Prostaglandins, Leukotrienes and Essential Fatty Acids 107 (2016) 43–49

Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

Long-chain saturated and monounsaturated fatty acids associate with development of premature infants up to 18 months of age

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ARTICLE INFO

Article history:
Received 17 September 2015
Received in revised form
18 December 2015
Accepted 12 January 2016

Keywords:
Elongase
Desaturase
LCPUFA
Lignoceric acid
Nervonic acid
Oleic acid

ABSTRACT

Myelination is important perinatally and highly dependent on long-chain saturated and monounsaturated fatty acids. Long-chain polyunsaturated fatty acids, nowadays often supplemented, inhibit oleic acid synthesis. Using data from a premature cohort, we studied if nervonic, lignoceric and oleic acids correlated to growth and early development up to 18 months corrected age. Small for gestational age infants had lower concentrations than infants appropriate for gestational age. Only oleic acid was negatively correlated to long-chain polyunsaturated fatty acids. Oleic and lignoceric acids correlated to social interaction at one month, and nervonic acid to mental, psychomotor and behavioral development at 6, 10 and 18 months, also when adjusted for several confounders. Negative association between oleic acid and long-chain polyunsaturated fatty acids suggests inhibition of delta-9 desaturase, and nervonic acid´s divergent correlation to lignoceric and oleic acids suggests different metabolism in neonatal period. Our results may have implications for the supplementation of premature infants.

1. Introduction

About 50 percent of the human brain weight consists of lipids and most importantly the long-chain polyunsaturated fatty acids (LCPUFA) with the highest accretion rate around the time of birth. Adequate supply is necessary for the developing brain in order to achieve an accelerated growth, including myelination [1,2]. Focus has mainly been given the LCPUFA, docosahexaenoic acid (22:6 n-3, DHA) and arachidonic acid (20:4 n-6, AA), but also other fatty acids and lipids are important for the developing brain. During the process of early myelination the pattern of fatty acids changes in the cerebral white matter both in humans and animals [3,4]. The 16- and 18-carbon saturated fatty acids are gradually decreasing with time, while the monounsaturated fatty acids are increasing [5]. Also the essential fatty acid composition in the phospholipids shows changes during the myelination process [4].

Nervonic acid (24:1n-9, NA) is found in lipids of white matter and is used in the biosynthesis of myelin, together with PUFA isolating the neurons. Previous studies have addressed the question whether NA accumulation in sphingomyelin is important for cerebral myelination in premature infants [5,6]. The study of Babin et al. [5] showed a remarkable increase of NA in red blood cell (RBC) membranes between the 32nd and the 37th gestational weeks. It was supposed to reflect brain maturity, which is supported by studies of glycerophospholipids and sphingomyelin in human brain tissue, showing a dramatic increase of NA in late gestation and early life [6]. White matter damage in areas of rich myelination has been associated with later cognitive disturbances and cerebral palsy [7].

Besides NA also oleic acid (18:1n-9, OA) and lignoceric acid (24:0, LiA) are important for myelination [6,8–10], but the relation of NA to these fatty acids have not been studied in the context of early development. LiA is synthesized directly from stearic acid (18:0, SA) by elongations [11]. It is generally considered that OA, the desaturation product of SA by the action of stearoyl-CoA-desaturase (Δ9 desaturase, SCD), is the exclusive precursor, including subsequent elongations, to form NA [12].

In a previous study we found that breast milk of mothers having premature infants contained sevenfold higher concentrations of NA

Abbreviations: AA, arachidonic acid; AGA, appropriate for gestational age; BNBAS, Brazelton Neonatal Behavioral Assessment Scale; BSID-II, Bayley Scales of Infant Development II; DHA, docosahexaenoic acid; GC, gas chromatography; HC, head circumference; LCPUFA, long-chain polyunsaturated fatty acids; LiA, lignoceric acid; MDI, mental developmental index; NA, nervonic acid; OA, oleic acid; PA, palmitic acid; PI, palmitoleic acid; PDI, psychomotor developmental index; RBC, red blood cells; SA, stearic acid; SCD, stearoyl-CoA-desaturase; SGA, small for gestational age.

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http://dx.doi.org/10.1016/j.plefa.2016.01.002
0952-3278/

than human donor milk, which is usually obtained from mothers delivering mature milk after term delivery [13]. This might be of importance if infants´ development associates with early NA concentrations. There are few studies during the latest decades on the influence of saturated and monunsaturated fatty acids on development; all interest being focused on the LCPUFA and brain development. However, those results have been equivocal and one confounding factor might be the influence of other fatty acids more involved in myelination, which is important for the neuronal integrity.

The aim of the present study was to investigate the neonatal concentrations of the saturated and monounsaturated fatty acids, NA, LiA and OA, and the relationship between them, in a cohort of premature infants, and to explore whether the concentration of these acids correlated with growth and development up to 18 months corrected age.

