Modulation of the Basolateral and Apical Step of Transepithelial Organic Anion Secretion in Proximal Tubular Opossum Kidney Cells

ACUTE EFFECTS OF EPIDERMAL GROWTH FACTOR AND MITOGEN-ACTIVATED PROTEIN KINASE*

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The organic anion transport system in the proximal tubule of the kidney is of major importance for the excretion of a variety of endogenous and potentially toxic exogenous substances. Furthermore, the clearance of model substrates (e.g. para-aminohippurate) of this system is used for the determination of renal blood flow. We investigated regulation of organic anion secretion in a way that allowed us to examine simultaneously regulation of overall transepithelial secretion and to estimate the separate contributions of regulation of the basolateral and apical transport steps to this overall regulation. The data were verified by measurement of initial basolateral uptake rate and initial apical efflux rate. Opossum kidney cells were used as a suitable model system for proximal tubule cells, and [14C]para-aminohippurate was utilized as an organic anion. Stimulation of protein kinase C inhibited transepithelial secretion because of inhibition of both apical efflux and basolateral uptake. Inhibition of the mitogen-activated protein kinase (MAPK) kinase MEK reduced transepithelial secretion via inhibition of basolateral uptake and apical efflux. Epidermal growth factor (EGF) enhanced transepithelial secretion via stimulation of basolateral uptake but did not affect apical efflux. EGF induced stimulation of basolateral uptake was abolished by inhibition of MEK. EGF led to phosphorylation of ERK1/2, which was also abolished by inhibition of MEK. Thus, EGF stimulated basolateral uptake of organic anions via MAPKs. Transepithelial organic anion secretion can be regulated at two sites, at least: basolateral uptake and apical efflux. Both steps are under control of protein kinase C and MAPK. The pathophysiologically relevant growth factor EGF enhances transepithelial secretion via stimulation of basolateral uptake. EGF stimulates basolateral uptake via MEK and ERK1/2. Thus, renal organic anion extraction may be modulated, especially under pathophysiological conditions.

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together, these studies give no detailed information concerning the contribution of the single transport steps to the regulation of transcellular secretion. To address this problem, we investigated transcellular secretion in combination with measurements of initial basolateral uptake rate and initial apical efflux rate.

In the present study, we determined the effect of epidermal growth factor (EGF) and MAPKs on PAH transport in OK cells. EGF and its receptor are known to be expressed in proximal tubular cells (23). EGF has been suggested as a mediator of normal tubulogenesis and tubular regeneration after injury. A reduction of renal EGF expression and/or urinary excretion has been reported during acute and chronic tubular injury (24). Additionally, EGF led to an increase in PAH excretion in rats (25), indicating an influence of EGF on proximal tubular organic anion transport. MAPKs are known to be involved in renal stress response and represent an important downstream signal of the EGF pathway (26).

Our data show that activation of PKC inhibits both the basolateral and the apical step of PAH secretion. Moreover, we show that MAPK activity is required for a proper activity of basolateral uptake step and the apical exit of PAH. EGF stimulates transepithelial secretion via stimulation of the basolateral uptake but does not affect the apical transport step. EGF leads to successive activation of the MAPKs, ERK kinase (MEK), and extracellular regulated kinase 1/2 (ERK1/2).

