Stimulation of oxidative phosphorylation by electrophoretic K$^+$ entry associated to electroneutral K$^+$/H$^+$ exchange in yeast mitochondria

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Abstract

The effect of the addition of KCl, at constant osmolarity, was investigated on oxidative phosphorylation in isolated yeast mitochondria. KCl stimulated both respiration and ATP synthesis rates without changing the ATP/O ratio. KCl did not change the relationships between respiration rates and the protonmotive force. Since the K$^+$/H$^+$ exchange activity was active under these conditions, the stimulatory effect of respiration could be explained by the net proton entry caused by the electrophoretic K$^+$ entry/electroneutral K$^+$/H$^+$ exchange cycle. On the other hand, K$^+$ entry stimulated phosphate accumulation and transport under non-phosphorylating conditions and decreased the kinetic control by phosphate transport under phosphorylating conditions. Additionally, the stimulation of ATP synthesis strongly depended on the activity of phosphate transport. Taken together, these data showed that electrophoretic K$^+$-entry and electroneutral K$^+$/H$^+$ exchange occurred in phosphorylating yeast mitochondria but did not promote any uncoupling between respiration and ATP synthesis.

Keywords: Respiration; ATP synthesis; Potassium ion transport; Phosphate transport; (Yeast mitochondria)

1. Introduction

According to the chemio-osmotic theory [1], mitochondria are able to couple the oxidation of reduced substrates and ATP synthesis via the creation and the maintaining of an electrochemical proton gradient through the inner mitochondrial membrane. It is implicit in this formulation that the inner mitochondrial membrane should be by itself nearly impermeant not only to protons but also to any cations, the reentry of which should dissipate the transmembrane potential which generally accounts for the main part of the electrochemical proton gradient. However, the hazards posed by diffusive and dissipative leaks of cations down the transmembrane potential were recognized by Mitchell, who postulated the existence of an electroneutral system of cation exit (cations/H$^+$ antiporter) preventing cation (particularly K$^+$) accumulation in the matrix [1]; the existence of this K$^+$/H$^+$ exchange is now well established ([2,3] for reviews).

In recent years, the view of the regulation of the inner membrane permeability has considerably evolved, following the demonstration, by different methods, of a number of K$^+$ and/or Na$^+$ uniporters [4–10] and of cation [11,12] or anion ([13–15] for reviews) conductances, although the physiological role of these electrophoretic pathways remains unclear. These pathways were observed under conditions (e.g., alkaline pH, Mg^{2+} depletion,...) far from those of typical measurements of oxidative phosphorylations. Therefore, the evidence that these electrophoretic, $\Delta\Psi$-consuming pathways could work under 'normal' conditions (i.e., when mitochondria are able to couple oxidations to ATP synthesis) is still lacking.

Systems equivalent to those described in mammalian mitochondria also exist in yeast mitochondria. Namely, yeast mitochondria contain a specific K$^+$ uniporter which, under non-energetic conditions, works only at alkaline pH [16]. Quite surprisingly, yeast mitochondria also support an ATP-induced channel, able to transport both anions and cations at neutral pH [17]. It has been shown that the respiration of yeast mitochondria was stimulated by KCl [18], this effect having been attributed to a 'protonophoric' effect of the electrophoretic K$^+$-entry associated to the electroneutral K$^+$(Na$^+$)/H$^+$ exchange [19,20].

In the present paper, we reinvestigated this stimulatory effect of KCl over both the respiration rates and the initial rates of ATP synthesis. We observed that, in addition to the expected stimulatory effect of KCl on the respiration rates, related to the protonophoric effect described above, the salt induced a marked stimulation of ATP synthesis, which appeared to be quite in contradiction with the effect on respiration. From the characteristics of phosphate transport and the estimation of the repartition of the kinetic control among the different steps involved in ATP synthesis, we conclude that the stimulation of ATP synthesis occurred via a secondary stimulation of phosphate transport. A preliminary report of these data has been communicated at the 6th BioThermoKinetics meeting [21].

