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# $K^+$ Secretion in Rat Distal Jejunum

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**Abstract.** The Ussing chamber technique was used to measure unidirectional $Rb^+$ fluxes under short-circuit conditions across tissue sheets from proximal, central, and distal jejunum of rats.

Whereas the proximal and central parts of the jejunum did not show any net transport of $Rb^+$, there was a net secretion of around 0.2 μmol $hr^{-1}$ $cm^{-2}$ in the distal segment. This secretion could not be influenced significantly by mucosal application of $K^+$ channel blockers such as $Ba^{2+}$ (5 mM), tetraethylammonium (20 mM) or quinine (1 mM). Serosal ouabain (1 mM) blocked net secretion by increasing mucoserosal flux. Blockers of $H^+/K^+$ ATPases could not alter net fluxes of $Rb^+$. Stimulation of $Cl^-$ secretion by forskolin (10 μM) or of $Na^+$ absorption by serine (10 mM) failed to influence the observed secretion of $Rb^+$. Adrenaline (10 μM) also had no effect on $Rb^+$ fluxes. Blocking $Na^+/H^+$ exchange by 5-(N-Ethyl-N-isopropyl)-amilorid (100 μM) blocked net secretion by increasing mucoserosal flux, as did the addition of $Na^+$ acetate (30 mM) to the mucosal solution.

We conclude that the distal jejunum of the rat secretes $K^+$ under short-circuit conditions. This secretion does not seem to occur via $K^+$ channels, but through a pH dependent mechanism.

**Key words:** Potassium transport — $K^+/H^+$ exchange — Jejunum — Rat

## Introduction

Over the past two decades, it has become apparent that not only the kidney, but that the colon as well contributes to $K^+$ homeostasis in mammals. This becomes evident in the event of renal insufficiency or in states of limited or increased alimentary $K^+$ supply [1, 15, 24, 47]. The hindgut is capable of actively secreting and absorbing $K^+$, the mechanisms of which have been studied in detail over the last years [3, 23].

In contrast to the colon, the ability of active potassium transport has been disputed for the small intestine. In both humans and rats, transepithelial $K^+$ flow is attributed solely to passive diffusion and solvent drag across the epithelium of jejunum and ileum [10, 18, 44].

In preliminary experiments performed with sheep small intestine, our group observed $K^+$ secretion in the distal segment with the Ussing chamber technique [7]. $Rb^+$ fluxes measured under short-circuit conditions in this tissue revealed a net secretion of $Rb^+$ in sheep distal jejunum. To our knowledge, such an effect has not been observed before in small intestine. Because a systematic investigation regarding this issue has not been carried out so far, we examined different parts of rat small intestine in Ussing chambers. $Rb^+$ fluxes were performed as a marker for $K^+$ transport across short-circuited epithelial tissue.

## Materials and Methods

### Tissue Preparation

Male ZUR:SD rats (Institut für Labortierkunde, Universität Zürich, Switzerland) were used which were kept on an artificial dark-light cycle of 12-hr duration. They were fed a diet high in carbohydrates with a $K^+$ content of 100 mmol/kg [9]. The animals had free access to water and food until the day of the experiment when they had reached a weight of 180–230 g. Animals were stunned by a blow to the head and killed by exsanguination. The proximal, central, and distal jejunum were localized as follows: proximal jejunum from the end of the plica duodenocolica to 10 cm distal of this point; central jejunum 30–40 cm distal to the plica; distal jejunum from the free end of the plica ileocaecalis to 10 cm proximal of this point. The respective intestinal segments were taken out immediately, flushed with cold standard so-

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lution (*see below*), cut open along the mesenteric line, and mounted in modified Ussing chambers.

### Determination of Electrophysiological Parameters

Sheets of tissue were mounted in Ussing chambers, bathed with a volume of 3.5 ml buffer solution on each side of the epithelium and continuously short-circuited by an automatic voltage-clamp device (Aachen Microclamp, AC Copy Datentechnik, Aachen, Germany) with correction for solution resistance. The standard solution contained (mM): 144 $Na^+$, 130 $Cl^-$, 4.7 $Rb^+$, 2.6 $Ca^{2+}$, 1.2 $Mg^{2+}$, 25 $HCO_3^-$, 1.2 $PO_4^{2-}$, and 10 glucose. $Rb^+$ was used instead of $K^+$ due to the flux measurements with $^{86}Rb^+$. Bathing solutions were continually gassed with 95% $O_2$ and 5% $CO_2$, which maintained the pH of the solution at 7.4. In one experimental series, $Cl^-$ was substituted for $HCO_3^-$. This solution contained 10 mM HEPES and was gassed with $O_2$. The exposed surface of the tissue was 1 $cm^2$. Tissue conductance ($G_t$) was measured by recording currents resulting from bipolar square voltage pulses (±2 mV) applied across the tissue at one minute intervals.

### Measurement of Unidirectional Ion Fluxes

Ten to fifteen minutes after mounting the tissue in the chambers, $^{86}Rb^+$ (75 kBq) was added to one side of the epithelium (labeled side). After an additional 60 min to allow isotope fluxes to reach a steady state, unidirectional ion fluxes (mucosa-to-serosa flux = $J_{ms}$, serosa-to-mucosa flux = $J_{sm}$) were determined by taking samples from the unlabeled side at 20-min intervals and replacing the taken amount of buffer. Samples were counted with a liquid scintillation counter (Packard Tricarb 1600TR). One 20-min period was taken as control period under basal conditions. Drugs were added immediately after this period. After an equilibration time of 20 min, another 20 min period was analyzed. From the measured unidirectional fluxes, net ion fluxes were calculated according to $J_{net} = J_{ms} - J_{sm}$ from the means of the unidirectional fluxes. In one experimental series $J_{sm}$ was measured at different transepithelial voltages ($\psi_{ms}$); $\psi_{ms}$ was clamped in random order at ±20, ±10, and 0 mV for 20 min each after a 60-min equilibration time under short-circuit conditions. This allowed to differentiate between active and passive components of $J_{sm}$ [16].

