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Omega-6 for Body, Omega-3 for Brain: Balance for Brain Development in Children (英文原文)

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Abstract: Food must supply a balance of nutrients to support both brain and body. The human brain makes us uniquely human. Essential fatty acids are part of the metabolic pathways that define tissue structure and function. Omega-6 (O6) linoleic acid (LA6) has long been known to be required for skin structure, and as a precursor for inflammatory, thrombotic, immune, and other signaling molecules. Omega-3 (O3) alpha-linolenic acid (ALA3) and particularly its long chain product docosahexaenoic acid (DHA3) has a key structural role in the brain, retina, and related neural tissue. In the 20th century western world, inexpensive, high quality oils primarily from LA6-rich/O3-poor vegetable seed oils became dominant fats produced by the food industry. Provision of LA6-rich/O3-poor oils as the sole source of fat in the diets of pregnant animals causes O3 deficiency and poor brain development, primarily because high LA6 antagonizes metabolism of all O3, creating an artificial metabolic demand for O3. Data developed over the last 2~3 decades show that provision of low LA6 combined with preformed DHA3 optimizes brain function. Recent studies emphasize the importance of nutrition to support brain development, with newer findings showing particular importance of fatty acid balance in malnourished children. The World Health Organization (WHO) through the Codex Alimentarius (“Code for Food”) is increasingly recognizing the primacy of brain health and in part on that basis recently acted to recommend balanced fat for Ready-to-Use-Therapeutic Foods used to treat children with severe acute malnutrition. Similar principles are likely to be important in older persons. Industry now has the tools to adjust the composition of oils to support brain health throughout the life cycle.

Key words: brain development; docosahexaenoic acid; Omega-3; Omega-6; high oleic oils; severe acute malnutrition; Ready to use therapeutic food; fatty acid balance

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ABBREVIATIONS

CVD: Cardiovascular disease
HUFA: Highly unsaturated fatty acids
HO: High oleic acid
PUFA: Polyunsaturated fatty acids
RUTF: Ready-to-Use Therapeutic Foods
O6: Omega-6 fatty acids
LA6: Linoleic acid Omega-6
ARA6: Arachidonic acid Omega-6
O3: Omega-3 fatty acids
ALA3: Alpha-linolenic acid Omega-3
EPA3: Eicosapentaenoic acid Omega-3
DHA3: Docosahexaenoic acid Omega-3

1. INTRODUCTION

Humans are the animal of the runaway brain[1-2]. The human brain is far larger and consumes far more energy as a percent of body weight than any comparably-sized terrestrial animal. In this sense human brains are unique.

The brains of all mammals have a unique composition compared to all other organs, but brains themselves are similar in their composition. They are dominated by specialized highly unsaturated fatty acids (HUFA), in particular Omega-3 (O3) docosahexaenoic acid (DHA3) and Omega-6 (O6) arachidonic acid (ARA6). This classic observation implies that size of mammalian brains is in some way limited by the ability of the animal to obtain through food the major components of the brain, and specifically DHA3[3].

Food supplies the essential fatty acids required for all metabolic functions. While the underlying metabolism of fatty acids is similar throughout the body, principles that govern the most obvious aspects of health are different for body and brain. Overt deficiency in the body is avoided with 2% of energy as O6 linoleic acid (LA6) with no O3, even though O3 deficiency causes abnormal development of the brain's higher functions. Our goal here is to review O6 and O3 nutritional principles with emphasis on recent studies on fatty acid nutrition in brain development of malnourished children.

2. HUFA SYNTHESIS, BRIEFLY

We have recently reviewed details of the biochemical pathway and genetics around polyunsaturated fatty acids(PUFA)[4-5] and will summarize key points here.

