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Review Article

Modern Ideas About the Role of Apt in the Act of Muscle Contraction

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Abstract

Muscle contraction is one of the fundamental manifestations of the vital activity of living organisms and has been the object of close attention of physiologists, biochemists and biophysicists for many decades. The central place in the study of the mechanism of muscular activity is occupied by the problem of converting chemical energy into mechanical work, as well as clarifying the role of macroergic compounds, primarily adenosine triphosphate (ATP), in this process. Classical concepts associate the act of contraction with the hydrolysis of ATP and the subsequent interaction of contractile proteins, actin and myosin; however, the accumulation of experimental data has led to the emergence of alternative views questioning the direct and unambiguous relationship between the breakdown of ATP and the development of muscle contraction.

Kew Words: modern ideas; atp; of muscle contraction

Introduction

Of particular interest are studies indicating the possibility of muscle fiber contraction without a noticeable decrease in the concentration of ATP and phosphocreatine, as well as studies demonstrating the involvement of other nucleoside triphosphates in the contractile process. These data necessitated the revision of a number of well-established concepts and contributed to the formation of new ideas about the molecular mechanisms of muscle activity, including ideas about the phases of the contractile cycle, the role of high-energy actomyosin bonds, and the regulatory significance of relaxation factors. The present work is devoted to the analysis of experimental and theoretical data on the role of ATP in the act of muscle contraction, as well as to the discussion of modern ideas about the mechanochemical and thermodynamic aspects of muscular activity. Investigation Of the Role of Atp in the Act of Muscle Contraction Recently, several attempts have been made to revise existing ideas regarding the role of ATP in the mechanism of muscle contraction; some authors even found it possible to predict the beginning of a revolution in the field of muscle biochemistry, similar to the one that occurred after the publication of Lundsgard's work in 1930, which overturned the then-seemingly unshakable theory of muscle activity by Meyerhof—Hill. The following facts served as the basis for such statements: there were a number of reports about the possibility of reducing muscle fibers without splitting ATP. The last author investigated shifts in the content of ATP and phosphocreatine during a single contraction and subsequent

relaxation of a muscle fiber. At the same time, a technique was applied that allows for the decomposition of minimal amounts of ATP (about 0.05—0.025 d).M per gram of tissue), as well as the formation of equivalent amounts of adenosine diphosphoric and adenylic acids. In addition, the breakdown of phosphocreatine was also taken into account. However, Mommerts failed to detect a noticeable breakdown of adenosine triphosphate and phosphocreatine and a corresponding increase in the concentration of adenosine diphosphoric and adenylic acids during a single contraction of muscle fiber. [4]

Similar conclusions had been reached somewhat earlier by Fleckenstein, Janke, Lechner, and Bauer, working with an isolated M. recti frog. According to these authors, the average ATP content per gram of fresh tissue (the method of quantitative chromatography of phosphorus fractions on paper was used) was 2.82 micromoles in the reduced m. recti at 0°; the ADP content in the contracted muscle was 0.71 micromoles per gram of tissue, respectively. Almost the same figures were obtained when determining the content of ATP and ADP in resting muscle. The ATP/ADP ratio (molar ratio) in the contracted muscle also almost did not differ from that in the resting muscle (4.29 in the first case and 4.27 in the second). [1]

It was not possible to detect changes in the content of ATP and ADP during rapid tetanic contraction of m. recti compared with resting muscle and at 20

°. Thus, the average ATP content in 12 contracted and 12 resting muscles was the same in both cases (about 2.77 micromoles per 1 g of tissue); the ADP content was expressed in figures of 0.87 cM/g of tissue and 0.91 cm/g of tissue, respectively. Based on these data, Fleckenstein et al. concludes that tetanic contraction can occur independently of the breakdown of ATP and creatine phosphate in muscle fiber. According to these authors, it is only with prolonged tetanus at 20 °C that noticeable cleavage of creatine phosphate can be detected within 1-2 seconds after the onset of irritation. The authors suggest that the energy of creatine phosphate breakdown in muscle fibers is used, as well as during the operation of the electrical organs of fish, only to charge discharged cell membranes. It should be noted, however, that all of the above data are in some contradiction with the results of the work of Manch-Petersen, who had previously discovered a noticeable formation of ADP during the contraction of the turtle muscle, which corresponded, according to her calculations, to the amount of decomposed adenosine triphosphate and the heat released. Lange, working with frog muscles, also observed the breakdown of ATP during the contraction phase with the formation of ADP and the subsequent decrease in creatine phosphate concentration. [6]

The contradictory conclusions drawn by various researchers who have worked on this issue are probably explained by the methodological difficulties encountered in carrying out this kind of work, and makes us consider their final assessment somewhat premature. However, there is no doubt that the resynthesis of ATP in the muscle occurs normally, in accordance with the previously available data, at an extremely high rate. It should also be emphasized that the observations of Fleckenstein et al. and Mommerts can probably be explained to some extent in the light of new data, which definitely suggests that the cleavage of ATP by actomyosin, accompanied by the reduction of this protein, is not a reaction quite specific to ATP, as previously assumed. As it turned out, actomyosin gels are capable of cleaving not only ATP, but also other purine ribose triphosphates, for example, inosine triphosphate (ITP) and guanosine triphosphate (GTP), and even pyrimidine ribose triphosphates such as uridine triphosphate (UTP) and cytidine triphosphate (CTP) (Spicer and Bowen, 1951; Bergquist and Deutsch, 1954; Blum, 1955). The cleavage of ITP, UTP, and CTF, as well as the cleavage of ATP, is accompanied by a reduction in actomyosin gels (Bergquist and Deutsch; Blum; Ranni; Portzel). According to Hasselbach, acetyl—ATP and GTP cause the same effect. [11]

The presence of small amounts of CTF, UTF, and GTF in living muscles has recently been shown by Bergquist and Deutsch, McLaughlin, Shifman, and St. Gyorgy. Thus, ATP may not be the only macro-ergome capable of interacting with contractile muscle protein in a living muscle. The latter assumption is confirmed, in particular, by the works of Fleckenstein, Janke, Davis and Krebs (Fleckenstein, Janke, Davies and Krebs), who found that under certain conditions muscle contraction, although not accompanied by a decrease in the concentration of ATP and phosphocreatine in it, is at the same time associated with a noticeable increase in the content of inorganic phosphate, apparently due to the decomposition of a phosphorous compound unidentified by the authors. [2]