### Chemicals

$^{86}RbCl$ was obtained from NEN Life Sciences (Vilvoorde, Belgium), omeprazole was kindly provided by Astra Hässle (Molndal, Sweden), SCH28080 by Schering Plough (Kenilworth), and adrenaline was from Siegfried (Zofingen, Switzerland). All other chemicals were obtained from Sigma. Drugs were added in small volumes from freshly prepared stock solutions. For drugs dissolved in DMSO, final DMSO concentration never exceeded 0.1% (v/v). Omeprazole was prepared in an acidic stock solution (ethanol with HCl) immediately before use.

### Statistics

Data are presented as means ± SEM. Short-circuit current ($I_{sc}$) and tissue conductance ($G_t$) were averaged over the respective flux period. SEM for $J_{net}$ were calculated according to the law of error propagation [35]. Statistical significance of $J_{net}$ was determined with the *t*-test (*vs.* zero) and comparisons between two flux periods were done with the paired or unpaired *t*-test, as appropriate. A value of $P < 0.05$ was considered significant. Indicated *n* is number of flux experiments; for electrical parameters number of experiments is twice *n* (sum of $J_{ms}$ and $J_{sm}$ experiments).

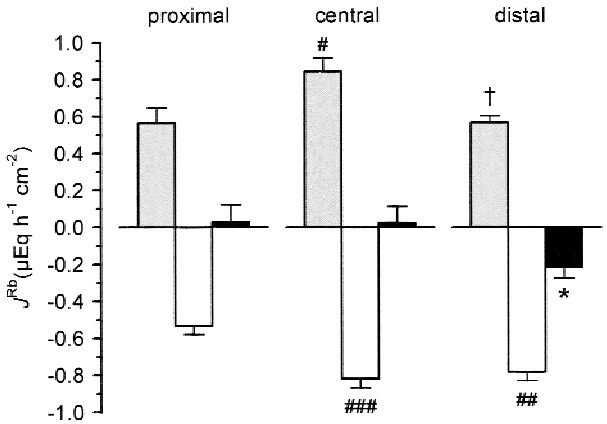


**Fig. 1.** Unidirectional and net $Rb^+$ fluxes in proximal, central, and distal segment of rat jejunum. Basal fluxes are shown for proximal jejunum on the left ($n = 10$), for central jejunum in the middle ($n = 10$), and for distal jejunum ($n = 24$) on the right side of the figure. Hatched bars represent $J_{ms}$, open bars $J_{sm}$, and black bars $J_{net}$. #, ##, ### significantly different from respective flux in proximal jejunum with $P < 0.05$, $P < 0.01$, or $P < 0.001$, respectively. † Significantly different from respective flux in central jejunum with $P < 0.001$. * Significantly different from zero with $P < 0.01$.

## Results

### Basal Values

Preliminary experiments showed that unidirectional $Rb^+$ fluxes were stable after the 60-min equilibration period and remained constant for at least 100 min, the longest duration of experiments conducted in this study. Electrical parameters were not different between central and distal jejunum. Short-circuit current ($I_{sc}$) was 3.5 ± 0.6 μEq $hr^{-1}$ $cm^{-2}$ and tissue conductance ($G_t$) was 50.0 ± 4.4 mS $cm^{-2}$ for central jejunum ($n = 20$). The respective values for distal jejunum were 3.7 ± 0.2 μEq $hr^{-1}$ $cm^{-2}$ ($I_{sc}$) and 44.6 ± 1.1 mS $cm^{-2}$ ($G_t$) ($n = 48$). In contrast to both the central and distal segment, proximal jejunum showed significantly lower $I_{sc}$ and $G_t$ values of 1.2 ± 0.2 μEq $hr^{-1}$ $cm^{-2}$ and 28.7 ± 2.1 mS $cm^{-2}$, respectively ($P < 0.001$ each; $n = 20$).

In accordance to the smaller $G_t$ in proximal jejunum, the unidirectional fluxes in the proximal segment were significantly smaller than in the central part, both net fluxes were, however, not significantly different from zero (Fig. 1). In distal jejunum, $J_{sm}$ was similar to $J_{sm}$ of central jejunum, but $J_{ms}$ was significantly smaller, resulting in a net $Rb^+$ secretion of 0.217 ± 0.058 μEq $hr^{-1}$ $cm^{-2}$ ($P < 0.01$; $n = 24$) (Fig. 1).

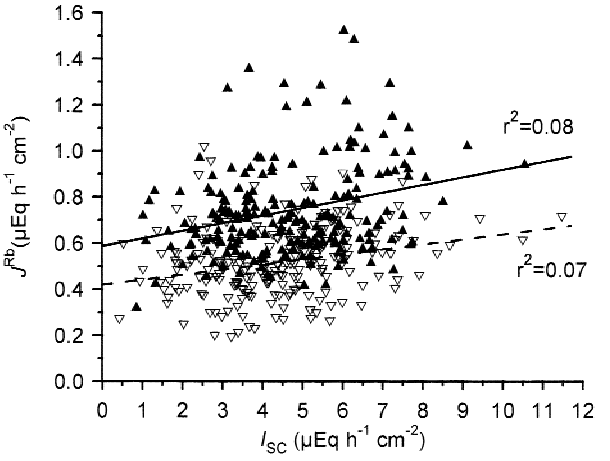


**Fig. 2.** Relation between unidirectional $Rb^+$ fluxes and short-circuit current in distal rat jejunum. Open triangles are $J_{ms}$ ($n = 213$), closed triangles represent $J_{sm}$ ($n = 211$) of control period. The linear regression line for $J_{ms}$ is hatched, whereas the linear regression line for $J_{sm}$ is solid. $r^2$ = coefficient of determination.