2. Materials and methods

The diploid wild-type strain Yeast Foam was grown aerobically in a 1% Yeast Extract (Gibco), 0.12% $(NH_4)_2SO_4$, 0.1% KH_2PO_4 medium supplemented with 2% DL-lactate (adjusted at pH 5.0 with NaOH). Cells were harvested in the mid-exponential growth phase and mitochondria were isolated as previously described [22]. Mannitol and sorbitol used in preparation buffers were routinely deionized. Mitochondria were frozen as small beads in liquid nitrogen and could be stored at $-80°C$ for weeks without significant alterations of their phosphorylating properties. Proteins were measured by the biuret method with bovine serum albumin as standard.

The basal medium for all the experiments was 0.6 M mannitol, 2 mM Tris/EGTA, 10 mM Tris/maleate, 0.3% bovine serum albumin (pH 6.8). When a salt was added to the medium, mannitol concentration was decreased to maintain a constant osmolarity.

Respiration rates and initial rates of ATP synthesis were measured simultaneously in a thermostated cuvette (28°C) equipped with a Clark electrode. The medium was supplemented with 5 mM $[^{32}P]P_i$ and mitochondria were suspended at 0.67 mg/ml. The respiratory substrate was 40 mM ethanol. ATP synthesis was initiated with 1 mM ADP and the reaction was stopped at different times by adding 0.3 ml aliquots to 0.05 ml 3 M trichloroacetic acid. After immediate centrifugation, the supernatant was mixed with 0.5 ml of a vegetal coal suspension (100 g/l in 0.2 M potassium phosphate (pH 7.1)) and the tubes could be stored at 4°C overnight without significant ATP hydrolysis. The suspension was then layered onto Whatman GF/C filters, abundantly washed with 0.2 M potassium phosphate and water, dried and counted. Under our conditions, the rates of ATP synthesis were linear for at least 1 min.

Matrix volumes, ΔpH and $\Delta \Psi$ were determined in parallel experiments. Mitochondria were suspended in the same medium as above at 3 mg/ml. The medium was continuously bubbled with air or oxygen to avoid mitochondria to reach anaerobiosis during the experiments.

Matrix volumes were determined from the repartition of $[^{14}C]$mannitol and ^3H_2O, ΔpH from the repartition of $[^3H]$acetate and $\Delta \Psi$ from the repartition of $[^3H]$triphenylmethylphosphonium.

Phosphate accumulation and phosphate transport were measured at 4°C in the same buffer as above with 1 mg/ml mitochondria, in the presence of oligomycin 10 $\mu g/ml$ [23]. Transport was stopped by adding 1 mM mersalyl and immediate centrifugation. All the measurements are given corrected by non-matricial phosphate content determined in the presence of 1 mM mersalyl.

Mitochondrial swelling was followed as the absorbance decrease at 520 nm.

3. Results

3.1. Stimulation of oxidative phosphorylation by KCl

Fig. 1A shows the effect of KCl addition, at constant osmolarity, on respiration rates and on initial rates of ATP synthesis. KCl stimulated both state 4 and state 3 with a marked increase of the respiratory control ratio (Fig. 1B). But KCl simultaneously stimulated the initial rates of ATP synthesis (Fig. 1A) so that the ATP/O ratio (J_{ATP}/state 3) remained approximately constant (Fig. 1B).

The lack of effect of KCl addition on the ATP/O ratio can be more clearly visualized by titrating both fluxes with
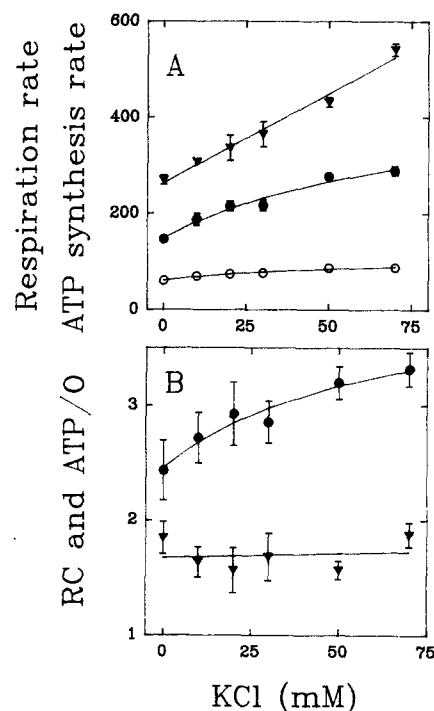

