Methylxanthines During Pregnancy and Early Postnatal Life

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Contents

Abstract World-wide, many fetuses and infants are exposed to methylxanthines via maternal consumption of coffee and other beverages containing these substances. Methylxanthines (caffeine, theophylline and aminophylline) are also commonly used as a medication for apnea of prematurity.

The metabolism of methylxanthines is impaired in pregnant women, fetuses and neonates, leading to accumulating levels thereof. Methylxanthines readily passes

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the placenta barrier and enters all tissues and thus may affect the fetus/newborn at any time during pregnancy or postnatal life, given that the effector systems are mature.

At clinically relevant doses, the major effector system for methylxanthines is adenosine receptors. Animal studies suggest that adenosine receptors in the cardiovascular, respiratory and immune system are developed at birth, but that cerebral adenosine receptors are not fully functional. Furthermore animal studies have shown protective positive effects of methylxanthines in situations of hypoxia/ischemia in neonates. Similarly, a positive long-term effect on lung function and CNS development was found in human preterm infants treated with high doses of caffeine for apneas. There is now evidence that the overall benefits from methylxanthine therapy for apnea of prematurity outweigh potential short-term risks.

On the other hand it is important to note that experimental studies have indicated that long-term effects of caffeine during pregnancy and postnatally may include altered behavior and altered respiratory control in the offspring, although there is currently no human data to support this.

Some epidemiology studies have reported negative effects on pregnancy and perinatal outcomes related to maternal ingestion of high doses of caffeine, but the results are inconclusive. The evidence base for adverse effects of caffeine in first third of pregnancy are stronger than for later parts of pregnancy and there is currently insufficient evidence to advise women to restrict caffeine intake after the first trimester.

Keywords Caffeine · Fetus · Methylxanthines · Neonatal · Newborn · Pregnancy · Theophylline

1 Introduction

The majority of expecting mothers in the Western world drink beverages containing methylxanthines during pregnancy and they continue their consumption during lactation. Many fetuses and infants are thus exposed to these substances. In addition, a large number of premature infants need pharmacological treatment for apnea of prematurity with methylxanthines.

There has been considerable concern over fetuses and infants being subjected to methylxanthines, with reported negative effects on pregnancy, perinatal, and long-term outcomes.

This chapter discusses how fetuses and newborns are subjected to methylxanthines, how the effects are mediated, and what information the current literature provides on the long-term effects of exposure to methylxanthines at clinically relevant doses.

2 Mechanisms of Action in the Neonate. Effector Systems and Their Maturation

2.1 Mechanisms of Action at Clinically Relevant Concentrations

The only known effect of caffeine at concentrations relevant to daily intake of coffee is blockade of adenosine A_1 and A_{2A} receptors that occurs at serum concentrations of 0.2–2 mg/L (0.001–0.01 mM; Fredholm et al. 1999). When pregnant women drink beverages containing caffeine, serum levels of caffeine soon become similar in the fetus and in the mother. When preterm infants are treated with caffeine for apnea of prematurity, more than 10 times higher serum levels are reached and then, in addition to adenosine A_1 and A_{2A} receptor blockade, an inhibitory effect on adenosine A_3 receptors, and a minimal blockade of phosphodiesterases, $GABA_A$ receptors, and Ca^{++} release can occur. The maturation of these effector systems may affect the way the fetus and the infant react to caffeine (see below).

It is now less common that fetuses and infants are exposed to theophylline than caffeine, since theophylline has been replaced in modern asthma therapy and for treatment of apneas in preterm infants, and caffeine is usually preferred to theophylline/aminophylline (see below). Theophylline is structurally related to caffeine and is thus a potent inhibitor of adenosine A_1, A_{2A}, and to some extent A_3 receptors at therapeutically relevant doses. The degree of inhibition of phosphodiesterases is minimal at these concentrations.

Methylxanthines have both pro- and anti-inflammatory properties. At therapeutic doses, most effects result from adenosine receptor antagonism and the proinflammatory actions may be more relevant (Haskó and Cronstein 2010; Ohta and Sitkovsky 2010), at least in adults. However, a recent study in umbilical cord blood monocytes indicated that caffeine inhibited TNF-α production in neonates, possibly via adenosine A_1 receptors (Chavez-Valdez et al. 2009).

