What Are the Real Differences Between EPA and DHA?

In the Zone by Barry Sears Ph.D.

To reduce cellular inflammation, you need more EPA than DHA.

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It is rapidly becoming acknowledged that omega-3 fatty acids are good for the brain. However, there are two eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Are they equivalent, different, or something in-between?

The first casualty of marketing is usually the truth. The reality is that the two key omega-3 fatty acids (EPA and DHA) do a lot of different things, and as a result, the benefits of EPA and DHA are often very different. That's why you need them both. But as to why let me go into more detail.

Benefits of EPA

The ultimate goal of using omega-3 fatty acids is the reduction of cellular inflammation. Since eicosanoids derived from arachidonic acid (AA), an omega-6 fatty acid, are the primary mediators of cellular inflammation, EPA becomes the most important of the omega-3 fatty acids to reduce cellular inflammation for a number of reasons. First, EPA is an inhibitor of the enzyme delta-5-desaturase (D5D) that produces AA (1). The more EPA you have in the diet, the less AA you produce. This essentially chokes off the supply of AA necessary for the production of pro-inflammatory eicosanoids (prostaglandins, thromboxanes, leukotrienes, etc.). DHA is not an inhibitor of this enzyme because it can't fit into the active catalytic site of the enzyme due to its larger spatial size.

As an additional insurance policy, EPA also competes with AA for the enzyme phospholipase A2 necessary to release AA from the membrane phospholipids (where it is stored). Inhibition of this enzyme is the mechanism of action used by corticosteroids. If you have adequate levels of EPA to compete with AA (i.e. a low AA/EPA ratio), you can realize many of the benefits of corticosteroids but without their side effects. That's because if you don't release AA from the cell membrane then you can't make inflammatory eicosanoids.

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Because of its increased spatial dimensions, DHA is not a good competitor of phospholipase A2 relative to EPA. On the other hand, EPA and AA are very similar spatially so they are in constant competition for the phospholipase A2 enzyme just as both fatty acids are in constant competition for the delta-5 desaturase enzyme. This is why measuring the AA/EPA ratio is such a powerful predictor of the state of cellular inflammation in your body.

The various enzymes (COX and LOX) that make inflammatory eicosanoids can accommodate both AA and EPA, but again due to the greater spatial size of DHA, these enzymes will have difficulty in converting DHA into eicosanoids. This makes DHA a poor substrate for these key inflammatory enzymes. Thus DHA again has little effect on cellular inflammation whereas EPA can have a powerful impact.

Finally, it is often assumed since there are not high levels of EPA in the brain, that it is not important for neurological function. Actually it is key for reducing neuro-inflammation by competing against AA for access to the same enzymes needed to produce inflammatory eicosanoids. However, once EPA enters the brain it is rapidly oxidized (2,3). This is not the case with DHA (4). The only way to control cellular inflammation in the brain is to maintain high levels of EPA in the blood. This is why all the work on depression, ADHD, brain trauma, etc. have demonstrated EPA to be superior to DHA (5).

Benefits of DHA

At this point, you might think that DHA is useless. Actually just the opposite, because DHA can do a lot of different things that EPA can’t do..

The first difference is in the area of omega-6 fatty acid metabolism. Whereas EPA is the inhibitor of the enzyme (D5D) that directly produces AA, DHA is an inhibitor of another key enzyme delta-6-desaturase (D6D) that produces the first metabolite from linoleic acid known as gamma-linolenic acid or GLA (6). However, this is not exactly an advantage. Even though the reduction of GLA will eventually decrease AA production, it also has the more immediate effect of reducing the production of the next metabolite known as dihomo gamma linolenic acid or DGLA. This can be a disaster as a great number of powerful anti-inflammatory eicosanoids are derived from DGLA. This is why if you use high-dose DHA it is essential to add back trace amounts of GLA to maintain sufficient levels of DGLA to continue to produce anti-inflammatory eicosanoids.

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In my opinion, the key benefit of DHA lies in its unique spatial characteristics. As mentioned earlier, the extra double bond (six in DHA vs. five in EPA) and increased carbon length (22 carbons in DHA vs. 20 in EPA) means that DHA takes up a lot more space than does EPA in the membrane. Although this increase in spatial volume makes DHA a poor substrate for phospholipase A2 as well as the COX and LOX enzymes, it does a great job of making membranes (especially those in the brain) a lot more fluid as the DHA sweeps out a much greater volume in the membrane than does EPA. This increase in membrane fluidity is critical for synaptic vesicles and the retina of the eye as it allows receptors to rotate more effectively thus increasing the transmission of signals from the surface of the membrane to the interior of the nerve cells. This is why DHA is a critical component of these highly fluid portions of the nerves (7). On the other hand, the myelin membrane is essentially an insulator so that relatively little DHA is found in that part of the membrane.

This constant sweeping motion of DHA also causes the breakup of lipid rafts in membranes (8). Disruption of these islands of relatively solid lipids makes it more difficult for cancer cells to continue to survive and more difficult for inflammatory cytokines to initiate the signaling responses to turn on inflammatory genes (9). In addition, the greater spatial characteristics of DHA increase the size of LDL particles to a greater extent compared to EPA.

As a result, DHA helps reduce the entry of these enlarged LDL particles into the muscle cells that line the artery thus reducing the likelihood of developing atherosclerotic lesions (10). Thus the increased spatial territory swept out by DHA is good news for making certain areas of membranes more fluid or lipoprotein particles larger, even though it reduces the benefits of DHA in competing with AA for key enzymes important in the development of cellular inflammation.

Common Effects for Both EPA and DHA

Not surprisingly, there are some areas in which both EPA and DHA appear to be equally beneficial. As an example, both are equally effective in reducing triglyceride levels (10). This is probably due to the relatively equivalent activation of the gene transcription factor (PPAR alpha) that causes the enhanced synthesis of the enzymes that oxidize fats in lipoprotein particles. There is also apparently equal activation of the anti-inflammatory gene transcription factor PPAR-gamma (11). Both seem to be equally effective in making powerful anti-inflammatory eicosanoids known as resolvins (12).

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Finally, although both have no effect on total cholesterol levels, DHA can increase the size of LDL particles to a greater extent than can EPA (10).

Summary

EPA and DHA do different things, so you need them both, especially for the brain. If your goal is reducing cellular inflammation, then you probably need more EPA than DHA. How much more? Probably twice the levels, nonetheless you always cover your bets with omega-3 fatty acids by using both EPA and DHA at the same time.

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What Are the Real Differences Between EPA and DHA?

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