

Interactions of Lithium and Protons with the Sodium-Proton Exchanger of Dog Red Blood Cells

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ABSTRACT Passive movements of Li in dog red blood cells (RBC) are like those of Na and protons in being stimulated by osmotic cell shrinkage and inhibited by amiloride. Li and protons have similar asymmetrical effects on Na-H exchange. When the intracellular fluid is made rich in Li or protons, Na-H exchange is stimulated. When the extracellular fluid is enriched in Li or protons, Na-H exchange is inhibited. In the case of protons, these effects can override alterations in driving force that are created by the experimental conditions. For example, acidification of the cytoplasm stimulates outward Na movements, while acidification of the medium inhibits Na efflux. Thus, protons (and, by analogy, Li) can interact with the Na-H exchanger not only as substrates but also as modulators. In previous experiments, the only way to activate the Na-H exchanger in dog RBC was to shrink the cells in hypertonic media. The influences of Li or protons, however, are so strong as to preempt the volume effects, so that the pathway can be activated even in swollen cells and deactivated in shrunken ones.

INTRODUCTION

The increase in passive Na flux that occurs when dog red blood cells (RBC) are osmotically shrunken (18) is mediated by an amiloride-sensitive, electroneutral Na-H exchanger in the plasma membrane (12, 16). Activation of this transporter is promptly reversed when the cells are brought back to a normal or high volume (13). Like similar pathways described in *Amphiuma* RBC (4) and human lymphocytes (5), the dog RBC Na-H exchanger can function as a volume regulator (17). In some cell types, Na-H countertransport serves other functions, such as cytoplasmic pH control or as part of a signaling system set in motion by the action of exogenous mitogens or hormones (2).

The present communication reports experiments designed to explore the interactions of Li and protons with the Na-H exchanger in dog RBC, particularly in light of evidence summarized by Aronson (1) that this transporter may respond to manipulation of its substrates in ways that may give clues as to its mode of

regulation *in vivo*. Specifically, internal protons have been reported in several systems to exert an allosteric activating effect on the Na-H exchanger that is independent of the role of protons as transportable substrates.

In dog RBC, Na-H exchange is activated reversibly by cell shrinkage. As yet there is no information about how the cell perceives its volume or how a volume stimulus might trigger the activation of a transport pathway. In the studies reported here, allosteric effects of protons on both the inner and outer face of the membrane are reported. Li has effects that are qualitatively similar to those of protons. In the case of Li (and presumably also protons), the activating effects of the ion are explicable in terms of a change in the threshold or set point for the volume stimulus. Some of the early results have been briefly summarized (14, 15).

MATERIALS AND METHODS

Dipyridamole and ATP were purchased from Sigma Chemical Co. (St. Louis, MO). Ethoxzolamide was obtained from The Upjohn Co. (Kalamazoo, MI) through the kindness of Drs. L. Mandel (Duke University, Durham, NC) and J. Funder (University of Copenhagen, Denmark). Amiloride was the generous gift of The Merck Institute (West Point, PA). ^{22}Na (9240 Ci/mol) was purchased from Amersham International plc (Amersham, England). All chemicals were reagent grade. Blood was drawn from healthy mongrel dogs into heparin-rinsed syringes within 30 min of each study. The RBC were freed of plasma and buffy coat by centrifugation and washing.

The procedures for analysis of RBC Na, K, Cl, and water were as previously published (16). Red cell Li was determined on an AutoCal model 643 flame photometer from Instrumentation Laboratories (Lexington, MA). As with the measurements of water and other ions, all values were determined per kilogram dry cell weight.

Measurements of isotopic Na influx were performed as noted previously (19). Briefly, ^{22}Na (1 $\mu\text{Ci/ml}$) was added to suspensions containing 1 vol of RBC per 10–20 vol of medium. At intervals, cells were pelleted and the radioactivity of cells and medium was determined with a Gamma 5500 Counting System from Beckman Instruments, Inc. (Fullerton, CA). Initial rates of isotope movement were shown to be obtainable from 30–60-min samples (19). Influx was calculated as the rate of isotope entry divided by the specific activity in the medium.

