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The Importance of Omega-3 for Cell Membrane Functionality

Analysis by Dr. Joseph Mercola Fact Checked | September 03, 2023

STORY AT-A-GLANCE

- The cellular membrane is the universal surface onto which, and into which, the cellular machinery is assembled. The integrity of the inner and outer membranes is vital for the function of the cell
- The cell membrane also hosts response elements and almost all signaling, except for hormones. Almost all short path signaling begins in the membrane
- Membranes are lipid structures made of phospholipids and other constituents. The food you eat provides the raw material substrate that is then assembled into the mitochondrial and cellular membranes, which is why the type of fats you consume is so important
- Most people aren't willing to forgo processed foods and end up with far too much LA, which then necessitates taking extra omega-3. By increasing your omega-3 intake, the EPA and DHA can push the omega-6 out of your membranes
- Lysophosphatidylcholine (LPC) shuttles EPA and DHA into your eyes, liver and, in pregnant women, the placenta. LPC is endogenously produced, but your capacity to produce it is dependent on choline

In this interview, Nils Hoem, Ph.D., — a research scientist with Aker Biomarine, the largest krill oil company in the world — takes a deep dive into omega-3s and the crucial role they play in the health and functionality of your cell membranes.

> *"In my academic life, I spent the first 20 years as a researcher at the University of Oslo. I got my master's and doctorate from the University of Oslo in pharmacology, and was an associate professor there ... Fifteen years ago, I came ... to work for Aker Biomarine ... as the chief scientist, but I'm, by heart and mind, really, a pharmacologist,"* Hoem says.

The Importance of Membranes

As explained by Hoem, the cellular membrane is the universal surface onto which, and into which, the cellular machinery is assembled. "Very little in the cell just floats around. It's a very complex structure and the integrity of membranes is absolutely vital for the function of the cell," he says.

The cell membrane also hosts response elements and almost all signaling, except for hormones. Almost all short path signaling begins in the membrane. Your mitochondria also have an inner and outer membrane, and the function of these are also crucial for health.

Membranes are lipid structures made of phospholipids and other constituents. Inside we find phosphatidylcholine and phosphatidylethanolamine, two ampholytic phospholipids, meaning they have a polar end and nonpolar end.

The food you eat provides the raw material substrate that is then assembled into the mitochondrial and cellular membranes, which is why the type of fats you consume is so important.

Omega-6 Competes Against Omega-3

As explained by Hoem, there are two polyunsaturated fats (PUFAs) that are considered to be essential in conventional medicine. One of them is the omega-6 linoleic acid (LA), which is an 18-carbon molecule. Although the level of LA needed is likely significantly lower than suggested, it is a moot point as virtually consuming 10 times the suggestion. The other is omega-3 alpha-linolenic acid (ALA), which also has 18 carbons.

Your body cannot make these fats, so you must get them from your diet. That said, since LA is found in nearly every food, and you need very small amounts, it's virtually impossible to become deficient in LA.

Others, such as the omega-3 EPA and DHA, which have 20 and 22 carbons respectively, can be synthesized in your body, provided you have enough available delta-6-desaturase, an enzyme responsible for their conversion.

The problem is that there's competitive inhibition for that enzyme, so when you have 10-fold (1,000%) more omega-6 in your system, then the delta-6-desaturase will be used to convert the omega-6 into arachidonic acid, instead of converting the ALA into EPA.

Processed foods are loaded with omega-6 fats, which radically skews the omega-3 to omega-6 ratio and inhibits your body's innate ability to synthesize EPA and DHA.

> *"A Japanese professor showed me data from inner Mongolia, where they eat no seafood at all, but eat a lot of meat and dairy products from grass fed cattle. They get a lot of ALA and very little omega-6, and they actually had pretty high levels of EPA and DHA despite not eating any seafood at all. So that tells the story, I think,"* Hoem says.

Most People Consume Far Too Much LA

Historically, LA used to account for only 1% to 2% of daily calories. Today, it's between 20% and 25%, which means most people have enormous stores of LA in their cells.

If you reduce your LA intake to historical norms, then there's not this competition for delta-6. And if you have a baseline level of the omega-3 ALA, then you can make substantial amounts of DHA and EPA and probably don't need supplements.

The problem is that most people aren't willing to forgo processed foods and end up with far too much LA, which then necessitates taking extra omega-3. Basically, if you're eating higher than historical amounts of LA, you have to either add more omega-3s or reduce your intake of omega-6. Ideally, you'd do both.