It may also be recalled here that according to Berg and Joklik, an enzyme that catalyzes the lerephosphorylation reaction between ATP and UTP can be isolated from muscle tissue. All this suggests that at present, apparently, there are no sufficiently serious grounds for revising existing views on the role of ATP (or macroerges close to ATP - purine ribose— or pyrimidine ribose triphosphates) in biphasic muscle activity. At least, the idea of the need for ATP to participate in the contractile process is fully preserved. The

possibility of contraction of macerated muscle fiber in vitro under the influence of ATP, UTF, and ITF, which proceeds anisodimentally and in many respects is similar to the contraction of living muscle, is irrefutable evidence of the existence of a close relationship between the act of muscle contraction and the interaction of contractile muscle protein with energy-rich phosphorous compounds. [5]

Reduction can only occur under certain conditions. Webberformulates these conditions, based on the work of both his school and the St. Gyorgy school, as follows: first of all, it is necessary that the pH of the medium remains within the physiological limits (between 6.5 and 8.0); the ionic strength of the solution should be about 0.15; Mg ions should be present in the solution; ATP, or other nucleoside triphosphates (NTPs), should be cleaved by actomyosin at a sufficient rate (>0.02 [x M per mg protein per minute). It goes without saying that ATP cleavage should occur under the action of actomyosin atpase, but not other phosphatases. The rate of cleavage of nucleoside triphosphates and the maximum stress developed during contraction varies among ATP analogues, according to Weber, as follows: ATP ~ acetyl — ATP~ATP > ITF > UTF > GTP, where CTP is cytidine triphosphate, ITP is inosine triphosphate, UTP is uridine triphosphate, GTP is guanosine triphosphate. [13] The data presented in the review article by Weber are also of interest, which indicates that the maximum tension (in kg/cm2) developed by contraction of various types of muscles corresponds to the tension generated by pr and shortening of the washed muscle fibers isolated from these muscles when exposed to ATP Thus, the idea of the reaction between actomyosin and ATP as the process underlying the phenomenon of muscle fiber contraction is convincingly confirmed in vivo. So, we will consider it proven that muscle fiber contraction occurs as a result of its interaction with ATP or some other purine or pyrimidine analogues of adenosine triphosphate containing macroergic phosphate bonds. At the same time, however, there is no doubt that events are brewing in muscle biochemistry and facts are accumulating, which may lead to a revision of some of the ideas that previously occupied the position of the cornerstone in the doctrine of muscle mechanochemistry. First of all, the idea of the ATPASE activity of myosin is under fire, as an inherent property of a contractile protein that determines the possibility of converting chemical energy in a muscle into mechanical work. [3]

Apparently, indeed, the ATP hydrolysis reaction catalyzed by myosin is only closely related to some other processes that directly supply the muscle with the energy needed for contraction, but it cannot be considered as a reaction that directly delivers energy to the contractile mechanism of the cell. The position that the energy released during the hydrolysis of ATP to form ADP and H3PO4 in the form of heat cannot be used in muscle for mechanical purposes is quite obvious, since living organisms do not work according to the principle of a heat engine. Consequently, during the utilization of energy accumulated in ATP during muscular activity, there must be some other more complex mechanism of interaction of ATP with the contractile protein. If we take this point of view, then the possibility of a single contraction of a muscle fiber without splitting into ADP and H3P04 during the reduction of ATP will no longer seem absolutely incredible. This possibility is indicated not only by the data of direct experiments, in which it was not possible to show a noticeable cleavage of ATP during single reduction (or relaxation) to form inorganic phosphate (see above), but also by many indirect considerations and observations (see Bowen and Martin). For example, there are reports of various effects of increased concentrations of CS1 on the degree of shortening of "glycerol" muscle fibers and the rate of dephosphorylation of ATP by them (Bowen; Morales and Bothe), Bowen and Kerwin). [1]

Particularly interesting data has been obtained recently by Chance and his collaborators (Chance and; see also Chance and Blachevsky; Chance and Williams; Chance and Connelly). Chance has developed a very precise spectrophotometric and fluorometric technique for examining living muscle fiber during its contraction. The principle of this method is based on a sharp increase in oxidative processes during the formation of ADP in the cell (as a result of the breakdown of ATP). An increase in the concentration of ADP in the tissue causes the oxidation of the corresponding amount of the reduced form of codehydrase (pyridine nucleotide). The last change is immediately detected using appropriate optical instruments that detect changes in the nature of fluorescence or absorption spectra. The measurements carried out by Chance and his collaborators did not allow us to detect the formation of ADP in amounts equivalent to the amount of work performed during single contractions of muscle fibers. [16] In these methodically advanced studies, it seems that only calculations aimed at showing the impossibility of sufficiently rapid ATP resynthesis with a single reduction need to be verified and confirmed. However, at present, the attention of many researchers is focused on the question of how the energy accumulated in the phosphate bonds of ATP is used during the work of muscles or the rhythmic contraction of various cellular organs of movement. Modern biochemistry and biophysics have already come close to studying at the molecular level the changes that the contractile protein system undergoes during muscle contraction. [4]

It has also already been mentioned that the data of electron microscopic examination allow us to consider it very likely that the interaction of ATP with the actomyosin system leads to a completely peculiar reaction — the penetration of the actin filamentous system into the myosin filamentous system. This type of chemical reactions, which are still almost unexpl ored, can obviously occur only between high-molecular compounds of a fibrous structure. This peculiar "sliding" of actin filaments along myosin filaments, which begins after exposure to the contractile system of ATP, accompanied by mechanical work, is apparently associated with the transformation of highly energetic bonds between actin and myosin into ordinary energy-poor bonds. According to Weber, highly ergic bonds between actin and myosin filaments are formed due to macroergic ATP bonds at the beginning of the working cycle

How can one imagine the mechanism of movement of actin filaments along myosin filaments in the presence of ATP? **Weber attempts to explain this phenomenon in the following way:** It is assumed that the reaction chain begins with the attachment of either ADP or H_3PO_4 to certain chemical groups of acting as a result of its interaction with ATP:

1) actin + ATP → actin~PO_3H_2 + ADP or 2) actin + ATP → actin~ADP + H_3PO_4.

