Distribution of Rat Organic Anion Transporting Polypeptide-E (oatp-E) in the Rat Eye

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PURPOSE. To examine the protein and mRNA expression levels of the recently cloned rat multifunctional Na+-independent organic anion transporting polypeptide (rat oatp-E), which is involved in the transport of thyroid hormone in the rat, the distribution and function of this transporter were investigated in the retina.

METHODS. Real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) was performed with gene-specific primers for oatp-E in rat ocular tissues. Western blot analysis was performed by raising a specific antibody against oatp-E in rat ocular tissues. Immunohistochemistry was performed with a specific antibody for oatp-E in paraffin sections of rat eyes. The expression of oatp-E in isolated and cultured rat retinal pigment epithelial (RPE) cells was confirmed by RT-PCR, Western blot analysis, and immunohistochemistry. In addition, oatp-E function was analyzed in cultured rat RPE cells by measuring the uptake of triiodothyronine (T3), which is a known substrate for oatp-E.

RESULTS. Using real-time quantitative RT-PCR, oatp-E mRNA was detected, in order of highest to lowest concentration, in the rat retina, cornea, and ciliary body-iris. A single band for oatp-E was observed by Western blot analysis in the rat brain retina, cornea, and ciliary body-iris. oatp-E immunostaining was predominantly expressed in the corneal epithelium, in the pigmented and nonpigmented epithelium of the ciliary body, and in the iris of the rat eye. In the rat retina, intense immunostaining was detected in the RPE, inner and outer nuclear layers, ganglion cell layer, and nerve fiber layer. In addition, oatp-E immunoreactivity in cultured rat RPE cells was expressed in the cell membrane and cytoplasm of RPE cells, a finding that was also confirmed by RT-PCR and Western blot analysis. RPE cells, which were shown to express high levels of oatp-E, transported T3 in a saturable and dose-dependent manner. Moreover, this uptake was significantly inhibited by sulfobromophthalein (BSP), an inhibitor of oatp, suggesting that oatp-E may in part contribute to this uptake.

CONCLUSIONS. Results from the present study revealed that oatp-E is localized mainly to the corneal epithelium, ciliary body, iris, and retina. Furthermore, the findings appear to suggest that transport of T3 in the RPE may have a functional role for organic anion (i.e., thyroid hormone) transport in the rat eye. (Invest Ophthal Vis Sci. 2003;44:4877–4884) DOI: 10.1167/iovs.02-1108

The organic anion transporter polypeptide (oatp) family plays important roles in the elimination of a variety of endogenous and exogenous substances from the body. This family of transporter peptides consists of membrane proteins with 12 putative membrane-spanning domains that function as sodium-independent exchangers or facilitators. Within the past decade, several members of multispecific oatps that mediate the elimination of organic anions in the liver and other organs have been identified.1–7 Recently, we have isolated two Na+-independent oatps, termed oatp22,3 and oatp3,2 that transport thyroid hormones from the rat retina. The tissue distribution patterns show that oatp2 and oatp3 are widely expressed.8 Thyroid hormone plays a key role in the neural function of the mammalian central nervous system, particularly during critical periods of its development.9,10 In the eye, the absence of thyroid hormone causes serious damage to the structural development and organization of the retina.11 However, in humans the molecular organization of organic anion transporters has diverged, and thus the responsible molecule for thyroid hormone transport in the human eye has not been clarified.

Recently, we isolated and characterized a novel human organic anion transporter, OATP-E from the human brain.12 The isolated cDNA encodes a polypeptide of 722 amino acids with 12 transmembrane domains. A rat counterpart, oatp-E, was also isolated from the rat retina. The overall amino acid sequence homology between rat oatp-E and human OATP-E was found to be 72.6%, where the transmembrane domain and the surrounding area are highly conserved. Human OATP-E transports thyroxine (T4), triiodothyronine (T3), and reverse T3 (rT3) in a Na+-independent manner.12 Although OATP-E was isolated from the human brain, OATP-E mRNA has also been shown to be abundantly expressed in various peripheral tissues, such as the heart, placenta, liver, skeletal muscle, kidney, pancreas, brain, spleen, thymus, prostate, testis, and small intestine. The rat counterpart, oatp-E also transports T3. However, little is known about the existence or cellular localization of oatp-E/OATP-E in the eye. In this study, we examined the...
expression and function of oatp-E in the rat eye and discuss its role in this specialized tissue.

