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Review Article

CELL MEMBRANE FATTY ACIDS AND HEALTH

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ABSTRACT

All living cells, prokaryotic and eukaryotic, have a plasma membrane that encloses their contents and serves as a semi-porous barrier to the outside environment. The basic matrix of the plasma membrane consists essentially of two sheets (a bilayer) of phospholipids molecules**.** Among the significant components of cell membranes are the phospholipids, which contain fatty acids. The types of fatty acids in the diet determine the types of fatty acids that are available to the composition of cell membranes. The cell membrane that contains phospholipids made from saturated fatty acids has a different structure and is less fluid than the one that incorporates essential fatty acids**.** Fatty acids carry out many functions that are necessary for normal physiological health. Saturated fatty acids are non-essential fatty acids and are harmful if ingested excessively in food. On the contrary, polyunsaturated fatty acids (PUFA) are designated as "essential" for good health as their metabolic precursors cannot be synthesized in the body and must be ingested by food intake. Increased dietary intake of omega-6 leads to production of prostaglandins, thromboxanes and leukotrienes and interferes with the incorporation of omega-3 in cell membrane phospholipids.Omega-3 has the most potent anti-inflammatory effects. Inflammation is at the base of many chronic diseases, including coronary heart disease, diabetes, arthritis, cancer and mental health. Dietary intake of omega-3 fatty acids may prevent the development of many diseases.

INTRODUCTION

Our diet contains a complex mixture of fats and oils whose basic structural components are fatty acids. We generally consume at least 20 different types of fatty acids, which are classified as saturated (SFA), monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA). Fatty acids have many fates in the body, including β-oxidation for energy, storage in depot fat or incorporation into phospholipids, which form the major structural components of all cellular membranes [1].

Fatty acids carry out many functions that are necessary for normal physiological health. Saturated fatty acids are non essential fatty acids and are harmful if ingested excessively in food. On the contrary, polyunsaturated fatty acids (PUFA) are designated as "essential" for good health as their metabolic precursors cannot be synthesized in the body and must be ingested by food intake. PUFA have important effects on the structure and physical properties of localised membrane domains. They modulate enzyme activities, carriers and membrane receptors (low density lipoprotein LDL receptors, insulin, antibodies neurotransmitters, drugs receptors, etc.) [2].

Endogenous fatty acids deficiency in cells leads to changes of phospholipids fatty acid composition and physicochemical properties of plasma membrane and lowering their fluidity [3].

Thus, it is from interest to study the reflection of dietary fat on the cell membrane and the role of cell membrane component especially fatty acids in improving health.

Cell membrane

All living cells, prokaryotic and eukaryotic, have a plasma membrane that encloses their contents and serves as a semi-porous barrier to the outside environment. The membrane acts as a boundary, holding the cell constituents together and keeping other substances from entering. The plasma membrane is permeable to specific molecules, however, and allows nutrients and other essential elements to enter the cell and waste materials to leave the cell. Small molecules, such as oxygen, carbon dioxide, and water, are able to pass freely across the membrane, but the passage of larger molecules, such as amino acids and sugars, is carefully regulated [4].

Cell membrane structure

The basic matrix of the plasma membrane consists essentially of two sheets (a bilayer) of phospholipids molecules (Figure 1). The phospholipids are amphoteric molecules (i.e. one end of the molecule is hydrophilic or water soluble and the other end is hydrophobic or water insoluble). Therefore, in an aqueous environment the two sheets adopt a phospholipids bilayer, with the hydrophobic ends of the molecules on the inside of the bilayer and the hydrophilic ends on the outside. Within this "sea" of phospholipids are embedded many different types of protein molecules, which have many specialist functions [5].

Cell membrane bilayer is composed of 40% lipids and glycolipids, and 60% integral proteins and glycoproteins. The lipids in the membrane bilayer are composed of phospholipids (75% to 88%), glycosphyngolipids (2% to 5%) and cholesterol (10% to 20%).The phospholipids include phosphatidylcholine (45% to 55%), phosphatidylethanolamine (15% to 25%), phosphatidylinositol (10% to 15%), phosphatidylserine (2% to 10%), phosphatidic acid (1% to 2%), sphyngomyelin (5% to 10%) and cardiolipin (2% to 5%) [6].

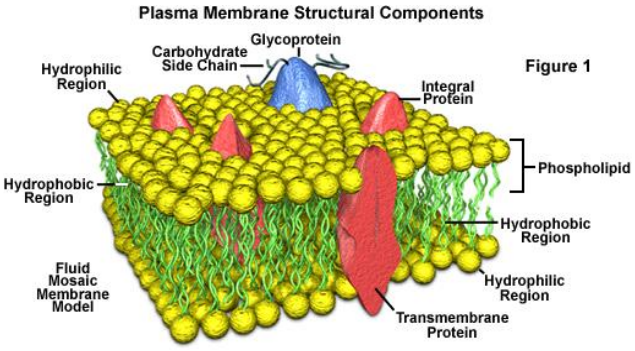

Fig. 1: Cell membrane structure [4]

Cell membrane proteins

The numerous types of protein molecule associated with plasma membrane can be broadly classified as extrinsic (peripheral) or intrinsic (integral) (Figure 2). Intrinsic proteins include receptors that span the width of the membrane; extrinsic protein includes various enzymes involved in mediating the intracellular effects of receptor activation by signaling molecules. Functionally, the membrane proteins can be divided into several distinct groups:

- Receptors-respond to the binding of specific signaling molecules.
- Ion channels-permit the passage of specific ions
- Transporters- carry important ions or molecules across the membrane, sometimes against a concentration gradient.

