DMD Fast Forward. Published on February 29, 2020 as DOI: 10.1124/dmd.119.089755
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DMD # 89755

Ontogeny and cross-species comparison of pathways involved in drug absorption, distribution, metabolism and excretion in neonates (Review): KIDNEY

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Running title: Cross-species comparison of kidney ADME ontogeny

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Number of text pages: 28

Number of tables: 5

Number of figures: 1

Number of words in Abstract: 250

Number of words in introduction: 408

Number of words in discussion: 257

Keywords: Kidney, ADME, ontogeny, species, human

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Abbreviations

ABC	ATP-binding cassette
ADME	Absorption, distribution, metabolism and excretion
ATP	Adenosine triphosphate
BCRP	Breast cancer resistance protein
BW	Body weight
CYP	Cytochrome P450
ENT	Equilibrative nucleoside transporter
EPHX	Epoxide hydrolase
GFR	Glomerular filtration rate
GST	Glutathione S-transferase
GW	Gestational weeks
HNFs	Hepatocyte nuclear factors
KW	Kidney weight
LDF	Laser doppler flowmetry
MATE	Multidrug and toxin extrusion
MDR	Multidrug resistance protein
MRI	Magnetic resonance imaging
MRP	Multidrug resistance-associated proteins
NATS	N-Acetyltransferase
NPT	Sodium-phosphate co-transporters
OAT	Organic anion transporters
OATP	Organic-anion-transporting polypeptide
OCT	Organic cation transporters
PAH	Para-amino hippurate
PAPS	3’-phospoadenosine-5’-phosphosulfate
PD	Pharmacodynamics
Pept	Peptide transporter
Pgp	P-glycoprotein
PK	Pharmacokinetics
PND	Postnatal day
PNW	Postnatal week
PXR	Pregnane X receptor
RBF	Renal blood flow
RPF	Renal plasma flow
RNA	Ribonucleic acid
SCP	sulphachlorpyridazine
SLC	Solute carrier
SULT	Sulfotransferase
TmPAH	Maximum tubular secretory capacity of PAH
mRNA	Messenger RNA
UDPGA	Uridine 5’-diphosphate glucuronic acid
UGT	Uridine 5'-diphospho-glucuronosyltransferase
URAT	Urate transporter

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Abstract

The kidneys play an important role in many processes, including urine formation, water conservation, acid-base equilibrium, and elimination of waste. The anatomical and functional development of the kidney has different maturation time points in humans versus animals, with critical differences between species in maturation before and after birth. Absorption, distribution, metabolism and excretion (ADME) of drugs vary depending on age and maturation, which will lead to differences in toxicity and efficacy. When neonate/juvenile laboratory animal studies are designed, a thorough knowledge of the differences in kidney development between newborns/children and laboratory animals is essential. The human and laboratory animal data must be combined to obtain a more complete picture of the development in the kidneys around the neonatal period and the complexity of ADME in newborns and children. This review examines the ontogeny and cross-species differences in ADME processes in the developing kidney in preterm and term laboratory animals and children. It provides an overview of insights into ADME functionality in the kidney by identifying what is currently known and which gaps still exist. Important renal function properties such as glomerular filtration rate, renal blood flow and ability to concentrate are generally well known, detailed knowledge about transporter and metabolism maturation is growing, but is still lacking. Preclinical data in those properties is limited to rodents and generally covers only the expression levels of transporter or enzyme-encoding genes. More knowledge on a functional level is needed to predict the kinetics and toxicity in neonate/juvenile toxicity and efficacy studies.

Significance statement: This review provides insight in cross-species developmental differences of ADME properties in the kidney, which should be considered in neonate/juvenile study interpretation, hypotheses generation and experimental design.

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1. Introduction

The kidneys play a pivotal role in a number of processes, i.e. 1) urine formation; 2) conservation of water, cations, anions, glucose, amino acids; and 3) elimination of endogenous and exogenous waste compounds (Gans and Mercer, 1984). These various functions are dependent on the specialized subcellular structural and functional properties of renal tubule epithelium, including their various transporters, metabolic activity, and membrane integrity. Therefore, the development and maturation of these processes in pediatric patients or in animals can have a profound effect on the disposition and fate of administered drug therapies that depend on the kidney for filtration, uptake, secretion and/or metabolism.

The anatomic and functional development of the kidney has different maturation time points in men compared with laboratory animals. In addition to the knowledge of kidney development in humans, several reviews have been published on the comparative ontogeny of the developing kidney in different laboratory animals, which describe critical species differences in renal development and functional maturation before and after birth (Owen and Heywood, 1986; Witte et al., 1986; Zoetis and Hurtt, 2003; Solhaug et al., 2004; McMahon, 2016; Frazier, 2017).

Factors in the neonatal kidney that influence absorption, distribution, metabolism and excretion (ADME) properties of drugs include renal blood flow (RBF), glomerular filtration rate (GFR), and the tubular mass and lack of tubule maturity with its impact on tubular secretion and absorption, maintenance of acid-base equilibrium and urine concentrating mechanisms. These functions are all reduced in the juvenile animal (Seely, 2017). In addition, the ontogeny of metabolizing enzymes, transporters and transcription factors in the kidney all play a major role. Better understanding of these factors is needed to improve prediction of the ADME characteristics of drugs and chemicals administered to neonates. There are numerous examples of drugs which behave quite differently in adults and neonates that can be explained by the lack

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of maturation of various transporters or metabolic enzymes such as propofol, pazopanib or dabrafenib, among many others (Groseclose et al., 2015; Frazier, 2017; Michelet et al., 2018; Frazier et al., 2019).

The aim of the current review is to provide an overview of the ontogeny and cross-species differences of pathways involved in ADME in the developing kidney in preterm and term neonatal animals and children. This review is part of a multi-sector collaborative research effort coordinated by the Health and Environmental Sciences Institute to increase the knowledge base in the nonclinical space to better inform clinical treatment decisions made for the pediatric population (De Schaepdrijver et al., 2019; Hausner et al., 2019; Neal-Kluever et al., 2019). The ontogeny and cross-species differences of ADME-related processes in the liver and other organs will be covered by other reviews. These manuscripts will provide a comprehensive overview of available data and insights on ADME functionality present in the maturing organs, to toxicologists, modelers and clinicians, by identifying what is currently known and which gaps still exist.

Laughon et al. (2014) stated that “Children are therapeutic orphans”. Currently, pediatric therapeutic guidelines are supported by a limited number of trials performed in pediatric populations, in combination with extrapolation from adult trials or case reports. The statement is also supported by the daily experience of clinicians, whereby a lack of “pediatric-adapted” drug information frequently requires off-label prescription of drugs, potentially leading to adverse events and dosage errors (Laughon et al., 2014; Skinner, 2014; Cuzzolin and Agostino, 2016). Over the last 10 to 20 years, an upsurge in pediatric drug research has been noted, partly based on legislative initiatives, leading to more pediatric labeling of drugs. Unfortunately, even with the increased regulatory efforts, today still >50% of the drugs used in the pediatric population and even >75% of the drugs used in the critically ill and neonates are unlicensed or

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prescribed off-label (Cuzzolin and Agostino, 2016). Most common drug classes are antiinfectives, respiratory drugs, antianemics, cardiovascular, central nervous system drugs and gastrointestinals (Cuzzolin and Agostino, 2016). Therefore, an improvement of current pediatric drug research conduct is required in order to attain information on age-appropriate dosage schemes, potential toxicity and adverse events. Extensive studies in the pediatric population are ethically not possible, whereby alternative approaches such as juvenile animal models and modeling and simulation tools emerge. The development and selection of appropriate juvenile animal models is key to build translatable models and to predict the effect on neonates and children, based on juvenile animal *in vivo* data. To be able to perform this selection, a thorough cross-species knowledge of the morphological and functional development of all organs involved in pharmacokinetics (PK), pharmacodynamics (PD) and toxicity is needed.

To assess and incorporate the vast amount of disparate data across species on this topic, a thorough literature search was performed in PubMed/Medline, Web of Science and EMBASE databases using a comprehensive list of keywords related to maturation of the kidney and the role of the kidney in the ADME processes. Additionally, previously published search strategies on kidney transporter ontogeny (Brouwer et al., 2015) were repeated and modified to include additional transporters, enzymes and species. The literature search was limited to peer-reviewed English language articles. The review was centered around humans and the most predominant used toxicology laboratory animal species, namely rat, mouse, dog, pig and monkey. All species were assessed for each parameter. When information is not listed for a particular parameter it indicates that no supporting data was found in our search. No additional animal or clinical experiments were performed for the construction of this review paper.

