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Sex-specific respiratory effects of acute and chronic caffeine administration in newborn rats

Hayet Kouchi [1], NagaPraveena Uppari [1], Vincent Joseph, Aida Bairam *

Centre de recherche de l'institut de cardiologie et de pneumologie de Québec, Département de Pédiatrie, Faculté de médicine, Université Laval, Québec, Québec, Canada

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ABSTRACT

Caffeine is widely used for the treatment of apnea of prematurity (AoP) but whether this effect varies with sex is unknown. To shed some light on this question, we present a summary of data obtained on the effects of caffeine on the respiratory chemoreflexes and apnea frequency in 1- and 12-days old male and female rats. Caffeine was either administered as a single acute injection (10 mg/kg, i.p.) or for 10 consecutive days (7.5 mg/kg/day between 3 and 12 days of life by gavage, simulating its clinical use). Acute caffeine had little effects on breathing in 1-day old male and female rats. In 12-days old female rats caffeine reduced the response to hypercapnia (not hypoxia) compared to males. During the steady state of hypoxia females had a lower frequency of apneas than males, and acute injection of caffeine decreased the frequency of apnea, suppressing the differences between males and females. In 12-days old rats chronic administration of caffeine stimulated basal breathing and decreased the frequency of apnea similarly in males and females. In response to hypoxia, chronic caffeine administration also masked the difference in respiratory frequency between males and females observed in control rats. Female rats had lower frequency of apnea than males with or without caffeine treatment. These observations indicate that sex influences the respiratory responses to caffeine and this effect seems to depend on the modality of administration (acute vs chronic) and environmental oxygen (normoxia vs hypoxia).

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* Corresponding author at: Centre de Recherche de l'Institut Universitaire, de Cardiologie et de Pneumologie de Québec, 2725, chemin Sainte-Foy, Québec (Québec) G1V 4G5, Canada.
E-mail addresses: joseph@fmed.ulaval.ca, aida.bairam@fmed.ulaval.ca (A. Bairam).
[1] Contribute equally to this review.

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1. Apnea in newborn

Apnea in newborn and particularly in preterm infants with gestational age of less than 34 weeks (apnea of prematurity – AoP) is the most prevalent respiratory disorders during neonatal period. AoP is related to a functional immaturity of the respiratory control system at the central (respiratory nuclei of the brainstem) and at the peripheral chemoreceptor level (mostly localized within the carotid bodies). AoP is developmentally regulated as its frequency decreases with advancing age in human (Darnall et al., 2006; Zhao et al., 2011), and in rats (Niane and Bairam, 2011; Niane and Bairam, 2012), in parallel with an increased maturation of the respiratory control system (Darnall et al., 2006; Martin and Wilson, 2012). However, AoP is a burden in neonatal units because of the associated bradycardia and desaturation. Although there is no general consensus to define these symptoms, bradycardia is considered as a decrease of heart rate below 100 beats/min, and a desaturation is a reduction of arterial oxygen saturation below 80% (Di Fiore et al., 2016; Fairchild et al., 2016; Vergales et al., 2014). These clinical manifestations of AoP increase the morbidity of the neonates and significantly prolong the duration of hospitalization. For instance, one of the first lines of physiological responses to apnea is a hemodynamic adjustment to redistribute peripheral blood to the brain. This protects the brain from the hypoxic/ischemic insults, but produces pallor and cyanosis, and reduces the intestinal circulation, which probably participates in the occurrence of necrotizing enterocolitis (Palmer et al., 1987; Thompson and Bizzarro, 2008). It has also been suggested that these repeated episodes of hypoxic-ischemic insults during the neonatal period have long-term consequences; longer period of AoP (days to weeks) is associated with a higher incidence of severe retinopathy (Di Fiore et al., 2010) and neurocognitive disorders at school age (Janvier et al., 2004; Pillekamp et al., 2007).