- Others (e.g. band 3' proteins and glycoprotein) [7].

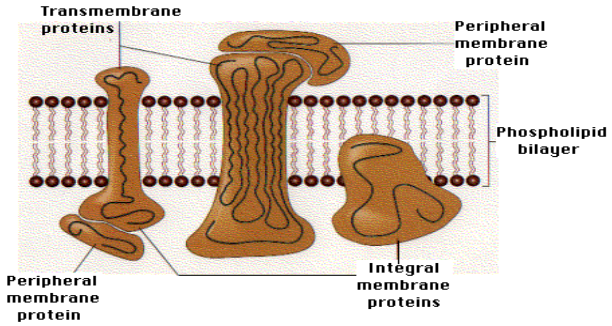

Fig. 2: Cell membrane proteins (peripheral and integral) [8]

Cell membrane phospholipids

Among the significant components of cell membranes are the phospholipids, which contain fatty acids. The types of fatty acids in the diet determine the types of fatty acids that are available to the composition of cell membranes. The cell membrane that contains phospholipids made from saturated fatty acids has a different structure and is less fluid than the one that incorporates essential fatty acids [9].

Phospholipids contain only two fatty acids tail attached to glycerol head; this occurs by a condensation reaction. The third alcohol group of the glycerol is attached to phosphate molecule and then attached to other small molecules such as choline. This phosphate group along with the glycerol group makes the head of the phospholipids hydrophilic, whereas the fatty acids tail is hydrophobic. Thus phospholipids are amphibatic: Water loving and water hating (Figure3). The most abundant phospholipids in the cell membrane are phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI) and sphyngomyelin (SM) [6].

Fatty acids

Fatty acids can be divided into four general categories: saturated, monounsaturated, polyunsaturated, and *trans* fats. In saturated fatty acids, the carbon chain has the maximum number of hydrogen atoms attached to every carbon atom. If a pair of hydrogen atoms is missing because of a double bond between two carbon atoms, it is called an unsaturated fatty acid (Figure 4). A fatty acid with a single double bond is monounsaturated, whereas a fatty acid with more than one double bond is polyunsaturated. The carbon-carbon double bond found in monounsaturated (MUFA) or polyunsaturated fatty acids (PUFA) can exist in the *cis* or *Trans* configuration. When the two hydrogen atoms are on opposite sides of the double bond, the configuration is called *Trans*. When the hydrogen atoms are on the same side of the double bond, the configuration is called cis [11].

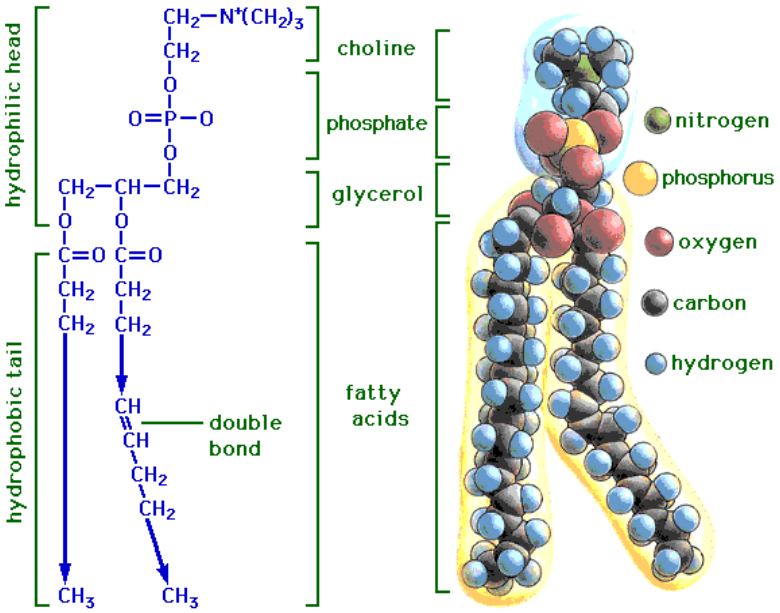

Fig. 3: Phospholipids structure [10]

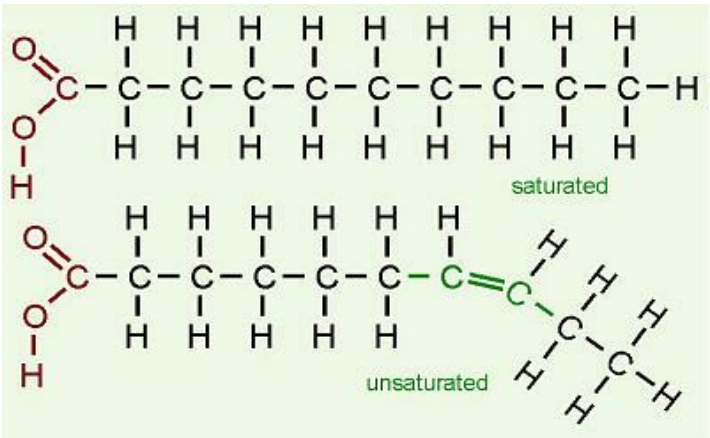

Fig. 4: Saturated and unsaturated fatty acids [12].

Chemically, PUFA belong to the class of simple lipids, as they are fatty acids with two or more double bonds in *cis* configuration. There are two main families of PUFA: n-3 and n-6. These fatty acids family are not convertible and have very different biochemical roles. Linoleic acid (n-6) (LA) and alpha-linolenic acid (n-3) (ALA) are two of the main representative compounds, known as dietary essential fatty acids (EFA) because they cannot be synthesized by humans [13].