Anatomical development

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Nephrogenesis

In 2017, a comparison of nephrogenesis by species was presented in detail by Frazier (2017), and included review of earlier authors (Owen and Heywood, 1986; Witte et al., 1986; Zoetis and Hurtt, 2003; Solhaug et al., 2004; Cappon and Hurtt, 2010; McMahon, 2016). An overview of renal development and the nephrogenesis of the different species can be found in Table 1. The three main phases of *in utero* renal development include pronephros, mesonephros and metanephros, with the latter forming the functioning kidney in vertebrates (Seely, 2017). Kidney formation involves a well-regulated balance between proliferation, differentiation, apoptosis and morphogenesis (Frazier, 2017). Nephrogenesis, which involves the final phases of kidney development and tubule differentiation, occurs in very different contexts between species (McMahon, 2016). In **humans**, morphologic renal development occurs exclusively *in utero*, with nephrogenesis and organogenesis occurring from gestational week (GW) 6 to 36. After GW 36, nephrogenesis is complete and each kidney has a full complement of nephrons (Solhaug et al., 2004). While nephrogenesis begins in the fetus and is completed in humans before birth, it continues postnatally in the **rat** and is not completed until postnatal day (PND) 11-15 (Zoetis and Hurtt, 2003). In **mice**, most nephrons are fully formed by the end of gestation based on histomorphology (Zoetis and Hurtt, 2003; Frazier, 2017). In contrast, evidence in mice indicating labeled progenitor cells do not disappear until a few days after birth suggests nephrogenesis is not complete in mice until PND 2-4 (Short et al., 2014; McMahon, 2016). Further, evidence from embryonic gene expression indicates that branching of the tips of renal tubules does not cease until PND 2 in mice (Short et al., 2014). In contrast, nephrogenesis is completed by GW 24 in most **nonhuman primates** (Frazier, 2017). Nephrogenesis in the **dog** and the **pig** proceeds approximately up to postnatal week (PNW) 2 and 3, respectively (Friis, 1980; Kleinman, 1982; Zoetis and Hurtt, 2003; Gasthuys et al., 2016).

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Postnatal maturation and growth of nephron segments encompassing tubule elongation continues throughout the first year in **human** infants and lasts up to 5 months postnatally in **nonhuman primates**. Tubule differentiation occurs up to PND 21 in **rats**, but is completed around the time of birth in **mice** (McMahon, 2016; Frazier, 2017). Tubule elongation in rodents slows considerably after PND 28. In **dogs**, the volume of nephron segments continues to grow from PNW 2 (when nephrogenesis ceases) to approximately PNW 28, enlarging by as much as 300% (Eisenbrandt and Phemister, 1979).

Vasculogenesis

In concert with nephrogenesis, **human** vasculogenesis is completed by GW 34-36. Vascular maturation in the kidney of **nonhuman primates** is also completed by birth. In **dogs** it is not completed until PNW 6. In **rats**, renal vasculogenesis is active as late as PND 12 and is not completed until PND 17 to 19, while in **mice** it is complete by PND 7 (Frazier, 2017).

Kidney size

The neonatal kidney in **all species** is smaller than the adult kidney and will increase in mass during the juvenile and pediatric growth period specific for that species (Frazier, 2017). It should be noted that the number of glomeruli is constant in an individual between the end of nephrogenesis and maturity, with the increase in renal volume attributable to an increase in tubular mass (Frazier, 2017). The lower tubular mass in juvenile kidneys results in diminished capacity for water and solute reabsorption and an increased risk of dehydration in neonates as compared with adults (Frazier, 2017).

In **mice**, the glomerular size relative to total kidney weight (KW) is smaller than in other species, including **rat**. Glomerular size tends to increase with age and can vary among strains of rodents (Frazier et al., 2012). Takasu et al. (2015) evaluated the kidney size of

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microminipigs (Fuji Micra Inc) (4-7 months of age) and **beagle dogs** (10 months of age). The kidney size (in cm^3) was comparable between the dogs and the 7-month-old pigs (right kidney: [27.9-34.9]; left kidney: [28.0-41.1]), when both species were approximately the same size. The kidney size of a **Hanford miniature swine** (BW: 25 kg) is 11 × 6 × 3 cm (KW: 120 g), which resembles the kidney of a 70 kg human (Swindle and Brown, 2016).

Functional development

Renal clearance encompasses three main processes: 1) glomerular filtration, 2) tubular secretion and 3) active/passive tubular reabsorption. Functional maturation is closely related to the morphogenesis of the kidney. In all species, functional development lags behind anatomic maturation (Seely, 2017). During gestation, the homeostasis is mainly preserved by the placenta, whereas the contribution of the kidney starts to emerge in the third trimester (Chevalier and Norwood, 2011). Functional maturity is dependent on many factors. Renal blood flow, GFR, tubular secretion and absorption, maintenance of acid-base equilibrium and urine concentrating mechanisms are all limited in the juvenile animal. The reduced tubular mass and lack of tubule maturity in neonatal or juvenile kidneys are responsible for a reduced capacity to maintain kidney homeostasis. Full maturation differs per species and ranges from approximately 1 month in rodents to up to 2 years in humans.

Renal blood flow

Renal blood flow progressively increases during gestation and achieves full-term levels by GW 32-35 in **humans**. The values at term are less than those observed in adults even when corrected for BW, KW, or body surface area. For the human kidney, the transition at birth is marked by striking physiologic functional changes that facilitate not only the immediate demands for adaptation to extra-uterine life but also the progressive maturation to adult renal function. The most striking postnatal transition occurs in an increase in RBF together with a marked change

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in glomerular filtration pressure, resulting in a rise in GFR. In contrast, urinary sodium output drops so that sodium and thereby water, may be retained, which is needed for new tissue formation in this period of rapid somatic growth.

Renal blood flow and flow velocity have been determined in children and adolescents (range 1-16 years) by duplex doppler and was shown to be 4.1 (standard deviation 1.2) ml/min/g KW, independent of age (Grunert et al., 1990). Another study in healthy neonates resulted in an RBF of 21 ml/min/kg BW (Visser et al., 1992). More values have been reported for the effective renal plasma flow (RPF) at different developmental stages being 20 ml/min/1.73 m^2 in the premature infant, 45 ml/min/1.73 m^2 by GW 35, 83 ml/min/1.73 m^2 in term infants, 300 ml/min/1.73 m^2 by toddler age, up to a rate of 650 ml/min/1.73 m^2 by 2 years of age (Jose et al., 1994).

In **rats** multiple protocols have been used over the years to measure RBF or RPF. Classically, methods started out to be indirect calculations via *para*-aminohippurate (PAH) clearance and evolved using surgical models with flow probes, transducers or microspheres. More recently, magnetic resonance imaging (MRI) techniques and awake-instrumented models have been developed. Most research has focused on a time period where RBF was already considered at its maximum capacity (>PND 20). Horster and Lewy (1970) showed that from PND 1-3 RPF decreased from 0.017 to 0.013 ml/min/g KW by PAH clearance. At PND 24-28 RBF (as measured by radiolabeled microspheres) showed a flow of approximately 4.5 ml/min for an average KW of 0.52-0.55 g (Chevalier and Thornhill, 1995). In adult rats, wider ranges have been reported. Cortical RBF has been evaluated by arterial spin labeling MRI and showed ranges between 1.2 and 4.2 ml/min/g KW (Liu et al., 2012; Zimmer et al., 2013; Tan et al., 2015; Romero et al., 2018). This method showed good correlations with PAH clearance in humans (Ritt et al., 2010). Additionally, it has been pointed out by other researchers that the

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microsphere method might lead to an overestimation of RBF (Prinzen and Bassingthwaighte, 2000). In 3- to 4-month-old Wistar rats, flow-probe instrumented conscious rats showed RBF rates ranging from 4.4 to 5.5 ml/min (Flemming et al., 2001). Even though a rough range of RBF in adult rats has been established, data for the first 3 PNW in rats are still lacking.

Just as in rats, different protocols have been used over the years to measure the RBF in **mice**. Adult male C57BL/6 mice have a PAH clearance of 6.3 ml/min/g BW (Cervenka et al., 1999). In another study PAH clearance in 14-month-old 129SV-C57BL/6 mice resulted in a mean RBF of 4.7 ml/min/g (Cullen-McEwen et al., 2003). A surgical approach with flowmeters resulted in an RBF of 0.59 ml/min in 10- to 14-week-old C57BL/6J mice (Mergia et al., 2018). Adult New Zealand inbred mice showed a baseline RBF of 0.83 ml/min in freely moving conscious instrumented mice (Iliescu et al., 2008). There is variation in RBF results between different methods in adult mice. Data on the first weeks after birth are sparse, but Barnett et al. (2017) showed a rapid increase in renal perfusion from PND 0 [70 laser doppler flowmetry (LDF) arbitrary units] to PND 3 (180 LDF arbitrary units) and PND 7 (280 LDF arbitrary units) in CD-1 mice.

More neonatal data are available for the **dog**. Renal perfusion flow was calculated in mongrel puppies from inulin clearance by Fick's law and ranged from 0.7 ml/min/g KW on PND 1 to 1.8 ml/min/g KW at 1 month of age, compared with the adult reference of 2.7 ml/min/g KW (Kleinman and Lubbe, 1972). Another study was performed measuring RBF by xenon washout and krypton audiography in mongrel dogs aged 18 h to 70 days by Aschinberg et al. (1975). They showed an increase in RBF from 0.39 ml/min/g KW in week 1 to 2.1 ml/min/g KW in week 6, which is in the same order of magnitude (Aschinberg et al., 1975). Noteworthy detail here was that the increase in RBF appeared rather linear between week 1 and week 6. Another study in newborn mongrel dogs, but with a microsphere model, showed a RBF of 0.43 ml/min/g

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KW for newborns, 2.1 ml/min/g KW for 6-week old dogs and 3.8 ml/min/g KW for adults (Olbing et al., 1973). These estimates were further confirmed by flow transducer experiments in 14- to 25-day-old mongrel puppies (RBF of 1.6 ml/min/g KW) and in adult dogs (RBF 3.7 ml/min/g KW) (Baer and Navar, 1973; Jose et al., 1975). Again, more recently, RBF measurements can be performed in conscious flow-probe instrumented dogs and flow rates of 214-310 ml/min were registered in foxhounds weighing 23-35 kg by Just et al. (1998).