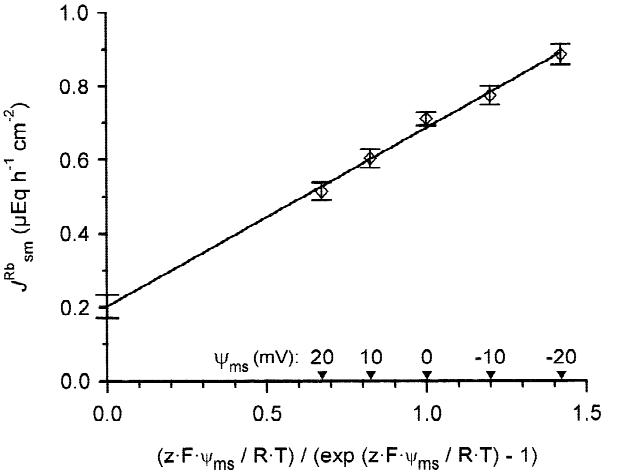


**Fig. 3.** Dependence of serosa-to-mucosa $Rb^+$ fluxes on transepithelial potential in distal rat jejunum. Serosa-to-mucosa fluxes of $Rb^+$ ($J^{Rb}_{sm}$) are plotted as a function of transepithelial potential ($\psi_{ms}$) ($n = 16$). For clarity, values of clamped $\psi_{ms}$ are indicated above abscissa. The intercept on the ordinate is at 0.202 ± 0.031 μEq hr$^{-1}$ cm$^{-2}$ and represents nondiffusional, $\psi_{ms}$ independent $J^{Rb}_{sm}$ ($P < 0.001$). The slope of the linear fit is 0.484 μEq hr$^{-1}$ cm$^{-2}$ per unit.

## Evidence for $K^+$ Secretion in Distal Jejunum

Due to the fact that the examined tissues had been mounted intact in the chambers, i.e., without removing serosal and muscle layers, the possibility of insufficient short-circuiting exists. This should be noticeable in a correlation between the unidirectional fluxes and the short-circuit current, as a residual transepithelial potential depends directly on $I_{sc}$ [42]. Therefore, all control fluxes were plotted against the $I_{sc}$ measured during the respective period (Fig. 2). Indeed, there was a significant correlation between $J_{ms}$ and $I_{sc}$ and also between $J_{sm}$ and the measured short-circuit current ($P < 0.001$ each). However, the coefficients of determination were rather small for both unidirectional fluxes, and the regression line for $J_{ms}$ also had a positive slope. $J_{net}$ for all fluxes under control condition was −0.227 ± 0.017 μEq hr$^{-1}$ cm$^{-2}$ ($n = 213$ for $J_{ms}$ and $n = 211$ for $J_{sm}$).

One method to differentiate between transepithelial potential ($\psi_{ms}$) dependent passive components and $\psi_{ms}$ independent non diffusional flux, is to examine $J_{sm}$ under various $\psi_{ms}$ [16]. The total serosa-to-mucosa flux of an ion $i$ is given by the following equation:

$$J^i_{sm} = {}_{0d}J^i_{sm} \cdot (zF \cdot \psi_{ms}/RT)/(\exp(zF \cdot \psi_{ms}/RT) - 1) + {}_mJ^i_{sm} \quad (1)$$

where $J^i_{sm}$ is the total serosa-to-mucosa flux of $i$ in the presence of any $\psi_{ms}$, ${}_{0d}J^i_{sm}$ is the diffusional flux of $i$ from serosa-to-mucosa under short-circuit conditions, and ${}_mJ^i_{sm}$ is the nondiffusional, $\psi_{ms}$ independent component of $J^i_{sm}$; $z$, $F$, $R$ and $T$ have their usual meanings. When $J^i_{sm}$ under various $\psi_{ms}$ is plotted as a function of

$$(zF \cdot \psi_{ms}/RT)/(\exp(zF \cdot \psi_{ms}/RT) - 1) \quad (2)$$

the slope of the line through $J^i_{sm}$ should be ${}_{0d}J^i_{sm}$, whereas the intercept on the ordinate is ${}_mJ^i_{sm}$, representing the nondiffusional, transcellular component of $J^i_{sm}$ [16]. To evaluate ${}_mJ^{Rb}_{sm}$, $J_{sm}$ was measured under various clamp potentials at ±20, ±10, and 0 mV in the distal jejunum and plotted as a function as described above. As can be seen in Fig. 3, the intercept on the ordinate was at 0.202 ± 0.031 μEq hr$^{-1}$ cm$^{-2}$, which was significantly different from zero ($P < 0.001$; $n = 16$). This value represents the $\psi_{ms}$ independent and nondiffusional component of $J_{sm}$.

## Effect of Mucosal $K^+$ Channel Blockers

$K^+$ secretion in mammalian colon occurs, at least partly, through apical $K^+$ channels. To investigate if $Rb^+$ was also secreted via $K^+$ channels in the distal jejunum of the rat, the rather unspecific $K^+$ channel blockers $Ba^{2+}$, tetraethylammonium (TEA), and quinine were applied to the mucosal side of the epithelium. $Ba^{2+}$ and quinine decreased $I_{sc}$ clearly, with quinine showing the strongest effect (Table 1). TEA had only a minor effect, the significant decrease of $I_{sc}$ 20 min after addition of TEA was due to a constant decrease of short-circuit current in this experimental series (Table 1). Among the three blockers employed, only quinine and TEA were able to reduce $G_t$ significantly. None of the blockers influenced unidirectional fluxes in a significant manner, although all of them showed a tendency to reduce $J_{sm}$ and therefore $J_{net}$

