Biochimica et Biophysica Acta, 550 (1979) 259—268

BBA 78244

ATP-P_i AND ITP-P_i EXCHANGE BY CARDIAC SARCOPLASMIC RETICULUM

BRIGITTE PLANK, GERTRUDE HELLMANN, CHRISTIAN PUNZENGRUBER and JOSEF SUKO

Institute of Pharmacology, University of Vienna, Währingerstrasse 13a, 1090 Vienna (Austria)

(Received May 10th, 1978)

Key words: NTP-P_i exchange; Ca^{2+} transport; ATPase; Phosphorylation; (Sarcoplasmic reticulum, Cardiac)

Summary

ATP-P_i and ITP-P_i exchange is demonstrated in cardiac sarcoplasmic reticulum isolated from dogs. Both reactions require calcium outside the sarcoplasmic reticulum and inside, as well as magnesium and ADP or IDP.

ATP-P_i or ITP-P_i exchange by sarcoplasmic reticulum is maximally activated at μM concentrations of calcium outside the sarcoplasmic reticulum, considerably inhibited by mM concentrations of calcium in the medium and abolished at nM concentrations of calcium in the medium; these last concentrations do not activate phosphorylation of the calcium transport ATPase by ATP or ITP. Phospholipase A-treated sarcoplasmic reticulum vesicles do not exhibit any nucleoside triphosphate-P_i exchange at calcium concentrations between 0.01 and 0.3 mM, but both reactions are partially activated by mM calcium concentrations, indicating that calcium in the mM range inside the sarcoplasmic reticulum is essential for nucleoside triphosphate-P_i exchange.

Drugs like prenylamine, chlorpromazine, quinidine, tetracaine and dibucaine inhibit ATP-P_i exchange and calcium-dependent ATPase to a similar extent. Inhibitors of mitochondrial ATP-P_i exchange do not affect ATP-P_i exchange by sarcoplasmic reticulum; dicyclohexyl carbodiimide was an exception in causing increased rate of phosphate exchange in sarcoplasmic reticulum.

It is suggested that nucleoside triphosphate-P_i exchange occurs via an exchange of inorganic phosphate with the phosphate of the phosphoprotein formed from nucleoside triphosphate, which is dephosphorylated by nucleoside diphosphate, resulting in ATP or ITP formation.

Abbreviations: NTP, nucleoside triphosphate; NDP, nucleoside diphosphate.

Introduction

ATP-P_i and ITP-P_i exchange by skeletal muscle sarcoplasmic reticulum was first shown by Makinose [1,2]. Both exchange reactions by native and leaky sarcoplasmic reticulum vesicles were extensively investigated by de Meis and coworkers [3—5]. ATP-P_i exchange also occured in reconstituted sarcoplasmic reticulum [6]. Forward and backward reactions of the calcium pump of skeletal muscle sarcoplasmic reticulum [7—10] participate in the NTP-P_i exchange mechanism [1—5].

In the case of cardiac sarcoplasmic reticulum, both the forward reactions (ATP-driven calcium transport from outside to the inside of sarcoplasmic reticulum and ATP hydrolysis [11—17], both proceeding via the phosphorylation of the transport ATPase by ATP [18—22]), and the backward reactions (ADP-induced, phosphate-dependent calcium release and calcium driven ATP synthesis from ADP and orthophosphate proceeding via the phosphorylation of the transport ATPase by orthophosphate [23,24]) have been demonstrated. NTP-P_i exchange by cardiac sarcoplasmic reticulum has not yet been reported. In order to characterize further the calcium transporting system of cardiac sarcoplasmic reticulum, NTP-P_i exchange was studied in dog heart sarcoplasmic reticulum. ATP-P_i and ITP-P_i exchange by cardiac sarcoplasmic reticulum both exhibit essentially the same features as in skeletal muscle sarcoplasmic reticulum [1—5].

Materials and Methods

Reagents

[^{32}P]Orthophosphate was purchased from the Radiochemical Centre (Amersham); ATP, ADP, ITP, IDP, oligomycin, tetraphenylarsonium and tetraphenylboron from Sigma (St. Louis); ITP, IDP, phospho*enol*pyruvate, pyruvate kinase and P^1,P^5-di(adenosine-5′)-pentaphosphate from Boehringer GmbH (Mannheim), ethyleneglycol-bis(2-aminoethylether)-*N*,*N*′-tetraacetic acid (EGTA) and *N*,*N*′-dicyclohexyl carbodiimide from Fluka AG (Buchs); and phospholipase A (*Naja naja*) from Koch Light (Colnbrook). Nigericin was a generous gift from Dr. R.L. Hamill (Eli Lilly and Comp., Indianapolis). All other chemicals were reagent grade from E. Merck (Darmstadt).

