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Drug transporters expressed in the human placenta and models for studying maternal-fetal drug transfer

André Dallmann, PhD[1,*], **Xiaomei I. Liu, PharmD**[2], **Gilbert J. Burckart, PharmD, FCP**[3], **John van den Anker, MD, PhD, FCP**[1,2]

[1]Pediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital Basel (UKBB), Switzerland [2]Division of Clinical Pharmacology, Children's National Medical Center, Washington, DC, USA [3]US Food and Drug Administration, Office of Clinical Pharmacology, Silver Spring, MD, USA

Abstract

Tremendous efforts have been directed to investigate the ontogeny of drug transporters in the fetus, neonates, infants, and children based on their importance for understanding drug pharmacokinetics. During development (i.e. in the fetus and newborn infant), there is a special interest in transporters expressed in the placenta which modulate placental drug transfer. Many of these transporters can decrease or increase drug concentrations in the fetus and at birth stressing the relevance of elucidating the expression in the placenta and potential gestational age-dependent changes therein. Hence, the main objective of this review was to summarize the current knowledge about expression and ontogeny of transporters in the human placenta in healthy pregnant women. Additionally, various *in vitro, ex vivo* and *in silico* models that can be used to investigate placental drug transfer, namely placental cancer cell lines, *ex vivo* cotyledon perfusion experiments and physiologically based pharmacokinetic (PBPK) models, are discussed together with their advantages and shortcomings. A particular focus was placed on PBPK models because these models can integrate different types of information, such as expression data, ontogeny information and observations obtained from the *ex vivo* cotyledon perfusion experiment. Such a mechanistic modeling framework may leverage the available information and ultimately help to improve the knowledge about the adequacy and safety of pharmacotherapy in pregnant women and their fetus.

Introduction

Drug transporters are of paramount importance for drug exposure and many research efforts have consequently been directed to elucidate the ontogeny of these transporters in the fetus, neonates, infants, and children.[1–3] In addition to the expression of these transporters in

Corresponding author: Dr. André Dallmann, Clinical Pharmacometrics, Research & Development, Pharmaceuticals, Bayer AG, Germany dallmann.a@gmail.com.

*Current address: Clinical Pharmacometrics, Research & Development, Pharmaceuticals, Bayer AG, Germany

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tissues such as the intestinal tract, drug exposure in preterm and term neonates may also be modulated by drug transfer via the placenta.[4] In fact, numerous transporters are expressed in the placenta transferring nutrients such as amino acids, vitamins and glucose, and xenobiotics such as drugs and environmental pollutants across the blood-placenta barrier. Many drug transporters may have a fetoprotective effect by acting as efflux transporters and lowering drug concentrations on the fetal side. For example, breast cancer resistance protein (BCRP) has been found to substantially limit glyburide transfer across the human placenta in both *in vitro* and *ex vivo* experiments.[5,6] Consistent with these findings, a clinical study involving pregnant women with gestational diabetes mellitus reported that glyburide concentrations in the umbilical vein were on average significantly lower compared to those measured in maternal plasma. Specifically, the reported median umbilical-to-maternal plasma glyburide concentration ratio was 0.81 (interquartile range: 0.46 – 1.27).[7]

Hence, a detailed understanding of transporters in the placenta including their ontogeny constitutes a crucial aspect for elucidating drug exposure *in utero* and in neonates. Quantitative information on the expression can be obtained from various experiments (e.g. with cultured placental cancer cell lines, such as the BeWo cell line, or primary (cyto)trophoblasts isolated from fresh placentae). Importantly, the latter experiment can also be used to study the ontogeny of transporters. *Ex vivo* cotyledon perfusion experiments are suitable to assess the kinetics of drug transfer across the placental barrier. Data from these experiments can eventually be leveraged in a mechanistic modeling framework, such as physiologically-based pharmacokinetic (PBPK) models, to investigate and predict the rate and extent of placental drug transfer and ultimately fetal and neonatal drug exposure *in silico*.[8] Since much of the success of integrating placental drug transfer *in vivo* depends on the availability and quality of data on transporter expression, the primary objective of this article is to review the expression and ontogeny of various transporters in the healthy human placenta. Additionally, *in vitro, ex vivo* and *in silico* methods that can be used to investigate placental drug transfer are discussed along with their advantages and shortcomings.

Although animal models have also been used for the investigation of placental drug transfer, histological and morphological differences between different species and humans make an extrapolation to pregnant women difficult.[9] Therefore, the current review does not include animal models.

Placental Transporters

The maternal-fetal interface in the placenta consists of a layer of syncytiotrophoblasts and cytotrophoblasts that separate the maternal from the fetal circulation. This cellular layer constitutes the blood-placenta-barrier and various transporters may be expressed in the apical or basolateral membrane of these cells. Transporters may additionally be expressed in the endothelial membrane lining the interior surface of the fetal blood vessels and separating the fetal blood from the stroma and trophoblasts.