Thus, some of the immunomodulatory mechanisms of methylxanthines are functioning at an early developmental stage, whereas other effects do not mature until later in infancy.

2.2 Maturation of Adenosine and $GABA_A$ Receptor Systems

As mentioned, the major effect of the methylxanthines caffeine and theophylline/aminophylline at therapeutic doses is antagonism of adenosine A_1 and A_{2A} receptors. The maturation of these receptor systems affects how the fetus and child react to methylxanthines. Data on the development of adenosine receptors are obtained from mice and rats, but there are no available data from human fetuses or infants to our knowledge.

Adenosine A_1 receptors are mainly present in the heart (conductive system and myocytes), brain (predominantly in cortex, hippocampus, cerebellum, pons, and medulla oblongata) kidney, testis, and adipose tissue. Adenosine-A_1-receptor-knockout mice appear to develop normally (Johansson et al. 2001), indicating that this receptor has no main effect on fetal development, but recent studies have pointed out differences in heart rate, body temperature, and locomotion in adult life of these mice (Yang et al. 2007). Adenosine A_1 receptors are present in a small amount early in brain development (Rivkees 1995; Aden et al. 2000), but are not functionally coupled to G proteins in the brain until adolescence (2–3 weeks of age in a mouse) (Aden et al. 2001). An important exception is the medulla oblongata, where functional coupling to G proteins was confirmed in rats just before birth using guanylyl-5′-*O*-(γ-[^{35}S]thio)-triphosphate binding (Herlenius et al. 2002). To this end, it is known that adenosine and adenosine A_1 receptor agonists depress respiratory rhythmogenesis in vivo and in vitro (Lagercrantz et al. 1984; Eldridge et al. 1985). Accordingly, methylxanthines exert profound stimulatory effects on respiration in newborns by antagonism of adenosine A_1 receptors in the pons and medulla oblongata (Lagercrantz et al. 1984; Tilley 2010).

An early functional coupling of adenosine A_1 receptors to G proteins was also reported in the heart (Aden et al. 2001), which is in agreement with the clinical observation that tachycardia is a frequently seen side effect of methylxanthines in premature infants. There are data indicating that adenosine A_1 receptors function in umbilical cord blood monocytes (Chavez-Valdez et al. 2009) Adenosine A_{2A} receptors are present in the brain and (predominantly in the basal ganglia), at endothelial cells, platelets, and on inflammatory cells (neutrophils, platelets, macrophages/microglial cells, and T cells), where they exhibit important anti-inflammatory properties (Haskó and Cronstein 2010; Ohta and Sitkovsky 2010, 2001). The first targeted disruption of the adenosine A_{2A} receptor gene in mice was reported in 1997 (Ledent et al. 1997) and in agreement with previous pharmacology studies, these animals had increased blood pressure and platelet aggregation. There were no major malformations in adenosine-A_{2A}-receptor-knockout mice, indicating that the stimulation of this receptor is not necessary for normal fetal development. The major development of cerebral adenosine A_{2A} receptors takes place after birth, as pointed out by rat studies (Rivkees 1995; Aden et al. 2000). It is not known whether adenosine A_{2A} receptors on inflammatory cells are functional early in life.

Adenosine A_3 receptors have a low affinity for caffeine and are therefore not considered as its primary target when ingested in beverages. However, therapeutic levels of methylxanthines given as therapy for preterm apneas may reach concentrations where adenosine A_3 receptors are blocked. Adenosine A_3 receptors are very scarce in the brain, but can be detected at low levels in several regions in the adult rodent brain. The functionality of these receptors in neurons remains unclear. It is, however, now evident that functional adenosine A_3 receptors are present on microglial cells and astrocytes (Hammarberg et al. 2003; Abbracchio et al. 2001; see Haskó and Cronstein 2010), but developmental data are lacking. Recent data show that deletion of adenosine A_3 receptors

(adenosine-A_3-receptor-knockout mice) during brain development leads to a reduced response to caffeine in adult life (Bjorklund et al. 2008a). Although the mechanisms have not been elucidated, a developmental role of adenosine A_3 receptors might therefore be indicated, in particular during circumstances when there is fetal exposure to caffeine.

