Basics and Dynamics of Neonatal and Pediatric Pharmacology

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Abstract Understanding the role of ontogeny in the disposition and actions of medicines is the most fundamental prerequisite for safe and effective pharmacotherapeutics in the pediatric population. The maturational process represents a continuum of growth, differentiation, and development, which extends from the very small preterm newborn infant through childhood, adolescence, and to young adulthood.

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Developmental changes in physiology and, consequently, in pharmacology influence the efficacy, toxicity, and dosing regimen of medicines. Relevant periods of development are characterized by changes in body composition and proportion, developmental changes of physiology with pathophysiology, exposure to unique safety hazards, changes in drug disposition by major organs of metabolism and elimination, ontogeny of drug targets (e.g., enzymes, transporters, receptors, and channels), and environmental influences. These developmental components that result in critical windows of development of immature organ systems that may lead to permanent effects later in life interact in a complex, nonlinear fashion.

The ontogeny of these physiologic processes provides the key to understanding the added dimension of development that defines the essential differences between children and adults. A basic understanding of the developmental dynamics in pediatric pharmacology is also essential to delineating the future directions and priority areas of pediatric drug research and development.

Keywords Ontogeny • Pediatric population • Classification • Maturation • Developmental changes • Pharmacokinetics • Pharmacodynamics • Neonatal pharmacology • Pediatric pharmacotherapeutics • Long-term safety

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ACE	Angiotensin-converting enzyme
ACh	Acetylcholine
AN	Anorexia nervosa
ATR	Angiotensin receptor
BN	Bulimia nervosa
CDL	Chronic lung disease
Clsys	Systemic clearance
CYP	CytochromeP450
DCT	Distal convoluted tubule
GABA	Gamma-aminobutyric acid
GnRH	Gonadotropin-releasing hormone
HPG	Hypothalamic–pituitary–gonadal
KCC2	Potassium-chloride cotransporter type 2
nAChRs	Nicotine acetylcholine receptors
NAT	*N*-Acetyltransferase
NEC	Necrotizing enterocolitis
NCCT	Sodium-chloride cotransporter
NKCC1	Sodium-potassium-2-chloride cotransporter type 1
PDA	Patent ductus arteriosus
PDE	Phosphodiesterase
P-gp	P-glycoprotein

RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SIDS	Sudden infant death syndrome
SLT	Salt-losing tubular disorder
SSRI's	Selective serotonin reuptake inhibitors
TDM	Therapeutic drug level monitoring
UGT	Uridine diphosphate glucuronosyltransferase
V(d)	Volume of distribution

1 Introduction

A safe and effective medication for children requires a fundamental understanding and integration of the role of ontogeny in the disposition and actions of medicines. As the most fundamental prerequisite, one has to consider the basic principle that children are not small adults!

The German-American and father of American pediatrics, Abraham Jacobi (1830–1919), recognized the importance of and the need for age-appropriate pharmacotherapy when he emphasized: "*Pediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but … has its own independent range and horizon*" (Kearns et al. 2003). Along that line of argumentation some years later the German pioneer of pediatric pharmacology, Rudolf Fischl (1862–1942), wrote: "*Die Therapie des Kindesalters bedeutet nicht lediglich eine Restriktion der Behandlung der Erwachsenen, sondern baut sich auf genaue Kenntnisse der Physiologie dieser Lebensepoche auf*" (Fischl 1902). Moreover, he stated: "*Viel Unglück hat schon die Mathematik in der Medizin angerichtet, und eine einfache Berechnung der sogenannten refrakten Dosen für das Kindersalter aus der Gewichtsdifferenz können leicht ebenfalls ein solches anrichten*" (Fischl 1902). Harry Shirkey (1916–1995), the well-known American pharmacist and pediatrician, wrote in his textbook on Pediatric Therapy with other words: "*The long list of dosage rules based on age, body weight or surface and their respective authors is testimony that no rule is entirely satisfactory in producing an exact fraction of the known adult dose that is applicable to a particular child*" (Shirkey 1975). This fundamental knowledge of determining the pediatric dosage of a medicine is even today – 100 years later – often ignored. Thus, as the first step for a successful approach to pediatric therapeutics, one must appreciate the differences among pediatric subpopulations with their typical features and health problems and the nonlinear and dynamic process of maturation. The ontogeny of basic physiologic processes provides guideposts for understanding the mechanisms underlying differences between different developmental stages within the pediatric and adult populations.

2 Classification of the Pediatric Population

The pediatric population represents a continuum of growth and development, which extends from the very small preterm newborn infant through childhood, adolescence, and to young adulthood (Fig. 1). The internationally agreed (Food and Drug Administration 2000), and to some extent arbitrary, classification of the pediatric population is as follows:

- Preterm infants (<37 weeks gestation)
- Term newborn infants (0–28 days)
- Infants and toddlers (>28 days to 23 months)
- Children (2–11 years)
- Adolescents (12 to 16–18 years, depending on the region)

Substantial changes in body composition and proportions accompany growth and development. Embedded within this continuum of growth and development is substantial individual variation. Developmental changes in physiology and, consequently, in pharmacology influence the efficacy, toxicity, and dosing regimen of medicines (posology) used in children. It is, therefore, important to review characteristics of the relevant periods of development from birth, through adolescence, to adulthood.

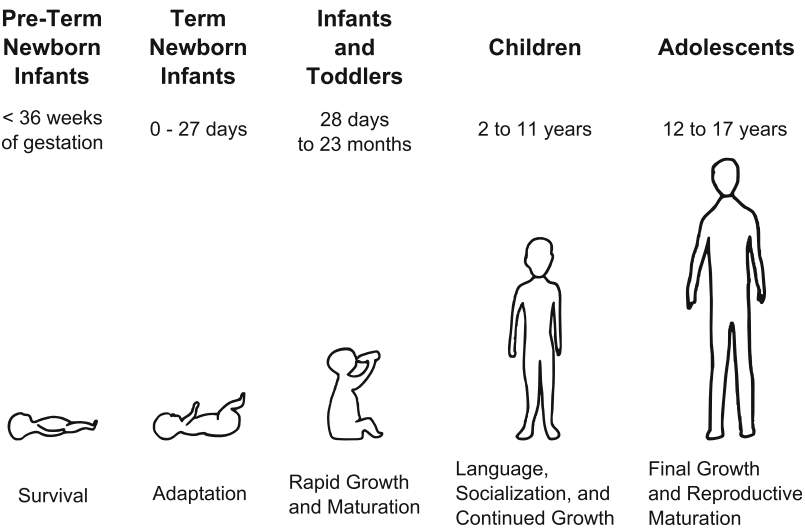

Fig. 1 Five stages of development. The pediatric population extends from the preterm and term newborn infant through childhood, and adolescence, or even to young adulthood. Each period of development has its own very specific characteristics, such as period of survival, period of adaptation, period of rapid growth and physiological maturation, period of language, socialization, and continued growth, and period of final growth and reproductive maturation

3 Description of the Five Relevant Periods of Development, Their Typical Features, Common Health Problems, and the Impact on Pediatric Pharmacotherapy

3.1 The Preterm Newborn: Period of Survival

3.1.1 Body Composition and Proportion

Body composition correlates with both gestational and postnatal age, and it continues to change significantly during the first year of life (Ahmad et al. 2010; Ellis 2000; Fomon and Nelson 2002). High body water content and extracellular/intracellular water ratio as well as very low body fat and muscle mass in the preterm infant are important contributors to altered volumes of distribution (V(d)) of hydrophilic and lipophilic medicines or highly tissue-bound drugs such as the cardiac glycosides. For example, the larger total body water content of the newborn infant (approximately 80% as compared with 60% of body weight by 5 months of age) results in a larger mg/kg-loading dose of water-soluble medicines, such as the aminoglycosides (Pacifici 2009).

The relatively large head circumference and cranial volume is the leading characteristic of the body proportion from the very preterm newborn to the older infant and toddler. Relatively large brain weight and cerebral blood flow, limited plasma protein binding capacity, as well as increased blood–brain barrier permeability all predispose the CNS to higher concentrations of administered medicines than later in life (Strolin Benedetti et al. 2005).

Likewise, increased skin permeability needs to be considered whenever a medicine is applied on the skin. Increased dermal absorption may increase risk of adverse effects as with antibacterial agents such as alcohol and hexachlorophene solution (Stewart and Hampton 1987) or provide an option for painless and noninvasive transdermal drug delivery in preterm newborns as with caffeine for apnea (Barrett and Rutter 1994).

3.1.2 Developmental Changes of Physiology with Their Pathophysiology and Safety Hazards

The Very Preterm Newborn (<30 Weeks of Gestation)

The very (extremely) preterm newborn around the 22–23 weeks of gestation is at the limit of viability because the incompletely developed complex pulmonary–cardiovascular system is not prepared to function well in the extrauterine environment, even with intensive support. The multiple hazards are as follows:

- *Respiratory distress syndrome (RDS)*
  Before primitive alveoli have formed and surfactant production has begun, the lung cannot adequately function as an organ of gas exchange. At an early and intermediate stage of pulmonary maturation, the very preterm newborn requires administration of exogenous surfactant and prolonged mechanical ventilation to prevent and/or treat severe RDS. These treatments, along with lung immaturity, are commonly associated with development of chronic lung disease of prematurity (Stevens et al. 2007).
- *Persistent fetal circulation*
  In this condition, the transitional from fetal to neonatal circulation is characterized by pulmonary hypertension and patent ductus arteriosus (PDA), which are responsible for marked right to left circulatory shunting and hypoxia.
- *Incomplete cerebral autoregulation*
  Impaired or completely missing cerebral autoregulation is a risk factor for intraventricular hemorrhage with parenchymal brain injury and posthemorrhagic complications later in life such as cerebral palsy, hydrocephalus, and cognitive deficits (Szabó et al. 2009).
- *Necrotizing enterocolitis (NEC)*
  Immaturity of the gastrointestinal tract and immune system predisposes the very preterm infant to NEC with life-threatening complications including fulminate septic shock (Neu 2007; Thompson and Bizzarro 2008).

