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Some characteristics of sodium-independent phosphate transport across renal basolateral membranes

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Sodium-independent phosphate transport was evaluated in porcine renal basolateral membrane vesicles. Phosphate uptake was saturable with an apparent K_m 10.1 ± 1.2 mM and V_{max} 13.6 ± 2.0 nmol (mg protein)$^{-1}$ min^{-1}, $n = 5$. Phosphate uptake was trans-stimulated with intravesicle phosphate and was enhanced with a positive transmembrane electrical potential. Arsenate and bicarbonate inhibited phosphate transport but other anions including sulfate and phosphonoformate were without effect. These studies indicate that phosphate uptake across basolateral membranes is present in the absence of sodium, is facilitated, and is specific for phosphate. The apparent affinity and rate of phosphate transport across the basolateral membrane is significantly higher than the respective parameters observed for the brush-border membrane.

Introduction

Phosphate enters the cell together with sodium via a sodium-phosphate cotransport system located in the brush-border membrane [1,2]. The electrochemical potential difference for sodium across the brush-border membrane (BBM) provides the driving force for the intracellular accumulation of phosphate [3,4]. Not yet understood is the transfer of phosphate across the cytoplasm and the exit at the basolateral cell side. Sodium-independent and sodium-dependent transport systems may be located within basolateral membrane (BLM) that facilitate the exit of phosphate out of the cell along its electrochemical gradient [5–8]. But it appears that normally the luminal entry mechanism is the rate-limiting step and thus is involved in the regulation of phosphate transport by kidney, epithelial cells [4,9].

Although the events occurring at the BBM have been extensively investigated, the transport of phosphate and other electrolytes across the BLM is not clearly understood. The early studies of Hoffmann et al. reported extensive phosphate uptake into BLM vesicles in the absence of sodium [3]. Grinstein and colleagues presented evidence suggesting a process of facilitated anionic diffusion with characteristics similar to the anionic transporter (band 3) reported for the erythrocyte [5]. Löw et al. extended these observations using vesicles prepared from renal BLM and sulfate as a prototypic anion [6]. They provided evidence for a common anion exchanger that accepts phosphate, sulfate, thiosulfate, bicarbonate, hydroxyl ions, chloride and a variety of organic anions. Independently, Pritchard and Renfro reported similar findings in rat BLM vesicles, although phosphate was not specifically examined in this study [10]. Hagenbuch et al. reported that sulfate may undergo facilitated exchange with a number of anions but not phosphate [7]. More recently, Grassl and Aronson have demonstrated the presence, of an anion exchanger in rabbit BLM vesicles that can mediate exchanges of sulfate for HCO_3^-, oxalate for HCO_3^-, and sulfate for oxalate [11,12]. This anion exchanger was sensitive to inhibition by the stilbene sulfonate derivative, DIDS, and did not require sodium. This exchanger was rather specific as it does not interact with other anions such as formate, lactate, *p*-aminohippuarate, urate, succinate, chloride and phos-

Abbreviations: BLM, basolateral membrane; BBM, brush-border membrane; Tris, tris(hydroxymethyl)aminomethane; Mes, 2-(*N*-morpholino)ethanesulfonic acid; Hepes, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; PMSF, phenylmethylsulfonyl fluoride; DIDS, 4,4′-diisothiocyanostilbene-2,2′-sulfonic acid; EDC, 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride; DCCD, *N*,*N*′-dicyclohexylcarbodiimide; DEPC, diethyl pyrocarbonate; NEM, *N*-ethyl maleimide; DMSO, dimethyl sulfoxide.

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phate. They provided evidence for $2HCO_3^-$ or $1CO_3^{2-}$ per sulfate or oxalate transported [12]. On balance, these reports support the notion of a transport process which moves phosphate across the BLM which is independent of sodium and in most instances is specific as it is not shared by anions such as sulfate.

Phosphate transport in BLM vesicles, isolated from porcine kidneys, was evaluated in the present study with an aim to defining the saturation kinetics and specificity of the transport process. Phosphate uptake, in the absence of sodium, was saturable and inhibited by a number of anions and amino acid reactive agents which supports the notion of a specific transport system in the BLM for phosphate.

