Evidence for the Role of Megalin in Renal Uptake of Transthyretin*

Mónica Mendes Sousa,a,b,c Anthony G. W. Norden,a Christian Jacobsen,c Thomas E. Willnow,f Erik Ilso Christensen,a Raj V. Thakker,h Pierre J. Verroust,i Søren K. Møestrup,c and Maria Joao Saraivaa,b,j

From the aAmyloid Unit, Instituto de Biologia Molecular e Celular and the bInstituto de Ciências Biomédicas Abel Salazar, University of Porto, Porto 4150, Portugal, the cDepartment of Clinical Biochemistry, Addenbrooke’s Hospital, Hills Road, Cambridge CB2 2QR, United Kingdom, the Departments of bMedical Biochemistry and aCell Biology, University of Aarhus, 8000 Aarhus C, Denmark, the Max-Delbrueck Center for Molecular Medicine, 13125 Berlin, Germany, the Molecular Endocrinology Group, Nuffield Department of Medicine, University of Oxford, Oxford OX3 9DU, United Kingdom, and the INSERM, U489, Hôpital Tenon, F-75020 Paris, France

The kidney is a major organ for uptake of the thyroid hormone thyroxine (T4) and its conversion to the active form, triiodothyronine. In the plasma, one of the T4 carriers is transthyretin (TTR). In the present study we observed that TTR, the transporter of both T4 and retinol-binding protein, binds to megalin, the multiligand receptor expressed on the luminal surface of various epithelia including the renal proximal tubules. In the kidney, megalin plays an important role in tubular uptake of macromolecules filtered through the glomerulus. To evaluate the importance of megalin for renal uptake of TTR, we performed binding/uptake assays using immobilized rat yolk sac cells with high expression levels of megalin. Radiolabeled TTR, free as well as in complex with thyroxine or retinol-binding protein, was rapidly taken up by the cells, and the uptake was strongly inhibited by a polyclonal megalin antibody and by the receptor-associated protein, a chaperone-like protein inhibiting ligand binding to megalin. In cell culture, different TTR mutations presented different levels of cell association and degradation, suggesting that the structure of TTR is important for megalin recognition. Both the apo form and the T4-bound form were taken up by the cells. Analysis of urine from patients with Dent’s disease, a renal tubular disorder that alters receptor-mediated endocytic reabsorption of proteins, identified TTR as an abundant excreted protein. Furthermore, analysis of kidney sections of megalin-deficient mice revealed no immunohistochemical TTR labeling in intracellular vesicles in the proximal tubule cells when compared with wild type control littermates. Taken together, the present data indicate that TTR represents a novel megalin ligand of importance in the thyroid hormone homeostasis.

Proximal tubules of the kidney serve an important function for the uptake of macromolecules passing the glomerular filtration barrier. Therefore, despite the massive influx of protein in the proximal tubules, human urine is virtually devoid of significant amounts of protein. By this way the proximal tubules salvage amino acids and essential protein-bound components such as lipids, hormones, and vitamins.

The receptor megalin plays an important role in the uptake mechanism. Megalin is a multiligand endocytic receptor expressed in clathrin-coated pits at the apical surface of a number of absorptive epithelia, including those of the proximal tubule (1) and yolk sac (2). Megalin is a member of the low density lipoprotein receptor family (3) and binds, as do the other members of this family, the ~40-kDa receptor-associated protein (RAP)1 (4), which functions as a specialized chaperone/escort protein during the biosynthesis of some of the members of the low density lipoprotein receptor family and in their delivery to the cell surface (5, 6).

Megalin ligands include vitamin carriers known to be filtered, such as transcobalamin (vitamin B12-binding protein) (7), vitamin D-binding protein (8), and retinol-binding protein (RBP) (9). The general importance of megalin was supported by the findings that knockout mice for the megalin gene result in high mortality, developmental abnormalities (10), and tubular reabsorption deficiency with excretion of low molecular weight plasma proteins in the urine (low molecular weight proteinuria) (11).

In the plasma, holo-RBP strongly interacts with transthyretin (TTR), and approximately 50% of TTR circulates as a 1:1 molar TTR-RBP complex (12). The formation of the TTR-RBP complex prevents to a certain extent the RBP-retinol complex from being filtered in the glomeruli. However, 4–5% of the circulating RBP-retinol is not bound to TTR (13) and is taken up by means of megalin in the proximal tubule (9). Apart from transporting retinol via binding to RBP, plasma TTR, a tetramer of four identical subunits of approximately 14 kDa (14), acts as a transport protein for the thyroid hormone thyroxine (T4). Most, if not all, of the active form of T4, triiodothyronine, is generated by deiodination of T4 mainly in the liver and in the proximal tubules of the kidney (15).

