Technical News Feature

Nutritional Attributes of Fatty Acids*

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When Wilhelm Normann hydrogenated a double bond of a fatty acid, who would have dreamed that the position of double bonds would be of utmost concern in human nutrition? The essential fatty acids were unkown, and at the end of the last century, fat was not regarded as essential because it could be synthesized in the body from carbohydrate (1).

The various families of unsaturated fatty acids now are designated by the biochemist and nutritionist according to the number of carbon atoms from the last double bond to the terminal methyl group, the (n-3) and (n-6) series of polyunsaturated fatty acids have become recognized as essential for normal development and health. The question of quantities of these fatty acids that should be present in the human diet has been hotly debated.

Successes in manipulating the fatty acid composition of oilseeds have highlighted the need for better information about nutritionally desirable levels of different fatty acids. No one source of fat is ideal for humans but the mix of fats and oils in the total diet determines the nature of the dietary fat. Where one type of oil has a prominent position in the food supply, there is a need to examine its contribution to dietary fatty acids and under some circumstances to modify the situation.

For countries with a high intake of fat and a prevalence of cardiovascular disease, it has been proposed that dietary fat should be comprised of equal quantities of saturated, monounsaturated and polyunsaturated fatty acids. The last group has to provide at least two essential nutrients to represent the (n-3) and (n-6) families.

ESSENTIALITY OF (n-3) FATTY ACIDS

Decades after the recognition of the role of linoleic acid in growth and reproduction, (n-3) linolenic acid appeared not to meet the traditional criteria for essentiality. The failure to find any effect of a linolenic deficiency on growth of experimental animals posed an uncertainty about the requirement in mammals (2). Life was maintained with no more than trace amounts of linolenic acid obtained as a contaminant from casein while the level of linoleic acid was about 300 times higher than that of linolenic acid. It appeared that if dietary linolenic acid or other (n-3) fatty acids were essential to life, the minimum level would be exceedingly low.

The distribution of (n-3) fatty acids and their concentration in particular tissues and phospholipids indicates that a strict metabolic control must be in operation. Docosahexaenoic acid, the last in the (n-3) series

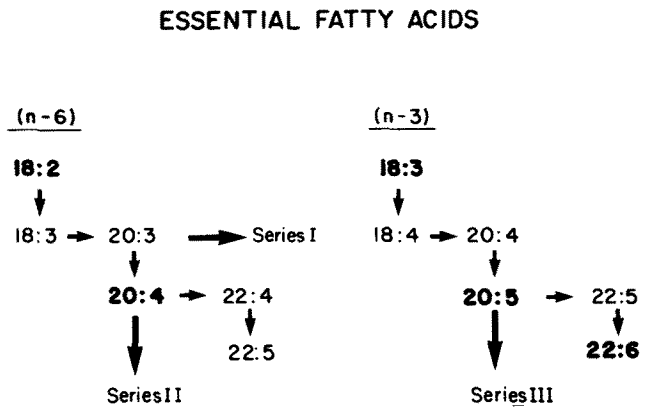

FIG. 1. The (n-6) and the (n-3) families of essential fatty acids and the steps at which eicosanoid series begin.

(Fig. 1), is also the most abundant member. It occurs most prominently in the retina, cerebral cortex, spermatozoa and testes and is suspected of having specific roles. The fine regulation of this fatty acid was suggested by its fairly constant level in the brain of different animal species (3).

The photoreceptor membranes of the retina are particularly rich in docosahexaenoic acid (4). With its six *cis* methylene-interrupted double bonds that cannot rotate, this fatty acid has a rather rigid structure. Its specific molecular roles in close proximity to rhodopsin of the retina, in cerebral grey matter or in reproductive cells have yet to be elucidated and remain a challenge for investigators.

The demonstration of the essentiality of (n-3) fatty acids in the retina was achieved in rhesus monkeys (5). When the only oil in the diet was safflower oil, containing 150 times more (n-6) than (n-3) fatty acids, and this was supplied before the female monekys conceived, during pregnancy and again in the infant formula the young monkeys, which were deficient in (n-3) fatty acids, exhibited impaired visual acuity as compared with those fed soybean oil. Because graduated amounts of the (n-3) fatty acids were not fed, the dietary requirement for normal visual acuity is yet to be determined. Nutrition experiments have tended to test extreme situations. In the deficient monkeys tested by Connor et al., the feeding of marine oil enhanced the level of (n-3) docosahexaenoic acid in the brain, particularly in the phosphatidyl ethanolamine (6). A reciprocal change in the (n-6) docosapentaenoic occurred. It is not known what functional changes might be associated with such substitution of membrane fatty acids.