**EXPERIMENTAL PROCEDURES**

**Cell Culture**

OK cells were obtained from Dr. Biber (Department of Physiology, University of Zurich). Cells were maintained in culture at 37 °C in a humidified 5% CO₂, 95% air atmosphere. The growth medium was minimal essential medium, pH 7.4, supplemented with Earl’s salts, nonessential amino acids, 10% (v/v) fetal calf serum (Biochrom KG, minimal essential medium, pH 7.4, supplemented with Earl’s salts, nonessential amino acids, 10% (v/v) fetal calf serum (Biochrom KG, University of Zurich). Cells were maintained in culture at 37 °C in a humidified 5% CO₂, 95% air atmosphere. The growth medium was minimal essential medium, pH 7.4, supplemented with Earl’s salts, nonessential amino acids, 10% (v/v) fetal calf serum (Biochrom KG, Franklin Lakes, NJ) for transport measurements. The effective growth area on one permeable support was 4.3 cm²/filter. All studies were performed between passages 60 and 100. The seeding density was 0.4-10⁶ cm⁻². The medium was changed every third day, and the monolayers were used for experiments at day 10 after seeding. The effect of 10⁻⁷ M phorbol 12-myristate 13-acetate or 5 × 10⁻⁵ M DOG on PAH secretion was determined in nonquiescent and quiescent cells, as shown in Fig. 1. OK cells were made quiescent by cultivating them in serum-deprived cell culture medium for 24 h before the experiments. In both cases, secretion (Fig. 1A) was reduced to a greater extent than cellular content (Fig. 1B), indicating that apical transport may be affected by PKC. Moreover, the effects were more pronounced in quiescent (means serum depleted for 24 h) cells (Fig. 1, right panel) as compared with nonquiescent cells (Fig. 1, left panel). In nonquiescent cells EGF showed no effect on cellular PAH content or transepithelial PAH secretion (data not shown). Because fetal calf serum contains a variety of chemokines, it is evident that investigation of the effect of an isolated chemokine is only possible in the absence of serum. As shown for PKC and mentioned for EGF, the effects on organic anion transport in OK cells were more pronounced or only apparent when cells were made quiescent. Thus, quiescent OK cells were used for all subsequent experiments.

**Transport Measurements**

The volumes of the apical and basolateral compartment were 1.3 and 2.5 ml to avoid hydrostatic pressure differences. Before each experiment, the cells were washed three times with phosphate-buffered Ringer (138 mmol/liter NaCl, 1 mmol/liter NaH₂PO₄, 4 mmol/liter Na₂HPO₄, 4 mmol/liter KCl, 1 mmol/liter MgCl₂, 1 mmol/liter CaCl₂, 5 mmol/liter glucose, pH 7.4). Transport measurements were performed in phosphate-buffered Ringer at pH 7.4 and 37 °C. The concentrations of the substrates applied to the basolateral compartment were: 1.5 × 10⁻⁶ mol/liter or 15 × 10⁻⁶ mol/liter [³¹⁴C]PAH, and 55 × 10⁻⁹ mol/liter [³¹⁴C]mannitol or 55 × 10⁻¹⁰ mol/liter [³¹⁴C]mannitol. [³¹⁴C]Mannitol was used to correct secretion for paracellular fluxes and to determine extracellular water space. At the end of the experiment, the apical and basolateral solutions were collected. Subsequently, the filters were washed twice with ice-cold PBS and cut with the supports. Radioactiv-

**FIG. 1. Effect of PKC stimulation in nonquiescent (left panel) and quiescent (right panel) OK cells on secretion (A) and cellular content (B) after 10 min. Phorbol 12-myristate 13-acetate (10⁻⁷ M) and DOG (5 × 10⁻⁵ M) were added to the transport buffer and were present throughout the 10 min of the transport process. 1.5 × 10⁻⁶ mol/liter [³¹⁴C]PAH was used as a substrate. Nonquiescent cells were cultivated in medium containing 10⁻⁷ M phorbol 12-myristate 13-acetate until the cell epithelia were experimentally used. For quiescent cells, experimental medium was replaced with medium without fetal calf serum 24 h prior to the experiments. n for every bar is shown in parentheses. *, p < 0.05 versus control.**