This reaction is similar to the one initiating, for example, the first steps of fatty acid synthesis during the interaction of acetate with ATP: ATP + acetate → AMP~acetate + PP_i (pyrophosphate).

It is then assumed that the fragment of ATP (ADP or PO_3H_2) in the complex with actin is replaced by the corresponding functional group of myosin:

P—actin + myosin → actin—myosin + P, where **P** is ADP or H_3PO_4.

During this process, inorganic phosphate (or ADP) is released, and a high-energy bond between actin and myosin is formed. A similar reaction occurs during fatty acid synthesis:

acetyl–AMP + CoA → acetyl–CoA + AMP. After the formation of the high-energy actin–myosin compound, the following reaction begins automatically: actin~myosin → actin—myosin → actin—myo— … → actin—myosin, that is, in other words, the actin chain begins to move sequentially from the first functional group of myosin to the second, third, and possibly to the fourth. It is assumed that the various functional groups of myosin filaments reacting with actin are arranged linearly. This leads to the fact that actin micelles begin to move along the myosin filaments during the reaction. [5]

It can be assumed, by analogy with the formation of acyl coenzymes A during the interaction of acyl pyrophosphates with HS — CoA, that the highly energetic bond between actin and myosin is formed due to one of the sulfhydryl groups (the first) of myosin. As for the mechanism of action micelles sliding or moving along the myosin chain, from one of its functional groupings to another, prototypes of such reactions are also apparently known. Something similar happens, for example, during the oxidative decarboxylation of pyruvic acid in some microorganisms, eventually forming acetyl coenzyme A In the theory of muscle contraction under consideration, the most important position is that the cleavage of ATP leads to the activation of functional groups of the contractile system and the formation of a highly ergic bond between actin and myosin. [9]

As a result of the movement of actin micelles along the myosin filaments, mechanical work is performed, the free energy of the system decreases and, consequently, the highly energetic bonds between myosin and actin formed at the beginning of the cycle turn into ordinary and, moreover, easily dissociating bonds at the end of the contractile process.

As mentioned above, the mechanism of activation of the ATP contractile protein can be imagined in two ways:

1) ATP + protein ^± protein ~ P + ADP and

2) ATP + protein ^zt protein ~ ADP + F

Using the isotope indication method, it turned out to be possible to find out which of these two mechanisms of actin activation actually takes place. It is easy to see that if equation 1 is correct, then when labeled ADP32 is added to the actin solution in the presence of ATP, a certain amount of labeled ATP (ATP32) should be formed, since the reaction proceeds both from left to right and from right to left. In the experiments of Ulbrecht and Ulbrecht, it was found that the formation of ATP32 from ADP32 due to myokinase and phosphocreatin-phosphokinase action did not exceed 5-10% of the total amount of exchanged F32. Nevertheless, it is impossible not to pay attention to the need for the strictest control during the conduct and interpretation of such experiments. [6]

The fact that the first phase of activation of the actomyosin system is the activation of actin, rather than myosin, follows from experiments on the exchange of ADP32 in myofibrils, from which myosin was previously extracted, but in which actin was preserved. Such myosin-free fibrils continue to form ATP32 from ADP32 at almost the same rate as fibrils that have not undergone extraction. Nevertheless, one cannot ignore the well-known fragility of this argument, since other protein substances that are not identical to actin remain in myofibrils after myosin extraction. Purified myosin (L-myosin of Weber), although it cleaves ATP, does not induce phosphate exchange reactions between ADPP2 and ATP. However, purified actin preparations do not induce this reaction either. Moreover, preparations of "artificial" actomyosin are also deprived of this ability. Thus, further research is required to solve the question of the actual mechanism of ATP-actomyosin interaction with the formation of a highly ergic form of contractile protein. [2]

In the new concepts, the position is particularly important, according to which the meaning of the interaction of ATP with muscle protein is reduced to the formation of "excitations" or a "highly energetic" form of actomyosin, capable of spontaneous contraction. From this point of view, actomyosin is charged with energy due to ATP, however, not in the phase of relaxation, which is possible without any input of energy from the outside, but at the moment of muscle activation before contraction, i.e. during its transition from an unexcited (inelastic) state to an excited state, in which the muscle acquires the ability to to spontaneous contraction. Let us recall here that such an idea was developed earlier by one of us (see Ivanov). Szent-Gyorgyi develops slightly different ideas about the mechanism of myosin-actin interaction at the molecular level. The reader can get acquainted with the views of this author through his original works and widely known monographs (see the list of references). [10]

Let us now turn to the question, what is currently known about the mechanism of muscle relaxation after contraction? Since it has been known since the first publications of St. Gyorgy and his school that ATP causes only a contraction of macerated muscle fiber or actomyosin filaments, which remain in a shortened state even after washing ATP, the idea arose that special conditions are required for relaxation of muscle fiber and, in particular, the presence of the so-called "relaxation factor". missing from the washed fibers. This notion seemed to be seriously confirmed in the works of Marsh and Bendall. The latter author was able to show that a muscle fiber contracted under the influence of ATP under stress enters a relaxed state and stretches to its original resting length (or even slightly longer) when a freshly obtained muscle extract containing a special factor, usually called the Marsh—Bendall factor, is introduced into the system. This factor is also called the relaxation factor. However, it should be emphasized right away that there did not seem to be sufficient grounds to call him that. [7]

In fact, the Marsh—Bendall factor only modifies (usually reduces) Atpase activity of actomyosin. Since the decrease in the ATP-aze activity of actomyosin by the Marsh—Bendall factor is not accompanied by the disappearance of the plasticizing or softening effect of ATP on living muscle, this factor can also be called a softening or plasticizing factor. In its presence, the contraction of muscle fiber under the influence of ATP becomes impossible, but the muscle does not lose its elasticity. Let us recall here that in the absence of ATP in a muscle or with a sharp decrease in ATP concentration, the muscle becomes rigid, as is observed, for example, with rigor mortis The mechanism of muscle fiber relaxation after the contractile act that has occurred under the influence of ATP should, apparently, be considered as part of a single two-phase work cycle. Indeed, a number of authors (Ranni; Bendall; I. I. Ivanov and G. P. Pinaev) found that the contraction of striated muscle fiber extracted with 50% glycerin when added to an ATP solution can, under certain experimental conditions, take on the character of an extremely delayed tetanic contraction.. The fiber initially contracts by lifting the load, but then in the same solution it loses its contractile force and returns to its original resting length under the influence of gravity of the load. In some cases, relaxation may be followed by a new, weaker contraction. [5]

