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KINETIC STUDIES ON THE ($Na^+ + K^+$)-DEPENDENT ATPase

EVIDENCE FOR COEXISTING SITES FOR Na^+, K^+ AND Mg^{2+}

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Na^+-ATPase activity of a dog kidney ($Na^+ + K^+$)-ATPase enzyme preparation was inhibited by a high concentration of NaCl (100 mM) in the presence of 30 μM ATP and 50 μM $MgCl_2$, but stimulated by 100 mM NaCl in the presence of 30 μM ATP and 3 mM $MgCl_2$. The $K_{0.5}$ for the effect of $MgCl_2$ was near 0.5 mM. Treatment of the enzyme with the organic mercurial thimerosal had little effect on Na^+-ATPase activity with 10 mM NaCl but lessened inhibition by 100 mM NaCl in the presence of 50 μM $MgCl_2$. Similar thimerosal treatment reduced ($Na^+ + K^+$)-ATPase activity by half but did not appreciably affect the $K_{0.5}$ for activation by either Na^+ or K^+, although it reduced inhibition by high Na^+ concentrations. These data are interpreted in terms of two classes of extracellularly-available low-affinity sites for Na^+: Na^+-discharge sites at which Na^+-binding can drive E_2-P back to E_1-P, thereby inhibiting Na^+-ATPase activity, and sites activating E_2-P hydrolysis and thereby stimulating Na^+-ATPase activity, corresponding to the K^+-acceptance sites. Since these two classes of sites cannot be identical, the data favor co-existing Na^+-discharge and K^+-acceptance sites. Mg^{2+} may stimulate Na^+-ATPase activity by favoring E_2-P over E_1-P, through occupying intracellular sites distinct from the phosphorylation site or Na^+-acceptance sites, perhaps at a coexisting low-affinity substrate site. Among other effects, thimerosal treatment appears to stimulate the Na^+-ATPase reaction and lessen Na^+-inhibition of the ($Na^+ + K^+$)-ATPase reaction by increasing the efficacy of Na^+ in activating E_2-P hydrolysis.

Introduction

Understanding the reaction sequence of the ($Na^+ + K^+$)-ATPase enzyme and the transport mechanism of the Na^+/K^+ pump, which this enzyme represents, obviously requires an account of the sites at which cations interact. Despite numerous descriptions of cation effects on enzyme and pump, even a cataloging of such sites has been elusive, largely due to the complexities of the reaction process [1–3]. Recently, Hara and Nakao [4], in a detailed analysis of the effects of high Na^+ concentrations on the phosphorylated enzyme, defined two distinct and antogonistic classes of actions, supporting earlier observations that high concentrations of extracellular Na^+ both can favor the E_1-P conformational state of the enzyme over E_2-P [5,6] and can activate hydrolysis of E_2-P [7,8]. These observations are extended here in kinetic studies on the ($Na^+ + K^+$)- and Na^+-ATPase reactions catalyzed by both the native and the thimerosal-treated [9–12] enzyme. The results, supplementing earlier studies on a different enzyme preparation [13], are considered in terms of the availability of sites for Na^+ and K^+, leading to reaction models requiring the simultaneous presence of extracellular discharge sites for Na^+ distinct from and coexisting with extracellular

acceptance sites for K^+ (on the same or separate peptides of the enzyme/pump complex). The models also require modulating sites for Mg^{2+} distinct from these monovalent cation sites and from the Mg^{2+}-site occupied during enzyme phosphorylation.

Methods and Materials

The enzyme was prepared from the medullae of frozen canine kidneys by a modification [14] of the procedure of Jørgensen [15].

