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Lithium Absorption in Tight and Leaky Segments of Intestine

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Summary. There is significant absorption of Li^+ by human jejunum and ileum, but negligible absorption by human colon. Thus, a proximal-to-distal gradient of decreasing Li^+ absorption and increasing junctional tightness exists in intestine as well as in renal tubule. For six leaky epithelia the relative permeabilities of K^+, Na^+, and Li^+ by the junctional route are in the sequence $P_K > P_{Na} > P_{Li}$ and all fall within a factor of 2.5. In contrast, for tight epithelia $P_{Li} \sim P_{Na} \gg P_K$ in the amiloride-sensitive channel of the apical membrane, but $P_K \gg P_{Li} \sim P_{Na}$ in the basolateral membrane. The ability of several tight epithelia to sustain nonzero transepithelial Li^+ absorption despite this basolateral barrier may be due to Na^+/Li^+ countertransport at the basolateral membrane, resulting in secondary active transport of Li^+ across the epithelium.

Key words lithium · tight junctions · leaky junctions · countertransport · intestine

Introduction

The renal tubular epithelium and the intestinal epithelium present interesting parallels in a proximal-to-distal gradient of junctional tightness. Proximal segments of both these tubes exhibit numerous hallmarks of leaky epithelia, while distal segments exhibit hallmarks of tight epithelia (Diamond, 1977). In the present paper we extend these parallels by examining whether the gradient in lithium absorption established for the kidney (Thomsen, 1968; Thomsen & Schou, 1968; Hayslett & Kashgarian, 1979; Corman, Roinel & de Rouffignac, 1981) also characterizes the human intestine.

The properties that characterize the renal proximal tubule as a leaky epithelium and renal distal tubule as a tight epithelium are well known. The proximal tubule absorbs Na^+ coupled to glucose, amino acid, and bicarbonate absorption, and is uninfluenced by aldosterone. Its electrical potential difference between identical bathing solutions, and its electrical resistance, are low because of the leaky junctions. In contrast, the distal tubule absorbs Na^+ under the control of aldosterone and not coupled to sugar, amino acid, or bicarbonate transport. The electrical resistance is high, and the electrical potential difference between identical Na^+-containing bathing solutions is also high because the transcellular potential arising from the Na^+ pump is not shunted out by leaky junctions. Osmotic water permeability is much higher in proximal tubule than in distal tubule.

A similar gradient of properties has been established along human intestine (Fordtran et al., 1965; Turnberg et al., 1970*a*, *b*; Fordtran, 1975; Davis et al., 1980, 1982; Krejs & Fordtran, 1980). The jejunum carries out active sodium absorption coupled to sugar absorption and active bicarbonate absorption and is uninfluenced by aldosterone, while the colon possesses aldosterone-controlled sodium transport and lacks sugar absorption. Osmotic water permeability decreases ninefold from jejunum to ileum. Reflection coefficients for urea, erythritol, and NaCl are 0.45–0.60 in jejunum but rise to nearly 1 by the ileum. The electrical resistance has not been measured, but the transepithelial electrical potential difference during perfusion with isotonic NaCl increases from −3 mV (lumen-negative) in jejunum to −31 mV in the distal colon, suggesting increasing junctional tightness and resistance towards the colon and hence decreasing shunting of pump voltages. Ionic selectivity properties inferred from NaCl dilution potentials also shift systematically along the intestine: P_{Na}/P_{Cl} exceeds 1 in the jejunum and ileum, is approximately 1 in the proximal colon, and is less than 1 in the distal colon. Similar properties but with some divergence of detail apply to the small and large intestine of other vertebrate species.

The renal proximal tubule absorbs Na^+ and Li^+ with approximately equal efficiencies, but the distal tubule absorbs Li^+ virtually not at all while

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absorbing Na^+ (*see* references in first paragraph). For human intestine, however, the site of Li^+ absorption has not been studied. We have therefore measured Li^+ absorption and also K^+ absorption for comparison at three sites along the human intestine: jejunum, ileum, and colon. It turns out that Li^+ absorption becomes negligible as one proceeds proximally to distally along the intestine, just as in the kidney. It remains to be seen whether differences in the relative handling of Na^+ and Li^+ can be added to the list of hallmarks distinguishing tight and leaky epithelia.