The Late Preterm Newborn (31–36 Weeks of Gestation)

At this stage, the infant is rarely in a life-threatening situation, but still is at risk for a series of serious health problems related to immaturity of several organ systems. These include:

- *Transient tachypnea*
  Lack of clearance of lung fluid and relative deficiency of pulmonary surfactant may cause transient tachypnea and RDS (Raju et al. 2006).
- *Relapse into fetal circulation*
  Partial relapse into fetal circulation may lead to pulmonary hypertension of the newborn. This condition may be associated with sepsis or sometimes with maternal use of selective serotonin reuptake inhibitors (SSRIs) (Konduri and Kim 2009; Koren and Boucher 2009; Ramachandrappa and Jain 2009).
- *Temparature instability and apnea*
  CNS immaturity may lead to poor temperature control (Raju et al. 2006) and failure of respiratory control with central apnea (Hunt 2006).
- *Peristaltic dysfunction*
  Immaturity of the gastrointestinal tract may lead to feeding problems related to peristaltic dysfunction and failure of sphincter control in the esophagus, stomach, and intestines (Lebenthal and Lebenthal 1999; Neu 2007).

– *Jaundice and hypoglycemia*
  Prolonged hyperbilirubinemia and hypoglycemia are risk factors for brain injury (Raju et al. 2006).
– *Susceptibility to infection*
  An incompetent (naïve) immune system increases susceptibility to infection and predisposes the infant to sepsis (Clapp 2006).

3.1.3 Major Organs of Metabolism and Elimination

Developmental immaturity has a major impact on drug disposition in preterm infants. Changes in the V(d) have already been mentioned in the context of body composition. The next most important pharmacokinetic factor for pediatric dosing is reduced systemic clearance (Cl_{sys}) due to immaturity of the liver and kidneys, the most important organs involved in the process of drug metabolism and elimination. The relatively large V_d and reduced Cl_{sys} in neonates commonly require a higher loading dose and lower maintenance dose of many drugs (Bartelink et al. 2006). The gray baby syndrome, a fatal cardiovascular collapse, is a frequently cited historical example of drug toxicity on the basis of immature hepatic glucuronidation of chloramphenicol leading to supratherapeutic systemic concentrations when infants were given doses used in older children (Asmar and Abdel-Haq 2005).

Hepatic Metabolism

Because of quantitative and qualitative differences in hepatic drug metabolism, medicines that are primarily metabolized by the liver may need to be administered in reduced doses until the age of about 2 months (Alcorn and McNamara 2002; Allegaert et al. 2007; Anderson and Lynn 2009; Bartelink et al. 2006). Enzymes most commonly involved in drug metabolism are those of the cytochrome P450 (CYP) family (phase I reactions) and the uridine diphosphate glucuronosyltransferase (UGT), sulfotransferase, glutathione-*S*-transferase, and *N*-acetyltransferase (NAT) families (phase II reactions). Each of the specific isozymes within a family matures at different rates during the first several years of life. The effect on metabolism of a specific medication depends on the dominant enzymatic pathway(s) responsible for metabolism of the drug. Several studies have been performed with medicines, which are frequently used in neonatology. Indomethacin is a substrate for CYP2C9 (Koukouritaki et al. 2004; Rodrigues AD 2005); phenobarbital is also a substrate for CYP2C9 in addition to CYP2C19 (Goto et al. 2007; Löscher et al. 2009); caffeine is metabolized by CYP1A2 and NAT2 (Pons et al. 1989); and morphine is a specific substrate for UGT2B7 (Coffman et al. 1997). These medicines function as markers for hepatic metabolic activity, which is low relative to older children and adults, leading to reduced total clearance of these drugs during the neonatal period (al-Alaiyan et al. 2001; Battino et al. 1995; Hartley et al. 1994; Yaffe et al. 1980).

A qualitative difference in hepatic drug metabolism is exemplified by the different metabolite profile of theophylline in newborns with the attendant risk of caffeine toxicity (Bory et al. 1979; Lowry et al. 2001). Theophylline and caffeine are frequenty used to treat apnea of prematurity. In contrast to adults, in preterm newborns caffeine is a biotransformation product of theophylline and may accumulate to toxic levels with chronic theophylline dosing. To avoid this complication, caffeine is the preferred methylxanthine to treat apnea of prematurity. This reduces the risk of methylxanthine toxicity and avoids the need for routine therapeutic drug level monitoring (TDM) (Charles et al. 2008; Natarajan et al. 2007; Steer and Henderson-Smart 2000).

Renal Elimination

At birth renal function is rather low, with a GFR down to 1 ml/min/kg, and does not approach adult levels before the age of 6–12 months (Alcorn and McNamara 2002). Tubular secretion matures more slowly and full renal function is reached at approximately 2–3 years of age (Fawer et al. 1979; Fettermann et al. 1965). Delayed maturation of tubular reabsorption leads to glomerulotubular imbalance with the risk of salt and water wasting (Alcorn and McNamara 2002; Bartelink et al. 2006; Celsi and Aperia 1993). On the positive side, the decreased ability to concentrate aminoglycosides in the tubular epithelium contributes to decreased nephrotoxicity of aminoglycosides in newborns (Fleck and Bräunlich 1995; McCracken 1986).

Thus, it is not surprising that furosemide, which is mainly excreted as a substrate of the PAH transport pathway unchanged in the urine, has a prolonged plasma half-life (often exceeding 24 h) and a very low renal clearance particularly in the very preterm newborns (Mirochnick et al. 1988; Peterson et al. 1980). Similarly, weak organic acids such as penicillins and cephalorins, which are frequently used in newborns, also have very low total clearances in preterm infants. The kidney almost exclusively excretes these medicines by an active tubular organic anion transport system, which has 20–30% of adult capacity at birth and approaches adult capacity at approximately 7–8 months (Alcorn and McNamara 2002).

3.1.4 Ontogeny of Drug Targets in the Perinatal Period

During the perinatal period many fundamental changes take place, which are unique to the newborn and are not observed again during infancy, childhood, and adolescence. To describe all these changes, which certainly have an impact on drug targets, would be far beyond the scope of this subsection. Thus, only selected aspects, where substantive progress is relevant to pediatric pharmacology, including molecular pharmacodynamics and pharmacogenetics, are discussed.

Receptors/Binding Sites

– *Adrenergic receptors*
The ontogeny of drug–receptor interactions, particularly of the adrenergic and cholinergic systems, has been of long-standing interest to pediatric pharmacologists (Boréus 1972). However, methods for isolation of homogeneous cells from organs of the fetus or the newborn ensuring that the cells and receptors have not been altered during isolation and purification have not been adequately developed (Whitsett et al. 1982). Nevertheless, there is ample direct and indirect experimental evidence of ontogenic regulation of receptor number and function. In the newborn rat brain, there are an increased number of β-adrenergic receptors during the first weeks of life, while at the same time the number of α-adrenergic receptors is declining after an initial rise in the rat brain shortly after birth (Whitsett et al. 1982). Unfortunately, due to methodological reasons, similar data in human tissue are often missing. Thus, more readily accessible circulating nucleated blood cells, e.g., leukocytes, have been used with the assumption that they may reflect the status of adrenergic receptors in the actual target organ of interest (Fraser et al. 1981). Decreased β-adrenergic receptor sites have been described in human cord blood neutrophils (PMN) of infants vaginally delivered at term (Roan and Galant 1982). These findings may reflect ontogenic differences between the neonatal and adult PMN. However, the effect of increasing catecholamine secretion during the stress of delivery resulting in downregulation of the β-adrenergic receptors cannot be ruled out.

More recent molecular pharmacology studies in the postnatal rat devoted to the ontogenesis of β-adrenergic signaling indicate that, in contrast to the receptor downregulation and desensitization of β-adrenergic receptors observed in the adult, the numbers and responsiveness of β-adrenergic receptors increase in most tissues of the immature organism in response to prolonged treatment with betamimetics during the postnatal period. This developmental stage of the rat approximately correlates with the mid-to-late second and early third trimester of human gestation (Slotkin et al. 2003). The process of downregulation and desensitization are not inherent properties, but rather acquired during the above-mentioned vulnerable time interval when pregnant women may be treated with betamimetics for preterm labor. Thus, intrauterine overstimulation with betamimetics during this critical period of prenatal development can induce a permanent shift in the balance of adrenergic-to-cholinergic tone with the risk of inducing functional and behavioral teratogenesis. This is a currently offered working hypothesis in an attempt to explain the association of prolonged (3–4 weeks) betamimetic treatment for tocolysis and bronchodilatation of the mother with increases in functional and behavioral disorders, including psychiatric disorders (e.g., autism), poor cognitive and motor function, and school performance as well as changes in blood pressure (e.g., hypertension) in the offspring (Witter et al. 2009).

– *Prostanoid receptors*
Prostanoids are abundantly generated throughout the perinatal period. They are thought to be key players in the regulation of ductus arteriosus tone and in the

autoregulation of blood flow to the brain and retina as well as to the renal and splanchnic vascular beds (Seyberth and Kühl 1988; Smith 1998; Wright et al. 2001). The rapid changes in vascular physiology during postnatal life are not only accomplished by rapid changes of the synthesis and metabolism of these autacoids, but also by rapid adjustments in the turnover of prostanoid receptor expression. This has been particularly well studied in the regulation of ductus arteriosus tone (Smith 1998).

In utero, the main factors maintaining patency of the ductus arteriosus are low oxygen tension and high levels of PGE_2 and PGI_2 (Fig. 2), which are acting through prostanoid EP_4 and IP receptors (Smith 1998; Smith and McGrath 1994; Leonhardt et al. 2003; Wright et al. 2001). Both receptors are coupled to adenylate cyclase (Boie et al. 1994; Honda et al. 1993). cAMP generated by this enzyme is considered to be the main intracellular second messenger involved in smooth muscle relaxation, which is consistent with the potent vasodilator effect PGE_2 and PGI_2 on the ductus. After birth, increased ductal oxygen tension and a fall of prostanoid levels, which is accompanied by a marked reduction of

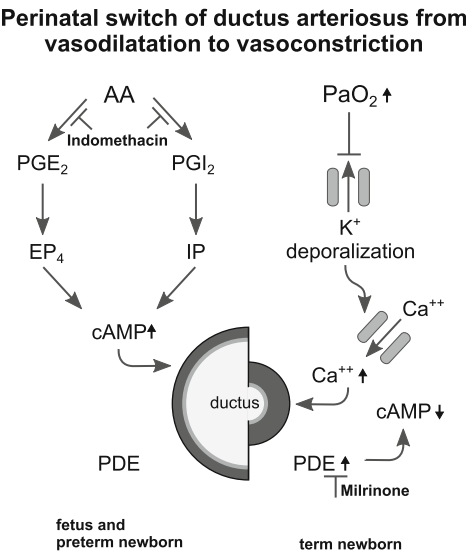

Fig. 2 Perinatal switch of ductus arteiosus from vasodilation to vasoconstriction. In utero, and to some extent in the pretem newborn, patency of the ductus arteriosus is maintained by high levels of PGE_2 and PGI_2 in addition to low oxygen tension. The potent vasodilator effect PGE_2 and PGI_2 on the ductus is mediated through PGE_2 and PGI_2 receptors, EP_4 and IP, respectively, by increasing cAMP. cAMP is considered to be the main intracellular second messenger involved in smooth muscle relaxation of the ductus. Postnatal increase in arterial PaO_2 plays an important role in functional closure of the ductus, which starts with oxygen-induced inhibition of O_2-sensitive potassium channels. This leads to smooth muscle cell depolarization and consequently to increased calcium influx through voltage-dependent L-type calcium channels. In parallel with advancing gestation, smooth muscle phosphodiesterase (PDE) isoforms in the ductus are increasingly expressed leading to decreased intracellular cAMP, thus supporting the shift from dilatation to constriction of the ductus arteriosus. PDE inhibitors such as milrinone, however, can prevent this shift

prostanoid receptor expression, induces closure, thus promoting contraction of the ductus arteriosus (Bouayad et al. 2001; Smith et al. 2001; Wright et al. 2001).