$GABA_A$ receptors may be a target for high doses of methylxanthines, for example, when given postnatally for the treatment of apnea of prematurity. This receptor system develops in the brain early during fetal life (Aden et al. 2000), but whereas activation of $GABA_A$ receptors in mature neurons results in membrane hyperpolarization, $GABA_A$ receptor activation during early stages of brain development (up until the first postnatal week in rodents, corresponding to term age in a human baby) causes depolarization of the postsynaptic membrane. The GABA-mediated depolarization is thought to regulate neurogenesis, synaptogenesis, and final neuron number by regulating second-messenger systems (Varani et al. 2005) and modulating DNA synthesis (Leinekugel et al. 1997). Blockade of $GABA_A$ receptors with methylxanthines has, therefore, a theoretic potential to affect brain development. However, it is completely unknown whether the net effect on outcome would be positive or negative.

3 Exposure to Methylxanthines During Fetal Life

As mentioned, it is nowadays uncommon that fetuses are exposed to theophylline, but many fetuses are subjected to caffeine because the majority (75%) of expecting mothers drink beverages containing caffeine (Eskenazi 1999).

3.1 Metabolism of Methylxanthines in the Pregnant Woman and in the Fetus

Methylxanthines are rapidly and completely absorbed from the gastrointestinal tract. There is only a minimal first-pass effect and once absorbed, methylxanthines pass blood–brain and placenta barriers, entering all tissues (Arnaud 1987). The half life of caffeine in pregnant women varies between 2 and 4.5 h during the first trimester, which is similar to that in nonpregnant women, but increases to 10 h at 17 weeks gestation and up to 18 h in the end of pregnancy, leading to an accumulation of caffeine in the mother and the fetus (Aldridge et al. 1981).

The main enzyme controlling caffeine metabolism is cytochrome P450 1A2 (CYP1A2). There are interindividual differences due to polymorphisms of this enzyme (Grosso and Bracken 2005). Another enzyme that regulates the metabolism to a lesser extent is *N*-acetyltransferase (Fenster et al. 1998). The activities of both of these enzymes are reduced during pregnancy (Tsutsumi et al. 2001), resulting in

gradually increasing plasma concentrations (to about twice the prepregnancy levels) of caffeine during pregnancy, despite little change in reported consumption (Cook et al. 1996). Both the fetus and the placenta lack the enzymes needed to metabolize methylxanthines (Kalow and Tang 1991) and therefore elimination in the fetus is almost entirely dependent upon renal excretion. The urinary excretion rate increases with dose in both mothers and fetuses.

3.2 *Exposure to Methylxanthines in Fetal Life and Perinatal Outcomes*

Since caffeine and its metabolites can pass the placenta barrier, maternal coffee consumption may affect the fetus at any time throughout pregnancy, given that the effector systems are mature (see earlier).

Some studies have raised concern about fetuses being exposed to caffeine during pregnancy, but others have failed to find any associations between maternal caffeine intake and adverse perinatal outcomes.

There is some evidence from animal studies that high doses of caffeine may result in malformations of the fetus, including cleft palate and cardiovascular malformations (for a review, see Nehlig and Debry 1994). Epidemiology studies, though, have not been able to detect significant risks for teratogenic effects of caffeine exposure in humans (Browne 2006). Some studies have shown that excessive maternal consumption of caffeine in humans (more than 300 mg/day) may be related to reduced fertility (Marie-Soleil and Graham 2010) and was associated with increased rate of spontaneous abortions (Godel et al. 1992; Klebanoff et al. 1999; Cnattingius et al. 2000; Wen et al. 2001), intrauterine growth restriction (Bracken et al. 2003a; Klebanoff et al. 2002; Vlajinac et al. 1997; CARE Study Group 2008), and still birth (Wisborg et al. 2003). One theoretically possible explanation for some of these effects may be that caffeine increases the levels of catecholamines in the mother and in the fetus, which may induce uteroplacental vasoconstriction (Kirkinen et al. 1983).