The described phenomenon may be a kind of model of tetanic contraction of living striated muscle fiber and, in any case, suggests that relaxation of the muscle fiber or, more precisely, a decrease in its contractile force occurs quite naturally and automatically after the contraction occurs, regardless of and not as a result of changes in the concentration of any substances in the environment (ATP, the "relaxation" factor, salt ions, etc.). The inability to observe a long series of alternating contractions and relaxes of macerated

muscle fiber under load in a solution of ATP, CO and MgCb undoubtedly depends on the onset of purely mechanical damage to the fiber with each of its stretching (see I. I. Ivanov). In an incomparably clearer form, the possibility of automatic two-phase activity of cellular organelles of movement in the presence of ATP can be observed on various glycerol cell models prepared according to Hoffmann-Berling (cell corpses of spermatozoa, ciliated epithelium, trypanosis, etc.). In these cases, alternating flexion and extension of the organelle of movement occurs with the usual for this type of cell This process continues as long as a known excess of ATP remains in the solution. [13]

All these facts irrefutably indicate that the relaxation of the organelle of motion is a passive process that occurs under the influence of elastic forces developed by an antagonistically acting extensor. The presence of such elastic extensors in a wide variety of cell movement organelles has been established by a number of authors. However, it is not difficult to see what a rapid return to the initial state (resting state) of an organelle of movement or a contracted muscle fiber is under the influence of an external force (elastic extensor, gravity of the load, tension of antagonist muscles, elastic pressure of certain structures of the muscle fiber stretched during contraction, for example, Z discs, etc. d.) it is possible only if the following conditions are met:: 1) the force developing during contraction should decrease sharply and, moreover, abruptly at the moment of complete contraction, and 2) the ability to contract with the same force should be sharply and suddenly abruptly restored after relaxation of the contractile organelle to the resting length. Indeed, if we assume that the force of contraction decreases gradually as the organelle of movement shortens, then at a certain point in time a state of equilibrium must inevitably be established between the force under the influence of which the organelle contracts and the force of elastic traction of the extensor antagonist (or the gravity of the load, if it is a question of muscle fiber contraction). Obviously, the periodic two-phase activity of the organelle will be impossible in this case. Let us recall here that this idea was developed by I. I. Ivanov, in a report at the IX All-Union Congress of Physiologists, Biochemists and Pharmacologists. [17]

What is the probable specific mechanism of the automatic abrupt change in the contractile force of the organelle of motion during the various phases of the contractile process? Currently, this kind of question can only be answered by stepping onto the shaky ground of scientific speculation. One can, for example, proceed from the theory of muscle contraction, formulated in general terms by Weber. According to this theory, for a pulling force to occur in a muscle fiber, two processes must occur: first, the attachment of ATP to actin and, secondly, the formation of a macroergic bond between actin and myosin. Both of these processes obviously take place over time. Since the formation of the highly ergic actin—myosin complex, a highly peculiar chain process occurs quite automatically, which is the direct cause of the contraction. As a result of actin filaments sliding along the myosin filaments, mechanical work is performed, and in the process of contraction, the actin-myosin complex passes through a number of energy levels several times, starting from the highest, when the actomyosin complex is connected through a macroergic bond, and ending with a state in which actin and myosin are held by bonds, the formation of which takes much less time. the amount of energy. Thus, the actomyosin complex is significantly less efficient at the end of the contractile process than at the beginning of the working cycle. [8]

It can also be said that by the end of the contraction, the pulling (or lifting) force of the fiber automatically decreases. Thus, after the onset of fiber

contraction, i.e., after the abrupt transition of the actin complex to a low energy level, it becomes quite possible to extract the actin filamentous system from the myosin filamentous system under the influence of the pulling force of elastic extensors or the weight of a load suspended from the muscle. From the moment the resting length is reached, when the system of actin filaments takes its initial position in relation to the system of myosin filaments, conditions are also automatically created for a new activation of actin due to its interaction with ATP, the re-formation of a highly energetic form of actomyosin and, consequently, the repetition of the entire contractile cycle. [20]

It seems to us that the following two positions follow from these ideas: first, we must assume that the tetanic contraction of a muscle fiber is a completely natural and natural reaction of the fiber to its interaction with a certain portion of ATP. Apparently, with each irritation of a muscle, such an amount of ATP is released from the nerve or acquires the ability to react with actomyosin, which can cause a whole series of twitches. The duration of tetanus should therefore depend on the amount of ATP mobilized by the nerve impulse. From the developed point of view, the difference between the mechanism of tetanic and tonic contraction is quite understandable. The latter type of contraction, as has been repeatedly noted, differs from tetanus in that due to the increased viscosity of the proteins that make up the smooth muscle myofibrils, the contractile process develops at an extremely slow pace. The process of relaxation of smooth muscles proceeds even more slowly, which occurs under the influence of external and internal forces striving to return the muscle to the resting length. With sufficient viscosity of the "easily soluble" myofibril proteins bound into a single functional complex with actomyosin, smooth muscle relaxation can be so prolonged over time that it will practically be equivalent to the development of a locking function. It is also obvious that in the phase of tonic resistance to stretching after contraction (in a state of blocking action), as well as in the phase of slow relaxation (more precisely, stretching), the contractile protein — actomyosin — is at a low energy level. [5]

The second important point that follows from the considered theory is that actomyosin can exist in two forms: as a complex containing highly ergic bonds, and as a complex without macroergic bonds. In the first modification, actomyosin is in a state of contraction (isotonic or isometric), and it passes into the second one after contraction. By the way, a similar formulation was expressed a few years ago by I. I. Ivanov (see also Tonomura, Matsumiya, Kitagawa and Morita). The third position, essentially developed in the new theory of muscle contraction, boils down to the denial of the leading role in the contractile act of the enzymatic (ATP-aze) activity of myosin. Indeed, as we have seen, the formation of a highly energetic form of actomyosin, capable of performing mechanical work, is associated with the interaction of ATP not with myosin, but with actin. It can be noted here that the same idea, although in a slightly different form, was developed back in 1950 by Straub and Feuer. According to recent authors, the breakdown of ATP under the influence of adenosine triphosphatase (myosin), contrary to existing ideas, cannot have a direct relationship to the change in the mechano-elastic properties of the muscle during its contraction. The reader can learn more about Straub's views on this issue from the original work of these authors (see also the review article by I. I. Ivanov in the yearbook "Successes of Biological Chemistry", vol. I). [9]