**Table 1.** Influence of mucosal $K^+$ channel blockers in distal rat jejunum

| | $J_{ms}$ (μEq $hr^{-1}$ $cm^{-2}$) | $J_{sm}$ (μEq $hr^{-1}$ $cm^{-2}$) | $J_{net}$ (μEq $hr^{-1}$ $cm^{-2}$) | $I_{sc}$ (μEq $hr^{-1}$ $cm^{-2}$) | $G_t$ (mS $cm^{-2}$) |
|---|---|---|---|---|---|
| Basal | 0.574 ± 0.062 | 0.808 ± 0.082 | −0.234 ± 0.103 | 5.6 ± 0.6 | 39.3 ± 2.3 |
| $Ba^{2+}$ (5 mM) | 0.562 ± 0.077 | 0.690 ± 0.061 | −0.128 ± 0.098 | 4.2 ± 0.5‡ | 37.5 ± 1.9 |
| Basal | 0.499 ± 0.064 | 1.050 ± 0.127 | −0.551 ± 0.142* | 5.1 ± 0.4 | 38.3 ± 1.9 |
| Quinine (1 mM) | 0.481 ± 0.052 | 0.852 ± 0.072 | −0.371 ± 0.089* | 1.5 ± 0.1‡ | 32.7 ± 1.9‡ |
| Basal | 0.363 ± 0.033 | 0.865 ± 0.083 | −0.502 ± 0.089** | 3.9 ± 0.1 | 32.4 ± 1.3 |
| TEA (20 mM) | 0.337 ± 0.038 | 0.728 ± 0.038 | −0.391 ± 0.054** | 2.9 ± 0.1‡ | 30.2 ± 1.6† |
| Basal[1] | 0.389 ± 0.023 | 0.566 ± 0.034 | −0.177 ± 0.041* | 6.0 ± 0.4 | 31.8 ± 0.7 |
| TEA + $BA^{2+}$ (20 mM ea.)[1] | 0.417 ± 0.018 | 0.528 ± 0.025 | −0.111 ± 0.031* | 3.8 ± 0.3‡ | 38.3 ± 1.1‡ |

Values are means ± SEM of paired experiments. $BaCl_2$, quinine and tetraethylammonium chloride (TEA) were added to the mucosal side, $n = 8$ for all blockers. In the experiments with TEA or with TEA plus $Ba^{2+}$, choline chloride (20 or 40 mM, respectively) was applied to the serosal side to balance osmotic and ionic gradients. †, ‡ Significantly different from basal period with $P < 0.05$ or $P < 0.001$, respectively. *, ** Significantly different from zero (for net fluxes) with $P < 0.01$ or $P < 0.001$, respectively. [1] In $HCO_3^-$ free solution with 10 mM HEPES.

(Table 1). This was confirmed in another experimental series, in which TEA and $Ba^{2+}$ were present at a concentration of 20 mM each (in $HCO_3^-$ free buffer to avoid precipitation of $BaCO_3$). Again, $J_{sm}$ decreased only slightly, which was not significant. Paradoxically, $G_t$ increased after the simultaneous addition of TEA and $Ba^{2+}$ (Table 1).

### Basolateral Uptake Mechanisms

Basolateral uptake of $K^+$ in mammalian colon depends on the cofunction of $Na^+/K^+/2Cl^-$ cotransport and $Na^+/K^+$ ATPase. Block of one of these mechanisms leads to inhibition of $K^+$ secretion in the large intestine. Bumetanide, a blocker of $Na^+/K^+/2Cl^-$ cotransport in colon and kidney, decreased $I_{sc}$ by 1.5 ± 0.1 μEq $hr^{-1}$ $cm^{-2}$ ($P < 0.001$) and increased $G_t$ by 4.4 + 0.9 mS $cm^{-2}$ ($P < 0.001$) in distal jejunum, when applied at a concentration of 1 mM serosally ($n = 18$). Inhibition of cotransport had no influence on unidirectional and net $Rb^+$ fluxes, though ($\Delta J_{ms} = 0.065 \pm 0.037$ μEq $hr^{-1}$ $cm^{-2}$, $\Delta J_{sm} = 0.007 \pm 0.043$ μEq $hr^{-1}$ $cm^{-2}$, $\Delta J_{net} = 0.072 \pm 0.057$ μEq $hr^{-1}$ $cm^{-2}$; $P > 0.05$ for all fluxes).

After $Na^+/K^+$ ATPase was blocked by serosal addition of 1 mM ouabain, $I_{sc}$ rapidly fell from 4.2 ± 0.4 μEq $hr^{-1}$ $cm^{-2}$ to 0.9 ± 0.1 μEq $hr^{-1}$ $cm^{-2}$ ($P < 0.001$; $n = 28$), whereas $G_t$ did not change (control: 37.8 ± 1.2 mS $cm^{-2}$, ouabain: 36.6 ± 1.0 mS $cm^{-2}$). $J_{sm}$ was not influenced by $Na^+/K^+$ ATPase inhibition, but $J_{ms}$ increased drastically with the consequence that net secretion was abolished (Fig. 4).

### Mucosal $H^+/K^+$ ATPase Inhibitors

In the colon, the active step for $K^+$ absorption is carried out by an ATPase in the apical membrane exchanging protons for $K^+$. Several colonic $H^+/K^+$ pumps have been identified with various blocker specificities. The apical proton pump of the guinea pig is very sensitive to ouabain [39], whereas the rabbit ATPase resembles the gastric proton pump in its sensitivity to SCH28080 [25]. The rat seems to possess at least two components, one ouabain-sensitive and another ouabain-insensitive component; the gastric proton pump inhibitors omeprazole and SCH28080 are ineffective in the rat [8, 41]. The various colonic $H^+/K^+$ pumps of rat, rabbit, and guinea pig can be blocked by the unspecific ATPase inhibitor orthovanadate [8, 25, 45]. Due to these differences in blocker specificity between the various $H^+/K^+$ ATPases found in mammalian colon, the inhibitors ouabain, orthovanadate, omeprazole and SCH28080 were tested. Mucosal ouabain (1 mM) or the gastric proton pump inhibitors omeprazole and SCH28080 (100 μM each) failed to show a clear effect on unidirectional and net

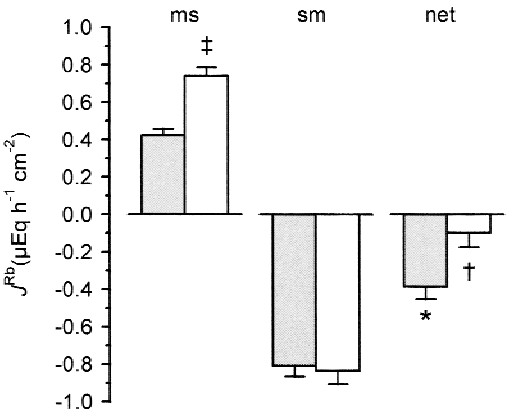


**Fig. 4.** Effect of $Na^+/K^+$ ATPase inhibition on $Rb^+$ fluxes in distal rat jejunum. Hatched bars are values for basal period, open bars represent the values in the presence of ouabain (1 mM serosal). Left $J_{ms}$, middle $J_{sm}$, right $J_{net}$ ($n = 14$). †, ‡ Significantly different from basal period with $P < 0.01$ or $P < 0.001$, respectively. * Significantly different from zero with $P < 0.001$.