On the other hand, several prospective epidemiology studies have shown no major effects of caffeine on ovulation (Chavarro et al. 2009; Chap. 21), intrauterine growth restriction, low birth weight, or preterm delivery (Bracken et al. 2003a).

The major limitations of the epidemiology studies in this field lie in their retrospective nature and the data on caffeine exposure are thus subject to recall and other types of bias and that some studies lack information on confounding variables such as smoking. Confounding due to pregnancy symptoms is another important issue that complicates the relation between caffeine consumption and spontaneous abortion. Nausea may influence the amount of caffeine consumed in early pregnancy and it is also a marker of fetal viability.

Only one randomized controlled study investigated the effect of caffeine versus restricted caffeine intake on pregnancy outcome (Bech et al. 2007). Caffeinated instant coffee was compared with decaffeinated coffee during the second and the

third trimester. A moderate caffeine reduction of 182 mg/day did not affect birth weight or length of gestation. Thus, there is currently insufficient evidence for advising mothers to avoid caffeine during the last two thirds of pregnancy.

The few studies that have examined theophylline in pregnancy in relation to perinatal outcomes have found no association between theophylline and low birth weight (Schatz et al. 2004) or small size for gestational age (Schatz et al. 2004; Stenius-Aarniala et al. 1995; Bracken et al. 2003b).

4 Exposure to Methylxanthines in Neonates

4.1 Absorption, Metabolism, and Elimination

Methylxanthines, from breast milk or given orally to infants for treatment of apneas, are rapidly and completely absorbed from the gastrointestinal tract of the neonate with a minimal first-pass effect (Arnaud 1987). Once absorbed, they freely enter all body tissues, including the brain and gonads (Arnaud 1987).

Pharmacokinetic studies have shown that newborn infants (up to about term-equivalent age) have a prolonged half life of caffeine of around 100 h (see Table 1), which decreases with gestational age (Aranda et al. 1979), reflecting the immaturity of the hepatic CYP1A2 enzyme system. The enzyme capacity then gradually improves and reaches adult function at about 3 months (Aranda et al. 1979) after birth.

Like caffeine, theophylline is readily absorbed orally (Ogilvie 1978) and no dose adjustment is needed when switching from intravenous to oral administration. Theophylline is, like caffeine, metabolized by CYP1A2, but has variable pharmacokinetics during the first few days in newborns, which is why monitoring of the plasma concentrations is required. Although there is a faster metabolic clearance of theophylline relative to caffeine in neonates, because theopylline can be back-methylated to caffeine, the net effect of methylxanthines may be the same since caffeine and theophylline exert similar biological actions. The half life in premature infants is 20–30 h.

Even though caffeine and theophylline are excreted in the urine mainly unchanged in the neonate, significant methylation of theophylline to caffeine occurs and the latter may exert additional pharmacological effects (Dani et al. 2000).

4.2 Methylxanthines and Breast Feeding

As mentioned already, although caffeine is excreted to a limited extent in breast milk, the immature metabolism of methylxanthines in neonates and, in particular, in preterm infants (Aranda et al. 1979) makes them at risk of accumulating

methylxanthines. Theophylline (e.g., given to the mother for asthma) and theobromine (from chocolate) are also present in breast milk after administration (Yurchak and Jusko 1976) and accumulate in the neonate (Aranda et al. 1976).

While some studies have suggested possible risk effects of methylxanthines in pregnancy (see Sect. 3.2), a growth-promoting effect has been demonstrated in breast-feeding rat pups (Hart and Grimble 1990), which was shown to be due to increased milk volume. By contrast, there are a few animal studies showing that theophylline (Milsap et al. 1980; Carnielli et al. 2000) and caffeine (Bauer et al. 2001) increase the metabolic rate, which would infer a negative effect on growth. Similarly, a minimal decrease in fetal growth was observed in humans after excessive maternal caffeine drinking (more than 600 mg/day, about six cups of coffee) (Bracken et al. 2003a).