Nevertheless, it should be noted that the developed concept obviously does not cover the whole problem, since the biological role and significance of the adenosine triphosphatase activity of the myosin component of the contractile system remains unexplained. This remark applies fully to the theory of

muscle contraction by Weber. Indeed, according to Weber's theory, the processes occurring during muscle contraction can be represented by the following two balance equations: actin + myosin + ATP —> actin ~ myosin+ADP + H3P04 and actin~ myosin —> actin + myosin + work. Based on the experimental data presented above, Weber assumes that the process begins with the formation of a highly energetic form of actin. As for the ATPASE activity of myosin, it does not appear at all in all subsequent discussions. However, it would hardly be correct to ignore the presence of ATP-aze activity in myosin when constructing any theory of muscle contraction. The need to preserve the ATP-aze activity of myosin for the formation of an active complex of myosin with actin has been repeatedly noted. It was also pointed out above that, according to Weber's own data, actomyosin possesses contractile properties only if its ATPASE activity is sufficiently pronounced. [10]

The Role of The March Relaxation Factor in Muscle Activity Let's now return to the question, what is the role of the Marsh—Bendall factor in muscle activity in the light of all currently available data? If we assume that there is a certain relationship between the amount of ATPASE activity of actomyosin and its ability to "charge" with energy due to the breakdown of ATP, then the function of the Marsh-Bendall factor can be associated with its regulation of both the enzymatic (ATPASE) activity of actomyosin and the ability of actomyosin to convert into its active form under the influence of ATP. Apparently, this factor only contributes to the creation of optimal conditions for the two-phase activity of the muscle fiber or cellular organelle of movement. In the absence of factor M-B (or when it is inactivated by Ca ions), the muscle fiber or organelle of movement (flagellum, cilia, etc.) contract vigorously and as much as possible. However, subsequent relaxation does not occur in this case, since the fiber retains high ATP-aze activity and the ability to interact with ATP to form an active "elastic" form of actomyosin. At the same time, the contractile protein apparently remains at one of the energy levels, at which it can still resist the forces that seek to return the contracted fiber or organelle of movement to its original resting state[19]

On the contrary, with an excessively high concentration of factor M-B, the ATP-aze activity (and, possibly, the ability to form a highly ergic form of actomyosin) of the contractile organelle or muscle fiber is already so reduced at the beginning of the contractile cycle that the tension developed due to interaction with ATP cannot overcome the resistance of the antagonist extensors (or the load applied to the muscle); contractions in this case do not occur at all. From all that has been said, it follows that the two—phase activity of organs and organelles of movement, carried out by the energy of cleavage of nucleoside triphosphates, is possible only under certain conditions: sufficient adenosine triphosphatase activity of contractile protein and sufficiently high, but not excessive elasticity of antagonists, extensors or other cellular structures performing the same function. In turn, the ATP-aze activity of the contractile protein is regulated by the Marsh—Bendall factor, the activity of which can change almost instantly over a wide range upon binding or release of Mg and, especially, Ca ions in the muscle fiber. [11]

The most important point here is the position according to which, at a certain ratio between the amount of ATPASE activity of actomyosin (which depends on a number of conditions- the concentration of factor M—B, Ca ions, etc.) and the force opposing the contraction of the fiber (or organelle of movement), rhythmic activity begins due to an automatic abrupt decrease with a reduction in pulling force contractile protein. It is very likely that this change in the pulling force of the contractile protein at different stages of the

contractile cycle is associated with an abrupt change in its ATP-aze activity (I. I. Ivanov and G. P. Pinaev).

This is, apparently, in general terms, the mechanism of autoregulation of the most complex process of two-phase contractile activity of various organs and organelles of movement.

Here you can also recall that Hasselbach and Weber develop similar ideas about the mechanism of action of the M-B factor. In their opinion, the effect of factor M-B is reduced to a kind of sensitization of actomyosin in relation to ATP and magnesium ions: concentrations of ATP, which in the absence of the factor cause a contraction of the washed muscle fiber in the presence of the factor are already "overoptimal". As a result, there is an inhibition of the ATPASE activity of actomyosin and the ability of the muscle fiber to contract. However, the mechanism of this "sensitizing" effect of factor M-B on muscle fiber remains unclear. [7]

Recent research by Portzel (cited by Weber) has shown that factor M-B is associated with muscle granules. This position is clearly demonstrated by the following diagrams.

As already mentioned, one of the most interesting features of the M-B factor is its ability to change its activity in the presence of Mg and Ca ions. Mg ions activate the M-B factor, Ca ions have a sharply depressing effect on its activity. In other words, in the presence of Ca ions, the inhibitory effect of factor M-B on ATP is . the azular activity of myosin is not manifested.

But what is the M-B factor in chemical terms? It must be admitted that quite numerous studies aimed at clarifying its nature have not yet fully clarified this issue.

Bendall identified this factor with myokinase. However, the mechanism of the relaxing effect of myokinase on washed muscle fiber under stress in the presence of ATP was not sufficiently satisfactorily explained by him. [3]

On the other hand, Gudall and St. Gyorgy, Lorand), and St. Gyorgy believed that the enzyme system contained in muscle extracts, consisting of creatine phosphokinase (ATP-creatine phosphorase), phosphocreatin, and Mg, causes a relaxing effect at pH 6. 2.. This system not only leads to relaxation of muscle fibers contracted under the influence of ATP, but also promotes the "dissolution" of superprecipitated actomyosin in the presence of adenzine triphosphate.

Recently, Lorand and Moose (see also Goodall) obtained data indicating the possibility of relaxation of contracted washed muscle fibers when exposed to enolphosphopyruvic acid at pH 7.0 in the presence of a corresponding phosphoperase strongly bound to the protein structures of the fiber.