Preterm infants with RDS and mechanically ventilated lungs are prone to develop a symptomatic PDA on the basis of persistent PGE_2 and PGI_2 release probably from the ventilated lung (Smith 1998; Seyberth et al. 1984). Thus, at the present time the most appropriate pharmacological intervention is the treatment with prostaglandin synthesis inhibitors (Fig. 2), such as indomethacin (Hammerman et al. 2008; Leonhardt and Seyberth 2003; Ohlsson et al. 2008). However, this systemic inhibition of endogenous prostanoid synthesis has some negative consequences. Firstly, all prostanoid effects are inhibited including those of TxA_2 and $PGF_{2\alpha}$, which do have additional vasoconstrictor potential via specific receptors on the ductus. Secondly, inhibition of all endogenously synthesized prostanoids has negative effects on a variety of physiological and protective functions of blood cells and organs such as platelets, kidney, and intestinal tract (Seyberth and Kühl 1988; Smith 1998; Wright et al. 2001). A potent and selective EP_4 receptor antagonist might be a more appropriate alternative for pharmacologically induced ductal closure (Momma et al. 2005b; Smith 1998; Wright et al. 2001). A selective EP_4 receptor agonist, on the other hand, could be an ideal tool in maintaining the ductus open in newborns with ductus-dependent congenital obstructive heart malformations (Momma et al. 2005a; Leonhardt et al. 2003; Smith 1998).

During experimental studies, predominately with fetal lambs, another important aspect of clinical relevance has become apparent. With increasing gestational age, and, certainly after birth, before irreversible anatomic remodeling of the ductus takes place there is a decreasing ductal sensitivity to vasodilatory prostanoids. This desensitization is not only accomplished by a reduction of PGE_2 receptor density but also by inhibition of the receptor-coupled mechanism, which leads to lower intracellular cAMP concentrations (Waleh et al. 2004). With advancing gestation, smooth muscle phosphodiesterase (PDE) isoforms in the ductus are increasingly expressed leading to increased cAMP degradation and decreased intracellular cAMP, thus inducing a shift from dilatation to constriction of the ductus arteriosus (Liu et al. 2008). This crucial role of these phosphodiesterases in the regulation of ductal tone needs to be considered when proposing use of PDE inhibitors such as milrinone for treatment of cardiac failure in preterm infants (Toyoshima et al. 2006) (Fig. 2). There is good experimental and clinical evidence that PDE 3 inhibitors prevent closure of the ductus arteriosus in preterm newborns, thus antagonizing the positive inotropic effect of these drugs in these infants (Paradisis et al. 2009; Toyoshima et al. 2006).

Channels and Transporters

– *Channel maturation and regulation of ductal tone during the perinatal period*
Developmental changes of channel activities have been studied during rapid physiological changes around birth. Besides the prostanoid system complex,

non-PG procontractile pathways are involved in the oxygen-induced functional closure of the ductus arteriosus. The postnatal increase in arterial PaO_2 plays an important role in active ductal constriction (Fig. 2). This functional closure of the ductus starts with oxygen-induced inhibition of O_2-sensitive potassium channels, which leads to smooth muscle cell depolarization and consequently to increased calcium influx through voltage-dependent L-type calcium channels (Nakanishi et al. 1993; Thébaud et al. 2004; Waleh et al. 2009). In preparation for extrauterine life, the expression of the calcium channels starts to increase during late gestation, while the inhibitory effect of the potassium channels declines (Clyman et al. 2007; Waleh et al. 2009). Thus, in preterm infants this maturation of active ductal vasoconstriction has not been fully completed, which contributes to persistent ductal patency. Since changes in membrane potential clearly play a critical role in regulating ductal tone, compounds acting at O_2-sensitive potassium channels are promising candidates for pharmacomanipulation of the ductus arteriosus after birth in both term and preterm infants (Smith 1998).

This understanding of the ontogenetic changes in tuning the muscular wall of the ductus is essential to understanding the mechanism by which chronic in utero inhibition of prostanoid synthesis is associated with temporary delay or even prevention of postnatal ductal closure. At the same time, when synthesis of relaxing prostanoids is inhibited, the expression of the O_2-sensitive potassium channel and calcium L-channel genes in the ductus wall is also reduced. In other words, the capability of O_2-induced ductal constriction has been weakened or even abolished (Momma et al. 2009; Reese et al. 2009). These experimental findings have been corroborated by clinical observations. The so-called paradoxical failure of ductal closure can be induced either after prenatal administration of indomethacin for preterm labor or after indomethacin treatment immediately after birth for prevention of patent ductus (Hammerman et al. 1998; Momma et al. 2009; Norton et al. 1993).

– *Channels and transporters involved in transepithelial electrolyte transport*
Another field, in which channels and transporters play an important role, is the transepithelial electrolyte transport in the developing kidney. Tubular reabsorption of salt and water begins maturing with very dynamic changes during the perinatal and early postnatal period (Alcorn and McNamara 2002). The so-called pharmacotyping of inherited hypokalemic salt-losing tubular disorders (SLT) associated with secondary hyperaldosteronism was extremely helpful in identifying common targets for mutations and developing interventions by pharmacologists (Reinalter et al. 2004) (Fig. 3). The furosemide-like SLT with a loop disorder and the thiazide-like SLT with a distal convoluted tubule (DCT) disorder are the two major types of SLT (Seyberth 2008). The phenotypes of the two genetic and the pharmacologically distinct "human knockouts" – defects of NKCC2 and NCCT – are almost identical, which include, in addition to hypokalemic alkalosis in both of them, polyuria, isosthenuria, and hypercalciuria for the furosemide type and hypomagnesemia and hypocalciuria for the thiazide type (Jeck et al. 2005; Peters et al. 2002). Moreover, patients with a loop disorder

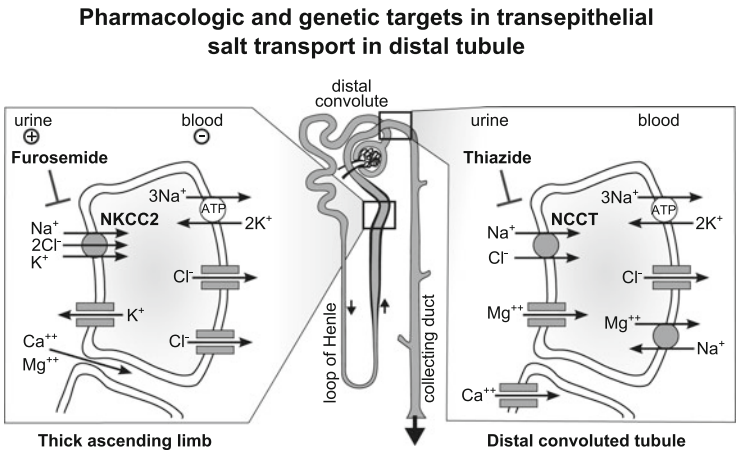

Fig. 3 Pharmacologic and genetic targets in transepithelial salt transport in distal tubule. Inherited hypokalemic salt-losing tubular disorders (SLT) associated with secondary hyperaldosteronism have common targets for mutations and pharmacological interventions such as the furosemide-sensitive sodium-potassium-chloride cotransporter (NKCC2) and the thiazide-sensitive sodium-chloride cotransporter (NCCT). The furosemide-like SLT is primarily a polyuric and hypercalciuric loop disorder, while the thiazide-like SLT is a distal convoluted tubule (DCT) disorder, which is characterized by persistent hypomagnesemia and hypocalciuria

do not respond to furosemide but do respond, as expected, to thiazide treatment (Köckerling et al. 1996). In contrast, the diuretic response in patients with a DCT defect is just the opposite (Colussi et al. 2007). The time of clinical presentation is another major difference between the two tubular disorders (Peters et al. 2002). While the loop defect presents in utero with fetal polyuria associated with the development of polyhydramnios and premature birth, the thiazide-like DCT defect rarely becomes symptomatic before late infancy with hypokalemic alkalosis as a consequence of a relatively mild salt and water diuresis.

From these experiments of nature one can predict that, in contrast to loop diuretics, thiazide diuretics are not going to be very efficacious in preterm infants. The NCCT in the DCT probably is not active and/or not expressed at that early stage of development. This hypothesis might be supported by the results of a well-controlled drug study with preterm infants (Green et al. 1983). While infants receiving furosemide clearly exhibited diuretic activity, *the response in those given chlorothiazide* (20 mg/kg/d) *was no different from patients not given diuretics*. Immunohistological studies with renal tissue of very preterm infants need to be done to prove this hypothesis directly.

