Journal of Nutrition & Intermediary Metabolism 5 (2016) 55–60

Contents lists available at ScienceDirect

Journal of Nutrition & Intermediary Metabolism

journal homepage: http://www.jnimonline.com/

Targeting inflammation in the preterm infant: The role of the omega-3 fatty acid docosahexaenoic acid

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ARTICLE INFO

Article history:
Received 4 December 2015
Received in revised form
20 March 2016
Accepted 22 March 2016
Available online 21 April 2016

Keywords:
Long-chain polyunsaturated fatty acid
Docosahexaenoic acid
Preterm infant
Inflammation
Immunoregulation

ABSTRACT

Long-chain polyunsaturated fatty acids are critical for the normal growth and development of preterm infants. Interest in these compounds rests in their anti-inflammatory properties. Clinical conditions with an inflammatory component such as bronchopulmonary dysplasia, necrotising enterocolitis and sepsis are risks to the survival of these infants. Dysregulation of inflammatory responses plays a central role in the aetiology of many of these neonatal disorders. There is evidence to suggest that the omega-3 long chain polyunsaturated fatty acid docosahexaenoic acid (DHA) can down-regulate local and systemic inflammation in adults and animal models; however, very little is known about its protective effects in infants, especially preterm infants. Due to their immunological immaturity, preterm infants are particularly sensitive to diseases with an inflammatory aetiology in the early postnatal period. This makes DHA supplementation immediately after birth to combat neonatal inflammation an attractive therapy. Mechanistic data for DHA use in preterm infants are lacking and results from adult and animal studies may not be relevant to this population because of fundamental immune system differences. While there is increasing evidence from randomised controlled trials to support a beneficial effect of DHA for the preterm infant, more evidence is required to establish short and long-term effects of DHA on the immune status of preterm infants.

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1. Introduction

Preterm birth, defined as birth at less than 37 completed weeks gestation, occurs in around 12% of deliveries worldwide with major implications for the long term health of the child [1,2]. Mortality rates of preterm infants have decreased substantially over the last few decades due to advancements in medical care [1]. However, morbidity rates, particularly in the very preterm infant (born less than 28 weeks gestation) have continued to rise [1]. Functionally and immunologically immature, the very preterm infant requires intensive support, and the medical interventions necessary for their survival can trigger a local or systemic inflammatory response [3].

Preterm infants have an under-developed immunoregulatory system, therefore there is the potential for chronic inflammation to develop [4]. Dysregulation of inflammatory responses plays a central role in the aetiology of many life-threatening neonatal disorders including bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC) and sepsis [3–7] and presents a continuing challenge to clinicians involved in their care. Interest is intensifying in dietary compounds that promote resolution of inflammation and confer a protective effect against development of neonatal inflammatory disorders [8]. There is some controversy as to whether or not preterm infants can synthesise sufficient long-chain polyunsaturated fatty acids (LCPUFA) such as docosahexaenoic acid (DHA) and arachidonic acid (AA) from essential fatty acid (EFA) precursors [9–13] because genetic variants in the fatty acid desaturase genes may affect rates of synthesis of LCPUFA [13,14]. However, all infants receive an exogenous source of EFA and/or LCPUFA, via breast milk, lipid emulsions, formula or a combination of these sources [15]. Interest in DHA supplementation and its

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http://dx.doi.org/10.1016/j.jnim.2016.03.004
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effect on clinical outcomes in preterm infants has escalated because these sources do not provide sufficient levels of DHA for these infants [16]. This review will focus specifically on the potential for the omega-3 LCPUFA DHA to act as an immunoregulatory agent to improve clinical outcomes in preterm infants.

2. Omega-3 LCPUFA and their role in early immune development

Preterm infants have a fundamentally different immune system to that of an adult or even a term infant, making them especially susceptible to an exaggerated immune activation [3]. The preterm infant relies heavily on the non-specific innate immune response for defence [3,17]. The antigen-specific adaptive immune system of preterm infants is also underdeveloped at birth, particularly with regard to T cells mediating inflammatory responses (T helper 1: Th1) and the important T cells involved in regulating the immune response (T-regulatory: T-reg) [3,18–20]. Ineffective T-reg function after birth, when the infant is exposed to a massive environmental antigenic onslaught from the birth process and neonatal intensive care unit (NICU), can result in excess inflammation and a lowered ability to down-regulate immune responses once initiated.