**MATERIALS AND METHODS**

**Animal Procedures**

All experiments were performed on 8-week-old male Sprague-Dawley rats (Charles River Japan Inc., Yokohama, Japan), weighing 200 to 250 g. All animals were kept under conditions of constant temperature and humidity in a 12-hour light-dark cycle in the animal house. Rats were killed with a lethal dose of pentobarbital sodium. All animal procedures were performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

**Cell Culture**

RPE cells were isolated, with slight modification, as described by Wang et al. and cultured in 75 cm² flasks with Dulbecco’s modified Eagle’s medium (DMEM)/nutrient mixture F12 (1:1) with HEPES containing 10% fetal bovine serum (Sigma-Aldrich, St. Louis, MO), 0.348% sodium bicarbonate, 1% (by volume) 200 nM glutatione, 0.1 mg/mL streptomycin, and 100 U/mL penicillin. The culture medium was replaced with fresh medium every other day, and cells were allowed to grow until they reached approximately 80% confluence. Subconfluent cultures were passed by dissociation in 0.05% trypsin and 0.02% EDTA in calcium-magnesium-free phosphate-buffered saline (PBS).

**Isolation of RNA from Rat Ocular Tissues and RPE Cells**

Animals were killed as described, and five eyes from three rats were immediately enucleated and prepared as previously reported. The cornea, ciliary body together with the iris, and the major part of the retina and RPE were homogenized. Total RNA was isolated from homogenized tissues using extraction reagent (TRizol; Invitrogen-Gibco, Gaithersburg, MD). Total RNA (5 μg) was prepared from the cornea, ciliary body-iris, retina, and RPE cells.

**cDNA Synthesis, PCR, and Real-Time Quantitative RT-PCR**

Reverse transcription (RT) was performed with a kit (Superscript RT; Amersham-Pharmacia, Piscataway, NJ) used according to the manufacturer’s instructions. cDNA was synthesized from 5 μg total RNA extracted from the cornea, ciliary body-iris, retina, and RPE cells. Polymerase chain reaction (PCR) was set up in a reaction volume of 25 μL, in which a 1:40 volume (0.5 μL) of synthesized cDNA was included. Each reaction contained master mix (Universal Master Mix; Perkin Elmer, Boston, MA), 900 nM forward primer, 900 nM reverse primer, and 200 nM TaqMan (Applied Biosystems, Foster City, CA) probe.

Primers for rat oatp-E were designed according to the sequence of rat oatp-E (1898-1908) expressed in the rat eye. The primers used for RT-PCR are listed in Table 1. DNA amplifications were performed in a 96-well reaction plate format in an automated sequence-detection system (GeneAmp 5700; Applied Biosystems). Each sample was analyzed in triplicate. Endogenous control rat GAPDH (Applied Biosystems) was used to normalize for mRNA quantity. Thermal cycling was initiated with a 2-minute incubation at 50°C, followed by an initial denaturation step for 10 minutes at 95°C and then 40 cycles at 95°C for 15 seconds and 60°C for 1 minute.

To compare the relative abundance of oatp-E mRNA, standard curves for both oatp-E and GAPDH were generated from cDNAs synthesized from 10-fold dilutions of cRNA (5, 0.5, and 0.05 pg, and 5, 0.5, and 0.05 fg), as described previously. For each rat ocular sample, the concentrations of oatp-E and GAPDH were determined from those standard curves. The resultant oatp-E concentration was divided by the concentration for GAPDH to obtain a normalized value. Normalized oatp-E values (oatp-E/GAPDH ratio) were subsequently divided by the normalized retinal oatp-E value to generate the relative expression levels of oatp-E mRNA.

Gene specific primers for oatp-E used in RT-PCR are listed in Table 2. Each sample was analyzed in triplicate. Endogenous control rat GAPDH sequence was used for the cDNA synthesis, PCR, and Real-Time Quantitative RT-PCR procedure as a negative control.