Materials and Methods

Solutions

The composition of all intestinal perfusion solutions included 140 mM NaCl, 4 mM KCl, 10 mM D-xylose, and 0.2% polyethylene glycol (a nonabsorbable volume marker). In addition, the solutions contained either 1, 4, or 10 mM LiCl. The solution containing 4 mM LiCl also contained 0.5 μCi/liter ^{42}K to measure potassium flux. All solutions were warmed to 37 °C and gassed with 5% CO_2/95% O_2. The resulting pH was 5.1 but equilibrated to 6.3 in the course of jejunal and ileal perfusion, 7.1 in the course of colonic perfusion.

Procedures

The experimental procedure consisted of standard double-lumen or triple-lumen perfusion techniques described elsewhere (Cooper et al., 1966; Fordtran, 1966; Davis et al., 1980). The double-lumen technique was used in jejunal and ileal studies, while the triple-lumen technique was used in colon studies to eliminate the risk of solution reflux into the terminal ileum. In the double-lumen technique an experimental solution is infused at a proximal site along the intestine and recovered at a distal site. Volume changes are calculated from the change in concentration of polyethylene glycol (PEG), and fluxes are calculated from changes in concentration of other solutes. Since fluid can also enter the perfused segment from the portion of the intestine proximal to the perfusion site, this method does not permit one to calculate net absorption or secretion of substances present in normal intestinal secretion, such as Na^+, K^+, HCO_3^-, and water, because differences between their amounts in the infused and collected solutions could partly reflect addition of proximal secretions. However, this method does permit one to calculate fluxes of Li^+ and ^{42}K, since they are absent from intestinal secretion. The triple-lumen technique differs in that fluid is infused from a proximal site and recovered from a medial site and also from a distal site. Solute fluxes in the segment between the medial and distal sites are calculated from differences in composition between the fluid collected at these sites. Since the fluid at the medial site is analyzed, the triple-lumen technique permits one to calculate absorption or secretion of all solutes, regardless of whether they are present in intestinal secretion entering the segment from upstream.

The subjects were normal healthy human volunteers with no history of gastrointestinal disease. Three were females, five males, with a mean age of 26 years (range, 24–29 years). None of the individuals studied was on any chronic medication. Informed written consent was obtained from each subject, and these experiments were approved by a Human Research Committee. Subjects were intubated by mouth with the double-lumen or triple-lumen polyvinyl tube. Under fluoroscopic control the infusion site was placed at the ligature of Treitz for jejunal studies, in the mid-ileum 250–300 cm from the incisors for the ileum study, and in the terminal ileum for the colon studies. Intestinal perfusion was begun after at least an 8-hr overnight fast. Test solutions were infused at a constant rate of 10 ml/min in the jejunal and ileal studies and at 20 ml/min in the colon studies with a Dasaga multichannel peristaltic pump (Brinkman Instruments, Westbury, New York). In the jejunal and ileal studies sampling was begun after a 25-min equilibration period from a collection site 20 cm from the infusion site and continued for 30 min at 1.5 ml/min. For the colon studies sampling was begun after a 30-min equilibration period from the medial collection site in the caecum and continued at a rate of 1.5 ml/min for 1 hr. A rectal tube inserted with its tip 17 cm from the anal verge served as the distal collection site. Fluid was allowed to drain freely from the rectal tube, and collection began 15 min after the start of the medial collection and continued for 1 hr. In each experiment the first solution to be perfused was the 1 mM Li^+ solution, then the 4 mM Li^+ solution containing ^{42}K, and finally the 10 mM Li^+ solution. The fluid collected over the 30-min (jejunum, ileum) or 1-hr (colon) sampling period was pooled for analysis.

