Regulation of the Synthesis and Hydrolysis of ATP by Mitochondrial ATPase

ROLE OF THE NATURAL ATPase INHIBITOR PROTEIN*

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The action of the natural ATPase inhibitor protein of Pullman and Monroy (Pullman, M. E., and Monroy, G. C. (1963) J. Biol. Chem. 238, 3762–3769) on the mechanisms of energy conservation of heart mitochondria has been explored. The synthesis and hydrolysis of ATP and the Pi-ATP exchange reaction were studied in submitochondrial particles that possess the ATPase-inhibitor protein complex in two distinguishable states. In addition to their different rates of hydrolysis, the two states of the complex have been identified from their different accessibility to antibodies directed against the inhibitor protein, and from the different action of antibodies and trypsin on the ATPase activity of the two types of particles studied. The steady state rates of hydrolysis and of the P1-ATP exchange reaction of the particles are determined by the state in which the ATPase-inhibitor complex exists. Apparently by modifying the rate of one of the steps involved in the catalytic reaction of the ATPase, the inhibitor protein determines the extent to which the enzyme is able to catalyze ATP hydrolysis and the P1-ATP exchange reaction. This action of the inhibitor protein also reflects the rate at which the particles carry out oxidative phosphorylation.

A question of central importance in the mechanism of energy conservation in mitochondria and other energy-transducing membranes is how the energy of electrochemical gradients is utilized for the synthesis of ATP. It is known that synthesis and hydrolysis of ATP are catalyzed by the F1 component of the ATPase (1, 2). F1-ATPase binds to the F0 portion of the membrane, which presumably channels H+ from the outside of the inner membrane of the mitochondria to F1-ATPase (for review, see Refs. 3 and 4), thus allowing the energy of the electrochemical gradient to be transformed into the chemical energy of ATP. It is of interest that most, if not all, energy-transducing membranes possess a low molecular weight protein that powerfully inhibits ATP hydrolysis (5–10), and all the ATP-dependent reactions of mitochondria (11, 12). For some years, the protein was considered a unidirectional inhibitor of the ATPase. However, in more recent years, it was found that steady state oxidative (13, 14) and photophosphorylation (15) took place only after a lag of several seconds. Since in membranes depleted of the inhibitor protein this time phase did not occur, it was concluded that the lag was due to the abolishment of an inhibitory action of the inhibitor protein in ATP synthesis.

In addition, studies with antibodies directed against the inhibitor protein indicated that electrochemical gradients induce the exposure of antigenic groups of the inhibitor protein (16). The data suggested that a change in the F1-inhibitor complex occurs upon establishment of electrochemical gradients. Along the same line, it was found that, in intact mitochondria during steady state phosphorylation, the inhibitor protein is attached to the F1 component in an inhibitory state of ATP hydrolysis (17).

These observations are strongly suggestive that the inhibitor protein exerts a regulatory action of the catalytic properties of mitochondrial ATPase, and that it plays an active role in the process of energy conservation. In this work, the possibility was examined by measuring the rates of hydrolysis and synthesis of ATP, and of the 32P-ATP exchange reaction of submitochondrial particles that possess the F1-inhibitor protein complex in two different states. The results indicate that the inhibitor protein exerts an active role in the mechanism of energy conservation.

MATERIALS AND METHODS

Preparation of Bovine Heart Mitochondria and Submitochondrial Particles—Mitochondria from bovine heart were prepared as described by Low and Vallin (18). “Heavy” mitochondria stored at −40 °C were used for the preparation of Mg-ATP (19), EDTA (20), and ammonia-Sephadex (6) submitochondrial particles. "State 3" particles were prepared from Mg-ATP particles as described by Van de Stadt et al. (21). After incubation in State 3 conditions, the particles were washed twice. Mg-ATP and State 3 particles were used immediately after preparation for the various assays.

Hydrolysis of ATP was measured in the conditions described under "Results." The amount of inorganic phosphate liberated was determined according to Sumner (22) after arrest of the reaction with 6% trichloroacetic acid. In some cases, the hydrolytic activity was assayed as in Ref. 1.

32P Incorporation—The incorporation of 32P into ATP, either through oxidative phosphorylation or in the F1-ATP exchange reaction, was carried out by incubation of the desired particles in mixtures that are detailed under results. 32P was used to measure the uptake of phosphate into ATP. After arresting the reaction with 6% trichloroacetic acid (final concentration), an aliquot of the supernatant was withdrawn and inorganic phosphate was extracted with isobutanol-benzene as described in the preceding article (23). Cerenkov radiation of the water phase was used to assay the uptake of 32P into ATP by counting it in the H channel of a Beckman scintillation counter. 32P from Amersham was purified as described elsewhere (24).