Comparing all these facts, one could conclude that the mechanism of action of factor M-B is played by the refosphorylation of adenosine diphosphate associated with certain functional groups of the actomyosin molecule. This refosphorylation of ADP into ATP can be achieved in various ways. The transformation of the bound form of ADP into the bound form of ATP causes the disappearance of the rigidity of the fiber, which leads to its relaxation, provided that the ATP-aze activity of actomyosin, which is part of the fiber, is suppressed. However, much remains completely unclear in this picture.

Recently, Kumagai, Eboshi, and Takeda showed that relaxation of washed muscle fibers contracted under the influence of ATP, which were preserved for a long time under certain conditions, can be observed only with the addition of freshly prepared muscle extract, but not purified phosphokinase system or myokinase preparations.

If this is the case, then it is quite likely that the factor causing the relaxation of myofibrils is only present in insufficiently purified preparations of phosphokinase and myokinase, but is not identical in chemical nature to these enzymes. [12]

Portzel published a paper that completely denied the identity of factor M-B to the phosphoperase system. This author has convincingly shown that phosphocreatine in the presence of creatine phosphokinase causes relaxation of muscle models that have contracted under the influence of ATP only if the concentration of ATP inside muscle fibers reaches superoptimal values as a result of enzymatic ATP resynthesis. If sufficiently thin muscle fibrils (with a radius of about 1 cm) are used for the experiment, then such fibrils contract under the influence of ATP equally well both in the absence and in the presence of the phosphocreatin-creatine phosphokinase system.

On the contrary, the ability of such fibrils to break down ATP and contract in the presence of ATP immediately disappears completely when the March relaxation factor isolated from the muscles is added in active form.

This makes it improbable to assume that the relaxation factor is identical to the phosphocreatin-creatine phosphokinase system and obviously other similar refosphorylating ADP systems.

Thus, the question of the mechanism of action of factor M-B and its chemical nature (i.e. belonging to a particular group of protein substances) It's still waiting for its final decision. [9]

Some Data on The Mechanochemistry and Thermodynamics of Muscular Activity The question of the mechanism of converting energy released during biochemical reactions into the mechanical work of muscle contraction has long attracted the attention of a wide range of specialists. Prior to the publication in 1939-1945 of widely known studies by the Soviet and Hungarian schools of biochemistry, sudden contraction of muscle fiber upon nerve irritation was usually associated with changes in surface tension in certain areas of the cell membrane, periodic changes in osmotic pressure, rapid swelling and swelling of plasma colloids due to recharging of protein particles, etc. [13]

Moreover, in almost all cases, the formation of acid- or alkali-reacting metabolic products (for example, lactic acid, H_3PO_4, ammonia, etc.) was considered the root cause of the onset of colloidal chemical changes in plasma proteins. All these ideas, at least in their original formulation, should now be considered too primitive. In the light of modern data on the mechanism of contraction of fibrillar contractile proteins of muscles and motile cells, the phenomenon of contractility of myofibrils and other cellular organelles of movement cannot be reduced to the simplest physico-chemical processes mentioned above. After publication, starting in 1939. a number of works by V. A. Engelhardt and M. N. It has become clear from Lyubimova, St. Gyorgy, Straub, Weber, and Hoffman-Berling that the contractility of the most diverse organelles of motion is due to the presence in them of special contractile proteins (or, more precisely, a system of two proteins) capable of changing their physical state as a result of chemical interaction with energy-rich compounds such as adenosine triphosphate. Contractile proteins, as it turned out, are at the same time enzymes capable of cleaving ATP and a number of its shurin and pyrimidine analogues with the cleavage of H_3PO_4 and the release of a large amount of energy. [11]

This discovery marked the beginning of a new direction in biochemistry, which V. A. Engelhardt proposed to call muscle mechanochemistry. However, until recently, the highly important question remained unclear whether the energy released by the breakdown of ATP is consumed in the

phase of muscle contraction or in the phase of relaxation. Let's look at this issue in more detail. Theoretically speaking, the mechanism of ATP interaction with the muscle contractile protein (actomyosin) could be imagined in two ways.

1) ATP attaches to actomyosin micelles, which in an unexcited muscle are in a stretched state (compared to their natural length). The addition of ATP somehow neutralizes the forces holding the actomyosin micelles in this state, resulting in their contraction (just as any rubber-like stretched body contracts after eliminating the cause that prevents it from shortening). From this point of view, adenosine triphosphate should not be cleaved during the muscle contraction phase, since contraction is a spontaneous process associated with a decrease in the free energy of the system. [14]

On the contrary, the muscle can return to a relaxed state only if the necessary amount of energy is injected into the system from the outside, without which stretching of any contracted rubber-like body is impossible. Thus, according to the proponents of this theory, known as the thermokinetic theory of muscular activity, the attachment of ATP to a contractile protein causes its contraction, but this contraction is not accompanied by the cleavage of adenosine triphosphate.

The hydrolysis of ATP, which proceeds according to the equation: ATP + H^O —"-g * ADP + H3P04, begins after contraction, and is released- There are a number of variants of thermokinetic theories of muscular activity. This issue is discussed in detail in a review article by V. I. Agola. 2) Another view is that muscle fiber contraction is not a spontaneous process, but is carried out at the expense of energy released by the breakdown of ATP by actomyosin. From this point of view, ATP hydrolysis obviously occurs in the phase of muscle contraction rather than relaxation. Muscle contraction is impossible without the enzymatic breakdown of ATP. Muscle relaxation, on the contrary, does not require an influx of energy from the outside, i.e. it is not associated with the use of energy from certain chemical processes occurring in the muscle tissue. [8]

It is easy to see that the main difference between the concepts developed in various versions of thermokinetic theories of muscular activity and theories linking the use of ATP breakdown energy with the contraction phase is the assumption that contractile proteins have the properties of rubber-like polymers; the latter are constructed from long, flexible, highly mobile macromolecules capable of changing their spatial configuration. This view might seem all the more likely because the most important component of the contractile protein complex, myosin, is indeed a fibrillar protein, i.e., a protein whose particles are constructed from a multitude of long polypeptide chains arranged more or less in parallel in a muscle fiber. From this fact, it was concluded that the phenomenon of muscle fiber contraction may be based on processes associated with a change in the configuration of flexible polypeptide chains, just as the shortening of rubber-like bodies is caused by the free thermal movement of individual units of long polymer macromolecules. [15]

