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Sulphate and phosphate transport in the renal proximal tubule

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Experiments performed on microperfused proximal tubules and brush-border membrane vesicles revealed that inorganic phosphate is actively reabsorbed in the proximal tubule involving a 2 Na^+–HPO_4^{2-} or $H_2PO_4^-$ co-transport step in the brush-border membrane and a sodium-independent exit step in the basolateral cell membrane. Na^+–phosphate co-transport is competitively inhibited by arsenate. The transtubular transport regulation is mirrored by the brush-border transport step: it is inhibited by parathyroid hormone intracellularly mediated by cyclic AMP. Transepithelial inorganic phosphate (P_i) transport and Na^+-dependent P_i transport across the brush-border membrane correlates inversely with the P_i content of the diet. Intraluminal acidification as well as intracellular alkalinization led to a reduction of transepithelial P_i transport. Data from brush-border membrane vesicles indicate that high luminal H^+ concentrations reduce the affinity for Na^+ of the Na^+-phosphate co-transport system, and that this mechanism might be responsible for the pH dependence of phosphate reabsorption. Contraluminal influx of P_i from the interstitium into the cell could be partly inhibited by 4,4′-diisothiocyanostilbene-2,2′-disulphonic acid (DIDS). It is not, however, changed when dicarboxylic acids are present or when the pH of the perfusate is reduced to pH 6.

Sulphate is actively reabsorbed, involving electroneutral 2 Na^+–SO_4^{2-} co-transport through the brush-border membrane. This transport step is inhibited by thiosulphate and molybdate, but not by phosphate or tungstate. The transtubular active sulphate reabsorption is not pH dependent, but is diminished by the absence of bicarbonate. The transport of sulphate through the contraluminal cell side is inhibited by DIDS and diminished when the capillary perfusate contains no bicarbonate or chloride. The latter data indicate the presence of an anion exchange system in the contraluminal cell membrane like that in the erythrocyte membrane.

Introduction

In the mammalian kidney, phosphate and sulphate are filtered in the glomeruli and reabsorbed in the proximal tubules by saturable transport processes (Pitts & Alexander 1944; Lotspeich 1947). In the elasmobranch fishes, instead of reabsorption, secretion of phosphate and sulphate takes place (Stolte *et al.* 1982). In contrast to Cl^-, which in the rat proximal tubule is more than 90 % reabsorbed by passive transport, i.e. by diffusion and solvent drag via the paracellular pathway, phosphate and sulphate are reabsorbed actively via the transcellular pathway. Paracellular passive fluxes of phosphate and sulphate play only a minor role. In this paper we shall show which factors influence the transtubular active transport of phosphate and sulphate, and we shall deal with the characteristics of the luminal and contraluminal transport steps.

Transtubular phosphate transport

Our first approach was to measure the transtubular zero net flux concentration difference of inorganic phosphate (P_i), which at a given permeability is a measure of the active transport rate (Ullrich 1973). The active transport rate of P_i in the early part of the proximal tubule is greater than in the later part, and vanishes if Na^+ is omitted from the perfusate (figure 1) (Baumann *et al.* 1975*a*, and our own unpublished results). Figure 2 shows 10 s phosphate reabsorption from animals that were parathyroidectomized 2 h before the experiments. In both

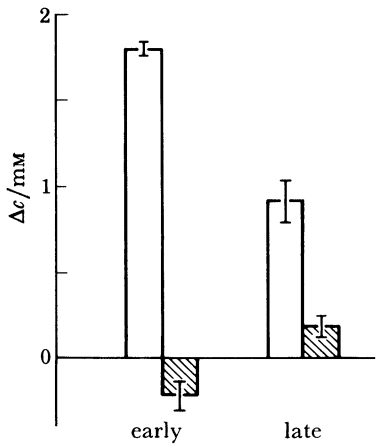

Figure 1.

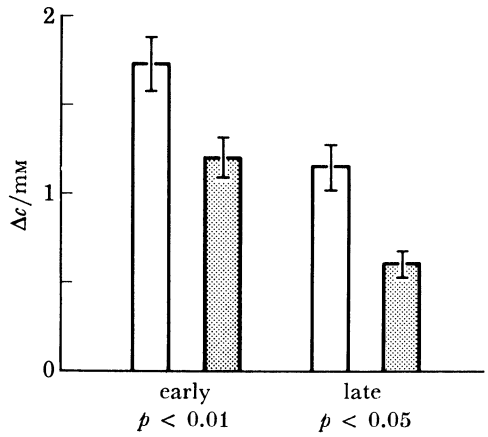

Figure 2.