**Preparation of Rabbit Antibodies**

A 14-amino acid peptide (DGLESALPSQSSA) corresponding to position 697-711 of the carboxyl terminus of rat oatp-E was synthesized. The oatp-E peptide was linked to a maleimide-activated key hole limpet hemocyanin (KHL; Pierce Inc., Rockford, IL). The KHL-linked peptide (1 mg/3 mg) was emulsified by mixing with an equal volume of Freund’s complete adjuvant and injected into female rabbits. Booster injections were performed every 2 weeks, and the animals were killed at 10 weeks. The antibodies were affinity purified using CNBr-activated Sepharose CL-4B (Amersham Pharmacia Biotech, Piscataway, NJ) coupled with synthetic peptides according to standard procedures.

**Western Blot Analysis**

Six rat eyes of three rats were enucleated and prepared as previously described. The cornea, ciliary body together with the iris, and the retina and RPE cells were homogenized in a buffer containing 0.23 M sucrose, 2 mM EDTA, 5 mM Tris-HCl (pH 7.5), 0.1 mM phenylmethylsulfonyl fluoride, 2 μg/mL aprotinin, 2 μg/mL leupeptin, and 2 μg/mL pepstatin A. The homogenate was centrifuged at 1000g for 15 minutes and 7500g for 15 minutes. The supernatant was further centrifuged at 100,000g for 1 hour.

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**Table 1. Primer Sets for Real-Time Quantitative RT-PCR**

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<th>Sequence (5'-3')</th>
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<td>Antisense primer</td>
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**Table 2. Primer Sets for RT-PCR**

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crude membrane fraction, was resuspended in a buffer of 0.23 M NaCl [pH 7.5], containing 0.1% Tween 20 at 4°C overnight and incubated with oatp-E/OATP-E antibody (2 μg/mL) for 1 hour at room temperature. The blots were then washed and incubated with anti-rabbit IgG conjugated with horseradish peroxidase (1:5000 dilution; Amersham Pharmacia Biotech) at room temperature for 1 hour. An enhanced chemiluminescence kit was used for detection (Amersham Pharmacia Biotech). To confirm antibody specificity, the antibody was incubated with 10 μg of the antigen peptide before use. Rat brain served as a positive control.

Immunohistochemistry

We prepared six eyes from three rats, and performed three replications. The systemic circulation was perfused through an intra-aortic administration of 4% periodate-lysine-4% paraformaldehyde in PBS. The whole eye was removed and immersed in the same fixation buffer followed by dehydration. The eyes were embedded in paraffin wax, and then thin sectioned at 3 μm. After incubation in PBS containing 1% bovine serum albumin and 0.05% Triton X-100, sections were incubated with primary antibody preabsorbed with 10 μg/mL antigen peptide overnight before use. Immunofluorescence was performed as described earlier. Stained RPE cells were analyzed by confocal laser microscopy (MRC 600; Bio-Rad).

Uptake Measurements in Cultured RPE Cells

For uptake experiments, RPE cells were seeded at a density of 0.5 × 10⁶ cells/well in 24-well culture plates and cultured in the presence of 1 mL/well culture medium. The medium was replaced every other day. Cultures were used for uptake measurements 3 days after seeding. Uptake of [¹²⁵I]T₃ (NEN Life Science Products, Boston, MA) into RPE cells was measured at room temperature for 15 minutes. The uptake buffer was composed of 142 mM NaCl, 4.83 mM KCl, 25.8 mM NaHCO₃, 0.96 mM KH₂PO₄, 1.2 mM MgSO₄·7H₂O, 1.53 mM CaCl₂, 5 mM glucose, and 12.6 mM HEPES (pH 7.5). To assess for experimental inhibition, the uptake buffer contained 0.1 μM T₃ and 100 μM sulfobromophthalein (BSP). After incubation, transport was terminated by aspiration of the uptake buffer followed by three washes with 2 mL ice-cold uptake buffer. The cells were then solubilized with 0.5 N NaOH and transferred to vials for quantification of the radioactivity associated with the cells. All experiments were repeated at least three times, with each experiment performed in triplicate.

