PUTTING DIETARY LIPIDS INTO PERSPECTIVE: A REVIEW

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SUMMARY

Much emphasis has been placed on dietary saturated fatty acids and cholesterol in recent years because of their implications in coronary heart disease and atherosclerosis. However, the polyunsaturated fatty acids may play an important role in coronary heart disease, as well as several other maladies, through their metabolism to a broad range of bioactive eicosanoids. This review attempts to shed some light on the ill effects of metabolites of polyunsaturated fatty acids with a notion that these essential nutrients may also be toxic when consumed in excess.

INTRODUCTION

Dietary lipids (fats and oils) have received much press in recent years in relation to animal and human health, and rightly so. As the role of lipids in health begins to unfold on the molecular physiological level, it becomes apparent that dietary lipids are important not only for energy and cellular constituents, but can also wreak havoc in the body. The purpose of this review is to shed some light on the relative importance of dietary modifications with regard to lowering serum cholesterol, which may decrease the risk to heart disease, while potentially increasing risk to other incapacitating diseases that may be influenced by diet, and especially by dietary polyunsaturated fatty acids (PUFAs).

Epidemiological studies have shown a correlation between high serum cholesterol and increased risk to atherosclerosis, heart disease and stroke. (Tyroler, 1984; Filip *et al., 1998*). Much emphasis is placed on the relationship of dietary saturated fats to serum cholesterol. Early studies showed that increasing the ratio of saturated fatty acids to PUFAs in dietary lipids tended to raise serum cholesterol levels (Keys, 1984).

Pyorala, 1987) has given an extensive review of this literature. The desire to make such correlations is based on the concept that animals and people with high serum cholesterol are at high risk to coronary heart disease than those with low serum cholesterol (Feinleib, 1984; Levy, 1984). However, many reports completely ignore the role genetic factors play in determining an individual's predisposition to high serum cholesterol and coronary heart disease. Numerous genetic

abnormalities associated with lipoprotein transport and increased susceptibility to coronary heart disease have been recognised (Breslow, 1991). Modifying the diet to lower serum cholesterol may provide substantial benefit to people and animals genetically prone to high risk for coronary heart disease, but such dietary modifications may not be necessary, or even prudent, for the majority of the population, especially if it means increasing the ratio of polyunsaturated to saturated fatty acids.

Furthermore, combining the correlation between dietary lipids and serum cholesterol with the correlation between serum cholesterol and coronary heart disease risk may not be necessarily valid in view of the many other factors involved in coronary heart disease. Reiser (1973) evaluated the literature regarding fatty acid composition of dietary lipids and serum cholesterol levels, pointing out many of the experimental flaws and misinterpretations made in the early studies. Elson (1992) has given an assessment of the literature regarding saturated vs. PUFAs in dietary lipids and their effects on health, stressing the unwarranted biases against tropical (palm and coconut) oils in terms of their effects on serum cholesterol.

A major contributing factor to the emphasis placed on monitoring serum cholesterol levels is the relative ease with which blood samples can be acquired from the population of people and animals at large and analysed for cholesterol, among other analytes.

BIOCHEMICAL OVERVIEW OF LIPIDS

From a nutritional viewpoint, fats and oils account for the bulk of lipids in the diet and account for a large percentage of the caloric intake. It was recognised more than half a century ago that some lipids are essential in the diet (Burr and Burr, 1929). Over the following decade or more it became apparent that linoleic acid was essential in the diet, but could be replaced by arachidonic acid, and to some extent, linolenic acid in order to alleviate the symptoms of deficiency (Evans *et al,* 1934; Quackenbush, *et al,* 1942). With our current understanding of the metabolism of these dietary PUFAs, it becomes apparent why these fatty acids are essential components of the diet for a healthy individual. The conversion of arachidonic acid, and other 20 carbon PUFAs to bioactive eicosanoids accounts for most of the observed deficiency symptoms. However, other physiological roles for these PUFAs cannot be completely ruled out.