> *"The amount of omega-6 is so huge compared with the omega-3s that the only feasible way of increasing your omega-3s in the membranes is through taking omega-3s,"* Hoem says. *"Then there is a 1-to-1 exchange of EPA and DHA for omega-6s in the membrane.*
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> *So, if you increase one molar amount of EPA and DHA in the membrane, then you kick out exactly the same amount of omega-6. And it's important to realize that the membrane will be a reflection of your intake of omega-6s versus omega-3s. You can't really do much with the omega-6s because they're everywhere, but you can fix it by increasing your intake of long chain omega-3s."*

That said, it is possible to dramatically reduce your intake of omega-6. I keep my intake below 1%, so it can be done. I've been doing it for about three or four years now. It takes about six or seven years to fully eliminate the stores of LA from your adipose tissue due to their long two-year half-life.

Upping Omega-3 Intake Is Necessary for Most People

Based on what Hoem is saying, you could facilitate the removal of LA by upping your omega-3 intake. The question is, how much omega-3 is needed to make a difference? And what happens to the omega-6 once it's displaced? Is it burned as fuel, or put back into the adipose cells? Unfortunately, Hoem doesn't have firm answers to those questions. His guess is that some of it gets burned as fuel and some gets stored.

> *"If you have a meal of salmon today, the EPA and DHA from that meal is going to wash around in your circulation and be exchanged within all different organs in your body for 14 days afterwards. We see that it undulates, so it goes in and out of plasma.*
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> *So, it increases in plasma, then it decreases in plasma, and increases again from six hours, then you have a 24-hour peak, and then you have another one usually, around 30 hours. When we look at how it's being incorporated into*

different tissues, that might give you some ideas. You see how, for example, the liver really, really wants EPA and DHA, as does the brain.

We've done experiments with lysophosphatidylcholine (LPC), which is the form that is being transported into the brain and into neuronal tissue ... The fatty acid is bound to lysophosphatidylcholine and that molecule is way more water soluble, 10 to the minus 4th actually.

Instead of being on its own, it's like EPA and DHA and a number of other fats sit on a ferry boat, and that ferry boat is lysophosphatidylcholine, that transports them into the brain ...

If you inject EPA and DHA LPC — lysophosphatidylcholine with EPA and DHA on it — it shoots into the brain and across the blood-retina barrier. So you see some organs that are very keen on grabbing these molecules. We call it infinite sink.

So, for example, what goes to the brain seems to stay in the brain until it's broken down. With half-life, that is probably hundreds of hours, while in the circulation, the half-life is pretty much like a hundred-ish hours longer for DHA than for EPA.

What this means is that when you change your intake, it takes about 600 hours, at least, until you are back at steady state. So, you can't fix anything fast with those fatty acid. You really need to be patient."

The Importance of Choline

The same transporter, LPC, also shuttles EPA and DHA into your eyes, liver and, in pregnant women, the placenta. Since LPC is so crucial, you also need to have a regular supply of phosphatidylcholine, and this is a common nutritional deficiency.

LPC is endogenously produced, but your capacity to produce it is dependent on choline. You also need the raw materials to make it, which means you need EPA and DHA.

Seafood is a great source of phosphatidylcholine. Many seafood sources also contain some EPA and DHA. For choline, the richest source is eggs.

> *"Research shows that if you increase your intake of choline, increase your intake of omega-3s, or basically increase your intake of phosphatidylcholine, you could actually reverse from nonalcoholic fatty liver back to a more normal liver, instead of sliding further down into steatosis and metabolic syndrome,"* Hoem notes.

What's the Best Omega-3 Supplement?

While many understand the importance of omega-3s, few realize that fish oil supplements aren't necessarily the best source. In most fish oil supplements, the omega-3 is in the form of ethyl ester, a synthetic form of omega-3. Natural omega-3 comes in three forms: triglyceride form, phospholipid form and free fatty acids. Contrary to these natural forms, ethyl esters are difficult to digest, so they must be taken with a fatty meal.