Fig. 1. Stimulation of oxidative phosphorylation by KCl. Respiration and ATP synthesis were measured simultaneously as indicated under the Methods section. (A) Open circles: state 4 respiration; full circles: state 3 respiration; triangles: initial rates of ATP synthesis. (B) Circles: respiratory control; triangles: ATP/O ratio.
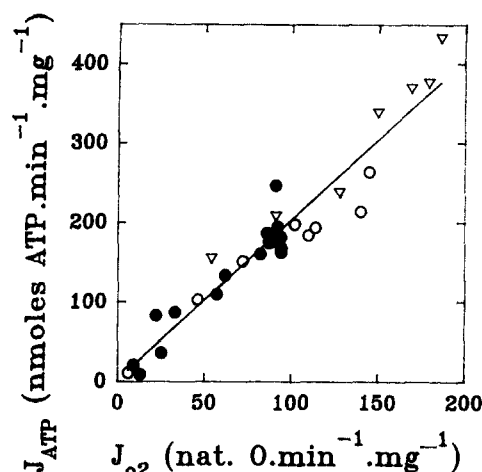
Fig. 2. Effect of KCl on J_{ATP} / J_{O2} relationships. Conditions as in Fig. 1. Both fluxes were titrated with antimycin A in the absence (filled circles) or in the presence of 30 mM (open circles) or 70 mM (triangles) KCl. Linear regressions gave values of ATP/O of 1.95 ± 0.18, 1.68 ± 0.15 and 2.03 ± 0.23, respectively.

antimycin A at different KCl concentrations (same experiment was done with KCN instead of antimycin A with simular results (not shown)). It can be seen in Fig. 2 that KCl did not significantly change the slope of the curve $J_{ATP} = f(J_{O2})$.

From this first set of experiments, it appeared that KCl was able to stimulate oxidative phosphorylation (i.e., ATP synthase + ADP/ATP translocase + P_i/H^+ cotransporter) with essentially no effect on the degree of coupling between the respiratory chain and the phosphorylation system.

We tested a number of other salts for their ability to replace KCl in this effect (Table 1). NaCl and LiCl had the same effect as KCl but significantly less marked. On the other hand, NH_4^+, which enters down the ΔpH, stimulated state 4 and significantly decreased both state 3 and J_{ATP}. Choline had no significant effect on respiration nor on ATP synthesis.

These results suggested that the stimulatory effect on the respiratory chain and on ATP synthesis are relatively specific and thus not caused by a simple ionic strength

Table 1
Effect of different chloride salts on oxidative phosphorylation

	nmol O/min per mg		nmol ATP/min per mg		
	State 4	State 3	J_{ATP}	RC	ATP/O
None	57	138	248	2.42	1.80
KCl	82	262	519	3.20	1.98
NaCl	88	249	428	2.83	1.72
LiCl	74	209	362	2.82	1.73
Chol·Cl	66	168	246	2.55	1.46
NH_4Cl	70	127	180	1.81	1.41

Conditions as in Fig. 1. All the salts were assayed at 70 mM. All the values of this table were obtained on a single mitochondria preparation. Similar results were obtained on three mitochondria preparations.

Table 2
Effect of KCl on ΔP

		Volumes (μl/mg prot)	Δ pH (mV)	$\Delta \Psi$ (mV)	ΔP (mV)
−KCl	state IV	1.6 ± 0.2	52 ± 4	125 ± 10	177 ± 14
	state III	1.5 ± 0.3	46 ± 6	98 ± 4	144 ± 10
+KCl 70 mM	state IV	1.7 ± 0.3	52 ± 5	112 ± 9	164 ± 14
	state III	1.5 ± 0.3	47 ± 2	89 ± 7	136 ± 9

ΔP was determined as indicated under Methods. Means of two independent determinations.

effect. Since Li^+ and Na^+, which are less permeant than K^+, could not completely replace it and choline and NH_4^+, which enter electroneutrally, could not do so at all, we concluded that only the cations able to enter electrophoretically could have this stimulatory effect.