**Table 2.** Effects of apical $H^+/K^+$ ATPase blockers in distal rat jejunum

| | $J_{ms}$ (μEq $hr^{-1}$ $cm^{-2}$) | $J_{sm}$ (μEq $hr^{-1}$ $cm^{-2}$) | $J_{net}$ (μEq $hr^{-1}$ $cm^{-2}$) | $I_{sc}$ (μEq $hr^{-1}$ $cm^{-2}$) | $G_t$ (mS $cm^{-2}$) |
|---|---|---|---|---|---|
| Basal | 0.609 ± 0.038 | 0.903 ± 0.056 | −0.294 ± 0.068** | 5.5 ± 0.5 | 41.0 ± 1.8 |
| Ouabain | 0.646 ± 0.037 | 0.837 ± 0.033 | −0.191 ± 0.050** | 4.1 ± 0.4‡ | 40.1 ± 1.7 |
| Basal | 0.556 ± 0.035 | 0.680 ± 0.034 | −0.124 ± 0.049* | 4.9 ± 0.4 | 36.3 ± 1.3 |
| Orthovanadate | 0.562 ± 0.047 | 0.780 ± 0.031† | −0.218 ± 0.056** | 2.2 ± 0.2‡ | 38.4 ± 1.8§ |
| Basal | 0.446 ± 0.040 | 0.765 ± 0.038 | −0.319 ± 0.055*** | 3.9 ± 0.5 | 35.3 ± 1.1 |
| Omeprazole | 0.502 ± 0.036 | 0.731 ± 0.034 | −0.229 ± 0.050** | 3.0 ± 0.4‡ | 35.9 ± 1.2 |
| Basal | 0.432 ± 0.048 | 0.732 ± 0.041 | −0.300 ± 0.062** | 3.6 ± 0.2 | 33.9 ± 1.5 |
| SCH28080 | 0.502 ± 0.051§ | 0.793 ± 0.092 | −0.291 ± 0.105* | 3.6 ± 0.2 | 34.9 ± 2.5 |

Ouabain (1 mM; $n = 8$), orthovanadate (1 mM; $n = 12$), omeprazole (100 μM; $n = 8$), and SCH28080 (100 μM; $n = 8$) were applied to the mucosal side. §, †, ‡ Significantly different from basal period with $P < 0.05$, $P < 0.01$ or $P < 0.001$, respectively. *, **, *** Significantly different from zero (for net fluxes) with $P < 0.05$, $P < 0.01$ or $P < 0.001$, respectively.

$Rb^+$ fluxes, besides a small increase in $J_{ms}$ (Table 2). After addition of SCH28080 a transient increase of $I_{sc}$ was observed, but $I_{sc}$ returned to basal values during the evaluation period. The significant decrease of $I_{sc}$ after 20 min in the presence of mucosal ouabain or omeprazole was due to a constant fall of short-circuit current in these experimental series (Table 2). In contrast to the other blockers, sodium orthovanadate showed a marked decrease of $I_{sc}$. Whereas $J_{ms}$ was not influenced by the drug, $J_{sm}$ increased by 0.1 μEq $hr^{-1}$ $cm^{-2}$, which, however, raised net secretion only marginally (Table 2).

### Interaction with Electrogenic Ion Transport

In the colon, $Cl^-$ secretion and $K^+$ secretion are often activated concurrently [12, 22, 33]. To investigate a possible interaction with electrogenic transport systems in small intestine, $Cl^-$ secretion was stimulated by the adenylate cyclase activator forskolin; in order to induce electrogenic $Na^+$ cotransport, the amino acid serine was added in another experimental series.

Forskolin (10 μM) induced $Cl^-$ secretion which was evident by a marked increase in $I_{sc}$ and $G_t$ (Table 3). Unidirectional and net $Rb^+$ fluxes were not influenced by this drug. The addition of the amino acid serine (10 mM) to both sides in order to avoid osmotic gradients led to an increase in $I_{sc}$ and $G_t$ due to electrogenic $Na^+$ absorption. This maneuver raised $J_{ms}$ and $J_{sm}$ significantly, but the increase of both unidirectional fluxes was equal, so that $J_{net}$ did not change (Table 3).

Adrenaline is known to stimulate $K^+$ secretion independent of $Cl^-$ secretion in the distal colon [22, 38]. Therefore, adrenaline was added to the serosal side at a concentration of 10 μM. The observed decrease of $I_{sc}$ and increase of $G_t$ after adrenaline (Table 3) on its own would fit to induction of a cation secretory process. The measured $Rb^+$ fluxes did not support this notion, however. Adrenaline did not change $J_{sm}$ at all, while it increased $J_{ms}$ slightly, but significantly, which led to a smaller $J_{net}$ instead of a larger one (Table 3). It is clear from these flux studies that adrenaline did not induce $K^+$ secretion.