The two families of essential fatty acids, PUFA, are supplied in modern diets primarily as LA6 for O6 and alpha-linolenic acid Omega-3 (ALA3) for the O3. These fatty acids are metabolically transformed into the bioactive HUFA by common enzymes coded by common genes (FADS2, FADS1, ELOVL5, ELOVL2), though some evidence shows that alternative transcripts modulate the specificity of the respective enzymes[6]. As a result, the balance between the dietary levels of the main C18 precursors of the two families of PUFA, LA6 and ALA3, are of key importance. The main PUFA/HUFA of importance are as follows, showing that LA6 and ALA3 are primarily precursors for ARA6 and eicosapentaenoic acid Omega-3(EPA3)/DHA3, respectively.

Omega-6 (O6): LA6→→→ARA6

Omega-3 (O3): ALA3→→→EPA3→DHA3

ARA6 is the precursor for more than 100 signaling molecules and appears to be a critical structural component for some neural membranes. DHA3 is required as a structural component of the neural system, and EPA3 is generally required to balance ARA6 signaling.

3. O6 FOR BODY

Diets with only LA6 and ALA3 could be achieved with a strict vegan diet, though veganism is a relatively recent practice: few if any ancestral human groups consume no animal products. The vast majority of human diets include HUFA from animal foods (meat and seafood, eggs, dairy) as well as seaplants and some other plants. Endogenous HUFA synthesis is suppressed by dietary HUFA via product inhibition. Recent data also show that many more saturated fatty acids than previously known can affect HUFA biosynthesis[5,7]. Thus, the overall mix of fatty acids in the diet, not only PUFA, affect HUFA synthesis. Nevertheless, concepts such as essential fatty acids, and the "parent" fatty acids were established with rodents primarily on diets with only LA6 and ALA3 and their biology should be understood in that limited context.

The only known metabolic function of LA6 that, apparently, cannot be satisfied by another fatty acid is as a component of skin lipids. The first known and most prominent symptom of essential fatty acid deficiency is a compromise in the barrier function of skin, leading to skin lesions and pathological evaporation of body water through the skin. While dietary LA6 rapidly cures this condition, so too does dietary ARA6, which is converted to LA6[8]. Moreover, it has long been known that diet ARA6 is more potent for improving skin integrity

than diet LA6.

Diets that have LA6 and little or no ALA3 support growth (weight and length gain) and apparently normal reproduction. These functions can be considered to support the body. Brain function is complex and subtle, and requires careful testing to reveal whether the higher mental functions such as problem solving and balanced mood are normal. Early studies did not test brain function and thus did not detect abnormalities that became obvious in later decades.

LA6 is special as a dietary FA. Conventional seed oils produced inexpensively and at high quality are generally rich in LA6, for instance soy oil (53% LA6), groundnut (25% LA6), rapeseed (25% LA6) and in the USA, sunflower and safflower oils (70% LA6). These levels compare to, for instance, teaseed oil (10% LA6) and fruit oils olive and palm oil (6%~15% LA6) and animal fats which are in the same low range. Widespread use of high LA6 oils is relatively new. Dietary LA6 suppresses tissue accumulation of all Omega-3 fatty acids, whether ALA3 or HUFA EPA3 and DHA3 by interfering with activation into the biochemical pathways by the acyl coA synthases, inhibiting HUFA biosynthesis, and inhibiting incorporation into tissue. LA6 also accumulates in white adipose to a far greater degree than any O3; this phenomenon is likely to be due to rapid damaging oxidation that O3's undergo.

LA6 drives ARA6 levels only up to about 4% of calories (cal)[9]. LA6 levels above about 4% of energy cause levels of the potently bioactive ARA6 to saturate in tissue. Further increases in ARA6 require consumption of preformed dietary ARA6. Most industrialized diets are on average far above 4%en LA6. As a comparison, American LA6 intake is above 10%cal. Halving dietary LA6 from 10% to 5% by substitution with an inert fatty acid (e.g. oleic acid, 18:1n-9) has no effect on circulating ARA6 because ARA6 is already maximal. Levels well below 4%cal are required to see changes.