3.2. Effect of KCl on J_{O2} / $\Delta \mu_{H^+}$ relationships

Table 2 shows the values of matrix volume, ΔpH, $\Delta \Psi$ and $\Delta \mu_H^+$ in the absence and in the presence of 70 mM KCl, respectively. It appeared that the matrix volume did not significantly increase in the presence of KCl. ΔpH did not change, whereas $\Delta \Psi$ decreased, both under state 4 and state 3.

Additionally J_{O2} was plotted vs. $\Delta \mu_H^+$ in the absence or in the presence of KCl by modulating either J_{O2} with antimycin A (Fig. 3A), or $\Delta \mu_H^+$ with ClCCP (Fig. 3B): in both cases, the presence of KCl did not change the relationships between J_{O2} and the protonmotive force. In the case of antimycin A titration, it could have been expected that the decrease in $\Delta \mu_H^+$ induced by KCl should promote a shift of the relationships to the left: we did not observe such a shift, probably because of the very low difference of $\Delta \mu_H^+$ in the presence and in the absence of KCl.

From these data, it was concluded that the stimulation of respiration rates by KCl could be simply explained by a partial dissipation of the transmembrane potential, very likely due to the appearance of unspecific K^+ leaks and/or the activation of K^+ uniporter. According to the interpretation of Dabadie et al. [18], the functionning of such electrophoretic K^+ transport pathways, associated to the electroneutral K^+/H^+ exchange is expected to result in a net H^+ reentry. The validity of this interpretation is based on the assumption that the K^+/H^+ exchange is active under these conditions. It is known that, under non-energetic conditions (both respiratory chain and ATPase being inhibited) and opposite to the behaviour of mammalian mitochondria [2,24], the K^+/H^+ exchange of yeast mitochondria is spontaneously activable [19,20], although the mechanism of its activation (e.g., depletion of divalent cations, swelling of mitochondrial matrix, etc.), is not well established. It remained to demonstrate that this exchange was also activated under energetic conditions.

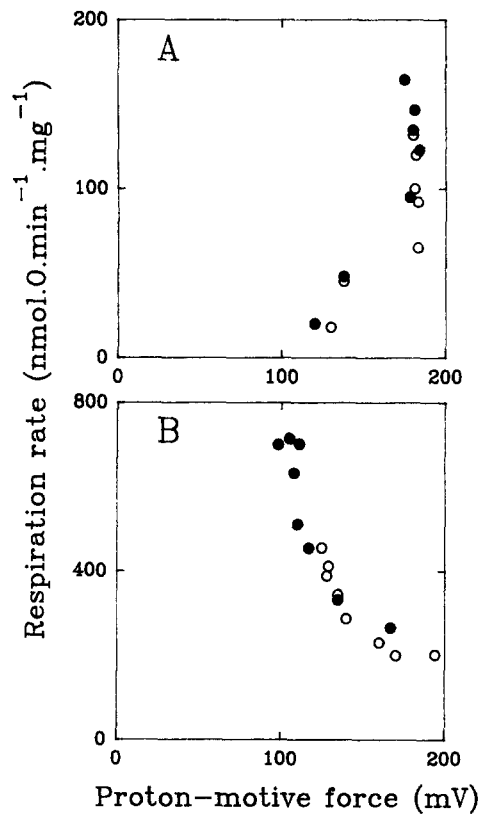Fig. 4 reports experiments of energetic swellings where

Fig. 3. Effect of KCl on $J_{O_2}/\Delta P$ relationships. Respiration rates and ΔP were determined as indicated under Methods. Other additions were 5 mM Tris/phosphate and 40 mM ethanol in the absence (open circles) or in the presence (filled circles) of 70 mM KCl. Both parameters were titrated with antimycin A (A) or ClCCP (B).

Fig. 4. Effect of propranolol on energetic swellings. Mitochondria were suspended in the basal medium added with 5 mM KAc, 10 μg/mg oligomycin, 0.4 μg/mg antimycin A and 0.25 μg/mg valinomycin. The swelling was followed as the apparent absorbance decrease at 520 nm. Additions: lactate 20 mM, KCN 100 μM, ClCCP 6 μM. (a) control; (b) plus 250 μM propranolol. Essentially similar results were obtained with ethanol as a substrate instead of lactate (+antimycin A), but the reversibility of the swelling was not total (not shown).

electrophoretic K^+ entry is induced by the respiratory chain in the presence of valinomycin. The swelling monitored under these conditions is activated by drugs known to inhibit the K^+/H^+ exchange, such as propranolol (trace b) or quinine and phenothiazines (not shown). These experiments demonstrated that the K^+/H^+ exchange was active under these conditions and partly prevented K^+ accumulation in the matrix down the transmembrane potential.