RESULTS

Real-Time Quantitative RT-PCR

Quantitative estimates of the relative abundance of oatp-E mRNA were obtained using real-time RT-PCR. mRNA levels for rat oatp-E were evaluated by real-time quantitative RT-PCR. oatp-E was expressed, in order of highest mRNA concentration, in the rat retina, cornea, and ciliary body-iris (Fig. 1). The rat retina expressed significantly higher levels of oatp-E mRNA—more than two times that of the cornea and five times that of the ciliary body-iris. Data are expressed as the mean ± SE (n = 3). Statistical significance was determined by an unpaired t-test (P < 0.05).

Western Blot Analysis

To analyze the expression of oatp-E at the protein level, we performed Western blot analysis. As shown in Figure 2, anti-oatp-E antibody recognized an apparent band in the rat retina and brain (68 kDa) and a faint band in the cornea and ciliary body/iris (68 kDa). These bands completely disappeared when the antibody was preabsorbed with the antigen peptide (data not shown), indicating the specificity of the detected band.
**Immunohistochemistry**

In the rat retina, oatp-E immunostaining was found to be widely expressed (Figs. 3A, 3B). In addition to the apparent immunostaining for oatp-E observed in the RPE (arrowhead), intense immunostaining for this peptide was also localized in the outer and inner plexiform layers and nerve fiber layer. In addition, oatp-E immunostaining was observed in the cytoplasm of ganglion cells (arrow) and the inner aspect of the inner nuclear layer. Moreover, oatp-E immunostaining was observed in the optic nerve, which was sectioned longitudinally, staining was seen in the glial cell processes (D, E, arrowhead) and nerve fibers. Apparent immunostaining was observed in the basal cells of the corneal epithelium (G, H, arrowhead) and corneal limbus (arrow), and faint staining was seen in the corneal endothelium (J, K, arrowhead). Immunostaining for oatp-E was detected in both the pigmented and nonpigmented epithelium of the iris (J, K, double arrows) and ciliary body (M, N, arrow). The muscular tissues of the ciliary body (M, N, arrowhead) and iris (J, K, arrowhead) were shown to be weakly immunopositive. (C, F, I, L, O) Negative control sections. For immunofluorescent chemistry, DAPI was counterstained to reveal the nucleus (blue).

**oatp-E Expression in Cultured RPE Cells**

Before characterizing the function of oatp-E in the eye, we confirmed the expression of oatp-E in rat RPE cells by RT-PCR.
In brief, RT-PCR was performed on total RNA isolated from rat RPE cells and rat retina (positive control). A gene-specific band for oatp-E, 635 bp in size, was identified in both of these tissues (Fig. 4A, top panel). When the RT-PCR products were subjected to Southern blot analysis and hybridized with an oatp-E-specific cDNA probe, gene-specific bands for oatp-E were detected in the retina and RPE cells (Fig. 4A, bottom panel). These data confirm that the RT-PCR product from rat RPE is indeed identical with oatp-E.

Western blot analysis revealed oatp-E expression at the protein level. oatp-E-specific bands (68 kDa) were detected in the rat retina and isolated RPE cells (Fig. 4B). However, a faint band was seen in rat liver. These bands completely disappeared when the antibody was preabsorbed with the antigen peptide (data not shown), indicating the specificity of the detected band.

To confirm the expression and membrane topology of oatp-E in RPE cells further, immunohistochemical analysis was performed. oatp-E was localized mainly to the plasma membrane and perinuclear portion of the cells (Fig. 4C). Because oatp-E-specific antibody recognizes the C terminus of oatp-E, only cells permeabilized by detergent were stained. No staining was seen without membrane permeabilization, which may explain the membrane’s topology (Fig. 4D). Precollection of the antibody with excess immunogen peptide resulted in the complete abolition of immunostaining for oatp-E (Fig. 4E).