In young rats, low levels of docosahexaenoic acid were produced by depriving females of (n-3) fatty acids during pregnancy and lactation (7). The dietary fats employed have been reminiscent of some primitive

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attempts to feed human infants with diets containing high levels of linoleic acid and no (n-3) fatty acids.

Results of discrimination learning tests in rats suggested that (n-3) fatty acids might be involved in cerebral functions (8). After two generations of rats were fed either soybean oil or safflower oil (no blends), the learning of correct responses was significantly better with the soybean oil that furnished (n-3) fatty acids. It is not known if visual acuity influenced this result from discrimination learning tests.

Human data on a (n-3) fatty acid deficiency are meager. A growing girl with a shortened bowel who parenterally received a lipid emulsion containing sunflower oil, which has a high level of linoleic acid but negligible linolenic acid, developed neurological symptoms and blurring of vision (9). The serum fatty acids were low in (n-3) fatty acids as compared with controls. This picture and the neurological symptoms disappeared when a soybean oil emulsion replaced the sunflower one. The report that a human linolenic acid deficiency had been produced caused skepticism because lecithin, a vehicle for choline known to affect neural transmission, was a constituent of the emulsion and the patient was being treated with long-term parenteral nutrition that can cause other metabolic disturbances (10). All of these caveats do not negate the apparent (n-3) deprivation that developed and that was corrected.

DIETARY SOURCES AND REQUIREMENTS OF (n-3) FATTY ACIDS

The shortest member of the (n-3) series, α-linolenic acid, is a constituent of soybean oil and also is found in rapeseed or canola oil. The chloroplasts in green vegetables supply (n-3) linolenic acid as a major fatty acid in low-fat foods. Examples of this in vegetables from Ottawa, Canada are shown in Table 1. Even cereal-based foods in which linoleic acid predominates provide appreciable amounts of (n-3) linolenic acid. (Table 2). The long-chain (n-3) fatty acids are provided by cold-water fish, which are rich sources of (n-3) eicosapentaenoic and docosahexaenoic acids, fatty acids that also are found in neural membranes. That humans can synthesize eicosapentaenoic and docosahexaenoic acids from dietary (n-3) linolenic acid is established since strict vegetarians do not consume the long-chain derivatives.

TABLE 1

(n-3) Fatty Acids in Vegetables

	m/100g
Celery	5
Iceberg lettuce	6
Spinach	10
Cabbage	17
Chicory	29
Romaine lettuce	55
Shallots	70
Parsley	84
Brussels sprouts	150
Broccoli	162

TABLE 2

Bread Fatty Acids (FA)

Bread	Total FA	(n-6) 18:2	(n-3) 18:3
	mg/g	%	%
Rye	14.5	21.4	1.4
Whole wheat	35.8	19.3	1.3
Bran	17.2	29.5	2.7
Pumpernickel	11.8	50.3	5.2
White	21.9	22.8	1.3

The requirement for (n-3) fatty acids may change during a lifespan. For a six-year-old, it was found that 0.54% energy was sufficient (9) but half of that intake met the need of immobilized elderly (11). The amount of (n-3) fatty acids ingested must be considered along with the amount of (n-6) fatty acids because the two families affect the metabolism of each other.

The ratio of the (n-6) to (n-3) fatty acid in the human fetus appeared to be 8:1 (12). In human milk, this ratio was found to be approximately 5:1 (13). It is recognized that (n-3) linolenic acid has a competitive advantage over linoleic acid for desaturation (14,15). The selectivity of acyltransferase ensures that arachidonic acid, a preferred substrate, is incorporated into membrane lipids (16).