4. CIRCULATING FATTY ACID LEVELS AND HEALTH: O3 INDEX AND OTHER FATTY ACIDS

Among the most reproducible phenomenon in mammalian biochemistry is the competitive nature of dietary fatty acids and specifically LA6 and ALA3. By the early 1960s, feeding studies showed that diets with only LA6 and ALA3 gave highly predicable responses in tissue levels of all PUFA[10-12]. These studies have been replicated many times since, and put on a quantitative basis[9,13-15]. The intake of food fatty acids and the genetics of the individual define the composition of tissue and in part its function.

In recent years laboratory blood tests have been developed to check fatty acid status and potentially recommend dietary changes. The most prominent of these are the O3 tests, though others are likely to emerge.

Dietary fatty acids and specifically the balance of saturated vs unsaturated fatty acids were considered to influence biomarkers of cardiovascular disease for many decades. Specifically, it is well established that oils rich in LA6 decrease serum cholesterol and LDL-cholesterol. However, LDL's role as a causal agent in cardiovascular disease, at least at levels below 200 mg/dL (5.2 mmol/L), is complicated by the various types of circulating LDL particles and thus is not straightforward. Substitution of LA6 by saturated fat raises LDL but does not increase cardiovascular disease (CVD) risk[16]. LDL below 200 mg/dL is not a risk factor for CVD in Japan[17].

Home compatible fatty acid tests are available. In these tests, a drop of blood from a finger prick is collected on treated paper and sealed, and mailed to a testing laboratory. Samples are extracted and analyzed for fatty acids that can be related to disease risk.

Over the past 15 years, whole blood O3 as a fraction of total PUFA and total HUFA has been developed and validated as a marker of CVD with at least as good predictive power than the cholesterol markers. The HS Omega-3 Index[18] and the Omega-3 HUFA Test[13,19] are examples.

Many other fatty acids can be reported in the same analyses, including an array of saturated fatty acids, monounsaturated fatty acids, and subset of these such as odd chain fatty acids. Until now these have been used for newborn screening primarily. In adults they are used for research purposes but the data strongly suggest that they will be of importance for individual cases as demand grows for insight into healthy eating practices.

5. BALANCING O6 AND O3 FOR BODY AND BRAIN

ALA3 has no known specific metabolic functions that depend upon it, unlike for LA6. Dietary ALA3 is not stored but is rapidly disposed of metabolically by one of three routes: a) oxidation to yield acetate

as a carbon source or CO_2/H_2O as an energy source, b) secretion onto the skin, c) conversion to long chain/more unsaturated PUFA that are required metabolically, specifically DHA3 and EPA3.

5.1 PUFA balance: excess LA6, not O6/O3 ratio, controls DHA3 levels

The levels of dietary LA6 and ALA3 influence the transformation of one another to HUFA. It is often said that DHA3 levels are controlled by the dietary ratio of O6 to O3. This is not correct in an important way.

Many animal[9,20] and human[21-22] studies have shown that circulating and tissue DHA3 is not controlled by the dietary ratio of O6/O3 when only LA6 and ALA3 are the sole sources of the two respective PUFA families. Consider an LA6/ALA3 (O6/O3) = 10. If ratio controlled DHA3 levels, then changing the ratio to 5 by either increasing ALA3 two-fold, or reducing LA6 by half, would increase DHA3 levels. The experimental fact is that increasing ALA3 never increases tissue DHA3 while decreasing LA6 increases DHA3. It is therefore more accurate to express the competition between dietary LA6 and ALA3 as one of excess LA6 as inhibitory. Thus, lowering LA6 is required to support DHA3 levels[13].

6. O3 AND BRAIN DEVELOPMENT THROUGH THE DECADES

DHA3 was discovered as a component of brain tissue by the 1950s, in the era when nutrition research focused on discovery of vitamins. The main bioactive fatty acid was considered to be LA6 because deficiency of this nutrient was obvious: it led to lesions and compromised the water barrier function of the skin[23]. O3 is not effective in repairing this defect. Looking back, we now know that O3 affects higher brain functions which are not as easily studied as skin lesions. Therefore the essentiality of O3 for human life was not well established until the mid-1980s, decades after O6 essentiality was established[24]. Even now the essentiality of O3 has not been fully corrected across all policy documents.

6.1 The brain requires O3; DHA3 is likely a required nutrient at least in some lifestages

It has been known since the 1970s that DHA3 is required to support detection of light in the retina, that is, the visual response[25-28]. About that time, expeditions to the arctic of North America revealed a relationship between high intake of O3 from seafood and low cardiovascular disease, a discovery that caused enormous interest in EPA3 and to a lesser extent DHA3 as a preventative or treatment for cardiovascular disease but did not address O3 as a required nutrient to prevent deficiency symptoms [29-30].

It was in this decade that O3 deficient diet first appeared, showing that replacement of all fats with an oil with high O6 but negligible O3 in diets of pregnant animals caused deficiency symptoms in rodents[31]. The use and expansion of these diets in the perinatal period for research into O3 expanded later.

The 1980s showed the first clinical studies of O3 as a key nutrient for brain development. The O3 deficit diet was refined and led to a series of influential papers showing that O3 deficiency caused replacement of DHA3 with the O6 analogue docosapentaenoic acid (DPA6) in rhesus monkeys[32-33]. These results matched findings of years earlier in rodents that also reported no changes in growth or reproduction, but looked at no measures of brain development[34] as was indicated by the knowledge that DHA3 accumulates in neural tissue, known for decades and demonstrated systematically for all wild animals a few years later[3]. In contrast, Neuringer and Connor showed that retinal function was dramatically compromised by O3 deficiency, and that retinal function was restored when dietary O3 was restored. A key lesson from this history is that measurements must target the function affected by the agent in question, in this case the growing brain and neural system[35].

In parallel, the first studies in infants were initiated, showing that the infant formulas of the time, with no DHA3, caused reductions in blood DHA3, similar to those seen in animals[36]. Around this time, reports of fatty acid concentrations in breastmilk using high resolution methods suitable for accurate analysis of DHA appeared and continued to the present[37]. Human clinical studies of the 1980s were concerned with preterm infants and the degree to which dietary preformed DHA3 is needed to maintain DHA3 status[38-41].

The 1990s were a decade of clinical studies on DHA3 and on O3 deficiency animal models similar to the earlier rhesus monkey studies. Both are too numerous to review here. In total, the clinical studies showed compellingly that preterm infants require preformed DHA3 in feeds while results were judged mixed though nevertheless compelling for term infants[42-43].

Animal studies of O3 deficiency are of key

importance in assessing foods for the general population. By 2011, at least 60 studies of functional outcomes of O3 deficiency appeared[44]. These studies provided diets similar to the rhesus monkey diets and showed that feeding numerous high LA6/low ALA3 oils as the sole source of fat to pregnant animals (rats, mice, pigs, primates) from conception to weaning cause all manner of abnormalities in neural function, from basic biochemical alterations not seen in free living/wild animals, to defects in maze running, visual acuity, neural signal transmission, balance, anxiety, aggression, impulse control, and many other non-neural defects such as abnormalities in circulating catecholamines. As usual, with ample dietary O6, animals grew and reproduced apparently normally though some studies suggested subtle abnormalities in litter size and other non-obvious outcomes (for example, reference [45]).

These experimental findings lead to a common, perhaps oversimplified but nevertheless accurate rule: *omega-6 supports the body, omega-3 supports the brain*.

7. SEVERE ACUTE MALNUTRITION AND PUFA

Severe acute malnutrition (SAM) caused by lack of food afflicts about 20 million children globally on an annual basis. Rehabilitation from SAM often leaves children with suboptimal mental functioning which can take the form of impaired ability to solve problems or inability to properly regulate mood. Impaired mood consisting of higher levels of depression, anxiety, aggression, as well as indirect risks to mood such as higher sensitivity to pain.

Therapeutic foods to rehabilitate children from SAM took the form of milks fortified with calories, protein, and micronutrients in the 1990s. Survival ("recovery") rates were in the range of 50% over a few months post treatment, showing some efficacy but leaving the hypothesis that many more children could be successfully treated.

7.1 A breakthrough: Ready-to-Use Therapeutic Foods (RUTF)

Ready-to-Use-Therapeutic Foods (RUTF) were developed around the year 2000[46]. RUTF are based on peanut (groundnut) butter, non-fat dry milk, sugar, vitamins/minerals, and oil, all sealed in a pouch and stable over 2 years at ambient temperature. Survival rates increased to over 90% by 2007, a major success that provides a suitable treatment for most malnourished children.

7.2 From survive to thrive

In human development, life-threatening conditions are first approached by the search for methods that enable survival. Once a treatment is found, research pediatricians turn attention to long term effects so to optimize the ability to live and thrive in the long term.

As with the story of preterm infants, the well-established human biology of PUFA nutrition was not a focus. And as with preterm infants, it was the O3 fatty acids that were of concern, though for different reasons. With preterm infants, the key issue was the inclusion of DHA3 in artificial feeds to parallel the composition of human milk more accurately.

With RUTF, the key issue was the use of oils with overwhelming amounts of LA6, as well as the lack of DHA3. This oversight was at least in part due to (a) the supply of vegetable oils available as ingredients for making RUTF, and (b) the lack of emphasis in global food standards for the interactions of nutrients within a diet, that is, that the level of one nutrient affects the requirements for the other. For RUTF, it was the high level of LA6 that causes a metabolic demand for all O3 by antagonizing O3 accretion in all tissues. Conventional peanuts, the main ingredient in RUTF, are high fat and contain high LA6 and no ALA3. Oils added to increase calorie content and with it, add some ALA3, were even higher in LA6 (for example, soy) and though they increased ALA3 they increased LA6 by more.

A 2010 conference in California brought together specialists in fatty acid nutrition and in malnutrition to consider aspects of PUFA nutrition. Emerging from that event was a collaborative team that established that, in fact, RUTF using the customary recipe could not achieve even modest ratio of LA6 to ALA3 (O6/O3) < 10 that was expected by the World Health Organization recommendations. Importantly some of the RUTF in use at that time had compositions similar to the O3-deficit diets that caused permanent neurological impairment in animal studies.

7.3 A smarter food for long term benefits

The availability of high oleic (HO) peanuts[47] opened the possibility to reformulate RUTF with oils that have lower levels of LA6 that will minimally antagonize O3. The most common HO oil in the west is olive oil which contains around 10% LA6 and over 80% oleic acid, with little ALA3

and no DHA3 or EPA3. This composition is similar to teaseed oil available in China. Early studies have shown that very low levels of dietary LA6 are needed to avoid deficiency symptoms[48], and that amounts above the minimum create a metabolic demand for DHA3[24]. The basic problem is that most *traditional* commercial oils, such as rapeseed, soy, sesame, contain high amounts of LA6 and low or zero O3. HO oils developed by traditional plant breeding, without artificial genetic modification, have a composition similar to olive and teaseed oil. HO peanut with their low LA6 and high oil content are a solution to the problem of high LA6 oils creating a metabolic demand for DHA3.

Studies in animals show that even extreme amounts of dietary ALA3 as the only source of O3 do not support tissue DHA3 in all neural tissue at the same levels as dietary preformed DHA3[49]. Even with HO oils and lower LA6, DHA3 may not reach the same levels as with preformed DHA3 in the diet. On this basis, we cast the hypothesis that RUTF with HO peanuts (lower LA6), and fortified with a modest amount of DHA3 would better support tissue levels of DHA3.

