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Expression, activity and pharmacokinetic impact of ocular transporters☆

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ABSTRACT

The eye is protected by several tissues that limit the permeability and entry of potentially harmful substances, but also hamper the delivery of drugs in the treatment of ocular diseases. Active transport across the ocular barriers may affect drug distribution, but the impact of drug transporters on ocular drug delivery is not well known. We have collected and critically reviewed the literature for ocular expression and activity of known drug transporters. The review concentrates on drug transporters that have been functionally characterized in ocular tissues or primary cells and on transporters for which there is available expression data at the protein level. Species differences are highlighted, since these may explain observed inconsistencies in the influence of specific transporters on drug disposition. There is variable evidence about the pharmacokinetic role of transporters in ocular tissues. The strongest evidence for the role of active transport is available for the blood-retinal barrier. We explored the role of active transport in the cornea and blood retinal barrier with pharmacokinetic simulations. The simulations show that the active transport is important only in the case of specific parameter combinations.

Contents

Abbreviations: ABC, ATP-binding cassette; AHUI, aqueous humor uptake index; AUC, area under the curve; BAB, blood-aqueous barrier; BBB, blood-brain barrier; BCRP, breast cancer resistance protein; BRB, blood-retinal barrier; BUI, brain uptake index; MATE1, multidrug and toxin extrusion protein 1; MCT, monocarboxylate transporter; MDR1, multidrug resistance protein 1; MRP, multidrug resistance associated protein; NPE, nonpigmented epithelial cell layer; OAT, organic anion transporters; OATP, organic anion transporting polypeptides; OCT, organic cation transporter; PCFT, proton-coupled folate transporter; PE, pigmented epithelial cell layer; QSPR, quantitative structure-property relationship; RFC1, reduced folate carrier 1; RPE, retinal pigment epithelium; SLC, solute carrier; TEA, tetraethylammonium.

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1. Introduction

Drug delivery is a challenge in the treatment of many ocular diseases. Drugs should reach the target site at concentrations that are effective, while maintaining the drug concentration at nontoxic levels in off-target tissues in the eye and elsewhere in the body. Topical administration is by far the most common way to treat ophthalmic diseases, even though the ocular bioavailability of topically applied drugs is generally <5% ([1]. The low bioavailability is partly explained by the fast removal of the drug from the surface of the eye, but it is also affected by the low permeability of the cornea [1–3]. Still, topical administration can be used to deliver small molecular drugs at sufficient levels to treat diseases in the anterior parts of the eye (cornea, anterior chamber and iris). In contrast, drug delivery to the posterior tissues (retina, choroid, vitreous) by topical administration is not feasible, because the drugs do not distribute easily from the anterior parts to the back of the eye [4]. Systemic delivery of drugs to the posterior eye tissues is limited by the blood-ocular barriers that protect the sensitive ocular tissues [1]. However, the ocular barriers are not completely impermeable as lipophilic small molecules are able to cross these barriers [5]. Additionally, many hydrophilic endogenous compounds can cross those barriers with the help of transport proteins. For instance, nutrients like glucose and amino acids are supplied to the posterior ocular tissues through these barriers by active transport, similarly as in the blood-brain barrier. Active transport is also utilized in removal of metabolites from the eye to the blood circulation. However, the impact of ocular transporters on drug disposition is still not well understood, even though transporters are known to have an important role in the disposition of many drugs and their metabolites elsewhere in the body [6]. In principle, the involvement of transporters in drug disposition may lead to nonlinear pharmacokinetics, drug-drug interactions as well as inter-individual variability. Thus, transporters may alter the safety and efficacy of drugs and therefore, an evaluation of the interactions of new drug molecules with selected transporters is required during drug development [7,8].

