RESEARCH UPDATE ON PUFAs (Polyunsaturated Fatty Acids) WITH A FOCUS ON DHA (Docosahexaenoic Acid)

In the December 2016 product newsletter #297, I introduced our new DHA product DHA 710 Select™. In that newsletter I focused on the aspects of DHA that revolve around optimizing neurologic function and acting as an anti-inflammatory agent. Interestingly, at the time I wrote that newsletter I felt confident that I had summed up all that needed to be stated about DHA from a published research point of view. Since that time, though, I did a more thorough examination of the published research on DHA and found my assumption that I stated everything that needed to be stated about DHA was, to put it mildly, in error. In fact, based on the amount of papers I found on DHA, DHA is now a subject of intense interest among researchers. Furthermore, this interest is not based purely on a desire for idle, academic knowledge. Rather, this interest is based on the idea that DHA supplementation may provide solutions to some of the most difficult to resolve clinical issues presented by chronically ill patients.

Why might DHA supplementation provide answers to chronic illness beyond the basics I presented earlier that revolved around neurologic support and what we have known for years about its anti-inflammatory properties? To begin to answer this question, I would like to present some lesser known basics about the properties of DHA as pointed out in the paper “Impact of DHA on metabolic diseases from womb to tomb” by Arnoldussen and Kiliaan (Arnoldussen IAC & Kiliaan AJ. Marine Drugs, Vol. 12, pp. 6190-6212, 2014).

DHA and membrane fluidity

As noted by Arnoldussen and Kiliaan, DHA is an extremely important component in maintaining optimal cell membrane fluidity:

“DHA is an essential component in phospholipids because it maintains membrane fluidity. Membrane fluidity can be defined as the optimum transition point between gel and liquid crystal where the neuronal lipid bilayer can exist.”

Why is this important? The authors state:

“This condition is of physiological importance for signal transmission. It can be strongly influenced by fatty acid composition and should therefore be maintained optimally. Dietary intake of specific fatty acids can modify the lipid composition of neurons up to a certain degree. Prolonged intake of DHA, for example, will modestly increase brain DHA content and decrease brain omega-6 PUFAs content simultaneously, particularly docosapentaenoic acid (DPA). High concentrations of DHA within the lipid bilayer provide neuronal membranes with the flexibility/fluidity that is required in order to function properly during axonal and synaptic growth, and improve functioning of ion-channels and receptors through better transmission.”

Can DHA cross the blood brain barrier?

“It has been demonstrated that in mammals, DHA, in free form, rapidly crosses the blood brain barrier (BBB), similar to freely diffusible lipophilic drugs.”

Of course, as mentioned above, no discussion of DHA is complete without acknowledging its impact of inflammation. In turn, Arnoldussen and Kiliaan point out that DHA has potent anti-inflammatory properties that are well known. However, as I will demonstrate, they also point out another way DHA impacts
inflammation that is much less well known but, incredibly important, particularly when trying to deal with the low-grade chronic inflammation that is now recognized to be an overwhelming driving force behind the signs and symptoms seen with virtually every chronically ill patient. The authors point out:

“DHA can be converted into potent novel molecules with anti-inflammatory and organ-protective properties such as the specialized pro-resolving lipid mediators (SPMs), including D- and E-series resolvins, neuroprotectins, and maresins via specialized chemical mediators.”

DHA and specialized pro-resolving lipid mediators (SPMs) – some introductory comments

For years we have known that the chief components of fish oil, EPA and DHA, have anti-inflammatory properties that are similar to substances such as curcumin and NSAIDS in that they reduce the production and impact of certain inflammatory mediators. Furthermore, for years we have assumed that this fairly simple mechanism totally explained why EPA and DHA have such a consistent and prolonged track record in assisting chronically ill patients for whom, as I mentioned, chronic inflammation is almost universal. As I will explain, this is only a small part of the EPA/DHA story in relationship to inflammation.