**Uptake of [125I] T3 in Cultured RPE Cells**

T₃ uptake by OATP-E and oatp-E was determined by using a Xenopus oocyte expression system.⁶ Because of the consistency of expression of oatp-E, we next examined T₃ uptake by RPE cells. T₃ uptake in RPE cells was dose dependent and saturable, according to saturation kinetics. The apparent Kₘ for thyroid hormone uptake varies from the nanomolar level in mouse neuroblastoma cells⁹ to the micromolar level in rat glia cells.⁸ In this study, results from quantitative RT-PCR demonstrated the expression of high levels of oatp-E mRNA in the rat retina rather than in the cornea and ciliary body-iris. Because thyroid hormones play an essential role in the neural function of the mammalian central nervous system,⁹–¹¹ it is not surprising to find oatp-E mRNA expressed most abundantly in the rat retina.

To date, there have been a few reports regarding thyroid hormone uptake in the central nervous system.¹⁹–²³ The reported Kₘ for thyroid hormone uptake varies from the nanomolar level in mouse neuroblastoma cells⁹ to the micromolar level in rat glia cells.⁸ The Kₘ for oatp-E obtained in this study was found to be within the same range of values as for cultured cerebrocortical neurons and rat glial cells.²⁰ The Kₘ for thyroid hormone uptake from rat RPE cells in this study was found to be similar to the rate for that of oatp-E-expressing Xenopus oocytes¹² and also significantly inhibited by BSP. These findings appear to suggest that thyroid hormone uptake may play a role in the transport of thyroid hormone into the retina.

By immunohistochemistry, we found oatp-E to be expressed at detectable levels throughout almost all retinal layers. Similar to oatp2,¹⁷ oatp-E immunostaining was also localized to...
the RPE. The RPE is also a unique source of transthyretin (TTR) synthesis. TTR is an important plasma transport protein for thyroid hormone. It is synthesized and secreted in the liver, the choroid plexus, and RPE. Intense immunostaining for TTR has been identified in the RPE, ciliary epithelium, iris epithelium, corneal endothelium, nerve fiber layer of the retina, and lens capsule. TTR protein has been suggested to be responsible for the transport of thyroid hormone in the eye. Based on the findings of TTR subcellular localization in cultured and native human retinal pigment epithelium, TTR labeling was observed in both mitochondrial and nuclear compartments and in close apposition to both apical and basal membranes, suggesting that TTR may function as a cytoplasmic carrier protein for thyroxine in the human RPE. The endothelium of the choriocapillaris was found to possess a system for binding and receptor-mediated transport of TTR. Thyroid hormone may be transported from the choriocapillaris to the RPE by oatp-E and/or an unknown carrier protein. It is assumed that interphotoreceptor retinoid-binding protein (IRBP) is the major protein present in the interphotoreceptor matrix (IPM) capable of shuttling visual-cycle retinoids between photoreceptors and the RPE. Adler et al. found that serum albumin may participate in visual cycle transport. Considering the conjugation of retinol binding protein to TTR in plasma, such a complex of proteins may be formed within RPE cells, which also incorporate thyroid hormones. It is possible that thyroid hormone may be transported from the RPE to the interphotoreceptor space of photoreceptor cells by oatp 2 and oatp-E cotransport, which may be involved in retinol cycling within the eye.

We also observed intense immunoreactivity in the outer plexiform layer, specifically within the synaptic interactions of photoreceptors, horizontal cells, and bipolar cells, and in the inner plexiform layers, which contain the cell processes and synaptic connections of retinal cells. Based on these observations, oatp-E may play an important role in transporting thyroid hormone in this specialized milieu. Thyroid hormone is essential for normal development of the vertebrate brain, influencing diverse processes such as neuronal migration, myelin formation, axonal maturation, and dendritic outgrowth. Even in the mature rat brain, increased RNA polymerase I activity stimulated by T3 in the neuronal nuclei has been detected. Thus, oatp-E similar to oatp 2 in the optic nerve may function as a means by which various organic anions are kept from reaching high concentrations in the optic nervous system and thyroid hormone-mediated aspects of ocular growth and development. In hypothyroid mice, the activity of both carbonic anhydrase and Na+/K(+)-ATPase was affected more in the myelin than in other subcellular fractions by deficiency of thyroid hormones. In addition, impairment of myelin compaction was demonstrated by experiments with 2′,3′-cyclic nucleotide 3′-phosphodiesterase immunohistochemistry in hypothyroid rats. Therefore, oatp-E may assume responsibility as an ordinary requirement of thyroid hormones to be restored in these ocular tissues. oatp-E immunostaining was also observed in the inner nuclear layer, which contains the nuclei of Müller cells, which are major retinal glia and the cellular component of optic nerves. Thyroid hormone has been reported to be transported into rat glial cells in primary culture through a saturable, stereospecific, and energy-independent carrier system. Our results also suggest that thyroid hormone is transported in the glial cells of the optic pathway by oatp-E.