In **pigs** experiments have been performed in 10- to 12-week-old animals both via microsphere and arterial spin labeling methodologies. Microsphere and arterial spin labeling MRI results were 3.7 ml/min/g KW and 2.0-2.1 ml/min/g KW, respectively (Artz et al., 2011). Additionally, microsphere experiments in piglets aged 6 h to 45 days showed mean RBF increased from 43 ml/min/m^2 body surface area to 760 ml/min/m^2 (Gruskin et al., 1970). This large increase is mainly driven by the normalization to body surface area and the rapid growth rate of pigs.

For cynomolgus **monkeys** RBF is at the maximum level at birth (Frazier, 2017). In rhesus monkeys between 3 and 5 days of age, RBF values of 2.5 ml/min/g KW were determined by microsphere methodology (Moore et al., 1974). Another study in infantile rhesus monkeys showed an RBF of 3.5 ml/min/g KW (Behrman and Lees, 1971). However adult rhesus monkeys showed higher normalized RBF values being 7.0-9.8 ml/min/g KW indicating that there may be differences in RBF maturation between species (Sivarajan et al., 1976).

Glomerular filtration rate

The GFR is widely used as a quantitative marker to assess renal clearance. In **humans**, GFR remains relatively low during gestation, increases quickly in the first weeks of life, after which it increases steadily and reaches adult levels at 1 to 2 years of age (Zoetis and Hurtt, 2003). During gestation, the increase in GFR is primarily attributed to nephrogenesis, which leads to an upsurge in new glomeruli. After birth, the rise in GFR is attributed to an increase in RBF, a

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higher capillary pressure, a drop in renal vascular resistance and a rise in cardiac output (Gruskin et al., 1970). In clinical practice, GFR is most often estimated (eGFR) in **humans**, rather than measured precisely, using the Cockcroft-Gault equation, Chronic Kidney Disease Epidemiology Collaboration equation, the Modification of Diet in Renal Disease (MDRD) equation, the Schwartz equation (in children), or other formulas. Actual measured values for GFR and reference ranges can be problematic to compare across species. In humans, GFR is normalized to a body surface area of 1.73 m^2 (once an average adult body surface area [body weight (BW): 70 kg)] and normal values represent approximately 20 ml/min/1.73 m^2 at birth, which increases to around 50 ml/min/1.73 m^2 by PNW 2 (Gomez et al., 1999; Vieux et al., 2010; Baum, 2016). Measured or estimated values of 100–120 ml/min/1.73 m^2 occur by 2 years of age and remain relatively constant into adulthood. Normalizing for BW results in a GFR of approximately 0.8 ml/min/kg shortly after birth (Wilkins, 1992), which increases to maximum values of approximately 3.2 ml/min/kg around the age of 2-3 years (Hayton, 2000). With increasing age, the GFR decreases to approximately 2.0 ml/min/kg in adults (Hayton, 2000).

In **dogs,** reference ranges have not been definitively agreed upon and variation in results have been reported in surveys of the GFR literature (Moe and Heiene, 1995). The primary reason why a reference range for GFR has not been produced is most likely due to variations in strains or protocols (i.e. markers used, assays for measurement of serum or urine marker concentration, urine or blood sampling times and PK models used for GFR calculation), as well as other factors such as circadian variation, hydration status, dietary protein and the use of sedation during measurement (Von Hendy-Willson and Pressler, 2011). Generally agreed upon values for normal GFR in the adult dog using several methods are approximately 3.7-4.3 ml/min/kg (Finco et al., 1993; Watson et al., 2002; Von Hendy-Willson and Pressler, 2011). At PND1, puppies have only approximately one-fourth of this value at just under 1 ml/min/kg (Kleinman, 1982).

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The variety of substrates and methods for determining the experimental value of GFR in laboratory **rats** have resulted in huge variances in published values and the way in which they are expressed can also confuse readers. Using iothalamate and I-hippuran, values of approximately 1.0 ml/min/100 g of BW were noted (de Vries et al., 1997). Using inulin clearance to assess GFR in experiments over 50 years ago, adult values were listed as 1.2 ml/min/g of KW (van Liew et al., 1967). In neonatal Sprague Dawley rats values of 0.044 ml/min/g KW at PND 3 were noted that increased to 0.3 ml/min/g KW by PND 18 (Horster and Lewy, 1970; Horster, 1977). In a study using female Han Wistar rats, values for GFR were similar and reported as 1.2 ml/min/g KW for adult rats and only slightly lower at PND 28. These data indicate that GFR matures around PNW 4 in rats even though maximum values and complete maturation are not completed until PND 42 (Guron, 2005; Frazier, 2017). In recent years, a variety of new imaging modalities that can measure GFR transdermally or via MRI in animals has become available. A typical GFR value obtained using these methods is 2.4 ml/min in adult rats weighing approximately 229 g (Yu et al., 2007).

The small size of **mice** and their sensitivity to blood loss pose a challenge to clearance studies, which normally require sequential assessment of plasma concentrations of inulin and/or other substrates. In some studies, GFR has been assessed by using radioisotope-labeled inulin and in others by chromotropic detection (Field et al., 1991). The measured values for GFR for adult mice differ by strain with lower values reported for C57BL mice. GFR averages 237 and 140 µl/min in adult male and female C57BL/6J mice, respectively, using bicompartmental analysis of inulin clearance. Other strains have reported GFR values between 0.8 and 1.4 ml/min/g BW (Qi et al., 2004; Qi and Breyer, 2009). Similar values of 240 µL/min were obtained using high throughput imaging techniques in CD-1 mice (Rieg, 2013). Using separate methodology, normal adult values of 1.0 ml/min/g BW have also been published (Field et al., 1991). Due to logistical problems in obtaining values in neonatal mice, standard ranges are not available for

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mice younger than two weeks.

For **minipigs,** values for GFR are very hard to compare based on age because of the marked increase in BW over time. Glomerular filtration rate values of 44-58 ml/min have been noted in minipigs at PNW 4, which corresponds to approximately 4.5 to 5 ml/min/kg. By PNW 15, GFR has increased to 101-116 ml/min but as they have now grown significantly the GFR value is down to 3-4 ml/min/kg which is roughly similar to the **dog** on a BW basis (Ransley et al., 1987). For **conventional pigs** (Belgian landrace × large white), the GFR indexed to body surface area increased in GFR from 46.6 to 100.9 ml/min/m^2 from 8 days to 7 weeks of age (Gasthuys et al., 2017). Kaskel and Kleinman (1976) and Friis (1979) also measured the GFR in growing conventional piglets indexed to KW and BW. The maturation of the GFR in those studies was similar to the trends observed by Gasthuys et al. (2017).

In healthy adult cynomolgus macaque **monkeys**, the GFR was found to be 3.1 ml/min/kg by two separate methods by one group (Iwama et al., 2014) and 2.5-2.8 ml/min/kg by another group using yet another method (Zhang et al., 2017). Similar values between 2.8 and 4 ml/min/kg have been noted in adult rhesus macaques (Rabito et al., 2010), but precise values for GFR in monkeys in the first week after birth are not available.

Tubular secretion

The renal tubules transfer substances, including drugs, to the urinary filtrate via tubular secretion. The level of maturation in the fetal and the juvenile kidney should be considered in drug administration because the drug excretion profile may undergo developmental changes. In general, the secretory capacity will increase as the kidney develops. Tubular secretory capacity can be measured via any one of a number of standard analytes but is difficult to assess prenatally. More practical physiologic assays in the postnatal period involve measuring

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excreted electrolytes directly in urine such as sodium or chloride to compare trends over time, but these analytes may only reflect concentrating ability rather than true excretion capacity as electrolytes are also filtered. It is known that the fetal renin-angiotensin system is active *in utero* and maintains the fetal renal excretion of sodium and water into the amniotic cavity, aiding the maternal system and ensuring an adequate volume of amniotic fluid for normal growth and development (Lumbers, 1995). In rodents and other animals, fractional excretion rate of solutes and water changes as a function of age and the urinary Na^+/K^+ concentration ratio often drops significantly at the time of birth. Secretory capacity can be measured directly by analyzing compounds in urine, which are not filtered or absorbed. It must be stressed that each specific transporter will mature at its own pace and lifecycle and thus a particular maximum secretory capacity or excretion rate will vary with the transporter a compound is associated with. In practice, excretion rates can be measured for compounds that are both filtered and secreted such as creatinine or PAH. Since PAH is efficiently transported by the organic anion transporter 1 (OAT1) in humans and animals, PAH can be used to measure the effective RPF and the maximum tubular secretory capacity (TmPAH) (i.e. the difference between the total rate of excretion and quantity filtered by the glomeruli), which for PAH is primarily attributable to OAT1 activity (Momper and Nigam, 2018). Upregulation of OAT1 and OAT3 in the proximal tubules during the postnatal period is a critical factor in tubular secretory capacity in both humans and rodents (Momper and Nigam, 2018). More details on transporters can be found in the transporter section of the manuscript.