Breast milk has long been considered the gold standard for infant nutrition and is essential for promoting appropriate immune development in newborns [21]. In addition to a full complement of LCPUFA, breast milk also contains a complex mixture of immunologically active components such as growth factors, lactoferrin, prostaglandins, immunoglobulins, cytokines and immune cells [22,23]. Together with LCPUFA, the immunoregulatory bioactives in breast milk such as interleukin (IL) 10, transforming growth factor (TGF) β and DHA serve as mediators to promote oral tolerance and they also modulate developing immune responses while the infant develops their own immunoregulatory ability [3,19,20,24–28]. This immune maturation is crucial in order for a complex and dynamic relationship to develop between the innate and adaptive immune system [4,18,19,29], allowing infants to respond effectively and appropriately to self and pathogenic environmental stimuli [25,30]. Without appropriate regulation, an unchecked inflammatory pathophysiology can result, leading to many neonatal morbidities [3,4,17].

3. Inflammatory disorders in the neonate and the role of DHA

A heightened immune response leading to an exaggerated release of inflammatory mediators is a hallmark of BPD and other inflammatory disorders in the neonatal period, such as sepsis, NEC and retinopathy of prematurity (ROP) [3]. These disorders have a multi-factorial pathogenesis for which a single medication or comprehensive treatment is not available. Data from both preterm infant [4,31] and animal studies [32,33] support the potential for DHA to serve as a general preventative agent against inflammation without inhibiting development or function of underdeveloped organs.

3.1. Bronchopulmonary dysplasia

BPD is a disorder of prematurity characterised by the need for assisted ventilation or supplemental oxygen at 36 weeks post-menstrual age and signs of impaired alveolarisation and vasculogenesis in the lungs [4,34]. BPD occurs in approximately 45% of infants born less than 29 weeks gestation that survive preterm birth [4,35]. Ongoing lung damage may be caused by the preterm infant's inability to down-regulate and maintain control of the inflammatory immune response, leading to a chronic inflammatory state [35–38]. Decreased levels of DHA have been found to be associated with respiratory disease in preterm infants [39,40] and results from a prospective observational study in preterm infants supports this trend [41]. The best evidence for the ability of DHA to improve respiratory outcomes in preterm infants comes from our "*Docosahexaenoic acid for Improvement in Neurodevelopmental Outcomes (DINO) trial*". In the subgroup of infants born weighing less than 1250 g, those who received higher-DHA breast milk or formula had a reduced rate of BPD [42]. A recent meta-analysis supports the potential for DHA as a preventative agent against adverse respiratory outcomes when administered early in life [4]. These data support the concept that there is an early window of opportunity for effective immunomodulation with DHA; the critical period is when the immune system is still developing and before clinical phenotypes have been established in the infant [8,43].

3.2. Necrotising enterocolitis

NEC is predominantly a disease of prematurity, it is the most common gastrointestinal illness in newborns and has a high mortality rate [44–46]. As the disease progresses, inflammation in the intestine worsens causing breakdown of the mucosal barrier and an escalating immune cascade leading to sepsis, shock and even death [6,44,47]. The risk for developing NEC is strongly influenced by commensal bacteria, which exert metabolic, nutritional and immunological effects on the host [48]. A preterm infant has very low bacterial diversity and the establishment of a more complex microbiome is easily disrupted by events related to premature birth, for example, early antibiotic administration and Caesarean sections [49–51]. This process, termed dysbiosis, is implicated in the development of both sepsis and NEC [48].

Breast milk is the first choice for nutrition in the preterm infant and its early introduction is critical due to known gastrointestinal benefits [52]. Breast milk promotes bacterial colonisation of the gut, which in turn, is a major promoter of the development of immunoregulatory pathways required to mediate inflammation and bring about immunological homoeostasis [53]. Enteral feeding regimens for preterm infants consist of breast milk, preterm formula, or more commonly in the first few weeks, a combination of the two [52]. Both are sources of DHA which has been shown to influence the composition of the microbiome, albeit with controversial efficacy [32,54–56]. It has been proposed that fat intake and type of fat (saturated vs. unsaturated) influences the distribution of beneficial and protective bacteria in preterm infants [51]. A meta-analyse of trials in which NEC was reported has shown no benefit for omega-3 LCPUFA [4]; however none of the included trials were specifically designed nor powered to determine the true effect of DHA on NEC. Data from neonatal animal models is promising, as it has been reported that omega-3 LCPUFA-enriched diets support the colonisation of beneficial bacteria and protect against growth of pathogenic bacteria [32] and are protective against NEC [57]. Further, large-scale studies are required to first determine if DHA can reduce the incidence of NEC, and secondly if it is through a direct anti-inflammatory action or if DHA influences microbial communities directly in the gut.

3.3. Sepsis

Sepsis is a systemic inflammation caused by infection. Globally, sepsis is responsible for approximately 15% of neonatal deaths [58], with rates of infection dependent on the geographic region [5,59,60]. In preterm infants, sepsis is classified as either early-onset (<72 h of life) or late-onset (>72 h of life), with the latter being a common complication associated with prolonged admission to NICU [59,60]. The distinction between the two is of clinical importance, as early-onset sepsis usually results from exposure to

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