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ORIGINAL ARTICLE

Influence of Fatty Acid Profile of Total Parenteral Nutrition Emulsions on the Fatty Acid Composition of Different Tissues of Piglets

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Abstract Total parenteral nutrition (TPN) studies in human babies of very-low-birth-weight suggest that the lipid emulsions currently available are not optimum for neonatal nutrition. Since fatty acid metabolism in human and pigs is very similar, the present study examines how lipid emulsions used in clinical TPN (i.e. ClinOleic, Intralipid, Lipofundin or Omegaven), with different fatty acid compositions, administered to neonatal piglets for 7 days, influenced their tissue fatty acid composition as compared to those enterally fed with a sow milk replacer. A positive linear relationship was found between the proportion of all individual fatty acids in the lipid emulsions or in the milk replacer versus those in plasma, skeletal muscle, subcutaneous fat, liver, heart, pancreas, stomach or intestine total lipids or in brain phospholipids, the latter showing the lowest correlation coefficient. With the exception of brain, the proportion of either oleic acid or α-linolenic acid in the individual tissues was correlated with those present in the corresponding lipid emulsion or milk replacer, whereas the proportion of linoleic acid correlated significantly with all the tissues studied. With the exception of brain phospholipids, both eicosapentaenoic and docosahexaenoic acids were higher in the tissues of piglets receiving Omegaven than in all other groups. In conclusion, with the exception of the brain, fatty acid composition of plasma and different tissues in piglets are strongly influenced by the fatty acid profile of TPN emulsions. Fatty acid composition of brain phospholipids are, however, much less influenced by dietary composition, indicating an active and efficient metabolism that ensures its appropriate composition at this key stage of development.

Keywords Total parenteral nutrition · Fatty acid profile · Neonatal pig

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Introduction

Total parenteral nutrition (TPN) has been used in routine nutritional care since the 1960s. The first lipid emulsion developed for TPN was a soybean oil-based lipid emulsion [1]. This lipid emulsion was marketed as Intralipid and is one of the most widely emulsions used in TPN administration [2]. Evidence has accumulated that, in addition to their nutritional role as energy source, lipid emulsions have numerous other biologic functions. In particular, it has been shown that the fatty acid composition of cell membranes is highly influenced by the fatty acid profile of dietary lipids [3], which may in turn affect their structural and regulatory properties [4]. Indeed, lipids can influence numerous physiological processes including some roles of the cellular membrane such as membrane permeability, receptor pathways and membrane-associated enzyme activities [5], and can also affect the immune function [6, 7].

Preterm infants often require a parenteral lipid emulsion in order to prevent essential fatty acid deficiency,

particularly if an adequate energy and lipid intake cannot be achieved by enteral feeding. The adequacy of soybean lipid emulsions for the nutritional needs of newborn and premature infants has been questioned [8]. Soybean-oil-based lipid emulsions contain only minor amounts of the long chain polyunsaturated fatty acids (LCPUFA). These long chain fatty acids, in particular arachidonic acid (AA) and docosahexaenoic acid (DHA), have essential functions for early visual and neural development [9–11]. In addition, AA is the main precursor for eicosanoids [12, 13] and is known to play a key role in neonatal growth [14, 15]. The endogenous synthesis of LCPUFA from precursor essential fatty acids (EFA), linoleic acid (LA) and α-linolenic acid (ALA), involves Δ6 and Δ5 desaturases, constituting the n-6 and n-3 PUFA metabolic pathways, respectively [16, 17]. Although intake of PUFA is required to prevent any EFA deficiency, it is known that excessive intake has detrimental effects. Thus, excessive intake of LA may inhibit Δ6 desaturase resulting in a decrease in the formation of DHA from ALA [18]. An excess of n-3 fatty acids has also been demonstrated to inhibit Δ-6 desaturase activity [19], which is responsible for a major decline in AA concentrations in rats fed a fish oil diet [20]. Desaturase activities are limited in preterm and term infants [21], and the large amounts of LA and ALA in soybean oil emulsions may further impair LCPUFA formation through substrate inhibition. Furthermore, the high supply of PUFA in soybean oil emulsions may enhance lipid peroxidation [22], which is of particular concern in preterm infants as it may for example cause liver damage [23]. The lipid content must be balanced to provide the correct fatty acids for brain development whilst avoiding the dangers of oxidative damage.

Total parenteral nutrition studies in human babies of very-low-birth-weight suggest that lipid emulsions currently available are not optimum for nutrition of the neonate [8]. The new lipid emulsions for clinical use are differentiated by their content in polyunsaturated (n-3 and n-6), monounsaturated, and saturated fatty acids. Due to similarities in the fatty acid metabolism in human and pigs [24], and for obvious ethical reasons, a piglet model of such treatments has been successfully developed in this study, and has enabled the effects of the treatments on tissue composition to be determined.

Materials and Methods

Experimental protocols were carried out as defined by the regulations of the Animals (Scientific Procedures) Act 1986, under the appropriate Home Office Licence and all procedures were agreed by the local ethical review board.

Experimental Design

Sixteen nulliparous sows (25% Meishan, 12.5% Duroc and 62.5% Large White X Landrace) were entered into the study. A routine caesarean section was carried out under anaesthesia at 113 days of gestation (term = 115 days). Anaesthesia was induced by administration of 2–5 mg/kg ketamine i.v. (Ketaset, Fort Dodge, Southampton, UK) and maintained using isoflurane 4–6 % (Schering-Plough Animal Health, Harefield, UK) oxygen (BOC, Manchester, UK). Following delivery, the piglets were given oxygen and an intramuscular injection of vitamin K (0.25 ml, Konakion MM 10 mg ml^{-1}, Roche Products Ltd, Lewes, UK) to assist blood clotting and allowed to recover from anaesthesia.