Na^+-ATPase activity was measured in terms of the production of [^{32}P]P_i from incubations at 37°C with [γ-^{32}P]ATP, as previously described [16]. The standard incubation medium for Na^+-ATPase activity contained 30 mM histidine-HCl/Tris (pH 7.8), 30 μM [γ-^{32}P]ATP, 50 μM $MgCl_2$, and 1 mM NaCl. ($Na^+ + K^+$)-ATPase activity was measured similarly, in the presence of KCl as well; with ATP concentrations higher than 0.1 mM production of P_i was measured colorimetrically, as previously described [17]. The standard incubation medium for ($Na^+ + K^+$)-ATPase activity contained 30 mM histidine-HCl/Tris (pH 7.8), 3 mM ATP, 3 mM $MgCl_2$, 90 mM NaCl, and 10 mM KCl. K^+-phosphatase activity was measured in terms of *p*-nitrophenol production from incubations at 37°C with *p*-nitrophenylphosphate, as previously described [18]. The standard incubation medium contained 30 mM histidine-HCl/Tris (pH 7.8), 3 mM *p*-nitrophenyl phosphate, 3 mM $MgCl_2$, and 10 mM KCl. Data presented are averages of four or more experiments, each performed in duplicate or triplicate, with the standard error of the mean where appropriate.

The enzyme preparation was reacted with 0.2 mM thimerosal by incubating it for 10 min at 22°C in 30 mM histidine-HCl/Tris (pH 7.8), followed by dilution with 0.25 M sucrose and washing by centrifugation [9].

Frozen dog kidneys were obtained from Pel-Freeze, [γ-^{32}P]ATP from Amersham, ATP (vanadate-free) and *p*-nitrophenyl phosphate from Sigma, and thimerosal (ethylmercurithiosalicylic acid) from Pfaltz and Bauer.

Results

Na^+-ATPase activity of the ($Na^+ + K^+$)-ATPase enzyme preparation is demonstrable in the absence of added K^+, but with a specific activity only one-tenth that of the ($Na^+ + K^+$)-ATPase when measured in the standard media described under Methods. In the presence of 30 μM ATP and 50 μM $MgCl_2$ the Na^+-ATPase reaction velocity rose with increasing NaCl concentrations up to 10 mM, but then fell (Fig. 1). The concentration of ATP also affected the extent of inhibition by 100 mM NaCl. In experiments with 1 μM ATP in place of 30 μM, increasing the NaCl concentration from 1 to 100 mM reduced Na^+-ATPase activity 13 ± 3% instead of 28 ± 4%.

In the presence of 30 μM ATP but with 3 mM $MgCl_2$, however, the Na^+-ATPase reaction velocity continued to rise with increasing NaCl concentrations over the range 1 to 100 mM in a seemingly biphasic fashion (Fig. 2). Although Na^+-ATPase activity with 3 mM $MgCl_2$ was less than that with 50 μM $MgCl_2$ at lower NaCl concentrations, the opposite was true at higher NaCl concentrations. Thus, with 100 mM NaCl the velocity in the presence of 3 mM $MgCl_2$ was nearly 50% greater than with the optimal NaCl concentration in the presence of 50 μM $MgCl_2$.

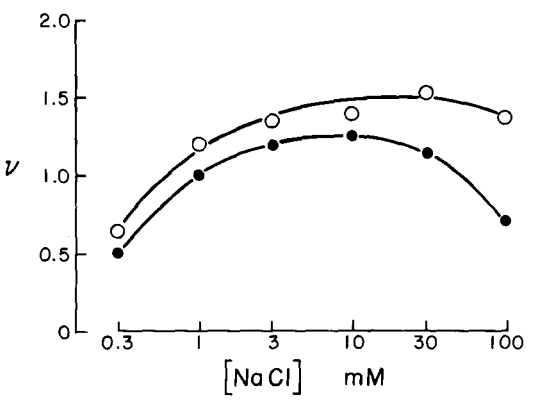

Fig. 1. Na^+-ATPase activity with 50 μM $MgCl_2$. Na^+-ATPase activity was measured in the standard medium containing 30 μM [γ-^{32}P-]ATP and 50 μM $MgCl_2$, as described under Methods, but with the NaCl concentrations indicated. Experiments were performed both with the untreated control enzyme preparation (●) and with the enzyme previously reacted with thimerosal (○). Velocities are expressed relative to that of the untreated enzyme in the standard medium, measured concurrently, defined as 1.0.