Endocrine/Paracrine System and Renal Function

Complex endocrine/paracrine interactions of the renin-angiotensin and the renal prostanoid system are critically involved in the protection and maintenance of

adequate renal blood perfusion and function. The extreme low blood pressure of the preterm infant with a mean arterial pressure of about 30 mm Hg makes an effective filtration pressure highly dependent on the activity of vasoconstrictive angiotensin II on the one hand and on vasodilatory renal prostanoids on the other hand (Evans and Moorcraft 1992; Guignard 2002; Prevot et al. 2002; Seyberth et al. 1991). This well-coordinated vasoconstriction and vasodilatation of the afferent and efferent glomerular vasculature renders renal function oversensitive to any angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor (ATR) antagonist and prostanoid synthesis inhibitor. Thus, besides their intrinsic potency one cannot expect any major differences in renal toxicity among ACE inhibitors and ATR antagonists as well as among prostanoid synthesis inhibitors (FitzGerald and Patrono 2001; Frölich 1997; Guignard 2002; Prevot et al. 2002). As long as one avoids a prolonged ineffective circulatory volume created by extreme fluid restriction, unnecessary furosemide treatment, and failure of ductal closure (all are additional stimuli for the renin-angiotensin system), no major renal damage to the preterm newborn is to be expected (Leonhardt et al. 2004; Seyberth et al. 1983). Under this condition, even a 10- to 100-fold overdose of indomethacin, caused by medication error, does not lead to significant deterioration of renal function (Narayanan et al. 1999; Schuster et al. 1990).

3.1.5 Environment and Critical Windows/Periods of Development of Immature Organ Systems with Resulting Permanent Effects on Phenotype

A classical pediatric example of this phenomenon – also sometimes called "programming" – is congenital hypothyroidism. If this condition remains undetected and untreated shortly after birth, it gives rise to lifelong phenotypic changes and learning difficulties. There is no comparable condition in adulthood because although hypothyroidism occurs in later life, the central nervous system has ceased developing. Now we discuss similar effects due to postnatally applied environmental and/or pharmacological factors.

Pathophysiology of Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is an instructive model to study the long-term consequences of an interruption of a complex maturation process by premature birth, particularly if it happens in the middle of a critical time window of development. In addition, the course of this vascular disease can be followed under clinical conditions by repeated inspections of the retina.

ROP remains an important cause of morbidity in the extremely preterm infant. The significantly improved survival of very premature infants due to advances in neonatal intensive care during the last decades has decreased mortality of the most immature newborns, but has not diminished the incidence of ROP worldwide

(Holmström et al. 2007; Wheatley et al. 2002). ROP is a multifactorial disease of the developing retinal vasculature under environmental, nutritional, and genetic influence. The postnatal interruption of a very vulnerable ongoing development around 26 weeks of gestation is a major trigger of this biphasic ocular disease (Hellström et al. 2009; Kermorvant-Duchemin et al. 2010). During the first ischemic phase after birth, premature exposure of the retina to hyperoxia induces an arrest in vascular development with a degeneration of already existing blood vessels. In the second, vasoproliferative phase the avascular and ischemic retina triggers a compensatory release of proangiogenic factors. This leads to abnormal, upregulated extraretinal neovascularization, which may progress to retinal detachment and finally to blindness. Basically, ROP is the result of an unbalanced activity of various proangiogenic (such as VEGF and IGF1) and antiangiogenic (such as thrombospondin-1) factors, interacting with protective effects of nutritional factors (such as docosahexaenoic acid), and cytotoxic effects of oxidative and nitro-oxidative stress-dependent mediators generated from interaction of *trans*-arachidonic acid with the nitrogen dioxide radical or its precursors (Balazy and Chemtob 2008; Kermorvant-Duchemin et al. 2010). This more complex view on the pathophysiology of ROP, however, poses new challenges for more rational pharmacologic interventions in the future. Presently, ROP-induced blindness in children, adolescents, and young adults has to be considered as a major cause of all visual disorders.

Postnatal Dexamethasone Treatment and Neurological Outcome

Over the past 20 years, corticosteroid use in the preterm infant has fallen in and out of favor. Steroids were introduced in the 1980s as a mode of preventing and treating chronic (inflammatory) lung disease (CLD) in the preterm infant population. This use has been targeted toward low birth weight infants who cannot be weaned off the ventilator. Dose, duration, and timing of treatment with dexamethasone, the steroid typically used in NICUs, have varied. Corticosteroids given postnatally are potentially neurotoxic when given in high dose or when used in the first 96 h of life. The mechanism by which they cause central nervous system damage is unknown, but may be related to increased risk of periventricular leukomalacia (Levene 2007). Unfortunately, there is still a need for long-term follow-up and reporting of late neurological and developmental outcomes, especially among surviving infants, in those who participated in randomized trials of early postnatal corticosteroid treatment and who have already been sent to school (Doyle et al. 2010).

3.2 The Newborn Term Infant: Period of Adaptation

3.2.1 Body Composition and Proportion

Body water content and extra/intracellular water ratio remain high as compared to infants and children. However, with each week of gestational age body fat content

increases when compared with preterm newborns (Ahmad et al. 2010; Ellis 2000; Fomon and Nelson 2002). Besides relatively large body surface area and head circumference as well as high permeability of blood–brain barrier and skin, rapid weight gain is a typical feature during this period of growth and development (Strolin Benedetti et al. 2005). Greater vulnerability to CNS drug toxicity (e.g., local anesthetic agents and opioids) is in part the consequence of the decreased blood–brain barrier (Latasch and Freye 2002)

3.2.2 Developmental Changes of Physiology with Their Pathophysiology and Safety Hazards

Although the term newborn is in a much more mature stage of development than the preterm newborn, they share several health problems with each other.

Drug Risk of Kernicterus

Icterus neonatorum (physiological jaundice) is certainly a safety hazard for both the term and preterm newborn. It is the result of increased bilirubin production following postnatal breakdown of fetal red blood cells combined with transient limitation in the conjugation of bilirubin by the liver. Excess circulating unconjugated bilirubin is bound to high-affinity acidic binding sites on plasma albumin, from where it can be displaced by highly bound acidic drugs, such as sulfisoxazole and ibuprofen, thereby increasing the concentration of free unconjugated bilirubin that may diffuse into the CNS. This increases the risk of kernicterus in newborn infants (Ahlfors 2004; Gal et al. 2006).

Metabolic Risk During Adaptation

Metabolic instability during the adaptation period shortly after birth may cause symptomatic hypoglycemia and hypocalcemia with seizures. This adaptive instability is often an endocrine/metabolic emergency situation leading to hospital admission (No authors listed 2004). Besides prematurity and intrauterine growth retardation, gestational diabetes is the most common cause for this neonatal complication (Jain et al. 2008a, b).

Immature Immune System

Immaturity of innate and adaptive immune responses in the perinatal period predisposes the neonate to increased infectious morbidity and mortality, the most common complications for all newborns (No authors listed 2004; Satwani et al. 2005).

Increased Susceptibility to Seizure

In addition to the anatomical and metabolic causes of seizures, the newborn brain is inherently prone to seizures as a consequence of incomplete neuronal maturation processes. The first months of postnatal life are critical for brain development (Ben-Ari and Holmes 2006; Dubois et al. 2008). At this age cerebral growth and maturation are intense and are influenced by multiple external stimuli encountered after birth. Besides dendritic growth and synaptic overproduction (in the gray matter), which is followed by synaptic pruning, myelination in white matter is essential for fast impulse conduction and for the structure maturation of functional networks (Ben-Ari and Holmes 2006; Dubois et al. 2008; Holopainen 2008). It is thought that at this stage the excitatory activity is enhanced and might contribute to the developing brain's greater capacity for activity-dependent plasticity. Myelination is a long nonlinear process that runs from the last trimester of gestation through the second decade of life with a peak in the first postnatal year. Besides these structural changes, complex changes in development and function of neurotransmitter systems also occur including the postnatal excitatory-to-inhibitory switch in gamma-aminobutyric acid (GABA) signaling. These functional changes are described in more detail in "Neurotransmitters, Transporters, and Channels".

3.2.3 Drug Disposition

Enteral Drug Absorption

Ongoing changes in growth, function, and differentiation of the gastrointestinal tract occur during adaptation to normal postnatal life. These changes may have significant effects on systemic delivery of medicines taken by the oral route. Obviously enteral drug absorption and bioavailability of medicines, which are administered by mouth, become quite important, as oral dosing is the most common and convenient route of administration.

In the first hours and days after birth, the intestinal weight and the mucosal mass almost double to accommodate the change from umbilical cord to oral feeding, which is similar to the change from parenteral to oral feeding (Commare and Tappenden 2007). This rapid intestinal growth and functional development is stimulated by feeding of colostrum, which is rich on peptide growth factors such as EGF, TGF alpha, and IGF-1. The large amount of secretory IgA in colostrum, which has a high systemic bioavailability, may also play a role in intestinal development in addition to providing immunologic protection (Commare and Tappenden 2007).

Several important examples illustrate the spectrum of dynamic developmental changes of the gastrointestinal tract during early infancy. These include altered gastric acid secretion, gastrointestinal transit time, and biliary and pancreatic exocrine function, all of which can significantly affect drug absorption and bioavailability of orally administered medicines in the first weeks of life.

Although parietal cells are well developed at term, the gastric pH is neutral at birth. Decreased capacity for hydrogen ion secretion persists throughout infancy, particularly represented by decreased acid production following pentogastrin stimulation (Anderson and Lynn 2009; Stewart and Hampton 1987; Strolin Benedetti et al. 2005). In addition, gastric contents are buffered by frequent feedings and gastric emptying is delayed. Altogether, these factors significantly influence the time course of drug absorption and bioavailability of acid-labile proteins and medicines such as growth factors and penicillins, respectively (Strolin Benedetti et al. 2005). Gastrointestinal absorption may also be facilitated for macromolecules such as lactalbumin from human milk or for aminoglycosides in early infancy as a consequence of the immature gastrointestinal mucosal barrier with increased permeability (Axelsson et al. 1989; Bhat and Meny 1984). In contrast, there are also examples of decreased absorption, such as the absorption of fat-soluble vitamins (vitamins D and E) in newborn infants probably because of the inadequate bile salt concentration in the ileum (Strolin Benedetti et al. 2005) or poor lipase hydrolysis of orally administered esters of a prodrug such as the palmitate ester of chloramphenicol (Shankaran and Kauffman 1984). Similarly, one step beyond intestinal absorption and hepatic uptake, the ester prodrug oseltamivir is only partially hydrolyzed to the active oseltamivir carboxylate by human carboxylasases. As the activity of these enzymes is not fully developed in fetuses and young children (Yang et al. 2009), one has to expect a low systemic bioavailability of the active metabolite and a low efficacy of this neuraminidase inhibitor in newborn infants and young children.