Figure 1. Effect of Na^+ on the transtubular active transport of phosphate in the early and late part of the proximal convolution. The zero net flux transtubular concentration difference ($\Delta c = c_{capillary} - c_{lumen}$), which at a given permeability is a measure of the active transport rate, was determined in the doubly perfused proximal tubule of the rat. The starting concentration of phosphate in both perfusates was 2 mM. Open column, controls; hatched columns, Na^+-free (Baumann *et al.* 1975*a*, and our own unpublished results).

Figure 2. Effect of parathyroid hormone (5 U initially and a continuous intravenous infusion of 12 U/h) on phosphate reabsorption (10 s values) in the early and late proximal convolution of acutely parathyroidectomized rats. $\Delta c = c_{lumen,\ time\ zero} - c_{lumen,\ 10s}$. The blood flow through the capillaries was not disturbed. Open columns, controls; shaded columns, PTH (Ullrich *et al.* 1977).

early and late proximal tubule, the phosphate transport can be inhibited by parathyroid hormone (PTH) injected into the animals 30 min before the microperfusion experiment (Ullrich *et al.* 1977*a*). Furthermore P_i reabsorption is higher in animals on a low-phosphate diet than in those on a high-phosphate diet (figure 3). In animals on a low P_i diet, PTH had no inhibitory effect in early proximal tubules, but did in late proximal tubules. However, acute parathyroidectomy increased phosphate reabsorption in the early as well as in the late proximal tubule. These data show that the transtubular phosphate transport is Na^+ dependent, under the influence of parathyroid hormone, and dependent on the phosphate content of the diet. Dietary adaptation of P_i transport is also observed in thyreoparathyroidectomized animals, i.e. in the absence of the parathyroid hormone system, and it seems that the P_i concentration in the blood plasma is somehow responsible for this effect.

With brush-border membrane vesicles it has been shown that a Na^+–phosphate co-transport mechanism exists at the luminal cell side (Hoffmann *et al.* 1976; Cheng & Sacktor 1981). With

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K^+ in the medium an exponential uptake of phosphate into the brush-border membrane vesicles was observed, which was almost identical whether the uptake was started under K^+-gradient or K^+-equilibrium conditions (figure 4). In the presence of Na^+, however, the uptake of phosphate was much larger. In the presence of an inward-directed Na^+ gradient, an overshoot was observed, i.e. the intravesicular phosphate concentration was transiently much larger

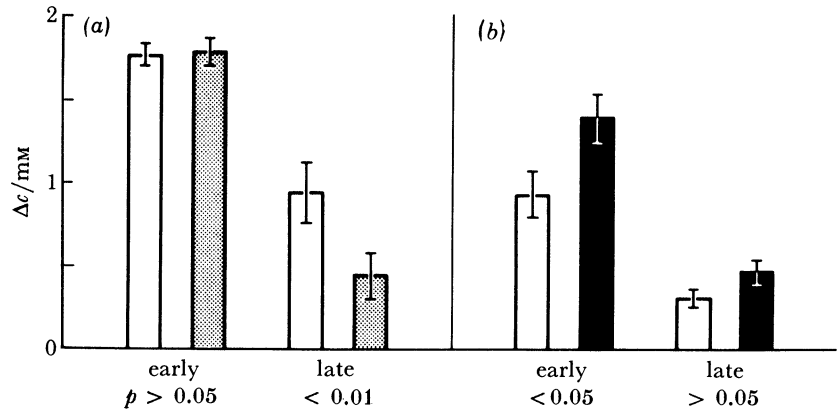

FIGURE 3. Effect of (*a*) low (less than 0.15%) and (*b*) high (2%) phosphate diets on 10 s phosphate efflux from the early and late proximal tubule. The effects of parathyroid hormone (PTH, shaded columns) and acute parathyroidectomy (PTX, black columns) are also shown (Ullrich *et al.* 1977).