**Western Blot Analysis**

OK cells were rinsed three times with PBS followed by a 10-min incubation with EGF and/or PD98059. Subsequently cells were washed with ice-cold PBS three times and lysed in ice-cold Triton X-100 lysis buffer (50 mM Tris·HCl, pH 7.5, 100 mM NaCl, 50 mM NaF, 5 mM EDTA, 40 mM β-glycerophosphate, 200 μM sodium orthovanadate, 0.1 mM phenylmethylsulfonyl fluoride, 1 μg/ml leupeptin, 1 μM pepstatin A, 1% Triton X-100) for 25 min at 4 °C. Insoluble material was removed by centrifugation at 12,000 × g for 15 min at 4 °C. The protein content was determined using a microbicinchoninic acid assay (Pierce) with bovine serum albumin as a standard. Cell lysates were matched for protein, separated by 12% SDS-polyacrylamide gel electrophoresis, and transferred to a polyvinylidene difluoride microporous membrane. Subsequently, membranes were blotted with rabbit anti-eERK1/2 (p42/p44) antibody (New England Biolabs). The primary antibody was detected using alkaline phosphatase-conjugated goat anti rabbit IgG visualized by ECL. Western blotting reagents and Hyperfilm ECL (Amersham Pharmacia Biotech). According to the manufacturer’s handbook Hyper-
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FIG. 2. Model showing the measured and calculated parameters describing the secretory transport of \[^{14}C\]PAH in OK cells. A, the cellular content of \[^{14}C\]PAH (parameter 1) and the transepithelial secretion of \[^{14}C\]PAH (parameter 2) are directly measured by liquid scintillation counting of the epithelium or the apical fluid, respectively. The parameter “basolateral uptake” (parameter 3) is the sum of the cellular content and the secretion of \[^{14}C\]PAH after 10 min and represents the total amount of \[^{14}C\]PAH that crossed the basolateral membrane during 10 min. The secretion-to-content ratio (parameter 4) is obtained by dividing transepithelial secretion by cellular content. B, according to data showing linearity for at least 1.5 min (right panel), initial basolateral uptake rate of \[^{14}C\]PAH was measured after 1 min. C, according to data showing linearity for at least 1.5 min (right panel), initial apical efflux rate was determined after 1 min.

Processing of Experimental Data

10-min transport—According to our measurements (Fig. 2A) secretory transport of organic anions in the OK clone used is detectable after 3–4 min and is then linear for at least 1 h (data not shown). Thus, secretory transport after 10 min represents the linear phase of secretion. Therefore, the amount of radiolabeled PAH in the apical compartment after 10 min was used to measure PAH secretion. The quantity of PAH in the cells is denominated cellular content. Summing up the values for PAH secretion and for cellular PAH content gives the basolateral uptake of PAH, i.e. the total amount of PAH transported across the basolateral membrane during 10 min. Additionally, we calculated the ratio of secretion to cellular content of PAH (the secretion-to-content ratio). Introducing these parameters enabled us to gain information regarding the contribution of basolateral and/or the apical transport steps to the overall secretion of PAH.

Basolateral Uptake during the First Minute—Under our experimental conditions uptake of PAH is linear at least during the first 1.5 min as shown in Fig. 2B (right panel), and no net secretion of PAH occurs (data not shown). Thus, the cellular PAH content after 1 min represents the initial basolateral uptake rate. Thus, the predictions concerning the basolateral transport derived from the 10-min transport experiments were verified by the 1-min data.

Apical Efflux of PAH during the First Minute—After preloading the cells as described above, we determined the apical efflux of \[^{14}C\]PAH during the first min as percentage of cellular PAH content at time 0. Because the volume of the apical compartment is about 1000 times that of the cells, there is a large outward gradient during the entire experimental period. According to Fig. 2C (right panel), efflux into the apical compartment is linear at least during 1.5 min, and, thus, the gradient is not collapsed in the time frame investigated. Therefore, the apical efflux during 1 min represents the initial apical efflux rate.

Data Analysis

Data are presented as the means ± S.E. n is given in the text or in the figures. n represents the number of culture plates or filters used. Statistical significance was determined by unpaired Student’s t test or analysis of variance as appropriate. Results were considered statistically different at p < 0.05. Significant differences are indicated by asterisks.

Materials

\[^{14}C\]PAH (55 mCi/mmol) and \[^{3}H\]mannitol (15 mCi/mmol) were purchased from American Radiolabeled Chemicals Inc. (St. Louis, MO). PD98059 was from Alexis Corp. (Läufelfingen, Switzerland). U0126 was from Promega Corp. (Madison, WI). Antibody against the phosphorylated form of ERK1/2 (pERK1/2) was from New England Biolabs Inc. If not stated otherwise, all other chemicals were from Sigma. EGF from Sigma was used as human, recombinant substance.