Preparation of sarcoplasmic reticulum

Cardiac sarcoplasmic reticulum was isolated from dogs [21] and usually stored at −20° C overnight in a medium containing 10 mM histidine buffer (pH 7.0) and 1 M sucrose. Protein was measured by the Folin method [25] standardized against bovine serum albumin.

Analyses

Calcium uptake by sarcoplasmic reticulum and calcium-dependent ATPase were assayed as detailed previously [15].

ATP-P_i exchange or ITP-P_i exchange was performed at 25° C in a medium containing 40 mM histidine buffer (pH 7.0), 100 mM KCl, 7 mM $MgCl_2$, 5 mM azide, 5—20 mM [^{32}P]orthophosphate, 5 mM ATP plus 2—10 mM ADP or

5 mM ITP plus 2—10 mM IDP, 0.01 or 0.1 mM $CaCl_2$ and 0.5 mg sarcoplasmic reticulum protein/ml. Variations of the assay conditions are given in the appropriate legends. The reaction was stopped by perchloric acid (final concentration 5%). Centrifugation was followed by neutralization of the supernatant with triethanolamine. Isolation of [^{32}P]ATP or [^{32}P]ITP was performed by ascending thin-layer chromatography on silica gel (aluminium sheets with silica gel 60 F_{254} from E. Merck, Darmstadt) as previously described [26] with the following modification in order to obtain separation of the nucelotides from [^{32}P]orthophosphate. After a 2-h run (solvent: *n*-propanol/ammonium (33%)/methanol/water (20 : 20 : 40 : 20, v/v) a high concentration of unlabelled orthophosphate (20 µl containing 3 µmol orthophosphate/2.5 cm) was applied between the ATP and ADP spots and run for a further 6 h; unlabelled orthophosphate was then reapplied just below the ATP spot, followed by a 15-h run. [^{32}P]ITP was isolated similarly, using the above solvent of the v/v ratio 45 : 30 : 15 : 10. [^{32}P]ATP or [^{32}P]ITP were counted in a liquid scintillation counter. The recovery of the nucleotides by this method was approx. 90%.

Phospholipase A treatment of sarcoplasmic reticulum was performed with 0.04 mg phospholipase A/mg sarcoplasmic reticulum protein in the presence of 1 mM $CaCl_2$ for 10 min at room temperature. The phospholipase A was boiled for 3—5 min prior to use [23].

Results

There are three essential requirements for the ATP-P_i exchange reaction by cardiac sarcoplasmic reticulum (Fig. 1; Table I).

1. A low calcium concentration in the medium is required in order to obtain

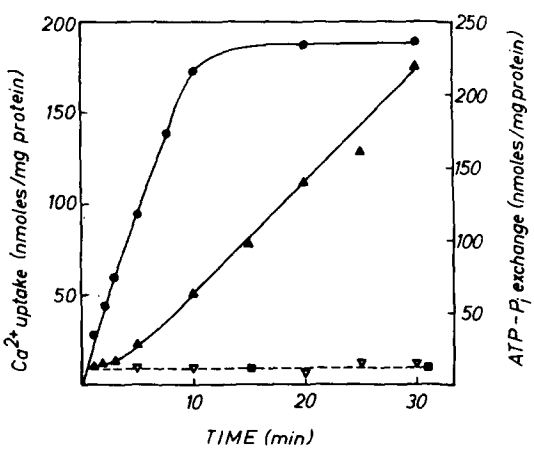


Fig. 1. Calcium uptake and ATP-P_i exchange by cardiac sarcoplasmic reticulum. Medium for calcium uptake and ATP-P_i exchange: 40 mM histidine buffer (pH 7.0), 100 mM KCl, 5 mM azide, 7 mM $MgCl_2$, 5 mM ATP, 2 mM ADP, 20 mM orthophosphate or [^{32}P]orthophosphate, 0.1 mM $CaCl_2$ or $^{45}CaCl_2$; 0.5 mg sarcoplasmic reticulum protein/ml. T = 25°C. Zero calcium: 10 mM EGTA, without addition of calcium. Zero ADP: 10 mM phospho*enol*pyruvate and 0.5 mg pyruvate kinase/ml, without addition of ADP. ●———●, calcium uptake; ATP-P_i exchange: ▲———▲, control; ▽— — —▽, zero calcium; ■— — —■, zero ADP.