Regulation of placental transporter expression

Knowledge about the specific effect of pregnancy on the regulation of transporter expression in the placenta is incomplete and most information is limited to the expression of the

adenosine triphosphate-binding cassette (ABC) B1 (encoding P-glycoprotein) and *ABCG2* (encoding BCRP). There is some evidence that treatment with progesterone and estrogen may upregulate the expression of *ABCB1* and *ABCG2* in placental cancer cell lines[10] and in primary trophoblasts isolated from term placentae.[11] Interestingly, although the plasma concentrations of these hormones rise dramatically during pregnancy, no increase in placental expression of *ABCB1* and *ABCG2* is observed *in vivo* stressing the importance of parallel pathways regulating the expression of these genes. For example, treatment of primary term trophoblasts with the inflammatory mediators tumor necrosis factor a (TNF-α) and interleukin (IL)-1β *in vitro* has been shown to decrease the expression of *ABCB1* and *ABCG2V* Since the human placenta constitutively produces these cytokines, their inhibitory effect on *ABCB1* and *ABCG2* expression may outweigh the activating effect exerted by progesterone and estrogen. Of note, a number of disorders are associated with elevated plasma concentrations of these cytokines compared to healthy controls, e.g. preeclampsia,[12] gestational diabetes,[13] intrauterine growth restriction (IUGR)[14] and intrauterine infection.[15] This raises the question to which extent the pregnancy-induced change in placental transporter expression is modified by diseases and drugs.

Furthermore, hypoxic conditions have been observed to significantly increase the production of TNF-α and IL-1β in cultured villous explants from human placentae.[16] However, although the placenta is poorly vascularized during early pregnancy,[17] the resulting hypoxia does not appear to translate into reduced placental transporter expression in the first trimester, stressing again the importance of parallel signalling pathways.

In addition to these factors regulating gene expression, the cellular tumor antigen p53 is another protein interacting with the *ABCB1* promotor region in cancer cell lines. This interaction leads either to repression or activation of the gene expression depending on the relative orientation of p53 binding sites in the *ABCB1* promoter region.[18] In placentae collected at term pregnancy, very high levels of p53 have been observed in the syncytiotrophoblast[19] which might be linked to the declining expression of *ABCB1*. In summary, a mechanistic understanding of the processes involved in the regulation of placental drug transporter expression is currently lacking and needs to be addressed by future studies.

Expression and ontogeny of placental transporters

Despite these knowledge gaps on the factors controlling gene expression, many studies have determined whether and to which extent drug transporters are expressed in the human placenta and how the expression pattern changes during the course of pregnancy. The subsequent sections address these aspects for each transporter. For reasons outlined below, the review of transporter expression has been limited to studies analysing fresh placenta tissue from healthy pregnant women since many diseases change the transporter expression in placenta, whereas transporter expression in placental cancer cell lines, such as BeWo cells, will not be reported here. Hence, the available information was generally derived from placentae collected at the end of the first trimester following abortion or in the second half of pregnancy following preterm or term delivery. Data from preterm delivery associated with intrauterine infections or other complications were not included here; if no such condition

was reported, the pregnant women were assumed to be healthy and data from preterm delivery were included in this analysis. Figure 1 schematically illustrates the drug transporters known to be expressed in the human placenta. The localization and change in transporter expression during pregnancy is also listed in Table 1 together with alternative names and examples of substrates of each transporter. The following information on transporter expression is exclusively derived from human placentae.

P-glycoprotein (P-gp): P-gp is an efflux transporter localized in the syncytiotrophoblasts and cytotrophoblasts as well as in the fetal and maternal endothelium of placental blood vessels.[20–23] Due to its importance in drug transport, numerous studies have investigated P-gp expression in the placenta from the 7th gestational week until term. The expression in these studies was quantified in relation to housekeeping genes, i.e. constitutive genes required for the maintenance of basic cellular functions that are expressed in all cells under normal and pathophysiological conditions, such as GAPDH, HPRT, YWHAZ, beta-actin and mRNA 18s. Although the results of one study suggested that P-gp was unchanged from the first trimester to term,[24] most studies show that P-gp expression decreases with advancing gestational age.[23,25–32]

Breast cancer resistance protein (BCRP): There are numerous studies on BCRP transporter expression in the placenta. Staining results indicate that the transporter is expressed in the apical membrane of the syncytiotrophoblasts and cytotrophoblasts as well as in fetal endothelial cells from the first trimester to term.[23,25,33–37] Various studies have quantified the expression of BCRP relative to the expression of housekeeping genes such as GAPDH, HPRT, YWHAZ, β-actin and 18S.[23,25–28,33,36,38–44] Although no clear pattern emerges from these studies, BCRP expression seems to decrease or remain unchanged between the first trimester and term.[23,25–28,39,43]

