The kidney, and more specifically the proximal tubule, is the main site of elimination of cationic endogenous metabolites and xenobiotics. Although numerous studies exist on renal organic cation transport of rat and rabbit, no information is available from humans. Therefore, we examined organic cation transport and its regulation across the basolateral membrane of isolated human proximal tubules. mRNA for the cation transporters hOCT1 and hOCT2 as well as hOCTN1 and hOCTN2 was detected in these tubules. Organic cation transport across the basolateral membrane of isolated collapsed proximal tubules was recorded with the fluorescent dye 4-(4-dimethylamino)styryl-N-methylpyridinium (ASP\(^+\)). Depolarization of the cells by rising extracellular K\(^+\) concentration to 145 mM reduced ASP\(^+\) uptake by 20 ± 5% (n = 15), indicating its electronegativity. The substrates of organic cation transport tetraethylammonium (K\(_{\text{m}}\) = 63 \mu M) and cimetidine (K\(_{\text{m}}\) = 11 \mu M) as well as the inhibitor quinine (K\(_{\text{m}}\) = 2.9 \mu M) reduced ASP\(^+\) uptake concentration dependently. Maximal inhibition reached with these substances was ~60%. Stimulation of protein kinase C with 1,2-dioctanoyl-sn-glycerol (DOG, 1 \mu M) or ATP (100 \mu M) inhibited ASP\(^+\) uptake by 30 ± 3 (n = 16) and 38 ± 13% (n = 6), respectively. The effect of DOG could be reduced with calphostin C (0.1 \mu M, n = 7). Activation of adenylyl cyclase by forskolin (1 \mu M) decreased ASP\(^+\) uptake by 29 ± 3% (n = 10). hANP (10 nm) or 8-bromo-cGMP (100 \mu M) also decreased ASP\(^+\) uptake by 17 ± 3 (n = 9) or 32 ± 5% (n = 10), respectively. We show for the first time that organic cation transport across the basolateral membrane of isolated human proximal tubules, most likely mediated via hOCT2, is electrogenic and regulated by protein kinase C, the cAMP- and the cGMP-dependent protein kinases.

The proximal tubule is the site of secretion and reabsorption of endogenous metabolites and xenobiotics in the kidney. Many of these substances are organic cations. As several drugs are among these organic cations, specific knowledge about properties of organic cation transport in the human proximal tubule is of great importance. The first organic cation transporter was cloned from rat (rOCT1) in 1994 (1). The first human organic cation transporters (hOCT1 and hOCT2) were cloned 3 years later (2, 3), and three other members of this family (hOCTN1, hOCTN2, and hOCT3, originally named EMT) followed (4–6). Previous functional studies (7, 8) on organic cation transport in the proximal tubule of the rat showed the differences between transport across the luminal or basolateral membrane. After cloning of the transporters from functional investigations of these transporters together with those obtained by microperfusion experiments and transport studies with membrane vesicles (8–12) led to a model of organic cation transport in the proximal tubule. OCTN1 was shown to be a H\(^{+}\)/organic cation exchanger (4, 13), whereas OCT1 has been characterized as a functionally different potential driven uniporter. Immunohistochemistry localized rOCT1 and rOCT2 to the basolateral membrane of proximal tubules (14–16). The OCTN1 is most likely located in the luminal membrane of proximal tubules (17, 18). Thus, organic cation transporters expressed in the luminal and basolateral membranes of the proximal tubule are molecularly and functionally very different members of this protein family.

After cloning of the first transporters, studies were performed to gain information on properties of these organic cation transporters expressed in Xenopus laevis oocytes or cell lines (19–21). From these studies we have information on their electronegativity, substrate specificities, and inhibitors with K\(_{\text{m}}\) and K\(_{\text{p}}\) values for the distinct cation transporters from rat and man. The homologous transporters of these two species differ in K\(_{\text{m}}\) and K\(_{\text{p}}\) values for the investigated cations (19–24). Properties found for the cloned rOCT1 and rOCT2 do not always match with the properties determined for the proximal tubule \textit{in vivo} obtained by micropuncture studies (7, 8, 19, 23, 25). These differences may be due to the fact that additional transporters are involved in the \textit{in vivo} situation or that transporter properties are modified \textit{in vivo} under the influence of protein kinases, for example. Consequently, it is impossible to transfer results on organic cation transport in rat proximal tubule or from cloned transporters studied in expression systems to that of humans. Therefore, studies of organic cation transporters in isolated human proximal tubules, which are described in this study for the very first time, are urgently needed. This point is even more important considering the fact that the first observations indicate that organic cation transporters are regulated by protein kinases (26–29). So far regulation of the basolateral organic cation transport via protein kinase C (PKC)\(^1\) was dem-

