

## **How Fatty Acids Fight Inflammation** **Narda G. Robinson, DO, DVM, MS**

Conventional wisdom dictates that nonsteroidal anti-inflammatory drugs (NSAIDs) constitute the best, first-line pharmacologic approach to arthritis pain. They work rapidly and provide substantive relief. But what's missing? Is inflammation "all bad"? New research on preemptive nutrition for pro-inflammatory states has revealed startling discoveries on ways through which the body fights pain and inflammation on its own, given the proper circumstances. Insights into the mechanisms of action of omega-3 fatty acids are revolutionizing our approach to the multimodal management of arthritis pain.

Acute inflammation, a defensive response mounted by the host, serves to rid afflicted tissues of the causes and consequences of injury. Chronic inflammation, however, keeps the body locked in a state of perpetuating pain and biochemical unrest. The omega-3 polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) facilitate the return of a homeostatic tissue environment. The mechanisms underlying these changes is catapulting the field of nutritional pharmacology and nutrigenomics to the forefront by providing nutritional approaches by which to help thwart the inflammatory march toward cancer, Alzheimer's disease, colitis, periodontal and heart disease.

When healthy individuals suffer trauma, inflammation ensues, but usually eventually disappears. Until recently, how redness, pain, heat, and swelling leave the site of injury received little scientific scrutiny; most assumed that once initiators of inflammation left, the body passively recovered. However, researchers at Harvard Medical School, have unearthed novel biochemical pathways and families of endogenous mediators derived from omega-3 polyunsaturated fatty acids that not only prevent but help resolve inflammation.<sup>1</sup> They named these mediator families "resolvins" (Rvs) and "protectins" (PDs), to connote their respective roles in controlling the acute inflammatory response and in effecting its resolution. EPA and DHA, most richly available in fish oil preparations, serve as precursors to resolvins and protectins, which have now joined the first family of mediators, lipoxins (LX) that were previously found to have anti-inflammatory and proresolving activities.

Possibly the most amazing aspect of the resolution angle occurs when polymorphonuclear neutrophils (PMNs) orchestrate the switch from a pro-inflammatory to an inflammation-resolving state. Instigated by microbes, trauma, or cytokines, PMNs incite inflammation by forming the arachidonic acid-derived eicosanoids, prostaglandins and leukotrienes. They accomplish this through enzymatic means, driven by cyclooxygenase (COX) and lipoxygenase (LOX) pathways. Although prostaglandins cause much of the pain and edema that clinicians reflexively squelch with NSAIDs, the prostaglandins PGE<sub>2</sub> and PGD<sub>2</sub> play a dual role by signaling an end to the inflammatory process. Selective COX-2 inhibitors block the production of both PGE<sub>2</sub> and PGD<sub>2</sub>, disrupt the mediator-switching process, and may delay the onset of resolution.

When PMNs enter an exudate and make contact with certain tissue constituents and leukocytes nearby, transcellular biosynthesis takes place. Based on their local environment and biochemical interactions, PMNs have the capacity to switch their phenotype and change their profile of lipid mediator production from leukotrienes to lipoxins. This switch stops more PMN's from entering the exudate and promotes the recruitment of nonphlogistic monocytes. Tissue macrophages engulf and phagocytize the apoptotic PMNs, clearing them from the formerly inflammatory environment and allowing resolution to occur. Depending on substrate availability, mediator switching can also change from eicosanoids to resolvins and protectins. This is where omega-3 fatty acids enter the scene; when EPA and DHA appear in inflammatory exudates, enzymatic mechanisms lead to the production of LXs, Rvs, and PDs. This shortens the time course of neutrophil infiltration and prompts clearance of apoptotic PMNs. Chemokine deposits clear from the inflammatory site, promoting instead the release of anti-inflammatory cytokines and reparative compounds such as transforming growth factor-  $\beta$ 1.

But the benefits of omega-3 PUFA's in treating pain go beyond resolving inflammation. Chronic pain and negative mood states display tight linkages.<sup>ii</sup> Emerging evidence shows that deficiencies in omega-3 fatty acid intake and increased omega-6 availability in the diet appear to be correlated in humans with disturbances in brain function, and may be associated with increased risk of depression, homicide and suicide.<sup>iii iv v</sup> Putative mechanisms explaining the impact of omega-3 fatty acids on psychiatric disorders relate to enhanced serotonergic neurotransmission, changes in dopamine function and other neurotransmitters and, modulation of vagal activity, prevention of neuronal apoptosis, regulated gene expression, competition of EPA with arachidonic acid for enzymatic activities and resultant anti-inflammation, and more.

Another pathway by which omega-3 PUFA's may reduce pain is by interacting directly with an ion channel found in nociceptive neurons and the brain. This capsaicin channel, known also as TRPV1 (for transient receptor potential vanilloid subtype 1), participates in inflammatory pain signaling and may modulate behavior. Although the differential effects of DHA and EPA on TRPV1 are only now coming to light, future work may reveal ways to optimally select for the desired effects through omega-3 supplementation.

Thus, although NSAIDs and omega-3 fatty acids both reduce the amount of pain inflammation in the body, they do so through markedly different processes. Both approaches offer vital elements in the multimodal analgesic plan for arthritis pain and inflammation, and most patients respond well to the combination.

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<sup>i</sup> Serhan CN, Yacoubian S, and Yang R. Anti-inflammatory and proresolving lipid mediators. *Annual Review of Pathology*. 2008;3:279-312.

<sup>ii</sup> Tang NK, Salkovskis PM, Hodges A, et al. Effects of mood on pain responses and pain tolerance: an experimental study in chronic back pain patients. *Pain*. 2008;Mar 4 [Epub ahead of print].

<sup>iii</sup> Hibbeln JR. From homicide to happiness – a commentary on omega-3 fatty acids and human society. *Nutrition and Health*. 2007;19:9-19.

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<sup>iv</sup> Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*. 2006;67:12.

<sup>v</sup> Sinclair AJ, Begg D, Mathai M, et al. Omega 3 fatty acids and the brain: review of studies in depression. *Asia Pac J Clin Nutr*. 2007;16(Supp 1):391-397.