Despite no detection of TTR mRNA in the adult kidney (16), which is one of the major extrahepatic sites of TTR degradation (18), positive staining was reported in the epithelium of the

1 The abbreviations used are: RAP, receptor associated protein; RBP, retinol-binding protein; TTR, transthyretin; T4, thyroxine; PBS, phosphate-buffered saline; BN, Brown Norway; SPR, surface plasmon resonance.

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1 To whom correspondence should be addressed: Amyloid Unit, Instituto de Biologia Molecular e Celular, Rua do Campo Alegre 823, Porto 4150, Portugal. Tel.: 351-22-6074900; Fax: 351-22-6099157; E-mail: mjsaraiva@ibmc.up.pt.
renal proximal tubules (17). However, the mechanism of TTR internalization and degradation remains to be elucidated, although a receptor-mediated uptake has been suggested (19). Because megalin has been implicated in the renal reuptake of plasma proteins that carry lipophilic compounds, we investigated the possibility that this receptor might also play a role in renal uptake of TTR.

EXPERIMENTAL PROCEDURES

Proteins and Antibodies—Recombinant TTR was purified from Escherichia coli D1210 transformed with plasmids carrying either wild type TTR (pINTR30 or the suitable mutant, pINTR119) according to Almeida et al. (20). Serum RBP was isolated by affinity in a TTR column and saturated with a molar excess of all-trans retinol (Sigma) by incubation at 37 °C in the dark for 1 h; excess retinol was separated from RBP by gel filtration in 10–ml Biogel P–6 DG columns (Bio-Rad). Recombinant RAP was expressed and purified as described previously (21). Megalin was purified by RAP affinity chromatography from human kidney cortex according to standard procedures (22). Purified sheep polyclonal antibodies against rat megalin have been described, and their specificity has been characterized (7). Purified sheep non-immune IgG was used as a negative control in binding experiments.

Isolation of TTR and RAP were iodinated following the iodogen method. Briefly, to reaction tubes coated with 10 μg of iodogen (Sigma), 100 μl of 0.25 mM phosphate buffer and 1 μCi (37 MBq) of Na125I (Amersham Pharmacia Biotech) were added, followed by 10 μg of protein in phosphate-buffered saline (PBS). The reaction was allowed to proceed in an ice bath for 10 min. Labeled protein was separated from free iodide in a 5–ml Sephadex G50 column (Amersham Pharmacia Biotech). For TTR, specific activities were determined after each iodination by a quantitative enzyme-linked immunosorbent assay using polyclonal anti-human TTR (Dako) as the coating antibody and peroxidase-conjugated anti-human TTR (The Binding Site) as secondary antibody. 125I-labeled TTR (125I-TTR) concentration was calculated from a standard curve ranging from 5 to 200 ng/ml. Characteristic specific activities were of 105 cpm/ng. 125I-TTR and 125I-TTRp5 (20%). Serum RBP was isolated by affinity in a TTR column and saturated with a molar excess of all-trans retinol (Sigma) by incubation at 37 °C in the dark for 1 h; excess retinol was separated from RBP by gel filtration in 10–ml Biogel P–6 DG columns (Bio-Rad). Recombinant RAP was expressed and purified as described previously (21). Megalin was purified by RAP affinity chromatography from human kidney cortex according to standard procedures (22). Purified sheep polyclonal antibodies against rat megalin have been described, and their specificity has been characterized (7). Purified sheep non-immune IgG was used as a negative control in binding experiments.

Uptake of TTR in Cultured Yolk Sac Cells—Megalin-expressing Brown Norway Rat yolk sac epithelial cells transformed with mouse sarcoma virus (BN cells) (24) were grown to confluence in 24-well plates (Nunc/A) in Dulbecco’s modified Eagle’s medium containing 10% (v/v) fetal calf serum, 100 units/ml penicillin, and 100 μg/ml streptomycin. Before incubation cells were washed with ice-cold PBS. Incubation with 125I-TTR was carried out in serum-free Dulbecco’s modified Eagle’s medium supplemented with 0.1% (w/v) ovalbumin for the indicated period of time, either at 4 or 37 °C. In some experiments 125I-TTR was added in the presence of RAP (1 μM), IgG antibody against megalin (200 μg/ml), IgG antibody against cubulin (200 μg/ml), or sheep non-immune IgG (200 μg/ml). Degradation of labeled protein was measured by precipitation of the incubation medium in 10% trichloroacetic acid. In all experiments, a control was included in which the amount of degradation was assessed in the absence of cells. Cell-associated radioactivity was determined by measuring radioactivity of the washed cell layer in ice-cold PBS followed by cell solubilization in 0.1 M NaOH. Total cellular protein was measured with the Bio-Rad protein assay kit (Bio-Rad), using bovine serum albumin as a standard. Cell association of 125I-TTR measured at a saturating concentration of unlabeled ligand (1 mg/ml) was considered nonspecific and subtracted from all values.