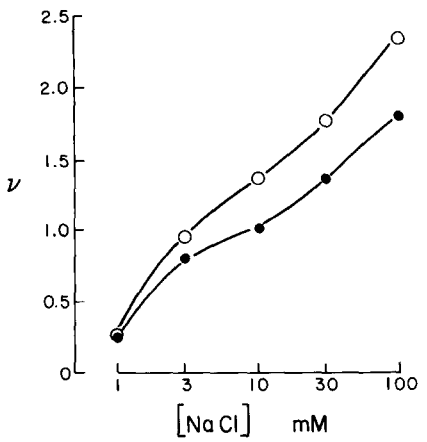

Fig. 2. Na^+-ATPase activity with 3 mM $MgCl_2$. The experiments were performed and the data are presented as in Fig. 1, except that the incubation medium contained 3 mM $MgCl_2$.

$MgCl_2$ stimulated Na^+-ATPase activity in the presence of 100 mM NaCl in a concentration-dependent fashion (Fig. 3). The $K_{0.5}$ was approx. 0.5 mM.

With 30 μM ATP, 50 μM $MgCl_2$, and 100 mM NaCl, the addition of KCl to the incubation medium increased ATPase activity 3-fold (Table I). This $(Na^+ + K^+)$-ATPase activity was unchanged by increasing the $MgCl_2$ concentration to 3 mM, although such an increase doubled Na^+-ATPase

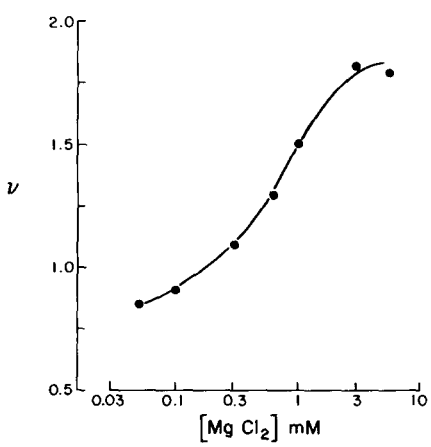

Fig. 3. Effect of $MgCl_2$ concentration on Na^+-ATPase activity. Na^+-ATPase activity of the untreated enzyme was measured in the presence of 30 μM ATP, 100 mM NaCl, and the concentrations of $MgCl_2$ indicated; the velocities are expressed relative to that in the standard medium, as in Fig. 1.

TABLE I

EFFECT OF $MgCl_2$ AND KCl ON ATPase ACTIVITY

ATPase activity was measured at 37°C in media containing 30 mM histidine-HCl/Tris (pH 7.8), 30 μM [γ-^{32}P]ATP, 100 mM NaCl, and either 50 μM or 3 mM $MgCl_2$, together with KCl as noted. Velocities are expressed relative to the Na^+-ATPase activity in the standard medium (1 mM NaCl and 50 μM $MgCl_2$), measured concurrently, defined as 1.0.

Additions	Relative ATPase activity	
	with 50 μM $MgCl_2$	with 3 mM $MgCl_2$
None	0.8 ± 0.1	1.7 ± 0.2
KCl, 1 mM	2.4 ± 0.3	2.3 ± 0.2
KCl, 10 mM	2.2 ± 0.2	1.9 ± 0.2

activity. Increasing the KCl concentration from 1 to 10 mM decreased, if anything, $(Na^+ + K^+)$-ATPase velocity under these conditions.

As Henderson and Askari [9,10] first demonstrated, treatment of the enzyme with the organic mercurial thimerosal alters the reaction properties variously. For the Na^+-ATPase reaction, prior treatment of the enzyme with 0.1 mM thimerosal stimulated Na^+-ATPase activity slightly when subsequently assayed in the standard medium (30 μM ATP, 50 μM $MgCl_2$, and 1 mM NaCl), to 117 ± 4% of control velocity (control enzyme preparation treated identically except for the addition of thimerosal). Moreover, the response of the thimerosal-treated enzyme to NaCl was altered: in the presence of 50 μM $MgCl_2$ inhibition by 100 mM NaCl was nearly abolished (Fig. 1), whereas in the presence of 3 mM $MgCl_2$ the percentage increase in velocity was nearly constant over the range of NaCl concentrations (Fig. 2). For the thimerosal-treated enzyme preparation as well as the untreated enzyme, Na^+-ATPase activity was greater with 3 mM $MgCl_2$ and 100 mM NaCl than with 50 μM $MgCl_2$ and any NaCl concentration tested.