Antibodies against the inhibitor protein were obtained as in Ref. 16. The labeling with 3H, and their binding to submitochondrial particles, was also made by following the methodology of Ref. 16. The conditions for the assay of their effect on the ATPase activity of submitochondrial particles is described under "Results."

Protein was assayed by the biuret method using bovine serum albumin as standard.

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The described conditions to obtain State 3 particles were prepared as described under "Materials and Methods." Their hydrolytic activity was assayed with an ATP-regenerating system (1). EDTA-Sephadex + inhibitor protein particles were prepared by incubating EDTA-Sephadex particles (1 mg of protein) with 20 µg of inhibitor protein in 500 µM Mg-ATP and 5 mM Tris-MES \(^2\) for 30 min at 30 °C. At this time, the particles were diluted with 0.25 M sucrose and centrifuged at 105,000 \(\times\) g for 30 min. The particles were suspended in 0.25 M sucrose and their ATPase and capacity to bind antibodies were tested. Binding of \(^{125}\)I-labeled antibodies or \(^{125}\)I-labeled pre-immune \(\gamma\)-globulins was measured by incubating overnight 1 mg of particles with 25 µg of antibodies or \(\gamma\)-globulins at 4 °C. The total number of counts was determined by counting the radioactivity of the whole tube. Subsequently, the tubes were centrifuged at 105,000 \(\times\) g for 15 min. The supernatant was discarded, and the amount of counts in the residue was measured. The counts present in particles incubated with pre-immune \(\gamma\)-globulins were subtracted from those obtained in particles incubated with antibodies to calculate specific binding.

**RESULTS**

It has been reported (16) that Mg-ATP particles, in which the large majority of the ATPases possess inhibitor protein in its inhibiting site, are less reactive to \(^{125}\)I-labeled antibodies directed against inhibitor protein than are State 3 particles. These observations were confirmed and extended (Table I). EDTA particles that had been passed through a Sephadex column (6) have a high hydrolytic activity, and do not bind antibodies (Table I). Moreover, these particles do not form precipitation bands in Ouchterlony plates when tested against the inhibitor protein (data not shown).

The data of Table I also indicate that added inhibitor protein induces as expected almost full inhibition of the ATPase activity of EDTA-Sephadex particles. However, these latter particles with an ATPase activity that is inhibited by the inhibitor protein fail to interact with antibodies directed against the protein. These observations indicate that the antigenic groups of the protein do not react with antibodies when the protein is in its full inhibitory state, such as that of Mg-ATP particles, or in those inhibited by added inhibitor protein. The results of Table I also show that particles that had been previously exposed to State 3 conditions possess inhibitor protein, but in a state that is accessible to antibodies.

It is important to stress that the hydrolytic activity of State 3 particles is not totally expressed. Our preparations of soluble F1,ATPase (25) have a specific activity of about 70 µmol min\(^{-1}\) mg\(^{-1}\). As F1-ATPase represents about 10% of the total protein of the inner membrane, particles with fully active ATPases should hydrolyze ATP at a rate of about 7 µmol min\(^{-1}\) mg\(^{-1}\). Our State 3 particles have a rate that has ranged from 1.2-2.5 µmol min\(^{-1}\) mg\(^{-1}\), a value much lower than the expected, if all the enzymes were fully active. As shown below (see Table II), State 3 particles carry out coupled ATP synthesis at a rate higher than Mg-ATP particles, which indicates that the described conditions to obtain State 3 particles (Ref. 21) do not induce damage of the preparation.

\(^1\) The abbreviation used is: MES, 4-morpholineethanesulfonic acid.

**TABLE I**

| Particles          | ATPase activity | Binding of antibodies |
|--------------------|-----------------|-----------------------|
|                    | µmol min\(^{-1}\) mg\(^{-1}\) | µg/mg                 |
| Mg-ATP             | 0.8             | 0.7                   |
| State 3            | 1.6             | 1.5                   |
| EDTA-Sephadex      | 2.7             | 0                     |
| EDTA-Sephadex + inhibitor protein | 0.1 | 0                     |

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The relatively low activity may be due to either of two alternatives: not all the ATPases are free of inhibitor protein, or the inhibitor protein is attached to all the ATPases, but in a form in which the hydrolytic activity of the enzymes is only partially inhibited.

**Effect of Antibodies**—To test these alternatives, the effect of antibodies directed against the inhibitor protein on the ATPase activity of State 3 particles was studied; as a control, pre-immune \(\gamma\)-globulins were tested. Fig. 1 shows that the antibodies induce stimulation of the rate of ATP hydrolysis of the State 3 particles. In Mg-ATP particles, stimulation of the ATPase activity also took place, but this was smaller than that attained in State 3 particles. The results indicate that the ATPase activity of State 3 particles is controlled by the inhibitor protein, and that this control is removed by inhibitor protein antibodies. Therefore, it seems that the inhibitor protein may exert two types of action: one in which strong but not full inhibition of the hydrolytic activity takes place, as in Mg-ATP particles or reconstituted systems (see Refs. 5-10) and another in which the inhibitor protein only diminishes the rate of ATP hydrolysis, as occurs in State 3 particles.