SUBSTITUTION OF (n-3) FOR (n-6) FATTY ACIDS

The extent to which eicosapentaenoic acid from fish oil can substitute for the (n-6) arachidonic acid in biomembranes is of considerable interest. The many studies on platelets confirm that the long chain (n-3) fatty acids from the diet increase in the membranes (17–19). They can be incorporated into all tissues and cells so far investigated. Red blood cells that are synthesized in bone marrow can be used as an index of their prolonged intake. When monkeys were fed 30% of their energy as fat with an equal distribution among saturated, monounsaturated and polyunsaturated fatty acids, the erythrocyte fatty acids were followed for 15 weeks (personal communication). The ratio of (n-6) to (n-3) fatty acids, including all derivatives, increased with a high linoleic, low (n-3) diet but with the diet containing linoleic and linolenic acids the ratio remained at a relatively constant level at about 2.5 and appeared metabolically regulated. In contrast, the longer chain (n-3) fatty acids from the fish oil, which did not have to be desaturated or elongated, increased progressively in the erythrocytes. The enhanced incorporation of the marine-type compared to the plant-type (n-3) fatty acids has been observed in human platelets (19,20) and

rat tissues, notably the heart (7-21). A supply of preformed fatty acid substrates for acyltransfer reactions permits an enhanced concentration of them in membrane lipids. This may be advantageous in some situations but does circumvent some metabolic control steps.

EICOSANOIDS

Large quantities of (n-6) and (n-3) fatty acids are incorporated into the 2-position of glycerol phospholipid but only a small amount of these polyunsaturated fatty acids may be used in the production of the potent eicosanoids. A thrombotic tendency was thought to be regulated by the balance between the proaggregatory thromboxane A_2 in the platelets and the antiaggregatory prostacyclin in the vessel endothelium (22,23). Thromboxane A_3 from eicosapentaenoic acid was found to be lacking in the proaggregatory properties that characterized thromboxane A_2 (24).

The low incidence of ischemic heart disease in the Greenland Eskimos (25) was attributed to the consumption of (n-3) fatty acids and the inhibition of eicosanoid production from arachidonic acid (26,27). Eicosapentaenoic acid was proposed as an antithrombotic agent. Among the hypotheses proposed for its action were competitive inhibition for cyclo-oxygenase (24,28) and enhanced synthesis of both thromboxane A_3 and prostacyclin I_3. In the in vivo situation, eicosapentaenoic acid was not incorporated into phosphatidylinositol but into phosphatidylcholine and phosphatidylethanolamine (29). As phosphatidylinositol, from which precursors for eicosanoid synthesis arise (30) appeared not to play a role, the metabolic pathway became questionable. Also there was a failure to find parallel effects between the uptake of eicosapentaenoic acid into platelet membranes and a diminished production of thromboxane B_2 (18). The mechanism by which dietary eicosapentaenoic acid alters haemostasis still is not clear but many findings have been well confirmed.

Arachidonic acid and, more particularly, eicosapentaenoic acid also are substrates for lipoxygenase. From studies on neutrophils, it was postulated that the (n-3) fatty acids of marine origin may have anti-inflammatory effects by inhibiting the 5-lipoxygenase pathway by which arachidonic acid is converted to 5-hydroperoxyeicosatetraenoic acid (5 HPETE) and subsequently to leukotriene A_4 and its more stable derivatives (31).

INFLUENCES OF MARINE FATTY ACIDS

A fall in blood pressure has accompanied the ingestion of marine oil (20,32). In Japan, a fishing population consuming more eicosapentaenoic acid than a farming population exhibited a lower blood viscosity (33). The addition of 10-20 ml per day of cod liver oil to a normal western diet increased bleeding time, decreased production of TXB_2, platelet aggregation and blood pressure (34). PGI_3 was detected within one day after the ingestion of marine oil (35). This also cast doubt on the original concept that the eicosanoid precursors must arise from the membrane phospholipids.

When the marine oils or concentrates of them have been administered to humans, the most consistent result has been lowering of the serum triacylglycerol levels (36-38). Some investigators also have found lowering of serum cholesterol. The effects obtained cannot be related easily to dose and duration because protocols have differed greatly. The greatest changes appear to have occurred in hyperlipidemic patients (39).

In a 20-year mortality study in Holland, the consumption of even one or two fish dishes per week has been claimed to prevent coronary heart disease (40). It appears that the level of intake of (n-3) fatty acids need not be above that easily obtained from food.

