

INFLAMMATION:

OMEGA-3 FATTY ACIDS AND THEIR HEALTH / DISEASE CONNECTION



ARIANNA CARUGHI

Ph.D., C.N.S.,
Nutrition Scientist,
Stanford Fellow,
GNLD SAB Member



KARSTEN GRONERT

M.S., Ph.D.
Associate Professor, Solon M. &
Pearl A. Braff Chair in
Clinical Optometric Science
Ocular Inflammation,
Vision Science Program
School of Optometry
University of California, Berkeley



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INFLAMMATION IS ESSENTIAL TO LIFE— PART OF THE BODY'S NATURAL RESPONSE TO INJURY OR INFECTION

When in appropriate balance, inflammation comes and goes on an “as needed” basis; doing its job and then going away. However an upset balance in the level of inflammation can make it persistent or chronic and can cause progressive damage to the body and lead to a variety of diseases. Current research shows that omega-3 fatty acids are building blocks for key compounds—resolvins and protectins—that are involved in the resolution of inflammation. Experimental and clinical data provide compelling evidence that low levels of these protective omega-3 derived compounds lead to misguided and uncontrolled inflammation. It is now recognized that this may increase risk of chronic disease and mortality.

INFLAMMATION— WHAT IS IT?

Inflammation is a natural part of a healthy immune system acting as the body's basic response to injury, stress, and infection. It is essential to health and survival of all living organisms¹. It is the result of a sequence of tightly controlled, complicated, and interrelated events. It works to protect a wound against invading bacteria/viruses, remove dead tissue and cells, and repair injured or stressed tissue. By design, a healthy inflammatory response is beneficial, temporary, resolves naturally, and restores normal function of the affected tissue/organ. At any given time in life there are many points where healthy and temporary inflammation goes unnoticed in the skin, gastrointestinal tract, mouth, eyes, blood vessels, and lungs providing routine protection against potential infection, repairing minor injuries, and maintaining normal organ function.

THE PROCESS— WHAT HAPPENS?

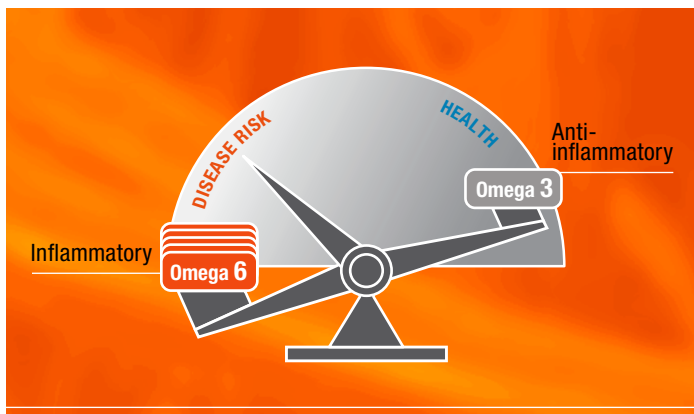
The complex inflammatory response is driven by white blood cells (*leukocytes*) that patrol the body and possess a potent arsenal of bactericidal agents and chemical messengers that regulate inflammation, immune responses, blood vessel formation, and wound healing. Injury or infection, for a short time, will attract leukocyte to the affected area where their activity is tightly controlled to let limited and specific release of the potent chemicals that kill harmful bacteria and promote wound healing, all the while trying to limit collateral damage to the surrounding tissue.



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INFLAMMATION AND DISEASE— WHEN A GOOD THING GOES WRONG

A complex assortment of chemical messengers that include lipid signals (molecules made from specific lipids) are released to trigger inflammation and activate patrolling immune system “guardians” called leukocytes. Unfortunately, the complex regulation of healthy inflammation is in a precarious balance that can tip towards causing unwanted tissue damage and lead to abnormal or chronic inflammation^{2,3}. Poor diet or overall state of health, environmental factors, and other influences can all tip healthy inflammatory balance toward an uncontrolled and disease causing “pro-inflammatory” state. Unregulated inflammation is now recognized as a major factor in the cause of cardiovascular diseases (atherosclerosis, heart attacks, stroke), asthma, arthritis, allergies, and cancer¹. Lipid signals have long been recognized as key messengers and regulators of inflammation and thus it is not surprising that they are key targets for drugs such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAID's such as aspirin and ibuprofen) that are the first treatment option for most symptoms of inflammation like pain, fever, and headaches, and inflammatory diseases like arthritis.



An imbalance of excessive omega-6 PUFA and deficient omega-3 PUFA (fish oils) consumption is associated with a higher risk of cardiovascular mortality and other inflammatory diseases.

DIETARY FATTY ACID INTAKE REGULATES INFLAMMATORY/ANTI-INFLAMMATORY BALANCE

Virtually every cell in the body can form lipid signals from key building blocks known as eicosanoids. The lipid messengers and regulators of inflammation are formed from the essential omega-6 polyunsaturated fatty acid (PUFA), arachidonic acid, while those for anti-inflammation are formed from omega-3 PUFA's. Both types of PUFA's are obtained directly through diet.