Essential fatty acids

There are two classes of essential fatty acids (EFA), omega-6 and omega-3. The distinction between omega-6 and omega-3 fatty acids is based on the location of the first double bond, counting from the methyl end of the fatty acid molecule. In the omega-6 fatty acids, the first double bond is between the 6th and 7th carbon atoms and for the omega-3 fatty acids the first double bond is between the 3rd and 4th carbon atoms (Figure 5). Monounsaturated are represented by oleic acid, an omega-9 fatty acid, which can be synthesized by all mammals including humans. Its double bond is between the 9th and 10th carbon atoms [15, 16].

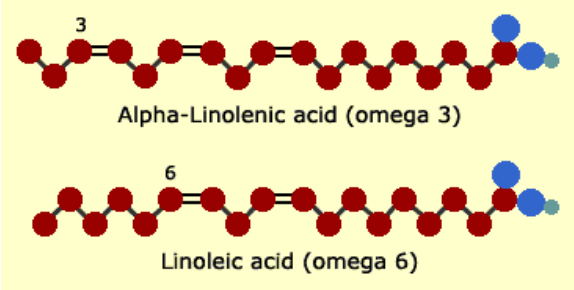

Fig. 5: Essential fatty acids: Omega-3 and omega-6 [14]

Omega-6 and omega-3 fatty acids are essential because humans like all mammals, cannot make them and must obtain them in their diet. Omega-6 fatty acids are represented by linoleic acid (LA; 18:2x6) and omega-3 fatty acids by a-linolenic acid (ALA; 18:3x3). LA is plentiful in nature and is found in the seeds of most plants except for coconut, cocoa, and palm. ALA on the other hand is found in the chloroplasts of green leafy vegetables, and in the seeds of flax, rape, chia, perilla and in walnuts [15].

Elongation and desaturation of essential fatty acids

Both EFA are metabolized to longer-chain fatty acids of 20 and 22 carbon atoms. LA is metabolized to arachidonic acid (AA; 20:4x6), and ALA to eicosapentaenoic acid (EPA) (20:5x3) and docosahexaenoic acid (DHA) (22:6x3), increasing the chain length and degree of unsaturation by adding extra double bonds to the carboxyl end of the fatty acid molecule [15] (Figure 6) .

Humans and other mammals, except for carnivores such as lions, can convert LA to AA and ALA to EPA and DHA, but it is slow. There is competition between omega- 6 and omega-3 fatty acids for the desaturation enzymes. However, both delta-4-desaturase (D-4) and delta-6-desaturase (D-6) prefer omega-3 to omega-6 fatty acids. But, a high LA intake interferes with the desaturation and elongation of ALA. Trans fatty acids interfere with the desaturation and elongation of both LA and ALA [15].

D-6 desaturase is the limiting enzyme and there is some evidence that it decreases with age. Premature infants, hypertensive individuals, and some diabetics are limited in their ability to make EPA and DHA from ALA. These findings are important and need to be considered when making dietary recommendations [15].

EPA and DHA are found in the oils of fish, particularly fatty fish. AA is found predominantly in the phospholipids of grain-fed animals and eggs [15].

ALA is found in triglycerides, in cholesteryl esters, and in very small amounts in phospholipids. EPA is found in cholesteryl esters, triglycerides, and phospholipids. DHA is found mostly in phospholipids [15].

In mammals, including humans, the cerebral cortex, retina, and testis and sperm are particularly rich in DHA. DHA is one of the most abundant components of the brain's structural lipids. DHA can be derived only from direct ingestion or by synthesis from dietary EPA or ALA [15].

Mammalian cells cannot convert omega-6 to omega-3 fatty acids because they lack the converting enzyme, omega- 3 desaturase. LA, the parent omega-6 fatty acid, and ALA, the parent omega-3 fatty acid, and their long-chain derivatives are important components of animal and plant cell membranes [15].

These two classes of EFA are not interconvertible, are metabolically and functionally distinct, and often have important opposing physiological functions. When humans ingest fish or fish oil, the EPA and DHA from the diet partially replace the omega-6 fatty acids, especially AA, in the membranes of probably all cells, but especially in the membranes of platelets, erythrocytes, neutrophils, monocytes, and liver cells. Whereas cellular proteins are genetically determined, the polyunsaturated fatty acid (PUFA) composition of cell membranes is to a great extent dependent on the dietary intake [15].

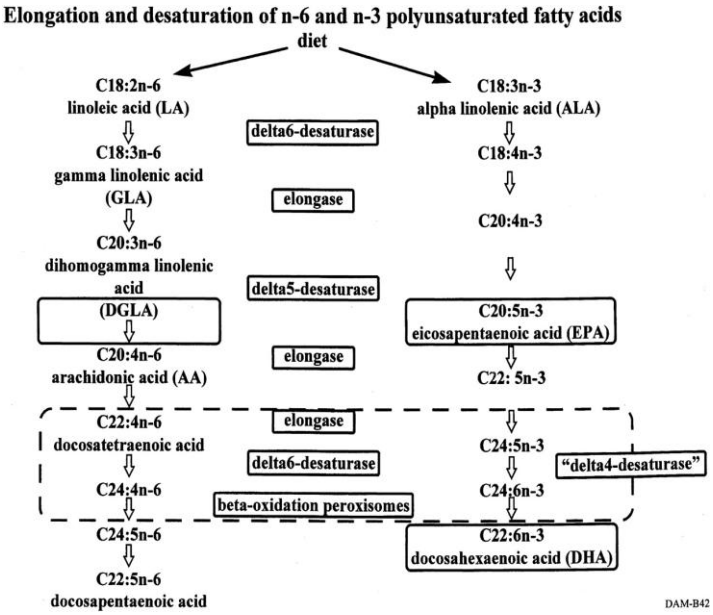

Fig. 6: Elongation and desaturation of omega-6 and omega-3 polyunsaturated fatty acids [15]