There has also been concern over the use of caffeine in mothers at the particular time point around delivery. Adenosine acting via adenosine receptors has endogenous neuroprotective effects in the adult brain (Fredholm 2007; Müller and Jacobson 2010). Although results in the neonate are complex (for a review, see Millar and Schmidt 2004), it was anticipated that the presence of the antagonist caffeine would possibly not be beneficial in a situation of birth asphyxia or postnatal apnea (with subsequent hypoxia). It was therefore surprising that when rat dams were given caffeine in their drinking water during pregnancy and lactation, in a dose that produced plasma concentrations similar to those achieved after 300–400 mg/day in humans, hypoxic ischemic brain damage was reduced by about 30% (Bona et al. 1995). No major effects on adenosine receptors or $GABA_A$ receptors were found (Aden et al. 2000). A similar perinatal exposure to caffeine prevented periventricular white matter damage in mice reared in hypoxia by enhancing myelination (Back et al. 2006). Further studies in adenosine-A_1-receptor-knockout mice (Turner et al. 2003) indicated that blockade of this receptor might contribute to the protective effect of caffeine in the immature brain. It is also possible that the anti-inflammatory effects of caffeine (Haskó and Cronstein 2010; Ohta and Sitkovsky 2010) may be partly instrumental for the beneficial effects of caffeine in the developing brain.

4.3 Methylxanthines for Apnea of Prematurity

More than three decades ago, it was demonstrated that methylxanthines can reduce the frequency of apneic episodes in premature infants (Kuzemko 1973; Aranda et al. 1977). Since then, methylxanthines have become part of the routine clinical management of apnea of prematurity. Apnea commonly occurs in premature infants below 34 weeks of gestational age and is a cessation of breathing due to immaturity of the respiratory drive, followed by decreased oxygen saturation in the blood and bradycardia. Recommended doses and desired plasma concentrations for

Table 1 Pharmacokinetics of methylxanthines in neonates. Data from Dani et'al. (2000) and Aranda et'al. (1976)

	Theophylline[a]	Caffeine
Plasma levels in neonates after moderate maternal coffee intake	No data available	0.2–1 mg/L (Neims and von Borstel 1983)
Route of administration	Intravenous, per os	Intravenous, per os
Dose (mg/kg)		
Loading	4–6	20
Maintenance	1.5-3 every 8-12 hr	5 (−10) every 24 hr
Plasma half life (h, range)	20–30	100 (40–230)
Therapeutic window (mg/L)	6–12	5–25
Adverse effects	Commonly include tachycardia, vomiting, hyperglycemia, irritability, sleeplessness	Usually mild, but includes tachycardia, vomiting restlessness

[a]Theophylline is often administered as the salt aminophylline, which consists of approximately 80% theophylline. If changing from intravenous administration of aminophylline to oral administration, the dose needs to be increased by 20%.

therapeutic use of caffeine and theophylline in premature neonates are shown in Table 1. It is important to note that the plasma concentration of caffeine used to treat this condition is 10–100 times higher than the plasma concentrations reached if the mother drinks moderate doses of coffee and the child is exposed via breast milk (Table 1). The methylxanthine therapy often goes on for several weeks until the premature child has matured.

Caffeine and theopylline exert similar effects, but have differences in pharmacokinetic properties (Table 1). In clinical practice, caffeine citrate has now become the methylxanthine of choice because it has a wider therapeutic range, has essentially complete full bioavailability, and can thus be given orally and routine measurements of blood concentrations are not needed.

As mentioned, given the neuroprotective effects of endogenous adenosine, there has been concern over the effects of high doses of methylxanthines in neonates at risk of apneas and postnatal hypoxic ischemia. It was therefore surprising that when rat pups were given theophylline in therapeutically relevant doses just before the induction of a hypoxia ischemia, the brain damage was reduced by almost 50% (Bona et al. 1997). The authors speculated that the mechanism for this protection might include anti-inflammatory effects of theophylline.

To this end, in a study where premature infants were randomized to either caffeine or a placebo for apnea of prematurity, it was shown that caffeine improved the rate of survival, decreased the number of children with severe respiratory sequelae (bronchopulmonary dysplasia), and reduced the incidences of cerebral palsy and cognitive delay at 18 months of age (Schmidt et al. 2007). With use of post hoc analysis, about half of the protective effect of caffeine was attributed to positive effects on the respiration, but half of the effect remained unexplained. These results indicate that caffeine has inherent direct or indirect neuroprotective effects.