RESULTS

Validation of the Cell Clone Used—We wanted to investigate regulation of organic anion secretion in a way that would allow us to examine regulation of overall transepithelial secretion and the separate contributions of the basolateral and apical transport steps to this overall regulation, simultaneously. For this purpose, we chose the proximal tubule-derived OK cell line
cultured on permeable supports, a well characterized model system to investigate organic anion secretion (27–29). Probenecid (10 mM), the classical inhibitor of organic anion transport, and a 1000-fold excess of unlabeled PAH, both inhibited uptake and secretion of [14C]PAH by more than 95% (data not shown). Thus, our particular cell clone transports organic anions in agreement with the published data mentioned in the introduction.

**PKC Affects Basolateral and Apical Transport**—Stimulation of PKC by 5 × 10^{-5} M DOG reduced secretion of PAH (Fig. 3A), whereas the cellular content (Fig. 3B) was not significantly different from control. Adding up secretion and cellular content of PAH gives the amount of PAH transported across the basolateral membrane (Fig. 3C). Transport across the basolateral membrane was reduced by DOG, in agreement with other studies (18–20). Furthermore, the decreased secretion-to-content ratio (Fig. 3D) indicates that the apical transport step is also inhibited by PKC. However, there is another possible explanation. The apical transport is carrier mediated and thus has a hyperbolic relationship to substrate concentration. A decrease in intracellular concentration could reduce this ratio, without inhibition of the apical step itself. Thus, experiments on initial transport rates will have to decide what kind of explanation applies to these data.

Simultaneous inhibition of apical and basolateral transport was confirmed by measurement of initial apical efflux rate and initial basolateral uptake rate. As shown in Fig. 4A, activation of PKC reduced the initial apical efflux rate, thereby leading to a decreased relative amount of PAH in the apical bath as compared with control. In addition, Fig. 4B shows that stimulation of PKC reduced the initial basolateral uptake rate of PAH. By contrast, inhibition of PKC with 10^{-7} M BIM increased basolateral uptake of PAH (data not shown). Thus, the basolateral organic anion transport in OK cells is regulated by PKC in agreement with data published previously (19, 20).

**EGF Stimulates Transepithelial Secretion**—EGF increased cellular content (Fig. 5B) and transepithelial secretion (Fig. 5A) of PAH. However, EGF did not affect secretion-to-content ratio for PAH (Fig. 5D) at all, indicating that EGF stimulates basolateral PAH transport in OK cells but does not affect the apical transport step. Initial efflux experiments showed no change in PAH efflux across the apical membrane in EGF treated cells (Fig. 6A). These data confirm the predictions derived from the 10-min transport experiments with EGF (Fig. 5). As shown in Fig. 6B, EGF stimulates the initial basolateral uptake rate of PAH in agreement with the prediction derived from the 10-min experiments.

**MAPKs Affect Basolateral and Apical Transport**—It is known that EGF uses the MAPK pathway also in OK cells (30). Therefore, we investigated the effect of substances that inhibit MAPK activation. Transepithelial secretion (Fig. 7A) and basolateral uptake (Fig. 7C) of PAH were reduced by PD98059 (inhibitor of MEK), whereas cellular PAH content (Fig. 7B) was increased 3-fold as compared with control. The secretion-to-content ratio (Fig. 7D) was dramatically decreased in the pres-
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Fig. 5. Effect of EGF (10 ng/ml) on 10 min transport of 1.5 × 10^{-6} \text{m} [^{14}C]PAH in quiescent OK cells. The following parameters describing transepithelial transport are shown: transepithelial secretion (A), cellular content (B), basolateral uptake (C), and the secretion content ratio (D). The parameters were determined and generated as described under “Experimental Procedures.” EGF was present in the transport buffer throughout the 10 min the transport was measured. n = 9 for every bar. *, p < 0.05 versus control.