TABLE I

ATP-P_i exchange and ITP-P_i exchange by native and leaky cardiac sarcoplasmic reticulum at different calcium concentrations. Medium: 40 mM histidine buffer (pH 7.0), 100 mM KCl, 10 mM $MgCl_2$, 5mM azide, 5 mM ATP plus 2 mM ADP or 5 mM ITP plus 5 mM IDP, 10 mM [^{32}P]orthophosphate, 0.5 mg sarcoplasmic reticulum protein/ml; total calcium was 0.01, 0.1 or 3 mM. $T = 25°C$. Phospholipase A treatment of sarcoplasmic reticulum vesicles was performed as described in Materials and Methods.

	ATP-P_i exchange (nmol/mg per 30 min)		ITP-P_i exchange (nmol/mg per 30 min)	
	Control	Phospho-lipase A	Control	Phospho-lipase A
Ca 0.01 mM	83.19	3.28	153.36	1.17
Ca 0.1 mM	71.03	2.80	143.36	0.64
Ca 3.0 mM	22.27	17.36	49.63	8.83
Zero Ca	—	2.05	3.46	0.58
Zero ADP, IDP	—	1.51	1.94	1.35

a maximum rate of ATP-P_i exchange. An initial total calcium concentration of 0.1 mM inhibits ATP-P_i exchange to a certain degree. The rate of orthophosphate exchange increases when the calcium in the medium is decreased by calcium uptake (Fig. 1). On the other hand, small amounts of calcium in the medium are necessary, since addition of sufficient EGTA to reduce free calcium outside the sarcoplasmic reticulum below concentrations which activate phosphorylation of the ATPase protein by ATP [20,21] abolishes the ATP-P_i exchange (Fig. 1; Table I). EGTA does not penetrate the sarcoplasmic reticulum at pH 7.0 [27].

2. Calcium inside the sarcoplasmic reticulum is obligatory for ATP-P_i exchange, which is achieved by calcium uptake in the above experiment. Treatment of sarcoplasmic reticulum with phosholipase A, which renders the sarcoplasmic reticulum vesicles permeable for calcium, completely eliminates ATP-P_i exchange at low calcium concentrations in the medium (ref. 1; Table I).

3. ADP is essential for the ATP-P_i exchange reaction, since phosphate exchange in the presence of an ATP regenerating system is reduced to levels observed with either EGTA in the medium or phospholipase A treatment of sarcoplasmic reticulum (Fig. 1; Table I).

Orthophosphate dependence of the ATP-P_i exchange reaction in the presence of 5 mM ATP, 2 mM ADP and 0.01 mM calcium initially reveals an apparent Michaelis constant for orthophosphate of around 20 mM and a maximum rate of ATP-P_i exchange of about 8 nmol/mg sarcoplasmic reticulum protein/min at 25°C (Fig. 2). This rate of ATP-P_i exchange is approximately 20 times lower than the rate of ATP splitting and about 40 times lower than the rate of ATP-ADP phosphate exchange by dog cardiac sarcoplasmic reticulum measured under the above conditions, i.e., in the presence of 5 mM ATP plus 2 mM ADP, but in the absence of orthophosphate [21].

Drugs such as prenylamine or chlorpromazine, which inhibit calcium uptake and ATP hydrolysis by skeletal muscle sarcoplasmic reticulum [28], are potent inhibitors of ATP-P_i exchange [1]. Furthermore, local anaesthetics such as tetracaine or dibucaine are inhibitors of both the forward and backward reactions of the calcium pump of skeletal muscle sarcoplasmic reticulum [26,29,