Little information regarding the clinical effects of ontogenetic changes of cytochrome P450 enzymes and transporter proteins such as P-glycoprotein (P-gp) in the small bowel is available (Johnson and Thomson 2008). Many oral medicines used in pediatrics are major substrates for intestinal forms of CYP3A. In duodenal biopsy specimens from pediatric patients aged 2 weeks to 17 years, CYP3A4 expression and function were continuously increased with age (Johnson et al. 2001). CYP3A4 was practically absent in the fetal duodenum and was expressed at relatively low levels in the newborn, indicating a low first-pass metabolism of pediatric medicines such as erythromycin (Johnson and Thomson 2008). There is also some evidence that expression of the transporter protein P-gp is very low in the intestines of term infants as compared to young adults (Miki et al. 2005).

Reduced expression of CYP3A and P-pg in newborns and young children can result in increased bioavailability of medicines. For example, a study on oral midazolam in preterm infants showed a higher bioavailability of 49% compared to 27–36% in children (de Wildt et al. 2002; Johnson and Thomson 2008). However, the effect of reduced intestinal and hepatic first-pass metabolism on bioavailability can offset several other bioavailability reducing factors such as altered gut physiology (see above), intraluminal pH, reduced gastric emptying, or intestinal transit time.

Major Organs of Metabolism and Elimination

Decreased systemic clearances for most medicines are mainly related to immaturity of hepatic and renal function (Alcorn and McNamara 2002; Rane 2005). Under normal conditions, parturition triggers the dramatic development of hepatic metabolism and renal function of the newborn term infant. However, there is marked variability in the various maturation processes among the individual drug-metabolizing enzymes and renal excretory functions, which often last over the whole first year of life. Thus, this situation is a rapidly changing transitional phase between the state of a newborn and that of an infant and a toddler (Alcorn and McNamara 2002; Bartelink et al. 2006; Strolin Benedetti et al. 2005). Clearly, at that early stage of development both genetic polymorphisms and ontogeny have a major impact on individualized pharmacotherapy (Allegaert et al. 2007).

The Breast-Fed Infant

Under certain circumstances, breast-feeding and maternal pharmacotherapy can become a neonatal risk. This has been demonstrated by fatal opioid poisoning in neonates, whose breast-feeding mothers are ultrarapid metabolizers of codeine to morphine (Madadi et al. 2009). In this situation, the high maternal morphine levels in breast milk can deliver an excessive morphine load to the low metabolizing infant, resulting in pharmacologically significant opioid levels. However, in general with a few exceptions such as bromocriptine, cocaine, ergotamine, or lithium most maternal medicines are relatively safe for nursing infants (Berlin 2005; Berlin et al. 2009).

3.2.4 Ontogeny of Drug Targets in the Neonatal and Postnatal Periods

Receptors/Binding Sites

Opioid receptors are not fully developed in the newborn rat – one of the most appropriate animal models to study the human species – and mature into adulthood (Freye 1996; Latasch and Freye 2002). A phenomenal increase in opioid binding sites occurs during maturation. Receptor density varies by brain region, with earlier development of caudal and later development in rostral parts of the CNS. Earlier development of opioid receptors in the medulla and pons, where the respiratory center is located, is consistent with the clinical observations that the mean plasma concentration of morphine that induces respiratory depression is in all pediatric age groups including the newborns in the same range, while the mean blood level to suppress pain is – with some overlap – about four to five times higher in newborns and young infants as compared to older infants and children (Bouwmeester et al. 2003; Lynn et al. 1993; Olkkola et al. 1988). These pharmacological differences of opioids in newborns, if neglected, may be a source of adverse drug reactions

(e.g., respiratory depression) when attempting to provide rapidly effective opioid analgesia in newborns.

Neurotransmitters, Transporters, and Channels

The present understanding of seizures in the developing brain is derived from animal models. Experimental models provide only a limited view of the complexity of clinical data; however, the electrophysiological, molecular, and anatomical features of seizures in the developing brain can usually transcend interspecies differences (Ben-Ari and Holmes 2006). In addition, during the early postnatal period, a time when the immature brain is highly susceptible to seizures, GABA exerts a paradoxical excitatory action in all animal species, including primates.

The mechanism of increased excitability of the immature brain is basically described as follows (Ben-Ari and Holmes 2006; Ben-Ari et al. 2007): During the early postnatal period, at a time when the immature brain is highly susceptible to seizures, GABA, which in the adult brain is the primary inhibitory neurotransmitter, exerts paradoxical excitatory action. GABA is initially excitatory because of a larger intracellular concentration of chloride in immature neurons compared to mature neurons. The shift from a depolarizing to a hyperpolarizing chloride current is mediated by an active sodium-potassium-2-chloride cotransporter type 1 (NKCC1) that facilitates the accumulation of chloride in neurons and by a delayed expression of a neuron-specific potassium-chloride cotransporter type 2 (KCC2) that extrudes chloride to establish adult concentrations of intracellular chloride. The depolarization by GABA of immature neurons is sufficient to generate sodium action potentials and to activate voltage-dependent calcium channels, leading to a large influx of calcium that in turn triggers long-term changes of synaptic efficacy. The synergistic action of GABA and calcium channels is unique to the developing brain and has many consequences on the impact of GABAergic synapses, such as seizure susceptibility. In addition, agents that interfere with the transport of chloride exert an antiepileptogenic action. With maturation, there is increasing function of KCC2 and decreasing function of NKCC1, which explain the declining strength of depolarization with age. For the clinical consequences of these ontogenetic changes in early infancy, see “Seizures”.

3.2.5 Environment and Critical Periods/Windows of Development of Immature Organ Systems with Resulting Permanent Effects

Two examples that demonstrate the sensitivity of time windows of the brain maturation and neuronal plasticity are presented.

Neonatal Painful Injuries and Their Long-Term Effects on Pain Response Later in Life is an Appropriate Example in This Context

The evidence that untreated or insufficiently treated pain in neonates and infants results in long-term adverse consequences (e.g., hyperalgesia) stems from several well-planned studies such as the randomized clinical trial on the effect of neonatal circumcision with and without a topical local anesthetic on pain response during subsequent vaccination 4–6 months later (Taddio et al. 1997). Even in extremely preterm infants, painful procedures during intensive care and surgery have an impact on somatosensory perception later in life (Walker et al. 2009; Hohmeister et al. 2010). Thus, the immature CNS is a challenge when managing pain treatment in infants with an emphasis on the need for a longer term view (Fitzgerald and Walker 2009).

Inappropriate Treatment of Neonatal Seizures Also Has Long-Term Effects on Brain Development and Function

Microcephaly, postnatal epilepsy, developmental delay, cerebral palsy, and behavioral problems are commonly associated with repeated or prolonged and electroencephalographically proven neonatal seizures (Glass and Wirrell 2009; Holmes 2009). While separating the consequences of seizure from consequences of the underlying etiology is clinically quite difficult, there is a considerable body of evidence from animal studies, which support the hypothesis that neonatal seizures can adversely interfere with the highly regulated developmental processes of the brain (Holmes 2009; Holopainen 2008). These animal data indicate that neonatal seizures, in contrast to seizures in a mature stage of the brain with fixed circuitry, are followed by long-lasting and persistent sequelae. These detrimental consequences are caused by alterations of developmental programs rather than by neuronal cell death, as occurs in adults. Decreases in neurogenesis and sprouting of mossy fibers, long-standing changes in signaling, and finally failure to construct efficient networks are the consequences of these alterations. These anatomic and physiologic changes correlate well with behavioral dysfunction and permanent handicaps later in life (Holmes 2009; Holopainen 2008).

All these reports provide good evidence for the need to prevent seizures in neonates. However, highly effective and safe anticonvulsive medicines for neonatal seizures with appropriate target- and age-specificity are not currently available, although some promising drug targets for the immature brain have been proposed (Glass and Wirrell 2009; Sankar and Painter 2005). The most commonly used first-line anticonvulsants, phenobarbital and phenytoin, are borderline effective and potentially neurotoxic for the developing brain (Bittigau et al. 2003).

3.3 The Infant and Toddler: Period of Rapid Growth and Physiological Maturation

3.3.1 Body Composition and Proportion

At this stage of development young children are still rapidly growing. Body weight typically doubles by 5 months of age and triples by 1 year. By the first birthday, body length and surface area increase by 50 and 200%, respectively. During this period of rapid growth, accumulation of fat is remarkably rapid during the first 6 months of age. In contrast, body water content, particularly the extracellular/intracellular ratio, continues to decrease throughout infancy (Fomon and Nelson 2002). From the drug disposition point of view, it is notable that the weight of liver and kidney relative to total body weight reaches maximum in the 1- to 2-year-old child, at the period of life when capacity for drug metabolism and elimination also tends to be greatest (Kauffman 2005; Murry et al. 1995)

3.3.2 Developmental Changes of Physiology with Their Pathophysiology and Typical Disorders with Their Health Problems

Respiratory Tract Infections

During the stage of intense lung growth and airway remodeling, small airway size predisposes the child to acute obstructive lower airway diseases, e.g., bronchiolitis (see also "Receptors/Binding Sites"), as well as to upper respiratory tract infections. These infections probably lead to edema and dysfunction of the Eustachian tube, which frequently contributes to middle ear infection (otitis media) (Kerschner 2007).

General Susceptibility to Infectious Diseases

Postnatal maturation of the immune system is not yet complete during early childhood, similar to the respiratory system (Holt et al. 2005). The reduced capability to express a sustained immune response predisposes young children to infectious diseases. In addition, this concurrent maturation of immunologic and respiratory functions may have implications for programming of long-term response patterns to exogenous inflammatory stimuli within the immune and respiratory systems (Holt et al. 2005).

Seizures

As already mentioned in "Increased Susceptibility to Seizure" and "Neurotransmitters, Transporters, and Channels", this period of maturation is associated with

the highest tendency for seizure activity of anytime in life. A large number of pathological processes may lead to seizures, including birth trauma and hypoxic–ischemic insults immediately after birth, systemic infections and metabolic imbalances in neonates, or fever in febrile seizures, which typically happen in infants and young children (Ben-Ari and Holmes 2006). The high excitatory state of the immature brain may also have some impact on the paradoxical effects of midazolam in the very young (Tobin 2008).

Neoplastic Diseases

Embryonic tumors such as neuroblastoma, nephroblastoma (Wilms tumor), and retinoblastoma are most common during the first year of life. These tumors are much less common in older children and adults after cell differentiation processes have slowed considerably (Kadan-Lottick 2007).