Ligand and Immuno blotting of BN Cells—Ligand and immunoblotting were performed essentially as described (7). Briefly, BN cells were exposed to SDS-polyacrylamide gel electrophoresis (4–16%) and electroblotted onto Immobilon membranes (Millipore). Membrane strips were incubated with immobilized RAP (10 μg/ml) in 10 mM Hepes, 140 mM NaCl, 2 mM CaCl2, 1 mM MgCl2, and 1% bovine serum albumin (pH 7.8). Similar strips for immunoblotting were blocked in 2% nonfat dry milk and 0.05% Tween 20 in the Hepes buffer and subsequently incubated with antibody in the Hepes buffer with 0.2% nonfat dry milk. Sheep anti-rat megalin antibody was used at a dilution of 1:10,000.

Surface Plasmon Resonance (SPR) Analysis—Receptor-ligand inter-

actions were assessed by SPR analysis on a BIACore 2000 instrument (Biacore) as described (25). Megalin was immobilized onto a CM5 sensor chip, using the amine-coupling kit as described by the supplier, at indicated densities. A control channel was routinely activated and blocked in the absence of protein. Binding to coated channels was measured for binding to noncoated channels. SPR analysis was assessed in 150 mM NaCl, 2 mM CaCl2, 0.005% (v/v) Tween 20, and 20 mM Hepes (pH 7.4) at 20 °C.

Preparation of Renal Tissue—Megalin-deficient mice were produced by gene targeting as described (11). Wild type littermates were used as controls. Mouse megalin knockout and control kidneys were fixed by perfusion through the heart with 4% paraformaldehyde in 0.1 M sodium cacodylate buffer. The tissue was trimmed into small blocks, further fixed by immersion for 1 h in 1% paraformaldehyde, infiltrated with 2.3 M sucrose containing 2% paraformaldehyde for 30 min, and frozen in liquid nitrogen.

Immunohistochemistry—For light microscopy, 0.8-μm cryosections were obtained at −80 °C with an FCS Reichert Ultracut cryoultramicrotome as described previously (1). For immunolabeling, the sections were incubated with rabbit anti-rat TTR primary antibody (26), diluted 1:200, at room temperature for 1 h after preincubation in PBS containing 0.05 mM glycine and 1% bovine serum albumin. The sections were subsequently incubated with peroxidase-conjugated secondary antibodies (Dako), and the peroxidase was visualized with diaminobenzidine. As control, sections were incubated with secondary antibodies alone or with nonspecific rabbit IgG. The sections were subsequently counterstained with Meiер’s stain for 2 min and examined in a Leica DMR microscope equipped with a Sony 3CCD color video camera attached to a Sony Digital still recorder. Images were processed using Adobe Photoshop 4.0.

Urine Samples—Overnight urine samples from six patients with Fanconi syndrome, four of whom had Dent’s disease (27) due to mutations of the renal chloride channel (28), and from three healthy control subjects were refrigerated immediately after collection and stored at −80 °C until processed for immunoblotting.

SDS-Polyacrylamide Gel Electrophoresis of Urine Samples—10-μl urine samples were electrophoresed in 8–16% SDS-polyacrylamide gel electrophoresis gels and subsequently transferred to nitrocellulose. Blots were blocked in 5% milk in PBS containing 0.1% Tween 20 for 1 h and incubated for 1 h at room temperature with anti-human TTR (Dako) in PBS containing 0.1% Tween 20. After washing in PBS containing 0.1% Tween 20, blots were incubated for 1 h with alkaline phosphatase-conjugated anti-rabbit IgG (Dako). Antibody binding was visualized using nitro blue tetrazolium and 5-bromo-1-chloro-3-indolyl phosphate color development substrates (Promega).