The remainder of the experimental procedures, including Li and proton flux measurements, are described in detail in the figure legends.

RESULTS

Movements of Li in Dog RBC

Fig. 1A shows Li entry into dog RBC in hypotonic (100 mM Li) and hypertonic (200 mM Li) media. The data resemble those for Na influx (19), both in the time course and the finding that Li entry is stimulated by cell shrinkage. In other studies (not shown), the effect of cell volume on Li influx was independent of the external Li concentration, i.e., cells bathed in media containing 100 mM Li plus 200 mM sucrose had a higher Li influx than cells bathed in 100 mM LiCl alone. Fig. 1B shows that 0.33 mM amiloride inhibited Li influx in shrunken cells by 50–60%. By comparison, Na influx was more sensitive to amiloride, being 50% inhibited at a drug concentration of ~ 0.010 mM (12).

Fig. 2 shows time courses for Li efflux as functions of external Na and amiloride. Cells were preloaded with Li by preincubation in hypertonic LiCl,

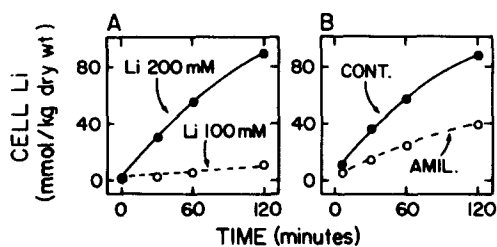


FIGURE 1. Intracellular Li as a function of time. Solutions used in these experiments contained (mM): 10 HEPES, 5 glucose, and 0.2 EDTA, and were adjusted with Tris base to a pH of 7.4 at 37°C. Fresh dog RBC were washed twice with a solution containing 100 mM LiCl. Cells were then incubated at 37°C in solutions with the following compositions: (A) 200 (solid symbols) or 100 (open symbols) mM LiCl; (B) 200 mM LiCl in the absence (solid symbols) or presence (open symbols) of 0.33 mM amiloride. Cells were removed from suspensions at the indicated intervals, washed with ice-cold 130 mM NaCl, and assayed for Li content. Each panel is representative of three similar studies.

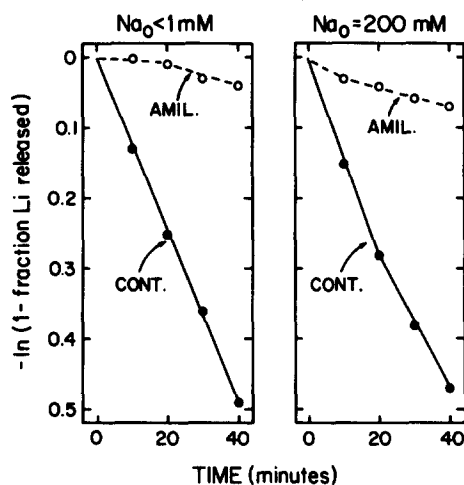


FIGURE 2. Release of Li from preloaded cells as a function of time, in the presence and absence of external Na, with and without amiloride. All solutions used in these experiments contained (mM): 10 HEPES, 5 glucose, and 0.2 EDTA, and were adjusted with Tris base to a pH of 7.4 at 37°C. Fresh dog RBC were washed twice in 150 mM LiCl and then incubated for 2 h in 200 mM LiCl at 37°C. All cells were then washed in 100 mM KCl, and resuspended at a cell/medium ratio of 1:10 in flux solutions containing 200 mM KCl (left panel) or 200 mM NaCl (right panel) in the presence (open symbols) or absence (solid symbols) of 1.3 mM amiloride. At the intervals shown on the abscissae, samples of suspensions were centrifuged and the supernatant was assayed for Li and hemoglobin. The Li and hemoglobin content of a sample of suspension in which all the cells had been lysed was measured. Hemolysis was <2% in all studies. Plotted on the ordinates are values for $[-\ln(1 - \text{fraction released})]$, where fraction released = Li in the supernatant/Li in the hemolyzed sample. Cell Li at the beginning of these studies was 26 mmol/kg dry cell solids. The initial amiloride-sensitive flux (computed from the slope of the curves between 0 and 20 min) in both Na-free and Na media was 19 mmol/kg dry cell solids·h. This study is representative of three similar ones.