What we are now learning is that EPA and DHA have an action that is much more powerful than just blocking inflammatory mediators. What is this action? To answer this question, we need to discuss an aspect of inflammation that we often see clinically but do not fully appreciate. Whether the condition is a cold or flu or a minor injury, we generally see production of inflammation and, at some point, elimination of the inflammation. Did you ever wonder why, in the above mentioned conditions, the inflammation goes away? I would guess that most of you would answer this question by stating the body produces the powerful anti-inflammatory cortisol. Interestingly, this is only part of the story. The body actually does much more to eliminate the inflammation than produce cortisol. It also produces eliminative compounds derived from EPA and DHA.

Of course, if the body always eliminated inflammation on its own without the need for our assistance, as with a cold, flu, or a minor injury, this aspect of EPA and DHA physiology would have little practical and clinical significance. Unfortunately, for the chronically ill and the almost universally present chronic, low-grade inflammation that can persist for years, it appears that there is a disturbance in the ability of the body to produce these EPA and DHA derived eliminative compounds. Could supplementation of EPA and DHA increase production of these eliminative compounds in addition to performing the task with which we are all familiar of blocking formation of inflammatory mediators? As I will demonstrate, a large body of research is now answering this question in the affirmative, making EPA and DHA supplementation more important than ever when attempting to address the needs of chronically ill patients, no matter what the clinical presentation.

What follows is a discussion of these EPA/DHA derived eliminative compounds which have been given the name in the research literature “Specialized pro-resolving lipid mediators (SPMs).”

Specialized pro-resolving lipid mediators (SPMs) – a detailed discussion

To begin this discussion I would like to present some quotes from the paper “DHA- and EPA-derived resolvins, protectins, and maresins in airway inflammation” by Duvall and Levy (Duvall MG & Levy BD, *Eur J Pharmacol*, Vol. 785, pp. 144–155, 2016). This first quote discusses the production of inflammation and, most pertinent to this discussion, the process of eliminating the inflammation:

“The hallmarks of acute inflammation include specific cellular events, including increased permeability of the endothelium and epithelium, infiltration of polymorphonuclear...
leukocytes, inflammatory macrophages, and lymphocytes to sites of infection or injury, and subsequent tissue edema. The cellular events of resolution oppose inflammation and in a process known as catabasis return the host tissues to a non-inflammatory state. Barrier integrity is restored and the permeability of endothelium and epithelium is reduced; neutrophils cease trafficking to sites of inflammation; macrophages clear the inflammatory milieu by phagocytosis of microbes and apoptotic neutrophils in a process termed efferocytosis; and neutrophils at the mucosal interface are released by CD55 from the apical surface of epithelial cells for luminal clearance. As tissue leukocytes recede from sites of acute inflammation, levels of proinflammatory cytokines and chemokines also decrease.”

The next quote discusses the extraordinary change that happens in terms of fatty acid metabolism as inflammation subsides:

“At this turning point, metabolism of polyunsaturated fatty acids switches from conversion to pro-inflammatory mediators, such as leukotrienes and prostaglandins, to pro-resolving mediators, such as lipoxins. These pro-resolving mediators act as agonists at specific receptors to contribute to the restoration of host tissues to a homeostatic state.”

What, specifically, are these specialized pro-resolving mediators (SPMs)? The authors state:

“These SPMs are comprised of several distinct families, including the omega-6 PUFA derived lipoxins, and the omega-3 PUFA derived D-series resolvins, E-series resolvins, protectins, and maresins.”

What, specifically, is the function of the SPMs?

“The SPMs act at subnanogram doses on specific receptors in diverse cells of the immune system, including neutrophils, macrophages, endothelial and epithelial cells, and lymphocytes. The actions of SPMs direct key features of inflammation resolution including inhibition of neutrophil migration, enhancement of macrophage phagocytosis of apoptotic neutrophils, and suppression of pro-inflammatory cytokines and chemokines.”

Why is this important clinically in terms of our efforts to address the needs of chronically ill patients? Duvall and Levy point out:

“This process appears to be defective in several common human lung diseases, such as asthma and COPD, which are characterized by chronic unrestrained inflammation and significant associated morbidity.”

