Decreased Prostaglandin E Turnover in Infants with Essential Fatty Acid Deficiency

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Summary

Sick low birth weight infants (LBWI) are prone to develop rapid onset of essential fatty acid (EFA) deficiency. EFAs serve as precursors for prostaglandins (PGs). We measured the excretion of the major urinary metabolite of prostaglandins E₁ and E₂, 7 α -hydroxy-5,11-diketotetranorprostane-1,16-dionic acid (PGE-M), in three EFA-deficient and in nine thriving neonates. There was no significant difference in PGE-M excretion between the sexes among thriving infants nor did PGE-M excretion appear to be affected by postconceptual age. However, a significant difference between the PGE-M excretion in the group of infants with EFA deficiency before and after treatment is apparent ($P < 0.05$). Significant differences in PGE-M excretion were also found between the control group and the EFA-deficient infants. The severity of the EFA deficiency correlates directly with the degree of PGs excretion. The biochemical evidences of EFA deficiency and the decreased levels of PGE-M excretion are rapidly corrected when patients resume a diet containing EFA.

Speculation

The decrease in PGE-M excretion in patients with EFA deficiency is most likely related to a decrease in the precursor EFA, although PG synthetase deficiency or altered PG metabolism has not been ruled out. Further investigation is needed into the pathophysiologic consequences of EFA deficiency as well as decreased PG biosynthesis and turnover in the sick low birth weight infant.

The development of EFA deficiency has been described in infants and children who have been maintained on fat-free diets (5) and fat-free iv alimentation (2). EFAs serve as precursors for prostaglandins (1, 6, 10, 15), which are a group of "local tissue hormones" with diverse biologic activities that involve almost every organ system. They are formed from endogenous intracellular polyunsaturated fatty acids in a sequence of complex enzyme reactions and then are released in response to various nervous, chemical and mechanical stimuli. Once formed, prostaglandins are rapidly metabolized (10).

There is some evidence that PG biosynthesis is reduced in the tissues of rabbits with EFA deficiency (14), but there is no information regarding the effects of EFA deficiency on PG biosynthesis and turnover in the human newborn. This relationship was studied in three EFA-deficient newborns by measuring the excretion of the major urinary metabolite of prostaglandins E₁ and E₂, 7 α -hydroxy-5,11-diketotetranorprostane-1,16-dionic acid (PGE-M) (4, 12). The results indicate that EFA deficiency state

correlates with a decreased prostaglandin E synthesis and turnover.

MATERIALS AND METHODS

PATIENTS

Case 1. Case 1 was a full term 3600-g male infant who required prolonged iv alimentation after repair of a large omphalocele. Fluid and calories were supplied solely by the iv route for 3 months. The solutions utilized included dextrose, electrolytes, trace elements, vitamins, and a parenteral alimentation mixture containing FreAmine II (McGaw Laboratories, Glendale, CA) but no fatty acids. Fluid intake varied from 100-200 ml/kg/24 hr and calories from 22-135 cal/kg/24 hr. During the 11th week on parenteral nutrition the infant developed a generalized scaly eruption which was most obvious over the forehead, face, and upper anterior chest. Cutaneous application of sunflower seed oil was then begun and continued for 3 weeks. Improvement and resolution of the skin rash was noted within 5 days of instituting treatment (3). At 15.5 weeks of age the infant underwent colostomy. Healing of the surgical wound was uneventful, and the infant is currently gaining weight and doing well on a diet of oral Portagen (Mead Johnson Laboratories, Evansville, IN).

Case 2. This male was born to a 20-year-old gravida 1 white female. Estimated gestational age was 26 weeks and birthweight was 800 g. The clinical course was complicated by recurrent apneic spells requiring application of continuous positive airway pressure and intermittent positive pressure breathing. Patent ductus arteriosus, congestive heart failure, necrotizing enterocolitis, hypoglycemia, hypocalcemia, and hyperbilirubinemia further complicated the clinical course. He was maintained on fat-free parenteral alimentation for the first 16 days of life. Similac (Ross Laboratories, Columbus, OH) was started on the 17th day. During the study period fluid intake varied between 60 and 190 ml/kg/24 hr and caloric intake was between 12 and 100 cal/kg/24 hr. The infant did well and was discharged on the 35th hospital day. Follow-up 6 weeks later revealed no evidence for patency of the ductus arteriosus.

Case 3. This male was born to a 22-year-old gravida 1 white female after an uneventful pregnancy. Estimated gestational age was 31 weeks and the birthweight was 975 g. The clinical course was complicated by recurrent apneic spells requiring endotracheal intubation and intermittent ventilatory assistance, patent ductus arteriosus, congestive heart failure, and necrotizing enterocolitis. The infant was maintained on iv dextrose, electrolytes, trace elements, and FreAmine II for the first 13 days of life. Oral feeding with Similac was started at 14 days of age. The fluid

intake varied between 72 and 200 ml/kg/24 hr and the caloric intake was between 20 and 120 cal/kg/24 hr. The infant was discharged well 6 weeks later, with no evidence of patency of the ductus arteriosus.

