Review

Interaction of lipids with immune function I: Biochemical effects of dietary lipids on plasma membranes

Michael D. Peck

University of Miami School of Medicine, Miami, FL USA

Lipids have especially potent and complex effects on the body's response to infection or stress. These effects are related to the diverse functions that lipids perform, especially as structural components and metabolic intermediates. In this article, the basic biochemical processes by which lipids modulate pathways occurring in plasma membranes will be reviewed. These processes include modulation of the biophysical properties of the phospholipid bilayer, production of lipid peroxides, metabolism of 20-carbon fatty acids to eicosanoid end-products, and the direct effects of fatty acids on signal transduction. In a subsequent article, the animal and human experimental data on the interactions of lipids with the immune system will be reviewed. (J. Nutr. Biochem. 5:466–478, 1994.)

Keywords: lipids; immunity; nutrition; membranes; eicosanoids; lipid peroxides; membrane fluidity

Lipid Biochemistry

In general, the fatty acid composition of adipose tissue and cell membranes reflects the dietary composition of lipids, and there are ample data to confirm that dietary lipids are incorporated into tissue lipids.[1–8] For example, Mori and associates found that daily supplementation of MaxEPA capsules (2.67 g eicosapentaenoic acid [EPA]/day and 1.72 g docosahexaenoic acid [DHA]/day) for 3 weeks decreases arachidonic acid (AA) and increases EPA and DHA in platelet phospholipids from healthy males.[3]

Of particular interest to discussion of the immune system is that dietary lipids alter phospholipid profiles of leukocytes such as lymphocytes,[4] macrophages,[5] and polymorphonuclear cells (PMNs).[6–9] For example, Cleland and associates found that membrane phospholipid fatty acid profiles of both induced peritoneal PMNs and resting splenic mononuclear cells reflect dietary lipid intake (olive, sunflower, linseed, or fish oils).[6] Although the length of time for maximal fatty acid incorporation into lymphocytes is 4 to 6 weeks,[4] significant incorporation of ω-3 polyunsaturated fatty acids (PUFA) has been found to occur as early as after 2 weeks of feeding.[5]

The differences in structure of lipids is critical, as they determine their functional characteristics.[10] Fatty acids are alkyl chains that terminate in carboxyl groups, and are classified primarily on the basis of chain length and degree of unsaturation (*Table 1*).[1] In addition, PUFA are classified by the position of the first double bond. Four classes of unsaturated fatty acids are recognized, the parent molecules being palmitoleic acid (16:1 ω-7), oleic acid (18:1 ω-9), linoleic acid (18:2 ω-6; LA), and α-linolenic acid (18:3 ω-3; ALA) (*Figure 1*).[11]* Each class is made up of a family of fatty acids that can be synthesized from the parent fatty acids, but a fatty acid of one class cannot be converted biologically to another class. For example, although oleic acid (18:1 ω-9) can be elongated and desaturated to eicosatrienoic acid (20:3 ω-9), it cannot be converted to AA (20:4 ω-6).

Very few ω-3 PUFA are naturally present in most oils and fats (*Table 2*). Canola and soybean oils, for example, which are commonly used in medical foods,[12] contain only 10% and 7% ALA, respectively. In contrast, some fish oils contain 25 to 35% ω-3 PUFA.[13] These oils are isolated from fish that live on vegetation that grows in cold water. For

Address reprint requests to Dr. Michael Peck at the University of Miami, Department of Surgery, P.O. Box 016310, Miami, FL USA.
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*Fatty acid structure is abbreviated as the length, followed by the number of double bonds, and finally by the position of the first double bond. The position of the first double bond can be identified in two ways: in the delta system (Δ), the carbon atoms are numbered from the carboxyl end; in the omega system (ω or n), the carbons are numbered from the methyl end. For example, 20:4 ω-6 refers to arachidonic acid, which is a 20 carbon acid with four double bonds, the first of which starts six carbons from the methyl end. Naturally occurring fatty acyl double bonds are in the *cis* position. *Trans*-unsaturation of double bonds may occur during hydrogenation or processing by intestinal bacteria in ruminants.

Table 1 Names and classes of fatty acids

Abbreviation	Common name	Chemical name*	Melting point (°C)
2:0	acetic	ethanoic	16.7
4:0	butyric	butanoic	−7.9
6:0	caproic	hexanoic	−3.4
8:0	caprylic	octanoic	16.7
10:0	capric	decanoic	31.6
12:0	lauric	dodecanoic	44.2
14:0	myristic	tetradecanoic	53.6
16:0	palmitic	hexadecanoic	63.1
16:1 ω-7	palmitoleic	hexadecanoic	0
18:0	stearic	octadecanoic	69.6
18:1 ω-9	oleic	*cis*-octadecenoic	13.2
18:1 ω-9	elaidic	*trans*-octadecenoic	44.0
18:2 ω-6	linoleic	*cis,cis*-octadecadienoic	−5.0
18:2 ω-6	linoelaidic	*trans, trans*-octadecadienoic	28.5
18:3 ω-3	α-linolenic	9, 12, 15-octadecatrienoic	−11.0
18:3 ω-6	γ-linolenic	6, 9, 12-octadecatrienoic	
20:3 ω-9		11, 14, 17-eicosatrienoic	
20:3 ω-6	γ-homolinolenic	8, 11, 14-eicosatrienoic	
20:4 ω-6	arachidonic	eicosatetraenoic	−49.5
20:5 ω-3	EPA	eicosapentaenoic	−54.1
22:1 ω-9	erucic	docosenoic	34.7
22:6 ω-3	DHA	docosahexaenoic	−44.3

This is adapted from the *CRC Handbook of Biochemistry and Molecular Biology, Lipids, Carbohydrates, and Steroids* (Fasman, G.D., ed., 3rd edition).
*Unless otherwise indicated, all double bonds are *cis*.