washed with hypotonic KCl media, and then resuspended in hypertonic KCl or NaCl, in the presence or absence of amiloride. Clearly, Li efflux from shrunken dog RBC is amiloride sensitive. The rate of Li efflux from the cells in this experiment seemed not to depend on whether the prevalent external cation was K or Na. The similarity in Li efflux in the two circumstances shown in Fig. 2 is remarkable in that the KCl-incubated cells should have had a progressively smaller volume than the NaCl-incubated cells. It may be that for Li transport through the Na-H exchanger there is a maximum velocity and that the cells represented in the two panels of Fig. 2 were both at that maximum. Further studies to pursue this point have not been done. The meaning of these results in terms of a possible Li-Na exchanger will be considered in the Discussion.

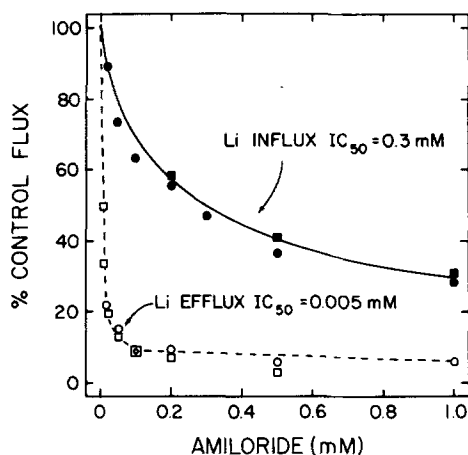


FIGURE 3. Li influx (solid symbols) and efflux (open symbols) as functions of external amiloride concentration. The methods were as noted in the legends for Figs. 1 (influx) and 2 (efflux). Influx was done in a 200 mM LiCl solution and efflux in a 200 mM KCl solution. Values for flux in the presence of amiloride were multiplied by 100 and divided by the flux in amiloride-free media. Different shaped symbols represent results of two separate experiments for each type of flux.

Fig. 3 shows that the concentration of amiloride that gave 50% inhibition was 0.3 mM for Li influx (with an external Li concentration of 200 mM) and 0.005 mM for Li efflux (with the initial external Li concentration nominally zero). The latter value agrees with data for amiloride inhibition of Na efflux, Na influx, and proton influx in shrunken dog RBC (12). The results of Fig. 3 suggest that there is competition at the external cell surface between Li and amiloride.

Influence of Internal Li on Na-H Exchange

Fig. 4 shows Na influx as a function of cell water content. Time courses of tracer Na entry in dog RBC have been published earlier (19); values for cell water were measured at the beginning and end of the flux period. The results confirm the observation that shrinking dog RBC below their physiological volume of ~66% cell water causes a sharp rise in Na influx (18, 19). Cells that were preloaded

with Li, however, had a shift in the volume-response curve: for any given volume (water content), the Li-loaded cells had a higher Na influx than controls. This increment in Na flux was amiloride sensitive, as shown in Fig. 5. At a cell water content of 66.1%, with no Li inside, there was a very small amiloride-sensitive flux. With increasing internal Li concentrations, the cell water content rose slightly (from 66.1 to 67.8%), and the amiloride-sensitive flux, instead of falling, rose, as would be expected when the cells swell, rose.

