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Bidirectional Active Transport of Thiosulfate in the Proximal Convolution of the Rat Kidney

K. J. Ullrich, G. Rumrich, and S. Klöss

Max-Planck-Institut für Biophysik, Kennedyallee 70, D-6000 Frankfurt/Main 70, Federal Republic of Germany

Abstract. Using the standing droplet method in the late proximal convolution and simultaneous microperfusion of the peritubular capillaries, the zero net flux transtubular concentration difference of thiosulfate at 45 s was determined, the latter being taken as a measure of active thiosulfate transport. Under control conditions, in the presence of Na^+, near zero Δc values were observed. When 1 mmol/l carinamide or paraaminohippurate (PAH) were added to the perfusates significant reabsorptive Δc arose. However, when 7.5 mmol/l sulfate was added to the Na^+ containing perfusates or when the perfusates were Na^+-free secretory Δc values were observed. Tested under Na^+-free conditions, the secretory Δc was not influenced by simultaneously present 5 mmol/l of SO_4^{2-} but was diminished by 50 mmol/l SO_4^{2-}. PAH (1 mmol/l), carinamide (0.2 mmol/l) and probenecid (1 mmol/l) decreased the secretory Δc by 48, 65 and 48%, respectively. The PAH secretion was not influenced, when thiosulfate or sulfate up to 50 mmol/l was added to both perfusates. Under Na^+-free conditions the Δc of thiosulfate in early loops of the proximal convolution is higher than in late loops, while for PAH this pattern is reversed. Taken together with the previously published inhibition of sulfate reabsorption by thiosulfate the data indicate 1. thiosulfate is reabsorved by the Na^+-dependent sulfate transport system and 2. thiosulfate is simultaneously secreted by a carinamide-, probenecid- and PAH-sensitive secretory system. The secretory system might also be shared by sulfate. The thiosulfate net flux is the result of the difference in the activity of the counteracting transporters, located at the luminal and contraluminal cell side. Is 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 cell side.

Key words: Renal tubule – Thiosulfate transport – Na^+ coupled transport – Sulfate transport – Paraaminohippurate transport.

Introduction

Thirty years ago it was shown that at low plasma concentrations thiosulfate undergoes tubular secretion [5, 6, 9, 12, 13] which was reduced when the plasma concentration was raised [5]. Furthermore, it was observed that thiosulfate secretion turned into reabsorption when carinamide was applied [6, 13]. Thus, under carinamide, a mutual competitive inhibition of sulfate and thiosulfate reabsorption could be documented [3]. With paraaminohippurate (PAH), however the findings were controversial; some authors working on cat and man observed an inhibitory effect of PAH on thiosulfate secretion [9, 12]; others working on dog and man could not observe it [7, 10]. Berglund et al. [2, 3], who did not obtain the expected thiosulfate secretory curve at rising plasma sulfate concentrations, concluded that sulfate must also have blocked thiosulfate secretion. Mudge et al. [15, 16] on the other hand, applying stop flow techniques, did not see a significant effect of sulfate on thiosulfate secretion. These discrepancies led to different models of thiosulfate transport. It is now possible for us to discriminate between thiosulfate reabsorption and secretion by applying the standing droplet technique to evaluate local transport rates and by omitting Na^+ from the perfusates. Our data are in agreement with the assumption that a Na^+-dependent, sulfate-thiosulfate reabsorptive mechanism and a separate thiosulfate- and possibly sulfate-secretory mechanism exists in the same tubular segment. The latter is inhibited by carinamide, probenecid and PAH but does not seem to be identical in all steps with the PAH secretory system.

Methods

The experiments were performed with male Wistar rats (Winkelmann, Kirchborchen/FRG) of 200–240 g body weight kept on Altromin standard diet and tap water. The rats were anesthetized with Inactin (Byk Gulden, Konstanz, FRG) by injecting 120–150 mg/kg body weight intraperitoneally. Mounted on a 37° C thermostated animal table the left kidney was exposed by flank incision and immobilized in a plastic cup [22]. The kidney was

