Transport of Monoamine Transmitters by the Organic Cation Transporter Type 2, OCT2*

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The recently cloned apical renal transport system for organic cations (OCT2) exists in dopamine-rich tissues such as kidney and some brain areas (Gründemann, D., Babin-Ebell, J., Martel, F., Örding, N., Schmidt, A., and Schömig, E. (1997) J. Biol. Chem. 272, 10408–10413). The study at hand was performed to answer the question of whether OCT2 accepts dopamine and other monoamine transmitters as substrate. 293 cells were stably transfected with the OCT2r cDNA resulting in the 293OCT2r cell line. Expression of OCT2r in 293 cells induces specific transport of tritiated dopamine, noradrenaline, adrenaline, and 5-hydroxytryptamine (5-HT). Initial rates of specific [3H]-dopamine, [3H]-noradrenaline, [3H]-adrenaline, and [3H]-5-HT transport were saturable, the K_m values being 2.1, 4.4, 1.9, and 3.6 mmol/liter, respectively. The corresponding v_max values were 3.9, 1.0, 0.59, and 2.5 mmol min⁻¹ mg of protein⁻¹, respectively. 1,1-diisopropyl-2,4-cyanine (disprocynium24), a known inhibitor of OCT2 with a potent eukaliuric diuretic activity, inhibited [3H]-dopamine uptake into 293OCT2r cells with an K_i of 5.1 (2.8, 9.9) nmol/liter. In situ hybridization reveals that, within the kidney, the OCT2r mRNA is restricted to the outer medulla and deep portions of the medullary rays indicating selective expression in the S3 segment of the proximal tubule. These findings open the possibility that OCT2r plays a role in renal dopamine handling.

The inactivation of released hormones and neurotransmitters is essential for chemical signal transduction. The inactivation of monoamine transmitters such as dopamine, noradrenaline, adrenaline, and 5-hydroxytryptamine is brought about by neuronal and non-neuronal (extraneuronal) membrane-bound transport systems. These transport mechanisms actively remove the monoamine transmitters from the extracellular space and thus terminate their biological actions. The primary structures of a variety of sodium-dependent neuronal transport systems for biogenic amines have recently been elucidated (1, 2). On the other hand, the molecular correlates of the transporter or transporters responsible for extraneuronal monoamine uptake are still unknown.

The use of a novel class of potent inhibitors of extraneuronal monoamine transport revealed that extraneuronal mechanisms contribute markedly to the inactivation of circulating catecholamines (3). The pharmacological characterization of extraneuronal monoamine transport in tissue culture suggests an unexpected but nevertheless close pharmacological relationship between extraneuronal monoamine transport and the secretion of organic cations through the apical plasma membrane of renal proximal tubule cells (4).

EXPERIMENTAL PROCEDURES

Construction of a Cell Line That Stably Expresses the Organic Cation Transporter OCT2r—If not stated otherwise, standard molecular biology techniques were employed (8). For the construction of pcDNA3OCT2r, the cDNA of OCT2r has been released from pBluescript II OCT2r by restriction with HindIII and XhoI and inserted into the corresponding polylinker site of pcDNA3 (Invitrogen, San Diego, CA). pcDNA3 is a eukaryotic expression vector that carries an aminoglycoside resistance cassette. Human embryonic kidney (HEK) 293 cells (ATCC CRL-1573) (9) were transfected by a cationic lipidosome technique with the Tfx-50 reagent (Promega, Mannheim, Germany) according to the recommendations of the manufacturer. Selection was carried out with the aminoglycoside Geneticin (Life Technologies, Inc.). The 293OCT2r cells were derived from an isolated transfected cell obtained by single cell cloning. Success of stable transfection of the 293OCT2r cells was tested by RT-PCR and functional experiments (see “Results”). For control purposes, 293pcDNA3 cells were constructed that were stably transfected with the empty expression vector pcDNA3. 293wt refers to wild-type 293 cells.