Identical treatment of the enzyme preparation with thimerosal had a greater effect on the subsequently-assayed $(Na^+ + K^+)$-ATPase velocity than on the Na^+-ATPase, in this case decreasing velocity to 58 ± 3% of control values after assay in the standard medium (3 mM ATP and 3 mM $MgCl_2$). Nevertheless, cation activation of the re-

action was affected negligibly, with the $K_{0.5}$ for NaCl measured at 8 vs. 7 mM (Fig. 4) and the $K_{0.5}$ for KCl remaining at 0.7 mM (Fig. 5); however, as previously noted by Askari et al. [11], the curvature of the double-reciprocal plots was decreased for the thimerosal-treated enzyme. The K_m for ATP was also unchanged by prior treatment with thimerosal, remaining at 0.4 mM (data not presented).

On the other hand, inhibition of $(Na^+ + K^+)$-ATPase activity by high concentrations of NaCl was markedly diminished by prior treatment with thimerosal when assayed in the presence of 10 mM KCl (Fig. 6), although such protection was far less apparent when the treated enzyme was assayed in the presence of only 1 mM KCl.

Increasing the $MgCl_2$ concentration from 3 mM in the standard assay medium to 6 mM had negligible effect on the $(Na^+ + K^+)$-ATPase activity of either the control or thimerosal-treated enzyme

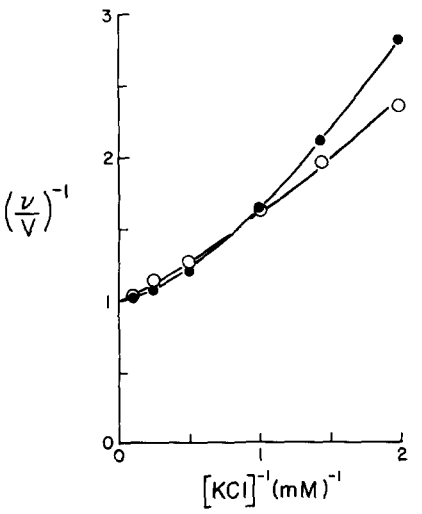

Fig. 5. Effect of KCl concentration on $(Na^+ + K^+)$-ATPase activity. The experiments were performed and the data are presented as in Fig. 4 except that the KCl concentrations were as indicated and the NaCl concentration was 90 mM throughout.

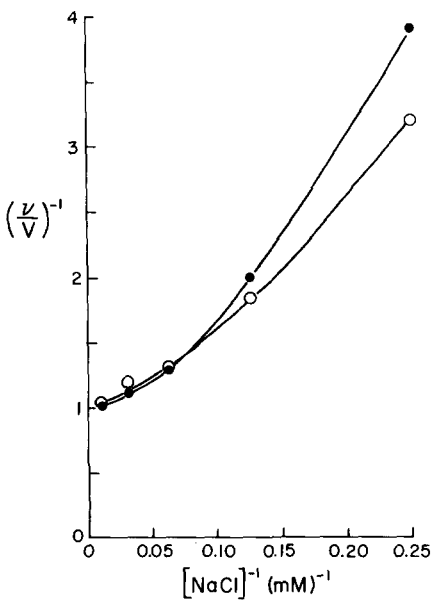

Fig. 4. Effect of NaCl concentration on $(Na^+ + K^+)$-ATPase activity. $(Na^+ + K^+)$-ATPase activity was measured in the standard medium containing 3 mM ATP, 3 mM $MgCl_2$, and 10 mM KCl, as described under Methods, but with the NaCl concentrations indicated. Experiments were performed both with the untreated control enzyme preparation (●) and with the enzyme previously reacted with thimerosal (○). Velocities are expressed as a function of the maximal velocity for each preparation, and the data are presented in double reciprocal form.