Values for maturation of excretion have been established for some species. Acquisition of filtration and secretion do not occur simultaneously. During the first months of life, the maximum tubular secretory capacity for organic anions is lower than GFR when compared to adults and there is significant intersubject variability.

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Human tubular secretory capacity in the kidney reaches maximum capacity at PNW 30 but is lowest in the first month of infancy (West et al., 1948). At PND 1–30 in humans, the TmPAH was shown to be only approximately 26% of the average during 1 year to 12 years of age (Rubin et al., 1949). In **rodents**, secretory capacity appears to increase from birth to PND 28 as overall kidney function matures (Frazier, 2017). It should be stressed that tubular secretory capacity is not necessarily equivalent to GFR as the rate of maturation in these processes is not identical within or among species.

Friis (1983) assessed the maturation of the active tubular secretion in **conventional pigs** by using PAH. Adult levels were reached at PNW 8 (PND 0-3: 0.8 ml/min/g KW and PNW 8: 1.9 ml/min/g KW). The TmPAH rose a fourfold from PND 0-3 to PNW 8.

Concentrating capacity

The concentrating capacity of the kidney depends on the medullary depth of a specific species. Greater depths of medulla results in the kidney to concentrate urine to a greater osmolality (Gans and Mercer, 1984). The relative medullary thickness for various species is: **human**: 3, **pig**: 1.6, **dog**: 4.3, **rat**: 5.8 (Schmidt-Nielsen and O'Dell, 1961). Maturation of the concentrating capacity is shown in Table 2.

Other functions

In **humans**, fetal urine formation starts during the first trimester of pregnancy (GW 10 to 11) (Abramovich, 1968). The hourly fetal urine production rate, estimated by regression analysis of bladder volumes, increases steadily during gestation (GW 20: 5 ml/h to GW 40: 51 ml/h), whereas the bladder storage interval remains unchanged (7-43 min) (Fagerquist, 2012). The increase in hourly fetal urine production rate is attributed to nephrogenesis and dynamic changes in RBF, GFR, tubular function and hormonal regulation (Chevalier and Norwood,

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2011).

Pharmacokinetic characteristics

Renal transporter maturation

The elucidation of transporter activity in various species and especially humans, has become increasingly important in predicting drug-drug interactions and for understanding the mechanism of some renal toxicities (Ennulat et al., 2018). However, to date, developmental data on transporters in pediatric patients and transporter ontogeny in general remains a significant gap in our understanding (Brouwer et al., 2015; Momper and Nigam, 2018).

Most renal transporters are localized to the proximal tubules (Frazier and Seely, 2018). In 2015, a comprehensive review of transporter maturation in **humans** has been compiled by Brouwer et al. (2015). We extended this review and the results are listed in Table 3a with localization shown in Figure 1. In general, data are limited about transporter ontogeny in human and non-rodent kidneys because most kidney transporter characterization has been performed in rodents. However a recent publication of Cheung et al. provides new insights on transporter maturation in humans using a more quantitative and novel technological approach with liquid chromatography-mass spectrometry (Cheung et al., 2019). There are several important differences in species between renal transporter expression, as well as in the timing of functional maturation of transport capacity (Sweeney et al., 2011). Transporter expression can be affected by both age and gender. In general, kidney transporters are largely immature at birth in humans and laboratory animals (Buist et al., 2002; Sweeney et al., 2011).

Among various transporters, the ATP-binding cassette (ABC) and solute carrier (SLC) families are responsible for the transport of most of the drugs handled by the kidney. Among the apical membrane (efflux) transporters of the proximal tubule, P-glycoprotein (Pgp), also termed

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multidrug resistance protein 1 (MDR1), is one of the most important for drug interactions. P-glycoprotein has been localized in **human** fetal kidneys by GW 5.5 using immunohistochemistry (Konieczna et al., 2011). Significant expression of Pgp has been demonstrated in humans at GW 11 in renal tubules and is present afterwards throughout gestation, increasing after birth to peak levels as an adult (van Kalken et al., 1992; Miki et al., 2005; Brouwer et al., 2015; Cheung et al., 2019). Protein abundance of Pgp is, however, already at adult level during childhood (Cheung et al., 2019). Low levels of Pgp expression has been noted in fetal **rat** kidneys, increasing at gestation and up through the early development period to weaning with maximum levels achieved between PND 11 and 26 (de Zwart et al., 2008; Sweeney et al., 2011; Xu et al., 2017). Peak Pgp expression in **mice** kidney has been noted at PND 20/21, but decreases sharply in males at PND 45 (Pinto et al., 2005; Cui et al., 2009).

Organic anion transporters are members of the SLC family and are involved in the movement of drugs, metabolites and toxins across the basolateral and apical membranes of the renal tubules, contributing to the secretion of a number of therapeutic agents and endogenous substrates (Burckhardt and Burckhardt, 2003). In **rats** and **mice**, renal OAT expression is low during gestation, but increases substantially during the postnatal period (Buist et al., 2002; Buist and Klaassen, 2004). The expression of OAT1 and OAT3 (which are critical carriers on the basolateral border), is significant enough for detection by approximately day 16-17 of gestation in **rodents** but rises considerably between birth and PNW 3 to reach adult levels by PNW 4 (Sweeney et al., 2011). The formation of new nephrons and extensive growth of established nephrons may contribute to the high upregulation levels of transporters in the postnatal kidney in some species. Protein levels of both transporters at PNW 3 largely resemble those of adults in both mice and rats (Nakajima et al., 2000; Hwang et al., 2010). However, using PAH secretion as a surrogate for OAT1 functional maturity, PAH clearance failed to reach maximal levels in rat until 8-10 weeks of age, suggesting either that OAT transporters are not fully mature

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at PND 21-28, or other renal factors may be confounding the data (Sweeney et al., 2011). The latter finding illustrates that expression at the ribonucleic acid (RNA) level does not necessarily equate with functional capacity, which makes interpretation of the scarce data even more challenging.

Many SLC carriers are present in early renal development, including Multidrug and toxin extrusion 1 (MATE) 1, Organic cation transporters 1 (OCT), OCT2, OCTn1, OCTn2, Urate transporter 1 (URAT) and Peptide transporter 2 (Pept). These transporters show similar expression patterns at least at the transcriptional level in **rodents** (Pavlova et al., 2000; Sweet et al., 2006). Organic cation transporters 1, OCT2, OCTn1 and OCTn2 messenger RNA (mRNA) expression in **mice** have been shown to approach adult levels by PNW 3 and although some of this family show gender differences in adult expression, the differences are not evident until about PND 30 (Alnouti et al., 2006). Multidrug and toxin extrusion 1 is an efflux cation transporter on the apical membrane. At PND 2, MATE1 expression in mice was only 12–14% compared to PND 45 when it reached adult levels and only 50% at PND 15. In **rats**, OCT2, OATP-4C1 and MATE1 expression levels were found to be low in fetal kidneys, increased gradually following birth and increased markedly on weaning, continuing to rise until adulthood. Although for OCT2 female expression does not increase after PNW3. Organic cation transporter 3 mRNA expression levels were low in fetal and newborn kidneys, but peaked at PND 35-40 in both sexes (Slitt et al., 2002; Xu et al., 2017). In **humans**, postnatal OAT1-mediated renal secretion is low in neonates and young infants relative to older children and adults (Momper and Nigam, 2018; Cheung et al., 2019). Organic anion transporter 3 expression is lowest in neonates and reaches adult levels before 2 years of age, but protein expression only reaches adult levels in adolescence (Cheung et al., 2019). Urate transporter 1mRNA expression is highest at the infant and child stage, however protein levels are more or less stable from childhood onwards (Cheung et al., 2019). Multidrug and toxin

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extrusion 1 shows similar expression and protein abundance from neonates up to adults (Cheung et al., 2019). Organic anion-transporting polypeptide B and OATP-D are both expressed in the human fetal kidney, but comparative expression has not yet been evaluated systematically throughout development (Brouwer et al., 2015).

Multidrug resistance-associated proteins (MRP) are a member of the ABC superfamily and include adenosine triphosphate-dependent efflux transporters which transport a wide variety of anionic and cationic compounds across membranes in the kidney and other tissues. Of the eight **mice** MRPs, six MRPs (MRP1-6) are significantly expressed in the kidney. The renal ontogeny of the MRP-carriers can be divided into three expression patterns in mice: 1) MRP1 expression remains relatively constant from birth to adulthood; 2) MRP2, 3 and 4 are expressed below adult levels at birth and increase during the first few weeks of age; and 3) highest expression of MRP5 is seen at birth and expression decreases during the first few weeks of life (Maher et al., 2005). Multidrug resistance-associated proteins do not exhibit mature expression levels until 1 month of age or later (Maher et al., 2005, 2006a). In a publication by Konieczna et al. (2011), immunohistochemistry of **human** fetal kidneys demonstrated MRP1 as early as GW 5.5 which increased during gestation. Expression of MRP 2 and 4 is similar between newborns and adults (Cheung et al., 2019). Unfortunately, there are no MRP mRNA expression data to support these results in human fetuses. Multidrug resistance-associated proteins 3 and 4 are expressed at much higher levels in adult female than male kidneys and are under hormonal influence in **mice**, **rats** and **humans** (Chen and Klaassen, 2004; Maher et al., 2006a).