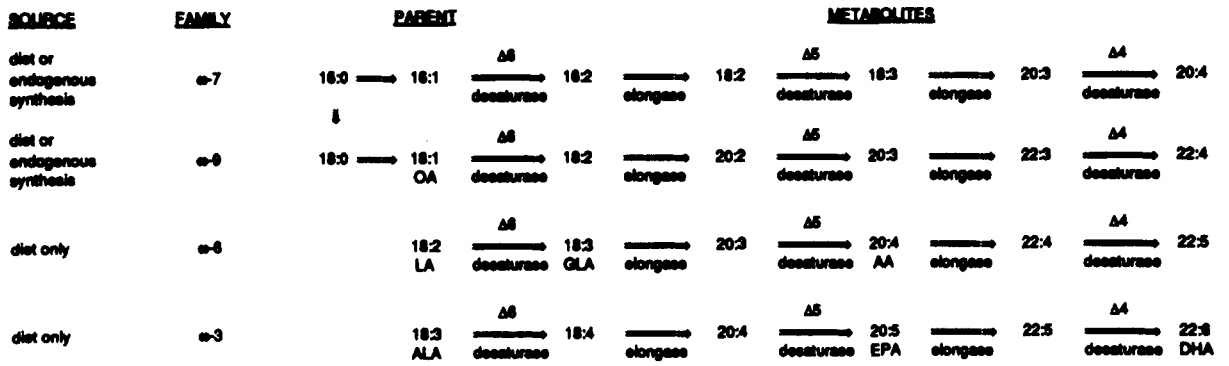

Figure 1 The four families of polyunsaturated fatty acids and their metabolism. Both palmitic (16:0) and stearic (18:0) acids are present in the diet and can by synthesized endogenously. Linoleic (18:2 ω-6) and linolenic (18:3 ω-3) acids can only be obtained from the diet. All four families of unsaturated fatty acids compete for the same desaturase and elongase enzymes. (Based on data from Montgomery et al[10] and Gurr.[11]) Abbreviations: OA, oleic acid; LA, linoleic acid; ALA, α-linolenic acid; GLA, γ-linolenic acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

example, the phytoplankter *Monochrysis lutheri*, which is found in the North Atlantic Ocean, has 22% EPA and 11% DHA (wt/wt).[14]

There are various ratios of saturated and unsaturated fats in natural foods (*Table 2*). Animal fats are generally more saturated than vegetable oils, except for coconut and palm oils. Plant oils are composed of only 10 to 20% saturated fats, compared with 40 to 60% in animal fats. The remainder of the fatty acids in plant oils are unsaturated, and vary from predominantly oleic acid-containing oils (such as olive oil with 79% oleic acid) to linoleic acid-containing oils (such as safflower oil with 76% LA).

Some lipids are essential to the diet. These essential lipids include fat-soluble vitamins (vitamins A, D, and E), and PUFA of the linoleic and α-linolenic acid groups (ω-6 and ω-3 PUFA).[15] ω-6 and ω-3 PUFA are destined more for structural positions in cell membranes than for storage depots of triglycerides. In addition, they have unique precursor roles as substrates for eicosanoid synthesis.

Essential fatty acids are those that the body cannot synthesize de novo, specifically, LA and ALA. The essential nature of these fatty acids was discovered by Burr and Burr in 1929.[15,16] The recommended minimum requirement for essential fatty acids is 1 en%,[11] although it may be as low as 0.2 to 0.3 en%.[8] Deficiency of these essential fatty acids for more than 6 to 8 weeks leads to a syndrome that includes stunted growth, dermatologic abnormalities (scaly skin, alopecia, and brittle nails), infertility, renal abnormalities (papil-

Table 2 Fatty acid composition of fats and oils (% composition)

	SFA	MFA	PFA	OA	LA	ALA	EPA	DHA	MP(°C)	iodine value
Coconut oil	82	5	1	5	1				25	10
Palm kernel oil	81	11	2	11	2				24	37
Beef tallow	54	39	2	36	2				42	50
Palm oil	49	37	37	9	2				35	54
Olive oil	13	79	7	79	7				−6	81
Peanut oil	17	46	32	45	32				3	93
Cottonseed oil	22	18	60	18	60				−1	106
Sesame oil	14	40	42	40	42				−6	107
Canola oil	6	61	30	61	21	9				115
Corn oil	12	31	56	31	56				−20	123
Sunflower oil	10	20	66	20	66				−17	126
Soybean oil	14	24	54	24	47	7			−16	130
Herring oil	19	60	16				7	4		140
Safflower oil	7	17	76	17	76					145
Cod liver oil	37	41	22	17	2	2	9	9		165
Menhaden oil	34	33	30				13	8		170
Linseed oil	8	20	72	20	18	54			−24	179
Perilla oil	8	18	73	18	15	58				195
MaxEPA oil	44	29	27	15	1	3	14	9		

(Based on Shils and Young,[146] Chee et al.,[13] and Altman.[147]

lary necrosis, hematuria, and hypertension), abnormal liver mitochondria, decreased capillary resistance, increased susceptibility to infection, decreased cardiac contractility, and erythrocyte fragility leading to osmotic hemolysis.[11,17]

Many if not all of these signs of deficiency may relate to changes in biomembranes and eicosanoid synthesis.[11] For example, the changes in hepatic mitochondria are due to increased permeability of the mitochondrial membranes to water and ions, leading to swelling of the mitochondria and decreased ATP production. This in turn leads to less efficient conversion of food energy into metabolic energy and results in stunted growth.

Both LA and ALA can prevent many of the signs of essential fatty acid deficiency. Supplementation of either of these essential fatty acids is adequate to maintain normal growth, capillary resistance, erythrocyte structure, and mitochondrial function. LA is, however, superior to ALA in treating dermatitis, infertility, neuropathies, and impaired wound healing.[11,17] It is not known whether these differences are due to differences in the relative effects of the two essential fatty acids on membrane structure and function or on eicosanoid production.

Cell membranes

The lipid bilayer forms the structural framework for all biomembranes.[18] It serves to define outside and inside compartments, and it regulates the nature of communication between the outside and inside of the cell (such as the passage of ions or molecules, or conformational changes in membrane components). Enzymes that catalyze transmembrane or intramembrane reactions may be attached to membranes. Most fundamental biochemical processes involve membranes at some point; examples include protein biosynthesis and secretion, bioenergetic reactions, and hormonal responses. The diversity of function of biomembranes is primarily due to different proteins present in the membrane.