Piglets were selected so as to balance experimental groups for sex, body weight at birth and maternal influences. Practically, each experimental group contained piglets from at least three sows and within each litter, male and female piglets were ranked according to weight, and any outliers removed. Within each gender, piglets were matched for weight, and randomly allocated to one of five treatment groups and fed either enterally (E) with a commercially-available sow milk replacer (4.5 kJ ml^{-1}, Primary Diets, Ripon, UK); or TPN solution (1,690 J/ml; 99.34 mg ml^{-1} glucose; 17.89 mg ml^{-1} amino acids; Portsmouth Hospital NHS Trust, Portsmouth, UK), plus one of the following commercially available lipid emulsions: Intralipid 20% (Fresenius Kabi Ltd., Runcorn, UK), ClinOleic 20% (Baxter Healthcare Ltd, Northampton, UK), Lipofundin 20% (Baxter Healthcare Ltd, Northampton, UK) or Omegaven 10% (Fresenius Kabi Ltd., Runcorn, UK). The fatty acid profile of the lipid emulsions is shown in Table 1. The TPN solution was formulated according to the prescription used by the local neonatal care centre (The William Harvey Hospital, Ashford, Kent). As humans and pigs have similar nutritional requirements [25] it is possible to provide adequate nutritional support in the pig using clinical TPN regimes, which is useful in establishing an animal model with clinical relevance [26].

At 2–4 h post-delivery, piglets of similar body weight were anaesthetized using isoflurane 0.5–2% (v:v; Schering-Plough Animal Health, Harefield, UK) and bilateral jugular catheters were inserted. One of these catheters was used for daily administration of TPN and the corresponding commercially available lipid emulsion, the other catheter was used to administer intravenous antibiotics, as required, and for blood sampling. The TPN solution was infused using a volumetric infusion pump (IVAC 598, Alaris medical, Basingstoke, UK) at 2.9 ml/h/kg. and lipid emulsion, via the same infusion line, using a syringe pump (IVAC P7000, Alaris medical, Basingstoke, UK) at 0.2 ml/h/kg for the

Table 1 Fatty acid profile in the lipid emulsions and the milk replacer

Fatty acid	Milk replacer	Clin oleic	Intralipid	Lipofundin	Omegaven
g/100 g fatty acid					
10:0	ND	ND	ND	21.7	ND
12:0	19.2	ND	ND	0.4	0.5
14:0	8.6	ND	0.1	0.1	5.8
16:0	23.2	13.0	12.3	9.8	13.0
18:0	6.5	3.8	3.6	3.9	2.5
18:1 (n-9)	33.3	60.3	23.5	17.9	16.0
18:2 (n-6)	6.5	18.4	52.8	39.6	3.3
18:3 (n-3)	0.9	2.1	5.6	4.8	1.3
20:4 (n-6)	ND	0.2	0.2	0.3	1.7
20:5 (n-3)	0.8	0.1	0.6	0.2	20.4
22:6 (n-3)	ND	0.1	0.2	0.1	17.5

All the analyses were carried out in triplicate, and data correspond to the mean values

ND non detectable

first 12 h. After 12 h the infusion rate of the TPN solution was increased to 5.8 ml/h/kg and lipid emulsion at 0.5 ml/h/kg and, after 24 h, piglets were receiving TPN solution at 5.8 ml/h/kg and lipid emulsion at 1.0 ml/h/kg. These rates were maintained throughout the remainder of the study. Other piglets, after recovering from surgery were fed enterally with a commercially-available sow milk replacer (Primary Diets, Ripon, UK). They were initially given 10 ml of milk replacer and subsequently supplied with 100 ml of milk at 4 h intervals, the volume of milk refused was recorded as a means of measuring intake. Piglets were weighed daily and given antibiotics i.v. (50 mg benzylpenicillin: Crystapen, Brittannia Ltd., Redhill, UK) twice daily.

On the final day of treatment (a few animals were slaughtered prior to the end of the study due to the varying ability of individual piglets to tolerate parenteral feeding), piglets were humanely slaughtered using pentobarbitone sodium (Euthatal, Rhone Merieux, Harlow, UK) and blood and tissue samples were taken. All tissue samples were frozen in liquid nitrogen and were kept at −80°C until analysis. Blood samples were taken into EDTA tubes (Teklab, Durham, UK) and centrifuged at 1,400 g in a bench centrifuge for 15 min at 4°C to produce plasma, which was stored at −20°C for subsequent analysis.