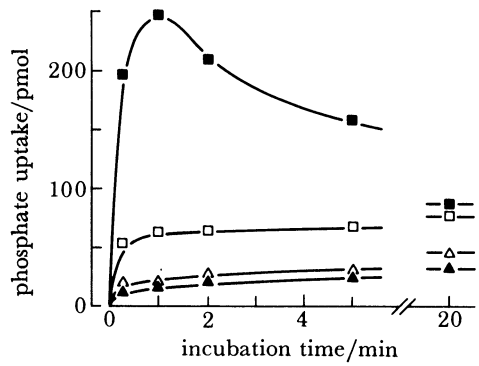

FIGURE 4. Uptake of phosphate in brush-border membrane vesicles in the presence of an inward-directed Na^+ gradient (■) or a K^+ gradient (▲) or at Na^+ (□) or K^+ (△) equilibrium; Na^+ and K^+ both 100 mM, as thiocyanate (Hoffmann *et al.* 1976).

than at the equilibrium. Na^+-dependent phosphate uptake was competitively inhibited by arsenate (Hoffmann *et al.* 1976). Vesicle studies (Hoffmann *et al.* 1976; Burckhardt *et al.* 1981) as well as intracellular electrical potential measurements (Samarzija *et al.* 1981) showed that the Na^+–phosphate co-transport in the rat is electrogenic at acidic pH values but electroneutral at alkaline pH values. These data are best explained with a transport mechanism that always accepts two Na^+ ions but can accept monovalent as well as divalent phosphate. Furthermore, it has been shown that the regulation of phosphate transport by parathyroid hormone (Evers *et al.* 1978; Stoll *et al.* 1979*b*; Hammerman *et al.* 1980) as well as by the phosphate content of the diet (Stoll *et al.* 1979*a*, *b*; Kempson *et al.* 1980) occurs at the level of the brush-border membrane. As can be seen in figure 5*a*, the phosphate uptake into brush-border membrane vesicles from

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rats that received parathyroid hormone 1 h before being killed is smaller than the uptake into vesicles from control rats. Similarly, the Na^+-gradient driven phosphate uptake into brush-border membrane vesicles from animals on a low P_i diet is higher than that from animals on a high P_i diet (figure 5*b*). Also, the defective renal phosphate reabsorption by the X-linked hypophosphataemic male mouse can be attributed to a specific loss of the Na^+-dependent phosphate transport system in the brush-border membrane (Tenenhouse *et al.* 1978). A body of evidence

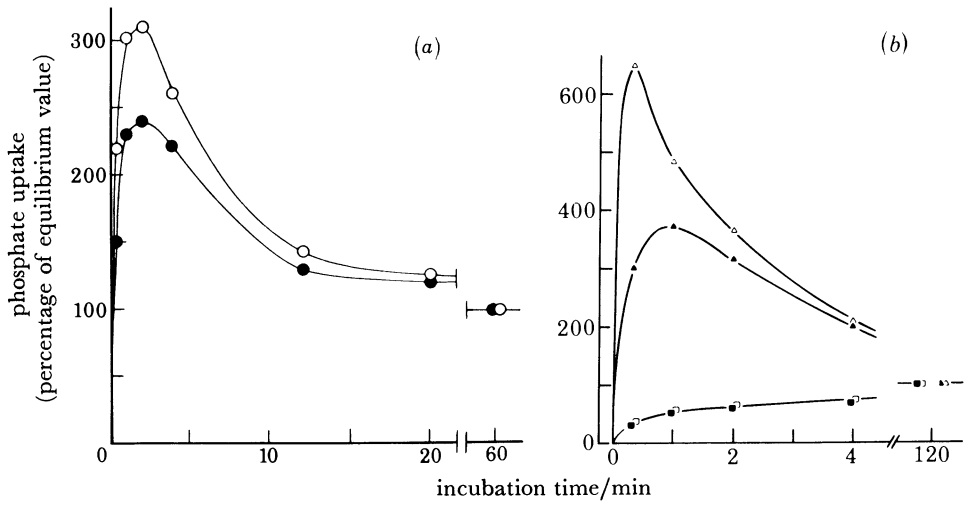

FIGURE 5. (*a*) Effect of parathyroid hormone (30 USP units given intramuscularly 1 h before killing) on the phosphate uptake into brush-border membrane vesicles in the presence of a Na^+ gradient. ○, Control rats; ●, PTH-treated rats (Evers *et al.* 1978). (*b*) Effect of low-phosphate (open symbols) and high-phosphate (closed symbols) diet on phosphate uptake in brush-border membrane vesicles. Triangles, phosphate uptake; squares, mannitol uptake (Stoll *et al.* 1979*b*).

