Expert Opinion

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Transporters and receptors in ocular drug delivery: opportunities and challenges

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In this editorial, the opportunities and challenges of transporter/receptor mediated ocular drug delivery are discussed.

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1. Transporter/receptor-mediated ocular drug delivery

Membrane transporters/receptors are involved in drug transport processes and play a key role in intestinal absorption, tissue distribution and elimination. An increasing number of drugs are currently being targeted to transporters and receptors to aid in site-specific carrier-mediated absorption. Drug targeting to specific transporters and receptors using carrier-mediated absorption is emerging as a novel and clinically significant approach. Transport processes in the eye have been targeted in an effort to increase ocular bioavailability of drugs following topical instillation. This editorial discusses the role of various transporters/receptors in ocular drug delivery.

1.1 Introduction to ocular drug delivery

The eye is one of the most important sensory organs and maintains connection with the body through a series of vascular networks, nerve fibres and muscular attachment. Because the eye is an isolated and protected organ, tissues inside the eye are not easily accessible from outside. The access is seriously constrained by numerous protective defence mechanisms that protect the eye from exogenous substances.

Recent progress in molecular cloning of transporter genes and functional analysis by expressing those genes in cultured cells has greatly contributed to our mechanistic understanding of structure and function of membrane transporters. These transmembrane proteins were initially thought to be responsible for transferring exo- and endogenous nutrients across the cell membranes, thereby strictly regulating the exchange of these compounds between intracellular and extracellular spaces. However, it is now clear that some of the transporters are involved in drug transport across various mucosae, and may play a key role in intestinal absorption, tissue distribution and elimination.

The utility of carrier-mediated drug absorption via membrane transporters/receptors is particularly significant when the parent drug or the prodrug is polar or ionised, where passive transcellular absorption is negligible. Therefore, the use of prodrugs has been actively pursued in several laboratories including the authors' to achieve very precise and direct effects at the site of action. The principal membrane barriers of the eye are located in the cornea, iris-ciliary body, lens epithelium and retina.

1.2 Strategy for site-specific drug delivery

Carrier-mediated drug transport is relatively unexplored in comparison with passive transcellular and paracellular drug transport. Prodrugs have been used to achieve site-directed delivery for enhanced absorption and reduced toxicity. The following three factors should be optimised for site-specific drug delivery [1]:

Table 1. Classification of various transporter types.

Transporter type	Mechanism of action	Example
Influx pumps	Transport solute from one side of plasma membrane to other. Requires ATP-derived energy	Na^+/K^+-ATPase
Channels	Transport ions, small solutes by passive diffusion	Na^+, Cl^- channels
Symporters	Transports solute and co-transported solute at the same time and direction	Na^+-glucose and Na^+/I^- symporters
Uniporters	Transports one solute at a time	Glucose transporter
Antiporters	Transports a solute 'in' and another 'out' in opposite direction	Cl^-/HCO_3^- exchanger
Efflux pumps	Effluxes molecules out of the plasma membrane	P-glycoprotein/ multidrug resistance proteins

- The prodrug must be readily transported to the site of action and its uptake by the target cells site must be rapid and the perfusion rate limited.
- Once at the site, the prodrug must be selectively cleaved to the active drug.
- The active drug, once regenerated, must be sufficiently retained by the target tissue to cause complete regeneration of the active drug.

The prodrugs can either be targeted to the transporters or enzymes for site-specific drug delivery. Enzymes can be recognised as presystemic metabolic sites or prodrug–drug *in vivo* reconversion sites [2]. The enzyme-targeted prodrug approach can be used to improve the oral drug absorption as well as site-specific drug delivery. An improvement in oral drug absorption can be achieved by targeting the gastrointestinal enzymes and using a nutrient moiety as a derivatising group in order to permit a more specific targeting to gastrointestinal enzymes. Targeting of enzymes for improved oral absorption and site-specific drug delivery has been made easy by the extensive literature present on the gastrointestinal enzymes, which provide necessary information such as enzyme distribution, activity and specificity for prodrug design. Recently, new approaches such as antibody- and gene-directed enzyme prodrug therapy have been proposed, which attempt the localisation of prodrug activation enzymes into specific cancer cells prior to prodrug administration.

On the other hand, prodrugs can be designed to resemble the intestinal nutrients structurally and be absorbed by specific carrier proteins. Prodrug targeting towards transporter/receptor requires considerable knowledge of the carrier proteins, including their distribution and substrate specificity.