Methods

Membrane preparation. Basolateral membrane vesicles were isolated from porcine renal cortex by a modification [11,13] of the Percoll gradient method previously described by Scalera et al. [14]. The kidneys from pigs, anesthetized with sodium pentobarbital, were immediately removed and placed in an ice-cold medium consisting of 250 mM sucrose, 2 mM EDTA and 10 mM Hepes (*N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid) titrated to pH 7.6 with tetramethylammonium (TMA) hydroxide. All subsequent steps of the procedures were carried out on ice or in refrigerated centrifuges. The kidneys were decapsulated and bisected. The cortices were then dissected, minced and homogenized (4 ml/g of cortex) in the same medium with 0.1 mM PMSF by completing twenty strokes with a Teflon-glass homogenizer at maximum speed. A sample of the homogenate was kept for protein and enzyme determinations. The homogenate was centrifugated at $1100 \times g$ for 10 min in a Sorval RC5C using a SS34 rotor. The resulting supernatant was saved and the pellet was resuspended, homogenized twenty strokes as before, recentrifuged at $1100 \times g$ for 10 min. The two supernatants were then combined and centrifuged at $48\,000 \times g$ for 30 min. The supernatant was discarded and the fluffy upper layer of the resulting pellet was resuspended in the buffered sucrose medium described above, and centrifuged at $48\,000 \times g$ for 30 min. This procedure was repeated twice. The fluffy upper layer from the last pellet was suspended in the buffered sucrose media. Percoll was added (final concentration 12%), and the suspension was mixed by completing five strokes with a Teflon-glass homogenizer at maximum speed. Centrifugation was then performed at $40\,000 \times g$ for 66 min, and the resulting Percoll gradient was aspirated from the top. Of the 26 ml contents in each tube, the first 5 ml were discarded and the next 4.5 ml were collected and saved. These fractions were then pooled and centrifuged at $200\,000 \times g$ for 60 min. The membranous material on top of the resulting hard Percoll pellet was resuspended in the buffer to be used as intravesicular medium in the phosphate uptake experiment and washed by further centrifugation at $48\,000 \times g$ for 20 min. The final pellet containing purified BLM was then resuspended in the last buffer mentioned above at a concentration 8–10 mg of membrane protein/ml.

Enzyme assays. The purity of the final vesicle suspension was assessed by assaying the enzyme activity associated with the BBM (δ-glutamyl transpeptidase) and BLM (ouabain-sensitive Na^+,K^+-ATPase). These enzyme activities were determined as previously reported [13,14]. Protein was determined by the method of Lowry et al. after treatment of the membranes with 5% sodium dodecyl sulfate (w/v); dilutions of bovine serum albumin were used as standards. The specific activity of δ-glutamyl transpeptidase was enriched 2.3 ± 0.3-fold, in BLM fractions relative to the homogenates and Na^+,K^+-ATPase activity was increased by 22.9 ± 0.9-fold. In some studies, porcine kidneys were obtained from a commercial slaughter house. The respective enzyme enrichments were 2.7 ± 0.3 and 11.0 ± 0.8. Transport was similar in kidneys obtained from both sources; accordingly, the results have been averaged.

Uptake measurements. The final membrane pellet was resuspended in appropriate concentrations of 42 mM Tris, 42 mM Hepes, 42 mM Mes, or combinations of these buffers with a final range of pH values of 6.0–8.0 as indicated with 20 mM mannitol, 21 mM TMA(OH) and 100 mM KCl. The incubation solutions were composed of the same buffer and pH as the vesicle suspension and contained in addition variable amounts of KH_2PO_4 and 20 μCi/ml of [^{32}P]phosphate to determine sodium-independent phosphate uptake. All studies were performed in the absence of sodium.

Uptake measurements were performed at 21°C in a 12×75 mm plastic test tube by adding 50 μl of incubation medium to 10 μl of membrane suspension. The reaction was started by mixing with a vortex and terminated by adding ice-cold stop solution containing (in mM): NaCl, 140; Na_2HAsO_4, 10; NaH_2PO_4, 0.5; Hepes, 2 (pH 7.5). The vesicle suspension was filtered through a Sartorius membrane filter (0.65 μm) and washed twice with 5 ml of cold stop solution. The filters were dried and then dissolved in Filter Count (Packard instruments), and counted in a liquid scintillation counter.