Transport Assays—The cell lines were grown in surface culture on standard tissue culture plastic materials. After a preincubation period of 30 min at 37 °C with buffer A (125 mmol/liter NaCl, 4.8 mmol/liter KCl, 1.2 mmol/liter CaCl2, 1.2 mmol/liter KH2PO4, 1.2 mmol/liter MgSO4, 25 mmol/liter HEPES/NaOH, pH 7.4, 5.6 mmol/liter D(+)-glucose), the cells were incubated with 100 mmol/liter 3H-labeled substrates in buffer A. Where appropriate, transport inhibitors were present during both the preincubation and incubation periods. Incubation was stopped by rinsing the cells four times with 3 ml of ice-cold buffer

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The abbreviations used are: OCT2, apical renal transport system for organic cations; 5-HT, 5-hydroxytryptamine; 293WT, wild-type 293; RT-PCR, reverse transcriptase polymerase chain reaction; PBS, phosphate-buffered saline; ANOVA, analysis of variance; 3H-MPP⁺, 3H-1-methyl-4-phenylpyridinium.
A. Subsequently, the cells were solubilized with 0.1% v/v Triton X-100 (dissolved in 5 mmol/liter Tris-HCl, pH 7.4), and radioactivity was measured by liquid scintillation counting. The specific activity of the used radiolabeled substrates was adjusted to result in uninhibited uptake values of about 500 cpm per culture dish. L(+)-α-ascorbic acid (1 mmol/liter) was present in all experiments. Where appropriate, intracellular metabolism via monoamine oxidase (MAO) and/or catechol-O-methyltransferase (COMT) was blocked by 10 μmol/liter pargyline alone (in the case of 5-HT) or by 10 μmol/liter pargyline and 10 μmol/liter U-0521 (in the case of dopamine, noradrenaline, or adrenaline).

In Situ Hybridization—The kidneys were removed from adult Sprague-Dawley rats perfused with 4% paraformaldehyde in phosphate-buffered saline (PBS), pH 7.4, and 18% sucrose solution in PBS. 14-μm cryostat sections were mounted on poly-L-lysine-coated slides and post-fixed for 20 min in 4% paraformaldehyde. The slides were washed in DEPC-treated water and subsequently in 0.1 M HCl. Next, the sections were acetylated for 20 min in 0.1 M triethanolamine (pH 8.0) containing 0.25% acetic anhydride and, after rinsing in PBS, dehydrated in ethanol (70 and 96%) and air-dried. Digoxigenin-labeling and nonradioactive in situ hybridization was carried out essentially as described elsewhere (11). Digoxigenin-11-UTP labeled sense and antisense RNA probes were prepared from a 6.3-kilobase fragment of the rat OCT2 cDNA and shortened by alkaline hydrolysis to an average length of 250 bases. The sections were hybridized at 42 °C for 16 h and washed at 49 °C in 1× SSC containing 50% formamide and finally in 0.5× and 0.2× SSC at 20 °C. Incubation with alkaline-phosphatase-coupled antidigoxigenin antibodies and the subsequent color reaction were done according to the protocol of the manufacturer (Boehringer Mannheim, Germany).

Protein Determination—Protein was determined by the method of Lowry (12).

Calculations and Statistics—The analysis of the time course of substrate accumulation was based on a 1-compartment model as described earlier (13). For the calculation of IC50 values, the parameters of the Hill equation for multisite inhibition (14) were fitted to the experimental data by nonlinear computer-assisted quasi Newton method (15). The IC50 values are identical with K values since nonsaturating substrate concentrations were used (16). Geometric means are given with 95% confidence limits, and arithmetic means are given with S.E. ANOVA was used to test for significance.

Drugs Used—(-)-N-Methyl-[3H]-adrenaline (2 kBq/pmol), (-)-[7-3H]noradrenaline (381 Bq/pmol), [3H]MPP+ (N-methyl-[3H]-4-phenylpyridinium acetate; 2.9 kBq/pmol) (NEN Life Science Products, Germany). (11), (12), and cocaine-HCl (Merck, Darmstadt); disprocynium22 (1,1-diethyl-2,4-cyanine iodide), dopamine hydrochloride, 5-hydroxytryptamine, cortisosterone, (–)-noradrenaline (Sigma, Munich, Germany); cocaine-HCl (Merck, Darmstadt); disprocynium24 (1,1-diisopropyl-2,4-cyanine iodide) was synthesized as described elsewhere (17).

RESULTS

Test for Stable Transfection of 293OCT2 Cells—Success of stable transfection was tested by RT-PCR. 8 weeks after transfection with pcDNA3OCT2r, total RNA was prepared from the Genetic-resistant clonal 293OCT2r cells and, for control purposes, from wild-type 293 cells. With RNA from 293OCT2r, RT-PCR with primers for OCT2r resulted in the amplification of the expected 795-base pair long PCR product. With RNA from 293WT cells, there was no amplification product. Stable transfection was also confirmed by functional testing. Upon incubation with 100 μmol/liter, initial rates of uptake of the prototypical organic cation (“H-MPP” in 293OCT2r cells and 293p<sub>kdNA3</sub> control cells amounted to 1.9 and 0.09 pmol min<sup>−1</sup> mg<sup>−1</sup> of protein<sup>−1</sup>, respectively (n = 2).