Processing of Samples

Fresh aliquots of each lipid emulsion as well as milk replacer, frozen plasma, liver, subcutaneous fat, brain, heart, pancreas, muscle, intestine and stomach were used for lipid extraction and purification [27]. To assess the fatty acid profile of the phospholipids in the brain, following the lipid extraction, lipids were separated by thin layer chromatography using Silicagel 60 F_{254} plates (Merck, Darmstadt, Germany) with *n*-heptane/diisopropyl ether/acetic acid (70:30:1 v/v/v) as the solvent system. The bands were visualized with 2′7′-dichlorofluorescein (Supelco, Bellafonte, PA, USA) and the phospholipid fractions were eluted from the plate. Total lipid or phospholipid fatty acids were simultaneously saponified and methylated following the method of Lepage and Roy [28, 29]. Fatty acid methyl esters were separated and quantified on a Perkin-Elmer gas chromatograph (Autosystem; Norwalk, CT, USA) with a flame ionisation detector and a 30 m × 0.25 mm Omegawax capillary column. Nitrogen was used as carrier gas, and the fatty acid methyl esters were compared with purified standards (Sigma Chemical Co., St. Louise, MO, USA). Individual fatty acids are expressed as percent of total fatty acids in the sample. Although all the fatty acids from 10:0 to 22:6 (n-3) were analyzed in every sample and used in calculating the corresponding proportions, in the tables and figures just those that have any significance due to their particular presence in the analyzed sample or are of interest due to their respective endogenous metabolism are given.

Statistical Analysis

Data are expressed as means ± SEM. Treatment effects (emulsions or enteral feeding) were analysed by one-way ANOVA with SPSS 12.0 for Windows. When treatment effects were significantly different ($P < 0.05$), means were tested by a Student–Newman–Keuls test. Linear regressions were calculated by the least-squares method [30]. To test the potential interrelationship in fatty acid composition between the emulsions given and the different tissues, correlations of the proportion of fatty acids in the emulsions and the mean value of individual fatty acids in each tissue were calculated.

Results

Plasma

The fatty acid profile of the plasma (Table 2) shows that the proportions of saturated and monounsaturated fatty acids were very similar between the groups with the only

Table 2 Fatty acid composition of plasma in piglets maintained on total parenteral nutrition (TPN) for up to 7 days ($n = 5$–9/group)

Fatty acid	Enteral	ClinOleic	Intralipid	Lipofundin	Omegaven
(g/100 g fatty acids)					
14:0	0.75 ± 0.27^{a}	0.60 ± 0.35^{a}	0.70 ± 0.26^{a}	1.22 ± 1.03^{a}	ND
16:0	18.15 ± 0.75^{ab}	17.05 ± 0.59^{ab}	17.78 ± 1.09^{ab}	14.58 ± 1.02^{b}	18.90 ± 0.67^{a}
18:0	10.07 ± 0.99^{a}	10.39 ± 0.35^{a}	10.40 ± 0.58^{a}	11.54 ± 1.31^{a}	11.01 ± 0.50^{a}
18:1 (n-9)	32.18 ± 2.04^{a}	32.63 ± 3.82^{a}	27.95 ± 2.79^{a}	21.12 ± 1.86^{a}	22.10 ± 1.07^{a}
18:2 (n-6)	17.95 ± 3.88^{a}	18.59 ± 2.29^{a}	24.05 ± 3.34^{a}	22.27 ± 9.38^{a}	15.26 ± 5.58^{a}
18:3 (n-3)	1.00 ± 0.50^{a}	0.98 ± 0.18^{a}	1.47 ± 0.40^{a}	0.80 ± 0.38^{a}	1.05 ± 0.67^{a}
20:4 (n-6)	9.17 ± 1.62^{a}	7.54 ± 0.74^{a}	7.41 ± 0.83^{a}	5.59 ± 2.20^{a}	5.77 ± 1.01^{a}
20:5 (n-3)	0.59 ± 0.11^{a}	0.96 ± 0.15^{a}	0.88 ± 0.24^{a}	3.92 ± 2.10^{b}	7.94 ± 2.02^{c}
22:6 (n-3)	3.06 ± 0.52^{a}	3.19 ± 0.61^{a}	2.49 ± 0.14^{a}	5.55 ± 3.49^{a}	12.19 ± 2.33^{b}

Values are expressed as means ± SEM. Student–Newman–Keuls test was used to determine differences between groups after ANOVA. Different superscripts in a row indicate significant differences ($P < 0.05$)

ND non detectable

exception being palmitic acid (16:0) which was the lowest in Lipofundin and highest in the Omegaven groups. The n-3 LCPUFA, eicosapentaenoic acid (EPA, 20:5 n-3) and also DHA (22:6 n-3) was higher in those animals given Omegaven compared to the other nutritional treatments (Table 2). AA (20:4 n-6) was almost non-detectable in the milk replacer and the lipid emulsions except for Omegaven (Table 1); however the plasma from all groups showed a considerable and similar proportion of AA (Table 2). There were no other changes observed in the PUFA between the groups, either in terms of the lipid of the nutrients supplied or in the plasma sampled from the animals.

Skeletal Muscle

The fatty acid composition of the skeletal muscle of piglets maintained on TPN with different lipid emulsions or enterally with milk replacer (Fig. 1) closely corresponded to the fatty acid composition of the TPN lipid emulsions or the milk replacer received by each group (Table 1). Of the saturated fatty acids the greatest proportion in all groups was palmitic acid and as it would be expected, myristic acid (14:0) was higher in the skeletal muscle of enterally fed piglets than in the TPN groups. Oleic acid (18:1n-9) was the predominant monounsaturated fatty acid in all the groups, being highest in the ClinOleic group, followed by the enterally fed group. Among n-6 fatty acids, linoleic acid (18:2 n-6) reached the greatest proportion in the Intralipid group followed by Lipofundin (Fig. 1), which fits with its larger proportion in these specific lipid emulsions (Table 1). The proportion of AA was similar in all the groups with a tendency of being slightly although not significantly higher in the Omegaven group than in the others. The proportion of α-linolenic acid (18:3n-3) in muscle, was greater in the Intralipid and Lipofundin groups than in the others (Fig. 1), in agreement with