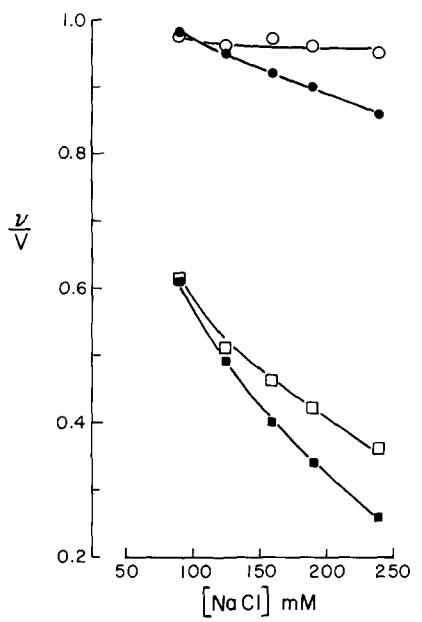

Fig. 6. Effect of high NaCl concentrations on $(Na^+ + K^+)$-ATPase activities. $(Na^+ + K^+)$-ATPase activity was measured in the presence of 3 mM ATP, 3 mM $MgCl_2$, the concentrations of NaCl indicated, and either 10 mM KCl (●, ○) or 1 mM KCl (■, □). Experiments were performed both with the untreated control enzyme preparation (●, ■) and with the enzyme previously reacted with thimerosal (○, □). Velocities are expressed as a function of the maximal velocity for each preparation, as in Fig. 4.

preparations (data not presented).

The enzyme also catalyzes a K^+-activated phosphatase reaction, and prior treatment of the enzyme with thimerosal had essentially no effect on the velocity in the standard medium, decreasing it only to 97 ± 2% of that with control enzyme. On the other hand, the $K_{0.5}$ for KCl was decreased slightly, from 1.3 ± 0.2 to 1.0 ± 0.1 mM (data not presented).

Discussion

A conventional [1–3,19] reaction scheme for the ($Na^+ + K^+$)-ATPase depicts high-affinity activating sites for Na^+ available on the cytoplasmic surface, low-affinity sites for discharge of Na^+ extracellularly, high-affinity activating sites for K^+ available on the extracellular surface, and low-affinity sites for discharge of K^+ cytoplasmically, with acceptance and discharge of Na^+ and K^+ following a ping-pong sequence (Fig. 7). The experiments described here bear on two major issues concerning the availability and functional role of specific cation sites: (i) those at which Na^+ can either inhibit (Fig. 1) or stimulate (Fig. 2) the Na^+-ATPase reaction, and (ii) those at which Mg^{2+} can regulate this inhibition/stimulation (Figs. 1–3).

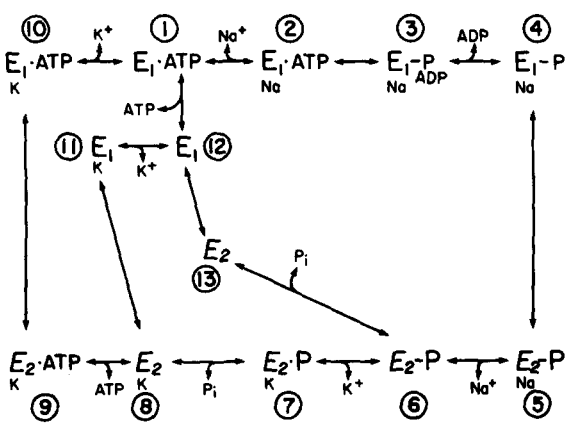

Fig. 7. Reaction sequence for the ($Na^+ + K^+$)-ATPase. A standard reaction sequence [1–3,19] is shown for the ($Na^+ + K^+$)-ATPase, including intermediates 1–10, and for the Na^+-ATPase, including intermediates 1–6 plus 13 and 12. Not shown is the possibility that Na^+ may bind in place of K^+ to the extracellularly-available sites on E_2-P of intermediate 7 with this Na^+-ATPase sequence continuing over 8, 11, and 12.

Previous studies [4–6] have shown that high concentrations of NaCl can stimulate ADP-dependent dephosphorylation of the enzyme and the ADP-ATP exchange reaction, interpretable as Na^+ at low-affinity sites shifting the K^+-sensitive E_2-P form of the enzyme toward the ADP-sensitive E_1-P. Since such effects are mediated through extracellularly-available sites [20,21] a plausible explanation is that Na^+ binding to its discharge sites on E_2-P can drive the reaction backward to E_1-P. On the other hand, stimulation of Na-ATPase activity by high concentrations of Na^+ is also mediated through extracellularly-available sites [4,7,8], and a plausible interpretation is that Na^+ acts through the high-affinity sites at which K^+ activates dephosphorylation of E_2-P [4,7,22], sites at which Na^+ has low affinity and low efficacy compared to K^+.