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decapsulated and the peritubular blood capillaries were punctured with 7–8 µm o.d., sharpened glass micropipettes and perfused at a rate of 1–3 µl/min. Simultaneously stop flow microperfusion was performed in either an early proximal tubule, i.e. at 0–20% of the proximal convolution or in a late proximal tubule i.e. at 80–95% of the proximal convolution. The tubule was situated in the perfused area 1–3 tubular diameters distant from the capillary infusion site. First the tubule was filled with colored castor oil thereby blocking the free flow. Then the tubule was also perfused with a rate of 50 nl/min in the orthograde direction. After 45 s of capillary and tubular perfusion with solutions containing $^{35}SSO_3^{2-}$ the luminal perfusion was stopped by a distal oil blockade. The stopped perfusate was withdrawn after 45 s contact time. The collection was repeated 2–3 times without interrupting the capillary perfusion. The first and second sample were pooled to get enough volume (0.5–1.5 nl) for analysis. To assure high accuracy in evaluating the effect of a test substance the crossed paired sampling technique [24] was applied. In that case, after the first 45 s luminal samples had been taken, the perfusion pipettes were removed and replaced by other pipettes containing different test solutions. After 45 s continuous perfusion with the new solutions a second series of 45 s luminal samples was obtained from the same tubular loop. In the course of each experiment the sequence control → test solution was alternately reversed. When the change (control → test) differed according to Student's *t*-test significantly from the crossed paired samples (test → control) it was concluded that the $S_2O_3^{2-}$ transport changed significantly. The same holds for measurements of the Δc of para-aminohippurate (PAH). The samples were placed under paraffin oil onto a siliconized glass dish and the sample size measured. The ^{35}S counts of the labelled $S_2O_3^{2-}$ in the capillary perfusate and the sampled luminal perfusates as well as the ^{3}H counts of PAH were measured in a Nuclear Chicago scintillation counter with Spectrafluor toluene as scintillation fluid.

Because the specific activity of $^{35}SSO_3$ in the luminal and capillary perfusate was the same, the radioactive counts were proportional to the chemical $S_2O_3^{2-}$ concentration. As pointed out in an earlier paper ([20], equation 10) at a given transtubular permeability the zero net flux transtubular electrochemical potential difference is a measure of the active transport rate. Under our zero net flux conditions the transtubular electrical potential difference is +1.9 mV, lumen-positive [10a] which according to the Nernst equation corresponds at equilibrium to a $[S_2O_3^{2-}]_l/[S_2O_3^{2-}]_0$ of 1.15. Thus, at the mean thiosulfate concentration present in our experiments the passive thiosulfate distribution would correspond to a Δc $(c_0 - c_l)S_2O_3^{2-}$ value of −0.075 mmol/l. This value is marked in the figures by a dotted line. Since the addition of mmolar concentrations of the test substances $S_2O_3^{2-}$, SO_4^{2-} and PAH do not change the transtubular potential difference (Samarzija and Frömter, unpublished results), and since there is no indication that they change the transtubular permeability, the observed changes of Δc after applying the test substances are taken as a measure of changes of the active transport rate.

The standard solution used for capillary perfusion contained in mmol/l: Na^+ 152, Cl^- 128, HCO_3^- 25, K^+ 3, Ca^{2+} 1.5, Mg^{2+} 1.0, $^{35}SSO_3^{2-}$ 0.5, acetate 6. It was gassed also with 95% O_2, 5% CO_2. Unless specified otherwise the luminal perfusate composition was Na^+ 136.5, Cl^- 133.5, HCO_3^- 4, K^+ 3, Ca^{2+} 1.5, Mg^{2+} 1.0, $^{35}SSO_3^{2-}$ 0.5, acetate 6, raffinose 31. It was gassed also with 95% O_2, 5% CO_2. The specific activity of $^{35}SSO_3^{2-}$ in the perfusates was 1.16 Ci/mmol. When Na^+-free solutions were used, all Na^+ of the capillary perfusate was replaced by choline. In the luminal perfusate the raffinose concentration was then lowered to 16 mmol/l and the other concentrations in the luminal perfusate were: $Choline^+$ 142, Cl^- 143, HCO_3^- 4, K^+ 5, Ca^{2+} 1.5, Mg^{2+} 1.0, $^{35}SSO_3^{2-}$ 0.5, acetate 6. When the Δc of PAH was measured both luminal and capillary perfusate contained tritiated PAH in the same concentration, 0.5 and 1.5 mmol/l, respectively. The specific activity of PAH was 0.4 Ci/mmol. Like the test substances (thiosulfate, PAH) all other substances, the influence of which on the respective Δc_s were tested, were added to the luminal as well as to the capillary perfusate in the same concentration. The only exemption is the experimental series 1, listed in the Table. $^{35}SSO_3^{2-}$ and tritiated PAH were obtained from NEN Chemicals, Boston/USA. Qualitative tests with $BaCl_2$ as well as silica gel thin layer chromatography [17] repeatedly performed during the course of the experiments gave no indication for sulfate impurity in the $^{35}SSO_3^{2-}$ stock. Carinamide and probenecid were gifts from Sharp and Dohme GmbH, München. Both substances are analogs of sulfamyl-benzoic acid and inhibit competitively the secretion of organic acids (PAH, phenol red, bromcresol green and many other substances) with a K_i around 10^{-5} M (for literature see [18]).