\(^{1}\) The abbreviations used are: PKC, protein kinase C; PKA, cAMP-dependent protein kinase; PKG, cGMP-dependent protein kinase; ASP\(^+\), 4-(4-dimethylamino)styryl-N-methylpyridinium; TEA\(^-\), tetraethylammonium; bp, base pair; RT-PCR, reverse transcriptase-polymerase chain reaction; 8-Br-cGMP, 8-bromo-cGMP; h, human; ANP, atrial natriuretic peptide.
onstrated for the S2 segments of rabbit proximal tubule (27). In the apical membrane of a human proximal tubule cell line (HIKE-1), we found organic cation transport, probably mediated by the OCTNs, to be under the regulation of PKC, cAMP-dependent protein kinase (PKA), and cGMP-dependent protein kinase (PKG) (29). Such a regulation could not be detected in a porcine cell line (LLC-PK-1), indicating the species differences also in the regulation of organic cation transport. Recently, we were able to demonstrate that the rat rOCT1 is activated by stimulation of PKA, PKC, and by tyrosine kinases (28). Until now no data have been reported for organic cation transport across the basolateral membrane of human proximal tubules and for regulation of the cloned human transporters. As the sequences of the basolateral human organic cation transporters show several putative phosphorylation sites for PKC, PKA, and casein kinase II, it appears likely that human organic cation transporters are also under the control of these kinases (2).

Here we present the first data on organic cation transport in freshly isolated human proximal tubules obtained from human tumor nephrectomies, which resemble more closely the in vivo situation than any cell culture or expression system. Our goal was to study for the first time the uptake of organic cations across the basolateral membrane of isolated human proximal tubules which is the first step in the elimination of cationic xenobiotics and endogenous metabolites via the kidney. By using the fluorescent dye 4-(4-(dimethylamino)styryl)-N-methylpyridinium (ASP™) and detecting the uptake with flurometrically recording organic cation transport in real time was as described in detail by us previously (28, 29, 34, 35). In short, an inverted microscope (Axiovert 135, Zeiss, Oberkochen, Germany) equipped with a 100× oil immersion objective was used. The excitation light was generated with a xenon quartz lamp (XBO 75 W, Zeiss). A pulsating excitation light was obtained by a filter wheel (Physiologisches Institut, Universitat Freiburg, Germany) rotating with 10 turns/s and equipped with a 450–490 nm bandpass filter. The excitation light was reflected to the perfusion chamber containing the isolated tubule by a dichroic mirror (560 nm). The emission light was measured after passing through a bandpass filter (575–640 nm) by a photon counting tube (Hamamatsu H 3460–04, Herrsching, Germany). The measurements were restricted to portions of the collapsed tubules with the aid of an adjustable diaphragm. The signal of the photon counting tube was transformed and recorded by a PC computer system with specific software (U. Frobe, Universitat Freiburg, Germany). The fluorescence signals of 10 pulses/s were averaged and plotted as a function of time. The base-line counts with no excitation light present (closed filter position) amounted to less than 5 counts/s and were subtracted from the specific signal.

Single isolated proximal tubules were transferred into a perfusion chamber with a glass bottom mounted in the focus of the microscope and were fixed with two holding pipettes. As the ends of the tubules were kept inside the holding pipettes and the tubules were collapsed, the cellular fluorescence increase upon addition of ASP™ to the perfusate was reflected organic cation transport across the basolateral membrane of the tubule only. The chamber was perfused with a flow rate of 10–12 ml/min with a HCO₃⁻–free Ringer-like solution (37 °C, pH 7.4, see below).