Breast cancer resistance protein (BCRP) has been shown by immunohistochemistry at multiple stages in the **human** fetus within renal proximal tubules on their apical border (Konieczna et al., 2011). Breast cancer resistance protein expression level is high in newborns and reduces with age, reaching adult levels before 2 years of age. Protein abundance is similar between

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newborns and adults (Cheung et al., 2019). In **mice**, BCRP expression is increased after gestation and increases until maturity (de Zwart et al., 2008; Sweeney et al., 2011).

There are several other transporters of note in the kidney, such as the sodium-phosphate co-transporters (NPT1, NPT2a, NPT2b and NPT2c) and the nucleoside transporters (equilibrative nucleoside transporter, ENT1, ENT2 and ENT3), but ontological data in any species for these groups are rather limited. Except for ENT2, all are minimally expressed in **mouse** kidneys until PND 15 and then increase until maturity (Cheng and Klaassen, 2009). ENT2 is highly expressed in mice during gestation and decreases from birth until PND 15 where it is maintained until adulthood (Cheng and Klaassen, 2009).

It should be noted that there are important mechanisms of regulation of transporters including the hepatocyte nuclear factors (HNFs) and the pregnane X receptor (PXR) during renal development. Hepatocyte nuclear factors 1a and 4a regulate the expression of many or most (21/32 tested in one study) proximal tubule transporters in ontogeny during intrauterine and later development (Maher et al., 2006b; Martovetsky et al., 2013). While PXR regulatory factor has a larger role in the maturation of enzymes related to metabolism, PXR also regulates some transporter genes during kidney development (Tolson and Wang, 2010).

Maturation of passive tubular reabsorption was assessed in **conventional pigs** by Friis (1983) using sulphachlorpyridazine (SCP). Although excretion of SCP comprises both secretion as well as reabsorption, an age-dependent increase in SCP/GFR clearance ratio was observed, implicating a relative decrease in reabsorption with age.

Metabolic enzyme maturation

Overall there is very little information on the ontogeny of metabolism in the kidney. Although ontogeny data in the liver has improved over the last decade after earlier gap analysis (de Wildt

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et al., 1999; Alcorn and McNamara, 2002), data on maturation in the kidney are still lacking. Data from liver studies demonstrated that levels of Uridine 5'-diphospho-glucuronosyltransferases (UGTs) are generally lower in neonates, but maturation depends on the isoform and possibly also on the tissue examined (Ekstrom et al., 2013). Unfortunately, most studies failed to include both fetal and adult kidney tissues in their experiments. Interpretation of results from human studies is difficult. Although studies have been performed with known substrates for specific metabolism pathways, it is not possible to discern liver from kidney related effects as there is a large overlap between enzymes in both tissues. Moreover, due to the many different techniques used, a comparison between studies is not always easy to make. The kidney plays a less prominent role in drug metabolism for most drugs compared with the liver, whereby only a small portion of the known metabolizing families are present.

CYP p450 family (table 3b)

In **human** kidney there is evidence for the expression of various cytochrome P450 (CYP) enzymes, such as CYP2B6, CYP3A5 and the CYP4 family, while presence of CYP2C8, CYP2C9 and CYP3A4 is considered equivocal (Knights et al., 2013). While some of these enzymes are also present in animals, it may be one of the other isoforms that has a similar function. A thorough overview of CYP isoforms between species was published by Martignoni et al. (2006).

The CYP2B6 enzyme is known for the metabolism of a wide range of drug classes including chemotherapeutics, anti-inflammatories, anti-retrovirals, anesthetics and benzodiazepines (Wang and Tompkins, 2008). Additionally, it metabolizes several insecticides and herbicides (Hodgson and Rose, 2007). Data on ontogeny and maturation in the kidney is however lacking in most **species**. Sparse data in **mice** showed CYP2B9 protein concentrations to be present between PNW 3 and 10. Between PNW 10 and 10 months of age the concentrations declined

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in females, but not in males using a proteomics approach (Hersman and Bumpus, 2014). In **pigs** CYP2B22 activity was present from birth and increased from PND10-15, where it remains stable into adulthood (Aleksa et al., 2004).

The CYP3A4/5 enzyme is known to metabolize a wide range of drugs including calcium channel blockers, HIV protease inhibitors, statins and benzodiazepines. The CYP3A4/5 enzymes are slightly higher expressed in the cortex compared with the medulla (Schuetz et al., 1992) and are detected in the **human** fetal kidney at GW 28 and onwards (Aleksa et al., 2005; Miki et al., 2005). With respect to the ontogeny and maturation of this enzyme in the kidney not much is known in **humans** and other **species**. The CYP3A4 enzyme was shown to slowly increase in expression with age in **pigs** (Aleksa et al., 2004). In **mice** protein concentrations of the predominant isoform CYP3A11 was undetected in kidney at PNW 3-4, 9-10 and 9-10 months of age. The CYP3A25 enzyme showed low levels at PNW 9-10 and 9-10 months of age in females. It was undetected in males (Hersman and Bumpus, 2014).

Several members of the CYP4 family have been identified in the kidney, including CYP4A11, CYP4F2, CYP4F8, CYP4F11 and CYP4F12. These enzymes are known to metabolize arachidonic-, docosahexaenoic and eicosapentenoic acids, but are not directly related to a drug class. Data on the ontogeny/maturation of the renal CYP4 family is lacking in **most species**, including **humans**. The CYP4F4 enzyme expression was analyzed in **rats** and showed a peak at 2 weeks of age (Kwekel et al., 2013). The CYP4F4 enzyme levels doubled at PNW 8, but thereafter declined sharply by PNW 12 and PNW 16. The CYP4F5 enzyme expression also decreased by 50% at PNW 12-18 when compared with the PNW 4 expression. The CYP4F6 enzyme levels, in contrast, increased by 40% at PNW 8 and 4-fold by PNW 12. However, at 18 PNW CYP4F6 levels were reduced to their 4-week levels (Kalsotra et al., 2005). In **mice** high protein concentrations of CYP4A12 were noted in both sexes at PNW 3-4 and 9-10. At 9-10

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months concentrations were significantly decreased in females only (Hersman and Bumpus, 2014).

The CYP2C8 enzyme is known to metabolize the following substrates: amodiaquine, chloroquine, paclitaxel, repaglinide and rosiglitazone. In **humans** this gene is expressed in the first trimester and more predominant in the proximal tubule compared with the distal tubules (Cizkova et al., 2014; Johansson et al., 2014). Expression is rather stable between 5 and 20 weeks of *intra uterine* development. In adults, expression of this gene is slightly higher in both proximal as well as distal tubules.

The CYP2C9 known substrates are losartan, NSAIDs, oral hypoglycemics and S-warfarin. In **humans** the CYP2C9 gene is expressed in the first trimester (GW 5-12) (Johansson et al., 2014). Moreover, Cizkova et al. (2014) showed expression in both proximal and distal tubules between GW 5 and GW 20. Expression was slightly less in the proximal tubule of adults compared with *in utero* development, in distal tubules expression was more-or-less similar (Cizkova et al., 2014). Limited data was available on the ontogeny of CYP2C8 and CYP2C9 isoforms in rodent species. The CYP2C23 enzyme expression was noted to increase progressively from birth until declining at PNW3 in the **rat** (Marie et al., 1993). In **mice** data was available on CYP2C29 and CYP2C37. The CYP2C29 protein concentrations were very low in males at PNW3-4, 9-10 and 9-10 months of age. In females, protein concentrations could only be detected at PNW 9-10. The CYP2C37 enzyme showed moderate protein concentrations from PNW 3-4 up till adulthood, with a peak in females at PNW 9-10 (Hersman and Bumpus, 2014).

Just as there is co-regulation for transporters, the function of enzymes is also dependent on other factors. In the case of the CYP p450 systems, CYP p450 oxidoreductase is required for function. The importance of this enzyme is apparent due to observed embryonic lethality in knockout mice around day 8-9 (Shen et al., 2002; Henderson et al., 2003). Postnatal deletion is however

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viable and demonstrated in a conditional knockout model (Wu et al., 2003). Although this model has been extensively used to study effects on CYP p450 reactions, ontogeny of this enzyme in the kidney has not been studied.

Other metabolism families (table 3c)

The major other route of metabolism in adults involves the UGT catalyzed conjugation reactions. Many of them are present in **human**, but few have been described regarding ontogeny or maturation in the kidney. Exceptions are UGT1A1, which was detected in both the mesonephros and metanephros stages (Hume et al., 1995) and UGT2B7, which was more abundant in the fetal kidney compared with the liver (Ekstrom et al., 2013). In other species no fetal-adult relations have been described. Recently, pharmacokinetic modelers hypothesised that the rate limiting step in human neonatal liver metabolism may not be the UGT enzymes themselves, but the availability of uridine 5'-diphosphate glucuronic acid (UDPGA) (Liu et al., 2019). Human fetal kidney concentrations (GW 17-25) of UDPGA are approximately 1.5 times lower compared with adult kidney concentrations and 5- and 25-fold lower compared with, respective fetal and adult liver concentrations (Cappiello et al., 2000).