The electrical potential difference (PD) between the intestinal lumen and a subcutaneous reference electrode was measured as described elsewhere (Read & Fordtran, 1979; Davis et al., 1980) and was found to average −4 mV (lumen negative) for jejunum, −7 mV for ileum, and −21 mV for colon.

Before and after each test solution was perfused, a serum sample was drawn to measure the concentration of Li^+ that had reached the bloodstream. The ^{42}K level in serum samples was found to be not significantly above background.

The length of the perfused segment was approximately 20 cm for the jejunal and ileal studies but was the whole colon (*ca.* 150 cm) for the colon studies. The jejunum, ileum, and colon were each studied in a total of four experiments on four different subjects. One subject was studied in all three segments, two subjects in both jejunum and ileum, three subjects in colon only, and one each in jejunum only and ileum only.

Analyses and Calculations

All samples were analyzed in duplicate. Na^+, K^+, Cl^-, HCO_3^-, and osmolality were determined by standard methods. PEG was analyzed by a modification of the method of Hyden (1955). Li^+ was analyzed by atomic absorption spectroscopy according to the ultramicro method of Ehrlich and Diamond (1978). ^{42}K was measured by a Packard 2425 liquid scintillation spectrometer. Net water and solute movements were calculated from standard nonabsorbable marker equations (Fordtran et al., 1965). The lumen-to-plasma flux of ^{42}K was calculated as $[(\text{vol})_I (\text{DPM})_I - (\text{vol})_F(\text{DPM})_F]\ (\text{K})_I/(\text{DPM})_I$, where subscript I denotes the infusion site in double-lumen studies and the medial collection site in triple-lumen studies, subscript F is the collection site at the end of the test segment in the jejunal and ileal studies and the rectal collection site in the colon studies, DPM is the disintegration per min of ^{42}K per ml of sample, vol represents the flow rate (ml/min) at the infusion site or collection site, and $(K)_I$ is the perfused K^+ concentration.

Results are expressed as the mean ± SEM. Ion concentrations in the intestinal lumen are expressed as the arithmetic mean of the concentration at the beginning and end of the test segment. Our flux measurements for the whole colon (150 cm) are multiplied by 20/150 in order that fluxes for all three segments will be expressed per 20 cm length for purposes of comparison.

Results

Changes in Solution Composition

As background to interpreting the measured Li^+ and ^{42}K fluxes, we summarize the changes that took place in solution composition along the length of the perfused segment.

Changes in osmolality and in concentrations of Na^+, Cl^+, K^+, and HCO_3^- were slight. In more detail, the average changes were as follows, citing in each case the jejunal change first, then the ileal change, and finally the colon change. Osmolality decreased by 9, 5, and 1 mOsm; Na^+ decreased by 4, 2, and 2 mM; Cl^- decreased by 5, 8, and 9 mM; HCO_3^- increased to 6, 4, and 11 mM; and K^+ increased by 0.5, 0.2, and 0.7 mM. The luminal concentrations of Li^+ and of ^{42}K tended to decrease along the perfused segment as these ions moved down their concentration gradient from lumen to bloodstream. The changes were greater for ^{42}K than for Li^+, indicating K^+ to be more rapidly absorbed than Li^+ in each intestinal segment. The changes were greatest in jejunum, less in ileum, and least in colon, indicating the absorption rates of these segments to decrease in that order. In the colon there was actually a slight rise in Li^+ concentration, because Li^+ absorption there is so low and because water absorption along the perfused segment tended to cause Li^+ concentration to rise. In more detail, the percent changes in Li^+ or ^{42}K concentration in the perfusate from the start to end of the perfused segment were as follows: jejunum, Li^+ −34%, ^{42}K −58%; ileum, Li^+ −18%, ^{42}K −37%; colon, Li^+ +6%, ^{42}K −1%. Since the Li^+ and ^{42}K concentrations did thus change along the perfused segment, the results for Li^+ or K^+ absorption as a function of perfusate concentration will be expressed with respect to the average of the concentration at the beginning and end of the perfused segment.