5 Short-Term Effects of Methylxanthines in the Infant

5.1 Physiological Effects

Methylxanthines exert profound stimulatory effects on respiratory drive in neonates by antagonism of adenosine A_1 receptors in the pons and medulla oblongata (Lagercrantz et al. 1984; Tilley 2010), improved chemoreceptor sensitivity to CO_2 (Davi et al. 1978), mainly via blockade of adenosine A_{2A} receptors (Conde et al. 2006), increased oxygen consumption (Bauer et al. 2001), and increased cardiac output (Walther et al. 1990). As mentioned already, experimental data show that adenosine A_1 receptors are clearly G-protein-coupled (Aden et al. 2001) and capable of function at birth in the heart. Accordingly, a commonly seen clinical effect/side effect of methylxanthines is tachycardia.

Adverse effects are similar for theophylline and caffeine (Table 1) but are milder and occur less often for caffeine. One specific adverse effect of theophylline is that cerebral blood hemodynamics are transiently affected (Dani et al. 2000), possibly via blockade of cerebrovascular adenosine A_{2A} receptors

Renal effects of methylxanthines include increased diuresis (via tubular adenosine A_1 receptors) and increased calcium excretion (Bauer et al. 2001; McPhee and Whiting 1989; Rieg et al. 2005).

Unfavorable symptoms can also occur in neonates if a chronic administration of methylxanthines during pregnancy suddenly ceases, i.e., if breast feeding is not established early after birth.

5.2 Withdrawal Symptoms

There are case reports in the literature on transient withdrawal symptoms in full-term neonates exposed to high concentrations of caffeine after excessive maternal ingestion of coffee, mate, or cola drinks (450–1,800 mg/day). These symptoms include jitteriness, high-pitched cry, hypertonia in the limbs, brisk tendon reflexes, and vomiting and resolved spontaneously within 1–2 days (Khanna and Somani 1984; McGowan et al. 1988). In these cases the withdrawal symptoms were preceded by lack of breast feeding.

It is also possible that some apneic episodes encountered in neonates who were exposed to caffeine during pregnancy but then were not breast-fed, may be due to a central withdrawal effect of caffeine at the pontomedullary level. This speculation was supported by experimental data from neonatal rat pups where caffeine was given in the drinking water to pregnant and lactating dams. If caffeine was withdrawn at birth, apneas could be induced and subsequent caffeine exposure during breast feeding was able to prevent apneas in the rat pups (Bodineau et al. 2006).

6 Long-Term Effects of Methylxanthines for the Developing Organism

Even though the short-term effects of caffeine, in relevant doses, seem to be largely beneficial, there has been considerable concern over the long-term effects of methylxanthines in the developing brain and other organs.

6.1 CNS Function

Exposure to psychostimulant drugs during brain development may lead to long-term effects beyond the time point when the drug exposure is withdrawn (Andersen 2005). There is some experimental evidence that high doses of methylxanthines induce long-lasting behavioral changes in the offspring (Nehlig and Debry 1994; Henderson et al. 1991; Nakamoto et al. 1991). Also, when a modest dose of caffeine (similar to plasma levels achieved in moderate maternal coffee drinking) was given in the drinking water to mice throughout pregnancy and lactation, the adult offspring exhibited increased locomotor activity in an open field (Nehlig and Debry 1994). A similar behavioral profile was found in mice heterozygous for the adenosine A_1 receptor gene, where signaling via adenosine A_1 receptors was reduced to about the same degree as after modest consumption of caffeine (Bjorklund et al. 2008b). Furthermore, it appeared that the mother's genotype, not the offspring's, was critical for behavioral changes in adult offspring, thus indicating that perinatal caffeine acting on adenosine A_1 receptors in the mother caused a long-term effect in the offspring (Bjorklund et al. 2008b). Interestingly, these effects even manifested themselves in the second generation (Bjorklund et al. 2008b).

