Controlling inflammation: a fat chance?

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The inflammatory response protects the body against infection and injury but can itself become deregulated with deleterious consequences to the host. It is now clear that several endogenous biochemical pathways activated during defense reactions can counterregulate inflammation. New experimental evidence adds resolvin E1 to this group of endogenous inhibitors and provides further rationale for the beneficial effects of dietary supplementation with fish oils. It also highlights an unexpected twist in the pharmacology of aspirin.

Polynsaturated fatty acids and diet

The discovery in the 1930s by George and Mildred Burr (1) that certain polyunsaturated fatty acids were “essential” to the health of mammals begged the question of why they were so crucial. Initially it was thought that their importance lay in their unique viscotropic effect on biological membranes, but the further discovery in the 1960s that all essential fatty acids were also substrates for prostaglandin synthesis by the cyclooxygenase enzymes (2) led to the realization that, in addition to being important structural components of the cell, these lipids were the precursors of potent hormones with widespread effects on the cardiovascular and immune systems. The subsequent demonstration that other mediators such as the leukotrienes (derived from the 5-lipoxygenase [3]) and, more recently, that the endocannabinoids (4) could also be derived from these same precursors, further highlighted this unusual property of these versatile lipids.

The essential fatty acids, which include arachidonic and eicosapentaenoic acids, cannot be synthesized by mammals de novo but must be supplied in the diet either as the native lipids or as intermediates produced by the diet. A number of studies have shown that increasing dietary proportions of these fatty acids results in reduced levels of arachidonic acid. Arachidonic acid is a 20-carbon fatty acid with 4 unsaturated double bonds located at positions (all cis) 5, 8, 11, and 14 in the hydrocarbon chain (counting from C1, the COOH terminal). Arachidonic acid belongs to a group of fatty acids sometimes known as \( \omega-6 \) fatty acids, so called because of the location of the final double bond from C20. Since the main source of essential fatty acids is foods—both plants and animals—the nature of the diet is important. Although arachidonic acid is abundant in the tissues of mammals, arachidonic acid is also a substrates for prostaglandin synthesis by the cyclooxygenase enzymes and its levels are regulated by endogenous inhibitors such as resolvin E1.

When oxidized by the cyclooxygenase enzyme systems, arachidonic acid gives rise to the “2” series of prostaglandins such as PGE2, PGE3, and so on, because of the loss of two unsaturated bonds during the cyclooxygenase reaction, and to the “4” series of leukotrienes, such as LTB4. However, the properties of eicosapentaenoic acid in this respect are quite different. To begin with, eicosapentaenoic acid is not a particularly good substrate for the cyclooxygenase and actually competitively inhibits arachidonic acid oxidation in vitro (6). PGE1 is produced from eicosapentaenoic acid by the cyclooxygenase but is less active than PGE2 in producing various biological effects relevant to inflammation (7). Eicosapentaenoic acid is, however, a good substrate for lipoxygenases, although LTB5 is ~30 times less active as an activator of neutrophils than LTB4 (8).

It had been deduced from epidemiological and dietary studies of different populations, such as the Greenland Eskimos (9), that a preponderance of fish in the diet was generally associated with a reduced incidence of inflammatory and cardiovascular disease. Over the years, a great number of studies have tested extracts of fish oil (which usually contain a mixture of eicosapentaenoic acid together with other associated fatty acids such as docosahexaenoic acid) as dietary supplements, finding a beneficial effect in a wide range of human inflammatory conditions including rheumatoid arthritis (10), cystic fibrosis (11), ulcerative colitis (12), UV-induced skin damage (13), septic shock (14), and asthma (15). Patients fed diets rich in eicosapentaenoic acid have been shown to express fewer inflammatory biomarkers (16), reduced leukocyte activation and mobility (17), and diminished production of prostaglandins and platelet-activating factor ex vivo (14); similar effects have been seen in many animal studies (18). Eicosapentaenoic acid is, therefore, one of the few “nutriceuticals” for which there is compelling evidence of efficacy, although the optimum dosage has perhaps yet to be established.

Explaining the beneficial effects

The most widely accepted explanation for the efficacy of eicosapentaenoic acid was that increasing proportions of this fatty acid incorporated into the cellular phospholipid pool reduces the net fraction of arachidonic acid released during cell activation, leading to less arachi-
whole idea of antiinflammatory lipids
Serhan’s group has now placed the extending his observations into man, phase of murine inflammation (24). By to be present during the resolution pound previously found by the group transformed to resolvin E1, a com-
pentaenoic acid) which is subsequently
hydroxy-6Z, 8E, 10E, 14Z, 16E-eicosa-
acyl-2, of a 15-epi product of eicos-
pirin, in a unique joint antiinflamma-
therapeutic agent, aspirin, as-
inhibited enzyme cannot produce pros-
taglandins it retains the ability to gener-
ate a monohydroxy fatty acid species. The most likely source of the COX-2 in this instance is the endothelial cell. In the presence of eicosapentaenoic acid and when “inhibited” by aspirin, COX-2 can release the 18R-hydroxy eicosapentaenoic acid precursor of res-
olvin E1. However, this moiety cannot
be further metabolized by the endothelial cell itself, and its transfor-
mation to resolvin E1 depends on the presence of the 5-lipoxygenase enzyme in adjacent leukocytes that are presum-
ably adherent to the vessel wall (Fig. 1). The resolvin E1 product was measured in bioactive concentrations in the plasma of volunteers taking both eicos-
apentaenoic acid (1 g) and low dose as-
pirin (160 mg).