It must be kept in mind that it may be possible to obtain excessive or toxic amounts of these nutrients, just as it is possible to consume toxic amounts of many minerals and vitamins, especially the lipid soluble vitamins (Olson, 1997). The toxicity of essential fatty acids is a subject that has not been addressed as such, since their metabolism is extremely complex and it is difficult to assign a disease state to excessive amounts of eicosanoids alone, since they normally function as comediators

with many other bioactive factors (hormones, parahormones, and other cellular stimuli).

The metabolic fate of dietary fats is quite varied. They may be stored as triacylglycerols (TAGs) in adipose tissue, metabolised for energy, utilised for synthesis of structural phospholipids, esterified to alcohols and sterols for special cellular functions or metabolised to other cellular products. When TAGs are stored, the adipose cells will incorporate cholesterol into the storage fat to maintain proper fluidity of these storage fats. The presence of PUFAs in the storage fats will impart fluidity to the TAGs and decrease the need for cholesterol. The same is true in phospholipid membranes. As the amount of PUFAs in membrane phospholipids increases, the amount of cholesterol decreases. These interactions account for the cholesterol lowering effect of PUFAs in the diet.

PUFAs may play other important physiological roles in phospholipid membranes through specific interactions with other membrane components; especially membrane bound enzymes and transport proteins (Lee *et al,* 1997). These effects may arise from the fluidity imparted to the membrane by the PUFAs or from structural considerations, such as chain length, that can alter activities of various proteins.

Most mammals synthesise primarily saturated fatty acids from carbohydrate if there is little fat in the diet. Warm-blooded mammals have evolved to incorporate cholesterol into the saturated fats to make them more fluid. The fluidity is important to cellular physiology, allowing communication with the environment through receptors on the membrane surface, and for the membrane remodelling that takes place when nutrients are brought into the cell or when substances are secreted from the cell. The chain elongation and desaturation of fatty acids is an important part of the regulation of further metabolism to bioactive eicosanoids. Through the combined action of the enzymes for elongation and desaturation, most land mammals can metabolise linoleic acid (18:2, w6) to arachidonic acid (20:4, w6). There seems to be a limit to the desaturation of fatty acids, in that the dehydrogenation reactions do not occur beyond the tenth carbon of the fatty acid chain (counting from the carboxylate group), and there is probably little desaturation of saturated fatty acids produced from the normal fatty acid synthesis pathway in most cells. Bonanome and Grundy, (1994) suggested that there is desaturation of dietary stearic acid to oleic acid, although the anatomic site of that reaction was not determined, nor was it determined that the plasma oleic acid was derived from dietary stearic acid.

Animals will tend to incorporate the fatty acids available from all sources, diet as well as new synthesis into the triglycerides for storage and into phospholipids of membranes. If the fatty acids available are predominantly saturated, cholesterol will need to be incorporated along with these fatty acids in order to maintain the proper fluidity. If the available fatty acids are predominantly the more fluid, unsaturated type, there will be much less cholesterol incorporated and the overall cholesterol levels in the body will tend to be much lower. When the stored fats are mobilised at a later time, the cholesterol will be mobilised along with them, accounting for the serum cholesterol levels observed on very low fat diets. This is a rather simplistic synopsis of fatty acid cholesterol interactions and the reader should consult the review by Elson, (1992) for discussions of the subtleties in these relationships.