> *"Your body doesn't recognize it as fat, so if you take pure ethyl esters on its own, it will just slide through your body. It actually ends up in your stool. But if you take it with a fatty meal, then your body recognizes fat and starts the digestion process. But I've seen ethyl esters glide through the gut almost unabsorbed,"* Hoem says.
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> *"Most seafood would have both triglyceride and phospholipids, and of course, the interchange form is the free fatty acids. Free fatty acids is really minor. You won't find much of free fatty acid. You find some, but it's really the two major classes of glycerolipids — triglycerides and phospholipids.*
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> *That's nature's way of doing it, so whenever you eat whole foods, that's what you get. Even though I work with phospholipids and krill oil, I won't talk down fish oils because that's how most people get their EPA and DHA, and it is way better than not getting it.*

> *But there is one thing that I really do not appreciate, and this is a particular for the United States. You're allowed to call ethyl esters fish oils, and frankly, I don't like that at all. It needs to be clearly labeled, so that is something that needs to be done.*
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> *One advantage of the ethyl esters is that you can take out environmental toxins. Now, the price you pay for that is that there is a high thermic load on the molecule. You know the history of partially hydrogenated fats and trans fats ... 50 years down the road, we found that it had killed a million Americans ... and now they're banned both in the U.S. and in Europe.*
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> *Trans fats are dangerous because they have the wrong geometry. They have the wrong structure. They bend in the wrong direction, and enzymes with certain response elements that read fat read them wrong. The way they are inserted into membranes, for example, is not normal, so you get a bent fat."*

Another downside of ethyl ester omega-3 is that it's highly unstable, even more unstable than omega-6 fats, which means it's perishable and highly susceptible to oxidative stressors. That leaves it predisposed to oxidation, which can spin off advanced lipoxidation end products (ALEs) that cause significant damage.

The key point here is that it's predisposed to doing this spontaneously. When you have a whole food version, you typically don't get this. Krill oil, for example, contains natural astaxanthin, which prevents this peroxidation. Phospholipids also do not oxidize as easily.

Krill Harvesting Is Carefully Regulated

In the interview, Hoem reviews how Aker Biomarine produces its krill oil, and what distinguishes it in terms of quality and sustainability. Aker is the world's largest harvester of krill, mostly from the Antarctic, where Hoem spends much of his time doing research.

> *"Krill is probably the largest single species marine biomass,"* he says. *"Around the Antarctic region, you find more than 500 million tons. In the region where we harvest it, in west Antarctica, the estimated biomass is 60 million tons. I've been on surveys to find out how much there is, and at least for now, the amount has not gone down.*
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> *So, for the last at least decade, or even longer, the amount seems to be stable around 60 million tons. At the same time, the number of whales has increased. Occasionally, you now see thousands of whales. So the whale population is back at where it was pretty much pre-whaling.*
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> *There is an international body called CAMLR that regulates all the fisheries in the Antarctic region. You find types of krill all over the globe, but the Antarctic krill is very particular. It is larger than other krill, and krill oil by definition only comes from Antarctic krill because in other parts of the world, the lipid structure will be different.*
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> *We are allowed to catch less than 1% or 1% of the total biomass, so 620,000 tons, and we've been around half a percent up until now. That's extremely conservative. And there isn't anything to suggest that what we do will harm the whale population."*

Antarctic krill harvesting is also certified by an international body called the Marine Stewardship Council. It's a third-party, independent body, not a paid-off front group, that oversees the harvesting. And, again, the amount of krill allowed to be harvested is very conservative, to ensure there are no adverse environmental impacts.

> *"Whales will eat way more krill than we harvest,"* Hoem says. *"I've seen a calculation that suggests whales, at a full population, will take out something in the neighborhood of up to 200 million tons a year.*
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> *Krill live for about six years and seems to have a tremendous ability, given enough algae, to increase its biomass. It increases its biomass up until levels*

regulated by other factors really. So, it's really the algae bloom in Antarctica that governs the amount of krill available."

Processing Dictates Quality

When it comes to the quality of an omega-3 supplement, the way it's processed makes all the difference, and this is true whether we're dealing with fish oil or krill oil. Hoem describes how Aker Biomarine assures the highest quality possible:

> *"We harvest krill in a continuous process. We have a trawl, which is a huge net, and then there is a suction pump at the end. The krill comes live onboard. We then immediately dry it at relatively low temperatures.*
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> *Then, we bring that on land and extract it, not by any type of heat treatment, but by ethanol extraction, which is very unusual for marine fats. Usually, you need a lot of heat. And this is because it's a phospholipid triglyceride mixture.*
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> *Triglycerides are not soluble in ethanol, but phospholipids are, and the phospholipids drag the triglycerides out together with them. So, the way we fish and process it is different for krill oil than for the other marine fats.*
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> *It's all about the processing. It's all about being fresh. People may not know this, but most of the cheaper fish oil products are made from fish oil that is stored in huge tanks for years. Then you would have to process that raw fish oil into something that has the quality that you want.*
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> *We don't do it that way. We take care of the raw material from second one. We don't store it away in large storage tanks and then refine it to the quality we need. We try to take care of the quality from the very beginning to the very end. And, by the way, we own the whole value chain ... We also have the infrastructure necessary. Quality is something that you get when you put quality into every step in your chain."*

