Potassium transport coupled to ATP hydrolysis in reconstituted proteoliposomes of yeast plasma membrane ATPase*

Antonio Villalobo†

From the Laboratoire d'Enzymologie, Université de Louvain, Place Croix du Sud, 1, 1348 Louvain-la-Neuve, Belgium

Potassium transport coupled to ATP hydrolysis has been reconstituted in proteoliposomes using a highly purified plasma membrane Mg2+-dependent ATPase of the yeast Schizosaccharomyces pombe.

The ATPase activity of the incorporated enzyme was strongly stimulated (2.2-fold) by the H+-conducting agent carbonyl cyanide m-chlorophenylhydrazone (CCCP). The H+/K+ exchanger nigericin (in the presence of K+) stimulated 1.6-fold the ATPase activity. When both ionophores were added together, the stimulation was increased up to 2.7-fold.

When a potassium concentration gradient (high K+i) was applied to the proteoliposome membrane, a significant drop in the CCCP-stimulated ATPase activity was observed. Inversion of the K+ concentration gradient (high K+i, no) did not decrease the stimulation by CCCP. High Na+i also decreased the stimulation induced by CCCP in the absence but not in the presence of external K+. However, high Li+i had no effect.

Direct potassium efflux from the proteoliposomes was detected upon addition of MgATP using a selective K+ electrode. The ATP-dependent potassium efflux was abolished in CCCP and/or nigericin-pretreated proteoliposomes. However, during steady state ATP hydrolysis, a transient and small K+ efflux was observed upon addition of a CCCP pulse.

I propose that the plasma membrane Mg2+-dependent ATPase in yeast cells not only carries out electrogenic H+ ejection but also drives the uptake of potassium via a voltage-sensitive gate which is closed in the absence and open in the presence of the membrane potential.

In order to maintain a high potassium concentration gradient across the plasma membrane, animal cells use the (Na+, K+)-ATPase (for review see Ref. 1). However, in plant cells, a (H+, K+)-ATPase has been suggested to be involved in K+ transport (for review see Ref. 2). In bacteria, several ATP-dependent systems for K+ uptake have also been described (3). The plasma membrane Mg2+-dependent ATPase of fission yeast has been proposed to carry out electrogenic proton translocation across the cell plasma membrane (for review see Ref. 4). We achieved the definitive demonstration of electrogenic proton translocation coupled to ATP hydrolysis in reconstituted proteoliposomes (5).

Recently we have suggested that a yeast plasma membrane ATPase could be directly involved in cellular potassium uptake because the high potassium concentration gradient across the plasma membrane appears to be higher than the gradient expected if the membrane potential (generated by an electrogenic pure H+ pump) was the only driving force for potassium uptake in metabolizing cells (6). In the present paper, we demonstrate that the purified yeast plasma membrane ATPase is able to carry out K+ transport in proteoliposomes. Taking into account the previously reported electrogenic H+ translocation by this enzyme (5) and the CCCP-sensitive K+ transport in the opposite direction (demonstrated in this present paper), we propose that the yeast plasma membrane ATPase could be an electrogenic H+/K+ pump in which potassium transport takes place through a channel which is controlled by the electrical gradient across the membrane. The K+ channel is closed in the absence and open in the presence of the membrane potential. This proposal does not necessarily imply that the K+ transport is stoichiometrically coupled to the H+ translocation in the opposite direction.

MATERIALS AND METHODS

Chemicals—ATP disodium salt (grade II) or magnesium salt, egg L-a-lyosphophatidylcholine, ovine brain L-a-phosphatidyethanolamine (II-S type), soybean L-a-phosphatidylcholine (II-S type and IV-S type), bovine heart diphosphatidyl glycerol (sodium salt), cholester, cholic acid (sodium salt), bovine serum albumin (fraction V), CCCP, and gramicidin S were purchased from Sigma. Valinomycin and A23187 were obtained from Calbiochem and nigericin (batch 477-19B) was a kind gift of Dr. J. W. Westley, The Roche Institute, Nutley, NJ.