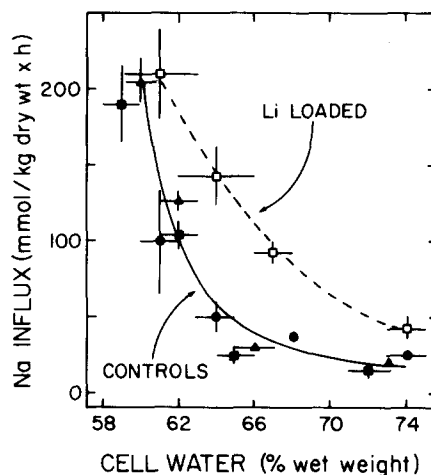


FIGURE 4. Na influx as a function of cell water content in Li-loaded cells (open symbols) and various controls (solid symbols). All solutions used in these experiments contained (mM): 10 HEPES, 5 glucose, and 0.2 EDTA, and were adjusted with Tris base to a pH of 7.4 at 37°C. Fresh dog RBC were divided into several aliquots. Some were preincubated for 60 min at 37°C in 200 mM LiCl (open symbols); others were preincubated in 100 mM LiCl (solid triangles), 220 mM NaCl (solid circles), or 100 mM NaCl (solid squares). After preincubation, each batch of cells was washed with ice-cold 140 mM NaCl and resuspended at a cell/medium ratio of 1:10 in a series of solutions of differing tonicity containing 90, 150, 190, and 225 mM NaCl. All suspensions were placed at 37°C and at time zero ^{22}Na was added. At 1 and 61 min, aliquots of each suspension were centrifuged for measurement of cell and supernatant radioactivity, supernatant Na concentration, and cell water. Na influx was expressed as the ratio of cell to supernatant counts times the supernatant Na concentration. Mean \pm SD for six experiments.

An alternative way to study the Na-H exchanger is to place dog RBC in unbuffered media containing no Na. The outward flow of Na down its concentration gradient causes protons to move into the cells, and the medium becomes alkaline. The effect is magnified if agents such as ethoxzolamide (22) and dipyridamole are added to retard the dissipation of a proton gradient across the membrane (16). Fig. 6 shows that cells preloaded with Li caused a greater alkalization of the medium than controls; the increment in proton uptake caused by Li loading was abolished when amiloride was included in the medium.

Influence of Internal Protons on Na-H Exchange

The above actions of internal Li were reminiscent of the modulatory effects of the cytoplasmic acidification on Na-H exchange reported in other tissues (1, 3, 5). The Na-H exchanger in dog RBC was similarly influenced by internal protons, but the demonstration of that fact is complicated by the changes in cell volume that accompany manipulations of internal pH.

When the cytoplasm of RBC is acidified, anionic groups on hemoglobin and

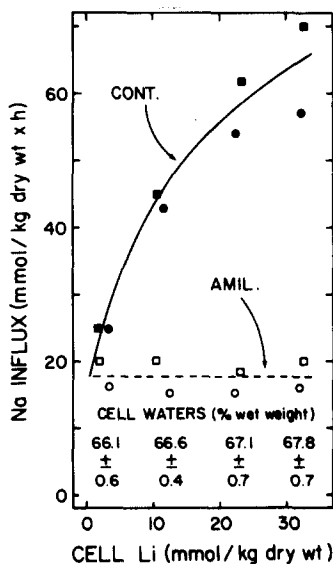


FIGURE 5. Na influx as a function of intracellular Li concentration in the presence and absence of amiloride, using mildly swollen RBC. All solutions used in these experiments contained (mM): 10 HEPES, 5 glucose, and 0.2 EDTA, and were adjusted with Tris base to a pH of 7.4 at 37°C. Fresh dog RBC were washed twice with 100 mM LiCl and then preincubated in 200 mM LiCl for time periods ranging from 0 to 50 min so as to take up increasing amounts of Li. At the end of the incubation period, cells were washed with 130 mM NaCl and resuspended in 130 mM NaCl with (open symbols) or without (solid symbols) 0.4 mM amiloride. Na influx and cell waters were determined as noted in the legend to Fig. 4. Squares and circles indicate identical experiments performed on blood from two dogs. Cell waters are given as mean \pm SD of eight determinations: two for each point, at the beginning and end of the 60-min flux period.