3.3. Stimulation of phosphate transport by KCl

In yeast mitochondria, as in mammalian mitochondria, phosphate transport is a strictly electroneutral phenomenon, thus depending on the extent of the ΔpH [25]. In the absence of any K^+/H^+ exchange, it is expected that the decrease in $\Delta\Psi$ induced by electrophoretic K^+ entry should increase ΔpH by the stimulation of the respiratory chain in response to the decrease of $\Delta\Psi$ and consequently stimulate phosphate transport activity.

Accumulation and transport of phosphate were measured at 4°C: at this temperature, the K^+/H^+ exchange activity (measured as the spontaneous swelling of mitochondria in potassium acetate) is almost non-existent (not shown).
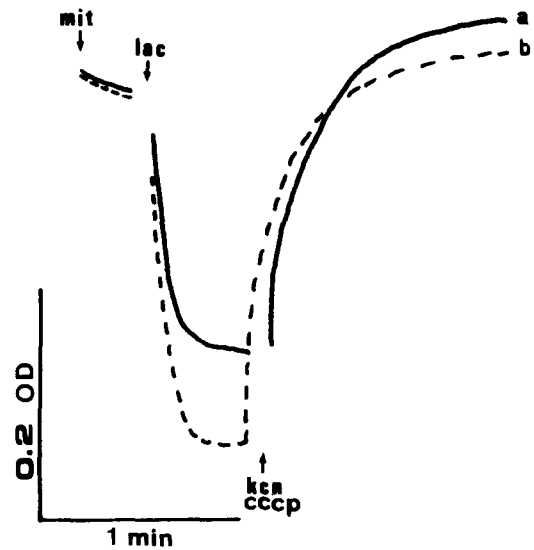
We first measured [^{32}P]P$_i$ accumulation in mitochondria at the equilibrium (Table 3): KCl stimulated this accumulation, strongly suggesting, in accordance to the direct relationships between ΔpH and phosphate accumulation [25], a marked increase of ΔpH.

When the rate of phosphate transport was measured in the presence of 100 mM KCl, it appeared that KCl markedly increased this rate, as compared to the experiment done in the absence of KCl (Table 3).

Kinetic parameters of phosphate transport were measured in the absence of KCl and in the presence of 100 mM KCl and valinomycin, which makes the membrane nearly freely permeable to potassium (Fig. 5): KCl increased the V_{max} (from 33.0 ± 1.5 to 95.6 ± 15.1 nmol/min

Table 3
Effect of KCl on phosphate accumulation and transport

	Accumulation (nmol P$_i$/mg)	Transport (nmol P$_i$/min per mg)
Without KCl		
control	30.0 ± 2.7 (n = 4)	22.0 ± 2.9 (n = 3)
+ mersalyl	21.0 ± 3.8 (n = 4)	–
+ ClCCP	23.2 ± 0.1 (n = 2)	n.d.
With KCl		
control	43.8 ± 7.3 (n = 4)	37.4 ± 2.3 (n = 3)
+ mersalyl	21.5 ± 2.6 (n = 4)	–
+ CCCP	22.2 ± 0.2 (n = 2)	n.d.

See conditions under Fig. 5. Accumulation was the amount of phosphate accumulated after 3 min at 3 mM external phosphate. Transport was measured at 1 mM. Means (±S.D.) of the determinations on the indicated n of mitochondria preparations.
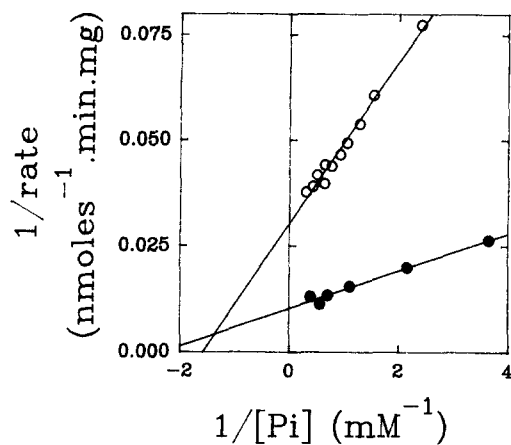
Fig. 5. Effect of KCl on phosphate transport. Mitochondria were suspended at 4°C in the basal medium added with 10 μg/mg oligomycin, 40 mM ethanol and a range of [^{32}P]phosphate concentrations in the absence (open circles) or in the presence (full circles) of 100 mM KCl + 0.2 μg/mg valinomycin. The transport was stopped at different times within 10 s by 1 mM mersalyl. Values are corrected by the value determined in the presence of 1 mM mersalyl before phosphate.