Recently, models of contractile proteins have even been created (Kachalsky) that can change their length when the reaction of the medium (pH) changes. These models consist of long macromolecules of polymers, which contain periodically repeating ionogenic groups. A change in the configuration of macromolecules as a result of the recharge of ionogenic groups under the influence of shifts in pH in the external environment can be a source of mechanical work, which can be compared with the work of muscle fiber contraction. In such polyelectrolyte systems, as in a living muscle, a direct transfer of chemical energy into mechanical work is carried out without the

intermediate formation of heat. However, there seems to be only an external analogy between the contraction of such models and muscle fiber. The theory of muscle contraction, expressed as early as 1929 by Meyer, is also of interest. By this time, it was already known that myosin belongs to the number of fibrillar proteins and a zwitterionic theory of protein structure was formulated. Based on the concepts developed in the zwitterionic theory of protein structure, Meyer suggested that in a non-excited muscle, only carboxylic ionic groups (for example, COOH groups of dicarboxylic amino acids) are dissociated in the myosin polypeptide chain. Thus, in this form, the myosin macromolecule has the character of a peculiar anion, which contains many periodically repeating ionic groups carrying charges of the same name. The polypeptide chain, of course, must be in a more or less straightened state. [12]

When a muscle is excited, according to Meyer, as a result of the formation of acid-reacting metabolic products in the muscle, myosin particles acquire a cytoteric structure.:In this case, hydrogen ions are bound by free amino groups, for example, amino groups of di-aminomonocarboxylic acid residues. As a result, the myosin polypeptide chain undergoes deformation due to the occurrence of electrostatic attractive forces between dissimilar electric charges. Thus, recharging the contractile protein leads, according to Meyer, to an increase in muscle elasticity at the time of arousal and contraction of muscle fibers. Note here that in Meyer's theory, as in various versions of thermokinetic theories of muscle activity, coj contraction of myofibrils is associated with a change in the internal structure of contractile muscle protein, more precisely with a change in the "spatial configuration" of myosin polypeptide chains.

Looking ahead a bit, it should be noted that, unfortunately, this at least completely unproven position with some variations appears in many manuals on muscle physiology at the present time. It is especially important that all theories of muscle activity that consider the contraction of myofibrils as a spontaneous process that does not require an influx of energy from outside are based on the premise of a change in the configuration of myosin polypeptide chains during muscle contraction. On the contrary, theories considering muscle contraction as a process inextricably linked with the use of chemical energy of metabolic processes are not limited by any ideas about the internal mechanism of changing the physical state of contractile protein. In this respect, they have a definite advantage over thermokinetic theories of muscular activity. [16]

Let's now see which of the two theories under consideration is in the best agreement with the totality of currently known facts and experimental data. Apparently, it can be assumed that the overwhelming majority of facts confirm the correctness of the idea that spontaneous muscle contraction is impossible without the breakdown of ATP. Let's recall some of them. 1) Data obtained by X-ray structural analysis. According to the research of Astbury and contrary to the earlier observations of Boehm and Weber, the contraction of living muscles is not accompanied by such changes in X-ray diffraction spectra that could correspond to the type of folding of polypeptide chains, in which there is a change in the distances between individual repeating amino acid residues (periods of identity). According to Astbury, radiographs of both relaxed and contracted Mytilus muscles, as well as m. sartorius frogs in a state of iodoacetate contracture belong to the same "-type. In other words, the periods of identity in the polypeptide chains of myosin, the protein that forms the bulk of the contractile substance of striated muscle fiber, do not change during muscle contraction. As was noted by one of us earlier (I. I. Ivanov), these data suggest that muscle contraction is not a consequence of intramolecular compression of polypeptide chains and has nothing in

common with the mechanism of elastic contraction of stretched rubber-like bodies or keratin-epidermal-fibrinogenic group proteins. More recently, similar considerations have been expressed by Weber. However, if biphasic muscle activity is not associated with a change in the spatial configuration of myosin polypeptide chains, then it is necessary to reject the assumption that myofibrils can contract without using the energy of macroergic ATP bonds or its purine and pyrimidine analogues (see, however, Morales).

2) Data obtained by electron and interference microscopy. As already mentioned, Hanson and Huxley, combining the method of electron microscopic examination with fractional extraction of myofibrillary proteins, showed that in relaxed myofibrils, myosin and actin are localized in various structures of the sarcomere. With the contraction of myofibrils, the actin system appears to enter the system of myosin filaments. In other words, shortening of striated myofibrils, according to electron microscopic examination, is associated with a peculiar sliding of actin filaments along myosin filaments. Here we return to the assumption made more than 10 years ago by St. Gyorgy, according to which actomyosin is formed in a muscle from myosin and actin only at the moment of its contraction. Of particular interest is the fact that, according to electron microscopic studies, the contraction of myofibrils is not associated with the "folding" of myosin polypeptide chains or a change in their length. Thus, thermokinetic theories of muscular activity are not supported from this side either. [17]

Weber even considers it possible to say that the experimental data of Huxley and Hanson mean, in essence, a set of elastic (or thermokinetic) theories of muscular activity. However, one should not think that exhaustive clarity has already been achieved in this regard. The studies conducted using the methods of electron and phase contrast microscopy, for all their indisputable importance, still need further development, detail and generalization. The question of the subtle mechanism of the interaction of actin and myosin filaments and the reduction of smooth muscles devoid of transverse striation, in particular, smooth locomotor muscles of invertebrates, remains unclear. The theory proposed by Weber explaining the mechanism of action filaments sliding along myosin filaments during the contraction of myofibrils needs to be specified and experimentally substantiated. One cannot ignore the criticism of Hansen and Huxley's data by Sjestrand, Hodge and other authors who refuse to consider the movement of thin (actin) filaments along thick (myosin) filaments in sarcomeres as the physico-chemical basis of the phenomenon of muscle contraction.