Our present concepts of the structure of biomembranes are based on the fluid-mosaic model suggested by Singer and Nicholson.[19] This model (*Figure 2*) describes a fluid-like phospholipid bilayer with freely diffusing globular proteins that are embedded to various degrees. Although the traditional model described a rather homogeneous interior, recent evidence suggests that membrane proteins do not diffuse freely, which may directly affect their function.[18] The lateral domains of membranes are heterogeneous and differentiated, and some regions may not be structured in the traditional homogeneous phospholipid bilayer. There is

Singer-Nicholson Fluid Mosaic Model

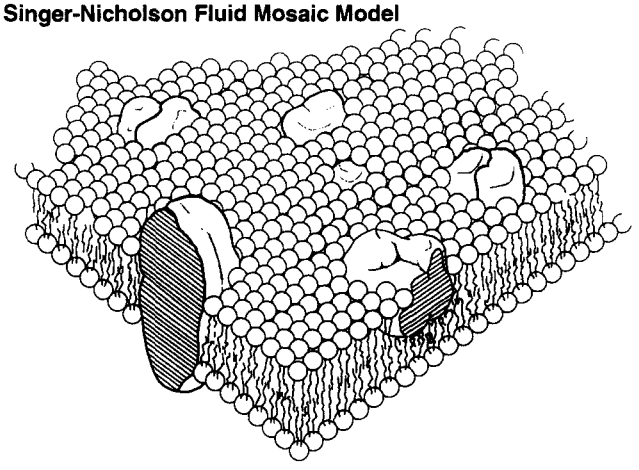

Figure 2 The Singer-Nicholson fluid mosaic model. The matrix of the membrane is formed by the phospholipid bilayer. Proteins are scattered throughout the bilayer of the plasma membrane in the pattern of a mosaic. Various types of proteins are associated with the lipid bilayer, including surface and transmembrane proteins. Proteins are not fixed in position and have lateral mobility and rotational freedom. Flip-flop, however, does not occur, so that the surface of a protein exposed to extracellular fluid does not flip over and become exposed to the cytoplasm. (Based on Singer and Nicholson.[19])

a nonrandom distribution of over 100 species of lipids in biomembranes; the reasons for this heterogeneity and the mechanism responsible for it are not known. The constraints on membrane structure are not rigid, however, because cell viability can be maintained within a wide range of lipid composition.[20]

The heterogeneity of biological membranes is due, to some degree, to the simultaneous existence of lipids in different phases. Mixtures of lipids in water can exist in four different phases.[21,22] The bulk of lipids in biological membranes exists in the lamellar liquid crystalline phase, in which there is a high degree of order of the polar head groups and disorder of the acyl chains (*Figure 3*). At lower temperatures, under experimental conditions, this mixture can exist as the lamellar gel phase, in which there is tighter packing and more order of the acyl chains. In the hexagonal I phase (H_I), lipids exist as cylinders packed in a hexagonal pattern with the polar head groups outside. In the hexagonal II phase (H_{II}), the polar head groups are inside. Hexagonal structures exist in small domains in biomembranes, such as hepatic microsomes, mitochondrial inner membranes, and retinal rod outer segments, and may be especially critical to membrane fusion.[23–25] In fact, membrane lipids are polymorphic and can exist in different phases. For example, phosphatidylethalomine prefers the H_{II} hexagonal phase.[21,26]

The transition of lipids from gel to liquid crystalline phases (conceptually similar to the transition of ice to liquid water) is characterized by the melting temperature, which is the midpoint of this transition. Several factors determine the melting temperature.[18] First, and most important, are the interactions among acyl chains even though polar head groups can also influence the melting temperature. Second, the longer the acyl chain length, the higher the melting temperature because of increased Van der Waals forces. Third, the presence of double bonds lowers the melting temperature because of increased disorder among the acyl chains; *cis*-double bonds lower the melting temperature much more than *trans*-double bonds (*Table 2*).

The maximal effect on melting temperature occurs when the double bond is in the middle of the acyl chain (for example, oleic acid, in which the double bond is at the ω-9 position in an 18 carbon chain).[27] In addition, the differences among the effects of increasing unsaturation (oleic, linoleic, and arachidonic acids) on membrane fluidity are relatively small compared with the changes noted between saturated (palmitic) and monounsaturated (oleic) fatty acids, suggesting that the first double bond plays the most important role.[28]

The heterogeneity of biomembranes is characterized by asymmetry in both lateral and transverse directions.[18] Transverse asymmetry has been documented in the lipid bilayers of the erythrocytes and Gram-negative bacteria, suggesting a physiologic role for this type of heterogeneity because different lipid compositions face different environments (that is, the interior and the exterior of the cell). Transbilayer motion, or flip-flop, is negligible for proteins, but does occur to some degree for membrane lipids. In the erythrocyte, for example, phosphatidylcholine and sphingomyelin are maintained at the exterior layer, and phosphatidylethanolamine and phosphatidylserine are maintained inside.[29] Transverse asymmetry is maintained by the physical requirements of membrane curvature, by interactions with the cytoskeleton,[30] and by ATP-dependent enzyme flipases.[31] All of these factors probably play a role in maintenance of transverse asymmetry because the rate of spontaneous lipid transbilayer motion, which normally occurs over several days, can be dramatically decreased by inhibitors of the cytoskeleton and of ATP.[18]

There are macroscopic lateral heterogeneities apparent in many cells, including sperm, rod, and nerve cells.[18] One of the best examples of macroscopic heterogeneity is the intestinal epithelial cell, where there is clear differentiation between the basolateral and apical regions. These macroscopic heterogeneities are maintained by protein-protein interactions, gap junctions, and cytoskeletal interactions, (such as patching and capping of surface antigens). Although more difficult to demonstrate, there are also microscopic lipid heterogeneities with distinct composition and physical properties. There may be regions of different fluidity, as both gel and liquid crystalline phases exist in different domains (*Figure 4*).[32] These different domains could be responsible for sequestration of enzymes, or could be areas for phase transitions that would allow increased flip-flop, increased permeability, or increased adhesion of lipid vesicles. For example, fusion between membrane organelles may involve a transition of lamellar liquid crystalline to H_{II} phases.[33]

As noted above, lateral heterogeneities are also maintained by interactions with the cytoskeleton, which interacts with the plasma membrane to provide structural support and perhaps to modulate signalling functions. The cytoskeleton, which is a network of filaments and other structures in eukaryotic cells, plays a mechanical role to support the plasma membrane, maintain the shape of the cell, attach to membrane sites of intracellular contact, and regulate the

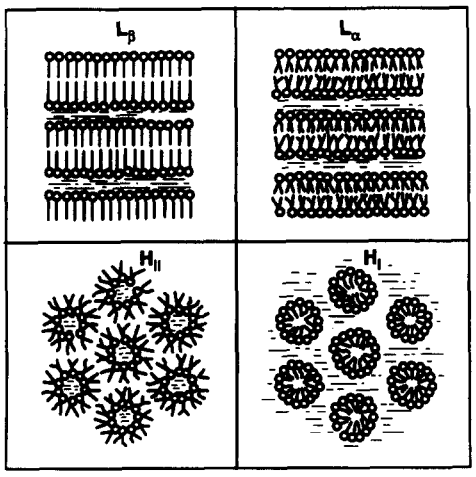

Figure 3 Schematic representations of lipid-water phases. L_β: lamellar gel phase, which is formed at low temperatures and in which the fatty acyl chains are packed more tightly together and are more highly ordered; $L\alpha$: lamellar liquid crystalline phase, which represents the bulk of lipids in biological membranes and in which there is considerable disorder of the acyl chains; H_{II}: hexagonal II phase in which the lipids are in the form of cylinders, with the polar groups facing the inside where there is a column of water; H_I: hexagonal I phase in which the lipids are in the form of cylinders, with the polar groups on the outside in contact with water. (Diagram based on Gennis,[18] adapted from Shipley et al.[21])