Li^+ and ^{42}K were absent from the bloodstream at the start of each experiment. As they were absorbed from the solution perfused through the intestinal segment, their concentration in the bloodstream would tend to rise (plasma ^{42}K actually remained undetectable). To minimize the effect of these blood concentration changes, we first perfused the 1 mM Li^+ solution, then the 4 mM solution, and last the 10 mM solution. The bloodstream Li^+ concentration rose highest in the jejunal studies, next highest in the ileal studies, and least in the colon studies, for two reasons. First, absorption in these three segments decreases in that order. Second, not all of the perfused fluid is collected at the distal site: some remained to be absorbed after the distal collecting site, and the length of the intestine remaining after the distal site is greatest for the jejunum and least for the colon. At the end of each study, the serum concentration of Li^+ was always less than 5% of the luminal concentration in jejunal experiments, less than 2% in ileal experiments, and less than 0.5% in colon experiments. Since these relative concentrations and the resulting backflux from bloodstream to lumen were so small, we neglected backflux in calculating absorption.

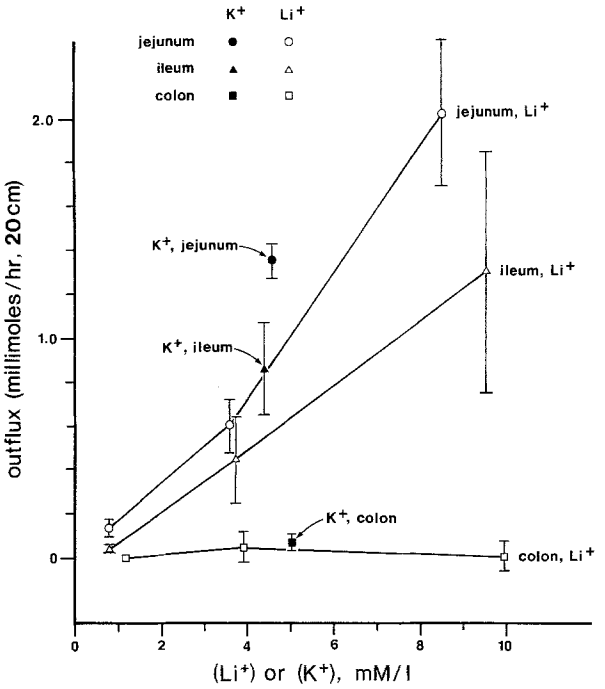

Fig. 1. Outflux of Li^+ or ^{42}K from human jejunum, ileum, or colon, as a function of luminal concentration. Units of outflux are millimoles per hr per 20 cm length of intestine. Each point is based on one experiment in each of four subjects. Error bars are ±1 SEM

Li^+ and ^{42}K Outflux

Figure 1 summarizes the measurements of Li^+ and ^{42}K outflux in each of the three intestinal segments. This figure yields the following conclusions:

In each segment the ^{42}K outflux at 4–5 mM exceeds the interpolated Li^+ outflux at the same concentration.

For each ion the outflux per 20 cm of intestine is maximal in the jejunum, less in the ileum, and least in the colon. Li^+ outflux from the colon does not differ significantly from zero at any of the three concentrations studied (mean Li^+ outflux ±1 SEM, 0±0.007 mM/hr, 20 cm at a Li^+ concentration of 1.16±0.06 mM, −0.33±0.54 at 3.90±0.19 mM,

and 0.08 ± 0.44 at 9.96 ± 0.31 mM). K^+ outflux from the colon at the one concentration studied (5.05 ± 0.20 mM) is very small but apparently real, 0.076 ± 0.031 mM/hr, 20 cm. We do not have values for the ratio of true intestinal surface area (taking account of villi and microvilli) to segment length in these three segments of human intestine. Since this ratio could vary with position, Fig. 1 does not suffice to prove that outflux expressed per cm^2 of true surface area is higher in jejunum than in ileum. However, it does suffice to prove that outflux in the colon is lower than that in the ileum or jejunum for Li^+, since Li^+ outflux in the colon is negligible. Figure 1 also suggests that K^+ outflux per cm^2 of true surface area is lower in the colon than in jejunum or ileum, since outflux of K^+ per 20 cm length is so much higher in the jejunum or ileum than in colon (18 times and 11 times higher, respectively) that this difference is unlikely to arise from differences in surface area per unit length alone.