Polyunsaturated Fatty Acids And Eicosanoids

Dietary PUFAs are considered essential fatty acids because the mammalian body cannot synthesise them from nonlipid nutrients or saturated fatty acid precursors and they are metabolised to extremely potent bioactive compounds - prostaglandins (PGs), thromboxanes (Txs) and leukotrienes (LTs). The major fatty acid precursors for these bioactive compounds contain 20 carbon atoms and 3,4 or 5 double bonds. Three major fatty acid precursors of the bioactive eicosanoids are 8,11,14-eicosatrienoic acid (dihomo-y-linolenic acid, DHLA: a w6 fatty acid), 5,8,11,14-eicosatetraenoic acid (arachidonic acid; also w6) and 5,8,11,14,17-eicosapentaenoic acid (EPA; a w3 fatty acid). There is also 5,8,11-eicosatrienoic acid (w9) formed from dietary oleic acid (Weiner and Sprecher, 1994), but the w9 fatty acids are not converted to bioactive eicosanoids (Wei *et al*, 1995). DHLA is converted to PGs and TXs of the 1 series (e.g., PGE_1 and TXA_1) and leukotrienes of the 3 series (e.g., LTB_3 or TXA_3). Arachidonic acid is converted to PGs and TXs of the 2 series (e.g., PGE_2 or TXA_2) and LTs of the 4 series (e.g., PGE_3 or TXA_3) and LTs of the 5 series (e.g., LTB_5). The numeric subscripts in each series represents the number of carbon-carbon double bonds in the compound and the letter indicates the chemical structure with respect to position of various substituent groups. In addition to the PGs, TXs and LTs, there are other bioactive substances produced from arachidonic acid, such as 5-HETE (5-hydroperoxy-6,8,11,14-eicosatetraenoic acid) and 15-HPETE (15-hydroperoxy-5, 8,11,13-eicosatetraenoic acid). The properties of the analogous substances derived from EPA have not been as thoroughly studied yet. These 20 carbon fatty acids and their 20 carbon bioactive metabolites are collectively known as eicosanoids. The bioactive products from these 3 different precursors are numerous and can have very different physiological activities in different tissues and species.

The physiological roles of eicosanoids are just beginning to unfold, and their involvement in a

wide variety of disease are only beginning to be understood, primarily because these extremely potent substances can have very different actions in most tissues, being destroyed nearly as fast as they are formed. Because of this fleeting existence, it is little wonder that our current understanding of this class of compounds in quite meagre, but growing rapidly due to technological advances in measurement of these substances and their consequent physiological responses. No attempt will be made to exhaustively review the literature regarding eicosanaoids and health, but a few general aspects will be discussed here, simply to shed some light on the complexity of the PUFAs picture and attempt to place these lipids in their proper perspective in a discussion of dietary fats and health.

Eicosanoids And Thrombosis

Thrombosis, or the formation of a blood clot, is a very complex process involving numerous clotting factors. One of the early events in the clotting process that is pertinent to lipid metabolism is the formation of thromboxane A_2 (TXA_2). TXA_2 is formed from arachidonic acid released from the phospholipid membrane of blood platelets upon stimulation by specific agents. When a blood vessel is punctured and blood begins seeping from the vessel, the platelets come in contact with collagen in the subendothelium of the vessel wall and become stimulated to release a variety of substances that promote platelet aggregation, vasoconstriction and release of clotting factors. TXA_2 is one of the most powerful substances known to promote platelet aggregation and vasoconstriction (Bang and Dyerberg, 1995). Its role in other physiological processes is beginning to be understood (Awara *et al.*, 1996).

A common and sometimes effective recommendation for patients after their first heart attack and patients at high risk for coronary heart disease is to take a single aspirin a day. This low dose of aspirin is sufficient to inhibit TXA_2 synthesis through irreversible inhibition of platelet cyclooxygenase; one of the best-understood actions of aspirin (Hans *et al.*, 1989, Dyken *et al.*, 1992, Krumholz *et al.*, 1995). The only way cyclooxygenase activity can be regained in platelets is by having the platelet forming cells of bone marrow synthesise this enzyme along with new platelets. Platelets have a normal life span of only a few days and are being formed continually in the bone marrow - they have no nucleus and cannot synthesise new protein after they mature.

Since aspirin comes in contact with blood components first when it is absorbed from the digestive tract, the cyclooxygenase in the blood components is the first to be inhibited; the low dose of aspirin is soon exhausted so it interferes with

prostaglandin metabolism very little in other parts of the body when taken in low doses. It is known that aspirin slows the blood clotting process (Hebert *et al.*, 1992, Rogers *et al.*, 1994).