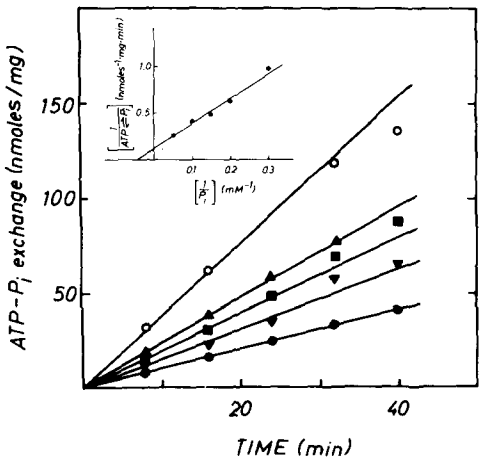


Fig. 2. Orthophosphate dependence of ATP-P_i exchange by cardiac sarcoplasmic reticulum. Medium: 40 mM histidine buffer (pH 7.0), 100 mM KCl, 5 mM azide, 7 mM $MgCl_2$, 5 mM ATP, 2 mM ADP, 0.01 mM $CaCl_2$, and 3.33 to 20 mM [^{32}P]orthophosphate, 0.5 mg sarcoplasmic reticulum protein/ml. T = 25°C. [^{32}P]orthophosphate concentrations (mM): ●———●, 3.33; ▼———▼, 5; ■———■, 6.66; ▲———▲, 10; ○———○, 20. Inset: Double reciprocal plot of the rates of ATP-P_i exchange vs. orthophosphate concentrations.

30]. The inhibition of ATP-P_i exchange by cardiac sarcoplasmic reticulum observed with prenylamine, chlorpromazine, quinidine, tetracaine or dibucaine, at drug concentrations indicated in Table II, is very close to the inhibition of the rate of calcium uptake and rate of calcium-dependent ATP hydrolysis measured in the presence of oxalate (ref. 30; Table II).

ITP drives the calcium uptake by cardiac sarcoplasmic reticulum associated with ITP hydrolysis and phosphorylation of the calcium transport protein by ITP like ATP, but the rates of calcium uptake and ITP splitting are only 10—20% of the rates of ATP-driven calcium uptake and calcium-dependent ATP hydrolysis [31]. Essentially the same requirements for ATP-P_i exchange

TABLE II

Inhibition of ATP-P_i exchange and Ca^{2+}-dependent ATP hydrolysis on cardiac sarcoplasmic reticulum by drugs. Medium for ATP-P_i exchange: 40 mM histidine buffer (pH 7.0), 100 mM KCl, 5 mM azide, 7 mM $MgCl_2$, 5 mM ATP, 2 mM ADP, 20 mM [^{32}P] orthophosphate, 0.1 mM $CaCl_2$, 0.5 mg sarcoplasmic reticulum protein/ml. T = 25°C. Medium for calcium-dependent ATP hydrolysis: 40 mM histidine buffer (pH 7.0), 100 mM KCl, 5 mM azide, 5 mM $MgCl_2$, 5 mM ATP, 2 mM phospho*enol*pyruvate, 0.02 mg pyruvate kinase/ml, 5 mM oxalate, 0.1 mM $CaCl_2$, 0.05 mg sarcoplasmic reticulum protein/ml. T = 25°C. The ATPase data were taken from ref. 30.

	Drug concentration (M)	ATP-P_i exchange (μmol/mg per 30 min)	Percent inhibition	Ca^{2+}-ATPase (μmol/mg per min)	Percent inhibition
Control	—	0.265	—	0.85	—
Prenylamine	10^{-4}	0.066	75.2	0.22	74.2
Chlorpromazine	10^{-4}	0.133	49.7	0.50	41.2
Quinidine	$3 \cdot 10^{-4}$	0.184	30.6	0.46	45.9
Tetracaine	10^{-3}	0.188	29.0	0.59	30.6
Dibucaine	$3 \cdot 10^{-4}$	0.150	43.5	0.55	35.3

hold true for ITP-P_i exchange (Fig. 3; Table I), but since IDP has a lower affinity than ADP for the calcium transport ATPase, higher concentrations of IDP have to be used in order to obtain a maximum rate of ITP-P_i exchange (Fig. 3 inset).

ATP-P_i exchange by sarcoplasmic reticulum vesicles made permeable for calcium by phospholipase A [1] or alkaline treatment [3—5] is zero at low calcium concentrations [1,3—5], but activated to some extent by high calcium concentrations in the medium [3—5]. This latter finding of de Meis and coworkers with skeletal muscle sarcoplasmic reticulum applies equally to the ATP-P_i or ITP-P_i exchange reaction by a cardiac sarcoplasmic reticulum (Fig. 4; Table I). Both exchange reactions by cardiac sarcoplasmic reticulum treated with phospholipase A are partially restored in the presence of 3 mM calcium in the medium. The ATP-P_i exchange by these leaky vesicles reached a plateau at approximately 2—4 mM $CaCl_2$, suggesting that calcium in the mM range inside the sarcoplasmic reticulum is necessary for the facilitation of the NTP-P_i exchange reaction [1,2,4,5].

