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Review

Caffeine, Bronchopulmonary Dysplasia and Neurodevelopmental Outcomes in Premature Infants

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ABSTRACT

Caffeine, a stimulant is the most widely used drug in the world in adults with increasing usage in children. It is commonly used in the treatment of apnea of prematurity in premature infants. Caffeine in a randomized trial has been shown to reduce the incidence of bronchopulmonary dysplasia in infants <1250 grams birth weight when used to treat apnea of prematurity in these infants. In the same cohort of infants, caffeine improved neurodevelopmental outcomes and survival at 18 months of age and was found to be safe without any adverse events up to 11 years of age. Caffeine is an adenosine receptor antagonist and inhibits adenosine receptors at physiologic concentrations with important effects on behavior and cognitive functions. However, higher doses of caffeine may inhibit the enzyme phosphodiesterase and affect vascular smooth muscle function. Anti-oxidant, anti-inflammatory and antiapoptotic properties of caffeine and its ability to scavenge reactive oxygen species may contribute to its lung and neuroprotective effects in premature infants. Animal studies on whether caffeine is protective to the lung are not conclusive at this time. Similarly, caffeine is demonstrated to have adverse effects on brain development in animal studies. Despite the beneficial effects of caffeine in premature infants when administered in the neonatal period, the long-term effects on adult-oriented disease such as cardio-metabolic disease and neurobehavioral states in children and adults needs further study.

Keywords

Caffeine; Premature infants; Bronchopulmonary dysplasia; Neurodevelopmental outcomes; Adenosine receptor.

INTRODUCTION

Caffeine is the most widely used psychoactive drug in adults and children in the world. Caffeine was consumed in some form for thousands of years in human history, however, it became popular as a beverage in the early 18th century. Its main beneficial effects include maintaining alertness, postponing fatigue and elevating mood by acting as a central nervous system stimulant in low to moderate doses. In a way, it is a magic drug for most of the world's population without a prescription! Moderate caffeine consumption very rarely leads to health risks. However, higher doses of caffeine produce symptoms such as anxiety, insomnia, restlessness, and tachycardia. The habitual use of caffeine can cause physical dependence that displays as caffeine withdrawal symptoms that harm normal functioning in adults. Recently, children and adolescents are the fastest segments of caffeine consumption with sales of energy drinks containing high doses of caffeine on the rise.[1] Energy drinks negatively impact health by disrupting sleep and increasing daytime sleepiness[2,3] and is associated with self-reported violent behavior and conduct disorder.[4] Caffeine is also correlated with stress, anxiety and depression in school children,[3] suggesting children are particularly vulnerable to the negative effects of caffeine, which could potentiate the effects of other substances such as alcohol and illicit drugs. Nonetheless, the use of caffeine has progressed and has become widespread in the neonatal populations, particularly in premature neonates. Caffeine is the drug of choice in the treatment of apneic events in premature infants. Since the reports of reduction in the incidence bronchopulmonary dysplasia with no effects on adverse neuro-developmental outcomes, caffeine use has become more widespread in intensive care units treating such newborns.The effects of caffeine in premature infants are related to unique pharmacokinetics and metabolism of

caffeine in premature neonates.

PHARMACOLOGY OF CAFFEINE IN PREMATURE NEONATES

Caffeine[1,3] is a plant alkaloid structurally similar to adenosine. Of the four adenosine receptors, A_1, A_{2a}, A_{2b} , and A_3 identified, micromolar concentrations of caffeine blocks the A_1 and A_{2a} receptors.[5] Caffeine is rapidly absorbed with 99% absorption within 45 minutes of ingestion.[6,7] Caffeine binds reversibly to plasma proteins, and protein-bound caffeine accounts for about 10-30% of the total plasma pool. In infants, the volume of distribution is 0.8 to 0.9 L/kg, suggesting that it is hydrophilic and distributes freely into the intracellular tissue water[7] and this is significantly influenced by postnatal age and current birth weight.[8] Caffeine is also sufficiently lipophilic to pass through all biological membranes and readily crosses the blood-brain barrier. Majority of premature infants achieve plasma concentrations of caffeine between 5-20 µg/ml following administration of standard doses of caffeine (loading dose: 20 mg/kg; maintenance dose: 5-8 mg/kg/day). Hence, therapeutic drug monitoring for caffeine levels is not necessary for the treatment of apnea of prematurity or more recently for prevention of BronchoPulmonary Dysplasia (BPD) in premature neonates.