Sulfotransferases (SULT) are present and active in the kidneys, but ontogeny or maturation data is only available for a limited number of enzymes. The SULT1A1 enzymes, one of the more prominent members of the family, was detected at PNW 15 and remained unchanged in the first 1.5 postnatal years in **humans** (Gilissen et al., 1994). Another member of the same family, SULT1A3, shows to be more active during the intrauterine development phase. Levels of this enzyme are higher in human fetal (GW 18-25) kidneys compared with adult kidneys (Cappiello et al., 1991; Pacifici et al., 1993). Other described sulfotransferases were SULT1C2, which was shown to be present in human fetal kidney (Her et al., 1997) and SULT2A1, which was detected in human kidneys from the second half of gestation onwards and reached adult levels in the

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neonate (Barker et al., 1994). Sulfotransferases have also been studied in rodent species. In **rats**, SULT1C1 and SULT1C2 expression has been studied and shown to be very little or highly expressed in the fetal kidney, respectively (Nagata et al., 1993; Dunn and Klaassen, 1998; Xiangrong et al., 2000). The SULT1C2 enzyme could also be confirmed on the protein level (Xiangrong et al., 2000). In **mice**, the SULT family has been studied in the C57BL/6 strain. At an age of PNW 8, very low or absent expression of SULT1B1, SULT1E1, SULT2A1/2, SULT2B1, SULT3A1 and SULT4A1 was noted. The SULT1C1 and SULT1D1 enzymes, however, increased over time from 2 days before birth to PND 45. The SULT1C2 enzyme increased in expression from 2 days before birth up till birth and remained stable expression up to PND 10. Thereafter, SULT1C2 expression further increased. Interestingly, expression levels started to decline in males, but not in females, at PND 22 (Alnouti and Klaassen, 2006).

Sulfotransferases can only function in there is enough 3'-Phosphoadenosine-5'-phosphosulfate (PAPS) available to donate the sulfonate group. 3'-Phosphoadenosine-5'-phosphosulfate is formed from dietary inorganic phosphate and adenosine triphosphate in a cascade of reactions catalyzed by the protein PAPSs. The isozyme PAPSs1 is stably expressed in kidneys of mice from birth till PND 15 after which it somewhat decreases (Alnouti and Klaassen, 2006). In adult rat, mouse and dog PAPS concentration in the kidney is rather similar and approximately 3-4 times higher compared with humans (Brzeznicka et al., 1987; Cappiello et al., 1989; Klaassen and Boles, 1997). Fetal kidney concentrations of PAPS in common laboratory species have not been reported.

The glutathione S-transferase (GST) family consist of nine subclasses, whereby the alpha, the mu and the pi classes have been mostly described in the kidney. **Human** data showed GSTα protein to be detectable in kidneys from GW 8 onwards with increasing function in the first 2 life years (Hiley et al., 1989; Beckett et al., 1990; Raijmakers et al., 2001). The GSTμ enzyme

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was also detectable on a protein level from GW 8 and slightly increased in GW 13. The protein levels remain fairly constant postnatally up to adulthood (Beckett et al., 1990; Raijmakers et al., 2001). The most prominent GST in the prenatal stages was GSTπ, which was detected at the protein level from GW 8 and was pronouncedly increased in GW 13 (Raijmakers et al., 2001). After birth levels declined and remained lower during adulthood (Beckett et al., 1990; Raijmakers et al., 2001). All three GST family members were also confirmed to show enzyme activity from GW 8, indicating these are all fully functional during the prenatal stages. In other species only limited data on GST ontogeny are available. In **rat**, GSTα was noted to increase between PNW 1 and PNW 4 and GSTπ showed a relatively stable signal between PNW 1-4 (Oberley et al., 1995).

Other minor metabolism pathways, such as epoxide hydrolases, N-acetyltransferases, methyltransferases and amino acid conjugates have been very poorly described in the kidney. **Human** data showed epoxide hydrolases to be present and increasing in the kidney from 7.5 to 25 GW (Pacifici et al., 1983; Omiecinski et al., 1994) and N-acetyltransferases were shown to be present in the kidney at a level somewhat comparable with adult kidney tissue (Pacifici et al., 1986). Data on expression in the kidney of **other species** is currently lacking.

Renal excretion maturation

Renal excretion of drugs is the net result of three main processes: 1) GFR, 2) tubular secretion and 3) tubular reabsorption. Maturation of the kidney function has an impact on the renal excretion of drugs on the one hand, but might also affect absorption, distribution, metabolism and nonrenal clearance of drugs on the other hand. Especially during the first 2 years of life, changes in kidney function can alter drug exposure and drug response, potentially leading to a shift in efficacy/safety balance (Rodieux et al., 2015). Immaturity of the kidney function results in alteration of plasma clearance and prolongation of elimination half-life of renally cleared

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drugs, necessitating adaptations of the dose and/or the dosing interval (Kearns et al., 2003). During the **human** neonatal period, renal excretion of drugs is decreased due to immature GFR and tubular secretion, whereas similar or even greater excretion was observed for many drugs during late infancy and/or childhood. The latter necessitates higher doses on a per-kilogram basis in infants and in children to reach sufficient plasma concentration levels (i.e. dose per-kilogram of digoxin is much higher in infants than in adults) (Fernandez et al., 2011).

Renal drug excretion represents unbound (= "free") drugs that will be filtered across the glomerular membrane into the renal tubules. Alterations in plasma/tissue protein binding will be reflected in lower or higher concentrations of unbound drugs. An increase in unbound drug concentration will lead to an increase in renal clearance, as there is more available for glomerular filtration and/or tubular secretion. Even though plasma/tissue protein binding is a major determinant of drug disposition, the clinical implication of altered plasma/tissue protein binding is rather limited, but can sometimes require dosage adaptations (Grandison and Boudinot, 2000).

Knowledge of which renal drug transporters (i.e. OCT and OATP) are involved in renal drug clearance and their impact on renal excretion in the pediatric population needs to be taken into account when considering whether pediatric-adapted dosing regimens are required ('t Jong, 2014). Moreover, as suggested by Rodieux et al. (2015), it is important to map the polymorphisms of genes encoding for drug-metabolizing enzymes, drug transporters and drug targets (pharmacogenomics), since it might influence drug disposition and thereby alter the efficacy/safety balance. As stated above, detailed knowledge on transporter- and metabolism maturation is still lacking, urging the need for additional research.

Over the years, allometric scaling equations have been used to predict the size-related changes in clearance between species on the one hand and within species (i.e. in humans: adults to

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children) on the other hand. In neonates and infants, simple allometric methods based on body size alone do not suffice, since body size is not representative for overall organ function throughout the pediatric population (Mahmood, 2014). Therefore, incorporation of the role of maturation and growth of i.e. the kidney in allometric models should be applied. The latter is confirmed by Peeters et al. (2010), who used allometric models developed in rats, children and adults to predict the propofol clearance in children. The authors concluded that these models, based on bodyweight, could be used to predict the propofol clearance in children older than 2 years, but additional maturational functions should be incorporated in order to be able to correctly predict the clearance in younger children. Mahmood and Tegenge (2019) compared the predictive capacity of physiologically based PK modeling and allometric scaling (age-dependent exponent model) for 73 drugs to predict drug clearance in the pediatric population (neonates to adolescents). The predictive power to predict drug clearance was equal for both methods. The simplicity of allometric scaling in comparison to PBPK modeling favors allometry to estimate pediatric drug clearance and consequently to perform first-in-pediatric dose estimations.

Conclusion

The paradigm that children should not be regarded as small adults in terms of drug handling, nor should neonates be regarded as small children, is now generally accepted. Unfortunately, our knowledge of kidney ADME ontogeny is still sparse in some areas. The major kidney function characteristics such as GFR, RBF and concentrating ability are generally well understood, however detailed knowledge on transporter- and metabolism maturation is still lacking. Preclinical data in those areas is mostly restricted to rat and mouse only and generally only covers the expression levels of transporter or enzyme-encoding genes. Such expression levels do not necessarily need to correspond with actual protein abundance and function as we

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learned from human data. It is the interaction between all these characteristics that is responsible for the majority of pronounced differences in toxicity of pharmaceutical agents noted between neonates and older children and between pediatric and adult patients. Of additional note, the developing kidney is prenatally as well as postnatally sensitive/vulnerable to morphological and functional disturbances during its different phases of growth and differentiation. Drug administration can result in both morphological and functional renal changes, depending on the timing, level and duration of the exposure. Primarily more knowledge on a functional level is needed to predict the kinetics and toxicity in neonate/juvenile toxicity or efficacy studies and improve the risk assessment to the human population. Nevertheless, there are a wide variety of species that can be used in preclinical embryofetal and juvenile toxicity studies focusing on renal development that can be extrapolated to human kidney development.

Authorship contributions:

Drafting the scope and outline: Bueters, Bael, Schreuder, Gasthuys, Chen, Frazier

Collecting the data: Bueters, Bael, Schreuder, Gasthuys, Frazier

Writing/editing the manuscript: Bueters, Bael, Schreuder, Gasthuys, Chen, Frazier

Reviewing the manuscript: Bueters, Bael, Schreuder, Gasthuys, Chen, Frazier.

All authors were supported by their own institutions during the preparation of this manuscript and had no conflict of interest.

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Figure 1: Overview of transporters in the human kidney discussed in this review

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Tables:

Table 1. Completion of nephrogenesis and vasculogenesis of different species.

Species	Nephrogenesis	Vasculogenesis
Human*	GW 36	GW 34-36
Rat	PND 11-15	PND 17-19
Mice	PND 2-4	PND 7
Dog	PNW 2	PNW 6
Nonhuman primates*	GW 24	By birth
Pig	PNW 3	PNW 8-12

GW: gestational weeks, PNW: postnatal weeks, PND: postnatal days
*: Average gestational period is 40 weeks in human and 23-34 weeks in nonhuman primates (depending on specific species)

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Table 2. Age at which full maturation of some physiological functions of the kidney is attained.