Uptake of Monoamine Transmitters in 293OCT2 Cells—Specific uptake of tritiated adrenaline, 5-hydroxytryptamine (5-HT), noradrenaline, and dopamine were analyzed in 293OCT2r cells and, for control purposes, in 293p<sub>kdNA3</sub> cells. After preincubation of 30 min in buffer A, the cells were incubated for 6 min at 37 °C in the presence of one of the labeled amines. Intracellular metabolism of the respective amine was blocked (for details, see “Experimental Procedures”). Specific uptake was defined as that fraction of total uptake which was sensitive to 1 μmol/liter decynium22. Decynium22 is a potent inhibitor of OCT2, the Ki being 5.6 mmol/liter (4). The expressed transport activity for a given substrate reflects the transport activity induced by the expression of OCT2r, i.e. transport activity in 293OCT2r cells minus uptake into 293p<sub>kdNA3</sub> control cells. The expression of OCT2r induced specific uptake of all tested monoamine transmitters (Fig. 1). The transport efficiencies ranged from 3.4 ± 0.3 μl/(mg of protein·min) for adrenaline to 1.0 ± 0.2 μl/(mg of protein·min) for dopamine.

Transport of dopamine by 293OCT2 cells was analyzed in more detail. For this purpose, 293OCT2r cells and 293p<sub>kdNA3</sub> cells were incubated with 100 μmol/liter [3H]-dopamine either in the absence or in the presence of 1 μmol/liter decynium22. [3H]-dopamine accumulation increased almost linearly for about 10 min (Fig. 2). The rate constants for total inwardly and outwardly directed [3H]-dopamine flux for 293OCT2r cells were 4.4 ± 0.5 μl/min<sup>−1</sup> (n = 15) and 0.05 ± 0.01 min<sup>−1</sup> (n = 15), respectively. In other words, an amount of 293OCT2r cells that corresponds to 1 mg of cell protein clears 4.4 μl of incubation medium of [3H]-dopamine/min, and simultaneously 5% of intracellular [3H]-dopamine leaves the cells per minute. At equi-
librium, the intracellular accumulation of $^3$H-dopamine amounted to $8.9 \pm 1.3$ pmol/mg of protein $^{-1}$ ($n = 15$) in 293_{OCT2} cells. Based on the known water space of 293 cells (18), this accumulation translates into a factor of intracellular accumulation at equilibrium of 13.

Initial rates of specific $^3$H-dopamine transport in 293_{OCT2} cells were saturable. The half-saturating concentration was 2.1 (0.7, 5.9) mmol/liter, and the maximal initial rate of $^3$H-dopamine uptake amounted to $3.9 \pm 0.8$ nmol/min $^{-1}$ mg of protein $^{-1}$ ($n = 15$). The corresponding Scatchard plot is compatible with simple Michaelis-Menten kinetics (Fig. 3 and Table I). For comparison, the corresponding kinetic constants for specific $^3$H-noradrenaline, $^3$H-adrenaline, and $^3$H-5-hydroxytryptamine uptake in 293_{OCT2} cells were determined (Table I).

The effects of known inhibitors of neuronal, vesicular, and extraneuronal monoamine transport systems were determined to distinguish dopamine transport via OCT2r from known monoamine transport systems. After preincubation of 20 min, 293_{OCT2} cells and 293_{pcDNA3} cells were incubated for 6 min at $37^\circ$C with 100 nmol/liter $^3$H-dopamine in the absence and presence of cocaine (1 mmol/liter), reserpine (30 nmol/liter), and O-methylisoprenaline (30 mmol/liter). The inhibitors were present during both the preincubation and incubation periods but failed to interact significantly with OCT2r (Fig. 4).

The inhibitory potencies of two known inhibitors of OCT2, disprocynium24 and corticosterone, were measured (Table I and Fig. 5). Because nonsaturating concentrations of the labeled substrates (0.1 mmol/liter) were used, the IC$_{50}$ values are identical with the corresponding $K_i$ values. Disprocynium24 and corticosterone inhibited monoamine transport by OCT2r with $K_i$ values of about 10 and 500 nmol/liter, respectively.