In adults caffeine is almost completely metabolized in the liver, with <3% excreted unchanged in the urine,[9] this is in contrast to neonates, wherein, 86% of caffeine is excreted unchanged in the urine.[10] Caffeine is metabolized almost exclusively in the microsomal enzyme system of the liver, predominantly by the enzyme CYP1A2. Biotransformation of caffeine by the microsomal cytochrome P450 mono-oxygenases and partially by xanthine oxidases is essentially a conversion to N-3 (paraxanthine), N-7 (theophylline) and N-1 (theobromine) demethylation.[11] The main route of metabolism in adults is through N-3 demethylation to paraxanthine (70-80%);[11] the predominant process in preterm infant is N-7 demethylation which matures at about four months of age.[12] The demethylation process in infants is postnatal age-dependent regardless of gestational age or birth weight. Females have a higher rate of caffeine metabolism than male neonates.[12] The half-life of caffeine is about 5 hours with an elimination half-life range between 1.5 to 9.5-hours in adults.[13] The serum half-life in infants and premature neonates varies from 40 to 230 hours exhibiting decreasing half-lives with advancing postmenstrual age until 60 weeks of age.[10] In infants born preterm, caffeine metabolism is limited by the immaturity of the microsomal enzyme system of the liver. In term and premature neonates caffeine clearance is determined by gestational age, postnatal age and parenteral nutrition.[14] As caffeine clearance increases with increasing Glomerular Filtration Rate (GFR) in both preterm and term infants, its elimination is slower at birth and increases with age.[14]

IS CAFFEINE, THE MAGIC BULLET IN PREMATURE NEONATES?

Caffeine therapy reduced the rates of BPD in very low birth weight (VLBW) infants in the caffeine for apnea of prematurity trial (CAP trial).[15] Infants with a birth weight of 500 to 1250 grams were randomly assigned within the first 10 days of birth to either caffeine or placebo until they no longer needed caffeine for apnea of prematurity. Caffeine administered at a dose of 20 mg/kg as a loading dose followed by a maintenance dose of 5-10 mg/kg/day depending on clinical symptoms. Infants administered caffeine came off positive pressure ventilation (PPV) an average one week early (median PMA-31 weeks; IQR-29.4-33.0 weeks) than infants in the placebo group (median PMA-32 weeks; IQR–30.3-34.0 weeks). Bronchopulmonary dysplasia, defined as oxygen requirement at 36 weeks post-menstrual age (PMA) was significantly less in the caffeine group compared to the placebo group in infants who survived [350/1006, 36% in caffeine group *versus* 447/1000, 47% in the placebo group; OR: 0.63 (0.52-0.76); $p<0.001$]. Infants in the caffeine group also had significantly less medical therapy for management of patent ductus arteriosus (PDA) (293/1006, 29.3% in caffeine group *versus* 381/1000, 38.1% in placebo group; $p<0.001$) and surgical closure of PDA (45/1006, 4.5% in caffeine group *versus* 126/1000, 12.6% in placebo group; $p<0.001$).[15]