	GFR	**RBF**	**Concentrating capacity**
Human	PNW 52-104	GW 32-35	PNW 52
Rat	PND 42	PND 16-24	PND 11
Mice	PND 28-32	PND 16-22	PND 21
Dog	PNW 8-10	PND 12	<PND 1
Nonhuman primate	PNW 26	<PND 1	PNW 20
Pigs	PNW 8[*1]	unknown	unknown

GFR: glomerular filtration rate; RBF: renal blood flow; PNW: postnatal week; PND: postnatal day, GW: gestational week
*1 conventional pig

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Table 3a. Cross-species overview of renal drug transporters.

Transporter	Human	Mice	Rat	Reference(s)
MDR1a/b (Pgp)	Expression of Pgp was noted from GW 5.5. Significant expression by GW 11 with increasing expression after birth and in adults. Protein abundance is lowest in newborns (PND 0-28)/infants (1-24 months) and reached adult (>16y) levels during the child stage (2-12y)	MDR1a/b was marginally expressed in newborns and was increased in the postnatal period, with a maximum expression on PND 21. At day 45 there was a decline in males, but not females.	Expression was marginal at birth and increased during postnatal stage with highest levels between PND 11-26.	van Kalken et al., 1992; Miki et al., 2005; Pinto et al., 2005; de Zwart et al., 2008; Cui et al., 2009; Konieczna et al., 2011; Sweeney et al., 2011; Xu et al., 2017; Cheung et al., 2019
BCRP	Significant expression was noted at GW 5.5 and 28. BCRP is upregulated in the term newborn and mostly reached adult levels before 2 years of age. Protein abundance is however similar between newborns and adults.	No fetal-adult relation described.	Expression was increased during postnatal stage compared with prenatal stage. During the postnatal stage expression was remained stable and highest expression was present in the adult stage.	de Zwart et al., 2008; Konieczna et al., 2011; Sweeney et al., 2011; Xu et al., 2017; Cheung et al., 2019
MRP1	Significant expression was noted at GW 5.5 and 28.	MRP1 was expressed at adult levels at birth. Female expression was predominant.	MRP1 was most highly expressed at birth.	Maher et al., 2005; de Zwart et al., 2008; Konieczna et al., 2011
MRP2	MRP2 shows similar gene expression levels from prematures (PND 0-28, GW<37) up till adult stages.	MRP2 levels was increased over time to reach adult levels during the first weeks of life.	Expression was increased in the postnatal stage compared with prenatal stage. During the postnatal stage expression was remained stable, but protein was increased and highest expression was presented in the mature stage.	Maher et al., 2005; de Zwart et al., 2008; Sweeney et al., 2011; Nomura et al., 2012; Cheung et al., 2019
MRP3	No fetal-adult relation described.	MRP3 levels were generally increased over time to reach adult levels. Female expression was predominant.	MRP3 was most highly expressed at birth.	Maher et al., 2005; de Zwart et al., 2008
MRP4	MRP4 shows similar gene expression levels from prematures up till adult stages.	MRP4 levels were generally increased over time to reach adult levels. Female expression was predominant.	Stable expression during fetal and early postnatal development. Higher expression in adult state.	Maher et al., 2005; Sweeney et al., 2011; Nomura et al., 2012; Xu et al., 2017; Cheung et al., 2019
OATP1A2 (rodent analogues OATP1,3-6)	No fetal-adult relation described.	OATP1A1 was hardly present at birth and showed high expression on PND 45 in males, but not females. OATP1A4 showed stable expression from PND -2 to 45. OATP1A6 expression started to increase 2 weeks after birth.	OATP1A4 peak levels were reached in the first week of birth and were then slowly decreased towards adult levels.	Cheng et al., 2005; de Zwart et al., 2008
OCT1	No fetal-adult relation described.	OCT1 expression was low before birth and was gradually increased in the first 2 PNW and peaked at PND 22, where after it remained rather stable.	OCT1 expression was increased from late prenatal development up till adult stage. Overall expression was only limited at birth.	Slitt et al., 2002; Alnouti et al., 2006; de Zwart et al., 2008; Sweeney et al., 2011; Ahmadimoghaddam et al., 2013; Xu et al., 2017
OCT2	Gene expression is lowest in the preterm newborn and reaches adult levels before 2 years of age. Protein abundance start to reach adult levels in the child stage.	OCT2 was undetected before birth, had a stable expression after birth and was increased somewhat at PND 22. From PND 30 onwards expression increased sharply in males, but remained unchanged in females.	OCT2 was slightly increased from the prenatal phase on but showed significantly increased expression at maturity.	Slitt et al., 2002; Alnouti et al., 2006; Sweeney et al., 2011; Xu et al., 2017; Cheung et al., 2019

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OAT1	OAT1 expression is lowest in preterm newborns and reaches adult levels at term birth or in infants. Protein abundance is lowest in term newborns and infants, levels in children and adolescents (12-16y) were approaching adult levels.	Expression was noted on day 15 of gestation and was increased progressively towards adulthood Organ culture showed positive transport activity.	OAT1 expression was increased during prenatal development, remained stable at postnatal development and was increased again at the mature age.	Lopez-Nieto et al., 1997; Nakajima et al., 2000; Pavlova et al., 2000; de Zwart et al., 2008; Truong et al., 2008; Hwang et al., 2010; Nagle et al., 2011; Sweeney et al., 2011; Nomura et al., 2012; Xu et al., 2017; Cheung et al., 2019
OAT3	OAT3 expression is lowest in the preterm newborn and reaches adult levels at the before 2 years of age. Protein abundance were lowest in term and newborn infants and rose to adult levels in the adolescent stage.	OAT3 was detected on day 14 of gestation and expression was gradually increased up to adulthood.	OAT3 expression was increased during the late prenatal development and kept increasing up till a mature age.	Pavlova et al., 2000; Buist and Klaassen, 2004; Hwang et al., 2010; Sweeney et al., 2011; Nomura et al., 2012; Xu et al., 2017
OCTn1	No fetal-adult relation described.	Expression was almost absent on PND -2, was gradually increased PNW 1 and doubles at PNW 2. From PNW 3 it increases again reaching maximum values around PND 40	OCTn1 showed 100-fold lower expression compared with adult levels at gestational day 13 and levels were started to increase at gestational day 18. Most pronounced upregulation was present in PNW 1 and PNW 4.	Slitt et al., 2002; Alnouti et al., 2006; Sweet et al., 2006; Sweeney et al., 2011
OCTn2	No fetal-adult relation described.	Very low expression at PND -2, which was increased pronouncedly at PNW 2. and reaches maximum expression around PND 35.	OCTn2 showed 10-fold lower expression compared with adult levels at gestational day 13 to 18. Most pronounced upregulation present in PNW 1; which was somewhat increased at PNW 4.	Slitt et al., 2002; Alnouti et al., 2006; Sweet et al., 2006; Sweeney et al., 2011
URAT1	URAT1 expression in infants and children is higher than in term newborns, adolescents and adults. URAT1 protein abundance was lower in term newborn and infants and reached adult levels at child stage.	URAT1 showed low expression at PND -2, which was greatly increased from PNW 2 onwards.	URAT1 main increase in expression was at PNW 1 and 4.	Cheng and Klaassen, 2009; Sweeney et al., 2011
PEPT2	No fetal-adult relation described.	Pept2 was expressed at PND -2 and was greatly increased at PNW 2.	Pept2 was increased at gestational day 18 and at PNW 4.	Sweeney et al., 2011
MATE1	MATE1 shows similar expression and protein abundance from premature up to adults.	MATE1 was present during PND -2 but was greatly increased from birth up to PNW 4.	MATE1 was increase steadily throughout gestational day 17 to 22 and increased more at PNW 4 MATE1 was even increased more at a later age of 6 months.	Lickteig et al., 2008; Sweeney et al., 2011; Xu et al., 2017; Cheung et al., 2019
NPT	No fetal-adult relation described.	NPT1, 2a and 2c were expressed at PND -2. Upregulation of the mRNA appears to start at postnatal PNW 2.	No fetal-adult relation described.	Cheng and Klaassen, 2009
ENT	No fetal-adult relation described.	ENT2 was expressed in a low amount at PND -2 and was decreased slightly in the first 2 PNW and is further reduced at PNW 7.	No fetal-adult relation described.	Cheng and Klaassen, 2009

Fetal-adult relations have not been described in nonhuman primates, dogs and pigs.
Abbreviations: MDR: multidrug resistance protein; Pgp: P-glycoprotein; BCRP: breast cancer resistance protein; MRP: multidrug resistance-associated proteins; OATP: organic anion transporter polypeptide; OCT organic cation transporter; OAT: organic anion transporter; OCTN organic cation novel transporter; URAT: urate transporter; PEPT: peptide transporter; MATE: multidrug and toxin extrusion; NPT: sodium-phosphate co-transporter; ENT: equilibrative nucleoside transporter; GW: gestational week; PND: postnatal day; PNW: postnatal week

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Table 3b. Cross-species overview of CYP p450 enzyme family.