In Situ Hybridization—Cryostat sections of adult rat kidney were hybridized with digoxigenin-labeled antisense RNA probes transcribed from a 1.63-base pair fragment of OCT2r. OCT2r transcripts were detected in tubule cells of the outer stripe of the medulla as well as in deep portions of the medullary rays (Fig. 6). This pattern indicates exclusive OCT2 mRNA expression in proximal tubule cells of the S3 segment. Proximal tubules of the S1 and S2 segment as well as other structures in renal cortex and medulla such as glomeruli, distal tubules, collecting ducts, and blood vessels were unreactive for the hybridization probe (Fig. 6). On alternate sections, the corresponding sense probe did not produce any detectable signal (not shown).

**TABLE I**

| Substrate               | $K_m$ (mmol/liter) | $V_{max}$ (nmol min$^{-1}$ mg$^{-1}$) | $K_i$ (nmol/liter) |
|-------------------------|------------------|---------------------------------|------------------|
| Dopamine                | 2.1 (0.7, 5.9)   | $3.9 \pm 0.8$                  | 5.1 (2.6, 9.9)   |
| (-)Noradrenaline        | 4.4 (1.2, 16)    | $1.0 \pm 0.3$                  | 13 (7, 23)       |
| (-)Adrenaline           | 1.9 (0.93, 3.7)  | $0.59 \pm 0.06$                | 12 (10, 14)      |
| 5-Hydroxytryptamine     | 3.6 (0.42, 3.1)  | $2.5 \pm 1.3$                  | 13 (7, 28)       |

$K_m$ values ($n = 12$) and $K_i$ values ($n = 5$) are given as geometric means with 95% confidence interval. $V_{max}$ values are given as means $\pm$ S.E. ($n = 12$).
DISCUSSION

The primary structure of a new renal transport system for organic cations (OCT2p) has recently been elucidated by molecular cloning from LLC-PK1 porcine kidney cells (5). OCT2p and OCT2r, the orthologue from rat kidney which has first been reported by Okuda et al. (6), upon heterologous expression in 293 cells, induce saturable transport of prototypical organic cations such as tetraethylammonium and 1-methyl-4-phenylpyridinium (MPP\(^+\)). The pharmacological properties clearly demonstrate that OCT2p is identical with the transport system for organic cations that is expressed in the apical but not the basolateral plasma membrane of LLC-PK1 cells (4, 5). LLC-PK1

FIG. 6. Localization by in situ hybridization of the OCT2r mRNA in the adult rat kidney. A, intense labeling occurs in proximal tubular profiles located in the outer stripe of the outer medulla and in deeper portions of the medullary rays. The distribution is compatible with the topographical arrangement of the S3 segment of the proximal tubule. B, OCT2r mRNA is expressed in proximal tubular cells of the S3 segment of the deeper part of a medullary ray but not in proximal tubule cells of the S1 and S2 segments located on the right side. G, glomerulus. C, OCT2r is transcribed in proximal tubules of the outer stripe but not in thick ascending limbs or collecting ducts (examples are indicated by stars). The scale bars in the lower right edges represent 400 (A), 65 (B), and 16 μm (C).
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cells, a widely used established cell line from porcine kidney
(19), display many properties characteristic of proximal tubu-
lar epithelial cells (20).

Two recently reported findings open the possibility that
OCT2 might be involved in transmembrane transport of mono-
amines, especially dopamine. Although the pharmacological
properties of OCT2 are characteristic of apical renal transport
of organic cations, the tissue distribution indicates that the role
of OCT2 might go beyond renal secretion of organic cations.
RT-PCR reveals that the OCT2r mRNA exists not only in the
kidney but is also transcribed in specific brain regions that are
especially rich in the monoamine transmitter dopamine such as
the nucleus accumbens, striatum, and substantia nigra (5).
Moreover, OCT2 is sensitive to corticosterone as well as to the
iso- and pseudoaocyanines which represent a novel group of
potent inhibitors of extraneuronal monoamine transport (5).
It should, however, be noted that, despite the evidence of a close
relationship, OCT2 and the extraneuronal monoamine trans-
porter are not identical. It is possible to distinguish these
transport systems pharmacologically with O-methylisoprena-
line. O-methylisoprenaline inhibits OCT2 about 500 times less
potently than the extraneuronal monoamine transporter (5, 21).

The present study was designed to clarify whether OCT2
transports dopamine and other monoamine transmitters. To
exclude transport-kinetic artifacts known to occur with isolated
organs and to minimize the influence of other transport mech-
nisms that might contribute to monoamine transport, a cell
line was created on the basis of human embryonic kidney cells
(293 cells) that stably expresses OCT2r (293_OCT2 cells). The
success of transfection was documented by RT-PCR and func-
tional testing. For control purposes, 293 cells were also trans-
fected with the empty eukaryotic expression vector pcDNA3
(293pcDNS cells).