1.3 Transporters/receptors: important drug delivery targets

Transporters are important to the cell because they aid in the entry and exit of essential nutrients and ions. Transporters can also act as an efflux pump by expelling toxic compounds out of the cell. All transmembrane transport processes are mediated by integral membrane proteins, sometimes functioning in conjunction with other receptors or protein domains. Usually transporters are thought to be localised in a polarised manner in the epithelium or endothelium for the purpose of transport of solutes. Transporters can be classified as follows (**Table 1**):

- influx pumps
- channels
- symporters
- uniporters
- antiporters
- efflux pumps

Various transporters/receptors have been found in the eye. They include peptide transporters, amino acid transporters (LAT1/2), glucose transporters, nucleoside/nucleobase transporters, vitamin transporters and a large number of nutrient receptors. A summary of all transporters/receptors present in various tissues on the anterior segment has been presented in **Table 2**.

1.4 Drug efflux pumps in the eye

Nearly 200 proteins are involved in the efflux of substrates across biological membranes. These efflux pumps belong to an ATP-binding cassette (ABC) superfamily, also termed traffic ATPases. These efflux pumps consist of two major efflux transporters: (i) P-glycoprotein (P-gp) and (ii) multidrug resistance-associated proteins (MRPs).

P-gp, considered as a versatile xenobiotic pump, is a member of a highly conserved group of the energy-dependent ABC transporters found in cells from various tissues. Mammalian P-gps display ~ 60 – 65% homology with most P-gps from other species, suggesting that their role in drug trafficking is highly conserved throughout their evolution [3]. It is an integral membrane protein composed of two homologous halves, each consisting of an N-terminal hydrophobic domain, with six transmembrane segments, which is separated from a hydrophilic domain, containing a nucleoside binding fold, by a flexible linker polypeptide. This transporter is encoded by a small multigene family (mdr class I, II, and III). P-gp belonging to all three classes are present in rodents, whereas human cells express P-gp belonging to classes I and III. P-gp has been found in various

Table 2. Transporters and receptors in various ocular tissues.

Transporter	Cornea	Conjunctiva	Iris-ciliary	Lens
Peptide	+*	-	-	-
Amino acids	+	-	-	-
Nucleoside	+	-	+	-
Glucose	+	+	+	+
Vitamin C	-	-	-	+
Acid/base	+	+	-	-
Glutathione	-	-	-	+
Efflux pump				
P-glycoprotein, MDR1	+	+	+	+
MRPs (1 – 9)	+*	+	NA	NA
Receptor				
Insulin/insulin like growth factor	+	+	+	+
Growth factors	+	+	+	+
Prostanoid		+	+	
Bradykinin/tachykinin	+	+	+	-
Muscarinic	+	+	+	+
Adrenergic	+	+	+	+
Histamine	+	+	+	+
Oestrogen	+	-	+	+
Progesterone	+	-	+	+
Prostanoid	+	+	+	+
Serotonin	+	-	+	-
Glucocorticoid	+	NA	+	+
Mineralocorticoid	+	NA	+	+
Tumour necrosis factor	+	-	+	-
Vascular endothelial growth factor	+	+	+	-
Hyaluronan	+	+	+*	+

*Exact subtype of transporter/receptor unknown; +: Presence of transporter/receptor; -: Absence of transporter/receptor.
MDR: Multidrug resistant; MRP: Multidrug resistance-associated protein; NA: No data available.

parts on the eye. Recently, the molecular presence and functional expression of P-gp in human and rabbit cornea has been confirmed. In the cornea, it has been shown to restrict drug uptake [4], thereby suggesting lower bioavailability of many ophthalmic drugs. Recently, there have been reports of P-gp expression of retinal pigment epithelial (RPE) and retinal blood vessels oriented towards the blood side, preventing substances from entering the ocular structures from systemic circulation.

The human MRPs play an important role in protecting the cells against carcinogenic drugs. MRPs are organic anion transporters; that is, they transport anionic drugs and neutral drugs conjugated to acidic ligands. MRPs also play a vital role in resistance development against nucleoside analogues in cancer chemotherapy. MRP1 has been found in rabbit conjunctival epithelial cells. However, the existence of MRPs in other ocular tissues has not been extensively explored.