ASP™ (500 nM) was added for 2 min and washed out at least for 10 min before it was added again. The highest initial rate of fluorescence increase was analyzed by linear regression. Two control additions of ASP™, together with another substrate or inhibitor, followed again by two control ASP™ additions. The influence of other substrates or inhibitors was analyzed as change in percent of averaged pre- and post-controls. For statistical analysis the agonists were added to the bath for 10 min before ASP™ was added in the continued presence of the agonist. Again ASP™ uptake rates in the presence of an agonist were compared with the averaged pre- and post-control values. The method of fluorometry, Uptake

**RESULTS**

Proximal tubules were isolated from kidney tissue from 34 male and 20 female patients. The average age of these patients was 58.6 ± 2.2 years, the youngest was 1 year and the oldest 79 years old. A total of 111 tubules was isolated from these kidneys and used for fluorescence measurements. From each of these kidney samples a minimum of one and a maximum of six
tubules was used successfully. All experiments were done on the same day of the nephrectomy. Three additional kidney samples were used for RT-PCR analyses.

Concentration Dependence of ASP\textsuperscript{+} Uptake—To demonstrate the concentration dependence of ASP\textsuperscript{+} uptake across the basolateral membrane of human proximal tubules, a concentration response curve for ASP\textsuperscript{+} uptake was generated. Fig. 1 shows an original recording of ASP\textsuperscript{+} with various concentrations of ASP\textsuperscript{+} added to the bath. As the repetitive addition of ASP\textsuperscript{+} (1 or 2 \(\mu\)M) shows, the uptake was reproducible. As indicated under “Experimental Procedures,” we evaluated the initial uptake rates of ASP\textsuperscript{+} as these reflect the transport step whereas the maximal fluorescence reached depends on export from the cells, cellular compartmentation, or bleaching of ASP\textsuperscript{+}. By using concentrations between 5 nM and 100 \(\mu\)M, the concentration response curve as shown in Fig. 2 was obtained. As can be seen from this figure the initial rate of ASP\textsuperscript{+} uptake was not saturated at 100 \(\mu\)M, which was the highest concentration we could get in solution. First significant uptake was obtained at 100 nM. For all further experiments we used 500 nM ASP\textsuperscript{+}, a concentration that resulted in a significant cellular fluorescence increase but allowed fast and complete wash out of the dye.

Electrogeneity of ASP\textsuperscript{+} Uptake—Next we determined whether ASP\textsuperscript{+} uptake depends on the membrane voltage of proximal tubule cells, as would be expected for an electrogenic transporter like hOCT1 or hOCT2. ASP\textsuperscript{+} uptake under resting voltages with an extracellular \(K^+\) concentration of 3.6 mM was compared with that of depolarized cells kept in a bath solution containing 145 mM \(K^+\). ASP\textsuperscript{+} uptake was inhibited under these conditions by 20 \(\pm\) 5\%(\(n = 15\), Fig. 3). This finding indicates that the uptake of organic cations across the basolateral membrane of human proximal tubules is indeed electrogenic.

Substrate Specificity—To gain information on the substrate specificities of the organic cation transport across the basolateral membrane of human proximal tubules, we tested the interference of different well known substrates for organic cation transporters (cimetidine, TEA\textsuperscript{−}, and amiloride) and an inhibitor of organic cation transport (quinine) with ASP\textsuperscript{+} uptake. All substrates reduced ASP\textsuperscript{+} uptake in a concentration-dependent manner (Fig. 4). Cimetidine inhibited the ASP\textsuperscript{+} uptake with an apparent \(K_i\) of 11 \(\mu\)M and TEA\textsuperscript{−} (\(n = 3–8\)) inhibited ASP\textsuperscript{+} uptake with \(K_i\) values of 11 and 63 \(\mu\)M, respectively. The inhibitor quinine (\(n = 5–10\)) reduced ASP\textsuperscript{+} uptake with a \(K_i\) of 3 \(\mu\)M. Inhibition of ASP\textsuperscript{+} uptake is shown in % of control mean values \(\pm\) S.E.