Biological Material—The fission yeast Schizosaccharomyces pombe 972a was grown in aerobic conditions in 5.8% (w/v) yeast extract at pH 4.5. The cells were harvested in exponential phase of growth.

Purification of the Plasma Membrane ATPase—The plasma membrane ATPase was purified by a modified procedure (6) of the one previously described (7).

Analytical Procedure—Protein concentration was determined by the method of Lowry et al. (8) using bovine serum albumin as a standard. Inorganic phosphate was determined as described by Pllman and Penefski (9). Potassium movements were monitored with a selective K+ electrode (Beckman 89047) using as reference electrode a small diameter combination pH glass electrode (A. M. Thomas 4094-L25 model) in a 2-ml thermostated chamber at 35 °C. The electrode outputs were amplified through two Beckman Expanding-Serie 82 pH meters connected in series and used in pH and millivolt modes for the pH and K+ electrodes, respectively, and fed into a dual channel Teckman Electronic Ltd. recorder adjusted to appropriate chart speed. Known amounts of standard solutions of KCl were added to calibrate the K+ electrode response in all of the experiments. Inversion of the K+ concentration gradient (high K+, 3) did not decrease the stimulation by CCCP. However, high Li+ had no effect.

In the present paper, we propose that the yeast plasma membrane ATPase could be an electrogenic H+/K+ pump in which potassium transport takes place through a channel which is controlled by the electrical gradient across the membrane. The K+ channel is closed in the absence and open in the presence of the membrane potential. This proposal does not necessarily imply that the K+ transport is stoichiometrically coupled to the H+ translocation in the opposite direction.

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*The abbreviations used are: CCCP, carbonyl cyanide m-chlorophenylhydrazone, Tris, Tris(hydroxymethyl)methylamine; EDTA, ethylenediaminetetraacetic acid; HRPES, 4-(2-hydroxymethyl)-1-piperazinethesulfonic acid.
Racker (10) was used to incorporate the purified ATPase in the phospholipid membrane vesicles. The phospholipids were added at a final concentration of 1.5% (w/v) and the cholate at a final concentration of 1% (w/v). The lipid/protein ratio (w/w) was usually about 200. When the ionic composition of the intraliposomal space was different from the external medium, a second dialysis was performed to change the external solutes.

RESULTS

Control of the Rate of ATP Hydrolysis by the Proton and Potassium Electrochemical Gradients—In a previous paper we have shown (5) that the rate of ATP hydrolysis was accelerated when the membrane potential across the ATPase proteoliposome membrane was collapsed. In the conditions described previously (pH 7.0, high buffer capacity, and equal Na⁺ and K⁺ concentration on both sides of the membrane), the maximum stimulatory effect was obtained upon addition of CCCP alone or by the combined addition of valinomycin plus nigericin. Nigericin alone had only little effect. From these results, we concluded that the membrane potential was generated by electrogenic proton pumping. This was confirmed by direct measurement of proton translocation (5). However, no direct indication in favor or against some sort of control of the rate of ATP hydrolysis by a potassium concentration gradient was obtained.

The experiments reported in the present paper were carried out at a more optimal pH for the ATPase assay (pH 6.2) than in the previous paper (5) with equal Na⁺ and K⁺ concentration on both sides of the membrane. In these new conditions (see Table I, experiment 1), the stimulatory effect of CCCP on the ATPase activity was about twice that previously reported (120% versus 60%). At pH 6.2, nigericin alone had a pronounced stimulatory effect (67%), but no significant stimulation was obtained either by valinomycin (4%) or by gramicidin S (2%). When CCCP plus nigericin were added together, a very strong stimulation (173%) was observed, well above the effect of CCCP alone (120%). CCCP stimulated also the ATPase activity in the presence of valinomycin and/or gramicidin S (see Table I). As previously reported (5), the combined addition of valinomycin plus nigericin was strongly stimulatory (134%), slightly above the effect of CCCP alone (120%). However, valinomycin plus gramicidin S had a small effect (12%), whereas nigericin plus gramicidin S stimulated appreciably (83%). When the buffer concentration was increased about 16 times (results not shown), the effects of CCCP alone (129%) or nigericin alone (66%) were similar to those observed at low buffer concentration. However, at this high buffer concentration, the combined addition of CCCP plus nigericin produced an increase of only 144%, slightly above the effect of CCCP alone (129%). Table I, experiment 2, also shows that the divalent cation/H⁺ exchanger A23187 (in the presence of Mg²⁺) does not have the same effect as nigericin, although both agents should similarly collapse any H⁺ concentration gradient across the proteoliposome membrane. As in the case of nigericin plus CCCP, the stimulatory effect of A23187 plus CCCP was better than of the one produced by CCCP alone (results not shown). Fig. 1 shows that the reconstituted ATPase activity is linear for at least 10 min in the absence as well as in the presence of CCCP and/or nigericin.