Results

In the presence of Na^+ the luminal thiosulfate concentration remains nearly the same as the peritubular thiosulfate concentration indicating no thiosulfate net transport (Fig. 1). When 1 mmol/l carinamide was added to the perfusates the luminal thiosulfate concentration is by 0.17 mmol/l (when corrected for pd, 0.25 mmol/l) lower than the peritubular thiosulfate concentration indicating thiosulfate reabsorption. Similarly with 1 mmol/l PAH in the perfusate a significant reabsorptive Δc can be seen. When, however, 7.5 mmol/l sulfate was added the Δc_s turned into secretory direction (Fig. 2). The secretory Δc_s were much more pronounced when the Na^+ in the perfusate were replaced by choline (Fig. 3). Therefore, while studying the secretory components, all following experiments were performed with Na^+-free solutions. As observed earlier the secretory Δc of PAH declines with time, no matter whether the solutions contain Na^+ or not. Similarly the first three samples in an experiment gave a secretory Δc of thiosulfate of -0.47 ± 0.07 and the next three samples one of -0.16 ± 0.05 mmol/l. Thus, in all experiments with Na^+-free solutions we took only three samples from each animal. Fig. 3 shows furthermore that the addition of 5 mmol/l sulfate did not change the secretory Δc of thiosulfate but the addition of 50 mmol/l sulfate decreased the Δc considerably. As shown in Figs. 4 and 5 the secretory Δc was significantly diminished when carinamide (0.2 mmol/l), probenecid (1 mmol/l) or PAH (1 mmol/l) were added to the perfusates. To find out whether thiosulfate or sulfate influenced PAH secretion thiosulfate or sulfate up to 50 mmol/l were added to the perfusates (Table 1). In neither case a significant influence of thiosulfate or sulfate on PAH secretion was observed. In order to find out whether the PAH and $S_2O_3^{2-}$ secretory pattern along the proximal tubule are the same, we measured the Δc_s of both substances with crossed paired experiments in the early and the late loops of the same proximal convolution. As shown in Fig. 6 the Δc for thiosulfate in the early loops is higher than in the late ones while for PAH the situation is reversed. Thus, the

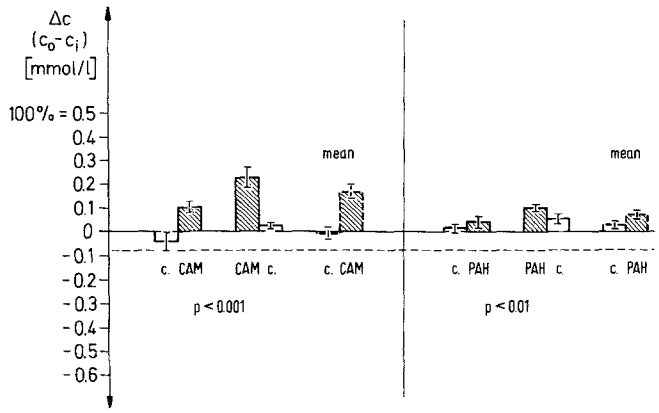

Fig. 1. Effect of carinamide (CAM, 1 mmol/l) and paraaminohippurate (PAH, 1 mmol/l) in both perfusates on the zero net flux transtubular concentration difference Δc ($c_{0=\text{blood side}} - c_{i=\text{lumen}}$) of thiosulfate (45 s values, Na^+ containing solutions, late proximal convolution). Crossed paired experiments were performed as described in the methods. At the same tubular segment two measurements were made. Between the first (control = open column) and second (test = hatched column) measurement (adjoining columns) an increase in Δc is seen when the test solution contained carinamide or PAH. When the sequence was reversed to test → control the Δc decreased. The significance between both sets of pairs is given in the figure. The third twin column gives the mean of both pairs (control → test and test → control). The dotted line indicates passive distribution as calculated under the assumption of a pd of +1.9 mV, lumen positive [10a]

