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Original article

Cholesterol and Linoleic Acid: a forgotten cooperation?

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Summary. This mini review proposes a reflection on the role of cholesterol in its cooperation with oxygen and linoleic acid. The authors deal with the logics of membrane mobility, where the concentrations of cholesterol and linoleic acid exert a strong influence on the dynamics of the greater or lesser entry of oxygen and, therefore, on the impact in the determinism of oxidative phenomena.

Key words: Cholesterol and oxygen relationship, Cholesterol and reactive oxygen species (ROS), Cholesterol and Linoleic Acid balance

Introduction

In the last decades, cholesterol has been the subject of many investigations because of its alleged role in ischemic heart disease: it is primarily involved in the maturation of the brain, in regulating the mobility of cell membranes, in the production of basic substances for the organism such as vitamin D and sex hormones. Guidelines have been created that have increasingly reduced the safety levels of circulating cholesterol to prevent cardiovascular diseases. Now, it seems that a total cholesterol of 180 mg / dl is considered safe. The following observations are not addressed to this new limit as a criticism, but they want to remind of some metabolic and not well-known functions of cholesterol in trying to balance bimolecular dynamics in the membrane. Cholesterol guarantees the membrane integrity and therefore allows the membranes to carry out their physiological function.

Cholesterol-Oxygen ratio

International literature shows an interesting relationship between cholesterol and the progressive increase of oxygen during evolution, i.e. cholesterol becomes important with the transition from prokaryotic to eukaryotic cell, and in particular it increases its concentration in cell membranes when the oxygen concentration increases (1). In support of this theory, it has been shown that in the metabolic pathway of cholesterol production, starting from squalene, there is a gradual concentration of oxygen accompanying the metabolic pathway of cholesterol synthesis until the final stage (2). This "friendly" relationship between cholesterol and oxygen led to the formulation of a further hypothesis, i.e. cholesterol has antioxidant properties. The hypothesis of the antioxidant role of cholesterol is more evident because of its correlation with the production of reactive oxygen species (ROS) and the function of ion channels. It has been shown that the depletion of cholesterol is associated with increasing of ROS production inside and outside of the cell. This seems to be mediated by NADPH oxidase, which generates hydrogen peroxide. The latter is then released into the extra cellular space, thus facilitating its passage in the cytoplasm through the membrane. In the case of a reduction of membrane cholesterol, ROS increase transiently for a short time, and this enables the increase of intracellular calcium and the spontaneous exocytosis (3). This would explain the importance of the role of ROS only in the initial stage of induction of exocytosis, e.g., for neurotransmitters. Moreover, a reduced concentration of cholesterol in the membranes can lead to

intensifying the mechanisms of phagocytosis and it is likely that the prolongation of this effect is caused by the activity of the protein kinase, ion channels, pumps and membrane fluidity. It is known that the conditions of the membrane mobility (viscosity and fluidity) affect the exposure of serotonin receptors, deeply involved in Mood Disorders (4). Other relationships that cholesterol has with oxygen are well described in reference to red blood cells, mitochondria, retina and brain (5-7). As far as concerns red blood cells, the literature reports that an increase of cholesterol in the membrane corresponds to a reduction of the oxygen transport, a clear evidence of the oxygen-cholesterol ratio (8). With regard to mitochondria, which contain reduced amounts of cholesterol compared to plasma membranes, an increase of the cholesterol can significantly reduce the mitochondrial respiration (9). It should not be forgotten, however, that substances inhibiting cholesterol synthesis inhibit also the coenzyme Q10, which is a fundamental component of mitochondrial respiration. A further confirmation of the relationship between cholesterol and oxygen concerns the cells of the lens, where a high concentration of cholesterol is usually found. Cholesterol helps to protect the cells of the lens from an excessive concentration of oxygen (10).

It is interesting to remember that the brain is equipped with a self-synthesis of cholesterol, with a very long half-life (6 months-5 years) and that the disposal of cholesterol through the blood brain barrier happens through its oxidation (11). Also in this case, there is an evident relationship between cholesterol and oxygen in maintaining cholesterol homeostasis.

Cholesterol and Linoleic Acid

Some research studies showed that there is a common characteristic in ischemic cardiovascular disease and mood disorders: a reduction of linoleic acid in the platelet membranes (12-16). This evidence, which significantly influences the adjustment of the mobility of the membrane, and that is mainly due to the characteristics of the melting point of linoleic acid, leads to a reflection on the relationship between linoleic acid and cholesterol, since the latter is a decisive element in the expression of membrane mobility.

