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Rwview

Linoleic acid: have we understood how it works in Psychopathologies and Ischemic Cardiovascular Diseases?

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Summary. The question about Linoleic Acid, which remains arguable, is whether the Linoleic Acid is inversely correlated to the Cardiovascular Disease or not and whether increasing the intake over the Recommended Daily Allowance (RDA) is positive or negative. The scientific literature, past and recent, is still controversial about the matter. To try to answer this controversy, it is important to remember the role of the Linoleic Acid in the membrane and its relationship with cholesterol. Furthermore, it is important to examine the effect of the oxidation of Linoleic Acid, its impact on the gut microbiota and the consequences on the gut epithelial integrity.

Highlights. Nutritional considerations about Linoleic Acid > Characteristic of oxidizability of Linoleic Acid with respect to the cell membrane function > Linoleic Acid in platelets > The position of Linoleic Acid with respect to Psychopathology and Ischemic Cardiovascular Disease > Linoleic Acid and its effect on gut bacteria adhesion to gut epithelial barrier.

Key words: linoleic acid, psychopatology, cardiovascular disease, membrane mobility

Nutrionional Characteristic of Linoleic Acid

The essentiality of Linoleic Acid (n-6), and alpha Linolenic Acid (n-3), was discovered by Burr & Burr in 1929 (1). It mainly consists in preventing tissue degeneration until death (1) and it is considered that the 1- 2% of total calories is the right amount to prevent deficiency (2). The assumption of 3-6 grams of Linoleic Acid is considered safe for average adults.

If we consider an average of 2000 Kcal per day, the amount of Linoleic Acid should be provided by about 4 grams of the fatty acid.

The increased consumption of vegetable oils has increased the intake of Linoleic Acid to about the 6% of total calories (3), which means that in diets with an intake of 2000 calories, the amount of Linoleic Acid has increased of about 3 times increasing the risk of oxidation.

Linoleic Acid: oxidizability and cell membrane mobility

There is a relationship between the molecular structure and the environmental behavior of all chemical species, both in chemical and biological systems, although it is not always the same for the two systems.

The interpretation of an event in complex systems such as biological ones is often also due to the knowledge of the molecular structures involved.

The fatty acids, that can be found bound or in their free form in different types of substances, have a

carboxyl group able to bind different chemical species, while the hydrocarbon chain can give chemicalphysical interactions of energy that is lower than in a bond, but still very important for biology (4).

By the existence of van der Waals forces, the hydrocarbon chains of different molecules can approach each other to produce an electrostatic attraction for the coupling of those linearly similar molecular parts due to the deformations of the electronic clouds, with the genesis of electrostatic effects. The presence of double bonds in the hydrocarbon chain keeps part of the juxtaposed chains and decreases the total energy due to van der Waals forces, appearing among the molecules involved as critical points of minor forces and greater spatial bulk. For molecular structures rich in hydrocarbon, linear or not, the melting point, the viscosity and the respective structural distances between molecules will be different and indicative of the "interaction" intensity. In a biological membrane, dominated by the presence of phospholipids and cholesterol, its fluidity and functionality will be conditioned by these molecular interactions, with variations due to the presence of all the minor components of the membrane.

In addition to these effects, the thermostatic control will be a necessity in order to facilitate the homeostasis of many interactions, maintained by a series of self-regulations, triggered by any changes that have occurred.

The diet influences the composition and behavior of the membranes, which the living being will rebalance in relation to their respective needs. For membranes, saturated fatty acids and cholesterol will be used to increase the stiffness of the membrane folds, while polyunsaturated fatty acids will have the task of fluidizing it. The oxidation of fatty acids or their derivatives is an inevitable event for the needs of living organisms to produce energy (beta-oxidation) and for chemical transformations, i.e., the synthesis of oxygenated derivatives (prostaglandins, thromboxanes, leukotrienes, etc.).

Unfortunately, alongside the needs of the desired oxidative process, other undesired ones may occur.

Reactive Oxygen Species (ROS), considered as the cause of undesired biological oxidation, are "buffered" by numerous antioxidant systems present in our body.

The problem of oxidation arises when its quantity is very high, and the antioxidant means are not enough.

The connection between oxidation and inflammation, with the possible consequences, increases the importance of the oxidation argument.

Lipid oxidation mechanisms have been studied extensively through research conducted on foods to protect them, but little in biological systems. Oxidation in the aqueous-lipidic system has a very different behavior from that of lipids in the homogeneous phase. In fact, in the latter, it follows the perfect correspondence of speed with the level of unsaturation of the fatty acids (5, 6), while in the aqueous-lipidic system the Linoleic Acid (LA) is the most oxidizable and the Docosahexaenoic Acid (DHA) the least oxidizable (7).