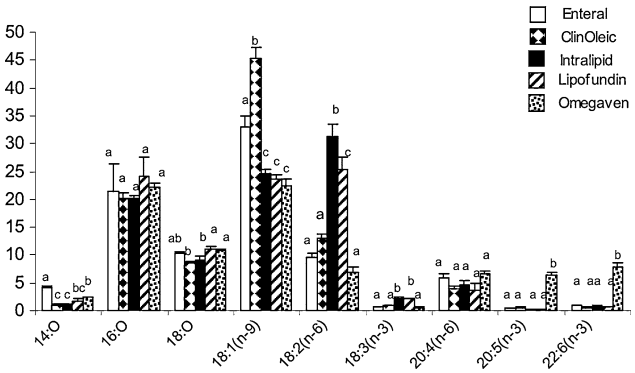

Fig. 1 Fatty acid profile (g/100 g fatty acids) of skeletal muscle in piglets maintained on total parenteral nutrition (TPN) for up to 7 days ($n = 5$–6/group). Values are expressed as means ± SEM. Student–Newman–Keuls test was used to determine differences between groups after ANOVA. *Different letters over each bar* indicate significant differences ($P < 0.05$)

their higher proportion in the corresponding lipid emulsion. Concerning the long chain n-3 PUFA (EPA and DHA), their proportions in muscle were much higher in the Omegaven group than in any of the others.

Subcutaneous Adipose Tissue

As shown in Table 3, the fatty acid profile of subcutaneous fat also mirrored that of the milk replacer given enterally or the lipid emulsion given during TPN and was markedly different between the groups. No differences among the groups were seen for the saturated fatty acids, whereas the proportion of oleic acid was higher in both the enterally fed and the ClinOleic groups than in the others. The proportions of both linoleic and α-linolenic acids in subcutaneous adipose tissue were higher in the Intralipid and Lipofundin groups whereas no differences among the groups were

Table 3 Fatty acid composition of subcutaneous fat in piglets maintained on TPN for up to 7 days (n = 5–11/group)

Fatty acid	Enteral	ClinOleic	Intralipid	Lipofundin	Omegaven
(g/100 g fatty acids)					
14:0	2.52 ± 1.25^{a}	0.63 ± 0.23^{a}	0.47 ± 0.17^{a}	0.11 ± 0.04^{a}	0.15 ± 0.07^{a}
16:0	22.09 ± 2.89^{a}	22.87 ± 1.60^{a}	18.28 ± 1.50^{a}	20.34 ± 3.48^{a}	19.53 ± 1.70^{a}
18:0	12.40 ± 1.21^{a}	10.07 ± 0.38^{a}	10.01 ± 0.80^{a}	20.79 ± 1.03^{b}	12.92 ± 1.05^{a}
18:1 (n-9)	40.14 ± 3.89^{a}	46.42 ± 1.94^{a}	29.92 ± 1.13^{b}	26.83 ± 1.55^{b}	27.02 ± 1.72^{b}
18:2 (n-6)	6.14 ± 0.59^{a}	8.93 ± 0.43^{b}	29.06 ± 1.12^{c}	19.79 ± 1.11^{d}	2.41 ± 0.14^{e}
18:3 (n-3)	0.6 ± 0.09^{a}	0.84 ± 0.12^{a}	2.97 ± 0.11^{b}	2.40 ± 0.15^{c}	0.68 ± 0.04^{a}
20:4 (n-6)	2.11 ± 0.74^{a}	1.59 ± 0.40^{a}	1.49 ± 0.28^{a}	2.38 ± 0.42^{a}	2.58 ± 0.22^{a}
20:5 (n-3)	3.03 ± 0.93^{a}	0.32 ± 0.11^{a}	0.41 ± 0.23^{a}	0.25 ± 0.04^{a}	11.73 ± 0.41^{b}
22:6 (n-3)	0.64 ± 0.35^{a}	0.45 ± 0.11^{a}	0.43 ± 0.07^{a}	0.74 ± 0.14^{a}	11.22 ± 0.51^{b}

Values are expressed as means ± SEM. Student–Newman–Keuls test was used to determine differences between groups after ANOVA. Different superscripts in a row indicate significant differences ($P < 0.05$)

found for AA. Here again, the proportion of both EPA and DHA was greater in the Omegaven group than in any of the others.

Liver

In liver, the composition of the fatty acids differ from the other tissues (Fig. 2). The proportion of saturated fatty acid was similar among the groups except for stearic acid (18:0) that was higher in the enterally fed group than in any of the others. Oleic acid reached the largest proportion in liver of the ClinOleic group, which fits with being the lipid emulsion containing the highest proportion of this fatty acid. The proportion of linoleic acid was highest in the Intralipid and the lowest in the Omegaven group. The proportion of α-linolenic acid in liver was higher in the Intralipid and Lipofundin groups than in any of the others. With AA, its highest proportion was reached by the enterally fed piglets, whereas the rest of the groups showed a similar proportion including the Omegaven group, which on the other hand showed the greatest proportion of n-3 LCPUFA, EPA and DHA (Fig. 2).