per mg) but did not strongly change the apparent k_T of phosphate transport (0.63 ± 0.05 and 0.48 ± 0.16 mM, in the absence and in the presence of KCl/valinomycin, respectively).

From these results we conclude that, in the absence of any K^+/H^+ exchange activity, the K^+ entry down the transmembrane potential, via valinomycin, stimulated phosphate transport by a stimulating effect of ΔpH. Moreover, in the absence of valinomycin, the inner mitochondrial membrane is sufficiently permeant to K^+ to observe this effect, although to a lesser extent.

3.4. Kinetic control of ATP synthesis

Under the experimental conditions we used to measure ATP synthesis (i.e., high external phosphate concentration), it had been demonstrated that the kinetic control over ATP synthesis was essentially shared between the respiratory chain and the phosphate/H^+ cotransporter [25,26]. The stimulatory effect of KCl on ATP synthesis could therefore be explained by a stimulation of phosphate transport and a release of its kinetic control over ATP synthesis.

From data reported above, phosphate transport could be stimulated by KCl under conditions where the K^+/H^+ exchange was nearly inactive. Could it also be under conditions where the K^+/H^+ exchange was active?

To answer the question, we estimated the repartition of the kinetic control over ATP synthesis by the different steps involved in ATP synthesis with the hypothesis that if phosphate transport is stimulated, its kinetic control over ATP synthesis should decrease.

Titration curves of ATP synthesis by the different inhibitors are reported in Fig. 6. We did not try to calculate the exact values of control coefficients, because of the

difficulty to obtain a sufficient precision of the rates of ATP synthesis. However, from the shape of the inhibition curves, some obvious conclusions can be drawn.

From mersalyl titrations, it clearly appeared that the sensitivity of ATP synthesis to weak inhibitions of the phosphate transport was significantly released by KCl. Since mersalyl is preincubated with mitochondria before being added to the medium, KCl could not affect its inhibitory properties. Therefore, the change in the inhibition curve most probably is the consequence of a real change of the kinetic control by this step. One can estimate the control coefficient decreasing from 0.40–0.55 in the absence of KCl to 0.10–0.15 in the presence of KCl.

From the titration curves by the other inhibitors, we tried to estimate whether the loss of control by phosphate
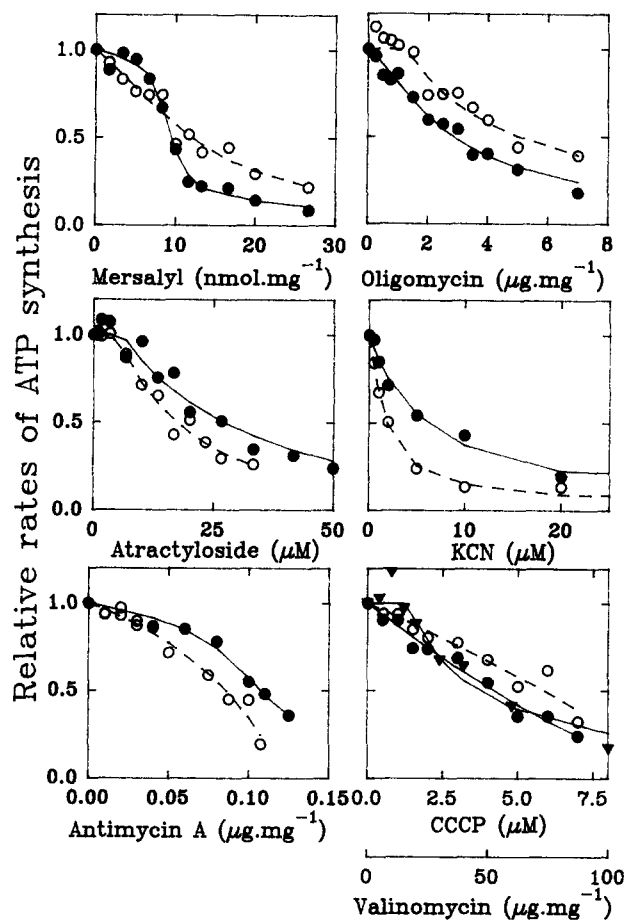