The two states of particulate ATPase-inhibitor protein complexes are also evidenced by their sensitivity to trypsin.

**FIG. 1. Effect of antibodies directed against the inhibitor protein on the hydrolytic activity of Mg-ATP and State 3 particles.** The indicated particles (50 µg) were incubated in 0.1 ml of 5 mM Tris-acetate, pH 7.4, with the indicated concentrations of antibodies (Abs) against inhibitor protein or pre-immune \(\gamma\)-globulins (\(\gamma\)-G) for 30 min. At this time, aliquots were withdrawn to assay ATPase activity (1).
conservation in two preparations which possessed ATPase-

ATPase activity. Therefore, the detected activation by trypsin

treated identically, to judge the action of trypsin on F, -
devoid of inhibitor protein (Refs. 6 and 27; Table I) were also

than of Mg-ATP particles (Fig. 2). Ammonia-Sephadex particles which are completely

inhibitor at various times, their ATPase activity was assayed

by trypsin. Subsequently, the ATPase activity of the particles was assayed (1). The ordinate shows the modification of the enzymatic activity induced by trypsin.

(6, 8, 26). It is known that trypsin induces activation of the ATPase, presumably through proteolytic cleavage of the inhibitor protein. Mg-ATP and State 3 particulates were incubated with trypsin, and after addition of soybean trypsin inhibitor at various times, their ATPase activity was assayed (Fig. 2). Ammonia-Sephadex particles which are completely devoid of inhibitor protein (Refs. 6 and 27; Table I) were also treated identically, to judge the action of trypsin on F, ATPase without inhibitor protein.

Trypsin induced a higher increase of the activity of State 3 than of Mg-ATP particles (Fig. 2). It is to be noted that, in ammonia-Sephadex particles, trypsin induced a decrease of ATPase activity. Therefore, the detected activation by trypsin in State 3 and Mg-ATP particles is most likely underestimated, since each point assayed represents the sum of the activation and the inactivation of the ATPase. In any case, the experiment does indicate that trypsin induces a higher activation in State 3 than in Mg-ATP particles. This confirms that in State 3 particles the ATPase activity is controlled by the inhibitor protein, and that in this state it is more susceptible to trypsin action (and more accessible to its antibodies) than in that which exists in Mg-ATP particles.

The Action of the Inhibitor Protein in ATP Synthesis in Mg-ATP and State 3 Particles—The aforementioned experiments indicate that, with respect to its interaction with the inhibitor protein, the ATPase complex may exist in two states. Therefore, it was possible to study the process of energy conservation in two preparations which possessed ATPase-inhibitor complex in two distinguishable states. With this idea, the $^{32}$P-ATP exchange reaction was assayed as a function of time in State 3 and Mg-ATP particles (Fig. 3). In Mg-ATP particles, the $^{32}$P-ATP exchange showed two clearly different phases, i.e. an initial phase in which the uptake of $^{32}$P was low, followed by a linear phase of rapid exchange. The lag that precedes steady state $^{32}$P-ATP exchange is reminiscent of the lag that precedes steady state oxidative phosphorylation (13, 14); however, in the present work, the phenomenon was not explored further. State 3 particles do not present this lag; therefore, in the initial seconds of the experiment, the rate was higher in State 3 than in Mg-ATP particles. However, after the initial seconds, the rate of $^{32}$P-ATP exchange was higher in Mg-ATP particles.

In the presence of added ADP, and in agreement with other authors (28, 29), the rate of $^{32}$P-ATP exchange was increased in the two types of particles studied (Fig. 3), but it may be observed that, with even added ADP, the rate of exchange remained higher in Mg-ATP particles. ADP did not abolish the lag in the onset of the exchange reaction in Mg-ATP particles.

In the preceding manuscript (23), it was shown that the capacity of mitochondrial ATPase to carry out hydrolysis and the $^{32}$P-ATP exchange reaction are regulated by Mg$^{2+}$ and ADP. Accordingly, the possible control by the inhibitor protein on these two reactions was studied in State 3 and Mg-ATP particles.

Fig. 4 shows the uptake of $^{32}$P into ATP and the amount of ATP hydrolyzed (measured under almost identical conditions) at various concentrations of particle protein. The results indicate that, regardless of the amount of ATP hydrolyzed, the exchange reaction is always higher in Mg-ATP particles. In contrast, the amount of ATP hydrolyzed is much higher with State 3 particles. In consequence, the ratio of ATP hydrolyzed to ATP that undergoes exchange is much lower in Mg-ATP particles, the decrease being the result of both a higher rate of exchange and a lower rate of ATP hydrolysis.

