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Review

Omega-3 fatty acids and their lipid mediators: Towards an understanding of resolvin and protectin formation
Omega-3 fatty acids and their resolvin/protectin mediators

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ABSTRACT

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have long been associated with decreased inflammation and are also implicated in the prevention of tumorigenesis. Conventional thinking attributed this mainly to a suppressive effect of these fatty acids on the formation of arachidonic acid-derived prostaglandins and leukotrienes. Recent years have seen the discovery of a new class of inflammation-dampening and resolution-promoting n-3 PUFA-derived lipid mediators called resolvins and protectins. Chemically, these compounds are hydroxylated derivatives of the parent n-3 PUFA eicosapentaenoic acid (EPA) for the E-resolvins, and docosahexaenoic acid (DHA) for the D-resolvins and protectin D1. While a relatively large number of these compounds have been identified and characterized until now, with differences in the positions of the hydroxyl-groups as well as in the chirality at the different carbon atoms, all compounds share common precursor metabolites, 17-hydroperoxydocosahexaenoic acid (17-H(p)DHA) for the DHA-derived compounds and 18-hydroperoxyeicosapentaenoic acid (18-H(p)EPE) for the EPA-derived compounds. In this review we summarize the current knowledge about EPA- and DHA-derived resolvins and protectins and explore the potential use of the pro-resolvins 17-hydroxydocosahexaenoic acid (17-HDHA) and 18-hydroxyeicosapentaenoic acid (18-HEPE) as indicators of anti-inflammatory n-3 PUFA mediator formation.

Contents

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1. Polyunsaturated fatty acids and inflammation

Essential omega-6 and omega-3 polyunsaturated fatty acids (n-6 and n-3 PUFAs) are precursors of a wide range of bioactive lipid mediators. Their nomenclature is based on the position of the first double bond counted from the methyl (omega) end of the respective polyunsaturated fatty acid.

The 20-carbon omega-6 polyunsaturated fatty acid arachidonic acid is the precursor of highly bioactive lipid mediators. Already in 1939, von Euler named a substance that he had isolated from certain genital glands prostaglandins (PG) [1]. In the 1970s Samuelsson coined the term leukotrienes (LT) [2], another group of bioactive compounds that, like prostaglandins, has an important role in inflammatory processes. Arachidonic acid derived lipid mediators comprise the subgroups of prostaglandins, thromboxanes, prostacyclins and leukotrienes and are widely appreciated for a variety of (often pro-inflammatory) activities [3,4].

While the molecular mechanisms of n-6 PUFA derived lipid mediator signal transduction and their effect on the organism have been well characterized, n-3 PUFAs have not been the focus of interest for many years. Interest in these compounds arose from observations in Greenland Eskimos showing mortality from coronary heart disease at only about 10% of that registered in epidemiologic studies for Danes and Americans [5,6]. Even though the amount of total fat in the diet of Eskimos and Americans was roughly the same, fat in the diet of native Eskimos was rich in n-3 PUFA [7]. Subsequent studies confirmed the importance of n-3 PUFAs such as DHA and EPA for the prevention of cardiovascular disease and decrease of cardiac mortality [8]. Besides coronary heart disease, the Greenland Eskimo population showed a lower prevalence of further diseases, such as psoriasis, inflammatory bowel disease, asthma, rheumatoid arthritis and other autoimmune diseases [9–12]. The inflammatory background of these diseases led to the assumption that n-3 PUFA may act through down-regulation of inflammatory stimuli.

Animal studies have demonstrated an anti-inflammatory effect of n-3 PUFAs in a wide variety of inflammation models and our previous work confirmed these findings in the fat-1 mouse model with endogenously increased n-3 PUFA tissue content in the context of allergic airway inflammation, colitis, pancreatitis and hepatitis as well as inflammation-triggered colon and liver tumorigenesis [13–18]. In humans, study results regarding the anti-inflammatory effect of n-3 PUFA are less clear (see e.g. [19]).

A common explanation for the effect of n-3 PUFAs is to assume that they might function as direct antagonists of arachidonic acid or as upstream suppressors of cyclooxygenase (COX) and lipoxygenase (LOX) enzyme expression, thereby inhibiting the formation of prostaglandins or leukotrienes [20]. Recent studies have now added an important twist to this, identifying n-3 PUFAs as precursors of a distinct set of lipid mediators that probably act through distinct receptors to unfold anti-inflammatory effects. These new n-3 PUFA-derived, anti-inflammatory mediators have been named protectins and resolvins. Serhan et al. identified resolvins in inflammatory exudates in the murine air pouch model of inflammation during the resolution phase, and named them accordingly "resolution phase interaction products" or resolvins [21]. Protectin D1 was initially found to attenuate damage of brain ischemia-reperfusion injury and thus named neuroprotectin D1 [22–24].