Materials

[^{32}P]Orthophosphate (carrier-free) was purchased from DuPont, New England Nuclear. Phenylglyoxal, DIDS, and diethyl-pyrocarbonate were from Sigma. EDC was obtained from Aldrich Chemicals Inc. Other chemicals were of the highest purity commercially available.

Results

Saturable sodium-independent phosphate transport

Phosphate is transported across the BLM into the vesicle (Fig. 1). The studies were performed in the presence of 1 mM phosphate and the absence of sodium. Uptake of phosphate into the BLM vesicles was linear from 0 to 9 s. Accordingly, uptake values determined prior to 9 s provide a reasonable estimate of transport at initial velocity.

Saturation studies were performed to determine if phosphate uptake across the BLM is facilitated and to find the apparent kinetic parameters of the transporters. Fig. 2 illustrates a typical concentration dependence of phosphate transport into BLM vesicles using a wide range of phosphate concentrations. Kinetic parameters were obtained from a Woolf-Augustinsson-Hofstee transformation with the use of a computer program (Lundon Software, Cleveland, OH). As described by Stevens et al. [15], a curvature of the Hofstee plot is compatible with diffusion and one major, high capacity saturable system. One major system was evident, the apparent V_{max} was 20.1 nmol (mg protein)$^{-1}$ min^{-1} and K_m 11.6 mM. The mean V_{max} was 13.6 ± 2.0 nmol (mg protein)$^{-1}$ min^{-1} and K_m 10.25 ± 0.9 mM, for five different membrane preparations.

Trans-stimulation of phosphate uptake

Next we performed trans-stimulation studies to support the contention that phosphate uptake was due to facilitated transport. Fig. 3 illustrates a typical experiment, one of three separate studies. Vesicles were prepared with 10 mM unlabelled phosphate inside and 5 mM [^{32}P]phosphate outside (final concentration) in the uptake solution. Transport of phosphate into BLM vesicles was consistently greater in those vesicles containing 10 mM phosphate than those prepared with no internal phosphate. The presence of trans-stimulation supports the notion that phosphate uptake into BLM vesicles is facilitated transport.

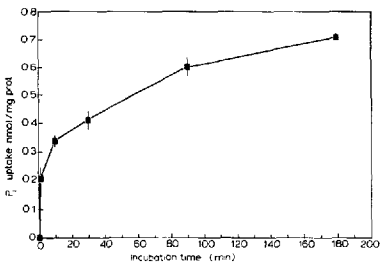

Fig. 1. Time course of phosphate uptake into BLM vesicles prepared from outer cortex of porcine kidneys. Vesicles were pre-equilibrated in 20 mM D-mannitol, 21 mM TMA(OH), 42 mM Hepes-Tris (pH 7.5), 100 mM KCl. Transport buffer consisted of 20 mM D-mannitol, 21 mM TMA(OH), 42 mM Hepes-Tris (pH 7.5), 99 mM KCl and 1 mM [^{32}P]phosphate. Isosmolarity was maintained with mannitol. Values are means ± S.E. of six determinations.

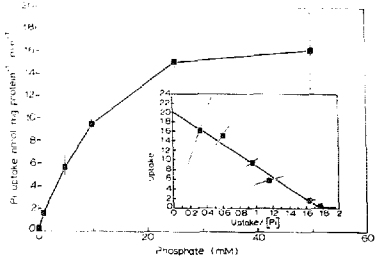

Fig. 2. Concentration dependence of phosphate uptake into renal BLM vesicles. Vesicles were preloaded with 100 mM KCl, 20 mM mannitol, 21 mM TMA(OH), 42 mM Hepes (pH 7.5). Incubations were performed at 21°C for 4.8 s in a medium containing appropriate amounts of KCl to insure a constant osmolarity, 20 mM mannitol, 21 mM TMA(OH), 42 mM Hepes (pH 7.5) and variable concentrations of phosphate, ranging from 0.1 to 50 mM. Data points are means ± S.E. of six determinations for each membrane preparation. The inset shows a Hofstee plot of the initial rate of phosphate uptake as a function of phosphate concentration.