In the cornea, oatp-E immunostaining was present in the epithelium. Moreover, the immunostaining was most prominent in the basal cells at the limbus. This structure, which is five to seven cells thick in the rat, is composed of three cell types: basal cells (innermost), which undergo mitosis to produce daughter cells that move toward the surface of the cornea; wing cells (middle), which are in an intermediate state of differentiation; and superficial cells (outermost), which are...
terminally differentiated and in the process of degenerating.
We found that immunoreactivity for oatp-E tended to be greater in the basal cells of the corneal epithelium than in the superficial cells. This pattern may be related to the fact that the basal cells are more metabolically active than superficial ones. It is well known that corneal stem cells exist among the basal cells at the limbus, which plays a major role in the regeneration of the corneal epithelium. Coulombre et al. have provided experimental proof of the role of thyroid hormone in corneal dehydration and transparency. Masterson and Edelhauser have reported that the development of both the endothelial and epithelial cell layers of the cornea is thyroxine dependent. The function of oatp-E in the cornea may relate to its ability to transport thyroid hormone into the cornea to maintain optical transparency. The corneal epithelium has been described as a “tight” ion-transporting cell layer that functions both as a protective barrier and as an accessory fluid-secreting layer that augments the endothelial regulation of stromal hydration. The most likely mechanism for the delivery mechanism of retinol to the cornea is by uptake, which has been shown to be time dependent and substrate saturable from the circulation and/or tears. Oatp-E may be involved in the transcellular movement of amphipathic compounds, including thyroid hormone and other organic anions.

In the ciliary body and iris, oatp-E was found to be abundant throughout both the pigmented and the nonpigmented epithelium. The oatp-E in these structures may be related to their roles in transporting thyroid hormone and other organic anions into the secretion of the aqueous humor. Moreover, the expression of oatp-E in these epithelia form the barrier between the blood, and the aqueous and vitreous chambers of the eye. The steady state concentrations of low-molecular-weight solutes in the aqueous reflect a dynamic equilibrium in which all substances continuously enter from the plasma or surrounding tissues and leave through the trabeculum and uveoscleral drainage. In addition, the specific concentrations of organic anion may be maintained by active secretion by the ciliary epithelium. The human trabecular meshwork tissue is known to have the capacity to respond to thyroid hormones.

In contrast, in humans, three organic anion transporters have been reported: liver-specific organic anion transporter LST-1 and LST-2 and human OATP. Compared with rat oatps, the expression of these isolated organic anion transporters is very much organ specific. LST-1 and -2 are exclusively expressed in the liver, whereas OATP is expressed in the brain. In addition, although LST-1 and -2, and OATP thyroid hormone concentrations into the brain and the liver, no molecules except OATP-E and mOATP, transporting thyroid hormone have been identified in other tissues. We have recently published work on the novel human organic anion transporter OATP-E, which transports thyroid hormone in various peripheral tissues. Our findings would also be helpful in understanding the delivery of thyroid hormone to ocular tissues in humans.

In conclusion, the expression of oatp-E in rat ocular tissues and its functional characterization suggest that oatp-E may have a role in facilitating the transport of thyroid hormones in the eye. Further study is necessary to characterize fully the distribution of oatp isoforms and to understand the intraocular cycling of thyroid hormone and other substances such as retinol. However, our findings may serve as a guide for the study of this unique transport system in the eye.

References