Control Newborns. Nine thriving low birth weight infants were selected at random from the Newborn Care Unit as control subjects. The clinical data for the five females and four males are shown in Table 1.

Neither mothers nor infants had received any drugs known to inhibit prostaglandin synthetase.

LIPID ANALYSIS

Whole blood, anticoagulated with EDTA, was obtained via a central line or peripheral venipuncture and centrifuged at 4°. The plasma was frozen and stored at -20° in 100% nitrogen until lipid extraction was begun. The various lipid fractions, including cholesterol esters, triglycerides, free fatty acids, and phospholipids, were separated by thin layer chromatography. The fatty acid composition of each lipid fraction was then determined by gas-liquid chromatography. These methods have been described previously (2).

PGE-M

Urine from each subject was collected in plastic bags for 16–24 hr during the period of EFA deficiency and on recovery. The specimens were stored in containers with toluene and kept frozen at -40° until analyzed for PGE-M according to the methods previously described (4). Urine creatinine was determined by the Jaffe reaction on the Technicon SMA 12-60. Urinary excretion of PGE-M is expressed as nanograms per mg creatinine, thus relating PGE-M excretion to an index of lean body mass.

STATISTICAL METHOD

Student's *t*-test for unpaired samples was used for statistical analysis.

RESULTS

PLASMA LIPIDS

All three patients demonstrated EFA deficiency by conventional criteria (6). In addition to severe depletion of linoleic and arachidonic acids there was a characteristic increase in 5,8,11-eicosatrienoic acid (Table 2). The ratio of 5,8,11-eicosatrienoic acid to arachidonic acid, the "trienoic/tetraenoic ratio," is ordinarily less than 0.4 (7). In these infants the ratio was 2.7 during EFA deficiency and less than 0.1 during recovery.

After treatment, the changes in the fatty acid composition of plasma phospholipids (Table 2) revealed an increase in arachidonate and linoleate and a decrease in 5,8,11-eicosatrienoic acid. These values were similar to those of control subjects. Changes involving palmitoleic, oleic, and other fatty acids were less consistent.

PGE-M

There was no significant difference in PGE-M excretion between the sexes among thriving infants (Figs. 1 and 2), nor did

PGE-M excretion appear to be affected by postconceptual age (Figs. 1 and 2). The differences between the PGE-M excretion in the group of infants with EFA deficiency before and after treatment is apparent ($P < 0.05$) from Figure 3. Differences in the urinary excretion of PGE-M were also found between the control group and the infants with EFA deficiency ($P < 0.05$). After treatment PGE-M levels were similar in control and study infants.

DISCUSSION

The EFAs are incorporated into the normal structure of biologic membranes and also serve as PG precursors (1, 6, 10, 15). Both arachidonate and linoleate are effective in the treatment of EFA deficiency (9); but, since linoleic acid is readily converted to arachidonic acid *in vivo* (6), it is the primary nutrient necessary linoleic acid—dietary fat, the prime source, and adipose tissue

Table 2. Percent of individual fatty acids in plasma phospholipid fraction of patients during EFA deficiency on recovery from EFA-D state and of control subjects¹

Fatty acid ²	Patients		Controls
	EFA deficiency	Recovery	
c16:0	33 ± 0.4	30.9 ± 3.2	33.6 ± 5.4
c16:1	7.1 ± 0.2	6.2 ± 0.4	0.8 ± 0.4
c18:0	9.3 ± 1.8	11.9 ± 2.3	11.8 ± 3.2
c18:1ω9	27.9 ± 0.4	12.8 ± 1.0	15.4 ± 4.9
c18:2ω6	2.8 ± 1.9	12.5 ± 3.5	12.6 ± 3.8
c20:3ω9	11.4 ± 0.9	0.1 ± 0.1	N.D. ³
c20:3ω6	N.D.	2.2 ± 1.7	2.8 ± 0.7
c20:4ω6	4.2 ± 2.2	16.0 ± 1.1	14.6 ± 4.2
HFA ⁴	4.0 ± 0.4	2.7 ± 0.4	6.4 ± 2.5

¹ Mean ± SEM.

² Palmitic (c16:0); palmitoleic (c16:1); stearic (c18:0); oleic (c18:1ω9); linoleic (c18:2ω6); 5,8,11-eicosatrienoic (c20:3ω9); dihomo-γ-linolenic (c20:3ω6); arachidonic (c20:4ω6). The abbreviated formula indicates the number of carbon atoms and the number of double bonds. The position of the double bond nearest to the methyl terminus is indicated by the symbol ω.

³ Level not detectable.

⁴ Higher fatty acids with carbon number >20.