Organic anion transporter (OAT) 1: No expression of OAT1 was detected in the placenta using Northern Blot analysis.[45]

OAT 2: There is only one study investigating OAT2 expression in pregnancy suggesting that OAT2 is not expressed in the placenta.[46]

OAT3: Findings from two studies using Northern Blotting techniques suggest that OAT3 is not expressed in the placenta.[45,47]

OAT4: OAT4 is an influx transporter which has been detected in the basolateral membrane of the syncytiotrophoblast and cytotrophoblast cells of the placenta in the third trimester.[37,47–49] Its ontogeny in the placenta is yet unknown.

OAT 10: Using RT-PCR and immunohistochemical staining, Uehara et al. demonstrated that OAT10 was expressed in syncytiotrophoblast cells of placentae collected between 26 and 41 weeks of gestation.[37]

Organic-anion-transporting polypeptide (OATP)-A: OATP-A is an influx transporter expressed in trophocytes responsible for the uptake of substrates, such as unconjugated

bilirubin, from the fetal blood.[50,51] Semi-quantitative expression analysis using real-time reverse transcriptase (RT) polymerase chain reaction (PCR) suggested that OATP-A expression relative to 18S rRNA decreases between the first and third trimester of pregnancy.[51]

OATP-1B1: Studies on OATP-1B1 (also known as OATP-C) expression in the placenta are not yet fully conclusive. In a previous study with isolated trophoblast cells from term placentae, mRNA of OATP-1B1 could not be detected by analytical RT-PCR, whereas weak levels were detected by real-time quantitative RT-PCR.[50] Another study that also used real-time quantitative RT-PCR with different primer and probe sequences detected a very low level of OATP-1B1 expression in 4 of the 8 placentae obtained between 9 and 12 weeks gestation and no expression in 6 placentae obtained between 38 and 40 weeks gestation.[51]

OATP-2B1: OATP-2B1, also called OATP-B, is an influx transporter expressed in the basolateral membrane of syncytiotrophoblast and cytotrophoblast cells.[48,52–54] Additionally, OATP-2B1 has been found to be also expressed to a much lesser extent in the apical membrane of these cells. Petrovic et al. reported that the expression of OATP-2B1, normalized to β-actin mRNA expression, is lower in placental samples obtained at term delivery (gestational age: 38.8 ± 0.8 (mean ± SD)) as compared with those at preterm delivery (gestational age: 32.8 ± 2.5).[28]

OATP-D: In a previous study, mRNA of OATP-D could be detected in microvillus fragments of the placenta through real-time quantitative RT-PCR expression.[51] Importantly, this study also compared the expression between the first and third trimester (9–12 weeks gestation and 38 and 40 weeks gestation, respectively). The results showed that OATP-D expression is significantly down-regulated towards the end of pregnancy with an averaged normalized expression of only 5.9% of that measured in the first trimester.[51] The cellular localization of OATP-D in the placenta is yet unknown.

OATP-E: OATP-E is an influx transporter located on the apical side of syncytiotrophoblast cells.[54] In the study by Patel et al., no significant difference in the expression levels between the first and third trimester was found.[51]

OATP-8: Expression of OATP-8 has been detected in term placentae where it may act as an influx transporter.[50]

Multidrug resistance protein (MRP) 1: There are several studies that show MRP1 expression in the placenta. The location of MRP1 was found to be on the basolateral side of syncytiotrophoblasts of the terminal and intermediate villi and, although not consistently observed in all studies, to a lesser extent also in fetal endothelial cells.[21,33,35,5220,55] Weak expression signals have, although rarely, also been detected in the apical membrane of syncytiotrophoblasts.[33] Three studies investigated the quantification of MRP1 expression normalized to that of housekeeping genes (GAPDH, HPRT and mRNA-18s). The results are somewhat conflicting showing that MRP1 expression between the 10th gestational week and term either increases or remains unchanged.[25,56]

MRP2: A few studies were conducted to investigate MRP2 expression in pregnancy.[25,52,53,57] The results show that MRP2 is an efflux transporter located on the apical side of syncytiotrophoblast cells.[52,53,57] Several studies have quantified MRP2 expression through real-time PCR demonstrating a relatively consistent increase in MRP2 expression during pregnancy.[53,56,58] One study reported a 2-fold increase in expression between 9–10 weeks of gestation and term[53], while another reported a 4.4-fold and 1.8-fold increase between gestational week 28 and term, and gestational week 34 and term, respectively.[59] Interestingly, the difference between gestational week 34 and term was not found in the MRP2 protein amount quantified by immunoblot analysis.[59]