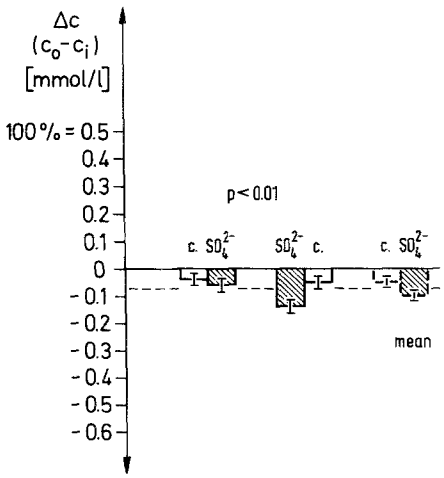

Fig. 2. Effect of sulfate (7.5 mM/l) in both perfusates on the Δc of thiosulfate in the late proximal convolution (Na^+ containing solution). Otherwise as in the legend to Fig. 1

secretory pattern of thiosulfate and paraaminohippurate along the proximal convolution are not identical.

Discussion

As pointed out by Mudge et al. [15] the clearance data on thiosulfate transport "provide only an overall

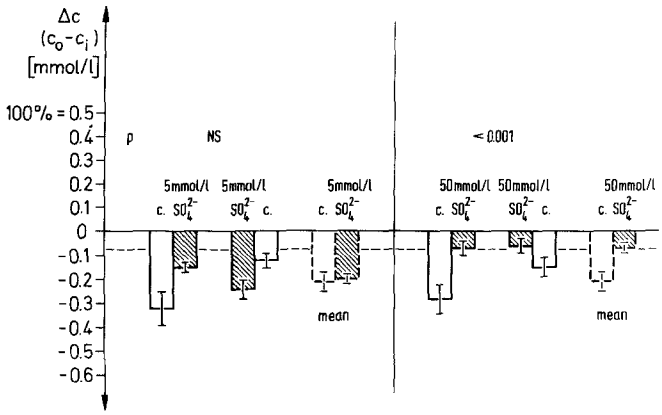

Fig. 3. Effect of sulfate on the secretory Δc of thiosulfate. Zero net flux concentration difference of thiosulfate in the late proximal convolution (45 s) with Na^+-free Ringer solutions. 5 mmol/l sulfate does not alter the secretory zero net flux concentration difference of thiosulfate. But if the solutions contain 50 mmol/l sulfate the secretory Δc of thiosulfate decreases considerably supposedly by competitive inhibition

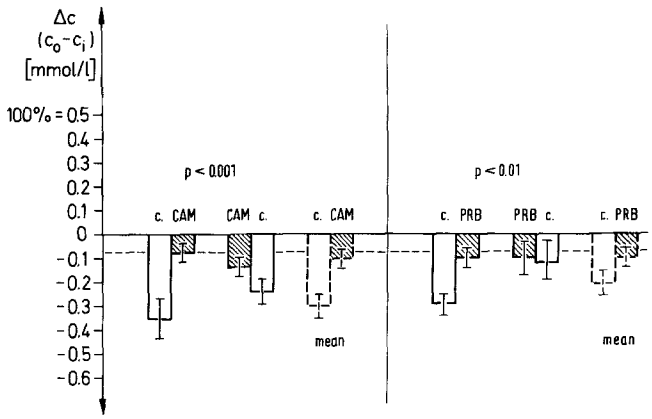

Fig. 4. Effect of carinamide (CAM, 0.2 mmol/l) and of probenecid (PRB, 1 mmol/l) in both perfusates on thiosulfate secretion in the late proximal convolution (45 s values with Na^+-free Ringer)

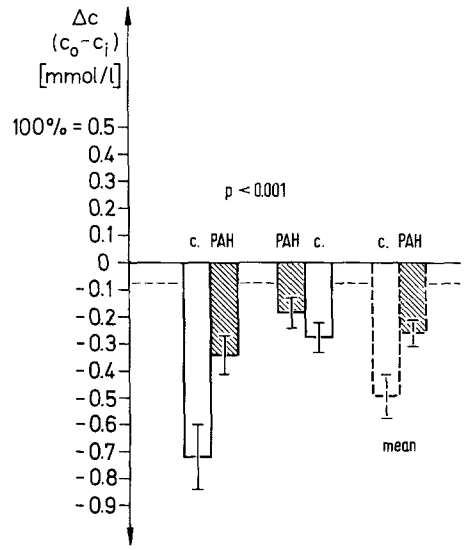

Fig. 5. Effect of PAH (1 mmol/l in both perfusates) on thiosulfate secretion in the late proximal convolution (45 s, Na^+-free Ringer)