The "inflammatory" omega-6 fatty acid (arachidonic acid) or its precursor linoleic acid is the predominant PUFA in the Western Diet. The excessive omega-6 consumption in the Western diet has been linked to amplified and prolonged inflammation. Conversely, the relative lack of "anti-inflammatory" omega-3's undermines the body's ability to resolve inflammation. Thus it is not surprising that an impressive body of clinical and experimental studies have shown that an imbalance of excessive omega-6 PUFA and deficient omega-3 PUFA (fish oils) consumption is associated with a higher risk of cardiovascular mortality and other inflammatory diseases⁴. According to the American Heart Association cardiovascular disease claimed 831,272 lives in 2006, which represents 1 of every 2.9 deaths in the USA. A recent scientific meeting on "omega-3 PUFA fatty acids—recommendations for therapeutics and prevention" concluded that increasing omega-3 PUFA in tissues may lower illnesses that account for the largest diseases burden worldwide⁴.

ENDING INFLAMMATION: RESOLUTION

Traditionally, it was assumed that healthy inflammation stopped due to the fact that inflammatory signals fizzle-out and leukocytes eventually leave the injured tissue. However, research in the last 10 years has uncovered that it is a very active process controlled by many chemical signals and highly specialized pathways for the removal of spent leukocytes^{3,5,6}. A meeting of leading world scientists in the field of inflammation in 2007³ defined that healthy inflammation requires activation of so called "resolution pathways" and more importantly identified lipid signals as key messengers and regulators of this essential process. Leading laboratories around the world are now focused on developing new drugs that amplify these "resolution pathways" rather than limiting drug options to non-specific inhibition of essential inflammation and immune responses^{7,8,9}. More importantly, several recent studies have demonstrated that increased dietary intake of omega-3 PUFA amplifies these "resolution pathways"^{12,13,14}.

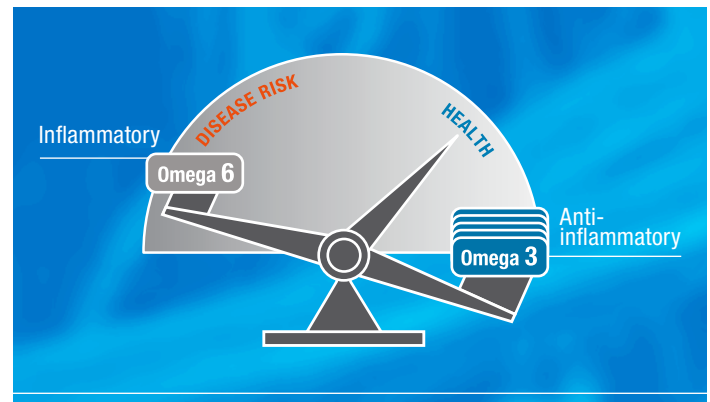
RESTORING BALANCE: OMEGA-3 FATTY ACIDS, RESOLVINS AND PROTECTINS

In early 2000, research teams at Harvard and Louisiana State University Health Science Center discovered that the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are converted to potent anti-inflammatory, neuroprotective and pro-resolving lipid signals called protectins and resolvins^{7,8,10,11}. This was a major breakthrough since decades of research have failed to produce a clear mechanism for the remarkable and essential properties of dietary omega-3 fatty acids. Intense research efforts and publications in leading scientific journals in the last 5 years have established that these protective EPA and DHA signals are specifically formed during the resolution of inflammation and that their potent actions offset pro-inflammatory signals, hold-back leukocyte activation, and promote termination of inflammation in models of stroke, asthma, inflammatory bowel disease, eye diseases, diabetes, and kidney failure^{7,8,10,12,13}. More importantly, recent experimental data demonstrates that dietary omega-3 fatty acids amplify this "resolution pathway" and that their remarkable protective effects that ensure healthy inflammation are carried out through the action of EPA and DHA derived protectins and resolvins^{12,14}.

OMEGA-3 FATTY ACID SUPPLEMENTATION ATTENUATES INFLAMMATORY RESPONSE

The normal levels of these protective DHA and EPA signals in healthy humans are currently unknown. To determine if these newly discovered compounds are indeed formed in healthy individuals and if increasing tissue levels of omega-3 fatty acids restrain leukocyte activation, we collaborated with the Health Research and Studies Center in a dietary intervention study. Thirty healthy individuals were enrolled and received daily DHA and EPA supplements (460 mg DHA, 480 mg EPA) for 8 weeks. Full profiles of lipid signals in the blood and markers for the activation of leukocytes were measured. The detailed analysis of lipid signals demonstrated that activated leukocyte in all enrolled subject generates significant levels of the protective DHA lipid signals (resolvins and protectins) prior to any dietary supplementation with omega-3 fatty acids. More importantly, 8 weeks of DHA and EPA supplementation prevented leukocytes from becoming fully activated during a vascular inflammatory stimulus, even though essential inflammatory responses such as blood clotting were unaffected by the fish oil supplementation.

In summation, it has long been known that a healthy balance between omega-6 and omega-3 fatty acids was important for health protection and disease prevention. Recent experimental and clinical data have established that omega-3 fatty acid are essential for the production of lipid signals that are the key components in inflammation “resolution pathways” that ensure healthy inflammation and promote natural healing processes. This represents yet another example of the remarkable protective effects of essential omega-3 fatty acids. Experimental and clinical data provide compelling evidence that low levels of protective EPA and DHA lipid signals lead to misguided and uncontrolled inflammation and leukocyte activation. More importantly, these protective pathways directly depend on and can readily be amplified by dietary intake of DHA and EPA.



Omega-3 fatty acid are essential for the production of lipid signals that are the key components in inflammation “resolution pathways” that ensure healthy inflammation and promote natural healing processes.

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