Fatty acids and health

Fatty acids carry out many functions that are necessary for normal physiological health. Saturated fatty acids are non essential fatty acids and are harmful if ingested excessively in food. On the contrary, polyunsaturated fatty acids (PUFA) are designated as "essential" for good health as their metabolic precursors cannot be synthesized in the body and must be ingested by food intake. PUFA have important effects on the structure and physical properties of localized membrane domains. They modulate enzyme activities, carriers and membrane receptors (low density lipoprotein (LDL) receptors, insulin, antibodies neurotransmitters, drugs receptors, etc.) [2].

Thus, PUFA deficiency in cell membranes leads to changes of phospholipids fatty acid composition and physicochemical properties of plasma membrane and lowering their fluidity [3].

Diet-induced changes in the polyunsaturated fatty acid composition of a cell membrane have an impact on the cell's function, partly because these fatty acids represent a reservoir of molecules that perform important signaling or communication roles within and between cells. In particular, dietary omega-3 fatty acids compete with the omega-6 family of dietary polyunsaturated fatty acids for incorporation into all cell membranes [16, 17] arguably; the most important of all cellular polyunsaturated fatty acids is the omega-6 family member arachidonic acid. When cells are activated by external stimuli, arachidonic acid is released from cell membranes and is transformed into powerful cellular mediators such as thromboxanes, prostaglandins and leukotrienes [18], hydroxy fatty acids, and lipoxins [19]. These compounds possess a range of activities, including activation of leukocytes and platelets, regulation of gastric secretions, induction of bronchoconstriction and signaling of pain in nerve cells (Figure 7). The importance of these compounds in health and disease is evident by the range of pharmaceutical products that target their biosynthesis or action [20] .Indeed, arachidonic acid metabolism is the target of nonsteroidal anti-inflammatory drugs (e.g., acetylsalicylic acid, ibuprofen), cyclooxygenase-2 (COX-2) inhibitors (e.g., rofecoxib, celecoxib) and leukotriene antagonists (e.g., montelukast, zafirlukast) [21].

Thus, a diet rich in omega-6 fatty acids shifts the physiological state to one that is prothrombotic and proaggregatory, with increases in blood viscosity, vasospasm, and vasoconstriction and decreases in bleeding time [19].

In the past, researchers looked mostly at the amount of omega-3 fatty acids present in the body to explain disease. However, an important part of the story includes the relationship that omega-3 have with omega-6 fatty acids in the body [22]

The ratio of the two types of fatty acids in the body becomes physiologically significant because AA competes with DHA and EPA for space in the cell membrane [19].

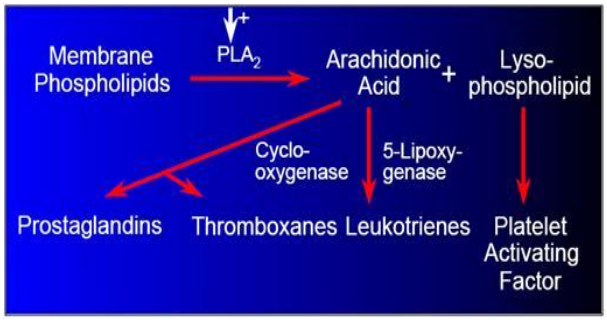

Fig. 7: The production of arachidonic acid (AA) as a result of free fatty acids (FFA) release causes a biochemical cascade ending with the production of thromboxane and leukotrienes [23]

Dietary omega-3 fatty acids directly affect arachidonic acid metabolism because they displace arachidonic acid from membranes and compete with arachidonic acid for the enzymes that catalyze the biosynthesis of thromboxanes, prostaglandins and leukotrienes [23]. Thus, the net effect of consuming foods enriched in omega-3 fatty acids is a diminished potential for cells like monocytes, neutrophils and eosinophils to synthesize these powerful arachidonic acid–derived mediators of inflammation and a diminished potential for platelets to produce the prothrombotic agent thromboxane A2 [17].

Fatty acids and inflammation

PUFA can modify the production and activity of various components of the immune system, thus it was reported that n-6 PUFA have pro-inflammatory effect although n-3 PUFA have anti-inflammatory effect. Several mechanisms had been proposed, including:

- Membrane fluidity (changes that might affect the capability of cytokines to bind to their respective receptors on the cell membrane)
- Lipid peroxidation (decrease or increase in free radical-induced tissue damage)
- Prostaglandin production (prostaglandins, which are derivatives of PUFA, modify cytokine activity)
- Regulation of gene expression (PUFA influences on the signal transduction pathways and modified mRNA activity) [9].