Regulation of ASP\textsuperscript{+} Uptake—To investigate the regulation of organic cation transport in these human proximal tubules, the ASP\textsuperscript{+} uptake rate under resting conditions was compared in paired experiments with that after a 10-min incubation with different activators of protein kinases. As shown in the original recordings of Fig. 5, incubation of the tubule for 10 min with either forskolin (1 \(\mu\)M), DOG (1 \(\mu\)M), or 8-Br-cGMP (100 \(\mu\)M) decreased the activity of organic cation transport. The results of these experiments are summarized in Fig. 6. Activation of the adenylate cyclase and consequently PKA via forskolin (1 \(\mu\)M) resulted in an inhibition of ASP\textsuperscript{+} uptake by 29 \(\pm\) 3\%(\(n = 10\)). Stimulation of PKC with DOG (1 \(\mu\)M), the membrane-permeable homolog of diacylglycerol, inhibited ASP\textsuperscript{+} uptake by 30 \(\pm\) 3\%(\(n = 16\)). ATP (10 \(\mu\)M) again stimulating PKC decreased the uptake by 38 \(\pm\) 13\%(\(n = 6\)). Incubation of proximal tubules with the membrane-permeable analog of GMP, 8-Br-cGMP (100 \(\mu\)M) or hANP (10 nM), both activating PKG, led to a
the knowledge of properties of organic cation transport especially in the human proximal tubule is desirable. So far no functional data from the human kidney or the isolated human proximal tubule are available at all. The reported significant differences in properties between the homologous transporters cloned from different species (22), however, indicate that it is not possible to simply extrapolate from findings in animals to the human situation. Furthermore, no data on the mechanisms and signaling pathways of the regulation of the cloned human transporters do exist up to now. As shown for the Na\(^{+}\)-glucose cotransporter 1 (SGLT1) (36) the transporters of humans and animals are under control of PKC, but in humans PKC activation shows the opposite effect. Our findings of regulation of the apical organic cation transport in a human (IHKE-1) and a porcine (LLC-PK-1) proximal tubule cell line show again that in different species this transport is not necessarily under regulation of the same kinases (29). Knowing that the basolateral organic cation transporters in rabbit proximal tubules are stimulated by activation of PKC (26–28) and that the cloned rOCT1 was also stimulated by activation of kinases (28), this study was designed to gain more information about the basal properties and mechanisms of regulation of organic cation transport across the basolateral membrane of proximal tubules of humans. We used the fluorescence technique recently established in our laboratory (29, 34, 35) to record organic cation uptake by proximal tubules in real time with ASP\(^{+}\) as fluorescent substrate.

As the source of living human renal tissue, we successfully used in this study healthy tissue samples surrounding the renal tumors of human tumor nephrectomies. This tissue was obtained with fairly high frequency and mechanical isolation of tubules for functional experiments was possible within 1 h under controlled cooling and oxygenation conditions. Experiments could be done successfully with these tubules for several hours.

Here we present the first measurements of organic cation transport in the human proximal tubule, identifying its electronegativity, substrate specificity, and regulation by PKA, PKC, and PKG. As the isolated tubules were collapsed and their ends were fixed in two holding pipettes, uptake of ASP\(^{+}\) was restricted to transport processes across the basolateral membrane. ASP\(^{+}\) uptake was concentration-dependent between 5 nm and 100 \(\mu\)M but did not reach saturation at 100 \(\mu\)M which was the highest concentration that could be dissolved in aqueous solution. These findings indicate that the \(K_m\) for ASP\(^{+}\) for this preparation is comparable to that determined for ASP\(^{+}\) uptake across the contraluminal side of rat proximal tubules in vivo (280 \(\mu\)M) (37). Alternatively, this concentration response curve extending over more than 3 decades points to the existence of two components responsible for ASP\(^{+}\) accumulation in the human proximal tubule as follows: a high affinity transport system with a \(K_m\) for ASP\(^{+}\) similar to that determined by us

decrease in ASP\(^{+}\) uptake of \(32 \pm 5\) \((n = 10)\) and \(17 \pm 3\%\) \((n = 9)\), respectively. The involvement of PKC in the effect induced by DOG was demonstrated by the combined incubation of the tubules with DOG (1 \(\mu\)M) and ATP (100 \(\mu\)M), and PKG was stimulated with 8-Br-cGMP (100 \(\mu\)M) and human ANP (10 nM). The last column shows the effects of incubation with ANP, DOG, and forskolin together. The tubules were incubated with the agonists for 10 min. ASP\(^{+}\) uptake was measured in presence of the agonists. Data are shown as mean values \pm S.E., \(n\) in parentheses indicate number of experiments.

