Can maternal DHA supplementation offer long-term protection against neonatal hyperoxic lung injury?

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Lingappan KD, Moorthy B. Can maternal DHA supplementation offer long-term protection against neonatal hyperoxic lung injury? Am J Physiol Lung Cell Mol Physiol 309: L1383–L1386, 2015. First published September 11, 2015; doi:10.1152/ajplung.00313.2015.—The effect of adverse perinatal environment (like maternal infection) has long-standing effects on many organ systems, including the respiratory system. Use of maternal nutritional supplements is an exciting therapeutic option that could be used to protect the developing fetus. In a recent issue of the journal, Ali and associates (Ali M, Heyob KM, Velten M, Tipple TE, Rogers LK. Am J Physiol Lung Cell Mol Physiol 309: L441–L448, 2015) specifically look at maternal docosahexaenoic acid (DHA) supplementation and its effect on chronic apoptosis in the lung in a mouse model of perinatal inflammation and postnatal hyperoxia. Strikingly, the authors show that pulmonary apoptosis was augmented even 8 wk after the hyperoxia-exposed mice had been returned to room air. This effect was significantly attenuated in mice that were subjected to maternal dietary DHA supplementation. These findings are novel, significantly advance our understanding of chronic effects of adverse perinatal and neonatal events on the developing lung, and thereby offer novel therapeutic options in the form of maternal dietary supplementation with DHA. This editorial reviews the long-term effects of adverse perinatal environment on postnatal lung development and the protective effects of dietary supplements such as DHA.

**docosahexaenoic acid; hyperoxia**

**MATERNAL INFLAMMATION** during pregnancy can occur by intra- or extraterine processes. Maternal infections both systemic (urinary tract infection, periodontitis) and chorioamnionitis have been associated with premature birth (17, 27, 36, 49). Chorioamnionitis leads to fetal lung inflammation in animal models (18, 28). The clinical correlation between chorioamnionitis and development of bronchopulmonary dysplasia (BPD) is not strong, with evidence being available both for and against the association (19, 41). In animal models, chorioamnionitis induces lung maturation (increase in surfactant proteins) but also causes delayed alveolarization and vascular injury (15, 18). Intra-amniotic lipopolysaccharide (LPS) on embryonic day 15 increases alveolar type II cell number through Toll-like receptor-4 signaling (33). Maternal inflammation can potentially initiate the inflammatory cascade in the fetal lung, which can be further potentiated by postnatal exposures such as hyperoxia (45). Antenatal corticosteroids (maternal β-methasone) given to pregnant ewes decrease intrauterine inflammation-induced TGF-β signaling in fetal lungs (9). Cao et al. showed that maternal exposure to systemic endotoxin in pregnant rats increases pulmonary inflammation in the pups, altered gene expression of molecules involved in alveologenesis, and delayed morphological maturation (6). Salminen et al. found that, following systemic maternal endotoxin administration, the inflammatory signal is rapidly transmitted to the fetus and in the fetal lungs; they noted an acute decrease in immune proteins, including surfactant proteins (SP-A and SP-D). This was different from the models of ascending inflammation (38).

Various murine models of BPD have been used by investigators to produce the lung phenotype seen in human BPD patients (3, 32). Multiple hits such as perinatal inflammation and postnatal hyperoxia may be common in human premature babies (22). Velten et al. showed that the combination of systemic maternal inflammation and postnatal hyperoxia persistently altered alveolarization, increased lung fibrosis, and impaired lung function at 8 wk (43, 44). Using the same model, the authors reported that maternal dietary supplementation with docosahexaenoic acid (DHA) improved alveolarization and pulmonary function at 8 wk (42).

The arrest in lung development caused by adverse perinatal and postnatal factors continues beyond the neonatal period. Many studies have shown that inflammatory markers are elevated in children diagnosed with BPD as neonates. Increased 8-isoprostane levels were detected in the exhaled breath condensate in adolescents born at ≤32 wk of gestation (12). Abnormalities in pulmonary function tests also persist (13, 46). These could predispose the neonates with BPD to the development of respiratory illnesses later in their life. Similar persistent findings into adulthood have been found in neonatal mice exposed to hyperoxia (4, 5, 34, 38, 48).

Several investigators have noted the protective effects of DHA and its downstream metabolites in various lung diseases. Levels of DHA decrease in premature neonates after birth (24), and this could potentially exacerbate the adverse effects of infection, inflammation, or oxidative stress. Martin et al. found that postnatal treatment with resolvins, a downstream metabolite of DHA, reverses the biochemical and histological changes of neonatal hyperoxia exposure (25). In a neonatal hyperoxia model, maternal DHA supplementation decreases leukocyte infiltration in the lungs (35). Similar beneficial results have been observed in adult animals in acute lung injury models (8, 11, 20, 47). Other pulmonary disease models where benefits were seen with DHA or its downstream metabolites include cystic fibrosis, asthma, and pulmonary fibrosis (29, 31, 51).

