Antiinflammatory Potential of Lipoxygenase-derived Eicosanoids: A Molecular Switch at 5 and 15 Positions?

Editorial

Arachidonic acid is the precursor to a broad array of structurally diverse and potent bioactive lipids that include prostaglandins, thromboxanes, leukotrienes (LT), and lipoxins (LX), as well as other oxygenated fatty acids; collectively, these molecules are termed eicosanoids (reviewed in references 1–3). In human tissues, eicosanoid biosynthesis is initiated by cyclooxygenases (present in two forms known as PGHS-1 and PGHS-2) that can give rise to PG, TX, and prostacyclin (PGI_2), as well as three major lipoxygenases (LO), designated 5-, 12-, and 15-LO. Each enzyme is distributed in cell type–specific fashion with its expression regulated by specific cytokines. Both within and among cells, compartmentalization and selective enzyme induction results in further diversity of the products produced via transcellular biosynthesis (3). One important concept that derives from these multiple molecules is that eicosanoids, generated from a common precursor, can display opposing physiological actions. For example, TX generation by platelets induces platelet aggregation, while PGI_2 production by endothelium regulates vascular tone and prevents platelet aggregation (1). Thus, an antiinflammatory action for specific eicosanoids is not surprising.

Of the two LOs associated with human leukocytes (i.e., 5- and 15-LO), it was quickly ascertained that the 5-LO generates LT that carry proinflammatory activities (2), while the actions of 15-LO were not well understood (1). More recently, the observation of opposing regulatory actions between LT and LX generated via 15-LO and cell–cell interactions has led to the concept that LX and products of 15-LO could serve as potential antiinflammatory mediators (reviewed in references 2, 3). In this regard, Vanderhoek et al. (4) first reported that 15-hydroxyeicosatetraenoic acid (15-HETE) inhibits 5-LO. The major action of 15-LO is to insert molecular oxygen in the 15 position of arachidonic acid, predominantly in the *S* configuration, to produce 15*S*-HpETE. This hydroperoxide undergoes rapid transformation to LX and/or reduction to the corresponding alcohol, namely 15*S*-HETE. An inverse relationship between the amounts of LT and LX biosynthesis has been established in human leukocytes in that, during LX formation, LT biosynthesis is blocked (3). LX are potent antiinflammatory molecules. LXA_4 blocks the vasoconstrictive actions of LTD_4 and inhibits leukocyte-dependent inflammation (reviewed in references 2, 3). Stable analogs of LXA_4 have been synthesized and found in nanomolar concentrations to inhibit neutrophil transmigration and adhesion (5). Thus, it appears that certain eicosanoids and products of 15-LO pathways can indeed downregulate key events in inflammation.

Interest in these pathways is heightened by the finding that aspirin, the widely used and well known inhibitor of PGHS, actually triggers biosynthesis of 15-epi-LX (the stereoisomer of LX with the chirality reversed at the 15 position). These novel "aspirin-triggered" compounds appear to mediate, at least in part, some of the beneficial aspects of aspirin by blocking neutrophil adhesion. When aspirin acetylates PGHS-2, the ability of this enzyme to generate the endoperoxide intermediate for PG is inhibited, while its enzymatic activity remains operative; this results in the formation of 15*R*-HETE from arachidonic acid, and this product is rapidly converted through cell–cell interactions to 15-epi-LX (2, 6). Although both 15-HpETE and 15-HETE can block certain proinflammatory events (3, 4), they are 100–1,000× less potent than LX stable analogs (5). The latter molecules, because of their stability and potency, are very useful experimental tools.

In this issue of the *Journal*, Ferrante et al. (7) report that 15-HpETE and arachidonic acid inhibit formation of TNF and thus raise additional evidence for a potential antiinflammatory role for 15-LO–derived products. 15-HpETE added to the Mono Mac 6 cell line reduced LPS-induced TNF mRNA expression and production and blocked translocation of protein kinase Cs. The authors provide evidence that 15-HpETE is more potent than either arachidonic acid or 15-HETE (in $\sim$ 1–30-μM concentrations), which are inhibitors of TNF production. Thus, 15-HpETE–derived products could be considered as potential antiinflammatory therapeutics. These suggestions are in line with previous observations from several laboratories, but also raise questions that need to be addressed. They are as follows: Are there stereochemical requirements for these actions of 15-HpETE on Mono Mac 6 cells? Can other positional hydroperoxy acids such as 5-HpETE or 12-HpETE inhibit TNF production? Is 15-HpETE further transformed to LX in these incubations with LPS? This appears likely, since Mono Mac 6 cells display 5-LO (8), but does this cell line possess sufficient 15-LO to produce 15-HpETE? Do LT act as intracellular signals in LPS signal transduction? Is the induction of 15-LO by IL-4 and IL-13 (9) important when considering the actions of LPS?

Avenues to address these questions (i.e., the role of 15-LO and its products) include selective 15-LO inhibitors (no agents that are selective for 15- vs. 5-LO are available) and genetic deletion of the enzyme. In this respect, it has been noteworthy that 15-LO induction is also proposed to be responsible for oxidative modification of LDL radicals and linked to processes such as atherosclerosis (see reference 10). The suggestion that 15-LO could act in a "nonselective" fashion to induce oxidative modifications of LDL contrasts the stereoselective and controlled actions of 15-LO in generating 15-HpETE. This dichotomy may illustrate the potential "normal" physiological activation of 15-LO in inflammation vs. a role in pathophysiologic settings. Nonetheless, the observation that 15-HpETE serves as the downregulator of a key proinflammatory cytokine such as TNF (7) warrants further study to elucidate the mechanism of action of this arachidonic acid derivative's potential antiinflammatory actions, particularly since most lipid hydroperoxides are generally viewed to be precursors of proinflammatory molecules or themselves indicators and initiators of oxidative damage.

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