To test whether activation of these different cellular signaling pathways together results in larger effects, tubules were incubated with a mixture of hANP (10 nM), DOG (1 \(\mu\)M) and forskolin (1 \(\mu\)M) for stimulation of PKG, ASP\(^{+}\) was given in addition to the agonists. The initial ASP\(^{+}\) uptake is shown for each agonist in comparison to its own paired control which was recorded immediately before the incubation with the respective agonists.

**DISCUSSION**

Specific transport systems are responsible for the excretion of organic cations such as endogenous metabolites and exogenous xenobiotics. As a large number of widely used drugs like antihypertensives, antibiotics, and others belong to these cationic xenobiotics and are substrates for these transporters (7),...
with the same method or with tracer flux measurements for the cloned rOCT1 expressed in HEK293 cells (around 1 µM) (28); a second component that might reflect other low affinity transport systems or sequestration of the fluorescent dye (18). To exclude such effects that could contribute to cellular ASP⁺ fluorescence, we evaluated the highest initial uptake rate after addition of very low concentrations of ASP⁺ (0.5 µM). The initial uptake rate should be due exclusively to the inward transport of the fluorescent dye. The fluorescence increase during the nonlinear portion of the curve certainly also involves outward transport as well as changes of fluorescence by sequestration of the fluorescent dye.

Most studies localize the organic cation transporters of the OCT-type to the basolateral membrane, whereas those of the OCTN-type probably reside in the apical membrane of polarized cells (14–16). Electrogeneity of the transport was reported for the cloned OCTs as well as for the basolateral organic cation transport in the proximal tubule in vivo or in vitro (2, 19). Strong depolarization of the proximal tubule cells in this study resulted in an inhibition of ASP⁺ uptake, indicating its electrogeneity. This suggests an involvement of the hOCT1 and/or hOCT2 in the ASP⁺ uptake across the basolateral membrane of human proximal tubules.

To characterize further the basal properties and mechanisms of organic cation transport across the basolateral membrane of the human proximal tubule and to identify the type of transporter involved in ASP⁺ uptake, we examined the interference of specific substrates and an inhibitor of the OCTs with this transport. The $K_i$ values determined for the competitive inhibition of organic cation transport can be compared with $K_a$ and $K_v$ values published for the cloned hOCT1 and hOCT2. It appears necessary to consider that these data were obtained with different methods in different expression systems. In addition, ASP⁺ uptake as well as organic cation transport in general across the basolateral membrane of the proximal tubule is probably not only due to one type of transport system. Nevertheless, the $K_i$ values for the substrates TEA⁺ or cimetidine and for the inhibitor quinine for the human proximal tubules obtained for the first time in this study are similar to the values reported for the hOCT2 and different from those for hOCT1 (2, 20). This comparison of $K_i$ values is shown in Table I. Analysis of the expression of mRNA for cloned human organic cation transporters detected hOCT1 and hOCT2 as well as hOCTN1 and hOCTN2 in these isolated proximal tubules. Considering the functional data hOCT2 apparently plays the main role in uptake of organic cations across the basolateral membrane of human proximal tubules. After cloning the human OCT1 and OCT2 the hOCT2 was immunohistochemically detected in distal convoluted tubules. Later the existence of hOCT2 has been demonstrated by RT-PCR in a human proximal tubule cell line (IHKE-1) (2) and in isolated human proximal tubules by us. Together with our functional data we now have evidence for the presence of the hOCT2 in the basolateral membrane of human proximal tubules.