The same cohort of infants from the caffeine for apnea of prematurity trial (CAP trial)[15] was found to have improved survival without neurodevelopmental disability at 18 to 21 months.[16] Of the 937 infants assigned to caffeine for whom data were available, 377 (40.2%) died or survived with neurodevelopmental disability in the caffeine group compared to 431 infants (46.2%) in the placebo group.[16] Prolonged PPV and apnea with hypoxic and desaturation episodes may explain adverse neurodevelopmental outcomes in the placebo group. The combined outcome of death or disability at 5 years of age was not significantly different for children assigned to the caffeine group (833 children, 21.1%) from those children assigned to the placebo group (807 children, 24.8%) (adjusted OR: 0.82; 95% CI, 0.65-1.03).[17] The rates of death, motor impairment, behavior problems, poor general health, deafness, and blindness did not differ significantly between the two groups. Neonatal caffeine therapy was no longer associated with a significantly improved rate of survival without disability in children when assessed at 5 years of age.[17] Similarly, caffeine did not significantly reduce the combined rate of academic, motor and behavioral impairments but reduced the rate of motor impairment at 11-years of age.[18]

More studies were conducted on the same cohort of infants who underwent the CAP trial in 2006. The first study to evaluate abnormalities in sleep architecture and breathing pattern in children aged 5-12-years, demonstrated that neonatal caffeine therapy has no long-term effects on sleep duration or sleep apnea during childhood.[19] Ex-preterm infants, regardless of caffeine status, are at risk for obstructive sleep apnea and periodic limb movements in later childhood. Caffeine treatment improved expiratory flow rates in mid-childhood, which is related to earlier extubations and less severity of BPD in these infants.[20] The studies suggest that neonatal caffeine therapy is effective and safe into middle school age (Figure 1). All the above studies on long-term effects on neurodevelopment and respiratory function are from the same cohort of infants originally enrolled in the CAP trial.

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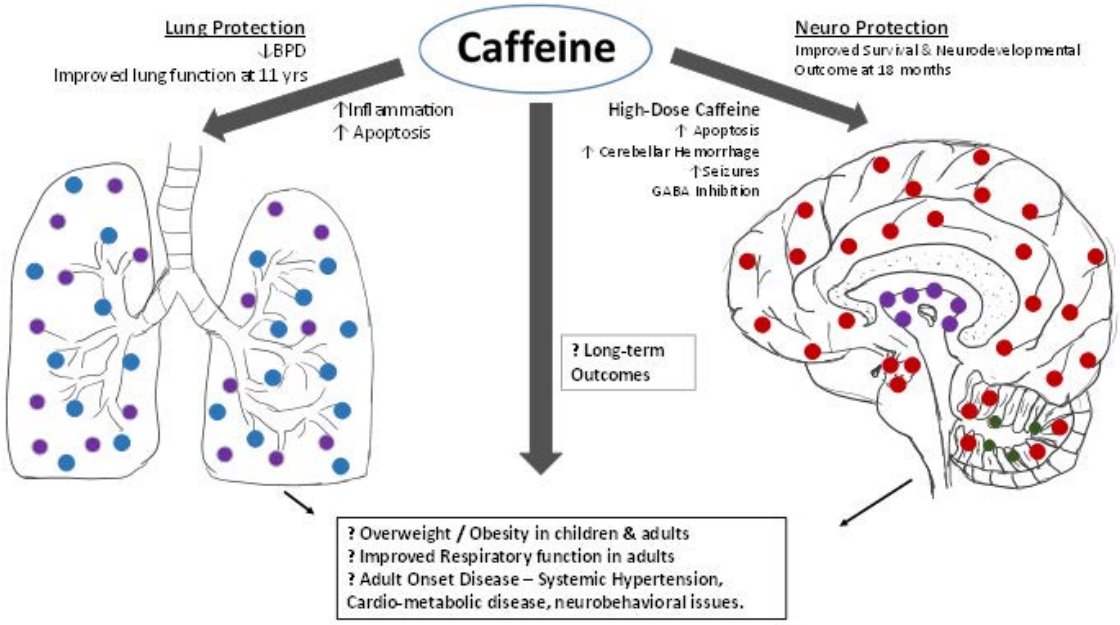
Figure 1. *Benefits of Caffeine in Premature Neonates. Caffeine Reduced Bronchopulmonary Dysplasia, Improved Survival and Neurodevelopmental Outcome at 18 Months in Premature Infants Weighing <1250 grams at Birth. Lung has Intermediate Concentrations of A_{2a} (Grey Circles) and A_{2b} (Light Blue Circles) Receptors; whereas Brain has High Concentrations of A_1 (Pink Circles–Cortex, Cerebellum, Hippocampus and Hypothalamus), A_{2a} (Grey Circles–Caudate, Putamen, Nucleus Accumbens and Olfactory Tubercle) and Intermediate Concentrations of A_3 (Light Green Circles-Cerebellum) Receptors.[64] The Long-Term Effects of Caffeine on Cardio-Metabolic and Neurobehavioral States are Not Well Studied and the Infants Needs Monitoring for Onset of Adult Oriented Disorders*