MRP3: Among all MRPs investigated, MRP3 has been found to be the most abundantly expressed transporter in the placenta. It is an efflux transporter with transport direction from the fetus to the maternal side. Several studies showed that MRP3 is located on the apical side of the syncytiotrophoblast cell predominantly in small terminal villi.[25,52,57] Quantitative real-time PCR showed no significant difference between the MRP3 expression in samples obtained at 9 – 10 weeks of gestation and those obtained at term. Although this study also reported that Western blot analysis did not detect MRP3 protein amount in term placentae, this negative result was noted to be likely due to a low reactivity of the antibodies used.[56]

MRP4: Real-time PCR and immunoblotting analysis indicated that MRP4 is present in the apical membrane of syncytiotrophoblast cells.[57]

MRP5: There are a few studies that show that MRP5 is located on the basolateral side of syncytiotrophoblast cells and fetal endothelial cells.[59] Quantification of MRP5 mRNA through real-time PCR indicated that MRP5 expression decreases significantly throughout pregnancy.[56,59] The same pattern could also be confirmed for the protein amount in term and pre-term placentae through quantification of band intensity of Western blot analysis.

Multidrug and toxin extrusion (MATE) 1: MATE1 is an efflux transporter located on the apical side of syncytiotrophoblast cells. Northern Blot analysis and quantitative RT-PCR indicated no expression or very weak expression of MATE1 in placentae collected in the first trimester and at term.[60–62]

MATE2: MATE2 is another efflux transporter expressed in the apical side of syncytiotrophoblast cells.[60–62] Analysis of MATE2 expression through RT-PCR showed a decrease between the first trimester and term, although the decrease was not significant due to large variability.[60]

Organic cation transporter (OCT) 1: Several studies demonstrate that OCT 1 is expressed in the placenta both at early and late stages of pregnancy; however, the exact localization has not yet been identified.[61,63–66] In one study by Ahmadimoghaddam et al., the OCT 1 expression quantified by RT-PCR was unchanged between the first trimester and term.[66]

OCT2: Several studies show that OCT2 is expressed in the placenta in the first and third trimester, but the localization is yet unknown.[61,63–65] OCT2 gene expression measured via

RT-PCR has been observed to decrease approximately 4-fold between placentae collected in the late first trimester and at term.[66]

OCT3: OCT3 is an influx transporter located in the basolateral membrane of syncytiotrophoblast cells.[61,67–69] Two studies have quantified the ontogeny of OCT3 by RT-PCR reporting varying results. Ahmadimoghaddam et al. observed a ~3.6-fold decrease between the late first trimester and term[60], whereas Lee et al. reported constant expression levels between the first trim ester, second trimester and term.[61] Interestingly, quantitative LC-MS/MS analysis by the latter authors revealed another pattern showing that protein levels of OCT3 were on average increased by 65% in the second trimester and by 57% at term compared to those in the first trimester.[61]

Organic cation/carnitine transporter (OCTN) 1: Two studies detected OCTN1 expression in the term placenta using Northern Blot and quantitative PCR.[70,71] The localization of OCTN1 in the placenta has not been determined yet.

OCTN2: OCTN2 is an influx transporter expressed in the apical membrane of syncytiotrophoblast cells and in fetal endothelial cells.[53,72] Compared to OCTN1, higher expression signals have been measured via quantitative PCR for OCTN2 in the term placenta. Additionally the mRNA expression, normalized to 18S rRNA, was observed to be around 15% higher in placentae obtained at around 32 weeks of gestation compared to those around 39 weeks of gestation, but this difference did not reach statistical significance.[53,70,72]

Plasma membrane monoamine transporter (PMAT): Weak expression levels of PMAT has been reported in the term placenta.[61] The localization of this transporter in the placenta is still unknown.

Bile salt export pump (BSEP): RT-PCR analysis indicated a weak expression of BSEP in placental specimens collected between 9 and 12 weeks of gestation and no expression at term.[51]

Multidrug resistance protein (MDR3): RT-PCR analysis showed that MDR3 is expressed in the placenta and that the expression increases between 9 – 12 weeks of gestation and term.[51]

Familial intrahepatic cholestasis (FIC) 1: FIC expression in the placenta as assessed by RT-PCR has been reported to decrease between 9 – 12 weeks of gestation and term.[51]

