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Review

Caffeine for apnea of prematurity: Effects on the developing brain

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ABSTRACT

Caffeine is a methylxanthine that is widely used to treat apnea of prematurity (AOP). In preterm infants, caffeine reduces the duration of respiratory support, improves survival rates and lowers the incidence of cerebral palsy and cognitive delay. There is, however, little evidence relating to the immediate and long-term effects of caffeine on brain development, especially at the cellular and molecular levels. Experimental data are conflicting, with studies showing that caffeine can have either adverse or benefical effects in the developing brain. The aim of this article is to review current understanding of how caffeine ameliorates AOP, the cellular and molecular mechanisms by which caffeine exerts its effects and the effects of caffeine on brain development. A better knowledge of the effects of caffeine on the developing brain at the cellular and/or molecular level is essential in order to understand the basis for the impact of caffeine on postnatal outcome. The studies reviewed here suggest that while caffeine has respiratory benefits for preterm infants, it may have adverse molecular and cellular effects on the developing brain; indeed a majority of experimental studies suggest that regardless of dose or duration of administration, caffeine leads to detrimental changes within the developing brain. Thus there is an urgent need to assess the impact of caffeine, at a range of doses, on the structure and function of the developing brain in preclinical studies, particularly using clinically relevant animal models. Future studies should focus on determining the maximal dose of caffeine that is safe for the preterm brain.

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1. Apnea of prematurity

Owing to immaturity of the lungs and other organs, preterm infants are susceptible to respiratory and metabolic abnormalities, which can result in hypoxemia, acidemia and hypoglycaemia. In spite of advances in neonatal intensive care, preterm infants are at risk of respiratory and neurological sequelae, with the risk being highest in those born very preterm (<32 weeks' gestational age) or extremely preterm (<28 weeks' gestational age) (Doyle et al., 2010b; Fanaroff et al., 2007). A common problem experienced by very and extremely preterm infants is apnea of prematurity (AOP), which is defined as a cessation in breathing lasting more than 15–20 s (Barrington and Finer, 1991; Miller and Martin, 2011). AOP occurs in 85% of infants born prior to 34 weeks' gestational age (Barrington and Finer, 1991). The incidence of AOP is inversely correlated with gestational age, occurring in 7% of infants born at 34–35 weeks, 15% at 32–34 weeks, 54% at 30–31 weeks, and in nearly all infants born prior to 30 weeks or with a birth weight <1000 g (Henderson-Smart, 1981; Robertson et al., 2009). If untreated, AOP can lead to hypoxemia, which can result in tissue hypoxia and hypoxic organ injury.

Cessation of respiratory airflow (apnea) can be caused by a cessation of the central respiratory rhythm, airway obstruction, or a combination of these. Thus, three main types of apnea are recognised: i) central apnea, characterised by a cessation of inspiratory efforts in the absence of airway obstruction, ii) obstructive apnea, when the infant attempts to breath against an obstructed upper airway, and iii) mixed apnea, when inspiratory efforts are obstructed, usually following periods of central apnea (Martin et al., 2004; Milner et al., 1980). AOP is believed to be a result of immaturity of respiratory control mechanisms (e.g. reduced sensitivity to CO_2 and hypoxia) as well as an exaggerated protective (laryngeal closure) response to laryngeal stimulation; recent evidence suggests that inflammation in the central nervous system (CNS) may also play a role (Morton and Smith, 2016).

The central respiratory rhythm is dependent upon input from chemoreceptors near the ventral surface of the medulla oblongata that respond to the ambient pH and partial pressure of carbon dioxide ($PaCO_2$); the rhythm is also affected by excitatory and inhibitory inputs from higher brain centres, mechanoreceptors in the upper airway and lungs, and chemoreceptors in the carotid bodies (Di Fiore et al., 2013; Martin and Wilson, 2012; Mathew, 2011). A cessation of the respiratory rhythm in the brainstem (central apnea) plays an important causative role in AOP as it will lead to a cessation in the inspiratory activation of the muscles of respiration, including the diaphragm, intercostal muscles and dilator muscles of the upper airway (larynx, pharynx, and tongue). As well as a cessation of inspiratory efforts, the upper airway may become closed; indeed it is likely that during central apnea, the glottis becomes actively closed, as it is in the fetus during periods of central apnea (Harding, 1984). In preterm infants, the soft tissues of the respiratory tract are highly compliant, predisposing these infants to upper airway collapse and obstruction during inspiratory efforts, especially in the absence of dilator muscle activity (Di Fiore et al., 2013).