The striking antiinflammatory activity of lipoxin A_4 (LXA_4) as an inhibitor of leukocyte activation, as earlier described by Serhan’s group (26), was rather surpris-

ingly manifested through interaction with a member of the formyl peptide receptor (FPR) family termed ALXR (or FPR-like 1). This finding was un-
expected, as this family of receptors, which comprises at least three subtypes
in humans, is generally considered to be a promoter rather than an inhibitor of leukocyte chemotaxis and activation (27). However, the recent notion that another endogenous antiinflammatory protein, annexin 1, also acts through ALXR reinforces the concept that this receptor may also have a protective anti-

inflammatory function (28).

As in the case of LXA_4, Serhan’s group has found that resolvin E1 exerts its antiinflammatory effects by acting through a G protein–coupled receptor to down-regulate NF-κB activation (22). This receptor (subsequently re-
ferred to as ChemR23), which seems fairly widely distributed in human tis-
ues, is related to ALXR and was origi-

![Image](https://example.com/image.png)
nally described as a receptor for a chemotactic peptide called chemerin. The promiscuity of the FPR family of seven-transmembrane G protein–coupled receptors may be gauged by the number and diversity of the ligands they recognize, which include lipids, peptides, proteins, bile acids, and even enzymes. It seems that Serhan’s group has uncovered an additional example of a series of lipids that exert their activities by binding to a receptor that might, under other circumstances, actually promote leukocyte chemotaxis (22). It is likely that receptors such as FPR, ALXR, and ChemR23 can assume ligand-specific conformations, hence transducing signals specific to each agonist. This concept has been advanced for several G protein–coupled receptors (29), including those of the FPR family (30).

The lure of endogenous antiinflammatories

The notion that the inflammatory response generates its own regulators in tandem with the better known proinflammatory mediators such as prostaglandins and leukotrienes makes sense from the cybernetic viewpoint as it is easier to control a process with both positive and negative regulatory inputs. Indeed, several other instances of endogenous regulators of the inflammatory response (31) have been characterized recently (32), adding support to the idea that this is a widely employed mechanism. Clearly, disturbances in such counterregulatory circuits could lead to exacerbated inflammatory responses just as effectively (although perhaps less obviously) than excessive activation of the proinflammatory cascades.

Aspirin: more than one mechanism?

This study also throws into sharp relief yet another previously unsuspected action of aspirin—its ability to facilitate the generation of antiinflammatory lipids from eicosapentaenoic acid and arachidonic acid (33). This property, which Serhan’s group has noted may be shared by indomethacin and acetaminophen (24), can now be added to the catalog of antiinflammatory effects of aspirin which have recently been the focus of other investigations (34). It is a sobering thought that aspirin, the first and arguably the simplest in chemical terms of all the modern antiinflammatory drugs, should have such complex and profound effects.

Clinical horizons

So where does this leave us in terms of practical therapeutics? It would seem that the antiinflammatory effects of eicosapentaenoic acid might be radically enhanced with low dose aspirin, and a priority should now be a formal clinical trial designed to test the additive action of these two agents in an inflammatory disease—perhaps rheumatoid arthritis—by monitoring plasma resolin E1 levels and disease outcome. We also need to know whether resolin E1 is found in vivo in the absence of aspirin treatment (and how) and whether other nonsteroidal antiinflammatory drugs such as indomethacin also promote its synthesis. But we should not overlook the cardiovascular implications of this work. Aspirin itself, of course, used already in low doses for the prophylactic treatment of patients at risk from myocardial infarction and other cardiovascular pathologies, and eicosapentaenoic acid has been shown already to be beneficial in these conditions as well. For example, the data reported in the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico) study (35), quoted by the authors, demonstrates a beneficial effect of eicosapentaenoic acid in patients at risk for myocardial infarct, many of whom were taking aspirin. In the light of the evidence presented by Serhan’s group (22), we should now also take a closer look at the aspirin–eicosapentaenoic acid interactions in the cardiovascular arena. We need to discover any direct effects resolin E1 may have on platelet function and to investigate whether any beneficial effects that may be seen in cardiovascular disease depend on the antiinflammatory effects of this compound or on other actions.

REFERENCES