### Influence of Intracellular pH

All of the experiments conducted so far lead to the suggestion that the mechanism by which $K^+$ is secreted in distal jejunum must be different from that in distal colon. We evaluated a possible effect of intracellular pH ($pH_i$) on the secretion observed. $Na^+/H^+$ exchange, especially the NHE-1 isoform located in the basolateral membrane of enterocytes, is responsible for $pH_i$ maintenance [30]. In order to reduce $pH_i$, we blocked $Na^+/H^+$ exchange with the amiloride analogue 5-(N-Ethyl-N-isopropyl)-amilorid (EIPA) [26]. 100 μM EIPA reduced $I_{sc}$ from 2.6 ± 0.3 μEq $hr^{-1}$ $cm^{-2}$ to 1.8 ± 0.2 μEq $hr^{-1}$ $cm^{-2}$ ($P < 0.001$; $n = 12$) whereas $G_t$ did not change significantly (control: 32.6 ± 0.9 mS $cm^{-2}$, EIPA: 34.0 ± 1.4 mS $cm^{-2}$). $J_{ms}$ increased in the presence of EIPA, whereas $J_{sm}$ remained unchanged, leading to an abolishment of net secretion (Fig. 5).

Another strategy to reduce $pH_i$ was to add 30 mM $Na^+$ acetate to the mucosal solution (the serosal solution received 30 mM $Na^+$ gluconate at the same time), as acetate and other short-chain fatty acids (SCFA) are known to acidify enterocytes [11, 29]. Mucosal acetate increased $I_{sc}$ by 0.9 ± 0.1 μEq $hr^{-1}$ $cm^{-2}$ and $G_t$ by 7.7 ± 0.5 mS $cm^{-2}$ ($P < 0.001$; $n = 48$) and enhanced $J_{ms}$, thereby abolishing $J_{net}$ (Fig. 6).

## Discussion

In contrast to the colon, literature dealing with $K^+$ transport in small intestine is rather sparse. Earlier studies using in vitro and in vivo perfusion of jejunal and ileal

**Table 3.** Influence of forskolin, adrenaline or serine in distal rat jejunum

| | $J_{ms}$ (μEq $hr^{-1}$ $cm^{-2}$) | $J_{sm}$ (μEq $hr^{-1}$ $cm^{-2}$) | $J_{net}$ (μEq $hr^{-1}$ $cm^{-2}$) | $I_{sc}$ (μEq $hr^{-1}$ $cm^{-2}$) | $G_t$ (mS $cm^{-2}$) |
|---|---|---|---|---|---|
| Basal | 0.619 ± 0.033 | 0.757 ± 0.045 | −0.138 ± 0.056* | 4.6 ± 0.2 | 41.5 ± 1.0 |
| Forskolin | 0.654 ± 0.35 | 0.786 ± 0.045 | −0.133 ± 0.057* | 7.6 ± 0.4‡ | 47.9 ± 1.6‡ |
| Basal | 0.567 ± 0.034 | 0.691 ± 0.037 | −0.124 ± 0.050* | 4.2 ± 0.3 | 41.5 ± 1.1 |
| Adrenaline | 0.647 ± 0.029§ | 0.713 ± 0.033 | −0.066 ± 0.044 | 2.5 ± 0.3‡ | 45.8 ± 1.7† |
| Basal | 0.532 ± 0.036 | 0.707 ± 0.036 | −0.175 ± 0.051** | 4.8 ± 0.3 | 38.4 ± 1.0 |
| Serine | 0.616 ± 0.037§ | 0.775 ± 0.035§ | −0.159 ± 0.051** | 5.6 ± 0.3‡ | 41.1 ± 1.2‡ |

Forskolin (10 μM; $n = 9$) and serine (10 mM; $n = 19$) were added to the mucosal and serosal side, adrenaline (10 μM; $n = 14$) was applied serosally only. §, †, ‡ Significantly different from basal period with $P < 0.05$, $P < 0.01$ or $P < 0.001$, respectively. *, ** Significantly different from zero (for net fluxes) with $P < 0.05$ or $P < 0.01$, respectively.

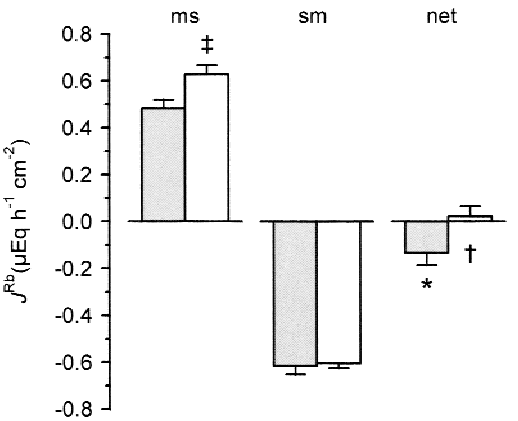


**Fig. 5.** Effect of $Na^+/H^+$ exchange inhibition on $Rb^+$ fluxes in distal rat jejunum. Hatched bars are values for basal period, open bars represent the values in the presence of EIPA (100 μM mucosal and serosal). Left $J_{ms}$, middle $J_{sm}$, right $J_{net}$ ($n = 6$). †, ‡ Significantly different from basal period with $P < 0.05$ or $P < 0.01$, respectively. * Significantly different from zero with $P < 0.05$.

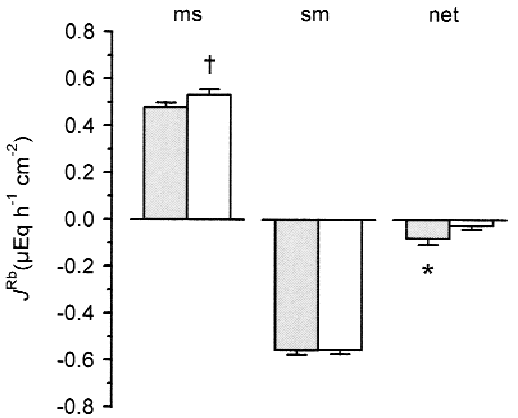


**Fig. 6.** Effect of $Na^+$ acetate on $Rb^+$ fluxes in distal rat jejunum. Hatched bars are values for basal period, open bars represent the values in the presence of acetate (30 mM mucosal). Left $J_{ms}$, middle $J_{sm}$, right $J_{net}$ ($n = 24$). † Significantly different from basal period with $P < 0.05$, * significantly different from zero with $P < 0.01$.

segments stated that $K^+$ movement across the wall of human and rat small intestine can be solely explained by passive movement [10, 18, 44]. Potassium is said to be only transported along its electrochemical gradient.