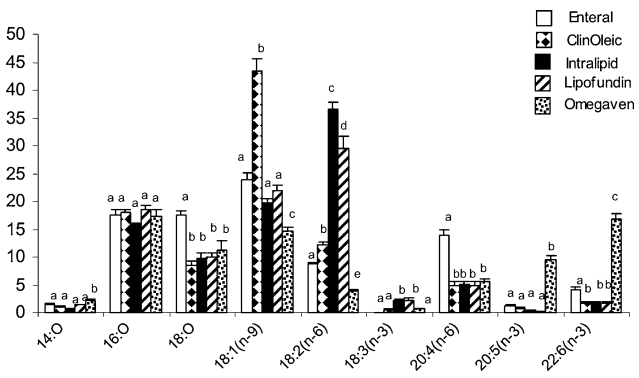

Fig. 2 Fatty acid profile (g/100 g fatty acids) of liver in piglets maintained on TPN for up to 7 days (n = 5–11/group). Values are expressed as means ± SEM. Student–Newman–Keuls test was used to determine differences between groups after ANOVA. *Different letters over each bar* indicate significant differences ($P < 0.05$)

Heart, Pancreas, Stomach and Intestine

Similar fatty acid profiles were found in heart (Table 4), pancreas (Table 5), and stomach (Table 6) and could be considered together: No major differences were detected for the saturated fatty acids, although values for stearic acid appeared lower in enterally fed and ClinOleic treated piglets than in the other groups in pancreas and stomach. Oleic acid tended to be higher in these tissues in the piglets receiving milk replacer enterally or the ClinOleic emulsion intravenously, than in the other groups. Both linoleic and α-linolenic acids were higher in these tissues in the groups given Intralipid and Lipofundin. AA showed a considerable proportion in these tissues in all the groups even though its proportion in the administered emulsions or enteral diet was very low, except for Omegaven. Piglets receiving the Omegaven emulsion showed the highest proportion of both EPA and DHA in these three tissues (Tables 4, 5, 6).

In the intestine there were some differences between the enterally fed piglets and those on TPN that require highlighting (Table 7). Higher proportions of lauric (12:0), myristic and oleic acid were found in the enterally fed group compared to any of the other groups. In contrast, proportions of stearic and AA were lower in the enterally fed piglets than in any of the other groups (Table 7). The Omegaven group also showed some differences in the intestine fatty acid profile compared to the other groups, with a lower proportion of both LA and ALA and a higher proportion of both EPA and DHA, all of which coincide with the relative proportions in the profile of the emulsion (Table 1).

Table 4 Fatty acid composition of heart in piglets maintained on TPN for up to 7 days ($n = 5$–6/group)

Fatty acid	Enteral	ClinOleic	Intralipid	Lipofundin	Omegaven
(g/100 g fatty acids)					
14:0	0.70 ± 0.09^{a}	0.27 ± 0.16^{b}	0.14 ± 0.02^{b}	0.15 ± 0.02^{b}	0.48 ± 0.16^{ab}
16:0	14.13 ± 0.46^{a}	13.15 ± 0.45^{ab}	12.98 ± 0.58^{ab}	12.19 ± 0.32^{b}	12.97 ± 0.32^{ab}
18:0	13.59 ± 0.36^{a}	13.12 ± 0.64^{a}	14.96 ± 0.59^{a}	15.72 ± 0.97^{a}	15.61 ± 0.46^{a}
18:1 (n-9)	24.91 ± 0.93^{ab}	27.62 ± 1.16^{a}	19.47 ± 2.52^{bc}	19.77 ± 1.49^{bc}	17.58 ± 0.45^{c}
18:2 (n-6)	16.16 ± 0.79^{a}	17.63 ± 0.84^{a}	30.28 ± 1.21^{b}	24.95 ± 2.35^{b}	12.64 ± 5.56^{a}
18:3 (n-3)	0.48 ± 0.08^{a}	0.56 ± 0.02^{a}	1.21 ± 0.02^{b}	1.02 ± 0.19^{b}	0.40 ± 0.04^{a}
20:4 (n-6)	14.29 ± 0.82^{a}	12.27 ± 0.66^{ab}	10.32 ± 0.90^{b}	11.56 ± 0.82^{ab}	12.85 ± 0.50^{ab}
20:5 (n-3)	0.42 ± 0.02^{a}	0.38 ± 0.01^{a}	0.31 ± 0.11^{a}	0.50 ± 0.15^{a}	11.08 ± 0.25^{b}
22:6 (n-3)	2.08 ± 0.43^{a}	1.88 ± 0.12^{a}	1.89 ± 0.37^{a}	1.91 ± 0.11^{a}	5.25 ± 1.30^{b}

Values are expressed as means ± SEM. Student–Newman–Keuls test was used to determine differences between groups after ANOVA. Different superscripts in a row indicate significant differences ($P < 0.05$)

Table 5 Fatty acid composition of pancreas in piglets maintained on TPN for up to 7 days ($n = 4$–7/group)

