below, in addition to these substances, ATP and Ph also play a role.

Chance and his collaborators attached the greatest importance to the concentration of ADP as the most important factor determining the respiration rate of both isolated mitochondria and intact cells [7]. A classic experiment is described in which Chance and Williams demonstrated the reaction of mitochondria to ADP. It turned out that the intensity of oxygen uptake by isolated mitochondria of the guinea pig liver in the presence of substrate and oxygen, but in the absence of ADP, is very low and is only 0.03 mmol 02 per 1 second. The addition of 390 mmol of ADP led to an immediate increase in respiratory intensity to 1.3 mmol 02 in 1 second, that is, approximately 43 times. Further, the intensity of respiration remains constant until there is a complete conversion of ADP into ATP; at this stage, there is a sharp decrease in the intensity of respiration to 0.02 mmol 02 in 1 second [8]. The quotient of the division of respiratory intensity in the presence of ADP (that is 1.3 mmol 02 in 1 sec) the respiratory rate in the absence of ADP (that is 0.03 mmol 02 in 1 second) is called the respiratory control coefficient or, more precisely, the coefficient of acceptor control; In this case, it is 43. "Strongly coupled" intact mitochondria are characterized by a very high coefficient of acceptor control [9]. "Labially conjugated" mitochondria, on the contrary, differ in a weakly pronounced dependence of respiratory intensity on ADP or the absence of such a dependence; in this case, the value of the coefficient of acceptor control is much lower and may approach unity [10].

Strongly conjugated mitochondria are characterized by a high coefficient of P: O, and for labile conjugated ones — usually low; however, this does not always happen; sometimes P: O can reach 3.0. Indeed, between the values of the coefficient of acceptor control and the coefficient of P:Oh, there is no simple quantitative ratio. It is interesting to note that a high coefficient of acceptor control is a stricter criterion for the integrity of the mitochondrial structure than a high coefficient of P : O.

One more conclusion can be drawn from Chance's experience mentioned above. During the period of intensive phosphorylating respiration (state 3), the oxygen concentration in the medium decreases by 56 mmol with the utilization of 390 mmol of ADP; therefore, the coefficient of ADP : O is 3.5. Since in strongly conjugated mitochondria, the coefficient of ADP : If O is quantitatively equal to the P : O coefficient, then the oxygen electrode turns out to be very convenient for measuring the P:O coefficient in intact mitochondria. However, the P : O coefficient of labially conjugated mitochondria and most submitochondrial systems cannot be determined based on changes in respiration with the addition of ADP.

Chance and Williams studied the sensitivity of the respiratory response of isolated mitochondria depending on the concentration of added ADP. Semi-maximal reactions can be caused by such a low concentration of ADP as 8 mmol. Therefore, at those concentrations of ADP that are common for the liver and kidneys, maximum respiration rate is possible. A low concentration of ADP in the muscle at rest can restrict breathing [11].

The respiratory stimulation of isolated mitochondria observed with the addition of ADP is more than 40 times consistent with those sharp fluctuations in respiratory intensity that are sometimes observed in intact tissues and depend on their functional activity. In support of their conclusion that the supply of ADP is the main factor in intracellular regulation of respiration, Chance and his collaborators conducted experiments to study the ratio between the amount of absorbed oxygen and the supply of ADP in intact cells and organs. They found that the cells of baker's yeast in a state of starvation are characterized by low respiratory intensity, which can be significantly increased by adding certain small amounts of ethyl alcohol. However, after that, the intensity of breathing decreases rapidly and ceases to increase even with the addition of such amounts of ethyl alcohol that are sufficient to further maintain breathing at a high level. Based on the spectroscopic study of the respiratory chain, it was concluded that the cessation of respiration in this case is associated with the use of ADP in the process of ethanol oxidation, i.e. there is a transition of the respiratory chain from state 3 to state 4. In these experiments, Chance discovered three crossing points in the respiratory chain of yeast cells, which are regulated by endogenous ADP, similar to how it occurs in isolated mitochondria [12]. Chance concluded that the P:O coefficient of intact yeast cells is approximately 3.0.

Chan also found that the respiration rate of a suspension of yeast cells in a state of starvation increases dramatically when small amounts of glucose are added to the medium [13]. After using the added glucose, the respiratory rate returned to the initial endogenous level. It was concluded that the addition of glucose to yeast cells causes the formation of equimolar amounts of ATP in the hexokinase reaction:

Glucose ATP -- Glucose-6-phosphate + ADP.