Fig. 6. Effect of EGF (10 ng/ml) on initial apical efflux rate of [^{14}C]PAH (A) and initial basolateral uptake rate of [^{14}C]PAH (B) in quiescent OK cells. A, apical efflux of [^{14}C]PAH during 1 min was determined as described under “Experimental Procedures.” EGF was present during the last 10 min before efflux. Apical efflux is presented as percentages of PAH content of the OK cells at efflux time. n = 3 for every bar. B, initial uptake of 15 × 10^{-6} \text{m} during 1 min was determined as described. The cells were incubated with EGF 10 min before the uptake was determined. In between, the cell epithelia were washed once with PBS. n = 6 for every bar. *, p < 0.05 versus control.

In summary, transepithelial secretion of PAH in OK cells is under the stimulatory control of the mitogen-activated protein kinase kinase MEK. Increased secretion when MEK is active results from a stimulation of both basolateral and apical transport (Fig. 9A). Similar results were obtained with another, structurally different, MEK inhibitor U0126 (data not shown).

EGF Acts on Basolateral Uptake via Successive Activation of MEK and ERK—As already mentioned, it is known that the MAPK pathway is stimulated by EGF in OK cells (30). Thus, we investigated whether the stimulatory effect of EGF on basolateral PAH transport is mediated by MAPK. As shown in Fig. 10, inhibition of the MAPK MEK by PD98059 or U0126 completely abolishes the stimulatory effect of EGF on initial basolateral PAH uptake. These data indicate that the stimulatory effect of EGF on basolateral uptake is mediated by the activation of MEK.

As shown in Fig. 11, EGF leads to increased phosphorylation of ERK1/2 in OK cells within 10 min. PD98059 alone, slightly but significantly, decreased the amount of pERK1/2 as compared with controls. These data are in good agreement with the effects on PAH transport. However, EGF increased phosphorylation of ERK1/2 is reduced by inhibition of MEK with PD98059, whereas EGF-stimulated uptake of PAH is totally abolished by PD98059. We explain this apparent discrepancy with the existence of intermediate signaling steps between ERK and basolateral organic anion transport, as discussed in detail later on.

Finally we tested whether preincubation for 10 min with EGF or PD98059 affects glutarate uptake in OK cells. Glutarate is a nonmetabolizable analogue of the dicarboxylate α-ketoglutarate. EGF and PD98059 did not affect basolateral uptake of glutarate (control: 1.2 ± 0.1, n = 3; 10 ng/ml EGF: 1.4 ± 0.1, n = 3; 5 μM PD98059: 1.3 ± 0.3, n = 6; in pmol/cm²·10 min⁻¹). Furthermore, EGF did not affect apical glutarate uptake (control: 0.9 ± 0.1, n = 3; 10 ng/ml EGF: 1.1 ± 0.1, n = 3;
in pmol·cm⁻²·10 min⁻¹). Thus, availability of intracellular counterions for PAH uptake is not altered by EGF or PD98059.

Previously published data showed no effect of PD98059 on basolateral glutarate uptake (19). Taken together, these data present strong evidence that EGF stimulates exchange of di-carboxylates and organic anions via stimulation of the ERK1/2 protein (Fig. 9A).

**DISCUSSION**

The Experimental Setup—The purpose of the present study was (a) to gain more information concerning the overall regulation of the proximal tubule organic anion transport and (b) to investigate the contribution of the basolateral and apical transport steps to this regulation. As shown for EGF, we were able to determine their effects on the basolateral and apical transport steps simultaneously with their effects on transepithelial secretion. However, inhibition of MEK by PD98059 led to a configuration (reduced secretion, increased content, reduced uptake, and reduced secretion-to-content ratio) where determination of the contribution of the basolateral transport step simultaneously with secretion was not possible, indicating the limitations of the method. This is also true for the DOG effect presented. However, with the help of initial apical efflux experiments and determination of the initial basolateral transport rate it is possible to investigate apical and basolateral transport steps separately. Nevertheless, we show that it is possible to estimate the site of action of a chemokine on the secretory transport simultaneously with transepithelial transport, although transport occurs across two membranes (and the cytosol). Thus, the particular processing of the 10-min transport data presented here is suitable to obtain a first estimate regarding the site of action of a given modulator of secretory transport.