CAFFEINE AND BRONCHOPULMONARY DYSPLASIA

With the exception of CAP trial, no other randomized studies have addressed the relationship between caffeine and BPD. In the CAP trial, caffeine administered infants were extubated a week early and hence received one week less of positive pressure ventilation (PPV) and supplemental oxygen accounting for lower BPD in these infants. Caffeine has been shown to facilitate successful extubations in premature infants less than one week of age[21]. Short-term benefits of successful extubations are more likely with a higher dose of caffeine (20 mg/kg/day)[22] although this needs to be balanced against the higher risk of cerebellar hemorrhage from these doses of caffeine.[23] Infants receiving early caffeine therapy (<3 days of life) had improved neonatal outcomes compared to infants receiving late caffeine therapy (>3 days of life) including death or BPD and PDA requiring treatment in a retrospective study.[24] Early caffeine therapy (0-2 days) was associated with improved survival without BPD compared to late caffeine (3-10 days) in premature infants,[25] suggesting that earlier the caffeine load better are its lung protective effects.

The benefits of earlier administration of caffeine on BPD may be related to the unique physiology of the fetus and the premature neonate modulated by the ductus arteriosus. Its ability to decrease PDA treatment may suggest that it favorably altering PDA closure attenuating the fluctuations in systemic blood pressures with substantial benefits to the cerebral circulation. Studies on cardiac and cerebral physiology with caffeine, especially in neonates are lacking at this time. However, several studies have tried to address mechanistic or molecular mechanisms of action, especially in animal hyperoxia models. Caffeine is thought to reduce inflammation,[26,27] attenuate endoplasmic stress[28] and prevents hyperoxia -induced functional and structural lung damage[26] in animal models. Potentially adverse role of caffeine on alveolar development with increased inflammation, apoptosis and decreased expression of A2a receptors is reported in murine model hyperoxia-induced alveolar hypoplasia.[29] Caffeine modulated TGF-β signaling in vitro and in vivo, however did not influence the course of blunted postnatal lung maturation in an experimental hyperoxia mouse model of BPD.[30] We have shown that caffeine administration in newborn mice improves alveolarization in adult mice[31] and most likely its effects are mediated by regulating angiogenesis in hyperoxia-induced lung injury.[32]

Caffeine increases cAMP by inhibiting phosphodiesterase's (PDEs) and also exerts actions on the vascular smooth muscle at non-physiological doses. The doses of caffeine administered to preterm infants are extremely high, compared to caffeine intake in normal adults. The loading dose of caffeine is almost equivalent 15 cups of brewed coffee per day and maintenance dose is equivalent to 6 cups of coffee per day.[33] Hence, the actions of caffeine on the lung may be by multiple mechanisms resulting from physiologic and supra-physiologic doses of caffeine. In a model of oleic-acid induced acute lung injury (ALI), chronic caffeine treatment (0.1g/L -0.25g/L) for 2-weeks, or acute caffeine treatment at high dose (50 mg/kg i.p.), significantly attenuated the lung edema, hemorrhage, neutrophil recruitment as well as the inflammatory cytokine tumor necrosis factor-α and interleukin-1 expressions in both the wild-type and A2aR knockout (KO) mice.[34] This was accompanied by an increase in cAMP levels and up-regulation of A2bR mRNAs in the lungs. In contrast, acute caffeine treatment at a low dose (5-15 mg/kg i.p.) before ALI, enhanced inflammation and lung damage