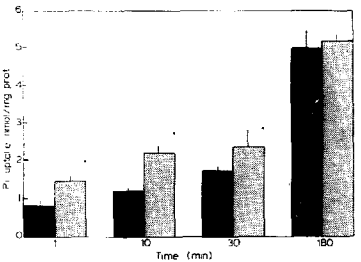

Fig. 3. Influence of phosphate trans-stimulation on phosphate uptake into BLM vesicles. Basolateral membrane vesicles were preloaded with 20 mM mannitol, 21 mM TMA(OH), 42 mM Hepes (pH 7.5), with or without 10 mM phosphate and appropriate amounts of KCl to insure a constant osmolarity. They were incubated at 21°C at variable times as indicated in medium containing 95 mM KCl, 20 mM mannitol, 21 mM TMA(OH), 42 mM Hepes (pH 7.5) and 5 mM phosphate. Values are means ± S.E. for six observations. Indicates significance ($P < 0.05$) from control values determined without intravesicle phosphate.

TABLE I

Specificity of phosphate uptake into BLM vesicles

The inhibitor was added to the transport solution at the indicated concentrations. Isosmolarity was maintained by replacing D-mannitol. [^{32}P]Phosphate concentration was 1.0 mM in the transport solution and uptake was terminated at 20 s. Values are means ± S.E.

Inhibition	Concentration	% of control	*n*
Arsenate	50 mM	44 ± 12 *	2
HCO_3^-	50 mM	75 ± 5 *	5
Sulfate	10 mM	95 ± 9	5
Sulfate	50 mM	108 ± 23	5
Acetate	50 mM	104 ± 8	5
Citrate	50 mM	86 ± 6	5
Formate	50 mM	99 ± 5	5
Succinate	50 mM	161 ± 33	5
PAH	50 mM	174 ± 26	5
Phosphonoformic acid	10 mM	120 ± 12	4

Specificity of phosphate uptake

A number of substrates were used to test the specificity of phosphate uptake into BLM vesicles prepared from porcine kidneys. Table I summarizes these observations. Large concentrations of sulfate, carboxylic acids, *p*-aminohippurate were without effect on phosphate uptake. Arsenate, a phosphate analogue, inhibits uptake by 54%. Bicarbonate also inhibited phosphate uptake into BLM vesicles which may be important in the intact cell in controlling phosphate movement across the renal cell. A number of phosphate analogues including phosphonocarboxylic acids, were also tested; these were without effect on BLM phosphate transport. This is in keeping with the previous observations of Dousa et al. who also observed no effect of phosphonoformate on BLM phosphate uptake [16]. This data suggests that the facilitative phosphate movement across the BLM is relatively specific for phosphate.

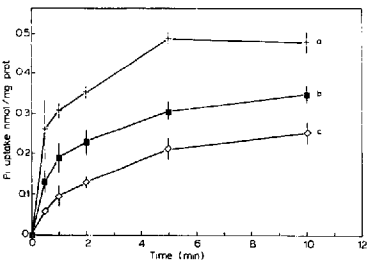

Fig. 4. Effect of transmembrane voltage or phosphate uptake. Vesicles were preloaded with 100 mM K gluconate (a,c) or 100 mM *N*-methyl-D-glucamine (NMDG) (b) in 20 mM mannitol, 21 mM TMA(OH), 42 mM Hepes (pH 7.5). The vesicles were then incubated with valinomycin, 12.5 μg/mg protein for 30 min at 20°C. P_i uptake was performed with 99 mM K gluconate (a,b) or 99 mM NMDG (c) in 20 mM mannitol, 21 mM TMA(OH), 42 mM Hepes and 1 mM KH_2PO_4.

Voltage-dependence of phosphate uptake

In order to test the effect of a transmembrane voltage gradient on phosphate uptake, a potassium diffusional potential was created across the BLM with and without valinomycin, a potassium ionophore. Fig. 4 summarizes this data. Phosphate uptake was greater in the presence of an internal positive potential indicating that transport is electrogenic in nature under these conditions.