3.3.3 Major Organs of Metabolism and Elimination

Frequently but not always, older infants, toddlers, and young children (see also "Functional and Physiological Processes with Their Pathophysiology and Typical Disorders and Their Health Problems") exhibit the greatest overall drug clearance, which is the result of the high metabolic and excretory function of liver and kidney. For example, the half-life of diazepam is shortest in infants and longest in preterm newborns and the elderly, with the magnitude of differences being more than threefold (Coffey et al. 1983; Kauffman 2005; Mandelli et al. 1978). This "toddler overshoot" may lead to therapeutic failure in cases where insufficient dose for age is administered (Anderson and Lynn 2009; Chen et al. 2006; Läer et al. 2005). (For more clinically relevant examples, see "Major Organs of Metabolism and Elimination".)

3.3.4 Ontogeny of Drug Targets

Receptors/Binding Sites

Obstructive bronchiolitis responds poorly to β-adrenergic agonists (betamimetics) due, at least in part, to reduced β-adrenergic receptor sites in the bronchial tree of the wheezing toddler (Chavasse et al. 2002; Gadomski and Bhasale 2006; Lenney and Milner 1978; Schindler 2002). Lack of betamimetic response may also be due to small airways, mucus secretion, and to vasodilatation with mucosal edema of the bronchial wall in bronchiolitis. Betamimetics probably have minimal effect on airway edema as opposed to bronchial smooth muscle contraction. Thus, the most likely explanation of this inconsistency or even failure of a bronchodilator response

is the heterogeneity of causes for infantile wheezing (Barr et al. 2000; Subbarao and Ratjen 2006).

Mediators

More recently, another mediator system has been discussed that might be involved in hyperresponsiveness of the tracheal–bronchial system of an infant or toddler. In a well-established guinea pig maturational model that utilizes tracheal strips from infant, juvenile, and adult animals, the role of airway smooth muscle in immature airway hyperresponsiveness has been studied (Chitano et al. 2005). In contrast to the adult, the infantile airway smooth muscle characteristically has a prostanoid-mediated reduction of spontaneous relaxation during electric field stimulation (Wang et al. 2008). Inhibition of prostanoid synthesis abolishes this reduced relaxation and the age difference. A major role for leukotrienes was excluded. Thus, it was concluded that the reduced spontaneous relaxation in immature airway smooth muscle of the guinea pig and probably the airway hyperresponsiveness in the young is associated with and most likely causally related to increased release of contractile prostanoid ($PGF_{2\alpha}$, PGD_2, and TXA_2) (Wang et al. 2008). However, extrapolation of the animal data to infants and toddlers with obstructive airway disease has not yet been validated through well-designed efficacy and toxicity studies with prostanoid synthesis inhibitors. Such well-controlled clinical studies would be quite helpful in resolving the debate as whether ibuprofen is deleterious or protective in children with asthma-related symptoms (Kanabar et al. 2007; Kauffman and Lieh-Lai 2004).

Immune function

Another system, which is subjected to a variety of maturation processes, is the complex in vivo immune system. This complexity makes it extremely difficult to assess its activity quantitatively. Thus, an in vitro model with peripheral blood monocytes has been established, which enables the quantification of cellular pharmacodynamics of the immunosuppressant cyclosporine (Marshall and Kearns 1999). Two surrogate biomarkers of effect have been chosen: Cell proliferation as a functional, yet nonspecific, marker of lymphocyte response to antigen and IL-2 expression as a specific marker of CD4 + lymphocyte activation. As reflected by significant age dependence in the derived pharmacodynamic parameters of IC_{50} (cell proliferation) and IC_{90} (IL-2 expression), the cellular targets for cyclosporine action obtained from infants (<12 months of age) showed a twofold or respectively a sevenfold higher sensitivity to cyclosporine as compared with children, adolescents, and young adults (Marshall and Kearns 1999). This factor, if neglected, may be a source of iatrogenic risk during immunosuppressive therapy of an infant, e.g., after allograft transplantation.

Thermoregulation

In a PK/PD study with ibuprofen, a more favorable antipyretic response was observed for infants compared with older children, despite a pharmacokinetic profile whose parameter estimates were independent of age (Kauffman and Nelson 1992). A mechanism for this age-related difference in the antipyretic response is postulated as follows: Relative surface area in infants is 1.7 times of that in children (>6 years). The skin is the primary organ through which heat is emitted. So the patient with the greatest body surface area relative to the body mass will be most efficient at decreasing body temperature (Kauffman and Nelson 1992).

3.3.5 Environment and Critical Window of Development

Tobacco Exposure Contributes to Sudden Infant Death Syndrome

A critical window of vulnerability of the nicotinic acetylcholine receptors (nAChRs) is hypothesized (Cnattingius 2004; Dwyer et al. 2009; Kinney 2009).

Sudden infant death syndrome (SIDS) remains the leading cause of postnatal infant mortality. There is a major association between intrauterine exposure to cigarette smoking and postnatal environmental tobacco smoke and the risk for SIDS. Furthermore, this risk of death is positively correlated with daily cigarette use (Hunt and Hauck 2007). In searching for an underlying biological mechanism (s), the "brainstem hypothesis" was born (Kinney 2009), which appears to be quite logical as the brainstem is the key brain region that controls the autonomic nervous system including breathing, blood pressure, chemosensitivity, temperature, and upper airway reflexes.

Although SIDS most likely results from a complex interaction of several dysfunctional neurotransmitter systems in the brainstem, there is good evidence from the clinical literature and experimental animal models that the diverse effects of nicotine exposure interfere with the critical regulatory role of nAChRs during prenatal, early postnatal, and even adolescent brain maturation (Dwyer et al. 2009). Various maturational processes in the brain are physiologically regulated by acetylcholine (ACh) via activation of nAChRs, which are ligand-gated ion channels. In accordance with the key regulatory role of ACh throughout ontogenesis, there is a transient appearance and alteration in the subunit composition of nAChRs, particularly during critical periods when brain maturation is most sensitive to perturbation (Dwyer et al. 2009). This is consistent with the key regulatory role of ACh of nAChR ontogenesis. Thus, it is not surprising that this transmitter system can be perturbed by exogenous nicotine exposure during vulnerable developmental windows, leading to serious and persisting consequences.

Methods to assess the function of the autonomic nervous system in infants of mothers who smoked will be essential to investigating the longer term effects of nicotine exposure. So far, during passive repositioning (60° head-up tilt) nicotine-exposed infants exhibit persistent (up to 1 year) cardiovascular stress

hyperreactivity with orthostatic dysregulation (Cohen et al. 2010). It remains to be explored, if this autonomic dysfunction in infants of smoking mothers leads to longer lasting "reprogramming" of infant blood pressure control mechanisms and eventually to hypertension. If this were found to be so, autonomic dysregulation in the infant would potentially be an early predictive test for long-term suseptibility to cardiovascular complications later in life.

3.4 The Child: Period of Language, Socialization, and Continued Growth

3.4.1 Body Composition and Proportion

This period is characterized by slower growth rate with slender figure, increasing muscular mass, and relative stable body habitus until the pubertal growth spurt. In general, the various composition compartments – except the extracellular water compartment – remain basically unchanged during this period of steady growth (Ellis 2000; Kauffman 2005).

3.4.2 Functional and Physiological Processes with Their Pathophysiology and Typical Disorders and Their Health Problems

Four Diseases with Immune Dysfunction

- *Rheumatic diseases* of childhood, including connective tissue and collagen diseases, are characterized by autoimmune activity of T- and B-lymphocytes. Typical systemic but nonspecific manifestations are arthralgia, weakness, and fever, which make it absolutely necessary to exclude infections and malignancies (Miller 2007).
- *Acute glomerulonephrits*, such as poststreptococcal glomerulonephritis, is mediated by nephritogenic immune complexes and activation of the complement system. It is most common in children aged 5–12 years and uncommon before the age of 3 years (Davis and Avner 2007).
- *Childhood asthma* represents the most common allergic disorder in children, with severe immune dysregulation and marked expansion of T helper type 2 (Th2) cells that secrete cytokines favoring IgE synthesis and eosinophilia (Leung 2007). Approximately 80% of all asthmatics report disease onset prior to 6 years of age (Liu et al. 2007).
- *Diabetes mellitus type 1* is the most common endocrine–metabolic disorder of childhood and adolescence with two peaks of presentation occurring at the age of 5–7 years and at the time of puberty. The first peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of

school (Alemzadeh and Wyatt 2007). The pathogenesis of this disorder is considered to be an autoimmune destruction of pancreatic islet β-cells, which eventually leads to insulin deficiency.

Epilepsy

Childhood absence epilepsy is the most common form of pediatric seizures. This benign idiopathic generalized epilepsy in an otherwise apparently healthy child is characterized by daily frequent but brief spells. It is uncommon before the age of 5 years and typically goes into remission at the age of 10–12 years with a generally good prognosis (Guerrini 2006).

Neoplastic Diseases

The most common lymphohematopoietic neoplastic diseases, i.e., acute lymphoblastic leukemia and lymphomas, have a striking peak incidence between 2 and 6 years of age. In addition to this age relationship, genetic and environmental risk factors have been observed such as Down syndrome and ionizing radiation (Kadan-Lottick 2007; Tubergen and Bleyer 2007). It is of note that pediatric neoplastic diseases differ markedly from adult malignancies (predominately solid cancers) in prognosis, distribution, tumor site, and molecular biology.

Neurobehavioral Disorders

This period is characterized by increased intellectual performance, rapid language acquisition, socialization, and appearance of behavior disorders. The most common neurobehavioral disorder of childhood and one of the most prevalent chronic health conditions affecting school-aged children are the attention-deficit/hyperactivity disorders (ADHD). Multiple factors have been implicated in the etiology of ADHD, such as perinatal complications (e.g., toxemia and traumatic delivery), maternal smoking and alcohol use, and genetic disposition (Raishevich and Jensen 2007). Unfortunately, a childhood diagnosis of ADHD often leads to persistent ADHD throughout the life span. Besides psychosocial and behaviorally oriented treatment, psychostimulant medication is a therapeutic option. However, this last option is not without risk, particularly when carried out over an extended period of time (see “Ontogeny of Drug Targets”).

Accidents

Intensified physical activity, practice of skills, and participation in competitive sports lead to increased risk of vehicular accidents and sports-related injuries at

schools or playground, particularly among middle-school-aged children (6–11years of age). Upper extremity and head injuries are by far most common.