The role of PUFA in immune function is complicated by the fact that n-3 and n-6 have differential effects on various immune components. Singer and Richterheinrich [24] indicated that n-3 fatty acids induce a decrease in lymphocyte proliferation in humans and rats, a decrease in interleukin-1(IL-1) production, and a decrease in interleukin-2 (IL-2) production in both humans and animals. In addition, n-3 FA decreases tumor necrosis factor- α (TNF-α) production in humans but increases it in mice macrophages, and also decreases natural killer (NK) cell activity. On the other hand, n-6 increases the production of IL-2 in mice and decreases production of TNF-α and NK cell activity. Still other studies have shown that linoleic acid (n-6) decreases the activity of IL-2 [25] and increases IL-1 production and tissue response to cytokines, while n-3 generally decreases IL-1 production and activity. Despite some disagreement among studies, it seems that n-3 fatty acids (α -linolenic acid, DHA, EPA) decrease the production and activity of the pro-inflammatory cytokines (IL-1, IL-6, TNF-α) [26] and that n-6 family has the opposite effect [27]. The ability of n-3 PUFA to reduce pro-inflammatory cytokines and prostaglandin leads to the proposal for the use of fish oil to relieve pain. Fish oil, rich in n-3 PUFA, has been shown to decrease IL-6, IL-10, IL-12, TNF-α and prostaglandin E2 (PGE2) [28]. Increasingly, the salutary effects of PUFA are being examined not only with respect to their absolute level in diet, supplementation, or serum and tissue content, but also with respect to their proportional relationship to other fatty acids (FAs) [9].

Fatty acids and menstrual pain

Menstrual pain or dysmenorrhea is the most common gynecological complaint among female adolescents and young women. The majority of dysmenorrhea has a physiologic cause, with occasional psychological components [2].

The high intake of n-6 fatty acids in the diet results in a predominance of these fatty acids in the cell membrane phospholipids. After the onset of progesterone withdrawal before menstruation, these n-6 fatty acids, particularly arachidonic acid, are released, and a cascade of prostaglandins and leukotrienes is initiated in the uterus .The inflammatory response, which is mediated by these eicosanoids produces both cramps and systemic symptoms such as nausea, vomiting and headaches. The prostaglandins E2 and F2α, cycloxygenase-2 (COX-2) metabolites of arachidonic acid, cause especially potent vasoconstriction and myometrial contractions, which lead to ischemia, pain and systemic symptoms of dysmenorrhea [2, 29] (Figure 8) .

Several double blind, placebo controlled trial studies have demonstrated that dietary supplementation with n-3 fatty acids has a beneficial effect on symptoms of dysmenorrhea. EPA and DHA compete with arachidonic acid for the production of prostaglandins and leukotrienes through the incorporation into cell membrane phospholipids and through competition at the

prostaglandin synthesis level. PUFA n-3 can also inhibit arachidonic acid formation at the level of the Δ6 desaturase enzyme. In the uterus, this competitive interaction between n-3 and n-6 fatty acids may result in the production of less potent prostaglandins and leukotrienes and may lead to a reduction in the systemic symptoms of dysmenorrhea [2].

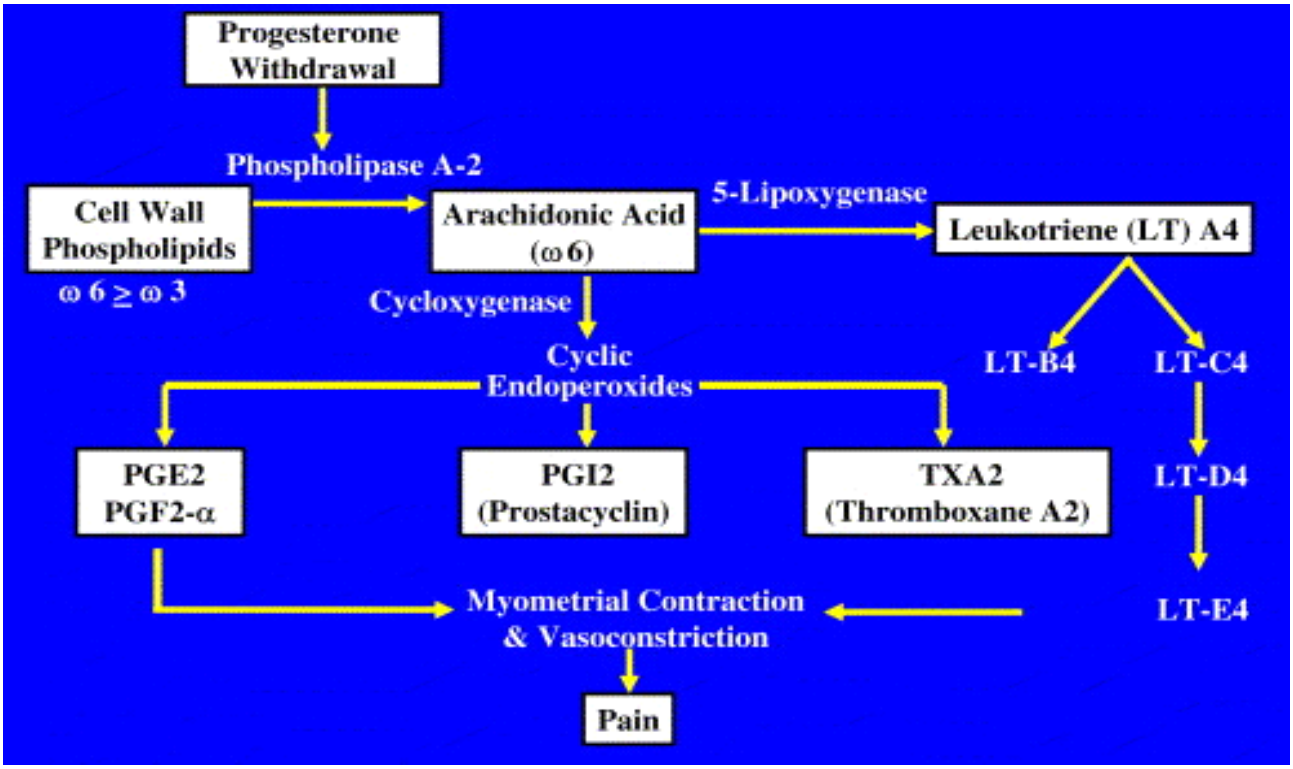

Fig. 8: Role of arachidonic acid in menstrual pain [29]