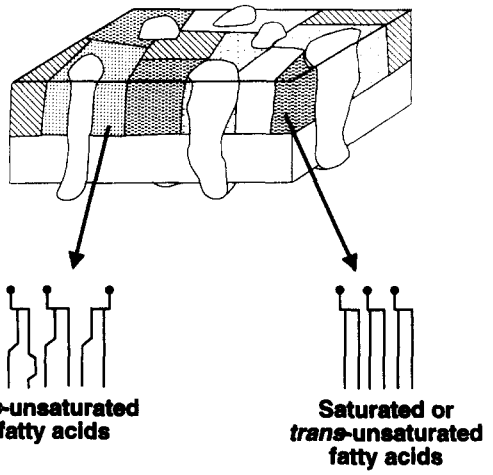

Figure 4 The structurally distinct domains of plasma membranes. In this highly schematized diagram of a plasma membrane, Klausner and associates have illustrated the diversity of lipid domains within membranes. These domains may represent lamellar gel, liquid crystalline, or hexagonal phases. Indeed, some may represent areas of increased or decreased fluidity of liquid crystalline phases. For instance, *cis*-unsaturated fatty acids may partition into a more disordered region than saturated or *trans*-unsaturated fatty acids; the function of the protein embedded in this domain may be altered by this difference in fluidity. (Based on Klausner et al.[32])

positions and movements of organelles.[34] Thus, the heterogeneity, or topography, of the plasma membrane is due to a number of factors, including cytoskeleton interactions, phospholipid phase transitions, ATP-dependent enzymes, and membrane curvature. Within each one of these distinct domains are unique biophysical characteristics related to the fluidity of the phospholipid tails.

Membrane fluidity

Membrane fluidity is a biophysical concept used to describe the resistance to movement of various types of molecules within membranes. Experimental assays used to estimate membrane fluidity utilize lipophilic probes that are inserted into the biomembranes by diffusion. The environmental restraints on probe rotation reflect lipid packing and membrane organization. Examples include electron spin resonance (ESR), nuclear magnetic resonance (NMR), and either time-resolved or steady-state fluorescent anisotropy, using probes such as diphenylhexatriene (DPH).[35]

Unfortunately, there are problems with all of these assays. First, biomembranes, as mentioned, are not homogeneous liquids, and the probes may diffuse into different domains within the membranes.[36,37] Second, the probes themselves have preferred orientation, and range is constrained. Third, the lipophilic probes will also diffuse nonselectively into lipid domains throughout the cell, including lipid droplets in the cytoplasm.[38] Finally, although the local rotations and oscillations of lipophilic probes can be quantitated by these methods, the lateral diffusion of intramembranous molecules may have more physiologic importance.[39] Lateral diffusion is better estimated by techniques such as photobleaching recovery. Despite the complexities and inadequacies of the assays available for estimation of membrane fluidity, these assays can yield useful information about changes in the biophysical characteristics of biomembranes, provided they are not too strictly interpreted.[35,40-42]

Membrane fluidity is strongly related to lipid packing or order. For, instance, fluidity can be altered by the cholesterol to phospholipid ratio, the degree of fatty acid unsaturation including the ratio of *cis* to *trans* double bonds, and environmental factors such temperature and pressure.[43-45] Biomembranes generally are kept in liquid crystalline phases in which fluidity is maintained to support life functions; membranes in gel states do not support biochemical reactions. For example, trout biomembranes will adjust their fatty acid content by increasing unsaturation to maintain membrane fluidity when they are exposed to cold waters.[46]

The lateral diffusion of lipids in biomembranes is also inversely related to lipid packing density.[18] Lateral diffusion can be estimated by photobleaching recovery in which laser light bleaches a uniformly labeled membrane. The rate of return of fluorescence to that area is a direct measurement of the lateral mobility of labeled molecule, whether lipid or protein. Lateral diffusion of intramembranous proteins may be constrained by increased viscosity of membranes, as well as by cytoskeletal attachments.[47]

Membrane fluidity can be altered by dietary lipids and disease. Experimentally, incubation of cells in culture with exogenous fatty acids produces changes in membrane fatty composition and fluidity.[36,38,48-50] Increasing the amount of PUFA in the diet increases the membrane ratio of polyunsaturated to saturated fatty acids (P/S ratio) and membrane fluidity.[27,51,52] Clinical studies have shown that membrane fluidity changes in injured patients, with both severe injury and sepsis resulting in decreased fluidity of peripheral blood cells,[53,54] although major burn injury increases fluidity of human peripheral blood lymphocytes.[55]

Changes in membrane fluidity brought about either by manipulation of dietary lipids or by exposure to carrier-bound free fatty acids in culture media can alter the function of cells. Murphy reviewed the experimental evidence associating changes in membrane phospholipid fatty acyl composition (and thereby membrane fluidity) with intramembranous enzyme function and concluded that membrane fluidity affects intramembranous protein function by stabilizing optimal protein conformation and by constraining the lateral mobility of proteins.[56]

There is evidence that increases in membrane fluidity increase the mobility of intramembranous proteins. For example, Borochov and Shinitzky found that cholesterol depletion, which increases membrane fluidity, decreases the exposure of membrane proteins to the outer environment.[57] In addition, Fernandes has noted that dietary fish oil increases lymphocyte IL-2 receptor expression, which may be caused by an increase in membrane fluidity.[51]

The study of patching and capping of surface proteins, which are early events in cell activation, reveals information about the lateral movement of membrane proteins, as well as their interactions with the cytoskeleton. Klausner and associates found that murine lymphocytes incubated with *cis*-unsaturated fatty acids have increased membrane fluidity and inhibited capping by anti-mouse gamma globulin.[36] Photobleaching recovery of the cross-linked membrane immunoglobulin showed that unsaturated free fatty acids do not

hinder the immobilization of cross linked receptors, suggesting that the inhibition by unsaturated free fatty acids occurs during the final energy-dependent aspect of capping that aggregates the immobilized receptors into a polar cap. *Cis*-fatty acids may alter lipid packing around crucial intramembranous proteins (like calcium-binding proteins), causing them to change their conformation, thus releasing calcium, and inhibiting capping by interfering with cytoskeleton interactions.[58]