In this case, a certain amount of ADP is formed, which leads to an increase in the intensity of respiration, however, this increase lasts until all ADP is used in the process of oxidative phosphorylation [14]. Analytical data show that for each molecule of added glucose there is a certain increase in oxygen consumption; it was concluded that the coefficient of ADP: The size of an intact cell ranges from 2.0 to 3.0. These data can be interpreted in a different way, however, such experiments on yeast cells, as well as on cells of the Ehrlich ascite tumor, are consistent with the assumption that the concentration of ADP in a cell can determine the intensity of respiration and, moreover, that the coefficient P:O of oxidative phosphorylation in these cells is high. Apparently, mitochondria in an intact cell can only respond to the blood pressure that is available to them, and do not respond to bound or spatially inaccessible ADP [15].

Chance and his collaborators also studied the role of ADP concentration in regulating the intensity of respiration in intact muscles at rest and during contraction. It is well known that the respiratory intensity of the skeletal muscle of a mammal can increase by 100 times, and the respiratory intensity of the flying muscle of an insect can increase by 1000 times during the transition from rest to active activity [16]. Although it is still difficult to interpret some of the data obtained on muscles, they are consistent with the assumption that a sharp increase in the intensity of respiration of some muscle types during contraction may be associated with an increase in the concentration of available ADP as a result of ATP breakdown; in some muscle types, this effect may be masked by rapid ATP regeneration due to creatine phosphate, and not in the process of oxidative phosphorylation.

The respiration rate of intact cells may depend on secretory activity also as a result of changes in the concentration of ADP. Whittam, for example, showed that respiration of renal tissue, which under normal conditions participates in ATP-dependent active transfer processes, can be suppressed by ouabain, a specific inhibitor of active transfer of Na+ and K+ and an inhibitor of Na+ and K+-dependent renal ATP-ase, which is responsible for the transfer of these ions. It can be assumed that the suppression of ATP utilization by ouabain during active transfer reduces the formation of ATP, which results in a decrease in respiratory intensity.

All these data on the regulation of respiration by adenosine diphosphate confirm Mitchell's concept that respiration and the functions associated with ATP consumption are finely coordinated; he suggested that the

endergonic reactions of ADP formation — active transfer and biosynthesis — regulate respiration through the ADP they form [17].

Research by the Klingenberg and Chance laboratories has shown that ATP concentration may also be a factor regulating the rate of respiration in tightly coupled mitochondria. It has been shown that mitochondrial NAD can be restored due to succinate and that this reaction depends on energy, the source of which in some conditions is ATP [18]. It is generally assumed that this reaction is the result of the reversal of the electron transfer associated with phosphorylation in the NAD — cytochrome B segment.

Further, Chance and Klingenberg showed that the reducing agent of NAD can be not only succinate, but also reduced cytochrome C. Indeed, Klingenberg and Schollmeyer found that the entire respiratory chain goes into a more restored state when ATP is added in the absence of ADP and Fn. Oxaloacetate, a relatively electropositive electron acceptor from mitochondrial NAD•H2, enhances this effect of ATP. They showed that the oxidation—reduction state of mitochondrial cytochrome c is a function of the [ATP]/[ADF] • [Fn]. Based on these data, Klingenberg and Schollmeyer were able to calculate the value of AO for the hydrolysis of the macroergic precursor of ATP, which turned out to be equal to 12 kcal/mol.The rate of succinate oxidation decreases with the addition of ATP. The addition of Fa and ADP leads to accelerated breathing.

Based on these important facts, which have shown that the oxidation—reduction state of the respiratory chain is a very sensitive function of the [ATP]/[ADP] • [Fn], i.e. the so-called phosphate potential, Klingenberg and Schollmeyer found that ATP suppresses respiration of strongly conjugated mitochondria. With a high coefficient of [ATP]/[ADF] • [Fn] this suppression is maximal [19].

Based on these data, it can be concluded that the mitochondrial respiration rate is regulated not only by ADP alone, as originally postulated by Chance and Williams, but also by ATP and Fnl. Data on the concentration of ATP, ADP and Ph in intact cells confirm the view that all three substances are involved in the regulation of respiration of intact cells. Finally, it is interesting to note that the suppression of respiration by adenosine triphosphate is probably the most sensitive of the known criteria for the integrity of the mitochondrial structure [20].

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