Table 1. Effect of thiosulfate and sulfate on the zero net flux concentrations (absolute values in mmol/l ± SE) of paraaminohippurate in the luminal perfusate of the proximal convolutions of the rat kidney. The starting PAH concentration of both luminal and capillary perfusate is given in column 1. While the capillary concentration remained constant the luminal concentrations, measured at the contact time, given in column 2, increased. 1. and 2. value referred to the concentrations in subsequent samples from the same tubular segment. The p, *T*-test refers to the crossed paired values. The last column gives the percent change of all Δc ($c_{\text{lumen}} - c_{\text{capillary}}$) values of one series brought about by the respective concentrations of thiosulfate or sulfate. In all solutions Na^+ was replaced by choline but the solutions with 5.0 mM $S_2O_3^{2-}$ (series 2) contained 2.5 meq Na^+, those with 15.0 mM $S_2O_3^{2-}$ (series 3) 12.5 mM Na^+, and in the solution with 50.0 mM $S_2O_3^{2-}$ (series 4) 100 meq choline were replaced by Li^+. In series 1 thiosulfate was added to the luminal perfusate only, but in all other series it was added to the luminal as well as to the capillary perfusate

PAH (mmol/l)	Contact time (s)	1. Value	2. Value	% changes of the paired values (1. value = 100%)	p, *T*-test	% changes of Δc combined values
0.5	5	$S_2O_3^{2-}$ 0.0 mM 0.73 ± 0.03 $S_2O_3^{2-}$ 0.5 mM 0.65 ± 0.03	0.5 mM 0.62 ± 0.036 0.0 mM 0.60 ± 0.046	−15.1 − 7.7	NS	−12.5
0.5	45	$S_2O_3^{2-}$ 0.0 mM 1.22 ± 0.12 $S_2O_3^{2-}$ 5 mM 1.22 ± 0.07	5.0 mM 0.79 ± 0.06 0.0 mM 0.93 ± 0.06	−35.2 −23.8	NS	−12.0
1.5	45	$S_2O_3^{2-}$ 0.0 mM 2.66 ± 0.12 $S_2O_3^{2-}$ 15.0 mM 3.05 ± 0.21	15.0 mM 2.18 ± 0.13 0.0 mM 2.60 ± 0.21	−18.0 −14.7	NS	− 0.8
0.5	45	$S_2O_3^{2-}$ 0.0 mM 1.37 ± 0.11 $S_2O_3^{2-}$ 50.0 mM 1.52 ± 0.05	50.0 mM 0.87 ± 0.06 0.0 mM 1.11 ± 0.06	−36.5 −27.0	NS	− 7.9
1.5	45	SO_4^{2-} 0.0 mM 2.45 ± 0.12 SO_4^{2-} 50.0 mM 2.63 ± 0.18	50.0 mM 1.94 ± 0.11 0.0 mM 2.41 ± 0.14	−20.8 − 8.4	NS	−17.3

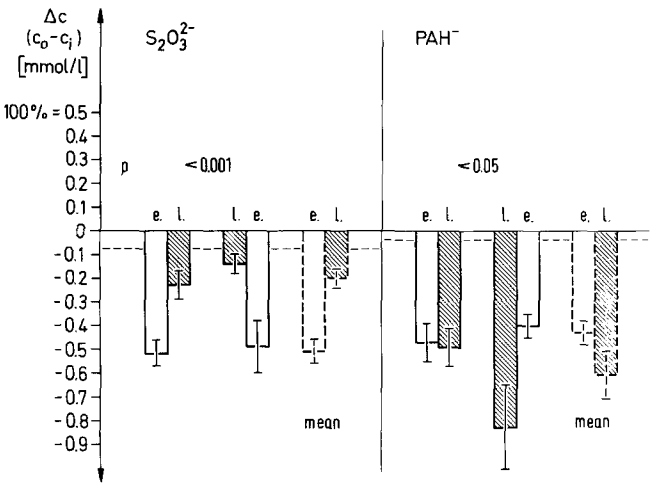

Fig. 6. Secretory Δc (45 s values) of thiosulfate and paraaminohippurate in the early (*e*) and late (*l*) loops of the proximal convolution. Crossed paired experiments were performed at the early and late loops of the same convolution under Na^+-free conditions