The influence of various mitochondrial uncouplers or energy transfer inhibitors on ATP-P_i exchange by sarcoplasmic reticulum fractions is shown in Table III. None of the agents, expect dicyclohexyl carbodiimide, had any appreciable

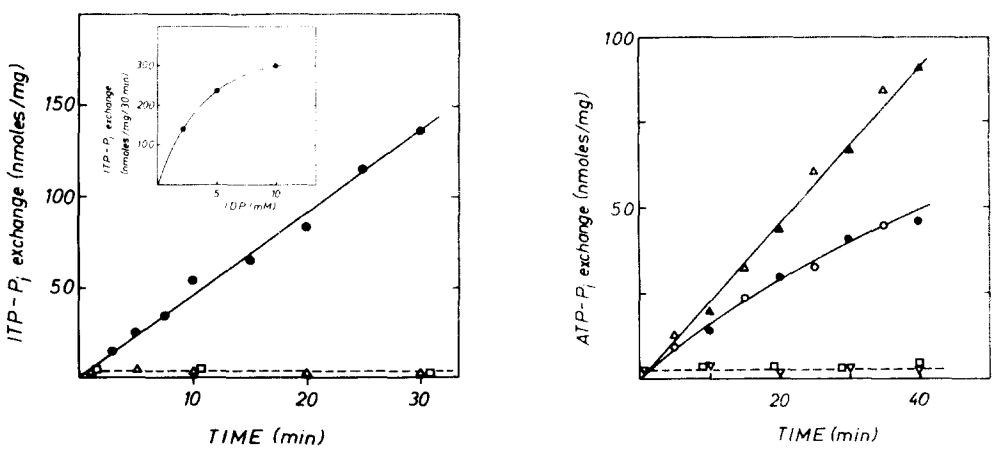


Fig. 3. Time course of ITP-P_i exchange by cardiac sarcoplasmic reticulum. Medium: 40 mM histidine buffer (pH 7.0), 100 mM KCl, 7 mM $MgCl_2$, 5 mM ITP, 2 mM IDP, 0.01 mM $CaCl_2$, 20 mM [^{32}P]orthophosphate, 0.5 mg sarcoplasmic reticulum protein/ml. T = 25° C. ●———●, control; △— — —△, zero calcium: 10 mM EGTA, without addition of calcium; □— — —□, zero IDP: 10 mM phospho*enol*pyruvate and 0.5 mg pyruvate kinase/ml, without addition of IDP. Control values were corrected for unspecific ITP formation in the presence of zero calcium in the medium. Inset: IDP-dependence of the ITP-P_i exchange.

Fig. 4. ATP-P_i exchange by native and phospholipase A treated cardiac sarcoplasmic reticulum at mM calcium concentrations. Medium: 40 mM histidine buffer (pH 7.0), 100 mM KCl, 5 mM azide, 20 mM $MgCl_2$, 5 mM ATP, 2 mM ADP, 3 mM $CaCl_2$ or 0.01 mM $CaCl_2$; 10 mM [^{32}P]orthophosphate, 0.5 mg sarcoplasmic reticulum protein/ml, nigericin (0.5 µg/ml) plus tetraphenylarsonium (0.05 mM) or nigericin (0.5 µg/ml) plus tetraphenylboron (0.05 mM). Zero calcium: 10 mM EGTA, without addition of calcium. T = 25° C. Native sarcoplasmic reticulum: 3 mM $CaCl_2$: ▲———▲, nigericin plus tetraphenylarsonium; △———△, nigericin plus tetraphenylboron; zero calcium: ▽— — —▽, nigericin plus tetraphenylarsonium. Phospholipase A-treated sarcoplasmic reticulum: 3 mM $CaCl_2$: ●———●, nigericin plus tetraphenylarsonium; ○———○, nigericin plus tetraphenylboron; 0.01 mM $CaCl_2$: □— — —□, nigericin plus tetraphenylarsonium.