As I will demonstrate, this defect in SPM function is not limited to issues of lung function. In fact, as I have repeatedly suggested, this defect in SPM function is probably a constant in chronically ill patients who are, almost always, chronically inflamed.

In the paper “Pro-resolving mediators produced from EPA and DHA: Overview of the pathways involved and their mechanisms in metabolic syndrome and related liver diseases” by Lopez-Vicario et al (Lopez-Vicario C et al. Eur J Pharmacology, Vol. 785, pp. 133-143, 2016) chronic inflammation and the role of SPMs in its resolution is considered in relation to many, if not most, of the illnesses we typically see in chronically ailing patients. The paper begins by reviewing the role of chronic inflammation in today’s most common chronic illnesses:

“Recent evidence indicates that unresolved, chronic inflammation in abdominal adipose tissue is the predominant underlying risk factor for the development of co-morbidities (i.e. insulin resistance, type 2 diabetes, dyslipidemia and non-alcoholic fatty liver disease (NAFLD)) in obese patients with underlying metabolic syndrome. In this condition, unresolved, chronic inflammation is characterized by a persistent ‘low-grade’ state of inflammation, which is aggravated by the recruitment of macrophages into the adipose tissue.”

The next quote discusses the need for resolution of chronic inflammation and the metabolic factors involved:

“A rapidly evolving field in managing inflammatory response is to modulate its dynamic resolution. Since unresolved inflammation is detrimental to the host, higher organisms have evolved protective
mechanisms to ensure resolution of the inflammatory response in a specific time-limited manner. Once considered a mere passive process of dilution, resolution is today envisioned as a highly-orchestrated process coordinated by a complex regulatory network of cells and mediators. Among the mediators that control the resolution process, lipid mediators derived from the metabolism of essential omega-3-polyunsaturated fatty acids have attracted the most attention.”

The next quote provides an overview of these mediators, much of which was discussed above:

“These mediators, generically known as ‘specialized pro-resolving mediators’ or SPM, comprise molecules designated as resolvins, protectins and maresins, and contrary to their metabolic substrates, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exert their biological actions at the nanomolar range. Indeed, the potency of these SPM is notable, with concentrations as low as 10 nM producing a 50 percent reduction in PMN transmigration in model systems.”

In particular, SPM metabolism is highly disturbed in inflamed obese adipose tissue. The authors of the paper note:

“Recent studies indicate that the formation of SPM is severely deregulated in inflamed obese adipose tissue. Since SPM act as ‘braking signals’ of the persistent vicious cycle leading to unremitting inflammation, in recent years these endogenous lipid mediators have attracted attention as a novel strategy to expedite the resolution process of inflamed adipose tissue in obesity.”

In the next quote the specific SPMs are discussed in terms of which ones are derived from EPA and which ones are derived from DHA:

“These novel bioactive lipid autocoids were termed resolvins (derived from resolution phase interaction products) and were classified as either resolvins of the E-series if the biosynthesis is initiated form EPA or resolvins of the D-series if they are generated from DHA. Protectins and maresins, macrophage mediators in resolving inflammation are also biosynthesized from DHA.”

How important are SPMs in terms of resolution of chronic inflammation? The authors of the paper make it clear that SPMs are central issues:

“…the presence of unresolved inflammation could be the consequence of a deregulated balance between the exacerbated levels of pro-inflammatory mediators and the reduced levels of mediators with anti-inflammatory and pro-resolution properties (i.e. SPM).”

Given that SPMs are derived from EPA and DHA, could supplementation of these fatty acids be of value in situations where SPM levels are suboptimal? The authors state:

“This deficit in SPM in obese adipose tissue appears to be a likely consequence of the structural deficiency in the tissue content of omega-3 fatty acids, namely DHA and EPA, as substrates of SPM biosynthesis. Therefore the use of dietary supplements enriched in omega-3-PUFAs, which favor the formation of endogenous anti-inflammatory and pro-resolving SPM in clinical practice, is more than justified. In this context, the supplementation of highly pure EPA and DHA to patients with NAFLD (non-alcoholic fatty liver disease) within a balanced nutritional guide is rapidly becoming an effective dietary intervention to prevent the hepatic complications associated with obesity and the metabolic syndrome.”

