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Personalized polyunsaturated fatty acids as a potential adjunctive treatment for anorexia nervosa☆

P. Betty Shih[a,*], Christophe Morisseau[b], Thu Le[a], Blake Woodside[c], J. Bruce German[b]

[a] University of California, San Diego, CA, USA
[b] University of California, Davis, CA, USA
[c] University of Toronto, Toronto, Canada

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ABSTRACT

Anorexia nervosa (AN) is a complex psychiatric disorder with high morbidity and mortality rates. While many individuals make full recoveries, up to a third of patients develop a chronic, treatment-resistant form of the illness that leads to a premature death in 15–20% of those affected. There have been few advances in treatment, both in terms of psychological or pharmacologic treatment over the last 30 years. Food aversion is commonly cited by patients with AN as a barrier to normalizing eating and weight. Our group has a keen interest in examining factors that might allow this to be addressed, thus improving treatment outcomes through personalized dietary plans or nutritional supplementation related to underlying genetic status.

We demonstrated that polyunsaturated fatty acids (PUFAs)-derived bioactive lipids (eicosanoids) are implicated in not only the risk of AN, but also with its comorbid psychopathology. Of interest, the differential postprandial omega 6-derived eicosanoid shift observed in AN highlights the possibility that the metabolism of PUFAs is an important mechanism underlying the profound food version, contributing to pathological food restriction in AN. A concise knowledge of the relationships among PUFAs, eicosanoids, and AN clinical course and psychopathology could be the key to developing personalized nutritional rehabilitative treatments for those suffering from AN.

This paper provides a comprehensive overview of the literature on PUFAs in AN. We also selectively reviewed the clinical benefits PUFA treatments exert in other psychiatric diseases, on weight and appetite regulation, and for resolution of inflammation, all of which are relevant in the disease course and outcome of AN. We propose that personalized PUFA formulation be developed and tested as a novel adjunctive treatment for patients with AN. We hypothesize that with personalized PUFA formulation, food aversion and anxiety about eating will decrease while mood, dietary behavior, and weight restoration will improve in AN, leading to improvements in the overall treatment outcome.

1. Introduction

Anorexia nervosa (AN) is a psychiatric disorder characterized by pathological restrictive eating patterns, an obsession of maintaining an unhealthy low weight, and body image disturbance. While some respond well to conventional treatments, many require multiple episodes of treatment over many years to get a good outcome, and one-third of patients go on to develop a chronic, treatment-resistant form of the illness that is associated with ongoing severe medical and psychiatric comorbidity, and high rates of premature death [1]. Research focused on understanding the etiology of AN, including core behaviors such as food avoidance, would be a major step in the direction of improving existing treatment outcomes and in developing new therapies.

Polyunsaturated fatty acids (PUFAs) include “essential fatty acids” linoleic (n-6) and alpha-linolenic (n-3(*n*-3) acids and long-chain fatty acids (LC n-PUFAs). Essential PUFAs are sourced from diet and serve as precursors to LC n-PUFAs such as n-3 eicosapentaenoic acid (EPA) and docosahexaenoic (DHA) acid, and n-6 arachidonic acid (ARA). The importance of PUFAs in weight restoration, a key clinical goal for patients with AN, was reported first in a 1930 rat study when Collin et al. stated that “Both linolenic acid and linoleic acid are effective in curing rats suffering from fat deficiency” [2]. Since then, PUFA treatments have shown to produce benefits in a small number of AN studies and in other psychiatric and neurobiological illnesses including schizophrenia, bipolar disease, major depressive disorder [3], and cognitive decline in Alzheimer’s disease [4]. Although the precise mechanism driving these clinical benefits is incompletely understood, PUFAs’ vital role in maintaining normal brain functions and inflammatory response regulation are likely the key factors to improve symptoms in patients with

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* Corresponding author.
E-mail address: pbshih@ucsd.edu (P.B. Shih).

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mental and neurodegenerative disease [5].

Although the health effects of individual PUFA have been established, the ratio of n-6 to n-3 PUFAs should also be considered as a significant determinant in health and disease outcomes given the complex, competitive relationship between n-3 and n-6 PUFAs and the resulting biological consequences [6–8]. The consideration of the ratio of n-6 to n-3 PUFAs is especially pertinent to today's world given the dramatic impact of food industrialization which changed how foods are sourced, processed, packaged, regulated and distributed in the western societies. Such major food industry evolution significantly alters the nutritional composition of our meals, thereby profoundly affected human health without population awareness. For example, the n-6:n-3 ratio found in the Paleolithic diets were estimated to be 0.79, yet the ratio in today's typical United States diet is estimated to be 16.74 [9,10]. While the effect of a high n-6 to n-3 ratio on human health has been determined as largely problematic [6,11], the increase in dietary n-6 also effects eicosanoids synthesis thereby disrupting resolution of inflammatory processes [12]. Eicosanoids are bioactive lipid mediators derived from the oxidation of several precursor PUFAs (including n-6 LA, and ARA, and n-3 ALA, EPA, and DHA) through enzymatic catalytic processing by cyclooxygenase (COX), lipoxygenase (LOX), or cytochrome P450 monooxygenases (CYP) pathways. Eicosanoids including prostaglandins, thromboxanes, leukotrienes, and epoxyeicosatrienoic acids form a complex regulatory network via competitive inhibition, displacement, or counteraction to regulate a number of important physiological processes including vascular permeability, platelet aggregation, and inflammation response and resolution (Fig. 1) [13,14].

Despite an abundance of studies demonstrating beneficial effects n-3 PUFAs have on various diseases and inflammation, there is a lack of comprehensive research on the role PUFAs play in AN risk and disease course. While a small number of studies suggest a potential for n-3 PUFAs to improve AN symptoms, the association between AN and specific PUFA is inconsistent, and the mechanisms by which PUFAs could benefit AN remain untested. We recently demonstrated that AN patients not only showed a significantly different pattern of PUFA concentration when compared with healthy controls [15], dysregulation in PUFA-derived eicosanoids were associated with AN risk [15] and comorbid psychopathology [16]. Of special interest is the finding that AN demonstrated a differential postprandial metabolism compared to healthy controls with n-6 ARA but not with n-3 PUFAs [16] (raw data in Table 1 of Ref 17)[17]. Our work to date highlights the possibility that the metabolism of PUFAs leading to increased production of proinflammatory bioactive lipid mediators may be a key mechanism underlying the profound food aversion in AN. This hypothesis is further supported by the finding that fat phobic-AN reported more episode and more severe gastrointestinal symptoms compared to nonfat phobic-AN [18].

Eating behavior and food selection of AN are characterized by an inadequate intake and a strong preference for low-fat foods [19]. Diet limited in total variety and specific food groups including "added fat" was associated with relapse risk in AN [20], highlighting the importance of dietary fat and adequate macronutrients for AN. Because correcting imbalanced nutritional state is a necessary step for weight restoration and healthy weight maintenance in AN, PUFA imbalance or deficiency is a critical missing link which should be researched and tested. The goal of this paper is to provide a comprehensive review on PUFAs and AN, and to present our conjectures through a selected review of PUFAs' effectiveness in diseases and phenotypes related to AN. We hypothesize that nutritional rehabilitative plans utilizing personalized PUFA formulation will lead to significant improvements in the overall treatment outcome for AN.

2. Discussion

2.1. n-3 and n-6 polyunsaturated fatty acids (PUFAs) in anorexia nervosa

The first report of PUFA abnormality in AN was published in 1985 when Langan et al. investigated essential fatty acid levels using both total and phospholipid fractions of the plasma fatty acid levels of 17 patients hospitalized for anorexia nervosa and 11 healthy females control. In plasma phospholipid, anorexia nervosa patients showed a lower level of n-6 LA (19.35 ± 5.65 vs 24.96 ± 2.24, $p < 0.01$) but higher n-3 DHA (2.3 ± 0.72 vs 1.68 ± 0.36, $p < 0.05$) compared to controls. AN also had a lower level of total n-6 PUFA. The total lipid plasma PUFA showed that LA trended lower in AN, but the only fatty acid found to be statistically different between two groups was stearic

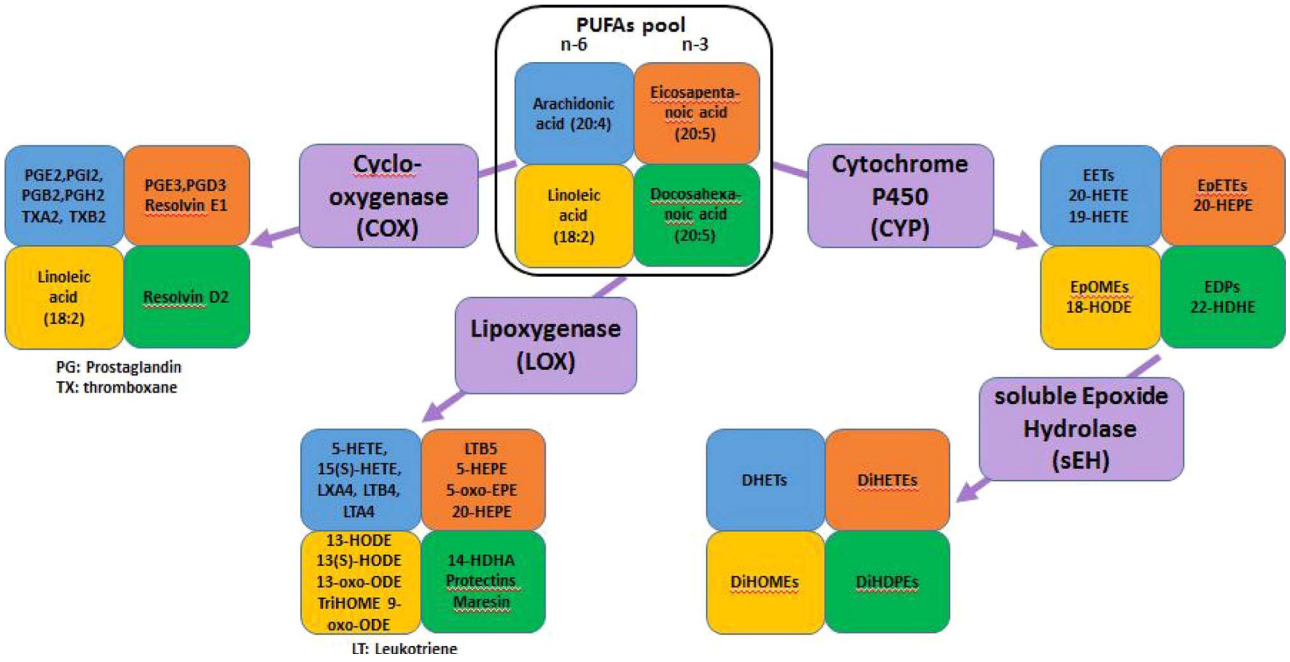

Fig. 1. Families of polyunsaturated fatty acids and related eicosanoids.
Figure Legend: Selected major polyunsaturated fatty acids, families of enzymes, and bioactive lipid mediators (eicosanoids) that are hypothesized as contributors to the risk and progression of anorexia nervosa and disordered eating behavior.