However, in humans, perinatal exposure to coffee per se was not related to any increased risk of having ADHD or hyperkinetic diagnosis (Linnet et al. 2009). Similarly, in a follow-up study of 500 pregnant women and their offspring, there was no association between perinatal caffeine exposure and IQ and attention tests at 7 years of age (Barr and Streissguth 1991). Furthermore in a large randomized controlled trial on caffeine (given postnatally in high doses) for apnea of prematurity, a reduced incidence of cerebral palsy and cognitive delay at 18 months of age was shown (Schmidt et al. 2007).

Although no detrimental long-term effects from perinatal methylxanthine exposure have been demonstrated in humans so far, studies on development of CNS functions require a very long follow-up period and complex neuropsychological testing; therefore, effects may nevertheless be present but difficult to detect.

6.2 Respiration and Cardiovascular Function

There is some experimental evidence that neonatal caffeine treatment with plasma levels comparable to these achieved with treatment for apnea of prematurity alters

the ventilatory response to hypercapnia and hypoxia in adolescence and adulthood (Montandon et al. 2008). Mainly adenosine A_1 receptors were found to be involved in these plasticity changes, which speculatively might have implications for diseases implied in respiratory control dysfunction such as SIDS and sleep apnea (Montandon et al. 2008).

It is also conceivable that perinatal exposure to caffeine may have persisting effects on cardiovascular function, since adenosine is an important regulator thereof (Riksen et al. 2010). Effector systems for adenosine receptors actually mature earlier in the cardiovascular system than in the CNS, at least in rats (Aden et al. 2001), and there is some evidence that early caffeine exposure can alter gene expression of adenosine and dopamine receptors and thyrosine hydroxylase in the carotid body and adrenal glands of rats (Montandon et al. 2008). Another study showed adverse effects of a dose of caffeine relevant to daily intake of coffee on embryonic arteries with transiently decreased blood flow. These effects were adenosine A_{2A} dependent (Momoi et al. 2008). It is thus possible that early exposure to caffeine might have long-lasting cardiovascular effects, but there is currently a lack of long-term follow-up data of cardiorespiratory function and human data.

As mentioned, an important positive influence of perinatal caffeine on lung function was seen in a randomized controlled study of apnea of prematurity, where caffeine decreased the number of children with a chronic respiratory disease (bronchopulmonary dysplasia) at 18 months of age (Schmidt et al. 2007). The major protective effect of caffeine in this context was that ventilator-induced lung injury was avoided to a large extent, because the caffeine-treated infants came off the ventilator earlier than the controls (Schmidt et al. 2007). Another possibly contributing effect might be that caffeine and other methylxanthines have inherent immunomodulatory mechanisms (Haskó and Cronstein 2010; Ohta and Sitkovsky 2010) that might protect both from lung and brain injury.

7 Conclusions

Many fetuses and neonates are exposed to low levels of methylxanthines owing to maternal drinking of coffee. Much higher doses of caffeine and theophylline are used in long-term pharmacological treatment of apneas in preterm infants. Pregnant women, fetuses, and neonates have an inability to detoxify methylxanthines, rendering the developing organism with accumulating levels of methylxanthines, which implies that there is a risk for adverse effects. Brain development is of particular concern.

Animal studies, however, suggest that the major effector system for methylxanthines, adenosine receptors, is not fully developed in the brain at birth. Furthermore, animal studies have shown protective positive effects of methylxanthines in situations of hypoxia/ischemia in neonates. Similarly, a positive long-term effect on lung function and CNS development was found in human preterm infants treated

with high doses of caffeine for apneas. There is now evidence that the overall benefits from methylxanthine therapy for apnea of prematurity outweigh potential risks in the short term.

Experimental studies, however, have indicated that long-term effects of low-dose caffeine during pregnancy and lactation may include altered behavior in the offspring, but there are currently no human data to support this.

Negative effects on pregnancy and perinatal outcomes have been reported in epidemiology studies, but the results are inconclusive. The evidence base for adverse effects of caffeine in first third of pregnancy is stronger than for later parts of pregnancy. Whereas it may be prudent for women in early pregnancy to limit caffeine intake (less than 300 mg/day), there is currently insufficient scientific evidence to advise mothers to avoid consuming caffeine during later parts of pregnancy.

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