Although others have also shown that free fatty acids inhibit patching and capping,[59,60] we have shown that mice fed diets with 40 en% safflower or fish oil have lymphocytes in which capping with anti-CD44 monoclonal antibodies is increased, compared with lymphocyte anti-CD44 capping in animals fed diets from coconut or olive oil (unpublished data, 1993). In addition, murine lymphocytes incubated with oleic acid show an increase in expression of CD44 antigens, and also an increase in CD44 receptor capping, compared to those incubated with stearic acid.[61]

Experimental models in which receptor capping is altered by lipids have also shown that lymphocyte blastogenesis is changed. For example, using mice fed as described above, we have shown that membrane fluidity increases with both safflower and fish oil diets, and that lymphocyte mitogenesis is inhibited.[62] These results are similar to those of Hoover and associates, who found that murine lymphocytes incubated with LA also show an increased expression of surface antigen but decreased mitogenesis.[50] They note that their results were similar with ALA (just as we found similar results with both safflower and fish oils), suggesting that these effects are not mediated by prostaglandins. It should be noted, however, that PGE_2 suppresses antigen presentation by peritoneal macrophages, suggesting that some component of surface protein activity is modulated by prostaglandins.[63] Hoover and associates propose that partitioning of fatty acids into particular lipid domains affects the protein/lipid interaction, protein conformation, and ultimately the linkage between the membrane and the cytoskeleton, resulting in altered capping properties.[50]

These observations are still somewhat dependent on the model used. In contrast to the findings above that increased lymphocyte membrane fluidity is associated with decreased mitogenesis, Hoover and associates noted that incubation of LA increases the response of BHK-21 cultured cells (a rat lymph node line) to mitogen stimulation.[50] Similarly, Traill and associates have shown that increasing cholesterol in chicken peripheral blood lymphocytes decreases fluidity and also blastogenesis, and that "activated lipid" (a unique phospholipid preparation) increases fluidity and PHA-induced blastogenesis.[44] This effect is dose dependent, as higher doses of activated lipid will suppress the PHA response. We have also shown that incubation of murine splenic lymphocytes with *cis*-unsaturated fatty acids increases both fluidity and blastogenesis at low doses.[64]

Macrophage function may also be altered by lipids via changes in membrane fluidity. Phagocytosis is a special form of endocytosis by macrophages in which large particles such as microorganisms and cell debris are ingested via large endocytic vesicles called phagosomes. After particles bind to the surface of the phagocyte, activated receptors transmit signals to the cell interior to initiate the response. Pseudopods are subsequently extended and engulf the particle and fuse at their tips.

A number of studies have documented that incubation with *cis*-unsaturated fatty acids increases phagocytosis by macrophages.[48,57,65–68] For example, Calder and associates found that murine thioglycollate-elicited peritoneal macrophages incubated with albumin-complexed unsaturated fatty acids (LA, ALA, AA, EPA, and DHA) have increased phagocytosis of zymosan particles.[68] The rate of phagocytosis correlates with the P/S ratio ($r = 0.747$). The correlation between phagocytosis and membrane phospholipid polyunsaturated fatty acid content is also very high ($r = 0.928$). The effects of DHA and EPA on phagocytosis, however, are not as marked as predicted based on the degree of unsaturation. Specifically, although linoleic acid increases phagocytosis to 145% of control, EPA increases it only to 126% and DHA to 135%.[68] This discrepancy between observed and predicted results suggests another mechanism for the action of PUFA, specifically that due to lipid peroxidation.

Lipid peroxides

PUFA are prone to peroxidation, or formation of free radicals, and as such can potentially damage cell membranes. Free radicals are molecules with unpaired electrons in the outer orbit (Freeman and Crapo,[69] Pryor,[70] Slater,[71] and Gerdin and Haglund[72]). As such, they are highly reactive and play integral roles as intermediates in normal biochemical reactions. They are produced either by radiation effects or through reduction-oxidation reactions with transition metals or enzymes. Tissue injury increases the production of free radicals, which in turn contribute to the pathophysiology of injury or disease.

Lipid peroxides are formed from autooxidation (from exposure of unsaturated fatty acids to molecular oxygen) or from peroxidation from attack by other free radicals. Most peroxidation in biomembranes involves AA and DHA.[71] Lipid domains that exist in the gel phase may be more susceptible to peroxidation.[73] The consequences of lipid peroxidation include decreased membrane fluidity (although the effect may vary with the model),[71] oxidation of thiol groups of enzymes in the membranes, and liberation of breakdown products (such as malondialdehyde [MDA]), which produce damage elsewhere. In fact, measurements of MDA or conjugated dienes (CD), are used as evidence of lipid peroxidation processes.

Cellular defenses against free radical damage include chain-breaking scavengers, many of which are lipid-soluble and act by scavenging the chain-carrying oxygen radicals.[74] Although β-carotene and retinoic acid play minor roles, vitamin E (especially α-tocopherol) is the major lipid peroxide scavenger. Vitamin C (ascorbic acid), which is itself a chain-breaking scavenger, contributes by regenerating reduced forms of vitamin E.[71,74] Selenium, an integral component of glutathione peroxidase, is effective at restoring many of the functions impaired by vitamin E deficiency.[75] Lymphocyte function is dependent on the intake of antioxidant vitamins, such a β-carotene, selenium, and vitamins A and E.[76]

Plasma membranes are critical sites for free radical reactions (Figure 5).[69] The plasma membrane, as the first site of contact with the cell's environment, encounters extracellular

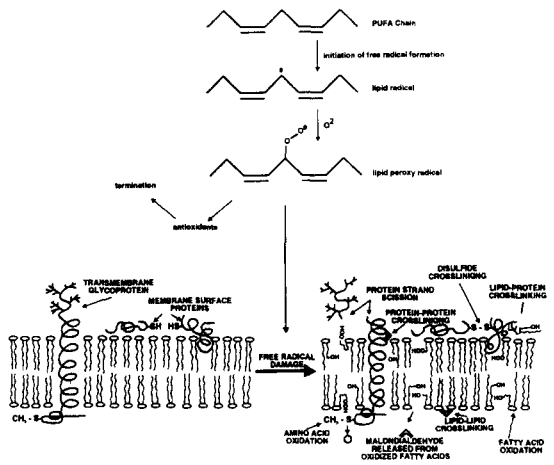

Figure 5 Free radical damage to membranes. Lipid peroxides are initiated by oxygen free radicals, forming lipid free radicals. Following initiation, there is rapidly accelerating propagation through chain reactions in which lipid radicals collide with each other and generate more lipid radicals. Often these react with oxygen to form lipid peroxyl radicals. If antioxidants (such as vitamin E) do not convert the lipid radicals into inactive molecules, these radicals can catalyze a number of damaging reactions in cell membranes, including amino acid oxidation, protein-protein cross-linking and protein strand scission. Malondialdehyde (MDA) is released from some of these reactions, and can mediate other damaging consequences. (Based on Freeman and Crapo.[69])

free radicals before other cell components. The perhydroxyl radical (the protonated form of the superoxide radical), partitions into lipids in the membrane, at which time unsaturated fatty acid and transmembrane proteins with oxidizable amino acids are attacked. Subsequent reactions may proceed to the interior of the cell.