2. Caffeine for the treatment of apnea of prematurity

Since the 1970s, methylxanthines, including caffeine, theophylline and aminophylline (the ethylenediamine salt of theophylline) have been the pharmacological drugs of choice for the treatment of AOP. Methylxanthines, combined with the prone sleeping position, continuous positive airway pressure or nasal intermittent positive pressure ventilation, comprise the current standard of care for AOP. Methylxanthines are able to reduce the incidence of apneic episodes via a number of pathways and have therefore become one of the most commonly prescribed drugs in neonatal medicine (Millar and Schmidt, 2004). Methylxanthines are believed to act by raising central sensitivity to CO_2 and improving respiratory muscle function, which together lead to an increase in minute ventilation (Abu-Shaweesh and Martin, 2008; Miller and Martin, 2011). Although it is well established that methylxanthines lead to an increase in respiratory neural output, the molecular and cellular basis of this effect is still unclear. The hydrophobic properties of caffeine allow it to pass through all biological membranes, including the blood-brain barrier (Lachance et al., 1983); thus it readily enters the CNS. The ability of methylxanthines to competitively antagonise adenosine receptors (ARs) within the CNS, in particular A_1 and A_{2A} ARs, has been proposed as the mechanism by which these agents stimulate the respiratory rhythm (Fredholm, 1995). A secondary mechanism may be via the effects of methylxanthines on gamma-aminobutyric acid (GABA) receptors, inhibition of phosphodiesterase (PDE) and calcium (Ca^{2+}) release; however these latter effects are unlikely to be seen owing to the extremely high (toxic) concentrations that are required (Fisone et al., 2004; Fredholm et al., 1999).

Numerous studies have compared the benefits and risks of methylxanthines in preterm infants. Although aminophylline and theophylline are just as effective in treating AOP as caffeine, they are associated with far more adverse effects than caffeine (Henderson-Smart and Steer, 2010; Larsen et al., 1995). Some of the well documented side-effects of methylxanthines include tachycardia, cardiac dysrhythmias, food intolerance, increased metabolic rate, increased O_2 consumption, and less frequently, seizures, all of which are uncommon with current therapeutic doses of caffeine (Abu-Shaweesh and Martin, 2008). Another advantage of caffeine is that it is more easily absorbed than aminophylline and theophylline, and has a wider therapeutic range and a longer half-life, allowing for once-a-day dosing (Henderson-Smart and De Paoli, 2010; Henderson-Smart and Steer, 2010; Millar and Schmidt, 2004). These benefits, along with the finding that caffeine improves respiratory and neurodevelopmental outcomes up to 21 months of age (Schmidt et al., 2006, 2007), have led to caffeine being the methylxanthine of choice when treating AOP. However, the dosing regimen of caffeine used in treating preterm infants varies between neonatal intensive care units around the world (Scanlon et al., 1992; Steer et al., 2003), and higher doses of caffeine are often administered when the standard dose is not sufficient to reduce the incidence of apnea. In addition, the timing of caffeine therapy in relation to birth is an important consideration (Schmidt et al., 2014). A preliminary randomized controlled trial of 21 neonates born at less than 29 weeks' gestational age who received caffeine (20 mg/kg) either prior to 2 h after birth or at 12 h after birth found no difference in ventilatory requirements; however, their hemodynamics improved more after early caffeine treatment compared with later treatment (Katheria et al., 2015). Whether early versus late caffeine therapy in preterm infants differentially affects brain development or the incidence of neonatal brain injury is yet to be determined.

3. Caffeine: mechanism of action

As caffeine has a range of molecular targets within the CNS, it has been difficult to determine the precise molecular and cellular mechanisms by which caffeine reduces the incidence of AOP. The major molecular target of caffeine within the CNS is antagonism of ARs, particularly the A_1 and A_{2A} receptors; at high concentrations, caffeine leads to the inhibition of PDE, release of intracellular Ca^{2+} and antagonism of $GABA_A$ receptors. The effect of clinical levels of caffeine on arousal and breathing is unlikely to be a result of its actions on PDE, intracellular Ca^{2+} and $GABA_A$ receptors (Fredholm et al., 1999), as these targets require very high concentrations of