Structure-function relationships of phosphate transport

Next, we used a number of selective and semi-selective reagents to study some of the characteristics of phosphate uptake into BLM vesicles. Preincubation of BLM vesicles with 15 mM, *N,N'*-dicyclohexylcarbodiimide, a COOH reactive agent for 30 min at 37°C lead to an inhibition of sodium-independent phosphate uptake of 33%. Similarly, 1-ethyl-3-[3-dimethylaminopropyl)carbodiimide, a water soluble COOH inhibitor, resulted in 34% inhibition. Diethyl pyrocarbonate, a histidine reagent, inhibits BLM phosphate uptake by 51%. The effects of DCCD, EDC, and DEPC were not due to a generalized membrane perturbation since the equilibrium values of [^{32}P]phosphate transport were not affected by these reagents. Phenylglyoxal (arginine reactive agent), $HgCl_2$ (sulfhydryl groups), and *N*-ethylmaleimide (sulfhydryl groups) was without effect at the concentrations used here. Interestingly, pretreatment of BLM vesicles with the stilbene derivative, DIDS, stimulated phosphate transport by 2–3-fold. We have no explanation for this observation at the present time.

Discussion

Evidence has been provided for both sodium-independent and sodium-dependent mechanisms for phosphate movement across the BLM. Although there is considerable contamination of the BLM preparation with BBM vesicles, as indicated by the marker enzymes for BBM, δ-glutamyl transpeptidase, and BLM, Na^+, K^+-ATPase, the transport observed here is likely to be due to BLM. There is very little, if any, sodium-independent phosphate transport into BBM vesicles prepared from renal cortical tissue [1–4]. The present studies characterized some aspects of phosphate uptake into vesicles prepared from the BLM.

Phosphate uptake into porcine BLM vesicles in the absence of sodium appears to be facilitated and selective for phosphate. This is consistent with previous reports in the rat, dog and rabbit [5,6,10,13]. The evidence for facilitation involves the observation that phosphate uptake is saturable and that it is trans-stimulated within internal phosphate. The apparent af-

finity is low, $K_m = 10.1 \pm 1.2$ mM, under the transport conditions used here. Although this may not accurately reflect what is occurring in the cell, it would suggest that the controls of phosphate absorption are not in the BLM. As the cytosolic free phosphate is in the order of 1–2 mM and the K_m for sodium-phosphate cotransport is 0.1–0.2 mM, the BLM phosphate transporter is set to regulate cell phosphate concentration rather than transcellular movement. The apparent kinetic values reported here may be altered by important influences such as transmembrane phosphate or some other cellular factors as indicated by the marked trans-stimulation.

A transmembrane positive voltage, outside-to-inside, stimulates phosphate uptake whereas a negative voltage inhibits transport. This clearly indicates that phosphate movement, either HPO_4^{2-} or $H_2PO_4^-$, is electrogenic. This is appropriate for phosphate movement from the cytosol across the BLM into the blood.

Phosphate uptake [4] into BLM vesicles is specific to phosphate and perhaps its close analogue, arsenate. Bicarbonate also inhibits phosphate uptake which may have some ramifications for transcellular phosphate movement [4]. Other anions, including sulfate and phosphonoformate had no apparent effect on sodium-independent phosphate transport across BLM. This is similar to the observations of some laboratories [10,11,17] but not others [4–6].

Selective and semi-selective reagents have been successfully used to investigate structure-function relationships [18,19]. Furthermore, these observations have become essential in describing tertiary structures from sequence data. Only a brief background will be given here for each of the reagents which were used. First, carbodiimides (DCCD and EDC) have been used to implicate critical carboxyl groups (under appropriate conditions there is also some interaction with tryosine groups) in sodium-dependent cotransporters [19,20,21, 22]. Weber et al. have shown that DCCD does not alter sodium-independent uptake but affects sodium-dependent mechanisms probably by reacting with a modifier site [20]. Under the conditions used here, DCCD and EDC inhibits sodium-independent phosphate uptake in porcine BLM vesicles. This apparently is also true for phosphate transport in band 3 of erythrocytes [23]. Diethyl pyrocarbonate (DEPC) inhibited BLM phosphate uptake (table 2). DEPC modifies histidine residues and has been shown to affect organic anion (PAH) exchanges [24] and sodium-glucose cotransport in BBM vesicles [25]. Hydroxylamine and dithiothreitol was used in the former case to specify histidine residues as opposed to imidazole moieties and sulfhydryl groups, respectively. These studies have not been performed in our BLM experiments; accordingly, specificity is yet to be established. However, the similarity of pK_a's values for phosphate and histidine may suggest that histidine residues may be important in phosphate transport. The present data support this contention. Phenylglyoxal has been used to affect arginine and lysine residues involved with sodium-dependent binding sites [26,27]. Béliveau and Strevey have successfully used this reagent to provide information on how the sodium-phosphate cotransporter works within the BBM [27]. Our data suggest that arginine (perhaps lysine residues) may not be critically involved with phosphate uptake in BLM vesicles or if it is, it is not exposed at the binding site. 2,3-Butanedione was not tested [26]. Other reagents such as flufenamate (Cl-binding sites), tetranitromethane (tyrosine), diazosulfanilic (histidine), and *N*-acetylimidazole (tyrosine and lysine) have not been used in BLM [28]. The latter was successfully used to label the sodium-phosphate cotransporter of OK cells [29]. Many of these reagents form covalent bonds with anionic and moieties thus they have been used to label proteins involved with functional studies such as transport [29]. This may be a possibility in the present studies.