One of the other effects of lipid peroxides may be to modulate eicosanoid synthesis. Farrukh and associates, for example, found that lipid peroxides increase cyclooxygenase and lipoxygenase products of AA.[77] On the other hand, Mosconi and associates found that the decrease in platelet thromboxane seen in rats gavaged with fish oil could be abrogated by vitamin E.[78]

Because of these diverse effects throughout the cell, free radical production plays an important role in many diseases.[79,80] Deficiency states of natural scavengers, such as deficiencies of vitamin E, vitamin C, or selenium, are associated with signs consistent with radical production, such as the increased fragility of erythrocytes in vitamin E deficiency. An excess of catalysts of free radical production, such as iron overload in hemochromatosis, causes both tissue damage and direct injury to tissues by toxins including paraquat, alcohol, and carbon tetrachloride.

The best-characterized example of free radical injury is reperfusion damage that occurs when blood flow is restored to a previously ischemic organ such as the intestine.[81] In reperfusion injury, tissue damage due to ischemia is exacerbated by xanthine dehydrogenase products; the tissue damage secondary to reperfusion can be blocked by superoxide dismutase, allopurinol, and desferoxamine. Similar tissue damage in the reperfused liver can be blocked by vitamin E, suggesting that reperfusion injury is related to lipid peroxide production.[82]

Shock states, in which there is inadequate tissue perfusion due to hemorrhage or inflammation, are also associated with free radical production.[83] The role of lipid peroxides in shock is suggested by the observation that α-tocopherol is protective against mortality from endotoxin in mice, restoring liver ATP stores by reducing the lipid peroxide load.[84,85]

Lipid peroxides may also contribute to the multiple organ failure syndrome (MOFS), which is characterized by the failure of two or more organ systems, commonly kidneys, liver, heart, or lungs, following a variety of inciting events, such as trauma, sepsis, or hemorrhagic shock. Oxygen free radical scavengers protect against lung, liver, and kidney damage in experimental models of MOFS.[72] The mechanism by which free radicals exacerbate MOFS may be through damage to the intestinal mucosa, thus allowing for bacterial translocation from the gut lumen.[86] In addition, free radicals may have their greatest effect through modulation of mediators, such as endothelium-derived relaxing factor (nitric oxide), which would worsen vasodilation and vascular collapse.[87,88]

Injuries are associated with increased appearance of lipid peroxidation products. Demling and LaLonde have shown an increase in plasma MDA and CD following burn injury in sheep.[89] The increase in plasma peroxidation products is associated with increased oxygen consumption, lung inflammation, and liver dysfunction, and is attenuated by allopurinol.[90] (The beneficial effects of allopurinol are limited to the lung; liver dysfunction is not affected.) Similarly, Horton and White have found lazaroids (inhibitors of lipid peroxidation) improve the cardiac dysfunction associated with burn injury.[91]

The contribution of lipid peroxides to shock and MOFS may also be related to direct effects on cell function and survival. For example, lymphocyte proliferation is suppressed by PUFA in vitro; because lymphocytes in culture are unable to elongate and desaturate 18-carbon fatty acids to AA—a failure that eliminates the possibility of suppression by eicosanoids—this phenomenon is probably due to lipid peroxidation.[92] Further evidence for the role of lipid peroxides on leucocyte function is the observation that the suppression of peripheral blood mononuclear cell proliferation in response to mitogens is reversed by vitamin E, and that there is a direct correlation between plasma α-tocopherol levels and blastogenesis in healthy males fed defined diets with 40 en% fish oil.[93]

More directly, PUFA have a pronounced cytotoxic effect in culture. For example, gram-positive cocci are sensitive to AA in culture, and can be protected by catalase and iron chelators.[94] Further, cytotoxicity of lymphocytes incubated with fatty acids is increased by decreasing fatty acyl chain length and by increasing unsaturation.[95] Finally, Begin has shown that PUFA have cytotoxic effects on both normal and transformed cells and can stimulate growth when fatty acid concentration is low (less than 20 μM) but are cytotoxic when levels are high (greater than 100 μM).[96,97] The cytotoxicity of the fatty acids is associated with their ability to induce lipid peroxidation and can be blocked by vitamin E, although, paradoxically, EPA and DHA do not always increase levels of MDA.

Although lipid peroxidation may play a significant role in the pathophysiology of disease and injury, the role of

dietary PUFA in increasing the body's burden of lipid peroxides is unknown. PUFA, especially highly unsaturated fatty acids such as EPA and DHA, can undergo rapid autoxidation.[98] At room temperature with exposure to atmosphere oxygen, fish oils lose a significant portion of their EPA and DHA to autooxidation. Feeding high amounts of fish oil to animals can lead to yellow fat disease, in which lipofuscin (the polymerized, peroxidized polyunsaturated fatty acid-protein complexes produced by high PUFA intake without adequate vitamin E) is deposited in tissues, especially cardiac muscle.[99] Nonetheless, there is little direct evidence that dietary lipid peroxides produce organ dysfunction, and Kinsella has concluded that the intake of dietary ω-3 PUFA should not exert any deleterious effects via peroxidation as long as adequate vitamin E is consumed.[98]

Eicosanoids

Eicosanoid synthesis

Eicosanoids are products formed from 20 carbon PUFA. They share a 5 carbon ring structure and sites of oxygenation. Most mammalian cells, except erythrocytes, can metabolize AA, but different cells generate different profiles of AA end-products.[100–102] Only a few cell lines, however, including leukocytes, hepatocytes, and gastric and adrenal cells, have specific prostaglandin receptors.[103] Furthermore, only minimal concentrations (10^{-9}g/g) are needed for physiologic effects in target cells. This necessity for small concentrations, together with the very short half-lives, suggest that eicosanoids have autocrine or paracrine effects on nearby cells, rather than on distant organ systems.[100–104]

Eicosanoid release is stimulated by a variety of substances. Collagen, thrombin, bradykinin, antigen-antibody complexes, oxygen free radicals, growth factors, and cytokines are all capable of stimulating release of esterified AA and further enzymatic modification to eicosanoid products.[102] The two major pathways of AA metabolism begin with the enzymes cyclooxygenase, which produces prostanoids (prostaglandins and thromboxanes), and lipoxygenase, which produces leukotrienes, hydroxyeicosatetraenoic acids, and lipoxins (*Figure 6*). (A third pathway, through cytochrome P_{450}, forms epoxides, which are converted to hydroxy-fatty acids.)