The explanation of this behavior is attributable to the ability of the DHA to twist itself, in a watery environment, based on the presence of six double bonds reaching a structure with minimal surface exposed to water, the exact opposite behavior with respect to the lipidic system (8).

These phenomena explain the central role of Linoleic Acid in the regulation of cell membrane mobility and explain how this fatty acid, whose molecular size is greater than any other fatty acid, conditions both, cholesterol levels and exposure of membrane receptors.

Linoleic Acid, membrane viscosity, Ischemic Heart Disease and Psychopathology

Fatty acids and membrane viscosity of platelets (cells primarily involved in cardiovascular pathologies), have been extensively studied in patients with Ischemic Cardiovascular Disease (ICVD) and Major Depression-Bipolar Disorder (9-14).

In these studies, Linoleic Acid in platelets is, by far, lower than in normal subjects and this finding could confirm that lower levels are characteristic of the ICVD and Depression-Bipolar Disorder.

The question is whether a higher intake of Linoleic Acid can reduce cardiovascular risks.

Linoleic Acid facts

To better understand the position of Linoleic Acid in ICVD and Depression-Bipolar Disorder risk, some arguments should be addressed:

Linoleic Acid concentration in platelets of ICVD and Depression-Bipolar Disorder subjects.

The platelet concentration of Linoleic Acid in ICVD subjects with respect to the pathologic subjects is higher at such extent that is practically impossible to reach normal conditions (19% vs 10% in ICVD subjects) (9,11,14).

The platelet concentration of Linoleic Acid in in suicide risk and severe heart ischemia reaches a very low concentration, about 5% (11, 15).

Linoleic Acid and Cholesterol have the same behavior in cell membrane

Linoleic Acid and Cholesterol act the same way in the membrane. The larger molecular dimension of the first increases the fluidity of the membrane, but an increase of cholesterol contrasts this to maintain the balance of the membrane mobility (16, 17).

Cholesterol protects Linoleic Acid from oxidation being the latter the trigger of endothelial activation which leads to pro inflammatory effects (18).

Linoleic Acid is, among all polyunsaturated fatty acids, the most oxidizable

It is demonstrated that Linoleic Acid, because of the above characteristic, is more oxidizable with respect to the other polyunsaturated fatty acids (19) and that the cell membrane has an increased risk of oxidation (20-22).

Despite the large number of scientific papers claiming a positive effect of Linoleic Acid in ICVD risk reduction, other papers claim the responsibility of Linoleic Acid in ICVD because of its peroxidative role in LDL, VLDL and HDL and the production of oxidized metabolites such as 9-HODE (9-hydroxy-10,12- octadecadienoic acid) and 4HNE (4-Hydroxynonenal) (23, 24).

Linoleic Acid influences the gut bacterial adhesion to the epithelial gut opening the door to the silent inflammation which is considered one of the major events in ICVD and Psychopathology

Complex cellular and inflammatory interactions are involved in the progress of vascular diseases, such as, for example, the association between pro-inflammatory cytokines with endothelial dysfunction and atherosclerosis (25, 26).

Several studies, including the ones conducted by Arif et al. (27) have demonstrated that the increased membrane fluidity of bacteria reduces the adhesion to the epithelial wall influencing the opening of the tight junctions and giving access to the pro-inflammatory cytokines.

The excessive presence of PUFAs in general, in particular Linoleic Acid, both in the culture media of the various bacterial strains and in the daily diet, such as seed oils, lecithin, etc. (28) should be avoided in order to prevent the silent inflammation involved in ICVD and in Psychopathologies. Further, it is of interest the activity of *B. longum* and *L. acidophilus* in their antioxidant capacity on the Linoleic Acid and in their scavenging activity on malondialdehyde (29).

Conclusion

The evidence of a reduced plasma and cellular concentration of Linoleic Acid in cardiovascular risk and in the course of ischemic cardiovascular disease has certainly led many researchers to believe that it is advisable to take a greater amount of Linoleic Acid than recommended.

This work is not a criticism against the opinion of researchers (29) who recommend increasing the intake of Linoleic Acid over the recommended amount; however, it wants to draw attention to the biochemical aspects of Linoleic Acid. Based on the tissue distribution of Linoleic Acid, ranging from about 1% of the brain (30) to about 20% of the cardiac cells (31) it is recognized the role that Linoleic Acid plays in the regulation of the ion channels flux (32, 33). The authors suggest respecting the quantities recommended to not compromise the delicate biochemical role of this fatty acid with the risk of an increased oxidizability with respect to the heart and brain functions (15).

Competing interests

The authors declare that they have no competing interests

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