In a recent issue of the journal, Ali and colleagues (1) elegantly show that apoptosis persists in the lungs of 8-wk-old mice who had been exposed to perinatal inflammation (maternal systemic inflammation) and postnatal hyperoxia [up to postnatal day (PND) 14] followed by return of the animals to room air. This was accompanied by upregulation of some of the proteins associated with the apoptotic pathways. Maternal dietary supplementation with DHA decreased apoptosis and the associated markers [poly (ADP-ribose) polymerase]...
(PARP); apoptotic protein activating factor (APAF); high mobility group box 1 (HMGB1)) in the lung. The authors have not specified the cell types (type I vs. type II epithelial, bronchial epithelial or endothelial) that were affected in this apoptotic process, and this could be important in carrying this story forward. Using cell-specific markers and colocalization studies, the anti-apoptotic protective effects could be narrowed down.

The authors also investigated the Notch pathway, which plays an important role in lung development, in mice exposed to perinatal inflammation and postnatal hyperoxia with and without maternal DHA supplementation. The implications of the findings, although interesting, need further studies. Delta like-1 (DLL1) and Presenilin enhancer 2 (PEN2) were significantly decreased in the DHA group compared with control mice exposed to LPS/O2. Notch downregulation is important for alveolar development (14). PEN2 is the regulatory component of a protease complex responsible for the proteolysis of the activated membrane-bound form of Notch. This releases intracellular notch cleavage product (NICD), which translocates to the nucleus and activates the Notch-target genes (39).

In view of the above, decreased PEN2 would be expected to decrease Notch activity and favor lung development. However, no differences were found in the levels of NICD by the authors. DLL1 is an essential Notch ligand, and DLL1-mediated Notch activation is crucial for postnatal arteriogenesis and vascular morphogenesis (21, 30). Decreased DLL1 (as found in this study)-mediated Notch activation would be expected to decrease postnatal pulmonary blood vessel development. Maternal DHA supplementation also decreased the levels of IL-6 (as a marker of inflammation) and F2 α-isoprostane levels (as a marker of lipid peroxidation) and increased glutathione-to-reduced glutathione ratios (improved antioxidant milieu).

The study raises several interesting questions about the translational aspects of this therapy for prevention of BPD. Would neonatal supplementation as shown by Martin et al., when combined with maternal supplementation, have additional beneficial effects in this model? This has been shown with supplements such as curcumin (37), vitamin A/retinoic acid (16), vitamin D (23), and β-naphthaflavone (10). Can specific downstream mediators of DHA like resolvin be tested in this model for greater specificity? In this model of systemic maternal inflammation during late pregnancy, maternal DHA supplementation was protective. It will be important test the protective effects in an intrauterine infection (chorioamnionitis) model. The protective effects can then potentially be extended to mothers with chorioamnionitis, which in many cases is clinically silent and is the major inflammatory pathway leading to preterm deliveries in humans. DHA has been shown to modulate angiogenesis through the vascular endothelial growth factor and other pathways (26, 50, 52). Because the endothelial-epithelial interaction is crucial for lung development (2), it will be interesting to see the effects of DHA on angiogenesis in the developing lung. The neonatal mice in this model probably received higher DHA in the milk from nursing dams receiving DHA than the controls fed normal chow. This may have provided added protection to the pups, since the postnatal hyperoxia extended to PND14 and probably also modulated lung repair until PND21 when the mice are usually weaned. This effect has also been shown in human studies, where breastfeeding mothers receiving DHA supplementation had higher DHA concentration in their breast milk (7, 40). This model would have clinical relevance for preterm neonates, since they may receive their mother’s own milk, donor human milk, or preterm formula in the neonatal intensive care unit. Last, to prove the beneficial effects of maternal DHA supplementation toward long-term lung health of the newborn, lung function studies in these groups would add important information (48).

In conclusion, this study highlights the fact that there are persistent deleterious effects of perinatal and neonatal exposures on the developing lung even after significant periods of recovery in room air, and maternal dietary supplementation with DHA can prevent these effects (Fig. 1). This is an important step forward in the prevention of BPD in a high-risk population and offers the opportunity for the development of novel prophylactic and treatment options for BPD in premature human infants.

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**AUTHOR CONTRIBUTIONS**

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![Diagram of possible processes that maternal docosahexaenoic acid (DHA) supplementation can modulate during the course of systemic maternal inflammation and postnatal hyperoxia.](http://ajplung.physiology.org/)

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**MATERNAL DHA AND NEONATAL LUNG INJURY**

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**Fig. 1.** Possible processes that maternal docosahexaenoic acid (DHA) supplementation can modulate during the course of systemic maternal inflammation and postnatal hyperoxia.