The first data on regulation of organic cation transport across the basolateral membrane of isolated proximal tubules of rabbit kidney suggested an up-regulation of this transport by activation of PKC (27). For human transporters only the data for the apical membrane of a cultured proximal tubule cell line are available. The apical transporters are activated by stimulation of PKA, PKC, and PKG. For the porcine proximal tubule cell line (LLC-PK-1) no influence of PKA and PKG could be shown (29). When the human OCT1 and OCT2 were cloned in 1997 (2), several putative phosphorylation sites in the intracellular domains were detected. Therefore, we investigated whether stimulation of PKA, PKC, or PKG had any effect on the transport activity in the human proximal tubule. With all tested agonists we measured significant inhibition of organic cation transport across the basolateral membrane of these tubules. This is the exact opposite effect compared with that reported for rat and rabbit organic cation transport. In case of DOG we could further identify the mechanism of regulation by proving an involvement of PKC as the effect was reduced by the PKC inhibitor calphostin C. For the OCT1 from rat expressed in HEK293 cells, we recently reported an activation of transport mediated by PKA and PKC stimulation (28). This effect was due to a direct phosphorylation of the transport protein and an increase in the substrate affinity. Preliminary data from our own group on regulation of the hOCT2 again expressed in HEK 293 cells revealed an inhibition of transport by stimulation of phospholipase C with ATP or carbamoyl.² Although the OCT1 share 82–96% and the OCT2 83–92% similarity on the amino acid level between species (37), an extrapolation of the regulatory properties of the OCT1 from rat to that of humans is not possible, and precise data on the regulation of the human OCT1 are needed. This is further supported, for example, by the completely different regulatory pattern of SGLT1 from different species by protein kinases when expressed in X. laevis oocytes (36). The inhibition of ASP⁺ uptake by forskolin in the present study parallels the findings for hOCT2² and is again opposite the effects on rOCT1 (28). Therefore, similar to our conclusions above from the apparent affinities for various substrates, the findings of these regulation experiments again indicate that the hOCT2 is responsible for ASP⁺ uptake across the basolateral membrane of these isolated human proximal tubules. The magnitude of the inhibition of ASP⁺ uptake by these agonists ranged between 20 and 40%. As inhibition of ASP⁺ uptake with maximal concentrations of other substrates or the inhibitor quinine did not exceed 60% of the total fluorescence accumulation, we have to conclude that a second mechanism is involved in ASP⁺ uptake which is not sensitive to these specific substances. The inhibition of ASP⁺ uptake at least by PKC activation was completely absent in the presence of maximal concentrations of TEA⁺ which means that OCT-mediated transport is reduced by 70–80% when this or presumably the other two protein kinases are fully activated. Finally, the absence of an apparent additivity of the inhibitory effects of agonists stimulating PKA, PKC, and PKG suggests that the investigated kinases probably lead to the same modification of the transport. Further studies are needed to examine whether these effects are due to a phosphorylation of the transporter itself or to changes in its trafficking as has been shown for SGLT1 (36).

In conclusion, we demonstrate for the first time the mechanisms and properties of specific organic cation transport across the basolateral membrane of isolated tubules from the human kidney using functional studies. Organic cation transport

| Substrate | hOCT1 $K_i$ (µM) | hOCT2 $K_i$ (µM) | hPT $K_i$ (µM) |
|-----------|-----------------|-----------------|----------------|
| TEA⁺      | 161             | 76              | 63             |
| Cimetidine| 166             | Not published   | 11             |
| Quinine   | 22.9            | 3.4             | 2.9            |

² I. Çetinkaya, T. Mehrens, J. R. Hirsch, and E. Schlutter, unpublished data.
across the basolateral membrane of the human proximal tubule is electrogenic and mediated via an OCT-type transporter to at least 60%. Again for the first time we demonstrate that this transport is regulated by various kinases. Examination of the signaling pathways shows that this transport is down-regulated when agonists stimulating PKA, PKC, or PKG are present. Substrate specificities, regulation of transport, and mRNA expression points toward hOCT2 as the transporter mediating this transport in human proximal tubules.

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Properties and Regulation of Organic Cation Transport in Freshly Isolated Human Proximal Tubules
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