Fig. 6. Effect of KCl on the inhibition curves of ATP synthesis by different inhibitors. Conditions as in Fig. 1 in the absence (open circles) or in the presence (filled circles) of 70 mM KCl. The titration with valinomycin in the presence of KCl was included in the bottom right graph (triangles). In the case of mersalyl, mitochondria were preincubated with the inhibitor for 2 min at 4°C before to be added to the reaction medium. The curves were obtained by non-linear regression by applying the equation of Gellerich et al. [28]. Although we obtained reasonnably good fits, the standard deviations on the parameters were too high to confirm the values found. All the titrations reported in this figure were done on a single mitochondria preparation. Similar results were obtained on two mitochondria preparations.

transport was compensated by an increase of control by another step. The inhibition curves by atractyloside, KCN and antimycin A did not reveal any increase of the control by the translocase, the cytochrome c oxidase and the bc_1 complex, respectively (in fact, the kinetic control by the respiratory complexes seemed to decrease).

The inhibition of ATP synthesis curves by ClCCP revealed a slight increase of the (negative) kinetic control by H^+ leaks. On the other hand, although ATP synthesis became obviously sensitive to K^+ leaks in the presence of KCl, the inhibition curve of ATP synthesis by valinomycin was typical of a non-controlling step.

The more ambiguous answer came from the inhibition by oligomycin. Although it is tempting to conclude to an increase of the kinetic control by the ATP synthase, one should keep in mind that low oligomycin concentrations may have a stimulatory effect of ATP synthesis due to the inhibitory effect of H^+ leaks possibly occurring through F_o sectors unbound to F_1 parts.

From these titration curves it can be seen that the kinetic control by phosphate transport was partly released; it was not, however, obviously reported on another step (with a doubt concerning ATP synthase) but, most likely, shared among all the steps.

3.5. Effect of phosphate transport on the ATP / O ratio

From the data reported above, one can deduce that the reason for the ATP/O ratio being maintained in the
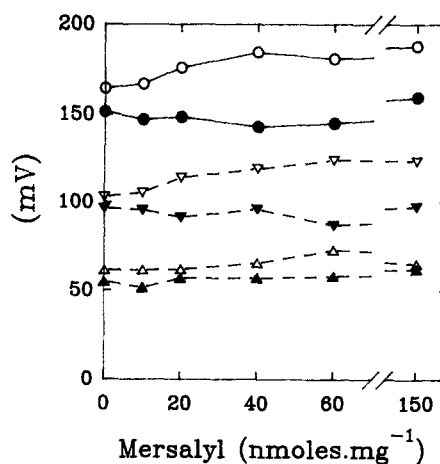
Fig. 8. Effect of mersalyl on the protonmotive force. Same conditions as in Fig. 3. Open symbols: no KCl; filled symbols: +100 mM KCl. Upward triangles: ΔpH; downward triangles: $\Delta\Psi$; circles: ΔP.

presence of KCl despite the slight decrease in the proton-motive force, is that phosphate transport was stimulated. Conversely, one should expect that, if phosphate transport cannot be stimulated, the ATP/O ratio should decrease.

Fig. 7 shows the values of ATP/O ratio when ATP synthesis is titrated by oligomycin, atractyloside or mersalyl. As expected, both in the absence or in the presence of KCl, oligomycin and atractyloside did not change the ATP/O ratio (except, of course, when the respiration rate approached state 4). In other words, oligomycin and atractyloside inhibited both fluxes in parallel.

In contrast, the effect of mersalyl depended on the presence of KCl: in the absence of KCl, ATP/O ratio remained constant, whereas in the presence of KCl, mersalyl decresed the ATP/O ratio, this corresponding to the fact that state 3 respiration was less affected by mersalyl than the ATP synthesis.