Stable transfection of 293 cells with OCT2r induced marked
transport of dopamine and other biogenic amines such as 5-HT,
noradrenaline, and adrenaline. Initial rates of dopamine trans-
port, mediated by OCT2r, were saturable and sensitive to
known inhibitors of the apical renal transport mechanism for
organic cations such as decynium24, disprocynium24, and
corticosterone (4, 5). Cocaine (1 µmol/liter), O-methylisoprenaline
(30 µmol/liter), and reserpine (30 nmol/liter), on the other
hand, failed to affect dopamine transport by OCT2r signifi-
cantly. Cocaine is a known inhibitor of the neuronal dopamine
transporter (DAT), the Kᵢ being about 0.1 µmol/liter (22). O-
Methylisoprenaline inhibits the extraneuronal monoamine
transporter with a Kᵢ of 1.5 µmol/liter (21) and reserpine the
vesicular monoamine transporters with a Kᵢ of 1 nmol/liter
(23).

These findings demonstrate that OCT2 has the capability of
transporting dopamine and other monoamine transmitters and,
hence, open the possibility of OCT2 being involved in
dopamine handling in both the kidney and the central nervous
system.

Recent evidence from in vivo experiments supports the hy-
thesis that OCT2 plays a role in renal dopamine handling. In
the anesthetized rabbit, intravenous treatment with disprocyn-
ium24 grossly reduces tubular secretion of dopamine (24). Renal proximal and distal tubule cells express the dopamine-
synthesizing enzyme L-aromatic amino acid decarboxylase (25),
and proximal tubule cells are known to form and secrete sub-
stantial amounts of dopamine (26). Several lines of evidence
support the concept that dopamine acts as an intrarenal natri-
uretic hormone, possibly through an indirect modulation of the
sodium/potassium-ATPase activity in tubular cells (27).

Disprocynium24 belongs to the new group of potent inhibi-
tors of OCT2 and the related extraneuronal monoamine trans-
porter (4, 17). It is, in fact, the most potent inhibitor of OCT2
reported so far. The Kᵢ for the inhibition of OCT2r has been
shown to be as low as 2.4 nmol/liter (5). This figure fits in with
the present results that reveal a Kᵢ of 5.1 nmol/liter of disprocynium24 for the inhibition of dopamine transport by OCT2T.

Interestingly enough, disprocynium24 does not only block tu-
bular secretion of dopamine but induces marked spill-over of
renal dopamine into the systemic circulation (24). This finding
is compatible with the concept that dopamine from proximal
tubule cells is normally secreted by OCT2 through the apical
membrane into the lumen of the tubule. When OCT2 is
blocked, intracellular dopamine rises and significant spill-over
into the peritubular fluid and, subsequently, systemic circula-
tion occurs. The localization of the OCT2r mRNA in the kidney
fits in with this concept. Our results indicate that high levels of
the OCT2r mRNA exists in proximal tubule cells of the S3
segment. Expression of OCT2h, a human homologue of OCT2r,
has been reported in the apical plasma membrane of distal
tubule cells. But there is also evidence for OCT2h to exist in
proximal tubule cells (7).

There is ample evidence that renal dopamine is involved in
the regulation of sodium excretion (27) and, surprisingly enough,
in the anaesthetized rat, disprocynium24 does not only block
dopamine excretion but acts as a high ceiling eucaillureic diuretic
and natriuretic (28). The exact mechanism of this new pharma-
cological effect of disprocynium24 has not yet been clarified.
An indirect activation of dopamine D1 and D2 receptors, however,
does not seem to be involved since pretreatment with the dopam-
iner receptor blockers SCH23390 and S(-)sulpiride fails to affect
the diuretic action of disprocynium24 (28).

The recently cloned apical renal transport systems for or-
ganic cations OCT2 exists in proximal tubule cells and in
dopamine-rich brain areas. For the first time, a cell line that
stably expresses OCT2 has been created (293_OCT2 cells) and
used to analyze the substrate specificity with special emphasis
on monoamine transmitters. The finding that OCT2 accepts
dopamine as a substrate opens the possibility that this trans-
porter is involved in dopaminergic signal transduction. To-
gether with recently published in vivo data, the findings at
hand suggest that OCT2 plays an important role in renal
dopamine handling and might be involved in the potent eu-
caillureic diuretic action of disprocynium24.

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