Pretreatment of BLM vesicles with the stilbene analogue, DIDS, increased phosphate uptake into BLM vesicles. We have no explanation for this observation. Myint and Butterworth have shown that DIDS does not alter phosphate efflux from intact chick proximal tubule cells [17]; however, Ullrich et al. using microperfusion

TABLE II

Effect of chemical modifiers on phosphate transport into BLM vesicles

Structure-function relationships of the putative BLM phosphate transporter. Basolateral membrane vesicles were preincubated in a solution containing 100 mM KCl, 20 mM mannitol, 21 mM TMA(OH), 42 mM Hepes (pH 7.5) and test amino acid modifiers (15 mM of *N,N'*-dicyclohexylcarbodiimide (DCCD) in 1.5% DMSO; 25 mM ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl (EDC); 25 mM diethyl pyrocarbonate (DPC); 15 mM phenylglyoxal in 1.5% DMSO; 25 mM *N*-ethylmaleimide (NEM); 25 mM $HgCl_2$. After 1 h incubation at room temperature, the vesicles were washed and suspended in the same buffer mentioned above with the exception of the amino acid modifiers. Incubations were then performed at room temperature in medium containing 99 mM KCl, 20 mM mannitol, 21 mM TMA(OH), 42 mM Hepes (pH 7.5) and 1 mM [^{32}P]phosphate. Isosmolarity was maintained with mannitol. For the amino acid modifiers dissolved in DMSO, the DMSO was also added to the control uptake studies. Values are means ± S.E. for the number of experiments performed (*n*).

Reagent	Concentration	% of control	*n*
N,N'-Dicyclohexylcarbodiimide (DCCD)	15 mM	67 ± 2 *	5
1-Ethyl-3-(3-dimethylamino-propyl) carbodiimide (EDC)	25 mM	66 ± 4 *	4
Diethyl pyrocarbonate (DEPC)	25 mM	39 ± 11 *	4
$HgCl_2$	25 mM	105 ± 10	3
N-Ethyl maleimide (NEM)	25 mM	136 ± 30	3
Phenylglyoxal	15 mM	94 ± 12	4
4,4'-Diisothiocyanostilbene-2,2'-disulfonate (DIDS)	10 mM	293 ± 45 *	3

experiments reported that DIDS inhibited diffusional phosphate flux [30]. Accordingly these descriptions remain to be explained.

The evidence, given here, indicates that phosphate uptake into porcine renal BLM vesicles is facilitated, specific for phosphate and, electrogenic. This suggests that either HPO_4^{2-} or $H_2PO_4^-$ is transported across the BLM. Phosphate is taken up by the BBM by a sodium-phosphate cotransporter, normally as $2Na^+$-HPO_4^{2-}. The major cotransporter possesses a high affinity, in the order of 0.1–0.2 mM and concentrates phosphate in the cytosol. We speculate that phosphate exits across the BLM by moving down an electrical gradient; as the cytosolic free phosphate concentration is about 1.0 mM and plasma 2.5–3.0 mM, the transmembrane voltage plays an important role in BLM transport. The facilitated BLM transporter is different from the BBM in that is has a relatively low affinity, $K_m = 10.1 \pm 2.9$ mM, for phosphate. Accordingly, the two transporters, one in the BBM and the other in BLM, are poised to accumulate phosphate within the cell and as such the BLM need not be highly regulated.

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