indicates that the inhibitory effect of parathyroid hormone is mediated by intracellular cyclic AMP (cAMP) (Aurbach & Heath 1974). Recently the parathyroid hormone effect could be mimicked by a complete *in vitro* system containing osmotically shocked vesicles, ATP and cAMP. Furthermore, cAMP-dependent brush-border membrane phosphorylation has been observed, which might be causally linked to the reduction of phosphate transport (Hammerman & Hruska 1982; Biber *et al.* 1982).

Special emphasis was given to the pH dependence of phosphate transport (for literature see Ullrich *et al.* 1981). In microperfusion experiments it has been observed that the phosphate transport is larger at alkaline pH than at acidic pH (Baumann *et al.* 1975*b*; Ullrich *et al.* 1978). The question was then whether the secondary phosphate ion is preferentially transported over the primary phosphate ion or whether the pH has an effect on the transport system of phosphate. In experiments with rat and rabbit renal brush-border membrane vesicles it has been confirmed that phosphate uptake was higher at alkaline pH than at acidic pH (figure 6) (Hoffmann *et al.* 1976; Sacktor & Cheng 1981; Burckhardt *et al.* 1981). But as can be seen from the inset of figure 6, the apparent K_m as well as V_{max} increased in the study with rat vesicles with increasing pH of the incubation medium. In the case where only secondary phosphate ions would be accepted by the transport system, an increase in pH should decrease K_m and leave V_{max} unchanged. The observed change in V_{max} indicates that pH might instead influence the phosphate transport system and that it does not act by changing the proportion of primary to secondary

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phosphate. Figure 7 shows indeed that increasing pH decreases the K_m for Na^+ to activate the phosphate transport system (Ullrich *et al.* 1981). The Na^+-concentration and thus most probably the saturation of the transporter with Na^+ determine the V_{max} of phosphate transport (Evers *et al.* 1978). Therefore, at physiological Na^+ concentrations, pH influences phosphate transport by varying the saturation of the transporter with Na^+. In rat renal brush-border

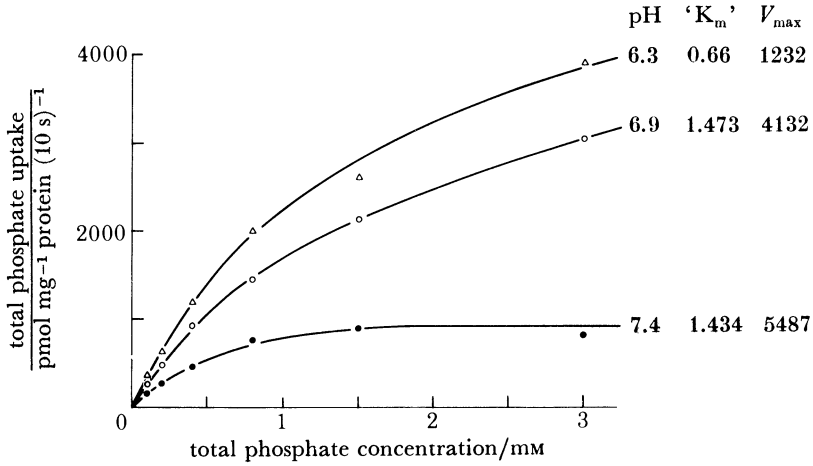

FIGURE 6. Phosphate uptake into brush-border membrane vesicles at different pH values of the incubation medium (Burckhardt *et al.* 1981).