Omega-3 Fatty Acids

Epidemiological studies from the 1940's showed that Eskimos have a very low incidence of heart disease, although it is seldom mentioned that their average life expectancy at that time was less than 30 years (Sinclair, 1953). However, most groups that consume large quantities of fish have a low incidence of heart disease. The fish oils contain relatively large amounts of w3 PUFAs, compared to w6 PUFAs that are commonly found in vegetable oils. Terrestrial animals and humans that consume primarily vegetable oils will tend to have an abundance of w6 PUFAs relative to other PUFAs. By consuming large quantities of fish and relatively small quantities of vegetable oils, the Eskimos incorporate a predominance of EPA, relative to arachidonic acid, into their phospholipid membranes, which, when released upon platelet stimulation, produces TXA_3. TXA_3 differs in chemical structure from TXA_2 only by having an additional double bond. However, this small chemical difference has a profound effect on the physiological action, resulting in weak platelet aggregation and weak vasoconstriction from TXA_3 (Dyerberg *et al.*, 1975).

It has been established that people and animals that eat relatively large quantities of marine lipids have much longer blood clotting time than those taking relatively little fish and large amounts of vegetable oils. This is due to increase formation of TAX_3 relative to TXA_2. For example, Eskimos living in Denmark have been found to have levels of linoleic acid (w6) in their blood that is comparable to that of the European population, yet their arachidonic acid levels remain very low (Dyerberg *et al.*, 1975). It has been suggested that Eskimos have a deficiency in one or more of the enzymes responsible for converting linoleic acid to arachidonic acid (Gibson and Sinclair, 1981). Bates *et al.*, (1992) studied a remote population of Native North Americans on the west coast of Vancouver Island and found they had low arachidonic acid levels in blood when fed a European diet that was relatively rich in linoleic acid to arachidonic acid, indicating they too may be deficient in one or more enzymes responsible for converting linoleic to arachidonic acid (Gibson and Sinclair, 1981). Perhaps further studies with other ethnic groups experiencing low incidence of cardiovascular disease will show similar lack of enzyme activities for arachidonic acid or TXA_2 synthesis.

Numerous studies have shown that w3 fish oil supplements in the diet of people and rats with high blood cholesterol resulted in a lowering of blood cholesterol and consequently, a decreased risk to cardiovascular disease (for reviews see Weaver and Holob, 1988; Herold and Kinsella, 1996). The action of the fish oils in decreasing risk to cardiovascular disease seems to be double

pronged. First, the highly polyunsaturated nature of the fish oils causes a decrease in blood cholesterol because of the fluidity it imparts to lipids. Second, the EPA in the fish oil results in increase production of TXA_3 relative to TXA_2 (Needleman *et al.,* 1979). Therefore, people and animals eating more fish oil and less vegetable oil should experience a reduction in thrombotic events. This translates into a longer bleeding time, as a result of a cut or scratch, but may bode well for reducing undesirable thrombosis in coronary or other arteries.

Fish oils may affect the levels of other thrombotic factors as well (Weaver and Holob, 1988). It is interesting to note that docosahexaenoic acid (another major w3 fatty acid found in marine lipids) may be converted to EPA in the body (Fischer *et al.,* 1987); therefore, these two marine oil fatty acids can be considered to have similar actions. Dietary linolenic acid (18:3,w3) and linoleic acid (18:2,w6) compete with one another for chain elongation and desaturation, so dietary fish oils would suppress arachidonic acid formation in the body and its subsequent metabolism to bioactive eicosanoids (Holman, 1997).

If dietary vegetable oils are diminished in the diet when fish oils are added, the relative amounts of arachidonic acid should consequently decrease. Whereas, if vegetable oils are maintained at previous levels in the diet, chances are arachidonic acid will be maintained or nearly maintained in the membrane phospholipids and be available for TXA_2 production, as well as production of other arachidonic acid metabolites (Corey et al., 1993). This would indicate that the optimum effect from fish oil supplements for the purpose of lowering cardiovascular disease risk, as well as for other health benefits, should occur when dietary vegetable oils are withheld or restricted. This design seems to be overlooked in many clinical trials investigating the effects of marine oil supplements on health. Attempting to restrict polyunsaturated vegetable oil during marine oil supplementation may seem to be unnecessary if one only considers the first effect of fish oil mentioned above, i.e., the effect on lipid fluidity. However, the eicosanoid effect should not be neglected, especially in view of the current understanding of the differences in potencies and physiological actions of eicosanoids derived from w3 vs. w6 fatty acids.