Fatty acids and coronary heart disease

The n-3 fatty acids of fish and fish oil have great potential for the prevention and treatment of patients with coronary artery disease. One of the most important effects of n-3 EPA and DHA is their ability to inhibit ventricular fibrillation and consequent cardiac arrest in primary and secondary prevention [30]. Several mechanisms had been proposed, including:

- EPA has antiarrhythmic effects and several antithrombotic actions, particularly inhibiting the synthesis of thromboxane A2, the prostaglandin that causes platelet aggregation and vasoconstriction.
- Reducing pro-inflammatory interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-α) and by inhibiting both cellular growth factors and the migration of monocytes.
- The n-3 fatty acids promote the synthesis of the beneficial nitric oxide in the endothelium.
- Experiments in humans indicate a hypolipemic effect of fish oil, especially the lowering of plasma triglyceride [2].
- Omega-3 fatty acids can also affect the function of membrane-associated proteins that are in direct contact with the lipid bilayer of cell membranes. Ion channels are membrane-associated proteins whose activity is modulated by omega-3 fatty acids .Sodium and calcium channels control voltage-gated sodium and calcium currents respectively. These currents are critical for the excitation of heart cells and contraction of the heart. Omega-3 fatty acids inhibit the activity of a number of cardiac ion-channel proteins, and this has been proposed to be partially responsible for their antiarrhythmic properties [31].

Fatty acids and hypertension

Different mechanisms appear to be involved in hypertension. Changes were reported in eicosanoid metabolism, loss of sodium, increase in potassium in cells and a decrease in intracellular calcium, among others [2].

In clinical studies, α-linolenic acid contributed to the lowering of blood pressure. In a population- based intervention trial it has been reported that a relationship may exist between n-3 fatty acid concentration in plasma phospholipids and blood pressure. There was a lower blood pressure at the baseline in subjects who habitually consume large quantities of fish, suggesting that supplementation with fish oils would be important from the primary prevention standpoint [2].

Fatty acids and diabetes

Diabetes mellitus is a complex of metabolic disease characterized by hyperglycemia, diminished insulin production, impaired insulin action, or a combination of both resulting in the inability of glucose to be transported from the blood stream into the tissues, which in turn results in high blood glucose levels and excretion of glucose in the urine . Cell functions involved in the action of insulin receptor binding enzyme and transporter activities are controlled by membrane properties [32].

Fatty acids (FA) composition of membrane phospholipids such as sphingomyelin (SM), phosphatidylethanolamine (PE) and phosphatidylcholine (PC) are tissue specific but are affected by the composition of the dietary fat. Changes in the fatty acids composition of erythrocyte membrane, which are easily accessible cells, reflects changes in that of membrane phospholipids of less accessible tissues [32].

The fatty acids composition of cell membrane can influence membrane associated phenomena such as the interaction between insulin and its receptors [33] .It was found that, fatty acids composition of the membrane phospholipids of insulin target tissues, such as liver and skeletal muscle, is a critical factor that influences both insulin secretion and its biological actions [34] thus,

membranes enriched in unsaturated fatty acids tend to bind more insulin than membrane enriched in saturated fatty acids [32].

The increase in free fatty acids concentration results in an increase in intracellular fatty acyl-CoA (FAcyl CoA) and diacylglycerol (DAG) concentrations ,results in activation of protein kinase C isoform (PKC-ε) leading to increase insulin receptor substrate-1(IRS-1) serine phosphorylation.This in turn leads to decrease IRS-1 tyrosine phosphorylation and decreas activation of IRS-1 associated phosphatidyleinositol 3-kinase (PI3-K) activity resulting in decreased insulin –stimulating glucose transport activity [35,36] (Figure 9).

Omega -3 fatty acids increased insulin sensitivity by increasing the residency time of glucose transporter -4(GLUT-4) in the plasma membrane , which leads to an expansion of intracellular pool of glucose-6- phosphate [37]. Moreover, Kato et al. [38] indicated that the amounts of skeletal muscle GLUT-4 in α-linolenic acid (omega-3) treated mice was increased to 250% compared to that in control mice (Figures10&11).

In the same line, Hussein et al. [39] indicated that flaxseed oil administration has a beneficial effect on decreasing insulin resistance in diabetic rats through the scavenging of free radicals and increasing antioxidant enzymes. This effect may be due to the fact that flaxseed oil contains high amount of unsaturated fatty acids, especially omega-3 [40] which upregulate gene expression of antioxidants enzymes and downregulate gene associated with production of reactive oxygen species [41].