2. Patients and methods

2.1. Subjects

Fifty-one premature infants were included with a gestational age ranging between 24 and 36 weeks, 57% being late-premature, i.e. born between 34.0–36.9 weeks of gestation. Nine infants were small for gestational age (SGA). The infants were born at a regional hospital and were unselectively and consecutively included at birth after acceptance of the parents. Extensive data of the cohort have previously been published [14]. All infants were breastfed and 36 infants were exclusively breastfed for a median of three months, the others were partially breastfed for the same time. The results were analyzed involving background factors, as sex of the infant, gestational age, birth weight, neonatal morbidity and smoking, morbidity and education of the mothers. None of the infants required intensive care but were classified as ill, if they showed some neonatal morbidity (registered as mechanical ventilation more than 10 min, hypoglycemia persisting more than 6 h, convulsions, or signs of severe infection) [14]. Standard deviation scores (*z*-scores) of weight, length and head circumference in relation to gestational age were computed according to Niklasson and Albertsson-Wikland [15].

2.2. Fatty acid analyses

Cord blood was collected in 26 infants. Plasma samples were taken from peripheral blood from the infants at one week after birth ($n=39$), at 40 weeks corresponding to term age ($n=36$) and at 44 weeks, corresponding to one month corrected age ($n=45$). Breast milk samples were collected at one week after birth ($n=50$). Fatty acids were analyzed in cord blood and plasma phospholipids with capillary GC as previously reported, and expressed as mol% [14]. The concentrations of all fatty acids except LiA have previously been reported [14].

2.3. Developmental assessments

The infants were examined at one month corrected age with Brazelton Neonatal Behavioral Assessment Scale (BNBAS) [16] by a psychologist (CL-P) certified at Harvard Medical School, and also at 3 ($n=48$), 6 ($n=47$), 10 ($n=51$) and 18 ($n=49$) months corrected age for motor, mental and behavioral development with Bayley Scales of Infant Development (BSID II) [17].

2.4. Ethics

The study was approved by the Ethics committee of the University of Gothenburg. Informed consent was obtained from all mothers and the study was performed in accordance with the Helsinki declaration.

2.5. Statistics

The statistical analysis was made using IBM SPSS statistics 21.0. Independent or dependent samples *t*-tests or non-parametric tests were used for the analyses when appropriate. Changes of group means over time were analyzed with ANOVA or Kruskall–Wallis test. The strength of relationship between developmental variables and fatty acids were first analyzed with Pearson product-moment correlation coefficient. Analyses of items in BNBAS were performed with Spearman correlation coefficient. Multiple linear regressions (backward method) included the significantly correlated fatty acids, background factors and also earlier reported significant correlations between omega-6 and omega-3 fatty acids and developmental variables [18,19]. Statistical significance was set at $p<0.05$.

3. Results

3.1. Nervonic acid

The concentration of NA in infants' early plasma phospholipids was nearly 10 times higher than in breast milk obtained at the same time. There was a significant decrease in the plasma concentrations with time from the first week after premature birth to one month corrected age ($p<0.001$) (Supplementary Table 1 and Fig. 1). NA in infants' plasma at one week showed significantly lower concentrations in SGA infants compared to appropriate for gestational age (AGA) infants, being 2.71(0.35) mol% ($n=7$) *vs* 3.37 (0.52) mol% ($n=32$), $p=0.003$. This difference was nearly abolished at one month corrected age ($p<0.05$), when the NA concentration in plasma phospholipids had decreased significantly ($p<0.001$) in the AGA infants, averaging 2.74 (0.47) mol% ($n=36$), but not significantly in SGA infants, 2.41(0.39) mol% ($n=9$). NA in breast milk was not significantly lower in the SGA group. Gestational age at birth had no association to the NA concentrations in cord blood or in plasma phospholipids at one week postpartum,

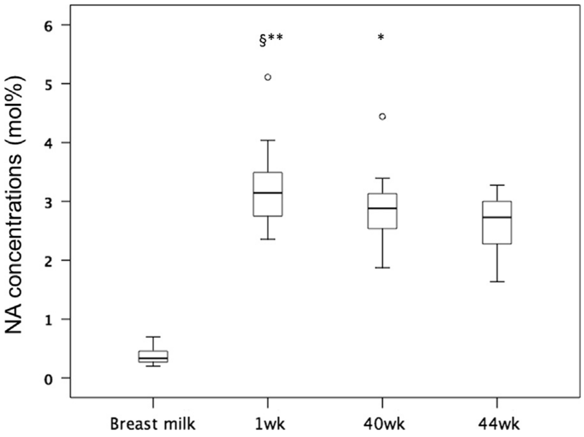

Fig. 1. The concentrations of nervonic acid (NA) in breast milk (BM) and infants' plasma phospholipids (P) at one week after birth and at the gestational ages of 40 and 44 weeks in 30 premature infants. Box plots show the median and interquartile range and the whiskers extreme cases of individual variables. Outliers indicated by single symbols. Mann-Whitney ** 1w–44w $p<0.0001$; § 1w–40w $p=0.001$; * 40w–44w $p=0.02$.