

Omega 3

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Phospholipids as physiological fatty acid carriers for the brain

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Abstract

Despite their ancient discovery and structure determination in the middle of the 19th century, phospholipids remained poorly studied for a long time. Their importance as cell membrane building blocks, as intracellular signals and as nutrients has been recently highlighted and is now gaining interest. The scientific studies tend to demonstrate their role as physiological carriers, and their essential implication for the nervous tissue supply in polyunsaturated fatty acids. Phospholipids appear to be better carriers of omega-3 fatty acids than triglycerides. The fatty acids linked to these polar lipids are more efficiently targeted to specific organs and incorporated in the membrane structures of cells. This is particularly the case for the central nervous system where phospholipids and omega-3 fatty acids, especially DHA, are both implicated in the regulation of nervous cell membrane functioning and brain performances.



INTRODUCTION

The description of the structure of the cell membrane led to the discovery that they are composed of phospholipids organized in bilayers. Phospholipids represent the building blocks of cell membranes and exert functional roles which are far beyond a simple barrier action.

The implication of phospholipids in food balance arose some years ago when the availability of the main natural sources for their food supply was blocked by the ESB crisis. Animal offal and liver were no longer available for human consumption which led some scientists to examine the potential consequences of this modification.

Moreover, the appearance of food ingredients where omega-3 fatty acids are primarily esterified to phospholipids permitted some comparisons between phospholipids and the currently used fish oil triglycerides.

These are mainly krill oil and fish roe extracts, and to some extent egg yolk phospholipids.

Are all these lipid sources equivalent for the supply of omega-3 fatty acids to the body? And what do we know about the importance of phospholipids as food nutrients?



PHYSICO-CHEMICAL CHARACTERISTICS OF PHOSPHOLIPIDS

Phospholipids are basically lipids that contain a phosphorus moiety. They are built either with a glycerol backbone and are then called glycerophospholipids, or with sphingosine from which arise the sphingolipids. Each glycerophospholipid contains two fatty acids whereas a sphingolipid contains only one fatty acid molecule.

The major and best known phospholipids present in lecithins are glycerophospholipids. The part of the molecule where the two fatty acids are located represents an apolar (lipophilic) zone. The phosphorylated end of the molecule bears a polar (hydrophilic) head which determines its final nature: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine or phosphatidylinositol. A free phosphorus end corresponds to phosphatidic acid.



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The phospholipids found in cell membrane structures or in natural oily extracts are mixtures of these different molecules. Their respective proportions vary according to their origin.

The presence of both lipophilic and hydrophilic parts in the same molecule gives to phospholipids their specific properties to organize in membrane bilayers or to play their functional role as food emulsifiers. These emulsifying properties will also facilitate the triglyceride digestion process in the digestive tract.

One of the interesting properties of phospholipids is the high oxidative protection they afford to the polyunsaturated fatty acids compared to the other forms available. Many studies have shown the higher stability of the complexes between omega-3 fatty acids and phospholipids. They have been reviewed by Henna Lu *et al* in 2011 (1). Depending on the experiments, phospholipids were 2-5 times more stable than triglycerides, the least resistant to oxidative degradation being fatty acid ethyl esters and free fatty acids.