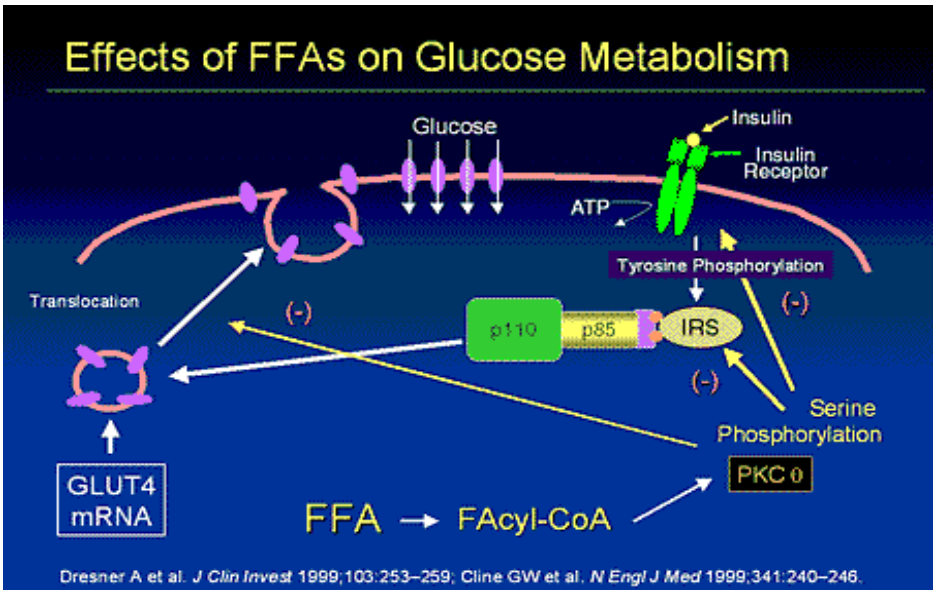

Fig. 9: Effect of fatty acids on glucose metabolism [36]

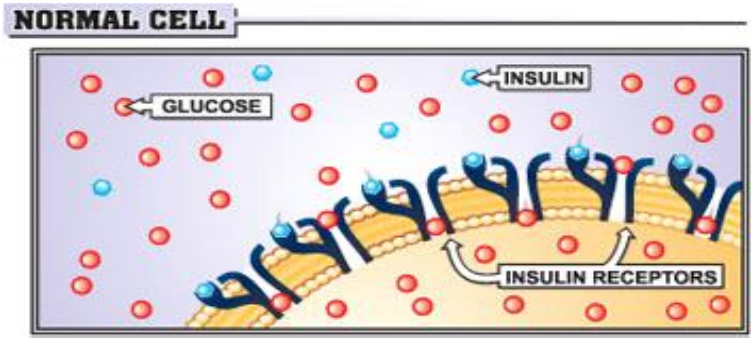

Fig. 10: Insulin receptors in normal cell [42]

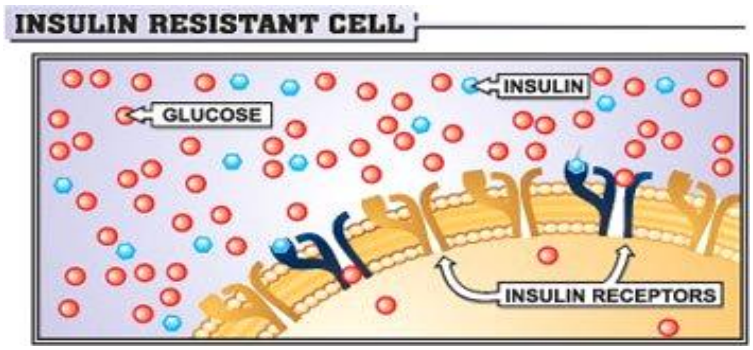

Fig. 11: Insulin receptors in insulin resistant cell [42]

Fatty acids and cancer

Several studies have demonstrated that dietary fat consumption modulates the risk of several types of cancer, especially breast, prostate and colorectal cancer. The relationship between the intake of specific fatty acids and the risk of cancer in humans has been investigated several times. Animal studies suggested that n-3 PUFA can inhibit the development of cancer, and that n-6 PUFA promote the development and growth of cancer [2].

Some authors observed that essential fatty acids and their metabolites can reverse and/or inhibit tumor cell drug resistance at least in vitro. In a clinical study using a case-control, the level of α-linolenic acid was inversely related to the risk of developing metastases in breast cancer patients. In a Japanese population study, an inverse association between prostate cancer mortality rate and serum n-3 PUFA levels appears to exist [2].

Several molecular mechanisms whereby n-3 PUFAs potentially affect carcinogenesis have been proposed, these mechanisms include:

- Suppression of arachidonic acid (AA, 20:4n-6)– derived eicosanoid biosynthesis, which results in altered immune response to cancer cells and modulation of inflammation, cell proliferation, apoptosis, metastasis, and angiogenesis (Figure12).
- Influences on transcription factor activity, gene expression, and signal transduction: Dietary PUFAs and their metabolites may exert some of their antitumor effects by affecting gene expression or the activities of signal transduction molecules involved in the control of cell growth, differentiation apoptosis, angiogenesis, and metastasis.
- Alteration of estrogen metabolism: high intake of n-3 PUFAs relative to that of n-6 PUFAs may decrease endogenous estrogen production, thus it is well known that estrogen has proliferative effects on estrogen-sensitive tissues and that high estrogen concentrations may increase the risk of breast cancer .
- Alteration the production of free radicals and reactive oxygen species [43].
- Mechanisms involving membrane fluidity and cell membrane permeability which provide more chances for anti-cancer elements to pass though the cell membrane and may be even intra-cellular membranes, such as the mitochondrial membrane [44, 45].