Recently, Hara and Nakao [4] examined these two antagonistic effects of Na^+ quantitatively in terms of a model (Fig. 8a) showing Na^+ driving E_2-P back toward E_1-P and of K^+ (or its substitute, high extracellular Na^+) activating dephosphorylation of E_2-P, driving the reaction forward. This model is kinetically equivalent to the scheme of Fig. 7; the pertinent steps are shown in Fig. 8b. Examination of the sequences in Figs. 8 a and b reveals that both Na^+ and K^+ bind to the same enzyme form, E_2-P, and if, as recent evidence strongly implies [22], Na^+ activates hydrolysis at the extracellular K^+-sites, then these Na^+-discharge sites and K^+-acceptance sites cannot be identical. It is impossible for Na^+ to bind to the same sites and both drive the reaction backward to E_1-P and forward to E_2-P hydrolysis.

Two possible resolutions of this dilemma are apparent. (i) There may be intervening step(s) between the enzyme form from which Na^+ is discharged and that to which K^+ (or Na^+) binds to activate hydrolysis (Fig. 8c) so the sites are then not identical. This model, however, requires a fixed ratio between the two enzyme forms binding, respectively, Na^+ and K^+ (E_x-P and E_y-P), a ratio that is independent of the Na^+ concentration and reflects merely the rate constants for this isomerization (assuming rapid equilibrium). The experiments of Hara and Nakao [4] clearly show this is not the case: as the Na^+ concentration is raised E_2-P hydrolysis is first favored and then E_1-P

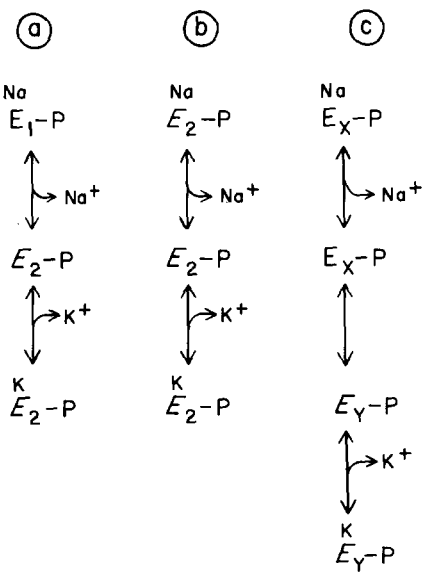

Fig. 8. Alternative schemes for effects of Na^+ on the phosphorylated enzyme. Sequence (a) is from Hara and Nakao [4]; sequence (b) is the corresponding path from Fig. 7; and sequence (c) includes an isomerization between the form from which Na^+ is discharged, E_x-P, and the form to which K^+ (or Na^+) binds to activate hydrolysis, E_y-P.

formation predominates. For Na^+ to alter this ratio requires mediation through yet another site to alter the rate constants for the isomerization. (ii) Alternatively, Na^+ and K^+ need not bind to the same sites on E_2-P. Moreover, to satisfy the strictures above, these distinct sites for Na^+ and for K^+ must coexist, on the same or different peptides of the functional enzyme complex. This resolution of the data is therefore inconsistent with the ping-pong reaction scheme of Fig. 7, although such a kinetic mechanism, as well as unitary transport schemes in which Na^+-sites are cyclically converted into K^+-sites, is still possible with dimeric transport models operating out of phase [1].

The ability of Mg^{2+} to convert inhibition of Na^+-ATPase activity by 100 mM NaCl into stimulation is interpretable, in this context, as Mg^{2+} favoring the conversion of E_1-P to E_2-P. As the Mg^{2+} concentration is raised sufficiently, then instead of Na^+ at the Na-discharge sites driving E_2-P toward E_1-P, Na^+ at the K^+-sites on E_2-P activates hydrolysis. Alternatively, Mg^{2+} might increase the affinity or efficacy of Na^+ at the K^+-sites (which is functionally equivalent to the shift from E_1-P to E_2-P). In the overall cycle of the Na^+-ATPase reaction Mg^{2+} might also stimulate by speeding the conversion of E_2 to E_1. A fourth alternative, that Mg^{2+} itself stimulates E_2-P hydrolysis by occupying an activating monovalent cation site is unlikely since Mg^{2+} acts at the cytoplasmic surface [21] and at saturating levels of cytoplasmic Na^+ to stimulate hydrolysis still further (Figs. 1, 2).