organic phosphates become protonated. Electroneutrality must be preserved, and since cations cannot leave the cell as readily as anions can enter, a rapid influx of anions occurs and the cells swell. Thus, studies of the influence of pH on RBC transport must be controlled for the attendant volume changes. Fig. 7 shows that net Na efflux into an Na-free medium, from cells preincubated and clamped at pH 6.0, exceeded that of cells clamped at pH 7.8, notwithstanding the higher water content at the more acid pH. The effect is even more remarkable in that the proton gradient driving Na efflux through an amiloride-sensitive Na-

H exchanger would be expected to be greater at an internal pH of 7.8 than at 6.0, given a constant external pH. It appears from this study that internal protons, like internal Li (Figs. 4–6), can activate the Na-H exchanger, even at relatively high cell volumes. Under normal conditions, the Na-H exchanger is not activated until cell water is reduced below 66–67% (Fig. 4).

Influence of External Protons on Na-H Exchange

Table I shows the results of studies in which external pH was varied while internal pH and cell volume were manipulated, using solutions of different

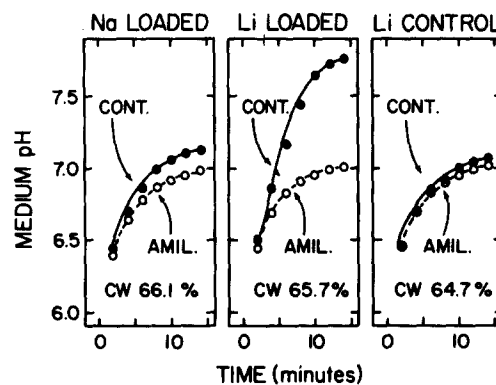


FIGURE 6. Medium pH as a function of time, in cells that were Na-loaded (left panel), Li-loaded (center panel), and incubated in hypotonic LiCl (right panel), and then washed and suspended in an unbuffered, isotonic KCl medium in the presence (open symbols) and absence (solid symbols) of amiloride. Fresh dog RBC were divided into three portions and washed and preincubated in solutions that contained (mM): 10 HEPES, 5 glucose, and 0.2 EDTA, and were adjusted with Tris base to a pH of 7.4 at 37°C. One-third of the cells were preincubated in 220 mM NaCl, one-third in 220 mM LiCl, and one-third in 90 mM LiCl, all for 15 min at 37°C. All three lots of cells were then washed with an unbuffered solution containing 100 mM NaCl, 5 mM glucose, 0.1 mM Na₂EDTA, 50 μM dipyridamole, and 10 μM ethoxzolamide. 1 vol of cells was then introduced into 50 vol unbuffered, prewarmed 37°C medium containing 140 mM KCl, 5 mM glucose, 0.05 mM EDTA, 50 μM dipyridamole, and 10 μM ethoxzolamide, with or without 0.4 mM amiloride. The suspension pH was recorded every 2 min and plotted as a function of time. An aliquot of cells was pelleted for determination of cell water. This study is representative of five similar ones.

osmolalities containing the impermeant anion gluconate. The results show that at comparable volumes (water contents), cells in a pH 6.1 medium had a lower net Na efflux into a Na-free medium than did cells in a pH 7.4 medium. This result is qualitatively paradoxical in that outward movements through the Na-H countertransport system are inhibited by raising the proton concentration on the external or *trans* side. In experiment 1, for example, the cells in flasks A and B had internal proton concentrations of ~60 nM and internal Na concentrations of ~170 mM. The external Na concentration in each case was nominally zero at the beginning of the flux period. The main difference between the two suspen-

sions was the external proton concentration: in flask A it was 39 nM, while in flask B it was 790 nM. On thermodynamic grounds, it would appear that the cells in flask B should have lost Na much faster than those in flask A through an Na-H exchanger. Moreover, the cells in flask B should have had their Na-H exchanger more activated than those in flask A, because they were more shrunken to start with. Clearly, the inhibitory effect of a low external pH on outward Na movements in this experiment involved something besides an alteration in driving force. A less well-controlled example of this phenomenon was reported earlier (16).