For jejunum and ileum, where Li^+ outflux is measurable, it is approximately linear with luminal Li^+ concentration.

Discussion

Mode and Route of Li^+ Absorption

Our results show that Li^+ absorption is negligible in human colon but substantial in human jejunum and ileum. The question therefore arises as to the mode (passive or against an electrochemical gradient) and route (transcellular or transjunctional) of jejunal and ileal Li^+ absorption. As background, recall that K^+ distributes passively in normal human jejunum and ileum and is secreted actively in colon, and that Na^+ is actively absorbed in human jejunum, ileum, and colon (Turnberg, 1970, 1971; Turnberg et al., 1970*a*, *b*; Hawker, Mashiter & Turnberg, 1978; Davis et al., 1982). Recall further that human jejunum and ileum possess the hallmarks of leaky epithelia, while human colon resembles tight epithelia. In other leaky and tight epithelia, transepithelial passive fluxes of small ions are known to be predominantly via the junctions and via the cells, respectively.

Our experiments do not provide direct evidence about the mode and route of Li^+ absorption in human intestine, but a reasonable inference can be drawn. Since Li^+ was virtually absent from plasma in our experiments, the Li^+ absorption observed was down Li^+'s concentration gradient. Our experiments do not indicate whether human intestine is also capable of absorbing Li^+ against an electrochemical gradient. However, with intraluminal (Na^+) at plasma levels, the efflux of tracer Na^+ from human jejunum and ileum considerably exceeds net Na^+ absorption (Davis et al., 1982), indicating that most tracer outflux, even for the actively absorbed Na^+, is passive rather than active. We therefore reason that most of the Li^+ absorption in our experiments was probably passive, hence probably via the junctions. Corman et al. (1981) reached a similar conclusion for Li^+ movements across rat proximal tubule.

Li^+ Pathways and Barriers in Leaky and Tight Epithelia

If one assumes that the flux/concentration relation for Li^+ in Fig. 1 is linear and interpolates to obtain the Li^+ outflux at a concentration equal to the concentration for which K^+ outflux was measured, one finds that the outflux ratio from solutions of equal concentration for Li^+ divided by K^+ is 0.69 for human jejunum, 0.42 for human ileum, and immeasurably low for human colon. Using the $^{24}Na^+$ outflux that Davis et al. (1980) measured in human jejunum under similar conditions (bicarbonate-free solutions, PD -4 mV), one obtains 0.72 for Na^+ outflux divided by K^+ outflux in human jejunum. Let us now compare these ratios with ratios measured for other epithelia.

Table 1 summarizes the passive permeability ratio P_{Li}/P_K for four other leaky epithelia: rabbit gallbladder, bullfrog gallbladder, frog choroid plexus, and frog jejunum. These values were obtained electrically from measurements of dilution potentials and biionic potentials, and hence certainly refer to passive permeation via the junctional pathway. The values range from 0.41 to 0.70, and thus are similar to the outflux ratio for human jejunum or ileum. In these four other epithelia as in human jejunum, Na^+ is slightly more permeable than Li^+ (P_{Na}/P_{Li} is unknown in human ileum), yielding the permeability sequence $P_K > P_{Na} > P_{Li}$. The main point to be emphasized is that the permeabilities of these three ions in these four leaky epithelia are quite similar and within at most a factor of $2\frac{1}{2}$ of each other, as in human jejunum and ileum. In another leaky epithelium, renal proximal tubule, Li^+ absorption is similar to Na^+ absorption (Corman et al., 1981), but the ratio P_{Li}/P_{Na} has not been specifically determined. As in our experiments on human intestine, the proximal tubule experiments do not specifically distinguish among possible modes of Li^+ transport.