Enzyme [1)]	Human	Pig	Mice	Rat	Reference
CYP3A4/CYP3A5	CYP3A4 was present in fetal kidney at GW 8. Levels were also present at pediatric age. Low levels were present in fetal and adult kidneys. CYP3A5 was present in fetal kidney at GW 28. CYP3A5 present in the pediatric population.	CYP3A4 expression was slowly increased from newborn to adult.	CYP3A11 protein was not detected at PNW 3-4, 9-10 and 9-10 months CYP3A25 protein showed low levels at PNW 9-10 and 9-10 months of age in females. It was undetected in males.	No fetal-adult relation described. No fetal-adult relation described.	Aleksa et al., 2004, 2005; Miki et al., 2005; Hersman and Bumpus, 2014
CYP2B6	No fetal-adult relation described.	CYP2b22 activity was present from birth and slightly lower on PND 1-10. Compared with PND 15-adulthood	CYP2b9 protein was stable between PNW 3-10 and decreased between PNW 10 and 10 months of age in females, but not in males.	No fetal-adult relation described.	Aleksa et al., 2004; Hersman and Bumpus, 2014
CYP2C8/CYP2C9	CYP2C8 was expressed in the first trimester (5-12 GW). CYP2C8 was expressed in all tubules from GW 5-20. Stronger expression was observed in adults. CYP2C9 incidental expression was observed in the first trimester (5-12 GW). CYP2C9 was expressed in all tubules from GW 5-20. Adult expression was slightly less in the proximal tubules.	No fetal-adult relation described.	CYP2C29 protein concentrations were very low in males at PNW 3-4, 9-10 and 8-10 months. In females presence was only noted at PNW 9-10. CYP2C37 showed moderate protein concentrations from PNW 3-4 till adulthood. With a peak in females at PNW 9-10. No fetal data available	CYP2c23 expression increased progressively from birth until declining at PNW 3.	Marie et al., 1993; Cizkova et al., 2014; Hersman and Bumpus, 2014; Johansson et al., 2014
CYP3A2	No fetal-adult relation described.	No fetal-adult relation described.	No fetal-adult relation described.	CYP3A2 young age (PNW 2) expression peak was observed.	Kwekel et al., 2013
CYP4A/F family	No fetal-adult relation described.	No fetal-adult relation described.	High protein concentration of CYP4A12 was noted in both sexes at PNW 3-4 and PNW 9-10. At 9-10 months concentrations were significantly decreased in females only.	CYP4F4 young age (PNW 2) expression peak was observed. CYP4F1 expression was stable between 4 and 18 PNW. CYP4F4 levels doubled at 8 PNW but thereafter declined sharply by 12 and 16 PNW. CYP4F5 expression also decreased by 50% at 12–18 PNW when compared with 4 PNW expression. CYP4F6	Kalsotra et al., 2005; Kwekel et al., 2013; Hersman and Bumpus, 2014

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			levels, in contrast, increased by 40% at 8 PNW and 4-fold by 12 PNW. However, at 18 PNW, 4F6 levels were reduced back to their 4 PNW levels.

1) Human Isoforms are listed for easy reference. Known animal isoforms were included in the evaluation.
Abbreviations: CYP: cytochrome-P450; GW: gestational week; PND: postnatal day; PNW: postnatal week
Fetal-adult relationships have not been described for dogs and nonhuman primates.

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Table 3c. Cross-species overview of other metabolizing enzyme families.

Enzyme	Human	Mice	Rat	Reference
UGT family	UGT1A1 was detected in mesonephros/metanephros stage. UGT2B7 was more abundant in fetal kidney than liver.	No fetal-adult relation described.	No fetal-adult relation described.	Lucier et al., 1977; Hume et al., 1995; Ekstrom et al., 2013
SULT family	SULT1A3 levels were higher in fetal (18-25 GW) kidneys than in adults. SULT1A1 was detected at 15 PNW and remained unchanged in the first 1.5 postnatal years. SULT2A1 was low to nondetectable before 25 GW but was then increased substantially during the latter half of gestation to approach adult levels during neonate. SULT1C2 was detected in fetal kidneys.	SULT 1b1, SULT1e1, SULT2a1/2, SULT2b1, SULT3A1, SULT4a1 levels were very low or absent (8 PNW). SULT1C1 and SULT1D1 increased over time from PND -2 to PND 45. PAPSs1 remained equal over this time period. Renal SULT1C2 mRNA was expressed at high levels in fetuses 2 days before birth and remained constant after birth until 10 PND, when mRNA levels began to increase. However, 22 PND, mRNA levels began to decline in male kidneys, whereas female levels remained constant.	SULT1C1 mRNA expression was mainly in liver, with very low or no expression in kidney, spleen, lung, colon, intestine, or brain. SULT1C2 mRNA and protein are highly expressed in kidney, followed by stomach and liver.	Cappiello et al., 1991; Nagata et al., 1993; Pacifici et al., 1993; Barker et al., 1994; Gilissen et al., 1994; Her et al., 1997; Dunn and Klaassen, 1998; Xiangrong et al., 2000; Alnouti and Klaassen, 2006
GSTA1/A2	GSTA1/A2 protein were detected and active in the kidney from 8 GW and increased in function in the first 2 life years	No fetal-adult relation described.	GSTA1 was increased from PNW 1 to 4, GSTA2 was only detected from PNW k3-4 No fetal data available.	Hiley et al., 1989; Beckett et al., 1990; Oberley et al., 1995; Raijmakers et al., 2001
GSTm	GSTm levels were constant pre- and postnatal. GSTm protein was detectable at GW 8 and slightly increased at GW 13. Concentration was on average similar in adult life.	No fetal-adult relation described.	No fetal-adult relation described.	Beckett et al., 1990; Raijmakers et al., 2001
GSTP1	GSTP1 activity was decreased from pre- to postnatal age. GSTP1 protein was detectable at GW 8 of and rapidly increased at GW 13. Concentration was lower in adult life.	No fetal-adult relation described.	GSTP showed a relatively stable signal at PNW 1 to 4 No fetal data available.	Beckett et al., 1990; Oberley et al., 1995; Raijmakers et al., 2001
EPHX	EPHX1 was present and increased from 7.5 to and 25 GW.	No fetal-adult relation described.	No fetal-adult relation described.	Pacifici et al., 1983; Omiecinski et al., 1994
NATS	NATS was present in fetuses and activity was somewhat comparable between fetal and adult tissue.	No fetal-adult relation described.	No fetal-adult relation described.	Pacifici et al., 1986

Fetal-adult relationships have not been described for nonhuman primates, dogs and pigs.
Abbreviations: UGT: Uridine 5'-diphospho-glucuronosyltransferase; SULT: sulfotransferase; GST: glutathione-s-transferase; EPHX: epoxide hydrolase; NATS: N-acetyltransferase; GW: gestational week; PND: postnatal day; PNW: postnatal week.

Figures:

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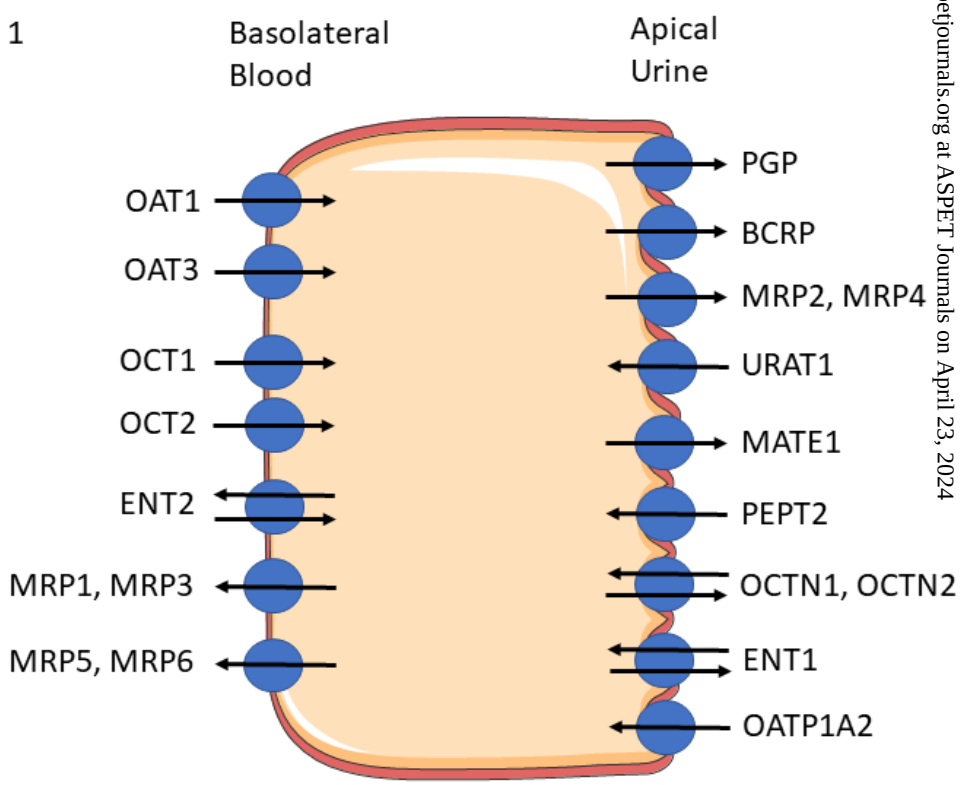

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