Linoleic acid, given its greater molecular size among all the other fatty acids, is the one that occupies, within the membrane lipid bilayer, the greatest space, and since the increasing number of cholesterol molecules within the membrane stabilizes the serotonin receptors, the same could apply to the Linoleic Acid when it decreases. Another, possible, hypothesis of the cooperation between cholesterol and linoleic acid (17). In this regard, we should remember that cholesterol protects the linoleic acid from the membrane oxidation. An example (18) is shown in the phosphatidylcholine fraction, since it is one of the richest in linoleic acid among the various biological districts of the body. Another interesting interaction between cholesterol and linoleic acid regards the mechanism of activation of endothelial cells triggered by linoleic acid (19). Also in this case, the presence of adequate amounts of cholesterol would have the ability to control the effects of linoleic acid in endothelial cells through a mechanism of protection from oxidative and pro inflammatory effects. It seems that this mechanism, which functions through signaling pathways that cause the activation of endothelial cells, is due to the amount of cholesterol. A moderate increase of cholesterol, therefore, appears to be beneficial.

The low concentration of linoleic acid recorded in platelets and the deep involvement of these cells in coronary heart disease (14,15) could mean, surprisingly, not that the low concentration of linoleic acid is an accidental marker of the phenomenon, but that it could be rather a defense mechanism that the body creates to reduce the phenomenon of activation of endothelial cells by linoleic acid.

Recent papers show some interesting aspects of the linoleic acid as a possible element of symmetry breaking of the brain and of evolutionary interest: all living beings have a very small (close to zero) brain concentration of the linoleic acid (essential fatty acid) during their whole life, from fetus to 80 years of age (20,21).

Other interesting scientific peculiarities about linoleic acid involve hibernating animals, fasting reptiles and the brain of different animal species and of the human being (22,23).

It has been shown that if a hibernating animal does not have a sufficient amount of linoleic acid in

brown adipose tissue, at the end of the torpor it could suffer a cardiac arrest. This is because of the effects that the reduced concentration of the linoleic acid in cardio myocytes has on calcium pumps of the endoplasmic reticulum, promoting an accumulation of calcium in the cytosol (24).

Recently, another relationship between linoleic acid and cholesterol (HDL) has been shown (25) about the strong link between the product of lipid peroxidation 4HNE (4-Hydroxynonenal), its potential precursor, i.e. linoleic acid, and HDL cholesterol. It seems that 4HNE increases proportionally to a reduction of HDL.

These observations tend to show that the organism has a specific need to maintain a balance between cholesterol and membrane fatty acids where these two elements are critical for the membrane mobility, the Gs alpha protein, the cytoskeleton and the ion channels' flow (26-29).

Conclusion

We need to reflect on the concept of homeostasis and reinterpret the phenomenon "cholesterol" which, in the collective imagery, is only seen as negative.

We need a re-reading of all the cholesterol functions, which is not mainly epidemiological and ideological but that considers, more precisely, what should be the real limits of the cholesterol level in blood and in cell membrane. The level should be compatible with the fulfillment of the cholesterol's important functions that are essential for the proper management of the body balance, and therefore for our health (30).