in WT mice with a decrease in cAMP but not in A2aR KO mice. These results indicate that caffeine either enhances lung damage by antagonizing A2a receptors or exerts protection against lung damage *via* A2aR-independent mechanisms, depending on the timing of exposure (chronic *vs.* acute) and the dose of administration (low *vs.* high).[34] Preclinical studies in animals with different doses of caffeine for varying durations have only resulted in contrasting effects on the lung. Some studies have demonstrated benefits from caffeine while others have reported detrimental effects on the lung. No two studies point towards a predominant mode of action of caffeine in the lung. Caffeine administered at differing doses (high *vs.* low) and for varying duration may determine the physiologic and supra-physiologic actions of caffeine. Ultimately, caffeine actions may be modulated by its pharmacodynamics and metabolism in preterm infants and this could influence a reduction in BPD in these infants.

CAFFEINE EFFECTS ON THE BRAIN

Data from the post hoc analysis of the CAP trial suggested that infants in the caffeine group who had received less positive pressure ventilation (PPV) derived the benefits from reduced motor impairments.[18] Prolonged mechanical ventilation is a strong risk factor for poor neurodevelopmental outcome at 18-months of age in preterm infants.[35] More recently, starting caffeine within two days of birth has been shown to significantly lower the odds of neurodevelopmental impairments at 18 to 24 months in premature infants <29 weeks gestation than in infants after 2-days of birth.[36] This may be suggestive of favorable effects on systemic and cerebral hemodynamics by caffeine, as neonates have unique transitional physiology at birth. Among extremely preterm infants who survived to 36-weeks' postmenstrual age, prolonged hypoxemic episodes during the first 2 to 3 months after birth are associated with adverse 18-month outcomes[37] and extended caffeine therapy reduces intermittent hypoxemic episodes in these premature infants.[38] Caffeine decreases apnea by stimulating the medullary respiratory centers, increasing the sensitivity to carbon dioxide and enhancing diaphragmatic function leading to increased minute ventilation and reduced hypoxic respiratory depression.[39] Caffeine administration in the delivery room improves minute volume and tidal volume in preterm infants at birth[40] and these improvements persist with daily maintenance therapy.[41] At least from clinical studies, the pulmonary benefits of caffeine may spill over to the cerebral circulation, if studies prove that it stabilizes the systemic and cerebral circulation in premature infants. It is reassuring that caffeine is safe in this cohort of preterm infants up to middle school years after its administration at birth.