RESULTS

To investigate the hypothesis that megalin might be responsible for the tubular uptake of TTR, by internalizing TTR, we analyzed TTR binding/uptake using an established immortalized rat yolk sac epithelial cell line with high expression of megalin (24). 125I-TTR bound efficiently and in a saturable manner to the cells at 4 °C (Fig. 1a), consistent with the existence of a TTR receptor. The apparent Kd for the 4 °C is 3 μM and the 4 °C binding to the cells was estimated to be approximately 500 nM when assuming one class of binding sites (Fig. 1b). 125I-TTR was rapidly taken up, and in accordance with an endocytic process, radiolabeled degradation products appeared in the medium after a lag time of approximately 30 min (Fig. 1c). Saturating concentrations of polyclonal antibodies against megalin showed a 63% inhibition in uptake, whereas no significant effect was seen with anti-cubulin antibody nor with non-immune IgG (Fig. 2a). Cubulin, an apical receptor expressed in the same tissues as megalin (29), is another apical receptor present in the BN cell line. The absence of significant inhibition of TTR uptake by the anti-cubulin antibody rules out the possibility of a nonspecific sterol effect produced by the anti-megalin antibody that could be responsible for the observed inhibition of TTR uptake. Therefore, the BN cell line presents specific megalin-mediated TTR degradation.

A strong inhibition in uptake was also observed with RAP (67%) (Fig. 2a). These data further suggest that the mechanism of TTR uptake presents features of a low density lipoprotein.

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receptor-mediated mechanism, namely, RAP sensitivity. BN cells were analyzed under non-reducing conditions by anti-megalin immunoblotting and ligand blotting with radiolabeled RAP (Fig. 2). The only RAP-binding protein observed was megalin, thus showing that in the BN cells, megalin is the prime RAP-binding receptor. Although these cells express cubilin, which has modest affinity for RAP, the involvement of this receptor in TTR internalization had been ruled out by competition experiments using the anti-cubilin antibody as described above.

SPR (data not shown) confirmed binding of purified TTR to immobilized megalin with an approximate $K_d$ of 5 μM at 20 °C, comparable with the low affinity of the interaction of RBP and megalin (9). The influence of T4 on TTR binding to megalin could not be assessed by SPR due to the well known hydrophobicity of the hormone, resulting in nonspecific binding to the SPR sensor chip.

The influence of TTR ligands on the interaction of the protein with megalin was further studied by uptake experiments of receptor-mediated mechanism, namely, RAP sensitivity. BN cells were analyzed under non-reducing conditions by anti-megalin immunoblotting and ligand blotting with radiolabeled RAP (Fig. 2). The only RAP-binding protein observed was megalin, thus showing that in the BN cells, megalin is the prime RAP-binding receptor. Although these cells express cubilin, which has modest affinity for RAP, the involvement of this receptor in TTR internalization had been ruled out by competition experiments using the anti-cubilin antibody as described above.

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The present study reveals that megalin is a receptor for tubular uptake of TTR in vivo. Megalin interaction with TTR was demonstrated in vitro by SPR analysis and by uptake studies of $^{125}$I-TTR in cells with high expression levels of megalin. Although the affinity of TTR for this receptor is relatively low, it is the same order of magnitude previously reported for other megalin ligands (11). Further evidence pointing to the in vivo relevance of this interaction came from the observations that patients with renal tubule failure excrete TTR in the urine and also that megalin knockout mice do not present lysosomal accumulation of TTR in renal tubules when compared with control wild type littermates. Because TTR is a carrier of T4 and retinol (in the latter case by the formation of a complex with RBP), it is possible that the presented mechanism is of potential importance in the transepithelial transport of retinol or thyroxine or both. Because RBP is also a megalin ligand (9), TTR might be more important for the renal uptake of T4.

Thyroid hormones are synthesized in the thyroid gland and are important in regulating basal metabolism and in controlling cellular growth and differentiation (33). T4 represents the form in the plasma. Triiodothyronine, the biologically active form of the hormone, derives mostly from T4 deiodination in the peripheral tissues including the kidney (15). Once secreted, more than 99% of the thyroid hormones in circulation are

![Graph](http://www.fbc.org)
bound to plasma proteins. In human plasma, TTR is one of the three proteins responsible for the transport of T₄, the main carrier being thyroxine-binding globulin; albumin is the third T₄-binding protein and the one that presents the lowest affinity for the hormone (14). In rodent serum, TTR is the major carrier of T₄. Interestingly, albumin is known to be taken up in the proximal tubules (39), pterins (40), chicken lu-

FIG. 5. Light microscope immunohistochemical labeling for TTR visualized by horseradish peroxidase in proximal tubules from control mice (a) and megalin-deficient mice (b). Labeling is seen as granular staining (arrows). The megalin-deficient mouse proximal tubules (b) are unlabeled. Magnification, × 1,050.

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