The purified ATPase was incorporated into different phospholipid vesicles using the same cholate dialysis method and the same batch of enzyme. Table II summarizes the specific activity of the incorporated ATPase and the stimulatory effects of CCCP or nigericin or both. Good tightly coupled proteoliposomes were obtained with both II-S and IV-S types of L-a-phosphatidylcholine either in the presence or in the absence of added cholesterol or diphasphatidyl glycerol. A dramatic decrease of the coupling was obtained when L-a-phosphatidylethanolamine was used either alone or in combination with L-a-phosphatidylcholine at a 1:1 ratio. This was demonstrated by the high specific activity of the incorporated ATPase and the absence of significant stimulation by ionophores. It was also observed that the further stimulation by nigericin above the CCCP control was dependent on the phospholipid composition of the liposomes.

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**Table I**

ATP hydrolysis control of the reconstituted plasma membrane ATPase by the H⁺ and K⁺ electrochemical gradients

The ATPase activity was assayed during 10 min at 25 °C in 1 ml of 50 mM KCl, 50 mM NaCl, 10 mM MgCl₂, 10 mM ATP (disodium salt), 3 mM K-HEPES, pH 6.2, and 0.2% (v/v) methanol. Purified ATPase 13.7 μg and 21.4 μg of protein in 2.97 mg and 4.28 mg of phospholipid liposomes (L-a-phosphatidylcholine, II-S type) were added for experiments 1 and 2, respectively. Where indicated, 2 μM CCCP, 1 μg·ml⁻¹ of nigericin, 1 μg·ml⁻¹ of valinomycin, 1 μg·ml⁻¹ of gramicidin S, and 1 μg·ml⁻¹ of A23187 were present.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Addition</th>
<th>ATPase activity</th>
<th>Relative activity</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>μmol·min⁻¹·mg⁻¹</td>
<td>% over control</td>
</tr>
<tr>
<td>1</td>
<td>None</td>
<td>2.44</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>CCCP</td>
<td>5.57</td>
<td>120</td>
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<tr>
<td></td>
<td>Nigericin</td>
<td>4.07</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Valinomycin</td>
<td>2.55</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Gramicidin S</td>
<td>2.49</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>CCCP + Nigericin</td>
<td>6.67</td>
<td>173</td>
</tr>
<tr>
<td></td>
<td>CCCP + valinomycin</td>
<td>5.58</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td>CCCP + gramicidin S</td>
<td>5.82</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>Valinomycin + Nigericin</td>
<td>5.71</td>
<td>134</td>
</tr>
<tr>
<td></td>
<td>Valinomycin + gramicidin S</td>
<td>2.78</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Nigericin + gramicidin S</td>
<td>4.48</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>1.93</td>
<td>100</td>
</tr>
<tr>
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<td>CCCP</td>
<td>3.75</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Nigericin</td>
<td>2.95</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>A23187</td>
<td>2.31</td>
<td>20</td>
</tr>
</tbody>
</table>