Fatty acid	Enteral	ClinOleic	Intralipid	Lipofundin	Omegaven
(g/100 g fatty acids)					
14:0	1.28 ± 0.46^{a}	0.18 ± 0.06^{a}	0.39 ± 0.09^{a}	0.37 ± 0.29^{a}	0.25 ± 0.21^{a}
16:0	22.74 ± 0.62^{b}	19.75 ± 0.58^{a}	21.04 ± 0.71^{ab}	23.35 ± 1.18^{b}	22.98 ± 0.66^{b}
18:0	10.70 ± 0.24^{a}	11.60 ± 0.42^{a}	13.75 ± 0.29^{b}	14.01 ± 0.90^{b}	13.83 ± 0.18^{b}
18:1 (n-9)	34.25 ± 1.20^{a}	32.68 ± 0.81^{a}	22.08 ± 0.63^{b}	22.05 ± 0.51^{b}	22.96 ± 0.30^{b}
18:2 (n-6)	11.57 ± 1.00^{a}	13.25 ± 0.71^{a}	22.58 ± 0.64^{b}	20.20 ± 1.48^{b}	7.25 ± 2.17^{c}
18:3 (n-3)	0.53 ± 0.06^{a}	0.37 ± 0.03^{a}	0.90 ± 0.08^{a}	0.85 ± 0.05^{a}	0.42 ± 0.07^{a}
20:4 (n-6)	7.74 ± 0.94^{a}	10.80 ± 0.37^{a}	8.90 ± 1.44^{a}	9.38 ± 0.69^{a}	9.40 ± 0.47^{a}
20:5 (n-3)	0.60 ± 0.07^{a}	0.88 ± 0.01^{a}	0.82 ± 0.03^{a}	0.84 ± 0.08^{a}	7.05 ± 1.54^{b}
22:6 (n-3)	1.36 ± 0.22^{a}	1.26 ± 0.10^{a}	1.37 ± 0.14^{a}	1.50 ± 0.41^{a}	3.74 ± 0.47^{b}

Values are expressed as means ± SEM. Student–Newman–Keuls test was used to determine differences between groups after ANOVA. Different superscripts in a row indicate significant differences ($P < 0.05$)

Table 6 Fatty acid composition of stomach in piglets maintained on TPN for up to 7 days ($n = 5$–11/group)

Fatty acid	Enteral	ClinOleic	Intralipid	Lipofundin	Omegaven
(g/100 g fatty acids)					
14:0	1.42 ± 0.16^{a}	0.31 ± 0.04^{b}	0.29 ± 0.02^{b}	0.38 ± 0.05^{b}	0.75 ± 0.13^{b}
16:0	20.99 ± 0.35^{a}	19.92 ± 0.67^{a}	18.69 ± 0.29^{a}	19.79 ± 0.56^{a}	21.71 ± 2.12^{a}
18:0	14.26 ± 0.34^{a}	14.73 ± 0.43^{a}	17.02 ± 0.56^{b}	16.81 ± 0.39^{b}	15.73 ± 0.87^{ab}
18:1 (n-9)	31.97 ± 0.47^{a}	32.60 ± 0.71^{a}	21.23 ± 0.29^{b}	21.46 ± 0.86^{b}	22.43 ± 0.49^{b}
18:2 (n-6)	10.28 ± 0.38^{a}	10.68 ± 0.51^{a}	19.53 ± 0.68^{b}	16.85 ± 1.20^{c}	4.78 ± 0.23^{d}
18:3 (n-3)	0.35 ± 0.04^{a}	0.36 ± 0.03^{a}	0.76 ± 0.10^{b}	0.65 ± 0.07^{b}	0.26 ± 0.02^{a}
20:4 (n-6)	10.19 ± 0.26^{a}	11.22 ± 0.31^{a}	10.94 ± 0.43^{a}	11.13 ± 0.15^{a}	9.93 ± 0.84^{a}
20:5 (n-3)	0.89 ± 0.03^{a}	0.87 ± 0.05^{a}	0.95 ± 0.03^{a}	1.07 ± 0.04^{a}	6.38 ± 0.38^{b}
22:6 (n-3)	2.05 ± 0.11^{a}	2.39 ± 0.14^{a}	2.59 ± 0.33^{a}	2.26 ± 0.15^{a}	5.04 ± 0.26^{b}

Values are expressed as means ± SEM. Student–Newman–Keuls test was used to determine differences between groups after ANOVA. Different superscripts in a row indicate significant differences ($P < 0.05$)

Brain

In relation to the fatty acid composition of brain phospholipids in piglets fed enterally or maintained on TPN (Fig. 3), it can be seen that there were no statistical differences in the proportions of the main saturated fatty acids (palmitic and stearic acids) between the different treatments. It is also interesting to notice that the proportion of

Table 7 Fatty acid composition of intestine in piglets maintained on TPN for up to 7 days ($n = 5$–11/group)

Fatty acid	Enteral	ClinOleic	Intralipid	Lipofundin	Omegaven
(g/100 g fatty acids)					
12:0	4.31 ± 1.13^{a}	0.06 ± 0.02^{b}	0.11 ± 0.05^{b}	0.05 ± 0.05^{b}	0.06 ± 0.04^{b}
14:0	3.21 ± 0.66^{a}	0.20 ± 0.03^{b}	0.22 ± 0.02^{b}	0.18 ± 0.05^{b}	0.52 ± 0.09^{b}
16:0	21.16 ± 0.54^{a}	20.28 ± 1.20^{a}	19.52 ± 0.48^{a}	17.25 ± 0.31^{b}	21.13 ± 0.69^{a}
18:0	12.05 ± 1.02^{a}	15.18 ± 1.04^{b}	17.38 ± 0.41^{bc}	19.39 ± 0.41^{c}	17.77 ± 0.77^{bc}
18:1 (n-9)	32.58 ± 0.88^{a}	28.59 ± 1.23^{b}	17.86 ± 0.41^{c}	18.70 ± 0.42^{c}	17.77 ± 0.73^{c}
18:2 (n-6)	13.11 ± 0.97^{a}	11.98 ± 0.60^{a}	22.10 ± 1.07^{b}	19.42 ± 1.16^{b}	4.51 ± 0.23^{c}
18:3 (n-3)	0.89 ± 0.07^{a}	0.46 ± 0.04^{b}	0.94 ± 0.10^{a}	1.00 ± 0.10^{a}	0.32 ± 0.02^{b}
20:4 (n-6)	6.15 ± 0.77^{a}	11.05 ± 0.84^{b}	10.83 ± 0.48^{b}	12.95 ± 0.69^{b}	11.30 ± 0.27^{b}
20:5 (n-3)	0.37 ± 0.04^{a}	0.51 ± 0.05^{a}	0.65 ± 0.06^{a}	0.52 ± 0.04^{a}	10.15 ± 0.29^{b}
22:6 (n-3)	1.45 ± 0.18^{a}	3.17 ± 0.27^{a}	3.08 ± 0.16^{a}	3.93 ± 0.21^{a}	8.49 ± 0.23^{b}