Models for placental drug transfer

In vitro models

Multiple *in vitro, ex vivo* and *in silico* models have been used to study transcellular drug transfer through the placenta.[73,74] In vitro model systems typically rely on different cell cultures that are experimentally applied in transport studies. For example, non-proliferative primary cytotrophoblasts can be isolated from human term placentae. Although easily cultured on semi-permeable membranes, these cells do not form a confluent cell monolayer

but aggregate with disrupted tight junctions.[75] Hemmings et al. reported a technique to grow multiple overlapping layers of syncytialised cells overcoming some of the problems observed with discontinuous membrane cultures of primary trophoblasts.[76] Human cancer cell lines constitute another *in vitro* system used for placental transfer studies. These cell lines include the JEG-3, the Jar, and the BeWo cell line (b30 clone),[77,79] which are all derived from choriocarcinoma cells. Among these, the BeWo cell line is the most frequently used for transfer studies. It grows relatively fast and forms confluent, polarized monolayers that are morphologically similar to normal trophoblasts.[80] Although these characteristics make it attractive for placental transfer studies, the BeWo cell line has a few disadvantages, in particular a different gene expression and protein amount of various transporters. For example, the mRNA level and protein amount of MDR1 and MDR3 has been found to be significantly lower in BeWo cells compared to primary trophoblasts isolated from term human placentae, whereas those of BCRP and MRP1 are much higher in BeWo cells.[81] Despite this discrepancy, a previous study has observed that the transport of antipyrine, benzoic acid, caffeine, and glyphosate across BeWo cell monolayers was overall in adequate agreement with results obtained from the *ex vivo* cotyledon perfusion experiment. However, the transfer rate measured in BeWo cells was much lower than in the *ex vivo* cotyledon perfusion experiment.[82] Consistent with these findings, another study demonstrated a good correlation between the relative transport rates in BeWo cells and the transfer indices measured in the *ex vivo* cotyledon perfusion experiment for a set of nine model compounds (including the previously investigated compounds antipyrine, benzoic acid, caffeine, and glyphosate).[83] Similar findings were also reported for non-dioxin-like polychlorinated biphenyls.[84] Recently, BeWo cells have also been employed to bioprint a 3D, bioengineered *in vitro* placenta model with biophysical properties that closely mimic those of the maternal decidua.[85] This model was developed to capture the chemotactic effect of epidermal growth factor on the migration of trophoblasts and human mesenchymal cells for studying preeclampsia. In future studies, this model might serve as a platform for printing more complex, physiological placental models capturing the *in vivo* physiology better than current 2D cell line models, thereby providing a more realistic framework for placental drug transfer.

Ex vivo cotyledon perfusion experiments

Ex vivo cotyledon perfusion experiments provide the only experimental model available to study human placental transfer within the physiological tissue architecture that is present *in vivo.* In this experiment, the physiological circulations in the placenta are reestablished by cannulating fetal and maternal blood vessels of an isolated cotyledon. Thereafter, a perfusate is circulated through the catheters at specific flow rates mimicking the physiological fetal and maternal blood flow rates through the placenta observed *in vivo.*[74] The circulation of the placenta can be either non-recirculating (open/single-pass) or recirculating (closed). The usage of this model started in 1962 by Panigel[86] and was subsequently refined by various groups.[87,88] Since the tissue for this experiment is collected from both vaginal birth and C-sections, the gestational age of the placentae utilized is usually around term gestation, which is one of the main limitations of the *ex vivo* perfusion experiment as earlier stages of pregnancy cannot be investigated. Another shortage of the experiment is that the concentrations of drug-binding proteins (e.g. albumin and α1-acid glycoprotein) are often

equal for the maternal and fetal circuit, which may not reflect the physiological conditions *in vivo.* Since only the unbound drug fraction can cross the placenta, the balance between maternal and fetal concentrations of drug-binding proteins is of particular importance. For example, the placental transfer of digoxin in the perfused cotyledons has been observed to be dependent on the albumin concentrations in both circuits.[89,90] Also, as discussed later on, the difference in the pH value between the maternal and fetal blood may be another relevant factor influencing the transfer of weakly basic drugs, which should be accounted for in these experiments. Despite these challenges, a recent study of 26 drugs showed that the prediction of *ex vivo* placenta perfusion matches the observed *in vivo* data well.[91]

PBPK models

PBPK models constitute another method for investigating placental drug transfer. Various models have previously been presented that allow the prediction of concentrations in the fetal blood or tissues.[92,9394–97] The two most promising approaches for predicting the transfer of a compound across the placenta were those presented by Mendes et al.[94,95] and by Zhang et al. [96] The approach suggested by Mendes et al. relies on experimental data obtained from the *ex vivo* cotyledon perfusion experiment. Briefly, a four compartment model is used to describe these data and the key parameters governing the placental transfer (the placental transfer constant and the partition coefficient) were initially fitted to the experimental data. Thereafter, these parameters were integrated in a whole-body PBPK model. It was shown that through this approach, the pharmacokinetics of emtricitabine, tenofovir and nevirapine observed at delivery could adequately be predicted by the PBPK model.[94,95] One shortcoming of this approach is that it cannot be readily extrapolated to other compounds for which no data from the ex *vivo* cotyledon perfusion experiment are available. Additionally, in case of highly protein-bound drugs, the experiment may not adequately reflect the *in vivo* situation unless different protein concentrations are used in the maternal and fetal circuit. Still, this approach can provide important insights into the placental transfer of compounds.