![Fig. 2. Effect of trypsin on the ATPase activity of Mg-ATP and State 3 particles.](http://www.jbc.org/)

![Fig. 3. The $^{32}$P-ATP exchange reaction of Mg-ATP and State 3 particles as a function of time.](http://www.jbc.org/)
employed, the rate of ATP synthesis is significantly higher in State 3 than in Mg-ATP particles. This would be expected if the velocity of step 4 of the reaction sequence is lower in Mg-ATP particles. Calculation of the apparent $K_a$ for ADP from Lineweaver-Burk plots (not shown) was 11 and 6 $\mu$M for the State 3 and Mg-ATP particles, respectively. Thus, it would appear that the different state of the inhibitor protein with respect to the ATPase reflects mainly on the velocity of the reaction, and not to a great extent on the $K_a$ for ADP.

**DISCUSSION**

It is accepted that the inhibitor protein of Pullman and Monroy (5) inhibits ATP hydrolysis and all the ATP-dependent reactions of mitochondria (5-12). However, from studies carried out in chloroplasts (15), heart submitochondrial particles (13, 14), and liver particles (33), it is becoming clear that the inhibitor protein also controls the onset of oxidative and photophosphorylation when initiated by an electrochemical gradient. However, it is not clear whether the protein exerts an active role in steady state phosphorylation. Indeed early studies in reconstituted particles devoid of inhibitor protein (6) indicated that the protein is not an essential component of ATP synthesis, but these latter studies do not invalidate the possibility that the inhibitor protein regulates the steps that lead to ATP synthesis.

In this work, it has been found that the inhibitor protein may exist in two states with respect to particulate F$_1$-ATPase: one that is observed in Mg-ATP and in which the protein strongly inhibits the hydrolytic activity, and another in which the inhibition of hydrolysis is much lower, as in State 3 particles. This latter state of the inhibitor protein was evidenced by the observation that, in State 3 particles, antibodies against the inhibitor protein induce an important activation of the hydrolytic activity. Also in agreement with these data, it was found that the inhibitor protein in F$_1$-ATPase of State 3 particles was more susceptible to proteolytic cleavage than in Mg-ATP particles. Thus, it would appear that Mg-ATP and State 3 particles possess ATPase-inhibitor protein complexes in two different states. The results of experiments with these two types of particles show that, regardless of the state of the ATPase-inhibitor complex, the enzyme is capable of carrying out ATP synthesis. Nevertheless, it was also found that the rate of the $^{32}$P-ATP exchange reaction is higher in Mg-ATP than in State 3 particles. In contrast and throughout steady state $^{32}$P-ATP exchange, the rate of hydrolysis is higher in State 3 than in Mg-ATP particles, notwithstanding the presence of high concentrations of ADP.

According to our working scheme of the reaction sequence and in line with the conclusions of the previous work (23), we think that the present results may be explained according to the following rationale.

In the proposed reaction sequence, the ratio of the relative velocities of steps 1, 2, and 3 to step 4 could determine the extent to which ATP becomes labeled, in relation to that which undergoes hydrolysis. In the parallel assay of the $^{32}$P-ATP exchange and hydrolysis, if step 4 is faster than steps 1-3, hydrolysis will predominate; in contrast, if the velocity of step 4 is lower than steps 1-3, the incorporation of $^{32}$P into ATP would be favored since the probability for reversal of steps 1-3 would increase. Therefore, the lower rate of hydrolysis and the higher rate of exchange of Mg-ATP particles, as compared to State 3 particles, could be the result of a lower rate of step 4 in the Mg-ATP particles as controlled by the inhibitor protein.

Moreover, the postulated lower rate of step 4 in both the backward and forward direction in Mg-ATP particles than in
State 3 particles satisfactorily explains why oxidative phosphorylation is slower in Mg-ATP particles, even though the rate of the "P-ATP exchange reaction is higher in these particles than in the State 3 particles.

It is important to point out that Galante et al. (34) have measured that P\(_{-}\)ATP exchange reaction and ATP hydrolysis in Complex V reconstituted with inhibitor protein; it was found that the protein induced a higher inhibition of hydrolysis than of the exchange reaction. In other words, it appears that these workers observed that, through the action of the inhibitor protein, the ratio of ATP hydrolysis/exchange diminishes. This would be in agreement with our findings.

In this respect, it must be pointed out that, in reference to the inhibitor protein, the ATPase complex can exist in more than two states that we describe here. The ATPase complex of "Sephadex particles" (6) is apparently free of the inhibitor protein, the ATPase complex can exist in more conservation in the mitochondrial membrane by controlling the rate of one of the steps of the catalytic process.

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