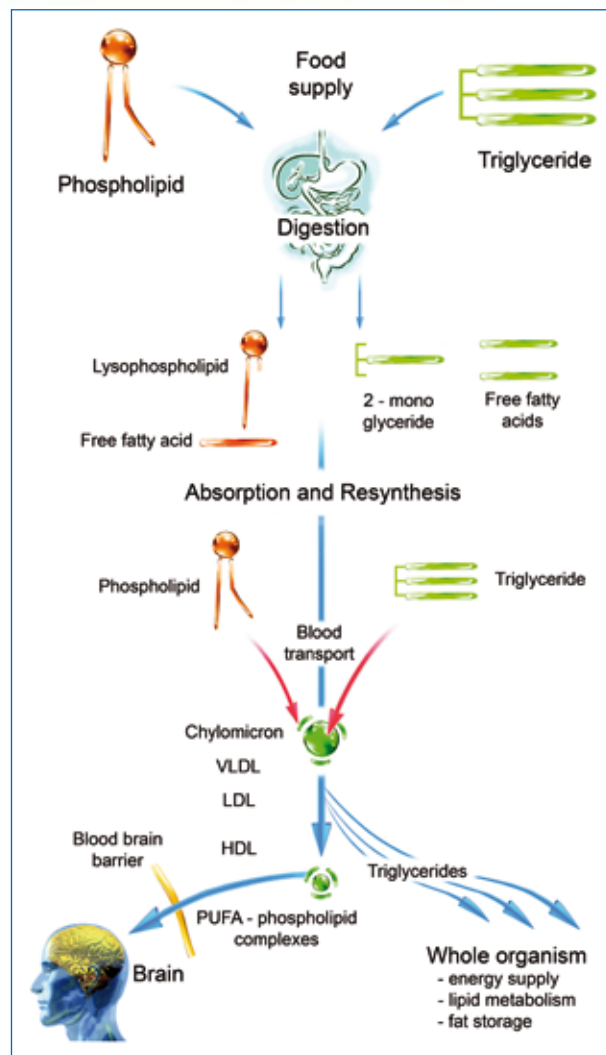
PHOSPHOLIPID METABOLISM AND FOOD SUPPLY

Phospholipids can be synthesized *de novo* in the endoplasmic reticulum of cells, mainly in adipocytes, liver and intestinal cells.

As the physiological requirements have not been calculated for phospholipids, there are no official daily recommendations for them. But it is estimated that the phospholipid food supply was approximately 6 g/day at the beginning of the 20th century. Since then it decreased regularly and is now 2-4 g/day.

The physiological synthesis of phospholipids may not be sufficient to cover all the needs of the body, and it is known that this synthesis activity decreases with age.

Moreover the synthesis of phosphatidylcholine, the main phospholipid of the cell membranes, from phosphatidylethanolamine requires several methyl group transfers. These methylation reactions use S-adenosylmethionine as a methyl donor and lead to the production of homocysteine which is suspected to increase the risk of cardiovascular disease.



The food supply of phospholipids appears thus to be an important and underestimated parameter of food balance also involved in health management.

The metabolic pathways of triglycerides and phospholipids are different. Their assimilation involves in both cases the progressive release of their fatty acid content (2). Whereas triglycerides need to be emulsified by bile salts for their enzymatic digestion, the emulsifying properties of phospholipids allow them to be fully accessible to digestive enzymes. The food phospholipids will also participate to the emulsification of triglycerides and optimize their assimilation.

The enzymatic digestion of the triglycerides begins in the stomach by lingual and gastric lipases, and continues in the small intestine. The enzymes release the two fatty acids situated at the external positions of glycerol and transform the triglycerides in 2-monoglycerides and free fatty acids which are absorbed by the enterocytes in the small intestine.





Phospholipids are digested and assimilated in the small intestine after the intervention of a pancreatic phospholipase A2 which releases the fatty acid situated at the internal position of the molecule. The resulting lysophospholipids and free fatty acids are then incorporated in the enterocytes.

distribution of their fatty acids in the bloodstream. They will progressively concentrate and be delivered without modifications to the cells.

Sinclair in 1974 (6) compared the assimilation and distribution of radiolabelled long chain PUFA (docosahexaenoic and arachidonic acids) to shorter PUFA (linoleic and alpha-linolenic acids). This study showed that long chain PUFA are more rapidly absorbed at the intestinal level, preferentially incorporated to phospholipids and recovered in the central nervous system. On the contrary, the radioactivity of linoleic and alpha-linolenic acids was recovered mainly in triglycerides, and then metabolized and dispatched in the entire organism.

These observations strongly suggest that fatty acids carried on phospholipids are not intended to produce energy and that they are also protected from dilution along their lymphatic and blood transports.

Target	Parameter	Model	Conclusion	Ref
Assimilation from food	Incorporation of LC-PUFA to plasmatic HDL	Piglets	Phospholipids more efficient than TG	4
Assimilation from food	DHA linked to phospholipids vs. TG	Rat	DHA twice as much absorbed from phospholipids than TG	3
Incorporation in brain from blood (perfusion)	DHA linked to phosphatidylcholine vs. free DHA	Rat	DHA 12 times as much absorbed from lyso-PC than free DHA.	8
Brain targeting after food supply	ARA linked to phospholipids vs. TG	Baboon	ARA twice as much incorporated in brain from phospholipids than TG	11
Brain targeting after food supply	DHA linked to phospholipids vs. TG	Rat	DHA twice as much incorporated in brain from phospholipids than TG	12

LC-PUFA: long chain polyunsaturated fatty acid; TG: triglyceride; Lyso-PC: Lyso-phosphatidylcholine

*Phospholipids as physiological fatty acid carriers for the brain.
Some examples of the efficiency of phospholipids as polyunsaturated fatty acid carriers.*

The free fatty acids are re-esterified to the monoglycerides and lysophospholipids in the enterocytes to rebuild new triglycerides and phospholipids which are then incorporated in globular structures called chylomicrons. Chylomicrons are released in the lymphatic system to transport the lipids supplied by food from the intestine to liver and adipose tissue. After their passage by the liver, they will be distributed to the different organs by similar structures called lipoproteins.