TABLE III

Effect of various agents on ATP-P_i exchange by cardiac sarcoplasmic reticulum. Medium: 40 mM histidine buffer (pH 7.0). 100 mM KCl, 7 mM $MgCl_2$, 5 mM ATP, 2 mM ADP, 20 mM [^{32}P]orthophosphate, 0.01 mM $CaCl_2$, 0.5 mg sarcoplasmic reticulum protein/ml. T = 25° C. All agents were added to the medium in the concentrations as indicated.

	ATP—P_i exchange (nmol/mg per 20 min)
Control	90.27
+ Azide (5 mM)	89.23
+ Dinitrophenol (0.1 mM)	101.71
+ Dicyclohexyl carbodiimide (0.5 mM)	150.88
+ Oligomycin (20 μg/ml)	79.81
+ Tetraphenylarsonium (0.05 mM)	85.00
+ Tetraphenylboron (0.05 mM)	90.53
+ Nigericin (0.5 μg/ml)	82.23
+ Nigericin (0.5 μg/ml) + tetraphenyl-arsonium (0.05 mM)	93.06
+ Nigericin (0.5 μg/ml) + tetraphenyl-boron (0.05 mM)	88.58
+ P^1, P^5-di(adenosine-5′)-pentaphosphate (0.5 mM)	113.92
Control: zero Calcium	9.09
Control: zero ADP	8.42

effect. A combination of nigericin plus tetraphenylarsonium or nigericin plus tetraphenylboron, which strongly inhibit ATP-P_i exchange by intact mitochondria or mitochondrial fragments [32] were without effect. These agents have no effect on phosphorylation of cardiac sarcoplasmic reticulum, either by ATP in the absence of orthophosphate [21], or phosphorylation from orthophosphate in the absence of ATP [23].

Dicyclohexyl carbodiimide increased the rate of ATP-P_i exchange by more than 50%. Similar effects of this agent on ATP-P_i or ITP-P_i exchange were also seen with skeletal muscle sarcoplasmic reticulum. Phosphorylation experiments on skeletal muscle sarcoplasmic reticulum with either radioactive ITP plus unlabelled orthophosphate or unlabelled ITP plus radioactive orthophosphate [5,33] indicate that dicyclohexyl carbodiimide decreases the phosphoprotein level formed from ITP and increases the incorporation of orthophosphate into the ATPase protein from inorganic phosphate (unpublished results). Makinose [34] has observed an increase in the rate of calcium uptake in the presence of low orthophosphate concentrations by dicyclohexyl carbodiimide. The inhibitor of adenylate kinase, P^1,P^5-di(adenosine-5′)-pentaphosphate produced a slight increase in ATP-P_i exchange in some experiments (Table III).

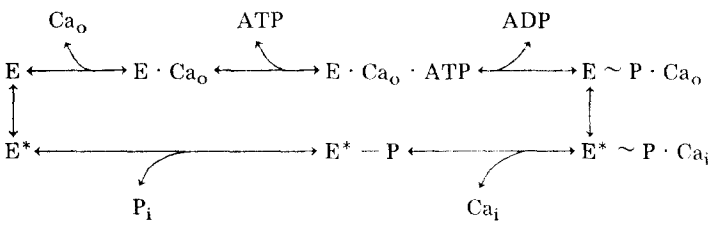
Discussion

There are several lines of evidence that the ATP-P_i exchange by cardiac sarcoplasmic reticulum fractions observed in the present study is derived from sarcoplasmic reticulum: a. The requirements for ATP-P_i exchange by cardiac

sarcoplasmic reticulum are essentially the same as reported for ATP-P_i exchange by skeletal muscle sarcoplasmic reticulum (Fig. 1, Fig. 3; Table I; refs. 1—5). b. Inhibition of ATP-P_i exchange by cardiac sarcoplasmic reticulum by drugs such as prenylamine, chlorpromazine, quinidine, tetracaine and dibucaine is of the same order of magnitude as the inhibition of the rate of calcium uptake and the rate of calcium-activated ATP hydrolysis (Table II; ref. 30). c. Inhibitors of mitochondrial ATP-P_i exchange have little effect on ATP-P_i exchange by cardiac sarcoplasmic reticulum (Table III). Furthermore, cardiac sarcoplasmic reticulum (Fig. 3; Table I) and skeletal muscle sarcoplasmic reticulum [2,4,5] catalyze ITP-P_i exchange, which does not occur in mitochondria [40]. ITP and IDP are not substrates for adenylatekinase.