**Fig. 1.** Effect of CCCP and/or nigericin on the time course of ATP hydrolysis by the incorporated ATPase. The incorporated enzyme (24.1 μg of protein in 4.8 mg of phospholipid vesicles of L-a-phosphatidylcholine II-S type) was assayed for ATPase activity at 25 °C for the indicated period of time in a total volume of 1 ml of 50 mM NaCl, 50 mM KCl, 10 mM MgCl₂, 10 mM ATP (sodium salt), 0.2% (v/v) methanol, and 3 mM K-HEPES, pH 6.2. Where indicated, 2 μM CCCP and/or 1 μg·ml⁻¹ of nigericin was added.
**Effects of CCCP and/or nigericin on the ATPase activity of the reconstituted enzyme in different phospholipid vesicles**

The ATPase activity was assayed during 10 min at 25 °C in 1 ml of 50 mM KCl, 50 mM NaCl, 10 mM MgCl₂, 10 mM ATP (disodium salt), 3 mM K-HEPES, pH 6.2, 0.2% (v/v) methanol, and 13.7 μg of protein of purified ATPase incorporated into different phospholipid vesicles as follows: 2.97 mg of L-α-phosphatidylcholine (II-S type), 2.97 mg of L-α-phosphatidylcholine (II-S type) + 0.3 mg of cholesterol, 2.97 mg of L-α-phosphatidylcholine (II-S type) + 0.74 mg of diphasophatidyl glycerol, 2.97 mg of L-α-phosphatidylcholine (II-S type), and 1.48 mg of L-α-phosphatidylcholine (II-S type) + 1.48 mg of L-α-phosphatidylethanolamine (II-S type) or 2.97 mg of L-α-phosphatidylethanolamine (II-S type). Where indicated, 2 μM CCCP and 1 μg·ml⁻¹ of nigericin were added.

<table>
<thead>
<tr>
<th>Phospholipid vesicles</th>
<th>ATPase activity (pmol·min⁻¹·mg⁻¹)</th>
<th>Relative activity (% over control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-α-Phosphatidylcholine (II-S type)</td>
<td>+CCCP</td>
<td>+NGERI-</td>
</tr>
<tr>
<td>2.44</td>
<td>5.37</td>
<td>4.07</td>
</tr>
<tr>
<td>2.57</td>
<td>5.18</td>
<td>3.93</td>
</tr>
<tr>
<td>2.04</td>
<td>4.86</td>
<td>3.97</td>
</tr>
<tr>
<td>L-α-Phosphatidylcholine (II-S type)</td>
<td>+ cholesterol (10:1)</td>
<td>2.84</td>
</tr>
<tr>
<td>6.51</td>
<td>7.51</td>
<td>7.23</td>
</tr>
<tr>
<td>L-α-Phosphatidylethanolamine (II-S type)</td>
<td>(1:1)</td>
<td>5.09</td>
</tr>
</tbody>
</table>

These experiments clearly suggest that not only the membrane potential, generated by the electrogenic H⁺ pumping, was an important contributor in the feedback control of the incorporated ATPase activity, but also suggested that a K⁺ gradient was also built up during the ATP hydrolysis (stronger stimulation of nigericin versus A23187). As expected, the stimulatory effect of nigericin alone was smaller than that of CCCP alone since the electroneutral exchange of H⁺ for K⁺ does not collapse the membrane potential.

**Potassium Transport Coupled to ATP Hydrolysis across the Proteoliposome Membrane**—Fig. 2 shows the direct measurement of potassium extrusion from the plasma membrane ATPase potassium-loaded proteoliposomes upon addition of MgATP. A fast potassium exit was observed that became progressively slower in rate. The slowing down in the rate of K⁺ exit was not related to the exhaustion of the intraliposomal content of potassium since addition of nigericin or valinomycin plus CCCP induced a fast and large potassium leak out of the proteoliposomes in exchange for H⁺ (results not shown). A further addition of CCCP (Fig. 2) induced a small and transient potassium exit as expected for an active transport. The ATP-dependent potassium exit was totally abolished after preincubation with the H⁺-conducting agent CCCP and consequently in the absence of a membrane potential. Fig. 3 shows that addition of MgATP to nigericin-treated proteoliposomes did not produce a net K⁺ exit as expected. However, a transient net K⁺ disappearance from the medium of unknown nature was observed. Again in the nigericin-treated proteoliposomes, the addition of CCCP induced again a net potassium exit. These results clearly show that in the reconstituted system there is a potassium transport directly coupled to the ATP hydrolysis which is not present in the absence of the membrane potential but can also be transiently shown upon addition of a CCCP pulse during ATP hydrolysis.