The main source of AA is membrane phospholipids, although free fatty acids are also a significant source of eicosanoid precursors.[105] Esterified AA is released by the action of phospholipase A_2, a membrane-bound enzyme activated by calcium that releases AA primarily from phosphatidylcholine, and by phospholipase C, which is specific for phosphatidylinositol (*Figure 6*).[101]

Eicosanoids primarily regulate cellular activity by altering intracellular levels of cAMP and cGMP.[101] For example, PGE_2 suppresses lymphocyte blastogenesis by increasing cAMP levels. Other eicosanoids, such as leukotrienes, increase cGMP levels, which have opposing effects to increases in cAMP levels. The cAMP to cGMP ratio, rather than the absolute amount of either cyclic nucleotide, ultimately determines the magnitude and direction of the cellular response.[101]

AA pathways are regulated both by dietary and pharmacologic means. ω-3 PUFA directly suppress the activity of cyclooxygenase, inhibiting formation of dienoic prostanoids (such as TXA_2 and PGE_2). In addition, dietary ω-3 PUFA provide substrates for eicosanoid production that result in less biologically potent end-products, such as PGE_3 and LTB_5.[105–109] There are also pharmacologic inhibitors specific for cyclooxygenase (such as aspirin, ibuprofen, and indomethacin) and for lipoxygenase (for which none have been approved for clinical use).[110]

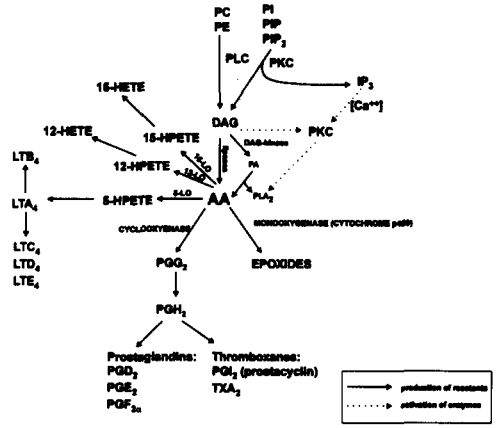

Figure 6 Proposed reactions that lead to the formation of eicosanoids from membrane phospholipids. Hydrolysis of PC or PE by PLC produces DAG, which is acted on by lipases to liberate AA. In addition, DAG-kinase phosphorylates DAG to form PA, a substrate for PLA_2, also producing AA. PKC hydrolyses PI, PIP, and PIP_2 to generate DAG and IP_3. IP_3 increases cytosolic calcium, which in turn stimulates PKC. DAG also stimulates PKC, which increases AA production by PLA_2. These lines of metabolism converge to liberate AA, which in turn is the substrate for oxygenase systems (see text). (Based on Levine.[102]) Abbreviations: DAG = Diacylglycerol; HETE = Hydroxyeicosatetraenoic Acid; HPETE = Hydroperoxyeicosatetraenoic Acid; IP_3 = Inositol Trisphosphate; LO = Lipoxygenase; PA = Phosphatidic Acid; PC = Phosphatidyl Choline; PE = Phosphatidyl Ethanolamine; PI = Phosphatidyl Inositol; PIP = Phosphatidylinositol Phosphate; PIP_2 = Phosphatidylinositol Bisphosphate; PKC = Protein Kinase C; PLA_2 = Phospholipase A_2; PLC = Phospholipase C.

The role of prostaglandins in modulation of immune processes is complex, depending on the concentration of PG, the length of PG-target cell interaction, and the state of differentiation of the target cell.[100] Prostaglandins do not play a critical role in the maintenance of normal immune responses in healthy humans, as evidenced by the absence of deleterious effects in patients chronically using nonsteroidal anti-inflammatory analgesics (NSAIDs).[100] Yet, when the immune system is stimulated, prostaglandins generally function to provide feedback inhibition.

Modulation of eicosanoid production by dietary lipids

The fatty acid composition of dietary lipids directly affects membrane phospholipid fatty acid profiles and in turn modulates eicosanoid synthesis. Marshall and Johnston studied rats fed diets with different ratios of linoleic to linolenic (that is, ω-6 to ω-3) fatty acids and found that dietary lipid composition is reflected in the phospholipid fatty acid profiles of splenocytes, thymocytes, lymphocytes, and mast cells.[111–112] The replacement of phospholipid fatty acids by ω-3 PUFA is due to competition for the Δ-6 desaturase

enzymes. Additionally, as the amount of ω-3 PUFA increases in diets, there are associated decreases in ω-6 metabolites, such as PGE_2, secondary to inhibition of PG synthetase complex and to decreased amounts of AA available as substrate.

Other studies have confirmed the displacement of AA from leucocyte plasma membranes,[4,113–118] and one has found a significant inverse linear correlation between dietary ω-3 PUFA and phospholipid AA concentration.[118] Other tissues, such as liver cells,[119] heart, and kidney cells,[120] similarly showed decreased AA and increased EPA and DHA in phospholipids from animals on fish oil diets. (Interestingly, there is tissue specificity regarding the uptake and/or subsequent elongation and desaturation of EPA and DHA: although renal cell membranes from rats fed tuna oil contain equal amounts of EPA and DHA, phospholipids from cardiac cells in the same animals show a 23 to 1 predominance of DHA over EPA.[120]) Although a direct correlation has been found between dietary ω-3 PUFA and triglyceride content, the response of tissue phospholipids is more complex: it is a competitive hyperbolic response, which can be predicted by the Lands equations.[121]

The suppression by ω-3 PUFA of dienoic prostanoids and tetraenoic leukotrienes has also been documented by a number of investigators.[109,113,115,119,122,124] In murine mastocytoma cells, the magnitude of the suppression of dienoic prostanoids and tetraenoic leukotrienes is greater than the enhancement of trienoic prostanoids and pentaenoic leukotrienes by EPA-enriched diets,[56] although humans supplemented with 4 g EPA daily have demonstrated only increased LTB_5 production by PMNs, without change in LTB_4.[125] There is, however, a direct correlation between the PMN membrane phospholipid EPA to AA ratio and PMN production of LTB_5/LTB_4.[125]