2. Strategies to improve ocular bioavailability by transporter-mediated drug delivery

2.1 Anterior segment

Topical ocular drug delivery is clinically significant in the treatment of diseases of the eye that affect the anterior chamber, such as corneal epithelial and stromal keratitis, glaucoma, conjunctivitis, and the posterior chamber, including bacterial endophthalmitis, retinitis and macular degeneration. One of the major challenges in ocular drug delivery has been to deliver drugs to the anterior and posterior chamber of the eye using topical dosage forms. The main disadvantages are related to the fact that the drug is diluted and washed off almost immediately due to a high tear turnover rate. Precorneal loss results in poor drug absorption and subtherapeutic drug concentrations in the eye. Several approaches have

been employed to increase bioavailability of drugs in the eye. Targeted prodrug design has proven to be an efficient strategy for site-directed delivery.

Various lipophilic prodrugs have shown increased ocular absorption, thus delivering more of the parent drug to the interior of the eye. Acyclovir (ACV) is used in the treatment of herpes simplex virus keratitis and is the drug of choice for viral infection in the eye. Owing to its limited bioavailability the drug has shown moderate antiviral efficacy following topical administration. For a compound to be effective topically and to be formulated into eye drops, it must possess sufficient hydrophilicty and at the same time exhibit sufficient permeation through the cornea to reach 3 – 5 times the minimum inhibitory concentration (MIC) levels. In order to overcome problems of insufficient solubility and transport of the parent drug ACV, dipeptide prodrugs have been synthesised in order to target the oligopeptide transporter on the cornea. The dipeptide prodrugs of ACV were found to be substrates of hPEPT1 and were transported across the intestinal cell line and isolated rabbit cornea owing to their recognition by the oligopeptide transporters.

2.2 Posterior segment

Expression of transporters on the retina, particularly on RPE and endothelial cells of the retinal blood vessels, provides us with an opportunity to increase the retinal and vitreal levels of various drugs, thereby increasing their efficacy and decreasing the required dose. Compounds can be targeted to the transporter by delivering through any of the three main routes: systemic, intravitreal and subconjunctival.

Different ocular routes that have been used to deliver drugs and prodrugs include cornea, conjunctiva, iris-ciliary body and lens epithelium. Transporters and receptors have been identified in these tissues and have been utilised to improve ocular drug delivery. On the other hand, discovery of efflux transporters (P-gp) identified on the cornea and conjunctiva will lead to a better understanding of restricted transport of drugs (anti-viral, antineoplastic etc.) to the inner compartment of the eye.

3. Expert opinion

Membrane transporters/receptors are involved in a variety of processes, including absorption, distribution and excretion. Recently, a significant number of transporters have been identified, cloned and expressed in various cell lines and tissues. Drug delivery utilising these transporters has been shown to have immense clinical significance. One of the challenges in ocular drug delivery has been to deliver drugs to the anterior and posterior chamber of the eye using topical dosage forms. However, it has certain disadvantages because the drug is diluted and washed off. The precorneal loss results in poor drug absorption and subtherapeutic drug concentrations in the eye. Several approaches have been employed to increase bioavailability of drugs in the eye. Targeted prodrug design has proven to be an efficient strategy for site-directed delivery. Various lipophilic prodrugs have shown to improve ocular absorption, thus delivering more of the parent drug to the interior of the eye. Different ocular routes have been used to deliver drugs and prodrugs. They include drugs delivered through the cornea, conjunctiva, iris-ciliary body and lens epithelium. Transporters and receptors have been identified in these tissues and have been utilised to improve ocular drug delivery. Efflux transporters (P-gp) identified on the cornea and conjunctiva will lead to a better understanding of restricted transport of drugs (antiviral, antineoplastic etc.) to the inner compartment of the eye for management of various ocular pathologies.

Bibliography

1. STELLA VJ, HIMMELSTEIN KJ: Prodrugs and site-specific drug delivery. *J. Med. Chem.* (1980) **23**:1275-1282.
2. HAN HK, AMIDON GL: Targeted prodrug design to optimize drug delivery. *AAPS PharmSci.* (2000) **2**:E6.
3. PAULSEN IT, BROWN MH, SKURRAY RA: Proton-dependent multidrug efflux systems. *Microbiol. Rev.* (1996) **60**:575-608.
4. DEY S, GUNDA S, MITRA AK: Pharmacokinetics of erythromycin in rabbit corneas after single-dose infusion: role of P-glycoprotein as a barrier to *in vivo* ocular drug absorption. *J. Pharmacol. Exp. Ther.* (2004) **311**:246-255.

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