**Specificity for Potassium Transport**—The ATP-dependent K⁺ efflux from potassium-loaded proteoliposomes, measured in Fig. 2, could, in principle, be interpreted as an unspecified extrusion of K⁺ down its concentration gradient drive by the generating membrane potential (positive inside) built it up by the electrogenic H⁺ pumping inside the liposomes (5). However, this process appears to be specific for potassium with some restrictions. In K⁺-loaded liposomes, the degree of stimulation by the H⁺-conducting agent CCCP dropped (see Table III, experiments 1 and 2) even when only a low concentration of K⁺ was present inside the liposomes. This effect which can be correlated with the K⁺ exit upon addition of MgATP observed in Fig. 2 appears to be electrophoretic since it was observed only when the membrane potential was present. It should be mentioned that this drop of the stimulation of the ATPase by CCCP is not only a consequence of an increase of

![Fig. 2](http://www.jbc.org/content/1826/3/1826/F2.large.jpg)

**FIG. 2.** Potassium transport coupled to ATP hydrolysis. Potassium movement was recorded with a K⁺-selective electrode in a thermostated chamber at 25 °C in a total volume of 2 ml. The ATPase (15±2 μg of protein) was incorporated in 30.8 μg of K⁺-loaded phospholipid vesicles (L-α-phosphatidylcholine II-S type). The composition of the medium in the internal proteoliposomes space was 100 mM KCl, 10 mM MgCl₂, and 50 mM Li-HEPES, pH 6.2. The external medium was 100 mM LiCl, 10 mM MgCl₂, and 50 mM Li-HEPES, pH 6.2. Where indicated, a pulse of 1 mM MgATP or 2 μM CCCP was added.

![Fig. 3](http://www.jbc.org/content/1826/3/1826/F3.large.jpg)

**FIG. 3.** Effect of nigericin on potassium transport. The experiment was carried out in the same conditions as described in Fig. 2 except that a pulse of 1 μg·ml⁻¹ of nigericin was added about 3 min before the first addition shown in the trace.
The incorporated enzyme (21.7 μg of protein in 4.35 mg of phospholipid vesicles of L-a-phosphatidylcholine (II-S type)) was assayed for ATPase activity for 10 min at 25 °C in a medium containing 10 mM MgATP, 3 mM HEPES, 0.1% methanol, and 100 mM concentration of the indicated chloride salt(s) at pH 6.2. The internal ionic composition of the proteoliposomes was as indicated except that MgATP was substituted for 10 mM MgCl₂. When indicated, 2 μM CCCP was added to the reaction mixture. The presented results are the average of two independent determinations.

We have demonstrated in a recent paper that the plasma membrane Mg²⁺-dependent ATPase of the yeast *S. pombe* carries out electrogenic H⁺ pumping (5). The direct measurement of proton translocation coupled to ATP hydrolysis across the membrane of reconstituted phospholipid vesicles was achieved using potassium (+valinomycin) as charge-compensating cation. The *S. pombe* and *Saccharomyces cerevisiae* enzymes have also been reconstituted into phospholipid vesicle by the freezing-thawing method. In these proteoliposomes, the quenching of 9-amino-6-chloro-2-methoxyacridine was observed during ATP hydrolysis and was released by uncouplers (11, 12). In the reconstituted enzyme of *S. cerevisiae*, a P:ATP exchange reaction was also measured (13).

In the present paper, three independent pieces of information suggest that this plasma membrane Mg²⁺-dependent ATPase of yeast could also be involved in K⁺ transport.