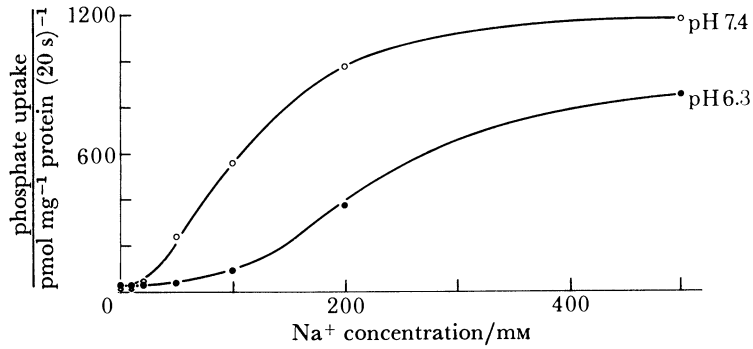

FIGURE 7. Na^+ dependence of phosphate uptake into brush-border membrane vesicles at pH 6.3 and 7.4 in the incubation medium (Burckhardt *et al.* 1981).

membrane vesicles, preferential uptake of secondary phosphate seems to play a minor role as a reason for the pH dependence of phosphate transport.

Only few data are available on phosphate transport through the contraluminal cell side. Hoffmann *et al.* (1976) found that vesicles from the basal lateral plasma membranes take up phosphate very rapidly. The basolateral phosphate transport is Na^+-independent. Applying a new method, we were able to measure the peritubular $^{32}P_i$ influx from the peritubular capillaries and interstitium into the tubular cells. Figure 8 shows the decrease of capillary P_i concentration with contact time, corrected for dilution by simultaneously measured changes of inulin concentrations. As can be seen, the presence of α-ketoglutarate, which competes with P_i transport in mitochondria, has no significant influence on peritubular P_i transport. Also,

decreasing the pH of the solution standing in the capillaries to pH 6 does not influence the peritubular P_i influx into the cell. DIDS (1 mM) inhibits the P_i influx. These data are in agreement with those of Grinstein *et al.* (1980), who measured phosphate efflux from basolateral cell membrane vesicles and observed a decrease of the phosphate efflux by 22 % when DIDS (50 μM) was in the solution.

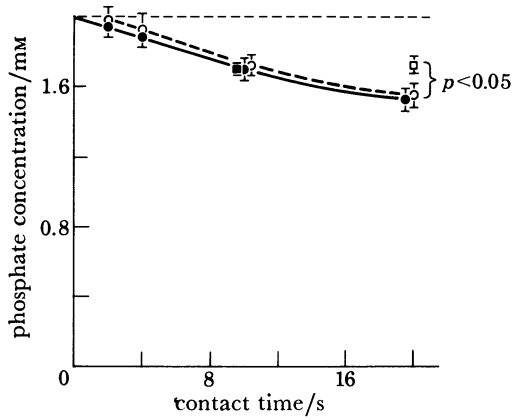

FIGURE 8. Contraluminal influx of phosphate (starting concentration 2.0 mM) from the capillaries into the kidney cells. ○, Control, pH 7.4; ●, in the presence of 3 mM α-ketoglutarate; ■, at pH 6; □, in the presence of 1 mM DIDS (K. J. Ullrich & G. Rumrich, unpublished results).

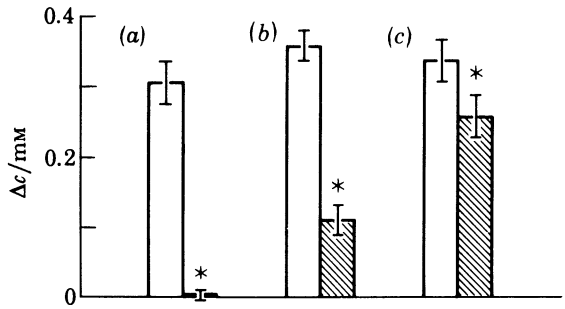

FIGURE 9. Active sulphate resorption in the proximal tubule of the rat kidney. Δc ($=c_{\text{capillary}}-c_{\text{lumen}}$ at zero net flux transtubular concentration difference) is at a given permeability a measure of the active transport rate. The starting concentration of SO_4^{2-} in the luminal and capillary perfusate was 0.5 mM. The inhibitory effect of omission of Na^+ (*a*) or addition of 1 mM thiosulphate (*b*) or molybdate (*c*) is shown (shaded columns). *, $p < 0.001$ (Ullrich *et al.* 1980*a*).