Transport proteins can be divided into two major families: the solute carrier (SLC) family and the ATP-binding cassette (ABC) family. The SLC transporters utilize facilitated diffusion or they couple an ion or electrochemical gradient to the transfer of their substrates across the cell membrane [9]. ABC transporters, on the other hand, use ATP as the energy source to drive the transport. The human ABC transporter family consists of 48 members divided into seven subfamilies, whereas the human SLC family is considerably larger with 52 subfamilies, comprising over 430 transporters in total [10]. Only a few of these transporters are known to transport drugs. Among the ABC transporters, members from the ABCB, ABCC and ABCG subfamilies efflux a wide variety of drugs and drug metabolites out from cells. The most widely studied ABC drug transporter is ABCB1, known as the multidrug resistance protein 1 (MDR1) or p-glycoprotein. Also, some other ABC transporters are involved in translocating a wide variety of drugs. These include multidrug resistance associated proteins (MRPs) (members of the ABCC subfamily) and the breast cancer resistance protein (BCRP) (ABCG2). As their names indicate, these transporters have been associated to drug resistance in cancer cells, where they are often overexpressed. However, these transporters are also widely expressed in healthy tissues, such as enterocytes lining the intestine, in canalicular cell membranes of the liver and proximal tubules of the kidney [6]. Depending on localization of transporters in these polarized cells, they may affect drug disposition by removing drugs and their metabolites from the cells into the intestinal lumen, bile or urine or alternatively to the blood circulation. Additionally, both MDR1 and BCRP are expressed in the capillary endothelium of the blood-brain barrier, where they efficiently prevent drug entry into the brain.

The most notable drug transporters within the SLC family include the organic anion transporting polypeptides (OATPs, SLCO family), organic anion transporters and organic cation transporters (OATs and OCTs, both belonging to the SLC22A family) [6]. In contrast to the human ABC transporters, which are all efflux transporters, the SLC proteins primarily assist the cellular uptake of drugs. Members of these subfamilies can be found in many epithelia, even though some transporters are expressed only in a specific cell type. For instance, OATP1B1 and OATP1B3 have been found only on the basolateral membrane of hepatocytes, where they extract their substrate drugs from the blood circulation to the liver [11]. The OCTs generally transport cations, while small, hydrophilic anions are substrates of OAT and larger, more hydrophobic anions are transported by OATPs.

There is considerable overlap in the substrate specificity of transporters, both between members within the subfamilies as well as between efflux and influx transporters. Due to the substrate overlap and to the lack of specific substrates and inhibitors, the activity of a specific transporter is difficult to assess *in vivo*. In addition, when evaluating the impact of transporter activity, it is important to consider the passive membrane permeability of the substrate, as the total permeation depends on both the passive diffusion and the active transport [12,13]. The passive diffusion is determined by the physicochemical properties of the drug, while the active transport depends both on the substrate affinity and transport rate, as well as the expression levels of the transporter at the barrier. The active transport (in either direction) may not significantly affect the total permeability of compounds that show high passive permeability, while the active transport can be responsible for most of drug permeation if the compound has limited passive diffusion through cellular barriers.

The effect of transporter activity on ocular drug disposition is not well understood, even though ocular transporter expression has been the subject of numerous studies. We have collected and critically reviewed the literature to include only robust and well-performed studies on ocular expression and function of transporters that are known to affect drug disposition. Many contradictory reports can be found in the scientific literature and problems arise in comparing the expression and impact of the transporters due to the diverse array of methods that have been used. Most of the early expression data comes from studies on the mRNA expression, which does not necessarily correlate with the protein levels [14]. In this review, we focus on the ocular transporters with evidence on expression at protein level. Quantitative information of the ocular transporter expression is mostly missing, even though this would be required to assess the pharmacokinetic impact of active transport. The expression levels can be used to scale the *in vitro* cellular transporter activity to *in vivo* situation, which in many cases is practically impossible to quantitate. Quantitative proteomic analysis of transporters using liquid chromatography combined to mass spectrometry provides a huge promise for determining protein expression levels [15]. It is important also to realize that transporter expression may differ in cultured cells compared to the *in vivo* situation, especially in the case of continuous cell lines [16]. Therefore, we have included data mainly from ocular tissues, but also from ocular primary cells or differentiated stem cells when tissue expression data is scarce. Data from continuous and transformed ocular cell lines was not included in the review.

Finally, it should be noted that almost all studies on ocular drug pharmacokinetics are done in animals, mainly in rabbits and rodents, but the transporter expression and substrate recognition may differ between species. When assessing species differences, it is important to realize that many studies use antibodies that are raised against human transporters, and therefore they may not correctly recognize orthologues in other species. The species differences in transporter expression and function and their implications on the translation to human pharmacokinetics will be examined in this review. In order to distinguish between transporters in human and animal species, human transporters are abbreviated in capital letters, while other transporters from other species are abbreviated in lower case letters. Overall, literature on ocular transporters is confounded by many factors. Therefore, caution is needed to draw solid conclusions in this field. We have tried to examine the literature critically in order to present a realistic