The mechanism of NTP-P_i exchange by sarcoplasmic reticulum includes reactions known from the unidirectional calcium translocation from outside to the inside and vice versa [1—5]. A minimum reaction sequence, which also applies to cardiac sarcoplasmic reticulum, is given in Scheme I ([2,5,35—39].

SCHEME I



Reaction scheme of calcium transport by sarcoplasmic reticulum. E = calcium transport ATPase; Ca_o = calcium outside; Ca_i = calcium inside the sarcoplasmic reticulum; E ~ P and E-P represent acid stable, hydroxylamine sensitive phosphoproteins. Calcium is liberated prior to phosphate according to Makinose [2].

Phosphorylation of the calcium transport ATPase by NTP [8—10, 20, 21] is essential for the NTP-P_i exchange (Fig. 1, Fig. 3; Table I); phosphorylation from orthophosphate appears to be a further prerequisite [8—10,23,41,42]. The maximum rate of NTP-P_i exchange is obtained at low calcium concentrations outside the sarcoplasmic reticulum, i.e., when the ratio of phosphoprotein formation from inorganic phosphate to phosphoprotein formation from NTP is high [2,4,5,23,33,43]. On the other hand, phosphorylation of the calcium transport ATPase by inorganic phosphate at pH 7.0 of sarcoplasmic reticulum from skeletal muscle [41—45] and cardiac muscle [23,24] is completely inhibited by calcium concentrations in the medium greater than 0.1 mM, irrespective of the presence or absence of a calcium load, but is demonstrable in the presence of NTP even at mM concentrations of calcium in the medium [4,5]. This indicates that phosphoprotein formation from NTP permits phosphate incorporation from orthophosphate into the ATPase protein at high calcium concentrations outside the sarcoplasmic reticulum, thereby explaining the reduced rate of NTP-P_i exchange at mM calcium concentrations by native as well as phospholipase A treated sarcoplasmic reticulum (Fig. 4; Table I). The NTP-P_i exchange by sarcoplasmic reticulum requires NDP (Fig. 1, Fig. 3; Table I; ref. 4), which allows dephosphorylation of the phosphoprotein formed

from NTP, i.e., the very conditions permitting ATP-ADP phosphate exchange [2,20,21,26,46,47] or ITP-ADP phosphate exchange [47]. ATP-P_i and ITP-P_i exchange reactions appear, therefore, to include an exchange of orthophosphate in the medium with the phosphate of the phosphoprotein formed from NTP, which is then dephosphorylated by ADP or IDP, resulting in ATP or ITP formation.

Acknowledgements

The authors wish to thank Dr. L. Adler-Kastner for help in preparing the manuscript and Mrs. E. Hafrank for typing the manuscript. This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung, Vienna, Austria.