Another approach was presented by Zhang et al. for compounds crossing the placenta exclusively via passive diffusion.[96,98] In this case, the fetal-to-maternal partition ratio was assumed to equal 1.0. According to this approach, the placental permeability of a compound is estimated from its apparent permeability measured *in vitro* (in e.g. Caco-2 cell lines) using midazolam as a calibrator compound. Although promising results were obtained for zidovudine and theophylline, [96] more examples are needed to corroborate these findings. The advantage of this approach is that it provides a rather simple and quick estimate of placental permeability. Yet, the main drawback remains the limitation to compounds crossing the placenta exclusively via passive diffusion.

To date, many maternal-fetal PBPK models have in common that they do not account for an explicit integration of placental drug transporters. While the active influx or efflux of drugs in the placenta can implicitly be factored into the permeability rate, a deconvolution of passive and active transfer processes is still desirable as it provides a greater mechanistic understanding of the transfer processes which ultimately facilitates extrapolation to earlier stages of pregnancy or even other compounds. Hence, the development of more mechanistic

PBPK models for the study of maternal-fetal drug transfer may benefit from the herein presented information on the expression and ontogeny of transporters in the placenta.

Apart from the explicit integration of placental transporters, these models may also benefit from a finer representation of the fetal physiology. Recently, several repositories have been published that review physiological changes in the fetus, such as organ growth, change in blood flow rates, tissue composition and drug-binding protein concentrations.[98–100] In addition, drug transfer may also be influenced by the pH difference between the fetal and maternal blood. Under normal conditions, the pH of the umbilical cord blood is about 0.1 log units lower than that of the maternal blood which can, in principle, lead to an increased fetal/maternal concentration ratio of weakly basic drugs. While the pH difference under normal conditions is probably insignificant, it may become relevant in cases of fetal acidosis and maternal alkalosis. For example, a lower pH value in the umbilical cord blood, as might occur in case of fetal asphyxia, may result in trapping the ionized form of weak bases, whereas in cases of maternal alkalosis, the non-dissociated fraction of weak bases available for transfer to the fetus may be increased.[101,102] Several reports in the literature demonstrate that lower pH values in umbilical cord blood at delivery are associated with increased fetal blood concentrations of the weakly basic anesthetics bupivacaine, mepivacaine and lidocaine which may lead to toxic effects in the fetus.[103–105] Placental drug transfer is also influenced by metabolism within the syncytiotrophoblasts and hence the expression of drug-metabolizing enzymes should also be considered. Although many of the previously published maternal-fetal PBPK models did not account for these factors, incorporating all these inherent physiologic functions, and possibly others, may substantially improve the mechanistic level of the model and lead to more accurate predictions of drug concentrations in the fetus.

Outlook

In summary, little is known about the mechanisms regulating the expression of drug transporters in the human placenta. Despite this knowledge gap, many studies investigated whether and to which extent drug transporters are present in the placenta and numerous transporters were found to be expressed at different levels throughout gestation. While there is abundant information on the ontogeny of some transporters in the placenta, such as P-gp, for other transporters this information is either conflicting or lacking. For these transporters, this review identifies important knowledge gaps where further research is needed. The *ex vivo* cotyledon perfusion experiment is currently being considered the gold standard for studying maternal-fetal drug transfer. However, attention should be given to those cases where the experimental conditions do not ideally reflect all factors affecting drug transfer *in vivo,* such as an altered pH value or protein concentration in the fetal circulation. Still, the results from these experiments provide very suitable information that can be incorporated in a mechanistic modeling framework. First attempts to inform PBPK models on the basis of *ex vivo* perfusion cotyledon experiments have shown promising results. To increase the mechanistic understanding of placental drug transfer, a refinement of these models with respect to the explicit incorporation of placental drug transporters seems necessary. This review provides important information on the expression and ontogeny of placental transporters that could be leveraged within a PBPK modeling context. Ultimately, these

models can help to improve the knowledge about the adequacy and safety of pharmacotherapy in pregnant women and their fetuses.