To our knowledge, a comprehensive study investigating $K^+$ transport in rat small intestine under short-circuit conditions is missing to date. Preliminary observations from sheep small intestine [7] persuaded us to examine this topic using different, anatomically well-defined locations of rat jejunum.

## Segmental Differences

From all examined segments of rat jejunum, only the distal portion showed a net $K^+$ secretion around 0.2 μEq $hr^{-1}$ $cm^{-2}$ in average. However, the individual fluxes scattered over a wide range (Fig. 2). This was noticeable in some experimental series, where basal net secretion was not significantly different from zero (*see* line 1 in Table 1). In this regard, it must be recalled that unidirectional fluxes were not paired to get $J_{net}$. Whereas the mean values of $J_{net}$ are the same both in paired and unpaired calculations, SEM values calculated by the law of error propagation from unidirectional fluxes, which are considered to be independent samples, result in larger standard errors [35]. This statistically more conservative method has the advantage of avoiding pairing of fluxes, which might be somewhat arbitrary, at the cost of needing larger samples or larger differences to gain significant differences.

## Is the Observed $K^+$ Secretion Real?

The intestinal segments used in this study were mounted intact in the chambers without removing serosal and muscular layers. The present subepithelial layers could have led to incomplete short-circuiting ("under-short-circuiting") of the epithelium [42]. The remaining transepithelial voltage could have been a driving force for

passive net ion movement which might have been the cause for the observed net $Rb^+$ secretion in distal jejunum. As this residual voltage is directly correlated to the short-circuit current [42], the driving force for $Rb^+$ secretion should increase to the same extent at higher $I_{sc}$ values as it decreases for $Rb^+$ absorption and, as a consequence, $J_{net}$ should considerably increase with a rise in short-circuit current. However, $J_{ms}$ increased similarly as $J_{sm}$ at higher $I_{sc}$ values. $J_{net}$ was, therefore, largely independent of $I_{sc}$, pointing out that incomplete short-circuiting of the tissue cannot explain the observed net secretion alone.

A further argument for the "correctness" of the measured net secretion comes from the comparison between the different jejunal segments. As proximal and mid jejunal tissues were prepared in the same manner as the distal segment, one would expect a similar effect on $J_{net}$. The lack of secretion in proximal and mid jejunum makes other explanations for distal $J_{net}$ more likely than incomplete short-circuiting.

Finally, $J_{sm}$ was analyzed under various clamp potentials to overcome the pitfalls of inadequate short-circuiting. This way allows to distinguish between active and passive components [16]. An $\psi_{ms}$ independent part was shown, which was in the same range as the observed secretory net fluxes under short-circuit conditions. According to the slope of the line in Fig. 3 (0.484 $\mu$Eq $hr^{-1}$ $cm^{-2}$), a transepithelial potential of 41 mV would be necessary to explain the secretion of 200 $\mu$Eq $hr^{-1}$ $cm^{-2}$ if ${}_mJ^i{}_{sm}$ were zero, i.e., in the absence of a nondiffusional flux component (according to eq. 1). The mean of the transepithelial potentials deduced from the measured $I_{sc}$ and $G_t$ values in our experiments was only 3.1 ± 0.1 mV. Together with the other points, this clearly demonstrated the occurrence of $K^+$ secretion in the distal part of rat jejunum, which cannot be explained by passive movement of $K^+$.

## Involvement of $K^+$ Channels and the $Na^+/K^+$ Pump

In mammalian colon the specific mechanisms for $K^+$ secretion are well defined. Basolateral uptake of $K^+$ occurs via $Na^+/K^+/2$ $Cl^-$ cotransport dependent on the ion gradients established by the $Na^+/K^+$ ATPase, whereas efflux on the apical membrane takes place via $K^+$ channels which can be blocked by $Ba^{2+}$ or TEA [22, 27, 40]. The failure of $Na^+/K^+/2$ $Cl^-$ cotransport inhibition by bumetanide to significantly influence $Rb^+$ fluxes in distal jejunum points to $K^+$ transport mechanisms different from those in colon. The $K^+$ channel blockers $Ba^{2+}$, TEA and quinine only showed a tendency to reduce $J_{sm}$. $Ba^{2+}$ and quinine had a marked effect on $I_{sc}$, which was most probably due to block of basolateral $K^+$ channels, depolarization of the membrane and, therefore, reduction of electrochemical gradients. The fact that $J_{net}$ was not significantly diminished by these blockers, though, makes it clear that $K^+$ channels like in colon cannot be held fully accountable for the observed secretion.

Among the specific inhibitors used, only ouabain was able to stop net secretion. This was not achieved by decreasing $J_{sm}$, as initially expected, but by raising $J_{ms}$ instead. A similar effect of basolateral $Na^+/K^+$ ATPase inhibition has been observed in pig jejunum [48]. An explanation for this was not provided by the authors. An increase of $J_{ms}$ by ouabain has also been described in colon, but, in these studies, block of basolateral $Na^+/K^+$ ATPase always decreased secretory fluxes, too [40, 46]. In rat distal jejunum, however, an effect of ouabain on $J_{sm}$ could not be detected.

## Involvement of Apical $H^+/K^+$ Pumps

In colon, $K^+$ absorption is accomplished by apical $H^+/K^+$ pumps with a distinct blocker profile among the various species tested [8, 25, 39].