The observed differences between triglycerides and phospholipids as fatty acids carriers begin at this point.

After introducing DHA in the stomach of rats, Cansell *et al* (3) measured that the quantity of DHA absorbed was nearly doubled when it is supplied esterified to phospholipids compared to fish oil triglycerides.

Polyunsaturated fatty acids appear to be better incorporated in plasmatic HDL lipoproteins when they are provided as phospholipids rather than triglycerides (4). This preferential uptake was also observed *in vitro* with the cellular model of intestinal absorption Caco-2 cells (5).



DHA SUPPLY TO BRAIN CELLS: A CHALLENGE FOR PHOSPHOLIPIDS.

The cell types for which membrane constitutes the support of the biological activity are highly dependent on their fatty acid and phospholipid compositions. This is particularly the case of nervous and retina cells and spermatozoa (7). In the case of nervous cells, it is known that phospholipids are specifically distributed between the two bilayers of the cell membrane. Phosphatidylserine appears to be preferentially concentrated at the cytoplasmic face. The phospholipid and fatty acid composition will influence the membrane fluidity in the direct environment and the functioning of membrane receptors and ionic channels. Moreover, the membrane composition of the synapses is different from the other parts of the cells.



PHOSPHOLIPIDS AS POLYUNSATURATED FATTY ACID CARRIERS FOR SPECIFIC TISSUES.

While triglycerides are incorporated in the core of chylomicrons and lipoproteins, phospholipids constitute their external layer. During their transport, the triglycerides will be continuously hydrolyzed by a specific lipoprotein lipase to provide fatty acids to tissues. A part of the released fatty acids will be oxidized and used as substrates for the production of energy.

Phospholipids escape to this hydrolysis and wide





In a comparative study between different tissues, Arterburn *et al* (7) observed that only two polyunsaturated fatty acids accumulate in nervous tissues: arachidonic acid (ARA or 20:4 ω 6) and docosahexaenoic acid (DHA or 22:6 ω 3). It is estimated that DHA accounts for approximately 10% of the total fatty acids in the whole human brain.

The endogen synthesis of DHA by enzymatic conversion from alpha-linolenic acid (ALA or 18:3 ω 3) is too low to fulfil to requirements of the brain. The presence of the blood-brain barrier makes the central nervous system a challenge for its supply in this essential fatty acid. This is where phospholipids will exhibit their main specificity as long-chain polyunsaturated fatty acid carriers.

The complexes between DHA and phospholipids appear to be a particularly important and efficient form of DHA supply to the brain compared to other organs (8). It had been reported that DHA is rapidly incorporated in red blood cells and then in brain cells when it is provided as phosphatidylcholine-DHA (9).

The blood-brain barrier cells are able to enzymatically modify the circulating phospholipids to make them cross the barrier. Phosphatidylethanolamine can be transformed into phosphatidylcholine and then lysophosphatidylcholine when incubated with isolated blood-brain barrier cell membranes (10). Phosphatidylcholine appears thus to be the carrier that allows DHA to cross the blood-brain barrier before being incorporated in the central nervous system.

An *in vivo* illustration was given by Wijendran and his colleagues in 2002 (11) who observed a two-fold accumulation of arachidonic acid in the brain of baboon neonates after feeding them with a phospholipid source compared to a triglyceride source of ARA. The same conclusion had been driven in rat after a food supply of DHA linked to phospholipids *versus* triglycerides with a twofold incorporation of DHA from the phospholipidic source (12).



CONCLUSION

Nervous cells are highly dependent on the fatty acid and phospholipid composition of their membranes for their optimal functioning. As the endogen synthesis of the long chain omega-3 fatty acid DHA and phospholipids cannot cover their requirements, the nervous cells depend on their external supply for these essential nutrients. This may be even more important during specific periods like pregnancy, fetal nervous system growth or aging.

It is also known that omega-3 fatty acids or phosphatidylserine are essential for optimal brain performances and memory. Reaching the nervous cell membranes is a mandatory condition for DHA and phospholipids to exert their positive effects. It constitutes a difficult challenge not only because of the absorption and transport steps but also because of the presence of the blood-brain barrier. Phospholipids appear to be the physiological answer to this challenge.

For the brain, the food supply of DHA in the form of DHA-phospholipid complexes represents not only a source of essential nutrients but also the most physiological and best carriers to maintain an optimal composition of its cell membranes.

The choice between the available natural sources of these complexes between long-chain polyunsaturated fatty acids and phospholipids will depend on their respective richness in the essential fatty acids to be provided, DHA and/or ARA.

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