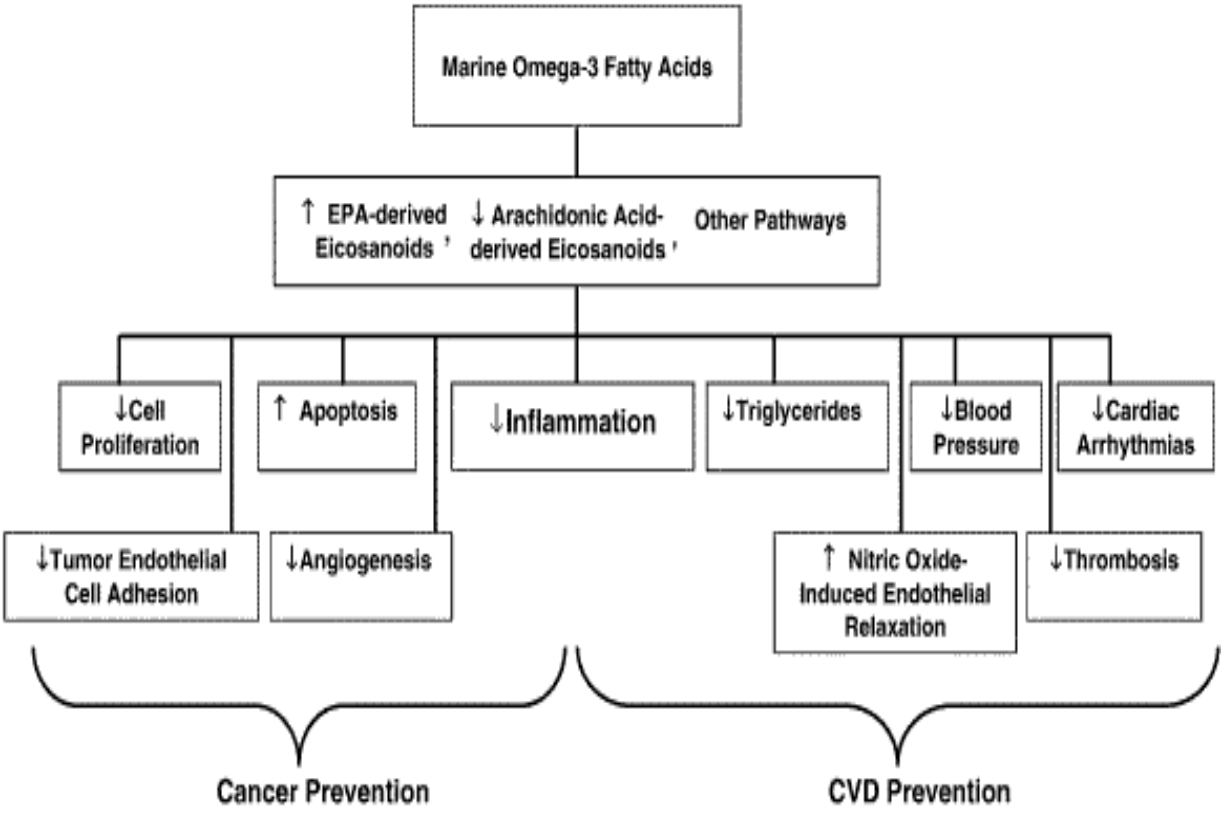

Fig. 12: Mechanism by which omega-3 fatty acids can lower cancer risk [45]

Fatty acids and brain

The cell membrane made from a saturated fats has a different structure and is less fluid than the one that incorporates an essential fatty acid. linoleic and alpha-linolenic acids have an effect on the neuronal membrane fluidity index. They are able to decrease the cholesterol level in the neuronal membrane, which would otherwise decrease membrane fluidity, which in turn would make it difficult for the cell to carry out its normal functions and increase the cell's susceptibility to injury and death [9].

These consequences for cell function are not restricted to absolute levels of FAs alone, rather it appears that the relative amounts of omega-3 fatty acids and omega-6 fatty acids in the cell membranes are responsible for affecting cellular function. At least six categories of PUFA effects on brain functions have been noted, namely:

- Modifications of membrane fluidity.
- Modifications of the activity of membrane bound enzymes.
- Modifications of the number and affinity of receptors.
- Modifications of the function of ion channels.
- Modifications of the production and activity of neurotransmitters.
- Signal transduction, which controls the activity of neurotransmitters and neuronal growth factors [9].

Determination of cell membrane fatty acids

Determination of cell membrane fatty acids is very complex and involves lipid extraction, methylation, separation steps and final analysis. Plasma fatty acids can also be measured. However, the RBCs profile is preferred because RBC fatty acids reveal long-term fatty acid balance in the tissues and is not influenced by recent dietary fat intake [46].

Extraction of cell membrane lipids

Total lipids in the cell membranes are extracted by chloroform: methanol method [47] modified from the method described by [48].

Extraction of cell membrane fatty acids

Extraction of cell membrane fatty acids is carried out by 2 % acetic acid- ethyl ether mixture (2:1 volume ratio) as described by [49].

Estimation of fatty acids

Fractionation and estimation of fatty acids are carried out by both gas chromatography (GC) as described by [50] and High performance liquid chromatography (HPLC) as described by [51,52].

CONCLUSION AND RECOMMENDATIONS

Conclusion

All living cells have plasma membrane , this membrane consists of two major categories, lipids and proteins, phospholipids are the most lipid component of the membrane and they consist of fatty acids saturated and unsaturated .Any change in the component of cell membrane especially fatty acids results in changes in membrane properties and functions .

The balance of omega-6/omega-3 fatty acids is an important determinant in decreasing the risk for many diseases.

Increased dietary intake of LA (omega-6) leads to production of prostaglandins, thromboxanes and leukotrienes and interferes with the incorporation of EPA and DHA in cell membrane phospholipids. EPA and DHA have the most potent anti-inflammatory effects. Inflammation is at the base of many chronic diseases, including coronary heart disease, diabetes, arthritis, cancer and mental health. Dietary intake of omega-3 fatty acids may prevent the development of many diseases.

Recommendations

- It is essential to increase the omega-3 and decrease the omega-6 fatty acids intake in order to have a balanced omega-6 and omega-3intake in the diet.
- Other research is required to determine the most effective omega 3 PUFA (EPA, DHA or a mixture of both).

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