Inflammation is an important component in the pathogenesis of numerous diseases. The elaborately orchestrated process of local inflammation is not only characterized by its swift initiation but also by means of controlled resolution in order to enable healing and to prevent inflammation from spinning out of control, threatening the entire organism. A key characteristic of inflammation resolution is the notion that inflammation does not only come to an end by a decline of pro-inflammatory stimuli and the subsequent fading of their effects until homeostasis is reached; the new understanding is that at a certain point of inflammation, i.e. the resolution phase, a different pattern of mediators is released. These mediators then have an active impact on resolution, not simply by antagonizing pro-inflammatory mediators but rather by actively promoting the return to health [25].

While initial observations regarding anti-inflammatory and pro-resolution lipid mediators were made in the field of arachidonic acid (and therefore n-6 PUFA) derived lipoxins, with the particular appreciation of the role of aspirin-triggered acetylation of COX-2 in one lipoxin synthesis pathway [26–28], recent years have added a large body of evidence towards an important role of a wide range of n-3 PUFA-derived resolvins in this context.

The purpose of this review is to summarize this knowledge with a particular focus on the initial biosynthesis step involved in the formation of resolvins from EPA and DHA as these compounds might offer an important new concept to explain the protective effect of n-3 PUFAs in a wide variety of pathophysiological contexts.

2. DHA-derived resolvins and protectins

DHA constitutes the origin for the D-series resolvins, as well as (neuro-)protectin D1. Formation happens through a 15-lipoxygenase (15-LOX) catalyzed hydroxylation of DHA at C17 leading to 17S-H(p)DHA [29]. These compounds are then further hydroxylated to give rise to trihydroxy compounds called resolvins D1, D2, D3 and D4 (RvD1–D4) and the dihydroxy compound protectin D1: all of these mediators share the 17S-configuration and could therefore also be called 17S-resolvin D class. Alternatively, the lipoxygenase-activity of the (aspirin-) acetylated COX-2 can catalyze the first hydroxylation step at C17 leading to 17R-H(p)DHA and the subsequent biosynthesis of (aspirin-triggered) resolvins D1–D4 (AT-RvD1–D4) [29], which could therefore also be summarized as 17R-resolvin D class. Aspirin triggered (R-) and 15-lipoxygenase dependent (S-) resolvins differ in the stereochemical configuration of their hydroxyl groups at C17 (Fig. 1): 17R- and 17S-resolvins D1 and D2 are formed from 17R-H(p)DHA or 17S-H(p)DHA respectively by epoxidation and 5-lipoxygenase action *via* 7S,(8)-epoxy or 7S-hydroperoxy intermediates, whereas epoxidation and lipoxygenase action *via* 4S,(5)-epoxy or 4S-hydroperoxy intermediates leads to the corresponding R- and S-resolvins D3 and D4.

17S-protectin D1 (10R,17S-dihydroxydocosahexaenoic acid) is formed through an enzymatic epoxidation mechanism involving the formation of a 17,16-epoxide from 17-H(p)DHA [30]. It is generated by a single enzyme (15-LOX) and is thus not classified with the resolvins, which are products of 15-LOX and 5-LOX interaction and are thus induced or amplified during inflammation resolution by 5-LOX carrying polymorphonuclear leukocytes (PMN).

17R-protectin D1 is triggered by aspirin and was found to also mediate anti-inflammatory and pro-resolution activity [31].

Bioactivity of several of these compounds has been characterized in a range of studies establishing anti-inflammatory and pro-resolution effects for 17S-resolvin D1 and 17R-resolvin D1, 17S-protectin D1, 17R-protectin D1, 17S-resolvin D2, 17R-HDHA and 17S-HDHA.

2.1. 17-HDHA

17-HDHA is a pathway marker for the formation of anti-inflammatory D-resolvins. Studies have also demonstrated a direct protective effect of 17S-HDHA in the context of renal reperfusion injury [32] and suppression of TNF-α secretion from murine macrophages by 17S-HDHA [33]. Similarly, 17R-HDHA was recently shown to be anti-inflammatory in the context of