The beneficial and adverse effects of caffeine during pregnancy and in the immediate newborn period has mostly come from animal studies. Daily high-dose caffeine (LD: 25 mg/kg; MD: 20 mg/kg) does not appear to adversely affect the developing white matter at the microstructural level such as oligodendrocyte density, myelination, axonal integrity, astrogliosis, apoptosis or neuronal density in the developing ovine brain.[42] However, high dose caffeine (80-100 mg/kg) transiently decrease myelin formation in newborn mice[43] and increase apoptosis when administered with morphine in rats,[44] suggesting its effects do not only do dose specific but also species specific. Even though, newborns tend to tolerate higher doses of caffeine, physiologically relevant doses of caffeine can significantly depress adult hippocampal neurogenesis.[45] In a mouse model of postnatal caffeine therapy similar to treatment for apnea of prematurity in premature infants, caffeine reduced astrocyte densities in various areas of the brain in first two postnatal weeks, probably involving the A2A receptor.[46] A recent study in preterm infants' ≤30 weeks gestation, randomized to high dose caffeine (80 mg/kg vs 20 mg/kg loading dose) had a higher incidence of cerebellar hemorrhage with early motor alterations at term age equivalent.[23] There were no differences in long-term neurodevelopmental outcomes between infants assigned to high-dose or the standard-dose groups; however, the study was not powered to study long-term outcomes.[23] Treatment of mouse dams with either caffeine or other A2AR antagonists during pregnancy and lactation led to delayed migration and insertion of g-aminobutyric acid (GABA) neurons into the hippocampal circuitry noted during the first postnatal week in offspring[47] Adult offspring of mouse dams displayed loss of hippocampal GABA neurons and some cognitive deficits with increased neuronal network excitability and increased susceptibility to seizures in response to a seizure-inducing agent. This may suggest that exposure to caffeine during pregnancy and lactation in rodents may have adverse effects on the neural development of their offspring.[47] Animal models of fetal drug exposure, be it cocaine or alcohol or caffeine consistently reveal an impairment of GABA neuron development.[48] Caffeine may also trigger a seizure in susceptible people and decrease the antiepileptic potency of certain drugs, especially topiramate.[49] Caffeine overdosage (36 mg/kg to 136 mg/kg) and perinatal asphyxia may precipitate or increase seizure activity in term neonates.[50] Early high-dose caffeine (80 mg/kg) is associated with an increasing trend of both seizure incidence and seizure burden in premature infant's ≤30 weeks GA.[51]

The data from both the animal and human studies presented above do not comply with the studies from the cohort of infants followed from 2006 in the CAP trial. Few contrasting points have to be made about the above studies and the CAP trial. Firstly, a distinction has to be made while translating findings from preclinical studies in animal models to human populations.[48] Despite the differences in brain development in rodents and primates, animal models are relevant to human brain development. High-dose caffeine is associated with adverse effects on brain development in both animal and human studies, which is unlikely to be used in human studies. Nonetheless, the standard dose (20 mg/kg loading dose with a maintenance dose of 5-10 mg/kg) needs to be studied further in premature infants. Studies should incorporate non-invasive imaging such as MRI in fetuses and in premature infants at term equivalent to study fetal brain development. Assessment of the systemic hemodynamics by echocardiography following the loading dose would help tease the physiologic effects of caffeine on the cardiovascular system. Newborn physiology is unique in terms of presence of PDA and the immature cerebral autoregulation in the developing brain. Benefits of caffeine within 48 to 72-hours of birth[24,25] and significantly less medical and surgical treatment of PDA in the CAP trial,[15] strengthen the possibility of caffeine stabilizing the fluctuations in systemic blood pressure and hence cerebral blood flow, offering neurologic benefits

in premature infants. Assessment of cerebral blood flow, cerebral oxygen saturation and cerebral autoregulation in these infants may offer additional clues to the physiologic benefits of caffeine. Studies need to link cardiovascular benefits to cerebral physiology to define caffeine benefits on the brain.

The protective effects of caffeine on common neurodegenerative diseases in adults such as Alzheimer's disease and Parkinson disease are reported in both human and animal studies.[52, 53] Reports have suggested that caffeine acts as a free radical scavenger. Electron spin resonance measurements provide evidence that a caffeine-deprived oxygen-centered radical is formed in the reaction of caffeine with hydroxyl radical (OH) explaining the anticarcinogenic properties of caffeine and related methylxanthine compounds.[54] Caffeine inhibits lipid peroxidation and oxidative damage from reactive oxygen species[55] and modulates hepatic response to exercise-induced oxidative stress in rat liver cells.[56] In newborn rats exposed to hyperoxia, pretreatment with caffeine reduced markers of oxidative stress, promoted anti-oxidant responses, down-regulated pro-inflammatory cytokines, modulated redox-sensitive transcription factor expression, reduced pro-apoptotic effectors and diminished extracellular matrix generation.[57] This may suggest that caffeine by its anti-oxidant, anti-inflammatory and anti-apoptotic properties, may be uniquely positioned to provide neuroprotection to the developing brain and some of its actions are mediated via the adenosine receptors.[58,59]

DOES NEONATAL CAFFEINE HAVE LONG-TERM EFFECTS?