In summary, present available evidence indicates that transtubular phosphate transport is Na^+-dependent and secondary active. The concentrative mechanism is located in the luminal membrane and has been identified as a Na^+–phosphate co-transport mechanism. Most of the regulatory phenomena in transtubular phosphate transport are expressed at the level of this co-transport mechanism. Contraluminal phosphate transport is Na^+-independent and sensitive to DIDS.

TRANSTUBULAR SULPHATE TRANSPORT

Sulphate is reabsorbed from the proximal convolution by a Na^+-dependent process that is inhibited by thiosulphate and molybdate, but not by tungstate and phosphate (figure 9) (Ullrich *et al.* 1980*a*). Results obtained with brush-border membrane vesicles were in agreement

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with these findings (Lücke *et al.* 1979). In the presence of an inward-directed Na^+ gradient an overshoot uptake of sulphate was observed (figure 10). Changing the electrical potential difference across the vesicle membrane by establishing different diffusion potentials did not alter Na^+-dependent sulphate uptake. An electrical signal of Na^+-sulphate co-transport could also not be seen in direct electrical cell potential messurements, indicating that sulphate co-transport

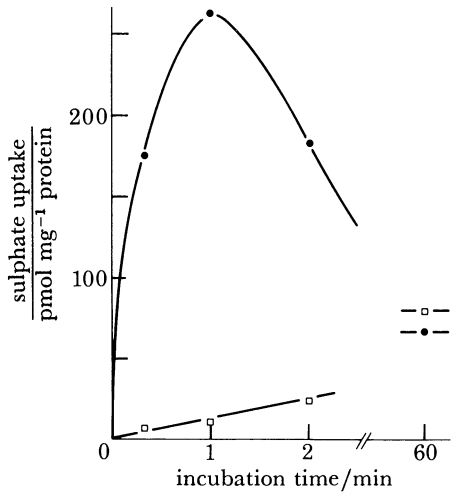

FIGURE 10. Sulphate uptake into brush-border membrane vesicles in the presence of an inward-directed Na^+ (●) or potassium (□) gradient (Lücke *et al.* 1979).

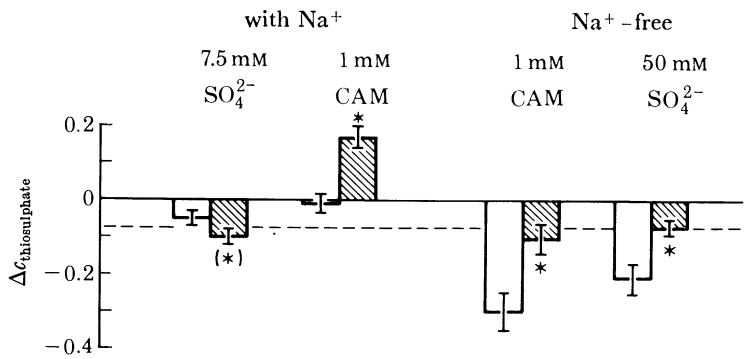

FIGURE 11. Zero net flux concentration differences ±s.e. of thiosulphate in the proximal tubule, which are a measure of the active transport rate. Positive Δc values indicate resorption, negative values secretion. Carinamide (CAM) was added to the perfusate at a concentration of 1 mM. The dotted line indicates passive distribution. (*), $p < 0.01$; *, $p < 0.001$. Open columns, controls; shaded columns, additions as indicated (Ullrich *et al.* 1980*b*).

proceeds with two Na^+ ions (Samarzija *et al.* 1981). With the technique of the double-perfused tubule *in situ* a typical bidirectional active transport was observed with thiosulphate. Thus under control conditions in the presence of Na^+, nearly zero Δc values were observed. However, when 7.5 mM sulphate was added to the Na^+-containing solution a secretory Δc arose, apparently by the inhibition of a reabsorptive component (figure 11). On the other hand, a significant reabsorptive Δc of thiosulphate was seen with Na^+-containing solutions when carinamide or *p*-aminohippurate (1 mM) were added to the perfusates, thereby inhibiting the

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secretory component. The largest secretion of thiosulphate was observed when the solutions were Na^+-free. Again, this secretion was inhibited by carinamide, probenecid and *p*-aminohippurate, but only by very large concentrations of sulphate (50 mM). On the other hand, *p*-aminohippurate secretion under Na^+-free conditions was not influenced by sulphate and thiosulphate at up to 50 mM. Our suggestion that thiosulphate secretion might be shared by