The literature is rich in describing the pathophysiological aspects of AoP and potential treatments (Darnall, 2010; Darnall et al., 2006; Gauda et al., 2004; Marchal et al., 1987; Martin and Wilson, 2012; Schoen et al., 2014; Zhao et al., 2011). Indeed, the use of methylxanthines (caffeine, theophylline or aminophylline) as respiratory stimulants is common and the reader can easily find a significant body of information on this subject (for reviews see: Di Fiore et al., 2016; Eichenwald, 2016; Marchal et al., 1987; Martin and Wilson, 2012; Morton and Smith, 2016; Schoen et al., 2014; Zhao et al., 2011). Although all xanthines are comparably efficient for the treatment of AoP, caffeine is now considered as the 1st choice for its pharmacological characteristics compared to other xanthines; particularly because of its longer half-life than theophylline or aminophylline allowing a treatment with one dose/day comparatively to 2 for the theophylline and 3 for aminophylline. Finally, caffeine has less secondary effects (Bairam et al., 1987; Henderson-Smart and Steer, 2010; Schoen et al., 2014). However, caffeine reduces, but does not eliminate apnea, and almost 50% of apneas persist despite adequate therapy (Erenberg et al., 2000). Males and females are pooled in these studies and so far it remains unknown if a sex-specific effect could contribute to this partial response to caffeine therapy.

In the aim to bring new insights to this question, we will present data from recent experiments performed to test the hypothesis that there are sex-specific effects on breathing and apnea frequency following acute and chronic administration of caffeine in newborn rats explaining in part the partial response to caffeine. The acute effect of caffeine was tested in 1 and 12 days-old rats; while the chronic effect was tested in 12 days-old rats. These ages may represent the neurological and respiratory behaviour of preterm infants and based on observations showing that i) in rats the development of central nervous system at birth corresponds roughly to preterm infant of 24–28 weeks of age (Clancy et al., 2007; Rice and Barone, 2000); ii) the respiratory response to hypoxia develops during the first 2 weeks of life and becomes similar to full term infants at the postnatal day 14–15; (Bissonnette, 2000); and iii) although transient, sudden changes in many excitatory and inhibitory transmitter systems in the brainstem and carotid body that would affect the pattern of breathing occur between 13–15 postnatal days (Holley et al., 2012; Wong-Riley and Liu, 2008; Wong-Riley et al., 2013).

The data presented in this review support that under certain circumstances, the respiratory effects of caffeine are sex-specific, and the underlying mechanisms need further investigation.

2. Clinical evidence for sex-specific pathophysiological conditions in human

In the following section, we will present observations showing that sex (male or female) is a factor in the prevalence or outcomes in some clinical situations in different ranges of age.

1) Evidence from studies in adult subjects

Several reports have pointed-out a sexual dimorphism in the occurrence or in the outcome of cardio-respiratory pathologies in adult human. A well-known example is the higher incident of sleep disordered breathing in men than women: between the ages of 30–49 years, about 10% of men and 3% of women suffer from sleep apnea, and this difference persists between 50 and 70 years, when 17% of men and 9% of women have sleep apnea (Peppard et al., 2013). There is also a clear sexual dimorphism in the morbidity and mortality related to sleep disordered-breathing: the mortality rate from cardiac and hemodynamic dysfunction is two times higher in men than in women (Punjabi et al., 2009). Another example of a clear sexual dimorphism is the higher preponderance of ischemic brain injury and brain stroke in men than in women, while the outcomes are less favorable in women than in men (Manwani and McCullough, 2011).

2) Evidence from studies in childhood subjects

The best example in children is a higher prevalence of asthma in obese boys than girls with a linear relationship with body mass index in boys (Chen et al., 2013). Some studies have also reported a higher prevalence of obstructive sleep apnea in boys than in girls (Brockmann et al., 2016; Lumeng and Chervin, 2008), and in prepubertal girls with high testosterone level (Brockmann et al., 2016), but much remains to be documented in this age group and there are still some inconsistencies between studies (Brockmann et al., 2016).

3) Evidence from studies in newborn subjects

It is well recognized that females are more resistant than males to hypoxic/ischemic injuries at birth, have a lower risk to develop respiratory distress syndrome (hyaline membrane disease), and show lower incidence of sudden infant death syndrome (2:1 M/F)(Condo et al., 2016; Kinney and Thach, 2009; Mage and Donner, 2004, 2014). Long-term consequences of apnea in preterm infants might also be sex-specific, following long period with persistent apnea (assessed as total days with apneas), girls have a lower probability of neurodevelopmental impairments at 3 years of age than boys (Janvier et al., 2004)