Antarctic Krill Is Very Clean

Aside from its high omega-3 content, Antarctic krill also contains a fair amount of copper — approximately five micrograms per gram — while being very low in environmental contaminants such as phosphates, PCBs and heavy metals like mercury.

> *"There is no phosphate pollution in Antarctica. You do see some PCBs, a very, very small amount. We analyze for heavy metals, and others have analyzed for it, and you find very low amounts of, for example, mercury and lead. They're not there. There are volcanoes in the area, for example, in what is called Deception Island, and there you can find it, but it's not spread around."*

Is Krill a Good Food Source for Humans?

One argument that many people have about consuming krill is that krill is not a natural food source for humans. Ancestral humans didn't consume krill. Hoem responds to this critique:

> *"Krill is a crustacean as good as any other crustacean, and certainly humans have been eating crustaceans. We haven't harvested Antarctic krill because it's where it is, but we certainly eat other types of krill. Shrimp are actually krill.*
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> *Nine out of 10 whales eat krill, so why shouldn't we do it? The first paper on the suggestion on eating krill was published in 1958, and a guy called Peloquin suggested in Scientific American that we should stop whaling and rather fish for krill.*
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> *Of course, we should harvest as far down in the food chain as we could. Now, ideally, we should have harvested algae, but don't ask me to harvest the microalgae that is five micrometers across. You won't be able to do that. And to me krill is just the sweet spot of it.*
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> *Krill does the algae harvesting for us, and then we harvest krill instead ... The Japanese also actually have eaten krill, what is called Pacific krill. If you go to*

Japan, in every bar, they will serve you dried Pacific krill as a snack."

Krill Oil Has Better Absorption Than Synthetic Fish Oil

Interestingly, the EPA and DHA found in krill is relatively low compared to your typical fish oil supplement — up to 90% lower — but the radically improved absorption and distribution within your body makes up for it.

> *"It doesn't really help you that much if your EPA and DHA reside in your white fat. So, it's really about the utility of it,"* Hoem says. *"Ethyl esters are special. They do have an absorption problem.*
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> *I would say neither phospholipids nor triglycerides really have an absorption problem. They're fairly well digested. Where you see the differences between them is in how they're distributed. And that's exactly why I think you need both.*
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> *So, I would never talk down fish oils. Now krill oil is more similar to what was called 18/12 oils. Krill is typically 8% to 9% DHA and 12% to 15% EPA, so they're not that different from what you find in other natural sources. You do not find any natural source with super-high concentrations of EPA and DHA. Then it is a concentrate of some kind.*
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> *I'm actually writing up a paper on some of this. To be able to analyze this, you have to use radiolabel substances. So, we've made them synthetic and then we've put in a radioligand, C14, because otherwise your experiment is going to be way too diluted.*
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> *By doing this, in animals, you can actually see exactly where the different labeled fatty acids go, and there is a clear difference between the different forms. Again, phospholipids have certain specifics when it comes to the brain, the eye, the liver.*
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> *Triglycerides seems to have some specifics when it comes to the heart muscle for example, but our heart is able to extract EPA and DHA from the circulation*

quite well. There is a very high lipase activity there. But what I can say is that it is a really diverse pattern, and what it tells me so far is that we need both forms.

Let me also point out that krill oil also contains EPA and DHA in triglyceride form. Krill oil really isn't an oil, it is lecithin. It's a mixture of triglycerides and phospholipids. So, nature provides both, and I think we need both."

EPA and DHA Are Required for Intercellular Communication

While certain tissues such as the brain, heart, liver, eyes and placenta need more EPA and DHA, they serve important functions in all tissues. As explained by Hoem, EPA and DHA serve as substrates for lipid-derived signaling between cells. This intercellular communication is part of how cells self-regulate to maintain health.

"The substrate for that signaling is usually fats or a fatty acid, and that's not strange at all, because those membranes are everywhere in the cell. Everything in the cell is connected to a membrane. And then, prostaglandins or prostacyclins or thromboxanes, they are made from fats excised from the membrane.