The mechanism for the action of (n-3) fatty acids in reducing platelet aggregation requires further study. It even has been suggested that levels of arachidonic acid that give rise to thromboxane A_2 may be determined genetically (41). For example, Indians living on an island off the West Coast of British Columbia who consume a traditional diet rich in eicosapentaenoic acid similar to the Eskimos maintain low levels of arachidonic acid in plasma even when they switched to non-marine foods. Eskimos and Indians may be more adapted to high fish diets than Hugh Sinclair (42), whose bleeding time increased abnormally on a diet of only marine foods.

Another manifestation of possible effects from a high intake of marine fat has been investigated in the Faroe Islands where birthweights are among the highest in the world and gestation periods are prolonged (43). It was postulated that there is an interference with the normal production of prostaglandins required to induce parturition. However, the diet on the Faroe Islands did not provide relief from cardiovascular disease, which was more prevalent than in Denmark (44).

MEMBRANE STRUCTURE

The major noneicosanoid function of essential fatty acids relates to their being integral compounds of membrane bilayers, in which they control the effectiveness of membranes through the conformational changes in the lipid surrounding intrinsic enzymes or transport proteins (45). In this regard, there appear to be distinctive functions in different membranes for the (n-3) and the (n-6) fatty acids. It has been suggested that mobility of insulin receptors on membranes is enhanced by many double bonds (46) but the mechanism by which blood glucose levels are elevated by the administration of fish oil is not known. This phenomenon appeared as a postprandial increase of plasma glucose in pigs fed mackerel oil (47) and in humans treated with a fish oil concentrate (48). If a change in the reactive sites for insulin occurs through ingestion of long chain (n-3) fatty acids, this apparent noneicosanoid influence may precipitate or worsen diabetes.

OTHER PRECAUTIONS

Another aspect of the ingestion of the (n-3) fatty acids is that they readily oxidize and when heated also cyclize and form geometric isomers (49). More information therefore is required on the composition of fatty acids in foods as eaten, particularly those rich in (n-3) fatty acids.

Elevated levels of docosahexaenoic acid in cardiac tissue may not be advantageous. Studies by Gudbjarnason and Hallgrisson (50) indicated that an elevated level of this acid in the heart might be an indication of cardiac lesions. With diets containing different amounts of (n-6) and (n-3) fatty acids, the level of docosahexaenoic acid in the tissue of experimental animals did not correlate with that in the diet, but did correlate the frequency of cardiac lesions (51).

Yellow fat disease developed in growing pigs receiving about 100 g of mackerel oil per day for four weeks, despite a supplement of 0.1% α-tocopheryl acetate in the oil (52). The production of yellow fat disease with the consumption of the highly unsaturated fatty acids in mackerel oil has been attributed to the number of double bonds and not to their position in the fatty acid molecule (53). A disctinction could not be made on the basis of (n-3) or (n-6) fatty acids but only on their degree of unsaturation. The increased requirements for tocopherol or other anti-oxidants in the presence of various (n-3) fatty acids have yet to be determined quantitatively. Caution has been urged with respect to the widespread use of diets high in (n-3) fatty acids (54).

It sometimes is not realized that fish oils contain cholesterol, a factor that usually has not been taken into account in either the design or the interpretation of experiments. The oils high in (n-6) fatty acids from vegetable oils have been hypocholesterolemic whereas the (n-3) fatty acids from marine oils have been consistently hypotriglyceridemic.

RANGE OF INTAKE

There is a need to determine the safe range of intake for the (n-3) fatty acids that is between inadequate intakes producing deficiency signs in membrane composition and an excessive intake that produces deleterious effects. If a concentrate with eicosapentaenoic acid is used as a drug to lower blood triglyceride levels, the patient must be monitored to ensure that blood glucose levels are not dangerously high. For normal nutrition, the challenge is to provide an appropriate proportion of (n-3) to (n-6) fatty acids and those in a suitable mix with other fatty acids.

A prime nutritional attribute of fatty acids is the energy value of the hydrocarbon chain. No other food component makes such a contribution; a situation that both comforts us in face of energy deficiency and alarms us in face of energy excess. What are the upper limits of safe intake of total fatty acids? A high level of saturates in maternal milk provides energy for the infant but in the diet of a mature adult increases blood cholesterol levels and the risk of cardiovascular disease. The level of various fatty acids should be such as to provide long-term health benefits.

The nutritional attributes of fatty acids can be expected to increase in importance as our understanding of them grows.

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