Among tight epithelia Li^+ absorption is negligible for renal distal tubule (Thomsen, 1978; Hays-

Table 1. Relative permeabilities of Li^+, Na^+, and K^+ in tight and leaky epithelia

Epithelium	Reference	P_{Li}/P_K	P_{Na}/P_K
Leaky epithelia, junctions			
Rabbit gallbladder	Moreno & Diamond (1974)	0.47	0.52
Bullfrog gallbladder	Moreno & Diamond (1974)	0.41	0.70
Bullfrog choroid plexus	Wright (1972)	0.70	0.82
Bullfrog jejunum	Wright (1972)	0.46	0.71
Human jejunum	This paper; Davis et al. (1980)	0.69	0.72
Human ileum	This paper	0.42	–
Tight epithelia, apical membrane			
Bullfrog skin	Lindley & Hoshiko (1964)	5.6	20.8
Leopard frog skin	Lindley & Hoshiko (1964)	5.3	13.5
Toad urinary bladder	Palmer (1982)	>700	>700
Tight epithelia, basolateral membrane			
Bullfrog skin	Lindley & Hoshiko (1964)	0.12	0.10
Leopard frog skin	Lindley & Hoshiko (1964)	0.14	0.09
Toad urinary bladder	Leb et al. (1965)	0.30	0.17

All values are ratios of passive permeability coefficients measured by electrical techniques, except that the values for human jejunum and ileum are ratios of tracer outfluxes and are believed to approximate junctional passive permeability coefficient ratios.

lett & Kashgarian, 1979) and human stomach (Ramsey et al., 1979) as for human colon, but is measurable across frog skin (Zerahn, 1955; Candia & Chiarandini, 1973; Reinach, Candia & Siegel, 1975; Benos, Mandel & Simon, 1980), toad urinary bladder (Herrera, Egea & Herrera, 1971; Macknight & Hughes, 1981; Palmer, 1982), and turtle colon (Sarracino & Dawson, 1979). Li^+ crossing the latter three tight epithelia does so via two barriers in series, the apical cell membrane and the basolateral cell membrane. These two barriers appear to behave very differently towards Li^+ (Table 1). The apical membrane is much more permeable to Li^+ and Na^+ than it is to K^+. Na^+ permeation through this membrane is via a specialized channel inhibited by amiloride. Several studies have shown that Li^+ can penetrate the amiloride-sensitive channel in several tight epithelia at least as readily as Na^+ (e.g., Nagel, 1977; Sarracino & Dawson, 1979; Palmer, 1982). In contrast, the basolateral cell membrane is far more permeable to K^+ than to either Li^+ or Na^+. This membrane has a slightly higher passive permeability to Li^+ than to Na^+ in both frog skin and toad urinary bladder (Table 1, based on Lindley & Hoshiko, 1964, and on Leb, Hoshiko & Lindley, 1965). However, Na^+ outflux across this membrane is largely via the ouabain-inhibited $Na^+ - K^+$ ATPase, whose Na^+ site has a negligible affinity for Li^+ (Gutman, Hochman & Wald, 1973; Reinach et al., 1975; Halm & Dawson, 1982). Thus, the main barrier to Li^+ movement across tight epithelia appears to be in the basolateral membrane.

This basolateral barrier makes it puzzling that several tight epithelia (frog skin, toad urinary bladder, turtle colon) can sustain any net Li^+ transport in the absence of external net driving forces. Toxic effects of Li^+, especially at high concentrations, limit the time for which transport can be sustained in Li^+-containing solutions. When transport is measured as short-circuit current (I_{sc}), part of the I_{sc} in Li^+-containing solutions represents Li^+ entry across the apical membrane and K^+ exit or Cl^- entry across the basolateral membrane (Macknight & Hughes, 1981). However, some of the I_{sc} is transepithelial transport of Li^+ itself. Li^+ readily enters the cell across the apical membrane by way of the amiloride-sensitive channel. How can it leave the cell across the basolateral membrane, given Li^+'s low affinity for the Na^+ site of the ouabain-sensitive ATPase?