Fig. 1. Urinary excretion of PGE-M expressed as nanograms per mg urinary creatinine in thriving neonates.

Table 1. Clinical data¹

Subjects (no.)	Sex		Gestational age, weeks	Postconceptual age at time of study, weeks		Birth wt, g	Weight at time of study, g	
	M	F		EFA deficiency	Recovery		EFA deficiency	Recovery
Patients (3)	3		33.0 ± 3.6	38.4 ± 6.8	40.7 ± 7.2	1791.7 ± 905.6	1763.3 ± 969.4	1943.3 ± 980.6
Controls (9)	4		29.8 ± 0.8		32.9 ± 1.4	1164.2 ± 84.2		1414.0 ± 183.0
		5	28.4 ± 0.5		35.9 ± 1.9	1090.6 ± 147.2		1560.0 ± 205.4

¹ Mean ± SEM.

Fig. 2. Urinary excretion of PGE-M expressed as micrograms per 24 hr in thriving neonates.

Fig. 3. Comparison of the urinary excretion of PGE-M expressed as nanograms per mg urinary creatinine, between infants with EFA deficiency, upon recovery and thriving neonates.

stores. In adults sufficient EFAs are present in tissue stores to meet body requirements for months or even years. In the fetus, however, the portion of linoleic acid in tissue phospholipids increases with advancing gestational age (11) so that the prematurely born infant is endowed with only limited stores. Because of their limited nonprotein caloric reserve, these infants must mobilize fatty acids early for caloric needs when faced with a deficient dietary intake. Adipose tissue triglycerides thus undergo constant hydrolysis with the release of EFAs and other fatty acids into the plasma. During hyperalimentation, however, the outflow of linoleic acid from adipose tissue is blocked, at least in part, by the high insulin levels accompanying glucose administration.

Prolonged feeding of an EFA-deficient diet has been associated with a specific clinical syndrome of deficiency in young animals and infants, resulting in acute dermatitis (case 1) and failure to thrive (3, 6). Nevertheless, as we have previously shown (2), very rapid onset of EFA deficiency can occur in the absence of clinical manifestations. Our second and third cases fall into this category. Our first case showed biochemical and clinical response to the inunction of sunflower seed oil within several days (3). Nevertheless, the linoleic acid level remained low in the plasma, even after 3 weeks of treatment. This may be secondary to extreme tissue

depletion, resulting in a higher requirement for the products of linoleic acid-arachidonic acid, prostaglandins and thromboxanes. The other two cases showed biochemical response to oral feedings with Similac, a formula containing EFA.

VanDorp *et al.* (14) studied the PG content of various parts of the kidney medulla, both in normal and EFA-deficient rabbits. These studies demonstrated clearly that EFA deficiency in rabbits is associated with prostaglandin deficiency. It was suspected, but not proven, that in the EFA-deficient animal there is a sharp decrease in precursor acids (14). Moreover, this hypothesis is supported by Kaa (8) who showed increased activity of PG synthetase *in vitro* in EFA-deficient rats.

In our three patients with EFA deficiency, the excretion of PGE-M was decreased in comparison with the levels excreted by the same infants after recovery, and with the control group (Fig. 3). Since PGE-M is the terminal product arising from sequential 15-dehydrogenation, $\Delta 13$ reduction and both β and ω oxidation of prostaglandins E_1 and E_2 , any decrease in its excretion reflects decreased prostaglandin synthesis and turnover in the body (4). This decrease is probably related to a decrease in the precursor EFA, although synthetase deficiency or altered PG metabolism has not been ruled out. Feeding arachidonate to humans increases the excretion of PGE-M (13), which indicates that the excretion of this prostaglandin metabolite is related to the amount of arachidonic acid in the precursor lipids. Because prostaglandins and thromboxanes are not stored in tissues (10), PGE-M excretion usually indicates biosynthetic activity for which both PG synthetase and substrate must be present. The severity of the EFA deficiency correlates directly with the degree of PGE-M excretion. Case 1, who has been on fat-free parenteral nutrition for 3 months and who developed severe clinical manifestations of EFA deficiency, demonstrated extremely low levels of PGE-M excretion in the urine. After recovery from EFA deficiency, the PGE-M excretion in this patient increased 15-fold, and all three patients increased urinary PGE-M excretion to levels similar to those of control infants. Hence, we conclude that the initial decrease in PGE-M excretion among those three patients reflected their EFA deficiency and consequent impairment of prostaglandin synthesis.

Both the biochemical evidence of EFA deficiency and the decreased levels of PGE-M excretion are rapidly corrected when patients resume a diet containing EFAs. Intravenous nutrition thus requires the supplemental administration of essential fat. Further investigation is needed into the pathophysiologic consequences of EFA deficiency as well as decreased prostaglandin and thromboxane biosynthesis and turnover in the newborn infant, particularly among those stressed low birth weight infants whose nutritional state and management invite EFA deficiency.

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