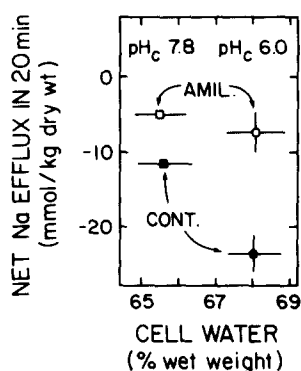


FIGURE 7. Net Na efflux as a function of initial cell water content in two groups of cells, one preincubated and clamped at pH 7.8 (squares), and the other at pH 6.0 (circles), in the absence (solid symbols) and presence (open symbols) of amiloride. All solutions used in these experiments contained (mM): 10 HEPES, 5 glucose, 1 KHCO_3 , 0.2 EDTA. Preincubation and clamping were done as follows. Fresh cells were divided into two equal portions, washed three times in media containing 120 mM KCl, and adjusted to pH values of 7.8 or 6.0 at 37°C. Each lot of cells was washed once more with the previous wash medium to which 50 μM dipyrindamole plus 10 μM ethoxzolamide had been added to retard dissipation of the pH gradient during the next incubation. Cells were then suspended at a cell/medium ratio of 1:10 in a 140 mM KCl medium (pH 7.4 at 37°C), containing dipyrindamole and ethoxzolamide as noted above. Cell pellets were analyzed for Na and water after 1 and 21 min incubation at 37°C. Mean and range for two studies on blood from different dogs.

DISCUSSION

Only a small fraction of the data needed to formulate a meaningful conceptual schema for Na-H exchange in dog RBC are available. One problem of arriving at an appropriate model derives from the fact that the Na-H transporter is modulated by cell volume. Since cell volume changes with time when the Na-H exchanger is activated, steady state flux data (from which affinities can be calculated) are difficult to obtain. Quantitative studies of the activation of the system by protons are difficult because of the influence of pH on cell volume. Finally, the phenomenon of Na-H exchange in dog RBC has been shown to be separable into two phases: the switching on of the transporter and the transport

itself. Thus, some perturbants of the mechanism may affect the cell signaling and activation process rather than the translocation of ions (13).

It is nevertheless possible to discuss some features of the mechanism that an adequate model would have to account for. Foremost among these is the observation (Fig. 7) that a high concentration of protons at the inner membrane surface can stimulate Na extrusion, when there is nothing on the *trans* side of

TABLE I
Net Na Loss into an Na-free Medium as a Function of External pH in Cells with Controlled Water Content and Internal pH Values

	Experiment 1			
	Flask A	Flask B	Flask C	Flask D
Extracellular pH	7.41	6.10	6.09	6.11
Intracellular pH	7.22	7.23	7.49	7.30
Initial cell water (percent wet weight)	61.2	58.7	60.5	61.1
Na loss (mmol/kg dry cell weight in 9 min)	52	14	17	15
	Experiment 2			
	Flask A	Flask B	Flask C	Flask D
Extracellular pH	7.40	6.10	6.12	6.12
Intracellular pH	7.23	7.12	7.44	7.25
Initial cell water (percent wet weight)	61.5	59.6	60.6	61.2
Na loss (mmol/kg dry cell weight in 9 min)	79	31	36	20

All solutions contained (mM): 5 HEPES, 5 MES, 5 glucose, 0.2 Na₂EDTA, and 1 KHCO₃. Fresh dog RBC were divided into four equal aliquots and washed twice in Na-containing media designed to vary external pH while keeping cell volume and internal pH comparable among the four cell samples. Wash A contained 180 mM NaCl. Washes B, C, and D contained 9, 5, and 7 mM NaCl, respectively, plus Na gluconate to make total Na salts equal to 190–200 mM. See table for extracellular pH (adjusted with Tris base at 37°C). Each lot of cells was then transferred to a flux solution identical to the one in which it had been washed, but with all the Na replaced by K. After 1 and 10 min at 37°C, the cells were rapidly pelleted in a cold centrifuge and analyzed for Na, K, water, and chloride content. Medium pH was measured at 37°C. Intracellular pH was calculated from the measured medium chloride, the cell chloride, and the medium pH by the formula:

$$pH_{\text{cell}} = pH_{\text{medium}} - \log_{10}(Cl_{\text{medium}}/Cl_{\text{cell}}).$$

the membrane that could return the carrier but protons. On purely thermodynamic grounds, cells with acidified cytoplasm would appear to have less of a driving force for outward Na movement through an Na-H exchanger than cells with an alkaline internal pH. A similar paradox is illustrated in the experiments of Table I: raising the proton concentration on the external surface of the cell inhibited Na efflux. The increased inward proton gradient in the cells placed in acid media would appear to favor Na loss through the Na-H exchanger. One

way to explain this sort of behavior would be to postulate "regulator sites" that are like the cell volume activation mechanism in that they control the switching on and off of Na-H exchange. These sites would be stimulated by internal protons and inhibited by external protons. The proton effects can overwhelm the influences of cell volume. Thus, acidifying the cytoplasm can turn on amiloride-sensitive flux, even in swollen cells (Fig. 7), while acidifying the medium can turn off the Na flux triggered by cell shrinkage (Table I). Modulatory effects of internal protons in renal epithelial membrane vesicles were first reported by Aronson et al. (3), and Grinstein et al. (5) subsequently reported such effects in lymphocytes. The meaning of these observations in relation to various kinetic models is discussed in Aronson's recent review (1).

Li ion is like hydrogen ion in that both species can be transported by, and each can modify, the Na-H exchanger. The opposing actions of Li at the inner and outer membrane surfaces mimic those of protons. Raising intracellular Li stimulates amiloride-sensitive Na and proton movements (Figs. 4-6), altering the volume-mediated control of the Na-H exchanger pathway in such a way that it functions even at normal or high volume. External Li is inhibitory to Na-H exchange (12). While quantitative experiments that relate volume, proton concentration, and flux are difficult in RBC (because of the effects of pH on volume), one can vary Li on both sides of the membrane while controlling volume. An interpretation of Fig. 4 might be that Li in some way alters the "set point" of the volume-sensing apparatus so that the cell behaves as if it were shrunken even at normal or high volumes. Perhaps the effect of internal protons is mediated in an analogous way, via the afferent limb of the volume-regulatory apparatus rather than directly on the Na-H exchanger. Such questions are approachable experimentally via the use of membrane fixatives and cross-linkers (13).

A possibility not addressed in the present paper is that the effects of internal Li are mediated via the influence of that ion on inositol phosphate metabolism (7, 20).

What is the relationship between Na-H exchange in dog RBC and Na-Li or Na-Na exchange in human RBC (6)? In a previous study, there was no *trans* stimulation of Na efflux by external Na (Fig. 6 of reference 12). In Fig. 2 of the present report, there was no stimulation of basal or amiloride-sensitive Li efflux by external Na. Interpretation of this experiment is confounded by the fact that the cell volumes cannot be comparable in the two circumstances: cells in a medium free of Li or Na shrink with time (11), whereas cells in an Na medium either swell or have a stable volume. But the criterion of *trans* stimulation could hardly be used as a test for Na-Li counterflow in a system that can also carry protons, unless it were possible to render one side or the other of the membrane virtually proton free. Because dog RBC do not tolerate even mild alkalization (21), such studies are at present impractical.¹ Jennings et al. (8) have recently presented evidence that rabbit RBC, which have a vigorous Na-Li exchanger, do not exchange Na for protons.

A final interaction of Li with the Na-H countertransporter is the decrease in

¹ Na-Na exchange can be demonstrated in dog RBC, but only when the cells are swollen. The counterflow appears to be mediated by the Ca-Na exchanger, which is completely shut down under the conditions of cell shrinkage that activate the Na-H exchanger (10).

apparent affinity for amiloride when Li is present externally at high concentration (Fig. 3). Similar effects were observed by Mahnensmith and Aronson (9) in renal epithelial vesicles. Those authors present evidence that Li and amiloride compete for a single site on the external membrane surface.

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