Assuming, then, that Mg^{2+} acts intracellularly to shift E_1-P toward E_2-P (or, perhaps, E_2 to E_1), what sites does it occupy? The high-affinity substrate site at which the enzyme is phosphorylated to form E_1-P necessarily binds Mg^{2+} at equimolar (and micromolar) concentrations, and Mg^{2+} remains with the enzyme at least through dephosphorylation of E_2-P [23]. Consequently, Mg^{2+} could then bind (with lower affinity) to E_2, after initial release of P_i and Mg^{2+}, and thereby favor conversion to E_1; several lines of evidence, however, argue for Mg^{2+} favoring E_2 over E_1 [24–26]. If, instead, Mg^{2+} stimulates Na^+-ATPase activity by favoring E_2-P over E_1-P, then such sites are not available. The remaining possibility is a separate low-affinity substrate site at which Mg^{2+} binds, on the same [27] or different peptide of the enzyme complex; actions of Mg^{2+} through such sites have been proposed previously to account for such phenomena as activation of the K^+-phosphatase reaction, inactivation of the enzyme by Be^{2+}, inhibition of the ADP-ATP exchange reaction, and alteration of Na^+-activation [28]: all these have the same concentration dependence as that seen here (Fig. 3).

The ability of thimerosal treatment to stimulate Na^+-ATPase activity at high Na^+ and low Mg^{2+} concentrations (Fig. 1) is similarly interpretable as: (i) favoring E_2-P over E_1-P; (ii) increasing affinity for Na^+ at the extracellular K^+ sites relative to that at the Na^+-discharge sites; or (iii) increasing the efficacy of Na^+ in activating E_2-P hydrolysis. Possibilities (i) and (ii) are unlikely since thimerosal treatment does not inhibit ADP-ATP exchange [10] nor does it affect the $K_{0.5}$ for Na^+- or K^+-activation of the ATPase reaction (Figs. 4,5). On the other hand, thimerosal treatment lessens inhibition of the ($Na^+ + K^+$)-ATPase reaction by high Na^+ (Fig. 6): this inhibition probably results both from Na^+ driving E_2-P back

to E_1-P and Na^+ competing for the K^+-sites activating hydrolysis. If thimerosal treatment does not favor E_2-P over E_1-P [10], and does not increase the affinity for K^+ (Fig. 5), then the lessened inhibition by Na^+ may be attributed to a greater efficacy for Na^+ in activating hydrolysis of E_2-P. However, such an effect clearly cannot account for the marked inhibition of $(Na^+ + K^+)$-ATPase activity. (A previous interpretation [29] of thimerosal treatment favoring E_1 over E_2 is contradicted by the effects on the K^+-phosphatase reaction, where there is a lack of inhibition and if anything a higher affinity for K^+, since this reaction and K^+-binding are hallmarks of the E_2 conformation.)

Earlier studies with a rat brain enzyme demonstrated that inhibition of Na^+-ATPase activity by 100 mM NaCl increased markedly with ATP concentration, rising from 10% inhibition with 1 μM ATP to 75% with 15 μM ATP [30]. With the dog kidney enzyme the contribution of ATP to inhibition in the presence of 100 mM NaCl was less striking, although inhibition increased 2-fold from 1 μM to 30 μM ATP. The mechanism by which ATP contributes to the inhibition of Na^+-ATPase activity is uncertain. If ATP can bind only to the unphosphorylated enzyme then this component of the inhibition seen with 100 mM NaCl must be mediated through the E_1 or E_2 enzyme forms, and presumably the latter in view of the high affinity of E_1 for ATP. Formation of an E_2(Na)ATP complex, analogous to E_2(K)ATP (Fig. 7, intermediate 9), might, in the absence of facilitating Mg^{2+} or thimerosal treatment, introduce a step in the reaction process slower than in the conventional Na^+-ATPase sequence (Fig. 7, intermediates 1–6 plus 13 and 12).

Acknowledgments

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