3.4.3 Major Organs of Metabolism and Elimination

The child at this stage of development is intermediate between the immature infant and the young adult (Kauffman 2005). The clearances of many hepatically metabolized medicines, such as theophylline (Hendeles and Weinberger 1983), omeprazole (Litalien et al. 2005), midazolam (Reed et al. 2001), and isoniazid (McIlleron et al. 2009) are increased in children (ages 2–11 years) compared with those of adults. This also applies to medicines, which are predominantly eliminated by the kidney, such as sotalol (Läer et al. 2005) and amikacin (Vogelstein et al. 1977). Consequently, higher doses are often required to achieve comparable therapeutic levels.

3.4.4 Ontogeny of Drug Targets

Glucose Metabolism

Recently, Hussain and coworkers reported hypoglycemia in children secondary to β-blocker treatment (Hussain et al. 2009). They presented five patients (1–5 years) out of 570 patients at their institution who were prescribed regular β-blockers over the same time period, who had severe hypoglycemic episodes while taking noncardioselective β-blockers (nadolol and propranolol) for prevention of arrhythmia. From these data, they estimated an overall risk of hypoglycemia to be around 1%. However, when only those children younger than six years of age were considered, they speculated that the hypoglycemic risk is threefold higher. Thus, at that age young children, who are per se prone to idiopathic ketotic hypoglycemia, have to be monitored very carefully when treated with β-blockers, which decreases glycogenolysis, gluconeogenesis, and lipolysis. At least two major possibilities for this instability of glucose homeostasis have to be considered: (1) maturational dysregulation in the adrenergic system, including particularly signal transduction via the β2-adrenergic receptors; or (2) some intrinsic hepatic weakness of glucose mobilization combined with some inappropriate feeding regimen during this phase of early childhood. Ongoing studies with propranolol for severe infantile hemangiomas may provide some additional data in a younger age group (Sans et al. 2009), which will be helpful to answer these questions.

Coagulation System

The age-dependent coagulation system can be described as an evolving and yet functional system in the young (Kuhle et al. 2003). For optimal prevention and

diagnosis of hemostatic problems, reference ranges for children of all age groups have been established. However, information on the developmental and maturational changes in the pharmacodynamics of anticoagulants such as warfarin is very limited. Apparently, Japanese children (1–11 years) with low plasma concentrations of vitamin K-dependent coagulation factors possess increased sensitivity to the anticoagulant effect of warfarin (Takahashi et al. 2000). Although prepubertal and adult patients showed comparable mean plasma concentrations of warfarin, prepubertal children showed significant lower plasma concentrations of protein C and prothrombin fragments 1 and 2 and higher INR. This augmented response to warfarin in children, e.g., with congenital heart disease and valve replacement, should be considered when estimating the most appropriate warfarin dose for them.

3.4.5 Environment and Critical Windows of Development

In this prepubescent pediatric population, one has primarily to consider the long-term consequences of drug treatment of patients with chronic diseases or conditions known as the "new pediatric morbidity" such as childhood asthma, neurodevelopmental disorders, and cancer as well as obesity, arterial hypertension, and type 2 diabetes (Cox et al. 2008; Hausner et al. 2008). The latter disorders are the consequences of "modern lifestyle" in Western as well as in emerging countries, characterized by a decline in physical activity and an increased consumption of "fast" processed food with high salt and caloric content. Consequently, there is a growing need for antihypertensives, antihyperlipidemics, and type 2 antidiabetic drugs in children (Cox et al. 2008). The long-term consequences over the whole life span are as yet unknown.

Chemotherapy

While cancer as a cause of morbity and mortality is not new to the pediatric population, as the survival rate has dramatically improved for a variety of neoplastic diseases over the past several decades, the prevalence and duration of chemotherapy has increased. This success in cancer survival is not without long-term effects on later maturation processes, such as those of the reproductive, immunological, skeletal, neural, behavioral, and cardiovascular systems. For example, the anthracycline doxorubicin, a very effective chemotherapeutic agent for certain childhood malignancies, is associated with a delayed serious and potentially life-threatening cardiotoxicity. Even years after completion of medication, particularly when treatment occurred during infancy and early childhood, persistent myocardiocyte loss, myocardial fibrosis, and failure of myocardial growth are observed as sequelae of former doxorubicin treatment (Hausner et al. 2008). In a more recent study, it has been shown that the relative hazard of congestive heart failure, pericardial disease, and valvular abnormities in adult survivors of childhood

and adolescent cancer treated with anthracyclines increased two to five times (Mulrooney et al. 2009).

Asthma-Controller Medication

The most common chronic medical condition of children is asthma. Accordingly, use of asthma-controller medication is the highest of all chronic medication use in children (Cox et al. 2008; Hausner et al. 2008). Unfortunately, the potentially negative effects of inhaled glucocorticoids on linear growth, even in the absence of hypothalamic–pituitary axis suppression, as well as long-term deleterious effects on the cardiovascular and pulmonary systems from early intervention with long-acting β-adrenergic receptor agonists are not sufficiently well studied Ducharme et al. 2010; Hausner et al. 2008).

ADHD Medication

In the treatment of ADHD, pharmacotherapy with psychostimulants is commonly employed in school-aged boys (less commonly in girls) to increase the ability to concentrate, improve overall school performance, and attenuate disturbing hyperactivity. With the marked increase in the prescription of these medicines, such as methylphenidate and amphetamines, the warnings about questionable cardiovascular safety of these compounds have become more and more insistent (Nissen 2006). All these sympathomimetic psychostimulants substantially increase heart rate and blood pressure, potentially predisposing the child to serious cardiovascular effects or sudden death, particularly in subgroups of individuals at heightened risk, such as those with congenital heart disorders and/or increased blood pressure. In addition, these agents may have negative effects on sleep, appetite, and growth; effects that are certainly not irrelevant during childhood and adolescence. Thus, it is of utmost importance to carefully consider the benefit-to-risk when prescribing psychostimulant medications.

3.5 The Adolescent: Period of Final Growth and Reproductive Maturation

3.5.1 Body Composition and Proportion

Puberty is another extremely important phase in the physical and psychosocial development of the adolescent. The age of onset of puberty varies as a function of ethnicity, health status, genetics, nutrition, and activity level. Generally, puberty

begins between 8 and 14 years and occurs almost two years earlier in females than males (Tanner and Davies 1985).

The main features of this maturation period are as follows: Pubertal growth spurt, which accounts for approximately 25% of final adult height, changes in the body habitus, and remodeling of the body over a relative short period of time with sexual maturation. This includes feminization with more fat content in females and masculinization with more muscular mass in males (Ellis 2000). Besides these changes in skeletal growth and alteration in body composition, cardiorespiratory changes take place such as doubling of the weight of the heart and rise in systolic blood pressure primarily in boys associated with increase in lung size and vital capacity and a drop in respiratory rate (Irwin 2003). Blood volume, red cell mass, and hematocrit increase throughout puberty in boys, while these parameters remain constant for girls. At the same time, dramatically increased levels of gonadal steroid hormones, which are secreted in a pulsatile manner, are involved in regulating plastic changes in neuronal structure and function. These modulation processes of brain circuits at puberty can have effects on changes in social behavior, risk-taking behaviors, and cognitive function at adolescence (Cameron 2004; Paus et al. 2008). Thus, it is not so surprising, when these processes are suboptimal in timing and/or magnitude that the risk of cognitive, affective, and addictive disorders increases (see below).

3.5.2 Functional and Physiological Processes and Their Pathophysiology and Typical Disorders and Their Health Problems

Growth Retardation

Growth retardation, also called stunting, may be a consequence of a variety of factors such as undernutrition, intestinal worm infections, vitamin D deficiency (rickets), chronic intoxication with arsenic and manganese (e.g., through household wells in South Asia), chronic and/or consumptive diseases, long-term drug-induced immunosuppression (e.g., posttransplantation), and premature pubertal development (precocious puberty). In general, optimal intrauterine, infant, and childhood growth is an important basis for satisfactory growth during adolescence.

Endocrine Dysfunctions

– *Precocious, markedly delayed, or absent puberty* are disorders of the hypothalamic–pituitary–gonadal (HPG) axis. Hormonal interventions are directed at both the acute and the long-term consequences of disturbed pubertal development, e.g., treatment of a patient with gonatropin-dependent early puberty (true precocious puberty) with gonadotropin-releasing hormone (GnRH) analogues to postpone pubertal maturation and to secure the pubertal growth spurt and final height by preventing premature closure of the long bone growth plates (Brämswig and

Dübbers 2009). In contrast, delayed pubertal development may be induced by substitution with gonadal steroid hormones in a teenager with absent puberty as a result of a gonadal disorder with hypergonatropic hypogonadism as seen in chromosomal anomalies, such as Ulrich–Turner syndrome.

- *Primary dysfunctional uterine bleeding and dysmenorrhea* remain leading reproductive complaints in menstruating female adolescents. This results from the immature HPG axis and painful prostaglandin-stimulated myometrial contraction, respectively. Thus, early longer term treatment with oral contraceptives and/or prostaglandin synthesis inhibitors appears to be justified (Moscicki 2003), although long-term consequences of this therapy on the reproductive system have not yet been studied.
- After the first peak of presentation in the early school age (see "Four Diseases with Immune Dysfunction"), *diabetes mellitus* type 1 has the second peak of disease onset. This is thought to be related to the pubertal growth spurt induced by gonadal steroids and growth hormone secretion, which antagonizes insulin (Alemzadeh and Wyatt 2007). In this context, it is of note that the second peak in onset occurs – as one would have expected – earlier in girls than in boys.

Malignancies

Malignancies, which are common in early adulthood, such as testicular and ovarian carcinoma, Hodgkin disease, the sarcomas such as osteosarcoma, Ewing sarcoma, and other soft-tissue sarcomas are the most common types of cancer in adolescence (Kadan-Lottick 2007).

Emotional Instability

It is believed that gonadal steroid hormones modulate the activity of a number of neurotransmitter systems, including cholinergic, serotonergic, noradrenergic, and dopaminergic neurons. These complex central nervous system pathways play central roles in regulating many higher order brain functions, including cognitive functions and emotional regulation (Cameron 2004). It is therefore not surprising that suicides, drug addiction, and risk-taking behavior are major health problems in adolescents.

- *Substance use and abuse* such as binge drinking and marijuana and cocaine use are quite common in the adolescent population particularly in the Western countries. Both cigarette use and alcohol use begin early in adolescence with a mean age of onset of about 12 years. Girls consistently report greater daily use of cigarettes than boys, whereas boys report greater use of alcohol than girls (Marcell and Irwin 2003a). Continued nicotine abuse in the female population into the childbearing years has grave implications for future pregnancies,

including increased risk of fetal growth restriction, preterm births, stillbirths, placental abruption, and possibly also sudden infant death syndrome (Cnattingius 2004).