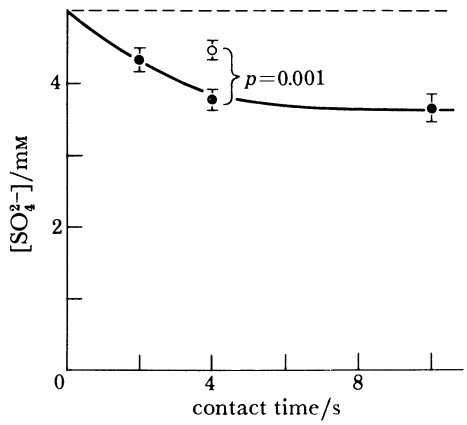

FIGURE 12. Contraluminal influx of sulphate (●, starting concentration 5 mM) from the capillaries into the kidney cells and the effect of 1 mM DIDS (○) on this influx (K. J. Ullrich & G. Rumrich, unpublished results).

sulphate was recently confirmed by Brazy & Dennis (1981), who measured the unidirectional sulphate fluxes. Thus a common reabsorptive system for sulphate and thiosulphate exists with a preference for sulphate and a common secretory system with a large preference for thiosulphate. The net flux seems to be the result of the difference in the activity of the counteracting transporters, located at the luminal and contraluminal cell side. It is possible that the higher activity of the transporter at one cell side leads to a reversal of the flux through the transporter at the other side. Our finding, that *p*-aminohippurate secretion is greater in the late proximal loops than in the early ones, whereas thiosulphate secretion is greater in the early loops, suggests the existence of several secretory systems with different affinities for different organic anions.

The contraluminal sulphate transport was tested with two methods: (1) by measuring the contraluminal influx from the peritubular capillaries into the tubular cells (figure 12) (Ullrich & Rumrich, unpublished), and (2) by flux measurement with vesicles from the contraluminal cell side (Grinstein *et al.* 1980). With both methods it was seen that sulphate transport was inhibited by DIDS. It must be emphasized that covalently bound SITS, which inhibited proximal buffer transport, when applied from the contraluminal cell side, inhibited neither *p*-aminohippurate nor sulphate transport (Ullrich *et al.* 1977*b*; Frömter & Ullrich 1980), but DIDS, which remained in contact with the membrane when the flux was measured, inhibited both. In the double-perfused tubule it was found that the sulphate reabsorption was not dependent on pH changes but on the presence of bicarbonate (Ullrich *et al.* 1980*a*). Recent data on the contraluminal transport of sulphate indicate that this transport step is indeed dependent on the presence of bicarbonate as well as of chloride, because the influx of sulphate from the interstitium into the tubular cells was diminished when bicarbonate was omitted from the perfusates

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or when chloride was replaced by gluconate (table 1). In these experiments intracellular bicarbonate and chloride most probably stimulated sulphate uptake by chloride–sulphate or bicarbonate–sulphate exchanges, assuming that the *trans*-stimulation of sulphate influx is greater than *cis*-inhibition of sulphate influx.

TABLE 1. CONTRALUMINAL SULPHATE INFLUX FROM THE INTERSTITIUM INTO PROXIMAL TUBULAR CELLS AS EVALUATED BY THE DECREASE OF SULPHATE CONCENTRATION IN A STANDING CAPILLARY PERFUSATE

(Percentage decreases ± s.e. of a perfusate containing 5 mM sulphate; p against control.)

control	Cl^--free	HCO_3^--free	$(Cl^- + HCO_3^-)$-free
22.1 ± 1.5	14.0 ± 2.0 $p < 0.01$	13.2 ± 3.5 $p < 0.05$	8.7 ± 1.9 $p < 0.001$

In summary, sulphate is reabsorbed in an electroneutral fashion by co-transport with Na^+ through the brush-border membrane. The system also accepts thiosulphate and molybdate. The contraluminal transport step of sulphate seems to occur in exchange for bicarbonate, chloride and possibly other anions, and is DIDS-sensitive. This contraluminal transport system may be common for sulphate and thiosulphate reabsorption, as well as for thiosulphate and possibly sulphate secretion.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES