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Emergence of omega-3 fatty acids in biomedical research

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Abstract

Shortly after the discovery that linoleic acid was an essential fatty acid in 1930, α -linolenic acid also was reported to prevent the fatty acid deficiency syndrome in animals. However, several prominent laboratories could not confirm the findings with α -linolenic acid, and as a result there was a loss of interest in omega-3 fatty acids in lipid research. Even the findings that a prostaglandin can be synthesized from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is necessary for optimum retinal function generated only limited interest in omega-3 fatty acids. The breakthrough came in the 1970s when Dyerberg and Bang reported that the low incidence of atherosclerotic coronary disease in Greenland Eskimos was due to the high marine lipid content of their diet. They subsequently found that EPA, which was increased in Eskimo plasma, inhibited platelet aggregation, and they concluded that the low incidence of coronary artery disease was due to the anti-thrombotic effect of EPA. This stimulated widespread interest and research in EPA and DHA, leading to the present view that, like their omega-6 counterparts, omega-3 fatty acids have important physiological functions and are essential fatty acids.

Keywords

essential fatty acid; α -linolenic acid; eicosapentaenoic acid (EPA); docosahexaenoic acid (DHA); linoleic acid; arachidonic acid; fatty acid deficiency syndrome

1. Introduction

Omega-3 fatty acids are a very active area of lipid research today, but they were generally overlooked for more than 40 years after the discovery of essential fatty acids [1]. The purpose of this review is to explain why omega-3 fatty acids were relegated to the background for so long and discuss the factors that led to the emergence of interest in the metabolism and function of these fatty acids in the 1980s.

In the late 1920s, Herbert Evans and George Burr described a deficiency disease that occurred in rats fed a fat-free diet [2,3]. Evans lost interest in the finding when it became

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clear that the disease was not due to a new vitamin deficiency. However, Burr decided to continue this work in collaboration with his wife, Mildred Burr, who maintained the rat colony and made many important observations on the pathophysiological effects of fat deficiency in the animals [4]. The Burrs demonstrated that addition of the fatty acid fraction of lard to the fat-free diet prevented the fatty acid deficiency syndrome [5], and in 1930, they discovered that linoleic acid was the active fatty acid and designated it as an essential fatty acid [6]. These findings were controversial initially because of the prevailing opinion that fatty acids were only a concentrated source of calories [7-9], but the effectiveness of linoleic acid was confirmed in many other laboratories [10-14], and there was general agreement by 1940 that linoleic acid is an essential nutrient for animals [4,15,16].

2. Controversy concerning α -linolenic acid¹

The Burrs predicted in their 1930 paper that like linoleic acid, other unsaturated fatty acids cannot be synthesized in adequate amounts by animals [6]. This prediction was confirmed for linolenic acid by Wesson and Burr [17], leading to the question of whether linolenic acid also was functionally essential. Burr, Burr and Miller tested this in 1932 by supplementing the fat-free diet with methyl linolenate and found that it was effective in curing the fatty acid deficiency syndrome in the rat [18]. They concluded that linolenic acid was about as potent as linoleic acid, but this result could not be confirmed by other prominent laboratories. In 1938, Hume et al. reported that methyl linolenate had no more than one-sixth the curative potency of methyl linoleate in fat-deficient rats [12]. Furthermore, in 1942, Quackenbush et al. reported that ethyl linolenate did not cure the reproductive defect or dermal symptoms of fat deficiency [19].

Although these negative results showed only that linolenic acid does not prevent the fatty acid deficiency syndrome, they were widely interpreted to indicate that linolenic acid is not an essential fatty acid. It should have been obvious that linoleic and linolenic acids would have different functional effects because of their known biochemical differences [20], but this was not considered. The conclusion that linolenic acid is not an essential fatty acid was generally accepted, resulting in a lack of interest in omega-3 fatty acids that persisted until the late 1970s.

3. Essential fatty acid research in the middle decades of the 20th century

The failure to confirm the essentiality of linolenic acid was the primary reason why omega-3 fatty acids were overlooked in the 1950s and 1960s, but it was not the only factor. Another important reason was the intense interest that developed during this period in cholesterol and prostaglandins and the relationship of these substances to omega-6 fatty acids. As a result, most lipid laboratories focused on linoleic and arachidonic acids, and omega-3 fatty acids were relegated to the background.

¹The prefix “ α -” for the omega-3 isomer of linolenic acid was not used in the biomedical literature until recently when it became necessary to distinguish it from the omega-6 isomer, γ -linolenic acid. The term “linolenic acid” was used to specifically indicate the omega-3 isomer in the references listed in this review, and it is used this way in the present text.

Atherosclerotic cardiovascular disease was at the forefront of biomedical research in the 1950s. There was increasing evidence that elevated plasma cholesterol was a risk factor for coronary heart disease [21], and plasma lipoproteins in the S_f 10-20 density range which have a high cholesterol content were found to be increased in patients with a history of coronary thrombosis [22]. Therefore, many studies were initiated to determine how the plasma cholesterol concentration and the metabolism of these cholesterol-rich lipoproteins were regulated.

The initial breakthrough came when Kinsell et al. observed that the serum cholesterol concentration in human subjects decreased when animal fat was replaced by plant fat in the diet [23]. Subsequent studies by Ahrens and colleagues using controlled formula diets showed that this also occurred in patients who had hypercholesterolemia [24]. They observed a substantial reduction in serum cholesterol when corn oil was substituted for coconut oil in the formula diet, and they attributed the decrease to the high linoleic acid content of the corn oil. Clinical investigation focused on determining how linoleic acid produced this cholesterol-lowering effect, and essential fatty acid research concentrated on the metabolism and function of linoleic acid.

Animals were known to metabolize linoleic acid to arachidonic acid [25-27], and like linoleic acid, arachidonic acid was shown to promote weight gain and cure the skin and reproductive abnormalities in fat-deficient rats [16,19,28]. In 1964, Van Dorp et al. and Bergström et al. independently discovered that arachidonic acid is the substrate for the synthesis of prostaglandin (PG) E₂ [29,30]. This occurred at a time when prostaglandins were of great interest in biomedical research because of their potent physiological actions [31-33], and Van Dorp et al. suggested that the function of essential fatty acids may be to act as precursors of prostaglandins [29]. As a result, the conversion of arachidonic acid to prostaglandins and the enzymatic mechanism of this process became the primary focus of essential fatty acid research in the latter half of the 1960s.

4. Omega-3 fatty acid research in the 1950s and 1960s

Although there were very few studies on omega-3 fatty acid during this period, several notable findings were made. Widmer and Holman demonstrated that animals convert linolenic acid to omega-3 fatty acids containing 5- and 6-double bonds [34], and Hammond and Lundberg identified the product containing 6-double bonds as docosahexaenoic acid (DHA) [35]. Klenk and Mohrhauer then found that large amounts of DHA were present in the brain [36], and Cotman et al. showed that DHA is enriched in synaptosomal membranes [37]. These findings had limited visibility because they were published in specialty journals with a small circulation in an era before electronic communication. Furthermore, there was no indication from these results that omega-3 fatty acids had a functional effect or were involved in any disease process. Therefore, these important findings were hardly noticed and had little overall impact.

4.1. Prostaglandin E₃ synthesis from EPA

Following their report that PGE₂ was synthesized from arachidonic acid [30], Bergström et al. found that PGE₃, the omega-3 analogue of PGE₂, was synthesized from eicosapentaenoic

acid (EPA) [38]. Furthermore, PGE₃ was detected in human seminal plasma, and like PGE₂, it was shown to have smooth muscle contractile activity [39]. The fact that the omega-3 analogue of arachidonic acid also is the substrate for a biologically active prostaglandin should have stimulated considerable interest in omega-3 fatty acids, but it was overlooked because the emphasis in the 1960s was on arachidonic acid and the physiological actions of the prostaglandins synthesized from it.

5. Emergence of interest in omega-3 fatty acids in the 1970s

Two key discoveries in the 1970s led to an awakening of interest in omega-3 fatty acids; enhancement of the retinal visual response by DHA [40,41], and linkage of the anti-thrombotic effect of EPA to protection against coronary thrombosis [42,43].

5.1. DHA and visual excitation

Studies in the early 1970s showed that phospholipids of the retinal rod outer segment contained large amounts of DHA [44-47]. Anderson and coworkers then discovered that the high DHA content of the retinal membranes enhanced the electrical response of the photoreceptor cells to illumination [40,41]. The original findings reported in 1973 are illustrated in Fig. 1 [40]. These results have been highly cited and were the stimulus for many studies of DHA function in the 1980s and 1990s [48,49]. Although this finding indicating that DHA has a functional effect in the central nervous system is crucial, it did not trigger widespread interest in omega-3 fatty acids.

5.2. Anti-atherogenic effect of EPA

The breakthrough came when Dyerberg and Bang reported that the very low incidence of coronary artery disease in the Greenland Eskimos was due to the high marine lipid content of their diet [50]. They found that the plasma of the Greenland Eskimos contained significantly lower amounts of atherogenic lipids and lipoproteins, including cholesterol, triglycerides, pre- β -lipoproteins and β -lipoproteins² than the plasma of either Eskimos living in Denmark or a corresponding group of Danes. This suggested that an environmental factor rather than genetics was responsible for the low plasma atherogenic lipid and lipoprotein levels in the Greenland Eskimos.

Dyerberg and Bang subsequently found that the plasma of the Greenland Eskimos contained more EPA and less arachidonic acid than the plasma of the Eskimos living in Denmark or corresponding Danes [51]. They also found that the marine lipid diet consumed by the Greenland Eskimos contained higher levels of EPA and DHA, but less linoleic acid and total polyunsaturated fatty acids, than the Western diet consumed in Denmark [52]. Based on these results, they concluded that the low plasma atherogenic lipid and lipoprotein concentrations were due to a special metabolic effect of the omega-3 fatty acids obtained from the marine lipid diet. Furthermore, they stated that these findings might relate to the difference in morbidity from coronary atherosclerotic disease between the Greenland Eskimos and Danes [52].

²Pre- β -lipoproteins are now designated as very low density lipoproteins (VLDL), and β -lipoproteins are now designated as low density lipoproteins (LDL).

5.3. Arachidonic acid, EPA and platelet aggregation

In 1975, Hamberg et al. reported that platelets convert the prostaglandin endoperoxide synthesized from arachidonic acid to thromboxane (TX) A₂ which causes platelet aggregation [53]. The following year, Needleman et al. found that the prostaglandin endoperoxide synthesized from EPA was similarly converted to TXA₃, but unlike TXA₂, TXA₃ did not cause platelet aggregation. However, they observed that both TXA₂ and TXA₃ produced vasoconstriction [54]. Despite the opposite effects of TXA₂ and TXA₃ on platelets, Needleman et al. did not emphasize the potential clinical significance of the anti-thrombotic effect of EPA and focused on the differences between the vasoconstrictor and platelet effects. As a result, the impact of their work was on prostaglandins and vascular biology rather than on the fatty acid field.

5.4. EPA and coronary thrombosis

In 1978 Dyerberg and Bang published a preliminary communication demonstrating that EPA inhibited ADP-induced platelet aggregation, as opposed to arachidonic acid which enhanced aggregation [42]. Their original finding demonstrating the difference between EPA and arachidonic acid is illustrated in Fig. 2. They also found that the plasma phospholipids of the Greenland Eskimos contained high levels of EPA and very little arachidonic acid, whereas the opposite occurred in the plasma phospholipids of the Danes. Based on this, Dyerberg and Bang concluded that:

... acute myocardial infarction is almost non-existent in Eskimos living in their native habitat partly because the atherogenic process is delayed and partly because C20:5 ω 3 protects against thrombocyte aggregation either by competitively inhibiting TXA₂ synthesis, or by generating prostaglandins which inhibit thrombocyte aggregation.