description of some complex interrelationships, so that more precise techniques are required in order to clarify the specific reactions". This is now possible by our technique to measure the zero net flux concentration differences (Δc_s) and our finding that the net transport of thiosulfate turned into reabsorption after carinamide and into secretion when the reabsorptive system is inhibited by intermediate sulfate concentrations or by omitting Na^+ from the perfusates. The inhibition of sulfate reabsorption by thiosulfate [25] and shift of thiosulfate transport toward secretion in the absence of Na^+ point to a reabsorptive Na^+-sulfate−Na^+-thiosulfate cotransport mechanism which, as recent experiments with brush border vesicles have shown [14], is located in the brush border membrane. Sulfate on the other hand inhibits the thiosulfate secretion, as measured under Na^+-free conditions, only at high concentrations. Thus, in the rat a rudiment of the sulfate secretory system, which is very active in fishes

[2, 11, 19], seems to exist. The question, whether thiosulfate secretion occurs via the organic acid secretory system, unfortunately cannot be answered unequivocally. Although carinamide, probenecid and PAH inhibit thiosulfate secretion under Na^+-free conditions (Figs. 4 and 5), the reverse, an effect of thiosulfate or sulfate on PAH secretion was not seen (Table 1), despite quite high concentrations of both solutes. One explanation is that the affinity of PAH for a common secretory mechanism is much greater than the affinity for thiosulfate. Another explanation is that there are two secretory systems. One, the organic acid (PAH) system, is not used by thiosulfate (sulfate). The other, transports thiosulfate and sulfate and has some affinity for PAH, probenecid and carinamide. Our finding that the secretory Δc pattern along the proximal convolution for PAH and for thiosulfate is not identical, seems to favour the latter interpretation. One has, however, to keep in mind that the same result could be obtained if the contraluminal entrance mechanisms would be indentical for thiosulfate and paraaminohippurate, but the exit systems, which accomplish the transport from cell into the lumen, would be quite different. Another question should be discussed here, namely whether the active secretory and reabsorptive thiosulfate transport are independent of each other or whether they interfere by using the same luminal and/or contraluminal transit mechanism. In principle it is possible that carinamide and paraaminohippurate are exerting at the contraluminal cell side both, in the absence of sodium inhibition of thiosulfate secretion by competition (cisinhibition) and in the presence of sodium acceleration of thiosulfate reabsorption by countertransport (transstimulation). Similarly in the presence of Na^+ it is conceivable that at the luminal cell side sulfate not only inhibits thiosulfate reabsorption by competition but rather augments thiosulfate secretion by countertransport. Thus, it seems that at the moment the question of mutual dependence or independence of the thiosulfate secretory and reabsorptive pathway can only be answered by studies with plasma membrane vesicles from each cell side [14].

The fact that thiosulfate secretion occurs under Na^+-free conditions raises the question about the driving forces for this active transport process. In previous experiments we observed that the secretory transport of PAH is almost unchanged under our short term Na^+-free conditions [21]. This finding contrasts with the strong inhibition of the other proximal transport processes, namely that of glucose, amino acids, Ca^{2+}, H^+-ions (for literature see [23], phosphate [1], sulfate [25], bile acids, lactate and malonate (unpublished results) when Na^+ was omitted from the perfusates. Furthermore, with plasma membrane vesicles of the contraluminal cell side a cotransport of Na^+ and paraaminohippurate could not be detected [4]. Thus, either a primary active PAH transport, driven by ATP or redox energy or a countertransport against substrate, formed in the intracellular metabolism, could be envisaged. The same as for paraaminohippurate may hold for thiosulfate secretion. In this regard it is worth noting that a strong decline of transport rates with time was in our laboratory only observed with the secretion of thiosulfate and paraaminohippurate and not with the transport of all other substances mentioned above. There is experimental evidence that at reduced intracellular ATP level the transcellular electrochemical gradient for Na^+ decays with some delay [8]. Therefore, if the cellular ATP level falls, the primary ATP-driven transport processes should be affected earlier than the secondary Na^+-gradient-driven transport processes.

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