Values are expressed as means ± SEM. Student–Newman–Keuls test was used to determine differences between groups after ANOVA. Different superscripts in a row indicate significant differences ($P < 0.05$)

stearic acid seen in brain phospholipids of all the groups is higher than that present in plasma or in any of the other tissues studied. The proportion of oleic acid (18:1n-9) was also similar in all the groups despite the differences in the proportion of this fatty acid in the emulsions used. In relation with PUFA, linoleic acid proportions in all the groups were lower than in any of the other tissues studied, and values were higher in the Intralipid group, followed by Lipofundin, which may be related to the high proportion of this fatty acid in the emulsion's composition. The proportion of α-linolenic acid was practically undetectable in brain phospholipids from all the groups, despite its significant proportion in the corresponding emulsions. Despite major differences in the proportions of LCPUFA in the emulsions or milk replacer, the brain phospholipids showed similar proportions across the different groups, with the exception of DHA, which showed a large proportion in all the groups, although the Omegaven group showed its greatest proportion (Fig. 3).

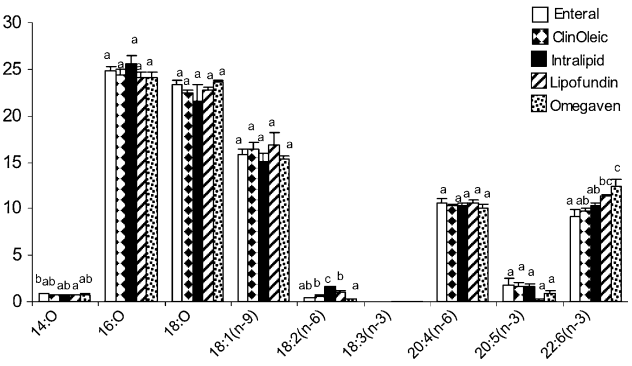

Fig. 3 Fatty acid profile (g/100 g fatty acids) of brain phospholipids in piglets maintained on TPN for up to 7 days ($n = 4$–11/group). Values are expressed as means ± SEM. Student–Newman–Keuls test was used to determine differences between groups after ANOVA. *Different letters over each bar* indicate significant differences ($P < 0.05$)

Relationship Between Emulsions and Tissues

There were positive significant linear correlations between the proportion of the fatty acids in the emulsions and the proportions of the same fatty acids in each of the tissues studied, with brain phospholipids showing the lowest correlation coefficient (data not shown). Besides, by calculating the relationship of individual fatty acids for each tissue vs. their proportion in the milk replacer or lipid emulsions or even in plasma, it was found that in case of the saturated fatty acids the correlations did not reach statistical significance whereas the proportions of oleic acid, linoleic acid, α-linolenic acid, EPA or DHA were significantly correlated in case of skeletal muscle, subcutaneous fat, liver, heart, pancreas, stomach or intestine, but not in brain phospholipids (data not shown).

Discussion

Tissue Fatty Acid Profiles in Piglets on TPN Emulsions with Different FA Compositions

The present study shows that the fatty acid composition of the skeletal muscle and subcutaneous adipose tissue from piglets enterally fed a milk replacer or intravenously administered ClinOleic, Intralipid, Lipofundin or Omegaven emulsions—having different fatty acids composition—for 7 days from birth, is clearly influenced by the dietary fatty acid composition, and it is consistent with a previous report that indicates that fatty acid composition of adipose tissue and muscle of 7-day-old pigs reflects milk

fatty acid composition [31]. This fits with the high lipoprotein lipase (LPL) activity that has been found in adipose tissue of these animals [31, 32], and although in muscle the LPL activity is lower, it has been found that there is no release of NEFA from skeletal muscle during high rates of LPL action, suggesting that in muscle LPL-derived fatty acids are effectively trapped in the tissue [33], which is in accordance with our results. Nevertheless, previous observations support the hypothesis that lipogenesis may be significant in adipose tissue of the neonatal pig [31, 34] and in our study the lack of difference in the proportion of palmitic acid in adipose tissue between the different groups studied, despite the fact that milk replacer contained nearly twofold the proportion of palmitic acid in the TPN emulsions, also supports this hypothesis.