Epidemiological evidence suggests that maternal nutritional influences affect the fetus growth and development and the risk of disease later in life.[60,61] The negative effects of caffeine consumption in pregnancy on fetal growth are well documented. Maternal caffeine intake may modify the overall weight growth trajectory of the child from birth to 8-years of age.[62] Any caffeine consumption during pregnancy is associated with a higher risk of excess infant growth and of childhood overweight, mainly in preschool ages.[62] In utero caffeine, exposure has been associated with an increased risk of childhood obesity.[63] Maternal caffeine exposure is also associated with low birth weight and increased risk of small for gestational age status or fetal growth restriction at birth.[64] Prenatal exposure to caffeine was shown to program the offspring towards excess growth and cardiometabolic changes through alterations in hypothalamic-pituitary-adrenal axis,[65,66] regulation of adenosine and its receptors that modulate development[67,68] and in placental expression and transport of leptins, essential for regulation of appetite.[69] In most of the studies, maternal caffeine intake was <200 mg/day (around 2 mg/kg/day). This is in contrast to the doses of caffeine administered at three to four-fold higher than maternal caffeine intake, in the context of the developing brain and other organ systems in premature infants. What we need is clear scientific data from human studies to be certain that caffeine use either during pregnancy or in premature neonates has no adverse long-term consequences on brain development. This is especially so since animal studies have convincingly demonstrated adverse effects on hippocampal GABA neurons in offspring of dams treated with caffeine. The effects of neonatal caffeine on adolescent behavior, cardio-metabolic profile and systemic hypertension and stress levels in adults are also not well studied. We have shown that neonatal caffeine has the potential to increase systemic blood pressure in adult mice with an increase in vessel reactivity, especially in male mice.[70,71] Programming at the hypothalamic-pituitary level from neonatal caffeine administration may be gender specific. Co-administration of substances of abuse in ex-preterm infants such as nicotine and more caffeine in adolescents and young adults are unknown at this time. Addiction to sugar and caffeine, in preterm infants prone to overweight and caffeine tolerance from neonatal exposure, are additional risk factors that need consideration. There are many unknowns at this time with respect to the risks for adult-onset diseases such as diabetes, cardio-metabolic disease, and psychosocial morbidities at this time in adults born preterm with caffeine exposure at birth (Figure. 1). Whether caffeine or other illicit drugs can alter cortical neuronal migration specifically GABA inhibitory neurons during brain development in humans is still uncertain. This could have implications not only on brain development but also on neurobehavioral and neuropsychiatric disorders in adult needs clarification.

CONCLUSION

With the extensive use of caffeine for apnea of prematurity and for management of BPD, there may be a therapeutic creep of caffeine from the delivery room to discharge of the preterm neonate. Surfactant administration in premature infants and use of inhaled nitric oxide for persistent pulmonary of the newborn (PPHN) in term infants are classic examples, wherein multiple randomized studies have demonstrated beneficial effects in both preclinical studies and in newborns. These have become standard of care in the current therapeutic armamentarium in the management of premature and term newborns. With the preclinical and animal studies demonstrating adverse effects from caffeine, uncertainty exists in the use of caffeine in premature infants. Should we rely heavily on the CAP trial and its benefits or should we proceed cautiously in the use of caffeine in these infants. All infants who received caffeine for prevention of BPD needs to be followed with close monitoring for early identification of adverse events as they grow into young adults. The risks and benefits of caffeine need to be appreciated from a long-term perspective of the preterm infant. More studies should address the relationship between neonatal caffeine exposure, the preterm lung and brain development in humans and its association with pathophysiologies such as BPD and neurobehavioral processes in premature infants.

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