Eicosanoids and the immune response

PGE_2 has been shown to play important roles in regulating the immune response. Its proinflammatory effects include fever, erythema, increased vascular permeability, vasodilation, and enhancement of the pain and edema caused by bradykinin and histamine.[103] PGE_2 also modulates leucocyte function, probably by increasing intracellular cAMP levels. Lymphocytes and macrophages both have receptors for and can secrete prostaglandins.[126] The different effects of prostaglandins on immune cells also appears to be related to the degree of differentiation of the cell populations because PG increase differentiation and maturation of immature lymphocytes.[103]

PGE_2 at physiologically relevant concentrations generally suppresses T cell function, such as mitogen-induced blastogenesis, clonal expansion, antigenic stimulation, E-rosette formation, lymphokine production, generation of cytotoxic cells, and lymphocyte migration.[100,101,103,127–130] (One subset of T cells, suppressor T cells, may be stimulated by prostaglandins, but the contribution of this effect overall will still be one of suppression of T-cell function.[130]) For example, T lymphocyte suppression in human diseases is associated with increased prostaglandin activity.[131,132] Moreover, monocytes, which are responsible for a large portion of PGE_2 production, also have increased activity in chronic inflammatory conditions.[100]

The effects of PGE_2 on B cell function and antibody production are dose dependent. At low doses, PGE_2 tends to enhance antibody production,[100,101,130,133] while it suppresses B-cell proliferation.[101,103,128]

PGE_2 suppresses cytokine release,[101,103,128,129,134] including IL-1 and tumor necrosis factor (TNF). Indeed, one of the primary roles of PGE_2 is to down-regulate the release of cytokines such as TNF, which has been implicated in the pathogenesis of septic shock.[130,134,135]

Prostaglandins suppress phagocyte function. PG depress chemotaxis, chemokinesis, aggregation, spreading, and oxidative metabolism of leukocytes.[103,128] Biphasic responses are also noted in natural killer cells and macrophages such that low doses enhance and high doses suppress cellular function.[100]

Lipoxygenase products (especially 5-lipoxygenase, or 5-LO) play important roles in allergic and immune reactions and are produced by all leukocytes except lymphocytes.[103,128] LTC, LTD, and LTE are the slow-reacting substances (SRS) released in response to IgE and are responsible for the smooth muscle restriction of anaphylactic reactions. Some researchers have argued that these leukotrienes (LTC_4, LTD_4, and LTE_4) also play an important role in the pathogenesis of shock.[136] Moreover, 5-LO products amplify platelet-activating factor by PMNs. The major 5-LO product involved in modulation of the immune system, however, is LTB_4.

LTB_4 is a major mediator of leucocyte activity. It stimulates aggregation lysosomal release and chemotaxis of PMNS. Most leukocytes do not synthesize 5-LO products on a constitutive basis; the main source of LTB_4 is PMNs.[137] The significance of 5-LO products in the immunosuppression associated with injury or infection is not well described. Nonetheless, Schonfeld and associates have shown that PMNs isolated from trauma patients show a decreased capacity to generate LTB_4 in the first week after injuries.[138]

The role of 5-LO products on lymphocyte function is not clear. Lymphocytes do not synthesize LO products, but lymphocyte function does seem to be suppressed by LTB_4.[137] LO inhibitors, on the other hand, have also been shown to suppress blastogenesis and natural killer cell function.[137,139]

Cell activation

Lymphocyte activation is initiated by appropriate ligand binding to surface receptors (*Figure 6*). These activated receptors, in turn, activate phospholipase C, which frees phosphatidylinositol-bisphosphate (PIP_2) to generate inositol trisphosphate ($InsP_3$) and diacylglycerol (DAG). $InsP_3$ releases calcium from the calcium-sequestering compartment, leading to proliferation. DAG can be cleaved to release AA, or it can activate protein kinase C, which can then phosphorylate a number of proteins with different functions.

Many steps of this signaling pathway can be affected by lipids. Incubation of fatty acids with a cell line of human colon cancer cells shows that LA decreases, and ALA increases the incorporation of $InsP_3$.[140] PI turnover, as well as intracellular calcium concentrations, are suppressed in rats fed fish oil diets.[141] On the contrary, Richieri and Kleinfeld observed that oleic acid compared with stearic acid inhibits

the rise in intracellular calcium in cytotoxic T cells following activation by target cells or by mitogens, but that it does so by altering less than 10 mol/mol/% of the fatty acid composition of the membrane without change in the production of IP metabolites.[142] Because these effects can be reversed by incubation of the cells with fatty acid-free albumin, the authors concluded that the effect was due to perturbation of the physical properties of membrane lipids, distal to cell surface recognition events and to phospholipase C activation.

Cis-unsaturated fatty acids also directly activate protein kinase C independent of changes in intracellular calcium. Unsaturated fatty acids activate protein kinase C in cellular preparations of central nervous system (CNS) homogenates and of human PMNs.[143–145] Protein kinase C in human PMNs is activated by unsaturated (oleic, linoleic, and linolenic) acids but not by saturated (palmitic and stearic) fatty acids.[143] This effect is not abrogated by inhibitors of either cyclooxygenase or lipoxygenase and appears to parallel the number of double bonds, with ALA having the most potent effect. Leach and Blumberg, however, found no correlation between the degree of fatty acyl unsaturation and protein kinase C-enhanced activity in CNS homogenates.[144] Nonetheless, they did confirm that all unsaturated fatty acids were more effective than saturated fatty acids at stimulating protein kinase C. Thus, unsaturated fatty acids may contribute to transmembrane signalling and cellular activation independent of eicosanoid metabolism.

Summary

Dietary lipids are distributed throughout the body, not only in storage form as adipose tissue, but also as the structural components of cell membranes. As such, they provide the pool of substrates for eicosanoid metabolism. The unique biochemical properties of fatty acids also allow them to act directly on transmembrane signalling processes, and, in the unstable form of free radicals, transmit damage to plasma membranes and the interior of the cell.

Essentially, all of the functional properties of lipids are vital to the maintenance of the normal immune response. For example, phagocytosis, the host's first defense against invading bacteria, is modulated by lipids at a number of steps: (a) influx of phagocytes to a site of inflammation; (b) endocytosis of particles or bacteria; (c) oxygen-dependent intracellular killing; and (d) regulation of phagocyte activity by cytokines or leukotrienes. In a subsequent review article, findings on the effects of lipids on specific areas of the immune system, including phagocytosis, lymphocyte function, and cytokine production, will be discussed, as will the results of manipulating lipids in models of transplantation, cancer, essential fatty acid deficiency, autoimmune disease, and infection.

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