Eicosanoids, Cancer and Immunity

The effects of alteration of the profile of dietary PUFAs are only beginning to be explored. The health effects of EPA have been reviewed by Weaver and Holob (1988) and the nutritional and health aspects of tropical oils have been reviewed by Elson (1992). A few examples of studies

demonstrating differences in the actions of dietary PUFAs from various sources are presented here to illustrate the importance of the eiosanoid connection in diseases other than heart disease. Dietary vegetable oils (rich in w6 PUFAs) have been found to promote chemically induced mammary tumours in rats, relative to diets containing predominantly saturated fatty acids or fish oil (Braden and Carroll, 1994). Dietary fish oils have been found to suppress tumor growth in *vitro,* as well, relative to dietary vegetable oils (Karmali, 1987). Carroll (1987) has summarised the effects of dietary fats on carcinogenesis in animal studies, with an emphasis on the role of PUFAs. McGiff (1987) has discussed the importance of bioactive eicosanoids with regard to tumour promotion.

One reassuring aspect of the relationship between PUFAs and tumour promotion is that, in general, the effect is dose dependent, i.e., the higher the level of fats, and especially polyunsaturated fats in the diet, the greater the tumour promotion one expects to see. It should be pointed out that some studies have found lower incidence of tumours with higher levels of PUFAs in the diets (Lawrence *et al.,* 1984; Nauss *et al.,* 1983), indicating there are many factors other than levels of dietary PUFAs that must be taken into consideration.

It is generally agreed that carcinogenesis is a multistep process involving initiation by mutagens, which alter the cellular DNA, followed by expression of the mutated genes to promote tumour growth (Sugimura, 1992). PUFAs may increase the incidence of cancer by either of these mechanisms. PUFAs are especially susceptible to peroxidation by free radical mechanisms, generating reactive species that may react with DNA (mutagenesis). PUFAs may also enhance the diacylglycerol-dependent activation of protein kinase C, an intracellular signalling /activating mechanism known to be activated by phorbol esters and other potent tumour promoting agents (Nishikuza, 1992).

These recent advances of our understanding of the effects of PUFAs on the molecular level, with regard to carcinogenesis, suggests that the PUFAs may be directly responsible for increasing carcinogenesis risk, without being metabolised to the bioactive eicosanoids. However, the role of eicosanoids in the immune response must be kept in mind, with regard to the body's ability to check the growth of tumours (Janniger and Racis, 1996). Clearly the role of lipids in carcinogenesis is complex, but having an abundance of lipids in the body, through excessive consumption of these nutrients, appears to be unhealthy and should be avoided.

Eicosanoids, Hypersensitivity and Inflammation

The eicosanoids derived from arachidonic acid are potent mediators of allergic reactions and inflammation (Samuelsson, 1983; Bisgaard, 1984; Higghs, 1986;

Bray, 1997). Dietary marine oil supplements have been found to suppress LTB_4 production by monocytes and neutrophils in humans and altered neutrophils function, suggesting an anti-inflammatory effect of marine oils (Lee *et al.*, 1997). Terano *et al.*, (1994) found that dietary EPA supplementation could suppress carrageenin induced inflammation in rats, compared to animals on a standard diet without EPA supplement. Another study showed that rats fed a beef fat diet had less inflammation from type II collagen induced arthritis, relative to animals fed a fish oil diet (Prickett, *et al*, 1984). Although the latter results would seem to be in conflict with the studies showing marine oils to be anti-inflammatory, they are easily explained by the fact that the beef fat diet had little PUFAs available for synthesis of bioactive ecosanoids to promote the immune response. Another study showed that rats fed a beef fat diet had little inflammation from adjuvant-induced arthritis, whereas dietary fish oil was only mildly inflammatory and vegetable oils, rich in linoleic acid, were strongly proinflammatory (Lawrence, 1990).