In our first study, we tested the hypothesis in a group of 81 children of mean age about 2 years and diagnosed with SAM in Malawi. We used only control and HO RUTF for a period of 4~12 weeks until body recovery was found. In four weeks, circulating phospholipid DHA3 dramatically decreased a stunning 25% on the control RUTF with 26% LA6 and <1% ALA3 (% by weight of fatty acids). In the HO diet with 13% LA6 and ALA3, DHA3 stabilized, showing that with balance the children could make sufficient DHA3 to supply tissue needs as the flood of calories and protein from RUTF were available to restart brain growth[50]. A similar study in a smaller number of children conducted by other researchers in Kenya that did not decrease LA6 but added ALA3 showed a non-significant decrease in DHA3[51]. This paper highlighted the importance of controlling LA6 levels and led to modest changes in RUTF composition.

Our most recent study was designed to evaluate brain function in over 1 000 children of 2 800 in the study[52]. The three groups received RUTF of various PUFA compositions: Control, HO formulated with HO peanuts with low LA6, and DHA-HO with added DHA (Table 1). Recovery of the body from malnutrition was similar in all groups as assessed by arm circumference. Children went home for six months and then their mental function was tested by the Malawi Developmental Aptitude Test. Compared to Control RUTF, the children receiving DHA3-HO RUTF performed significantly better six months after completing treatment with no intervention during the time away (Figure 1). Though the HO RUTF was not overall significantly improved, the trend to improvement was apparent in all components of the testing, and the social score was the highest in HO RUTF group.

Table 1 RUTF PUFA composition from[50]

	LA6/g	ALA3/g	DHA3/mg
Control	5.8	0.5	0
HO	2.1	1.4	0
DHA-HO	2.2	1.5	72

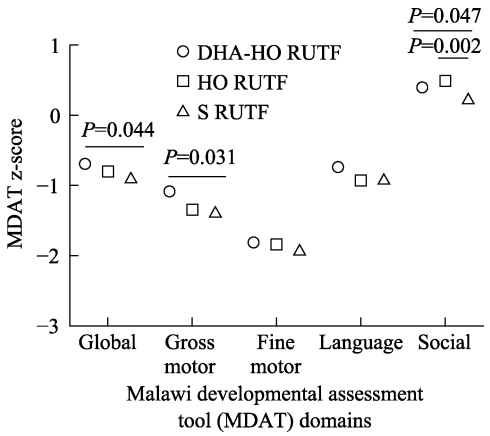

Fig.1 Long term mental function

Note: Children recovered from severe acute malnutrition score higher on the global MDAT *six months after recovery*. From Stephenson et al. Am J Clin Nutr 2021.

Thus, in the long term, six months post treatment with no intervention, the DHA-HO RUTF supported superior brain function, with most significant effects in the gross motor and social domains.

8. CONCLUSIONS: WHO RECOMMENDATIONS AND IMPLICATIONS

The World Health Organization Codex Alimentarius meets annually in November to consider recommendations for composition of foods. The process for considering proposed recommendations is highly structured, inviting input from country delegates worldwide. The responsible 2021 Codex committee finalized recommendations[53] for the composition of RUTF in part based on our findings in Malawi. Maximal LA6 was set at 780 mg and minimum ALA was set at 110 mg per 100 kcal,

compromise levels proposed prior to the time our study[52] appeared. These recommendations are a major improvement over the previous proposed higher LA6 and lower ALA3 levels. DHA3 addition is permitted and is being added to RUTFs by some manufacturers.

The emphasis on brain development reflected by the unanimous action of Codex may represent a change in attitude toward brain health in general. Malnourished children are among the vulnerable populations, but these results translate to all populations and life stages even if the effects on calorie/protein-replete children/adults/elderly are smaller. In this author's opinion, research should emphasize development of the organ that makes us human, the brain, and body health will follow.

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See in its Chinese version P13-P15.