References

1. Galea AM, Brown AJ. Special relationship between sterols and oxygen: were sterols an adaptation to aerobic life? Free Radic Biol Med 2009; 47:880–9.
2. Smith LL. Another cholesterol hypothesis: Cholesterol as antioxidant. Free Radic Biol Med 1991; 11:47–61.
3. Petrov AM, Yakovleva AA, Zefirov AL. Role of membrane cholesterol in spontaneous exocytosis at frog neuromuscular synapses: reactive oxygen species-calcium interplay. J Physiol. Blackwell Publishing Ltd; 2014; 592:4995– 5009.
4. Saxena R, Chattopadhyay A. Membrane cholesterol stabilizes the human serotonin(1A) receptor. Biochim Biophys Acta 2012; 818:2936–42.
5. Baggetto LG, Clottes E, Vial C. Low mitochondrial proton leak due to high membrane cholesterol content and cytosolic creatine kinase as two features of the deviant bioenergetics of Ehrlich and AS30-D tumor cells. Cancer Res 1992; 52:4935–41.
6. Pikuleva IA, Curcio CA. Cholesterol in the retina: The best is yet to come. Prog Retin Eye Res. Elsevier Ltd; 2014: 41:64–89.
7. Björkhem I, Meaney S. Brain cholesterol: long secret life behind a barrier. Arterioscler Thromb Vasc Biol 2004; 24:806–15.
8. Menchaca HJ, Michalek VN, Rohde TD, Hirsch AT, Tuna N, Buchwald H. Improvement of blood oxygen diffusion capacity and anginal symptoms by cholesterol lowering with simvastatin. J Appl Res 2004; 4:410–8.
9. Kennedy BE, Madreiter CT, Vishnu N, Malli R, Graier WF, Karten B. Adaptations of energy metabolism associated with increased levels of mitochondrial cholesterol in Niemann-Pick type C1-deficient cells. J Biol Chem. American Society for Biochemistry and Molecular Biology Inc.; 2014; 289:16278–89.
10. Subczynski WK, Raguz M, Widomska J, Mainali L, Konovalov A. Functions of cholesterol and the cholesterol bilayer domain specific to the fiber-cell plasma membrane of the eye lens. J Membr Biol 2012; 245:51–68.
11. De Fabiani E. Lipids in the brain: Crossing the "insurmountable" barrier for a fatty, happy life. Eur J Lipid Sci. Wiley-VCH Verlag; 2014; 116:941–2.
12. Benedetti S, Bucciarelli S, Canestrari F, Catalani S, Mandolini S, Marconi V, et al. Platelet's Fatty Acids and Differential Diagnosis of Major Depression and Bipolar Disorder through the Use of an Unsupervised Competitive-Learning Network Algorithm (SOM). Open J Depress 2014; 3:52–73.
13. Cocchi M, Tonello L. Bio molecular considerations in Major Depression and Ischemic Cardiovascular Disease: Central Nervous System Agents in Medicinal Chemistry 2010; 9: 2-11
14. Cocchi M, Gabrielli F, Tonello L. Platelet's Fatty Acids Secrets in Coronary Artery Disease (CAD), Lett to Ed BMJ. 2013; Oct 28th.
15. Cocchi M, Tonello L, Bosi S, Cremonesi A, Castriota F, Puri B TS. Platelet oleic acid as Ischemic Cardiovascular disease marker. BMJ. 2004; 329:1447.
16. Cocchi M, Tonello L, Lercker G. Fatty acids, membrane viscosity, serotonin and ischemic heart disease. Lipids Health Dis 2010; 9:97.
17. Cocchi M, Tonello L, Tuszynski J. Connection Between the Linoleic Acid and Psychopathology: A Symmetry-Breaking Phenomenon in the Brain? Commun to Ital Soc Exp Biol (Bologna Section) April, 2015.
18. Mazari A, Iwamoto S, Yamauchi R. Effects of linoleic acid position in phosphatidylcholines and cholesterol addition on their rates of peroxidation in unilamellar liposomes.

Biosci Biotechnol Biochem 2015; 74:1013–7.
19. Lee YW, Park HJ, Hennig B, Toborek M. Linoleic acid induces MCP-1 gene expression in human microvascular endothelial cells through an oxidative mechanism. The Journal of Nutritional Biochemistry 2001; 12:648-654.
20. Cocchi M, Tonello L, Gabrielli F, Minuto C. Human and Animal Brain Phospholipids Fatty Acids, Evolution and Mood Disorders. J Phylogen Evol Biol 2014; 2:2.
21. Svennerholm . Distribution and fatty acid composition of phosphoglycerides in normal human brain. J Lipid Res 1968; 9:570-579.
22. Lamine F, Bouguerra R, Jabrane J, Marrakchi Z, Rayana MC Ben, Slama C Ben, et al. Food intake and high density lipoprotein cholesterol levels changes during Ramadan fasting in healthy young subjects. Tunisie Medicale 2006; 84:647–50.
23. McCue MD. Fatty acid analyses may provide insight into the progression of starvation among squamate reptiles. Comp Biochem Physiol 2008; part A151:239–46.
24. Giroud S, Frare C, Strijkstra A, Boerema A, Arnold W, Ruf T. Membrane phospholipid fatty acid composition regulates cardiac SERCA activity in a hibernator, the Syrian hamster (Mesocricetus auratus). PLoS One 2013; 8(5): e63111.
25. Asselin C, Ducharme A, Ntimbane T, Ruiz M, Fortier A, Guertin M-C, et al. Circulating levels of linoleic acid and HDL-cholesterol are major determinants of 4-hydroxynonenal protein adducts in patients with heart failure. Redox Biol 2014; 2:148–55.
26. Cocchi M, Tonello L. Gabrielli F. Possible Roles of Cell Membrane & Cytoskeleton in Quantum Aspect of Psychiatry. J Conscious Explor Res 2012; 3:1082–100.
27. Tonello L, Cocchi M. The cell membrane: Is it a bridge from psychiatry to quantum consciousness? [Internet]. Neuro-Quantology 2010; 1:54–60.
28. Cocchi M, Tonello L, Rasenick MM. Human depression: a new approach in quantitative psychiatry. Ann Gen Psychiatry 2010; 9:25.
29. Summhammer J, Sulyok G, Bernroider G, and Cocchi M. Forces from Lipids and Ionic Diffusion: Probing lateral membrane effects by an optimized filter region of voltage dependent K+ channels. arXiv. Org. Physics 2020.
30. Cocchi M, Tonello L, Gabrielli F. Cholesterol on Sunset Boulevard: the decline of a myth. Letter to the Editor. BMJ 2016.

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