References

1 Makinose, M. (1971) FEBS Lett. 12, 269—270
2 Makinose, M. (1973) FEBS Lett. 37, 140—143
3 De Meis, L. and Carvalho, M.G.C. (1974) Biochemistry 13, 5032—5038
4 De Meis, L. and Sorenson, M.M. (1975) Biochemistry 14, 2739—2744
5 Carvalho, M.G.C., de Souza, D.G. and de Meis, L. (1976) J. Biol. Chem. 251, 3629—3636
6 Racker, E. (1972) J. Biol. Chem. 247, 8198—8200
7 Ebashi, S. and Endo, M. (1968) Prog. Biophys. Mol. Biol. 18, 123—183
8 Hasselbach, W. (1974) The Enzymes, Vol. 10, pp. 431—467, Academic Press, New York
9 Hasselbach, W. (1978) Biochim. Biophys. Acta 515, 23—53
10 Tada, M., Yamamoto, T. and Tonomura, Y. (1978) Physiol. Rev. 58, 1—79
11 Carsten, M.E. (1964) Proc. Natl. Acad. Sci. U.S. 52, 1456—1462
12 Fanburg, B.F. and Gergely, J. (1965) J. Biol. Chem. 240, 2412—2428
13 Lain, R.F., Hess, M.L., Gertz, E.W. and Briggs, F.N. (1968) Circulation Res. 23, 597—604
14 Pretorius, P.J., Pohl, W.G., Smithen, C.S. and Inesi, G. (1969) Circ. Res. 25, 487—409
15 Suko, J., Vogel, H.K. and Chidsey, C.A. (1970) Circ. Res. 27, 235—327
16 Suko, J. (1973) J. Physiol. (Lond.) 238, 563—582
17 Tada, M., Kirchberger, M.A., Repke, D.I. and Katz, A.M. (1974) J. Biol. Chem. 249, 6174—6180
18 Namm, D.H., Wodds, E.L. and Zucker, L. (1972) Circ. Res. 31, 308—316
19 Pang, D.C. and Briggs, N.F. (1973) Biochemistry 12, 4905—4911
20 Suko, J. and Hasselbach, W. (1975) in Recent Advances in Studies on Cardiac Structure and Metabolism (Fleckenstein, A. and Dhalla, N.S., eds.) Vol. 5, pp. 116—123, University Park Press, Baltimore, Md.
21 Suko, J. and Hasselbach, W. (1976) Eur. J. Biochem. 64, 123—130
22 Shigekawa, M., Finegan, J.A.M. and Katz, A. (1976) J. Biol. Chem. 251, 6894—6900
23 Winkler, F. and Suko, J. (1977) Eur. J. Biochem. 77, 611—619
24 Suko, J., Hellmann, G. and Winkler, F. (1977) Basic Res. Cardiol. 72, 147—152
25 Daughaday, W.H., Lowry, O.H., Rosebrough, N.J. and Fields, W.S. (1952) J. Lab. Clin. Med. 39, 663—665
26 Suko, J., Winkler, F., Scharinger, B. and Hellmann, G. (1976) Biochim. Biophys. Acta 443, 571—586
27 Weber, A., Herz, R. and Reiss, I. (1966) Biochem. Z. 345, 518—528
28 Balzer, H., Makinose, M. and Hasselbach, W. (1968) Naunyn-Schmiedeberg's Arch. Pharmacol. 260, 444—455
29 Balzer, H. (1972) Naunyn-Schmiedeberg's Arch. Pharmacol. 274, 256—272
30 Suko, J., Winkler, F., Scharinger, B. and Hellmann, G. (1975) in Calcium Transport in Contraction and Secretion (Carfoli, E., Clementi, F., Drabikowski, W. and Margareth, A., eds.), pp. 299—311, North-Holland, Amsterdam
31 Suko, J., Placheta, P. and Hellmann, G. (1974) Naunyn-Schmiedeberg's Arch. Pharmacol., Suppl. to Vol. 285, R 77
32 Kagawa, Y. and Racker, E. (1971) J. Biol. Chem. 246, 5477—5487
33 Makinose, M. (1973) 9. Int. Congr. Biochem., Stockholm, p. 260, Abstr. no. 5c5
34 Makinose, M. (1975) in Calcium Transport in Contraction and Secretion (Carfoli, E., Clementi, F., Drabikowski, W. and Margareth, A., eds.), pp. 367—372, North-Holland, Amsterdam

35 Kanazawa, T., Yamada, S., Yamamoto, T. and Tonomura, Y. (1971) J. Biochem. Tokyo 70, 95—123
36 Kanazawa, T. and Boyer, P.D. (1973) J. Biol. Chem. 248, 3163—3172
37 Martonosi, A., Lagawinska, E. and Oliver, M. (1974) Ann. N.Y. Acad. Sci. 227, 549—567
38 Hasselbach, W., Suko, J., Stromer, M.H. and The, R. (1975) Ann. N.Y. Acad. Sci. 264, 335—349
39 Fröhlich, J.P. and Taylor, E.W. (1976) J. Biol. Chem. 251, 2307—2315
40 Boyer, P.D., Luchsinger, W.W. and Falcone, A.B. (1956) J. Biol. Chem. 223, 405—421
41 Makinose, M. (1972) FEBS Lett. 25, 113—115
42 Yamada, S., Sumida, M. and Tonomura, Y. (1972) J. Biochem. Tokyo 72, 1537—1548
43 De Meis, L. and Madsuda, H. (1974) Biochemistry 13, 2057—2062
44 Kanazawa, T. (1975) J. Biol. Chem. 250, 113—119
45 Beil, F.U., Chak, D. and Hasselbach, W. (1977) Eur. J. Biochem. 81, 151—164
46 Hasselbach, W. and Makinose, M. (1962) Biochem. Biophys. Res. Commun. 7, 132—136
47 Makinose, M. (1966) Biochem. Z. 345, 80—86