We suspect that Na^+/Li^+ countertransport will prove to be the explanation for basolateral Li^+ extrusion in those tight epithelia capable of some Li^+ transport (Fig. 2). This mechanism has been extensively studied in erythrocytes, which maintain intracellular (Li^+) below electrochemical equilibrium. Li^+ uphill extrusion is coupled to Na^+ entry down the Na^+ gradient maintained by ouabain-sensitive active extrusion of Na^+. Thus, the energy for Li^+ movement against its electrochemical gradient comes directly from the Na^+ gradient, not from ATP (Haas, Scholler & Tosteson, 1975; Duhm et al., 1976; Ehrlich & Diamond, 1979). Evidence for a role of countertransport in maintaining intracellular (Li^+) below electrochemical equi-

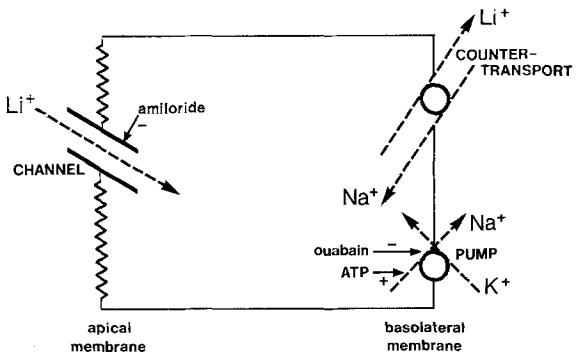

Fig. 2. Proposed model to explain how some tight epithelia (frog skin, toad urinary bladder, and turtle colon, but not human colon) carry out transepithelial uphill Li^+ transport. At the apical membrane Li^+ enters the cell down its electrochemical gradient via the amiloride-sensitive channel. At the basolateral membrane Li^+ leaves the cell up its electrochemical gradient by countertransport, in exchange for Na^+ entering the cell down its gradient. Cell (Na^+) is maintained low by the ouabain-sensitive, ATP-driven Na^+/K^+ exchange pump at the basolateral membrane

librium is strong for nerve (Ehrlich & Russell, 1981), and suggestive for muscle (Ehrlich, Clausen, & Diamond, 1980; Ehrlich & Diamond, 1980) and for choroid plexus epithelial cells (Ehrlich & Wright, 1982). Recently Kirk and Dawson (1982) have produced direct evidence for Na^+/Li^+ countertransport in turtle colon.

If the scheme of Fig. 2 proves to be correct, Li^+ transport in certain tight epithelia would exemplify "secondary active transport" (Stein, 1967). This expression refers to a net transmembrane flux of a solute in a direction opposite to that solute's electrochemical gradient, but with the energy for the flux coming from a transmembrane flux of a second solute. The two coupled fluxes are in the same direction (cotransport) for the best-studied epithelial case of secondary active transport, that of sugars and amino acids driven by Na^+. Our scheme for secondary active transport of Li^+ differs in that the coupled fluxes involve countertransport rather than cotransport, and occur in the basolateral membrane rather than in the apical membrane.

Table 1 and Fig. 2 suggest the following synthesis of Li^+ movements in tight and leaky epithelia. Li^+ is absorbed readily by leaky epithelia, because its passive permeability there in the junctional pathway is nearly as high as that of Na^+ and not much below that of K^+. In tight epithelia Li^+ absorption is low or negligible, despite the fact that Li^+ is nearly as permeant as Na^+ in the amiloride-sensitive channel of the apical membrane. The main barrier to Li^+ movement across tight epithelia is the basolateral membrane, across which Li^+ and Na^+ have similarly low passive permeabilities and across which Na^+ but not Li^+ is actively transported. In some tight epithelia Li^+ may be able to cross the basolateral membrane by countertransport exchange for Na^+, resulting in secondary active transport across the epithelium. With our experiments, the intestine joins the renal tubule in illustrating that these differences in Li^+ handling between tight and leaky epithelia can be observed in different segments of the same tubular organ.

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