The PUFAs from vegetable oils may have adverse effects on the immune system, especially with respect to hypersensitivity reactions in allergic response (Bisgaard, 1984), inflammatory skin diseases (Burton, 1989), and psoriasis (Zibon *et al.*, 1986), and may be important in modulation of autoimmune responses in diseases such as rheumatoid arthritis (Belch *et al.*, 1988) and systemic lupus erythematosus (Suryaprabha, *et al.*, 1991). Clearly more research needs to be done to determine the role of dietary fats in immune and allergic responses and in inflammation, but the results to date suggest that high levels of vegetable oils, providing precursors for arachidonic acid and subsequent eicosanoids, may augment many hypersensitivity, inflammatory and autoimmune responses.

Eicosanoids In The Nervous System

Eicosanoids are important mediators of neurotransmission (Wolfe, 1982; Axelrod, *et al.*, 1997). Prostaglandins of the D and E type have been shown to suppress convulsive seizures in laboratory animals (Rosenkranz and Killam, 1979); Forstermann *et al.*, 1992). Dietary PUFAs were found to suppress chemically induced seizures in mice. Corn oil (rich in w6 fatty acids) was more potent than fish oil in suppressing seizures, compared to mice fed a lard diet (Lawrence, 1986). These results suggest that arachidonic acid and/or its metabolites appear to be important in suppressing excitotoxic events in the nervous system. Considering the known effects of eicosanoids on neurotransmission, there is great potential for these substances to elicit a wide variety of physiological, as well as behavioural, effects in humans and animals. The effects or

dietary manipulations on many neurological diseases (e.g., epilepsy) remain to be explored.

CONCLUSIONS

Because this article has attempted to cover many health related aspects of dietary lipids, it could not be very thorough in any of these areas. The main purpose of this presentation is to bring several areas of lipid metabolism into a single picture to give a broader perspective of the problems we can face in trying to make intelligent dietary recommendations. Heart disease is one of the leading killers in many industrialised nations and is an emerging disease in developing nations. Coronary heart disease seems to hold a high priority status for broad-based dietary recommendations made to the general public. Entrepreneurs have taken advantage of this statistic in marketing products - whether their claims are valid or not.

Many of the dietary recommendations for cancer my also be good recommendations for heart disease and vice versa, such as getting sufficient fibre in the diet and decreasing the amount of fat consumed overall. However, when it comes to the types of fat in the diet, it seems that polyunsaturated fats can decrease blood cholesterol and lower risk to heart disease, but may increase one's risk to cancer and have numerous untold effects on many other aspects of an individual's and animal's well being.

The concern about saturated fats from coconut and palm oil seems to be greatly overemphasised. Careless use of rancid polyunsaturated oils by people and feeding of animals may be cause for additional concern.

Should we be looking for substitutes for commercially used lipids that constitute a large portion of our diet and that of animal feeds? if so, what do we look for in a substitute? Hydrogenated vegetable oils contain trans-fatty acids, which may or may not have adverse health effects (Kritchevsky, 1982). Holman and Mohfouz (1981) have shown that trans-unsaturated fatty acids can be metabolised to cis-polyunsaturated fatty acids. Glucose polymer, and similar noncaloric fat substitutes, still haven't been studied thoroughly enough to assure they are benign with prolonged consumption.

We need to keep our wits about our animals and us and approach the problem of dietary fats with intelligence and reason. There may not be a single diet or a single type of dietary fat that will solve all of health problems. Eliminating fats from the diet completely is not only unfeasible, but probably is not going to solve health problems either. Basically the dietary recommendations are quite reasonable. Keep the dietary intake of all fats low, below 30 percent of calories in the diet, and preferably as low as 20 percent. Provide sufficient amounts of essential fatty acids, but avoid excessive amounts of the latter, in view of their potential for production of adverse,

as well as beneficial, eicosanoids. Monounsaturated fats may be most preferable in view of their innocuous nature with regard to both plasma cholesterol levels and lack of bioactive eicosanoid production. Fish oils seem to be beneficial for some health conditions, but they may not be palatable as a substitute for other dietary lipids and, although eating more fish may be a good recommendation from the standpoint of dietary lipids, fish are known to harbour many toxic pollutants that have ended up in our waters. The best advice may be that handed down to us through the age, which is moderation in all things.

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