You could excise either omega-6s or omega-3s from the membranes, and that's dependent on the amount of these in the membrane. From this, you get two classes of signaling molecules. When you make the signaling molecules from EPA, for example, you get PGE-3 and not PGE-2. And the same goes for a number of these super important signaling molecules.

Further down the road, there is a type of molecule called resolving. Inflammation is there to fix a problem, but then it needs to be stopped, to be resolved, [which is what resolving does]. Resolvins are absolutely necessary to stop inflammation from overdoing its job. That's the key to healthy inflammation."

Resolvins are produced in situ, but to have a good specialized pro-resolving mediator (SPM) response, you need to load your membranes with EPA and DHA.

EPA and DHA Roles in Membranes

EPA and DHA are also incorporated into the inner membranes of the cell, and likely the mitochondrial membranes as well.

> *"Mitochondria need to communicate, so there will also be lipid-derived signals there. But now I'm easily ending into something that scientists shouldn't do; we end up in speculation. But I think we have to realize that these are white spots on the map. We have been viewing lipids as energy for decades, and not as structure, despite the fact that we're made of lipids.*
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> *The phospholipid membrane defines life. It defines the border between me and the environment outside. Without the membrane, there's no life. So we are at the very, very core of our own definition.*
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> *The unsaturated fatty acid in general, and in particular EPA and DHA, are bulky fatty acids. And they're bulky simply because they have these double bonds fixed. DHA is more of a linear bulky structure, while EPA is more of a circular bulky structure, and it can't rotate around its carbon, so it's really fixed. I think of them more as architectural building blocks.*
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> *And then you have to start asking yourself, 'What's going on in the membrane?' Well, the membrane has response elements in it — transporters, iron channels, the electron transport chain, you name it. All of this is connected to the membrane, and a lot of response elements needs to flow transversely in the membrane.*
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> *So, when I say fluidity of the membrane, don't necessarily think of it as it's flexible on its outside, but more of how response elements can flow transversely in the membrane, how element A can reach to element B, because,*

quite often, you have two or three such elements that need to coalesce into one element to be activated.

Now, if we go to signaling substance, the best way to describe this is to be specific. And if we take prostaglandin, which is a universal inflammatory signal, it is being made from arachidonic acid, an omega-6. The enzyme that is doing this sits on the inside of the membrane, in the cytosolic part of the membrane.

And it sits there, closely to the membrane, because the substrate is a fat. The fat isn't soluble in water. So, phospholipase A-2, for example, is excising out a fatty acid and feeds it directly into the hydrophobic pocket of that molecule. So, it doesn't have to traverse water to get in there. And it's not really one enzyme, it's two enzymes in one. So it's an epoxidase and an oxidase. And instead of arachidonic acid, it spits out PGE-2.

If instead phospholipase A-2 takes out an EPA, it spits out PGE-3. And PGE-3 has been shown to be less inflammatory, usually, than PGE-2. So that's one. So the omega-3s are not anti-inflammatory. They are modulators of inflammation, and they're part of a measured inflammatory response.

And then, downstream, PGE-3 is formed into moracins, the resolvins, and actually actively stops the inflammation and starts restoration instead. The omega-6s do not do that to the same extent. So you need EPA, DHA and DPA to have this resolving function going as it should."

Closing Remarks

So, in closing, the summary take-home from all this is that most people probably need omega-3 supplementation, especially if you've been eating a lot of processed foods and therefore have high LA stores. Again, as your omega-3 intake increases, the EPA and DHA start replacing the omega-6s in your membranes at a ratio of 1 to 1.

Hoem recommends getting an omega-3 index test once a year. Ideally, you'd want to have an index of 7 or higher.

> *“Just remember, the kinetics is very slow,”* he says. *“So if you double your dose, it will take the best part of three to six months until you are at a steady state again. The same goes for if you reduce your dose to half; it also takes three to six months. It's exactly the reverse. This is something that makes this tricky, because you won't recognize from day one to day two your change, but you will recognize it in six months. So it's long-term.*
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> *This is not pharmacology, it is nutrition. And it's a question about being prepared when you need your lipid-based systems to function correctly. If you do not take care of your membranes with regards to the right fatty acids, when you need them to respond correctly or in a measured way, it's too late to take them.”*

Once your LA stores are depleted (which can take up to seven years, provided you’re not loading more in), and provided you’re consuming enough ALA, then your body will likely have the ability to endogenously produce the EPA and DHA it needs.