Therefore, the effects of the gastric proton pump inhibitors, SCH28080 and omeprazole, of the $Na^+/K^+$ pump inhibitor ouabain, and of the rather unspecific ATP-dependent pump inhibitor orthovanadate were tested in rat distal jejunum. Among the different drugs, omeprazole and SCH28080 increased $J_{ms}$ slightly, but this had no effect on net fluxes. Orthovanadate, on the other side, induced a small increase of $J_{sm}$, but the drug did not alter $J_{ms}$, something that would have been expected if it blocked a $H^+/K^+$ ATPase responsible for $K^+$ absorption in the tissue investigated. The biological significance of this effect in regard to $K^+$ transport must be considered with respect to the fact that orthovanadate also had a marked impact on $I_{sc}$. Because $H^+/K^+$ ATPase is electroneutral, no change in $I_{sc}$ should occur by blocking this pump. Orthovanadate is known to have an impact on a variety of systems, e.g., on protein-phosphotyrosine phosphatases [20]. The reason for the fall of $I_{sc}$ due to orthovanadate was not further investigated in the present study, but this leaves other factors than $H^+/K^+$ pump inhibition likely to be the cause for the $J_{sm}$ increase induced by this drug.

From the data obtained in this study, a participation of apical $H^+/K^+$ ATPases in the transepithelial transport of $K^+$ across rat distal jejunum can be excluded.

## Interaction with Different Electrogenic Transport Systems

$K^+$ secretion in colon is often linked to $Cl^-$ secretion [12, 22, 33]. The distinct $Cl^-$ secretion induced by forskolin in the present study failed to influence $Rb^+$ fluxes. Adrenaline, which is known to stimulate colonic $K^+$ secretion independent of $Cl^-$ secretion [22, 33, 38], also was ineffective in raising $K^+$ secretory processes. The

decrease of $I_{sc}$ induced by the catecholamine is most likely related to inhibition of electrogenic $HCO_3^-$ secretion [13, 14, 36]. Both forms of $K^+$ secretion, the one dependent on $Cl^-$ secretion as well as the one independent from it, rely upon basolateral potassium uptake via $Na^+/K^+/2\ Cl^-$ cotransport [12, 22, 33]. Thus, the inability of forskolin or adrenaline to stimulate $J_{sm}$ together with the inefficiency of bumetanide to alter $Rb^+$ fluxes point to a mechanism of secretion which is different from the one in large intestine.

A possible interaction of $Rb^+$ fluxes with electrogenic $Na^+$ absorption was investigated by inducing $Na^+$/serine cotransport. This maneuver increased both unidirectional fluxes to an equal amount, therefore leaving $J_{net}$ unchanged. The rise in $J_{ms}$ and $J_{sm}$ can be explained by an increase in paracellular permeability due to the $Na^+$ coupled active transport of serine [31].

### Role of Intracellular pH

The issue of $pH_i$ regulation in enterocytes in regard to side specificity is still controversial. Some studies demonstrated that apical application of SCFA acidified enterocytes and activated preferably apical $Na^+/H^+$ exchange [34, 37], whereas others showed that SCFA influenced $pH_i$ only after serosal, but not after mucosal addition [5, 6]. However, a recent study from the latter group showed that the SCFA butyrate reduced $pH_i$ when added to the apical side, although serosal addition had a greater effect [17]. This can be explained by the existence of pH gradients in the cytosol and also in the adjacent areas of the apical and basolateral membrane of enterocytes [19, 29]. It is very likely that there exists a subapical microdomain analogous to the extracellular surface pH-microclimate which has been shown to be largely independent of solution pH [17]. Therefore, pH changes in this subapical microdomain could be different from cytosolic $pH_i$, yet decisive for pH dependent transport processes via the mucosal membrane.

To acidify $pH_i$, we either blocked $Na^+/H^+$ exchange with EIPA on both sides [26, 30] or added the SCFA acetate mucosally [29, 37]. Despite their different effects on electrical parameters, both strategies increased $J_{ms}$ and, therefore, abolished net secretion of $Rb^+$. From this, we conclude that the $K^+$ secretion in distal small intestine is dependent on pH. Binder and Murer (1986) described an apical $K^+/H^+$ exchange in a segment of rat small intestine, which includes the distal jejunum examined in the present study [2]. This $K^+/H^+$ exchange could explain the $K^+$ secretion we observed. Decreasing intracellular pH would establish a $H^+$ gradient that favors $H^+$ efflux and turns $K^+$ secretion into $K^+$ influx via the brush border membrane, something consistent with the action of EIPA and mucosal acetate on $J_{ms}$. However, $J_{sm}$ should have parallelly decreased. The existence of such an exchange mechanism could also explain the effect of ouabain on absorptive fluxes. The block of $Na^+/K^+$ ATPase decreases intracellular $K^+$ concentration [43], something that could establish a $H^+/K^+$ gradient in favor of $K^+$ influx via the exchanger. As a result, secretory fluxes should have diminished, something that was never observed in our experiments. We cannot give a coherent explanation for this at present. One might argue that unidirectional $K^+$ fluxes in distal small intestine are not independent from each other. This is, however, very speculative at this point. Meanwhile, the existence of a $K^+/H^+$ exchanger distinct from $Na^+/H^+$ exchange has been reported also in chick small intestine [32]. Binder and Murer (1986) speculated that $K^+/H^+$ exchange could play a role in transcellular $K^+$ transport or cell volume regulation [2]. However, studies with rabbit corneal epithelium or OK opossum kidney cells suggest that the physiological role of this exchanger is to be a counterpart of $Na^+/H^+$ exchange. Whereas the latter one increases $pH_i$, $K^+/H^+$ exchange works as a cell acidifier in these tissues [4, 21]. Therefore, it might be possible that the observed $K^+$ secretion is an expression of $pH_i$ regulation mediated via $K^+/H^+$ exchange restricted to distal rat jejunum, at least under the conditions of the present study. The presence of this $K^+/H^+$ exchanger in the distal small intestine might also partly explain why the microclimate at the surface of this epithelium is less acidic than in proximal small intestine [28]. However, since specific blockers for such a $K^+/H^+$ exchanger are missing, it is difficult to directly prove the involvement of this transporter in the observed $Rb^+$ secretion.

In summary, this study demonstrated a $K^+$ secretion in rat jejunum, which is restricted to the distal parts of the small intestine. This secretion is mediated by mechanisms different from that in colon and depends on intracellular pH. It is likely that the observed $K^+$ secretion expresses specific $pH_i$ regulatory mechanisms of enterocytes in the distal jejunum.

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