3) Data from myothermic studies. Myothermic studies also do not confirm the idea of muscle contraction as a shortening of a stretched elastic body, which contracts due to changes in internal energy If this were the case, one would expect significant consumption of chemical energy during the relaxation phase of the muscle to charge it. In fact, heat generation during two-phase muscular activity, by the nature of which it is possible to monitor the progress of energy-producing chemical processes, proceeds in a completely different way. As is known, during muscle contraction under aerobic conditions, heat develops both in the contraction phase and in the rest phase. The warmth of rest is released within a few minutes after relaxation (warmth of rest or delayed warmth). In an oxygen atmosphere, the amount of heat released in the resting phase (delayed heat generation) corresponds to the total amount of heat released in the reduction phase. Thus, the heat of rest is the heat of oxidation of the products of the anaerobic decomposition of energy substances that disappear during the reduction phase. But the muscle can contract and then relax in a nitrogen atmosphere. In this case, the warmth of rest is reduced to a very low value. In this case, heat generation reflects the course of anaerobic reduction reactions, which

can be ignored in further considerations. The increase in heat generation observed during relaxation (during anaerobic contraction), as special studies show, can have real significance only if it is a question of relaxing a muscle that has contracted under stress. In this case, the amount of heat released exactly corresponds to the amount of kinetic energy lost by the falling load. In other words, at the moment of relaxation in anaerobic conditions, there is no heat generation associated with the implementation of certain chemical reactions. Moreover, according to Hill, at the moment of relaxation of an unencumbered muscle, the formation of heat cannot be registered at all. [18]

All these facts do not correspond to the idea of the need to expend chemical energy in the relaxation phase of the muscle to "charge" it. There is other evidence to support this conclusion. The heat generated in the contraction phase, as it turns out, consists of two parts: 1) the heat of activation released before the start of contraction. The amount of this heat is only not much less than the heat of shortening and 2) the heat of shortening, which develops during the shortening of the muscle and is proportional to the amount of shortening. Thus, the total amount of energy released during muscle contraction is equal to the sum of: the heat of activation + the heat of shortening + the work done. The high value of the activation heat released before the start of contraction is also poorly compatible with the idea of muscle contraction as a spontaneous process. Finally, a number of data confirming the need to expend chemical energy in the phase of contraction rather than muscle relaxation were obtained by studying the course of heat generation during stretching of both contracted and relaxed muscles. However, we cannot elaborate on this last series of studies here and refer readers who would like to get a closer look at the data obtained to the relevant review articles (see, for example, the summary of Buchtal, Svensmark and Rosenfalk. Summarizing all that has been said, we come to the conclusion that the vast majority of established and verified facts allow us to consider experimentally justified only those theories of muscle activity that are based on the assumption that spontaneous contraction of muscle fibers is impossible without the expenditure of chemical energy. In the following sections of the book, the authors will proceed from this position when presenting individual issues. Here it is only necessary to emphasize that, speaking about the impossibility of spontaneous contraction of muscle fiber without the expenditure of chemical energy (splitting of ATP), we leave aside the question of the moment of interaction of ATP with actomyosin. [19]

It has already been pointed out above that this interaction appears to occur at the moment of muscle activation. It is at this moment that increased heat generation is observed, and actinomyosin enters a contractile state. Muscle relaxation— returning it to its original resting length—is undoubtedly a purely passive process (see Chapter III). It is especially necessary to focus on the works of Needham and collaborators — Dante, Kleinzeller, Lawrence, Mial, Needham—by determining the double refraction of myosin in a stream. The results of these studies, according to a number of authors (Blum and Morales; Jordan and Oster), confirm the assumption that it is possible to change the configuration of myosin polypeptide chains during the interaction of the micelles of this protein with ATP. Indeed, according to Needham and co-workers, the DLP of myosin solutions in 0.6 M KS1 decreases sharply with the addition of ATP. It was these observations that made it possible to speak of myosin as a "contractile enzyme."

In most cases, it was tacitly assumed that this should be a real shortening of myosin polypeptide chains under the influence of ATP, associated with a change in identity periods (distances between individual repeating atomic groupings in polypeptide chains). Regarding these experimental data, however, it is necessary to note the following: first of all, in the work of

Needham and co-workers, not pure myosin was used, but myosin with a greater or lesser admixture of actomyosin. Meanwhile, according to St. Gyorgy, pronounced DLP is observed in solutions of actomyosin. The DLP of actomyosin solutions decreases sharply with the addition of ATP. On the other hand, solutions of pure myosin in the presence of ATP do not alter DLP (see M. B. Kalmakarova).

According to Noda and Mariam, the change (decrease) DLP of actomyosin in 0.6 M KOH solution in the presence of ATP should be interpreted as the result of dissociation of actomyosin into its components (myosin and actin). The same point of view is shared by Lucky, Snellman and Erdos and Weber. Thus, in the light of currently available experimental data, there is no sufficient reason to consider a change in the DLP of actomyosin in saline solutions with high ionic strength when ATP is added as a manifestation of the contractility of myosin molecules.

The reaction with ATP does indeed lead to a change in the shape and size of the micelles of the contractile protein actomyosin, but this process is based not on the folding of polypeptide chains (a change in their configuration), but on a completely different mechanism (dissociation of actomyosin). [20]

Conclusion

The analysis of experimental data and theoretical concepts allows us to conclude that the role of ATP in the mechanism of muscle contraction is more complex and multilevel than it was assumed in the framework of classical concepts. Despite the existence of studies that fail to record noticeable ATP hydrolysis during single contractions, the totality of morphological, biochemical, myothermic, and electron microscopic data strongly suggests the impossibility of spontaneous contraction of muscle fiber without the participation of macroergic compounds. Modern concepts are increasingly shifting the focus from the direct use of ATP hydrolysis energy to the activation of the contractile system, the formation of high-energy forms of actomyosin and the subsequent performance of mechanical work. In this context, ATP is considered not only as an energy source, but also as a key regulator of the molecular interactions between actin and myosin. A significant role in ensuring the two—phase activity of the muscle fiber is also played by the system of regulation of ATPase activity, including the so-called Marsh-Bendall relaxation factor and ionic control mechanisms. Thus, muscle contraction should be considered as the result of a coordinated mechanochemical cycle involving activation of the contractile protein complex, performance of work, and passive relaxation. Further study of the molecular basis of these processes remains an urgent task of modern biochemistry and biophysics and is of fundamental importance for understanding both normal muscle physiology and pathological conditions accompanied by impaired contractile function.

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