Stimulation of PKC inhibits basolateral uptake rate and inhibition of MEK decreases basolateral uptake rate of PAH (Fig. 9A). These data are in agreement with the action of PKC (18–20) and MAPK (19) in isolated proximal tubules and again show the suitability of the OK cell system used. Additionally, we show for the first time that PKC inhibits and MEK stimulates the apical step of organic anion secretory transport in a proximal tubule derived cell line (Fig. 9A). Because the specific PKC inhibitors calphostin C and bisindolylmaleimide stimulate basolateral uptake of PAH, the observed inhibitory action of DOG is due to an interaction with regulatory cascades and not due to nonspecific or even toxic action. Furthermore, the calphostin C-induced stimulation of PAH uptake was prevented by both phorbol 12-myristate 13-acetate and DOG (data not shown). Systematic changes in mannitol flux were not observed with any of the substances used. Thus, no changes in epithelial tightness were induced, and the measured changes in PAH transport are not due to altered paracellular flux. The unchanged epithelial tightness, together with the short exposure time (10 min) and the moderate concentrations used, make it highly unlikely that any observed effect is due to...
unspecific toxic actions.

**EGF Stimulates Organic Anion Secretion**—As the above mentioned maneuvers act directly on intracellular signaling pathways, we investigated the effect of more physiologically or pathophysiologically relevant stimuli, namely EGF. We show for the first time that EGF increases the secretion of PAH in OK cells by a stimulation of the basolateral uptake step. EGF does not affect the apical transport step (Fig. 9B).

The effect of EGF on basolateral uptake is mediated by MEK, because two specific, structurally distinct inhibitors of MEK (PD98059 and U0126) completely abolished EGF induced stimulation of initial basolateral PAH uptake. As shown in Fig. 8B, 5 μM PD98059 led to a slight decrease of initial PAH uptake. This is in parallel with the decrease of ERK1/2 phosphorylation induced by 5 μM PD98059. However, the same concentration of PD98059 completely prevented the EGF-induced stimulation of initial basolateral PAH uptake. This was also the case for the structurally distinct MEK inhibitor U0126. The fact that inhibition of MEK decreased uptake only slightly but abolished EGF-stimulated uptake completely is strong evidence for the fact that EGF acts on basolateral transport via stimulation of MEK. Moreover, as already mentioned above, no secretion of organic anions in OK cells was detected during the first min. Thus, alterations of the apical transport step should not influence initial basolateral uptake rate.

Inhibition of MEK prevented EGF-induced stimulation of basolateral PAH uptake completely; however, it reduced EGF

**Fig. 9. Summary models.** +, stimulatory effects; –, inhibitory effects. A and B, effects of PKC and MEK (A) and EGF (B) on the basolateral and the apical transport step of transepithelial secretion of PAH in the OK cell model of the proximal tubule. C, hypothesized model of the stimulation of the basolateral exchange step of PAH and dicarboxylates by EGF. EGF stimulates the PAH/dicarboxylate exchanger via activation of the MAPKs MEK and ERK1/2. ERK1/2 action on the PAH/dicarboxylate exchanger is mediated via at least one intermediate signaling step.

**Fig. 10. Effect of inhibitors of MEK (PD98059 or U0126) on EGF stimulation of initial basolateral uptake rate of [14C]PAH.** The cells were incubated with EGF alone (10 ng/ml) and in presence of PD98059 (5 × 10⁻⁶ M) or U0126 (25 × 10⁻⁶ M) for 10 min before the uptake was determined. Reference values are untreated controls and uptake in presence of PD98059 or U0126, respectively. Thus the part of initial basolateral uptake rate of [14C]PAH that is stimulated by EGF is given by the difference in uptake after EGF and untreated controls, the difference in uptake after EGF in presence of PD98059 and PD98059 alone, and the difference in uptake after EGF in presence of U0126 and U0126 alone. Epithelia were washed once with PBS between incubation and uptake measurement. n = 9 for every bar. *, p < 0.05 versus 0.
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Western blot of OK cell protein with anti-ERK1/2 activation (data not shown). These data again support basolateral PAH uptake as compared with those with a lower ERK1/2 activation threshold that has to be exceeded to stimulate the downstream signals. Thus, we hypothesize that EGF stimulates the basolateral uptake of organic anions via ERK1/2 activation.
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