These EPA findings were published in the Lancet, a very high impact biomedical journal, and they attracted immediate attention.

In a follow-up study also published in the Lancet in 1978, Dyerberg and colleagues provided more details regarding the contrasting effects of EPA and arachidonic acid on platelet aggregation [43]. They also reported that EPA was converted by blood vessels to substance that inhibits platelet aggregation. Previously, Moncada and colleagues had shown that blood vessels convert arachidonic acid to prostacyclin, a prostaglandin that prevents platelet aggregation [55]. By analogy, Dyerberg and colleagues hypothesized that the anti-aggregatory substance synthesized from EPA by the blood vessels most likely was ¹⁷-prostacyclin (PGI₃), the omega-3 analogue of prostacyclin [43]. They concluded that the elevated amount of EPA in the plasma leads to the formation of an anti-thrombotic state due to the production of PGI₃ and TXA₃, and they stated that:

... enrichment of tissue lipids with E.P.A., either by dietary change or by supplementation may reduce the development of thrombosis and atherosclerosis in the Western World.

The linkage of the anti-thrombotic effect of EPA to protection against coronary thrombosis, a primary disease target in the 1970s, triggered an immediate outpouring of interest in omega-3 fatty acids in biology and medicine.

6. Essentiality of omega-3 fatty acids

In 1982, Holman and colleagues stated that [56]:

... linolenic acid is a required dietary nutrient for humans...the essentiality of linolenic acid resides in the polyunsaturated fatty acids formed from it.

This conclusion is now generally accepted, particularly for the significant role of DHA and its metabolites in the brain. The fact that DHA is necessary for proper development and optimum function of the nervous system may be the primary reason why omega-3 fatty acids are essential [57]. However, it was the discovery that EPA afforded protection against coronary thrombosis by Dyerberg and colleagues that stimulated extensive interest and research in omega-3 fatty acids in the 1980s. This has persisted, and the consensus opinion today is that omega-3 fatty acids, like their omega-6 counterparts, have important physiological functions and are essential fatty acids.

Understanding the mistakes and distractions that led to the long delay in recognizing the essentiality of omega-3 fatty acids should help us avoid similar pitfalls in dealing with new findings and thereby allow us to benefit more quickly from advances in lipid research in the years to come.

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Highlights

- The importance of omega-3 fatty acids was overlooked for more than 40 years after the discovery of essential fatty acids
- The breakthrough came in the 1970s when Dyerberg and Bang reported that the very low incidence of coronary artery disease in the Greenland Eskimos was due to the high marine lipid content of their diet and linked the protection to the anti-thrombotic effect of EPA

Fig. 1.

Original figure showing that DHA enhances the electrical response to illumination in the retina. Electroretinograms are from control rats (open symbols) and rats on fat-free diet (filled symbols). The rod outer segment phosphatidylethanolamine contained 45.3% DHA in the control rats and 19.0% DHA in the rats fed the fat-free diet. The average peak amplitude of the retinal a- and b-waves is higher in the control rats that have the higher retinal DHA content. From [R. M. Benolken, R. E. Anderson, T. G. Wheeler, Membrane fatty acids associated with the electrical response in visual excitation, *Science* 182 (1973) 1253-1254]. Reprinted with permission from AAAS.

Fig. 2. Original figure comparing the effect of EPA and arachidonic acid on platelet aggregation. Platelet-rich plasma was stimulated with 2.8 μM ADP and then incubated for 3 min with (A) 160 μM arachidonic acid, (B) saline solution, or (C) 160 μM EPA. Aggregation is enhanced by arachidonic acid but is inhibited by EPA. From [J. Dyerberg, H. O. Bang, Dietary fat and thrombosis, *Lancet*. 311 (1978) 152]. Reprinted with permission from Copyright Clearance Center's RightsLink service.