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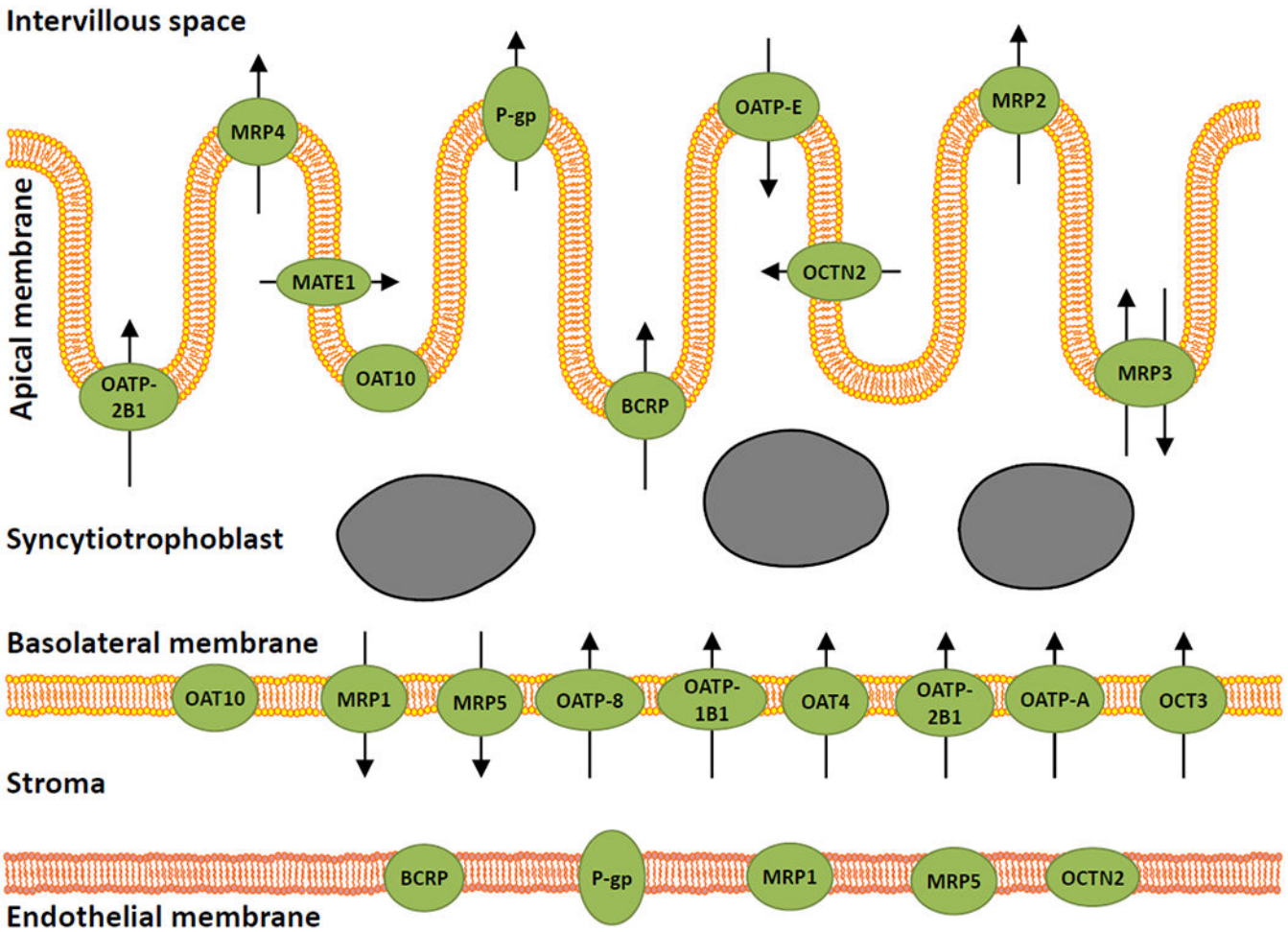

Figure 1.

Expression and localization of drug transporters in the placenta. Transporters are shown as green symbols, and the arrows indicate the direction of the transport, if reported.BCRP, breast cancer resistance protein; MATE, multidrug and toxin extrusion; MRP, multidrug resistance-associated protein; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; OCTN, organic cation/carnitine transporter; P-gp, P-glycoprotein.

Table 1:

Transporters Expressed in the Human Placenta and Examples of Substrates

Transporter name	Alternative names	Localization in the placenta	Change in expression during pregnancy	Substrate(s)
P-gp	ABCB1; MDR1	Syncytiotrophoblast, cytotrophoblast, fetal and maternal endothelium	↓, ↔	Dabigatran etexilate, dexamethasone, digoxin, fexofenadine, glyburide, methotrexate, carvedilol, methotrexate, talinolol
BCRP	ABCG2; MXR	Syncytiotrophoblast, cytotrophoblast, fetal endothelium	↓	glyburide, atorvastatin, rosuvastatin, zidovudine, cimetidine, methotrexate
OAT 1	SLC22A6	No expression in placenta	NA	beta-lactam antibiotics, non-steroidal antiinflammatory drugs, furodemide, tenofovir
OAT2	SLC22A7	No expression in placenta	NA	salicylate, furosemide, acyclovir, ganciclovir
OAT3	SLC22A8	No expression in placenta	NA	beta-lactam antibiotics, cephalosporin antibiotics non-steroidal antiinflammatory drugs, cimetidine, furosemide, methotrexate
OAT4	SLC22A9; SLC22A11	Syncytiotrophoblast, cytotrophoblast	NA	uric acid, methotrexate
OAT 10	SLC22A13	Syncytiotrophoblast[a]	NA	urate
OATP-A	OATP1A2; SLCO1A2; SLC21A3	Trophocytes	↓	ciprofloxacin, fexofenadine, glyburide, atorvastatin, pravastatin, rosuvastatin, atenolol, methotrexate, sumatriptan
OATP-1B1	SLCO1B1 ; OATP-C; HBLRR; LST1; SLC21A6	Trophoblast	↓	bile acid, enalapril, cefazolin, atorvastatin, pravastatin, rosuvastatin, methotrexate, glyburide, fexofenadine
OATP-2B1	OATP-B; SLC21A9	Syncytiotrophoblast, cytotrophoblast	↓	atorvastatin, pravastatin, rosuvastatin, glyburide, fexofenadine, sumatriptan, methotrexate
OATP-D	SLCO3A1 ; OATP3A1; SLC21A11	NA	↓	thyroxine, vasopressin
OATP-E	SLCO4A1; OATP4A1; OATP1; OATPE; OATPRP1; SLC21A12	Syncytiotrophoblast	↔	benzylpenicillin, thyroxine
OATP-8	SLC21A8	NA	NA	bile acid
MRP1	ABCC1	Syncytiotrophoblast, fetal endothelium	↔	Ritonavir, methotrexate
MRP2	ABCC2, CMRP, CMOAT	Syncytiotrophoblast	↑	atenolol, carvedilol, pravastatin, methotrexate
MRP3	ABCC3	Syncytiotrophoblast	↔	methotrexate
MRP4	ABCC4	Syncytiotrophoblast	NA	tenofovir, methotrexate
MRP5	ABCC5	Syncytiotrophoblast, fetal endothelium	↓	cGMP, methotrexate
OCTN1	SLC22A4	NA	NA	gabapentin
OCTN2	SLC22A5	Syncytiotrophoblast, fetal endothelium	↓	carnitine

Transporter name	Alternative names	Localization in the placenta	Change in expression during pregnancy	Substrate(s)
OCT1	SLC22A1	NA	↔	Metformin, sumatriptan, atenolol
OCT2	SLC22A2	NA	↓	Atenolol, , metformin, , procainamide
OCT3	SLC22A3; EMT	Syncytiotrophoblast	↓	metformin
MATE1	SLC47A1	Syncytiotrophoblast	↔	Atenolol, metformin, ganciclovir, cimetidine, acyclovir
MATE2	SLC47A2	Syncytiotrophoblast	↓	Atenolol, metformin, acyclovir, ganciclovir, cimetidine
PMAT	SLC29A4; ENT4	NA	NA	Metformin, atenolol
BSEP	ABCB11	NA	↓	pravastatin, fexofenadine
MDR3	ABCB4	NA	↑	digoxin, ursodiol
FIC1	ATP8B1	NA	↓	phosphatidylserine, phosphatidylethanolamine

[a]Expression in placenta not detected in all studies

Note: ↑ denotes increasing expression during pregnancy, ↓ denotes decreasing expression during pregnancy and ↔ denotes constant expression during pregnancy

Abbreviations'. ABC: Adenosine triphosphate-binding cassette; ATP8B1: ATPase phospholipid transporting 8B1; BCRP: breast cancer resistance protein; BSEP: Bile salt export pump; CMOAT: Canalicular multispecific organic anion transporter; CMRP: Canalicular multidrug resistance protein; EMT: Extraneuronal monoamine transporter; ENT: Equilibrative nucleoside transporter; FIC: Familial intrahepatic cholestasis; HBLRR: Hyperbilirubinemia, Rotor type; LST: Liver specific transporter; MATE: Multidrug and toxin extrusion; MDR: Multidrug resistance protein; MRP: Multidrug resistance-associated protein; MXR: Multixenobiotic resistance; NA: not available; OAT: Organic anion transporter; OATP: Organic anion transporting polypeptide; OATPRP: Organic anion transporting polypeptide-related protein; OCT: Organic cation transporter; OCTN: Organic cation/carnitine transporter; P-gp: P-glycoprotein; PMAT: Plasma membrane monoamine transporter; SLC: Solute carrier; SLCO: Solute carrier organic anion transporter.