We had shown (Tables I and II and Fig. 1) that the rate of ATP hydrolysis catalyzed by the incorporated enzyme appears to be controlled not only by the electrochemical proton gradient but also by a potassium concentration gradient across the phospholipid membrane. The fact that the enzymes were strongly stimulated by the H⁺/K⁺ exchanger nigericin strongly supports the idea that a potassium concentration gradient has been built up during ATP hydrolysis, especially since the Ca⁺⁺ or Mg⁺⁺/2H⁺ exchanger A23187 had smaller effect.

Moreover, we showed a direct exit of potassium of the proteoliposomes coupled to ATP hydrolysis. The fact that the potassium transport was abolished by pretreatment of the proteoliposomes with CCCP suggests that the potassium transport takes place via a potassium channel of the ATPase which is open only in the presence of the membrane potential generated by the electrogenic proton transport (5). Although the hydrophobic potassium channel without involvement of a polypeptide has been proposed to exist in phospholipid membranes (14), the probability that such translocation takes place appears to be highly improbable at normal temperature (15). There are several lines of evidence that make unlikely the interpretation that the potassium exit of the liposome is only due to an unspecific leak of the internal potassium pushed by the membrane potential (positive inside). (a) The ATP-induced K⁺ exits rapidly slow down with time, indicating that some sort of control of the potassium pumping is under way. This should not be the case if an unspecific leak was the reason for this K⁺ exit since there was not an exhaustion of the internal potassium (result not shown). (b) If a significant potassium permeability of the proteoliposome membrane was the reason for the potassium leak down the concentration gradient in the K⁺-loaded proteoliposomes, the K⁺ exit should be induced by the simple addition of CCCP in the absence of ATP because the H⁺ could then be able to compensate for the charge imbalance produced during K⁺ exit from the liposome down the concentration gradient. However, this was not the case (see Fig. 1). Even more important, during steady state ATP hydrolysis, a pulse of CCCP induces a transient and small K⁺ exit from the proteoliposomes, as expected for an active potassium transport. This could be interpreted assuming that the total collapse of the membrane potential upon addition of CCCP lasts several seconds and/or the K⁺ gate takes several seconds to be closed after a sudden drop in the membrane potential. We should emphasize that the slope of the potassium trace observed in Fig. 2 before the addition of any reagent was not a real K⁺ translocation because it was also observed in the absence of added proteoliposomes. This drift of the K⁺ electrode response is likely to be due to some K⁺ leak out from the reference electrode when used in a potassium-free medium as is the case in our experimental conditions. (c) Our results also demonstrate that this K⁺ efflux from the proteoliposomes is accompanied by a drop in the stimulation of the ATPase induced by CCCP. This effect is not only due to an increase of the ATPase activity in the absence of the uncoupler but, what is more important, is also a consequence of a significant decrease of the enzymatic activity in the presence of CCCP. Although at the present time a clear interpretation of these data is not possible, a simple uncoupling effect by the internal K⁺ is excluded because, in this case, only an increase of the ATPase activity in the absence of CCCP would be expected. Moreover, no ionic effect on the catalytic site of the ATPase could account for these results since the ATPase activity was assayed in the presence of the same ionic composition in the external medium.
transport by the plasma membrane ATPase of yeast can be drawn, further work is required to study the H+ and K+ as well as the H+/K+ stoichiometric ratios. Also, it should be very interesting to study the specificity of the potassium channel for other monovalent cations in the absence of ATP hydrolysis as well as its affinity for potassium. In conclusion, we point out that the present paper is the first direct proof that the plasma membrane ATPase of yeast is responsible for the active transport of potassium inside living cells. From theoretical considerations concerning yeast cells (6) and from other experimental evidences available in bacteria (16) and plant cells (17), it has been proposed that the direct transport of K+ inside the cell by a plasma membrane ATPase could be more efficient than a simple electrophoretic K+ uptake via an independent carrier and driven by the membrane potential generated by a primary H+ pump. Our model could better account for the high K+ concentration gradient across the plasma membrane of living cells since part of the free energy of the ATP hydrolysis could be directly utilized not only for H+ extrusion of the cell but also for the potassium uptake that already is favored by the membrane potential (negative inside) across the cell membrane.

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A Villalobo


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