In liver, the fatty acid composition must be modulated by in situ metabolism of fatty acids and the influx of fatty acids from the diet and/or from the de novo synthesis in the adipose tissue. Although it has been reported that the rate of lipogenesis in the liver of newborn piglets is low [35], a high rate of desaturase activities is found in the liver of piglets [19, 36]. As a result of this, and even though Omegaven emulsion is the only one that contains AA in its composition, all the groups produce high proportions of AA in liver. It is known that high proportions of long-chain n-3 fatty acids decrease Δ-6 desaturase activity [37, 38], the main enzyme responsible for the synthesis of AA from linoleic acid, but this effect could be compensated for by the presence of AA in the Omegaven emulsion, causing the Omegaven group to have a similar amount of AA in liver in comparison with the rest of the TPN fed groups. Moreover, it is important to point out that the highest proportion of AA in liver is observed in the enterally fed group, and the lower AA proportion in the TPN treated groups could be the result of lower rates of desaturation that have been already reported in other studies as a consequence of TPN treatments [39]. This lower proportion of AA following TPN occurs even after treatment with Intralipid, which contains the highest proportion of linoleic acid as compared to other emulsions and more than eight times higher than the milk replacer. It could well be that the high dietary intake of linoleic acid in this group inhibits AA synthesis or competes with AA for acylation, as it has been previously proposed [40]. Fatty acid composition of liver is also influenced by its LPL activity, allowing circulating triacylglycerols to be hydrolyzed and fatty acids to be taken up by the tissue. In contrast to what occurs in adults, the liver of the newborn in different species expresses LPL [41, 42] and the pig is not an exception [32]. In fact, we have previously shown that the piglets receiving TPN develop fatty liver, the effect being probably mediated by the action of LPL contributing to the tissue uptake of circulating fatty acids [32].

The fatty acid proportion in plasma must be the result of the influx of fatty acids from the emulsions, plus those from the metabolic changes taking place in liver and/or adipose tissue. The fact that no differences were found between the groups in oleic, linoleic, ALA and even AA in plasma, despite major differences in their respective proportion in the different lipid emulsions or milk replacers, would indicate that they represent a combination of these different sources. These metabolic changes also influence the fatty acid composition of other tissues such as heart, pancreas, stomach and intestine. Among them, the one that follows most closely the differences found in the lipid emulsions or milk replacer fatty acid composition is the heart, which has been reported not to exhibit desaturase activities [19, 43].

Relationship Between the Fatty Acid Profiles of the TPN Emulsions and in Different Tissues

In order to obtain an approximation of the influence of administered fatty acids, with the different emulsions or milk replacer, on the tissue fatty acid composition, linear correlations were made. Strong linear correlations were found between the fatty acids in the TPN emulsion given and the fatty acid composition of plasma and several tissues of piglets, the lowest correlation being found for brain phospholipids. In an attempt to analyze in more detail the influence that each fatty acid present in the emulsion has in its corresponding proportion in the different tissues, correlations were performed and it was found that the proportions of palmitic and stearic fatty acids, the main saturated fatty acids, did not correlate with their proportion in the TPN or in the milk replacer. This finding is consistent with the results found in other studies where it is observed that lipogenesis is significant in adipose tissue and muscle of neonatal pigs [31] and in developing brain [44, 45]. However, different to other tissues, oleic acid in brain phospholipids did not correlate with this fatty acid in the TPN emulsions or milk replacer, and its precursor, stearic acid shows the highest proportion in brain phospholipids than in any of the other tissues studied. Although we have not measured the actual rate of lipogenesis, these findings indicate an active elongase process in brain allowing the efficient conversion of palmitic acid into stearic acid, and the efficient Δ6 desaturation of the later, all of which agree with the active lipid metabolism known to take place in brain [46], and with the high stearoyl-CoA desaturase present in brain during the perinatal period [47]. The correlation between the proportion of tissue fatty acids and those present in the TPN emulsions and milk replacer were particularly significant for the PUFA, which agrees with similar previously described findings in adipose tissue [48]. EFA cannot be synthesized endogenously. The proportion of LA in the emulsions or milk replacer is strongly

correlated with the proportion found in each of the tissues studied, including brain phospholipids. However, the LA derivative, AA, reach a proportion in different tissues that is independent of its presence (or absence) in the diets. This indicates an active endogenous synthesis of AA in all the studied tissues, including brain, where it has been described that is active during development [49]. Concerning the n-3 LCPUFA, present findings indicate that with exception of brain phospholipids, the presence of both EPA and DHA in the different tissues is very much dependent on their presence in the corresponding emulsion or milk replacer, since despite of the presence of their precursor in the diets and tissues both fatty acids reached significant proportions only in the tissues of the TPN-Omegaven group, indicating that their endogenous synthesis in the neonatal pig is relatively low. This situation completely differs in brain phospholipids, where the proportion of EPA did not differ in the piglets receiving Omegaven compared to any of the other groups and in case of DHA, its comparative proportion in brain of animals on Omegaven versus the rest of the groups is much smaller than for any of the other studied tissues. This occurs despite the brain having the lowest proportion of ALA in all the groups, suggesting a rapid and efficient conversion to their LCPUFA derivatives, EPA and DHA.

Final Considerations

It is not possible to directly compare present findings to the condition present in premature human neonates on TPN. However, the premature piglet has previously been used as a model for the premature infant [50–52], and by using an experimental design similar to that previously used, we have recently found that during TPN, the piglets show typical responses previously reported in human infants [32]. Thus, with the appropriate caution, the findings here reported can be used to understand some of the responses to TPN in human premature neonates.

In conclusion, with the exception of the brain, the fatty acid composition of plasma and of different tissues of piglets are strongly influenced by the fatty acid profile of TPN emulsions. However, fatty acid composition in brain phospholipids is much less dependent on dietary composition, indicating an active and efficient metabolism that ensures the appropriate composition in this key stage of its development. It is proposed that an appropriate availability of essential fatty acids, rather than synthesized LCPUFA is needed to ensure an appropriate fatty acid profile in the brain during its developmental stage.

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