This high rate of respiration when ATP synthesis was inhibited by mersalyl actually corresponded to the mainte-nance of a low value of $\Delta\Psi$ (Fig. 8).

4. Discussion

The data reported in this paper are in good accordance with the assumption that yeast mitochondria, under phos-phorylating conditions, support active electrogenic K^+ pathways.

The effect of KCl on respiration rates was, as expected, a partial dissipation of the transmembrane potential (Table 2). This dissipation is linked to the spontaneous activity of the electroneutral K^+/H^+ exchange (Fig. 4) following the electrophoretic entry of K^+, the sum of both probably resulting in a protonophoric effect. However, this effect is very limited, as demonstrated by the poor extent of the stimulation of state 4 respiration by KCl.

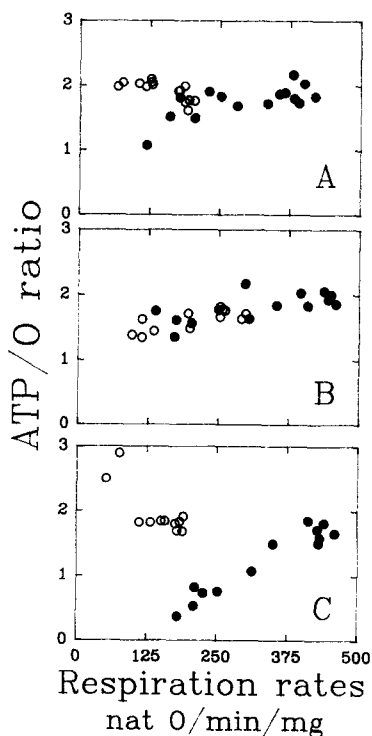The unexpected effect we observed was the stimulation

Fig. 7. Effect of oligomycin, atractyloside and mersalyl over the ATP/O ratio. Values were determined from titration experiments similar to that reported in Fig. 6 with (A) oligomycin, (B) atractyloside or (C) mersalyl. Open circles: no KCl; filled symbols: +70 mM KCl.

of the rate of ATP synthesis. This result, which at first sight appeared to be in contradiction with the (slight) dissipation of $\Delta\Psi$, could be explained by the peculiar behaviour of the kinetic control in yeast mitochondria. Indeed, in addition to the cytochrome c oxidase, the main controlling step in yeast mitochondria is the phosphate/H^+ cotransporter [26], whereas in mammalian mitochondria the main controlling step is the ADP/ATP translocator [27].

We observed that the maximal activity (not the apparent k_T) of the yeast phosphate/H^+ cotransport was stimulated by KCl entry. This was related to an increase of ΔpH, revealed from the higher level of phosphate accumulation.

Under phosphorylation conditions, one can expect the same feature to occur. The electrophoretic K^+ entry decreased $\Delta\Psi$ which is followed by a stimulation of the respiration rate and thus of H^+ excretion. Obviously, we did not observe any increase of the steady-state ΔpH, since H^+ reentry occurred more rapidly, both by the P_i/H^+ cotransporter and the K^+/H^+ exchange (which is active under these conditions). In other words, although the steady-state ΔpH did not change (Table 2), the rate of the proton cycle should be increased.

This activation of P_i transport can also be deduced from the partial release of the kinetic control by this step.

It should be noted that the maintaining of a good efficiency (i.e., ATP/O ratio) of oxidative phosphorylation in the presence of KCl is conditionned by a high rate of ATP synthesis and thus an optimal activity of the P_i/H^+ cotransporter. Since respiration can be stimulated by the K^+ cycle independently on the activity of phosphate transport, the inhibition of ATP synthesis by mersalyl induced a lost of efficiency of the system. This uncoupling induced by KCl when phosphate transport is not stimulatable clearly supports the hypothesis that the stimulation of phosphate transport was responsible for the absence of uncoupling observed under normal conditions.

This activation of ATP synthesis by KCl is of interest, since it showed that K^+ can actually enter the matrix via electrophoretic pathways without uncoupling of respiration and ATP synthesis. This is a good indication that such electrogenic pathways are able to work under physiological conditions and not only, as generally considered, under pathological conditions.

Acknowledgements

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