The impact of EPA and DHA supplementation on optimization of SPM levels

Given that much of the research on SPMs and their relationship with EPA and DHA has come from animal studies, the question needs to be asked if EPA and DHA supplementation is effective in optimizing SPM levels in humans. This question was answered by the paper “Short-term n-3 fatty acid supplementation but not aspirin increases plasma proresolving mediators of inflammation” by Barden et al (Barden A et al. J Lipid Res, Vol. 55, pp. 2401-2407, 2014). The paper begins with an overview of SPMs and their relationship with EPA and DHA:

“There is increasing interest in the role of the specialized proresolving mediators (SPMs)
that actively stimulate resolution of inflammation. In particular, recent attention has focused on those SPM derived from the long-chain n-3 fatty acids EPA and DHA. The SPMs formed from EPA are known as E-series resolvins, while those formed from DHA include protectins, D-series resolvins, and maresins.”

In the study that forms the basis for this paper 21 healthy volunteers aged 40 to 70 years were evaluated. For 7 days all were supplemented with fish oil capsules which provided a total of 1.4 g EPA and 1 g DHA per day. To assess efficacy precursors of maresin and E-series and D-series resolvins were measured in plasma. Many, but not all of these precursors significantly increased after EPA/DHA supplementation. The authors conclude:

“Taken together, our results suggest that n-3 supplementation with EPA and DHA can effectively increase a number of biologically active SPMs, which may in part explain the benefits of n-3 fatty acids in cardiovascular disease. The overall increase observed in the upstream precursors of the E- and D-series resolvins and 14R/S-HDHA with n-3 fatty acids supplementation could be a useful preventive strategy to limit the damage resulting from an impending inflammatory challenge.”

**SOME FINAL THOUGHTS ON CURRENT RESEARCH ON EPA AND DHA**

As we all know, fish oil supplementation has been a staple of clinical practice for years. Interestingly, much of the early research indicated that the clinical impact of fish oil supplementation was mainly related to its EPA content. While the impact of the DHA component was thought to be significant, it was generally regarded to be secondary to EPA. As I have demonstrated using the research discussed in this newsletter and the December 2016 product newsletter, we need to re-evaluate traditional thinking on the clinical value of fish oil and the predominant focus on EPA. Concerning the optimization of inflammatory mediators, EPA and DHA not only function as highly effective anti-inflammatory compounds but major components in optimizing the body’s endogenous ability to resolve the inflammation that is a universal constant in chronic illness. In addition, we can no longer think of EPA as the most important component of fish oil in this respect. Both are extremely important and, in certain situations, DHA may demonstrate superior performance clinically.

When considering the role of EPA and DHA in physiological functions other than metabolism of inflammatory mediators, it now appears that DHA is the star performer. Therefore, when considering the need to optimize cell membrane physiology and neurologic function in your patients, be sure to consider the use of DHA 710 Select™ in your supplemental protocol.

**Supplemental considerations to maximize both the anti-inflammatory and SPM enhancing aspects of EPA/DHA supplementation**

In the December 2016 product newsletter, I focused on a study by Allaire et al that considered the anti-inflammatory properties of EPA and DHA. In that study, at a level of about 2.5 g per day DHA supplementation demonstrated superior performance compared with EPA supplementation in terms of an anti-inflammatory impact. In terms of SPM enhancement, as suggested by the Barden et al study discussed above, it appears that 1 – 1.5 g per day of both EPA and DHA is effective. Based on this information, consider the following supplemental program that, for most patients, should provide both an excellent anti-inflammatory impact and significant increases in SPM production:

- **EPA/DHA HP Select®** – 4 softgels per day with meals. Each soft gel capsule provides 360 mg of EPA and 240 mg of DHA.
- **DHA 710 Select™** – 2 softgels per day with meals. Each soft gel capsule provides 710 mg of DHA and 50 mg of DHA.

For pricing, please visit our website.