– *Unintentional injuries*, as the result of a high risk-taking behavior in combination with alcohol consumption, are the primary cause of premature mortality in adolescents, accounting for more than 50% of deaths in that age group. It is not surprising that the mortality rate in male teenagers is nearly twice that of girls. Acute traumatic injuries resulting from nonfatal accidents account for the largest number of hospital days and outpatient physician visits for both adolescent boys and girls (Marcell and Irwin 2003b).

Sexual Behavior

Adolescents continue to initiate sexual activity early in the second decade of life. Again age of menarche, ethnic origin, and social status may have a significant influence on the age of first sexual intercourse; but one can assume that more than 50% of middle teen adolescents will have this experience and are prone to sexually transmitted diseases and ectopic pregnancies (Marcell and Irwin 2003c; Dalton 2007).

– *Covariation of risk behaviors*
  As already mentioned above, there is a close association of alcohol and unintentional injury. There also appears to be a relationship between cigarette smoking and the use of illicit substances as well as failure to use effective contraception leading to unintended pregnancy (Marcell and Irwin 2003d). In the worst case, the sequence of progression can be as follows: alcohol and cigarettes precede marijuana use, which is followed by other illicit drugs (including psychedelics, cocaine, heroin, and prescribed and nonprescribed stimulants, sedatives, and tranquilizers), leading to a cumulative effect of all substances and sometimes to high-risk teenage pregnancies.

Mental Health Problems During Adolescence

– *Depression and suicide*
  Transient depressive feelings are common during adolescence. Among these patients, the risk of suicide is increased significantly. Presently, it is the third leading cause of death in adolescents (Boris and Dalton 2007). Rates of completed suicide increase steadily across the teen years, peaking in the early 20s. The male:female ratio for completed suicide is approximately 4:1. For every completed suicide, it is estimated that there are many more (about 50) suicide attempts with significant underreporting and female predominance. Most female suicide attempts involve drug ingestions or superficial cutting, whereas males use more lethal means such as firearms and hanging (Boris and Dalton 2007).

Although adolescent females are more at risk for depression compared to males, males are generally more aggressive and impulsive than females.

– *Eating disorders*
Anorexia nervosa (AN) and bulimia nervosa (BN) are common psychiatric disorders in adolescents and young adults with high rates of morbidity and mortality. The incidence of both disorders has increased in the general population over the last two decades and remains eight times higher in the female than male teenage population (Abraham and Stafford 2007).

Extreme feelings of dissatisfaction with weight and shape and fear of gaining weight are the main causes of these disorders, leading typically to amenorrhea and to a maintenance weight of 15% below the ideal body weight in AN. Other clinical manifestations of eating disorders include severe malnutrition, self-induced vomiting (particularly in BN with episodes of compulsive overeating), and use of laxatives and/or diuretics. This may lead to dehydration, peripheral vasoconstriction, hypothermia, bradycardia, severe electrolyte imbalance with cardiac arrhythmia, osteopenia with stress fractures, hypoproteinemia with peripheral edema, and decreased glomerular filtration. This complex clinical condition is associated with severe medical and psychiatric comorbidity for which pharmacotherapy has a limited role at the present time. Nevertheless, the drugs mainly used in the treatment of eating disorders are antidepressants such as SSRIs, tricyclics, and atypical antipsychotic agents (Powers and Bruty 2009). However, dosing, side-effect profile, and long-term effects of these medications in children and adolescents are not well studied (Hausner et al. 2008).

3.5.3 Major Organs of Metabolism and Elimination

Around the onset of puberty with increased growth hormone levels and activation of the reproductive axis, drug-metabolizing enzyme capacity begins gradually to decline. This decline continues throughout adolescence and concludes with attainment of adult capacity at the completion of pubertal development (Kennedy 2008). During this period of marked hormonal changes and fluctuation, an apparent inverse relationship between levels of growth and sex hormones and drug-metabolizing activity can be observed. For example, a Tanner stage-dependent decrease in CYP1A2-mediated caffeine clearance has been described in healthy adolescents (Lambert et al. 1986). A more direct demonstration of this relationship was observed among growth hormone-deficient prepubertal children in whom physiological growth hormone replacement was associated with a twofold increase in the half-life of amobarbital, a probe of hepatic microsomal drug metabolism (Redmond et al. 1978). At least in part, changes in body composition may also have an effect on the V(d) as illustrated by a highly significant positive correlation of Tanner stage with theophylline elimination half-life and lean body mass and between lean body mass and V(d) in adolescents with asthma (Cary et al. 1991).

Gender differences in drug disposition also become more apparent during puberty (Beierle et al. 1999; Kennedy 2008; Lambert et al. 1986).

Thus, the effects of rapid growth, sexual maturation, and the large amount of variability in the timing of these developmental events on pharmacokinetics must be considered during studies with teenagers. The concept of developmental rather than chronological age should be applied whenever it is possible (Cary et al. 1991; Finkelstein 1994; Kennedy 2008).

These ontogenetic and pharmacokinetic changes during this stage of growth and sexual maturation are especially important when treating common chronic illnesses of adolescence, such as asthma, diabetes, epilepsy, and depression. This complex hormonal and pharmacotherapeutic interplay can further be complicated by on and off oral contraceptive therapy, teenage pregnancy, smoking, self-medication, and illicit drug use.

With respect to renal elimination, it is of note that glomerular filtration and tubular absorption are not influenced by sexual maturation, in contrast to tubular secretion of medicines, e.g., tubular secretion of digoxin, which declines during adolescence to the level seen in adults (Linday et al. 1984; Linday et al. 1981). Methotrexate, which is excreted by the kidney via glomerular filtration and tubular secretion, also shows reduced clearance as a function of age through adolescence (Donelli et al. 1995).

3.5.4 Ontogeny of Drug Targets

The effects of physical growth and sexual maturation on the expression of important drug targets, such as receptors, transporters, and channels, remain essentially unexplored. This is in contrast to the available comprehensive knowledge about ontogenetic differences in pharmacodynamics in the perinatal period. A major obstacle (hurdle) may be greater difficulties in monitoring quantitatively the relevant clinical end points or appropriate surrogate markers of drug action, efficacy, and toxicity throughout the course of pubertal development and sexual maturation. Moreover, pediatricians have relatively neglected research in the area of adolescent medicine in the past.

3.5.5 Environment and Critical Windows of Development

Long-term safety of medicines and, even more so, the long-term consequences of addictive substances use and drug abuse are of major concern in this pediatric population, e.g., tobacco and alcohol consumption and doping with central stimulants or androgens (Dwyer et al. 2009; Hausner et al. 2008; Sjöqvist et al. 2008).

Nicotine as a Gateway Drug

There is ample experimental and some epidemiological evidence that tobacco or nicotine administration particularly during adolescence is a gateway drug that increases the likelihood of subsequent use of other addictive substances (Dwyer et al. 2009). The ability of nicotine to interfere via the AChRs directly or indirectly with various transmitter systems such as the acetycholinergic, dopaminergic, or serotonergic systems may play a role in subsequent addictive behavior. Although the functional role of nAChRs in adolescent maturational processes has not been fully explored, neurochemical and behavioral studies with experimental animals suggest that they may regulate limbic system circuitry that is undergoing critical experience-dependent reshaping during this period (Dwyer et al. 2009). Thus, adolescence may be a particularly vulnerable period, during which nicotine exposure might produce long-term changes in function of the limbic system. This system supports a variety of functions including emotion, behavior, and long-term memory and is hereby involved in addictive disorders.

Anabolic Androgenic Steroids

The misuse of performance-enhancing drugs such as anabolic androgenic steroids is another example of the potential for long-term effects when used during this vulnerable period of maturation. Unfortunately, use of performance enhancers is quite common in young sportspeople, both in high schools and in noncompeting amateurs with a high predominance of male students. The estimated percentage in this adolescent population is at least 3–5% (Sjöqvist et al. 2008). In early adolescents (age 10–13 years), a typical adverse effect with permanent long-term consequences from this kind of doping is premature closure of epiphysial growth plates with ultimate stunted linear growth. In middle and late adolescence testicular atrophy and gynecomastia in males and virilization and long-term amenorrhea in females dominate the endocrine effects. The major cardiovascular side effects are hypertrophic cardiomyopathy and hypertension. In addition, common neuropsychiatric side effects include mood changes, such as mania, hypermania, depression, and increased aggressive behavior (Sjöqvist et al. 2008). In combination with alcohol and central stimulants, anabolic androgenic steroids seem to be strongly synergistic in producing impulsive violent behavior or suicide and homicide, respectively. The whole spectrum of the long-lasting effects of these steroids in humans is not well studied, but at least the effects on muscular fibers last much longer than a couple of years.

Psychostimulants

The long-term risk of extended use and misuse of central stimulants as performance-enhancing drugs has already been mentioned and briefly discussed in

"ADHD Medication". These risks are particularly relevant for the male teenage population at secondary school, in which the diagnosis of ADHD is frequently made with a prevalence of about 8% as compared to only 2% in girls (Huss et al. 2008).

4 Future Directions

There is a permanent need to fill the gaps of our knowledge about the continuous developmental changes of therapeutic targets (e.g., enzymes, transporters, receptors, and channels) from the fetus to young adult. These gaps include following sections.

4.1 Appropriate Tools for Assessment of Drug Action

Development of age-appropriate methods and tools for the assessment of drug actions and effects in the pediatric population, such as intermediate end point or surrogate markers, biomarkers, functional tests, scores, scales, and PK/PD analyses.

4.2 Appropriate Animals and Cell Models

Development of appropriate and predictive animal models, cell systems, in vitro tests, and in silico simulation; all tools which are important and helpful to manage – at least in part – the delicate and ethically and legally complex situation of research in a very vulnerable population.

4.3 Appropriate Methods for Long-Term Safety Effects

Development of appropriate epidemiological methods for the evaluation of long-term safety and potential programming effects of pharmacological interventions at an early stage of development, assessment of predictive value of surrogate end points in predicting long-term efficacy and toxicity (particularly with chronic exposures), identification of vulnerable windows of developmentally immature organ systems (e.g., cardiovascular, neurological, immunological, and reproductive systems) that might be especially sensitive to pharmacological perturbation, and additional study to evaluate the impact of a disease state that is unique to children.

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