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Resolvins and Protectins: Natural Pharmacophores For Resolution Biology

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Abstract

Dietary ingestion of fish is associated with a reduced risk for many common human illnesses. Fish oils are enriched with n-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid. Resolvins and protectins are newly discovered mediators that are enzymatically generated from these n-3 fatty acid precursors to orchestrate inflammation resolution. These natural compounds and their mimetics are providing intriguing evidence in model systems and translational research for cellular and molecular mechanisms that are active during catabasis. This review provides information on the biosynthesis and actions of these recently identified chemical mediators with particular reference to resolution of mucosal inflammatory responses.

Keywords

inflammation; resolvins; protectins; resolution; fish oils

1. Introduction

The resolution of acute inflammation is a complex active process that involves several distinct molecular and cellular mechanisms. In most cases, acute inflammation spontaneously resolves to restore homeostasis. The events directing resolution are not merely a passive dilution of pro-inflammatory signals and effectors. Rather, tissue resolution is a tightly orchestrated and multifaceted host response (1). It has its origins early in acute inflammation. In the first few minutes to hours in acutely injured, infected or inflamed tissues, biosynthetic circuits are created for chemical mediators that have anti-inflammatory properties and promote resolution (2). These counter-regulatory signals provide tissue level control over the intensity of the inflammatory response, and ultimately lead the process of catabasis. Specific pro-resolving mediators are generated that serve as agonists at specific receptors (3). Disruption of their biosynthesis or sites of action by genetic susceptibility or pharmacologic intervention can prove to be harmful to resolution, delaying the restoration of tissue homeostasis (4,5). In addition, many common diseases are characterized by chronic inflammation that fails to resolve. Recent

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identification of pro-resolving mediators has uncovered a shared pathobiology in several of these conditions of a defect in the generation of these protective compounds (6-11).

Acute tissue inflammation is characterized by specific cellular events, including increased endothelial and epithelial permeability, infiltration of polymorphonuclear leukocytes (PMNs) and inflammatory macrophages and lymphocytes (12). As the tissue resolves, barrier integrity is reestablished and further infiltration of PMNs is blocked. Cell clearance from the inflamed tissue is critical to resolution and is driven both by apoptosis of leukocytes (13-15) and egress from tissues (16). Clearance of the inflammatory site is mediated in part via the non-phlogistic recruitment of monocytes that, as macrophages, participate in the phagocytosis of apoptotic cells and microbes (5,17). In addition, mechanisms unique to mucosal surfaces exist to release PMNs from the apical surfaces of epithelial cells into the lumen for tissue clearance (18). These cellular events can be tracked by microscopy or tissue histology, leading to the development of several resolution indices to determine the extent of inflammation (19). Most common in current use are the maximal number of leukocytes (ϕ_{max}) and the resolution interval (R_i), which is the interval of time from the ϕ_{max} to the half-maximal response during resolution (19). These metrics are particularly useful when determining the impact of gene expression or pharmacologic intervention on the pace of resolution. If the resolution interval decreases, then resolution has been accelerated. In contrast, if the resolution interval lengthens then there has been an adverse impact on leukocyte resolution – independent of the intervention's impact on early pro-inflammatory events.

As cell numbers decline in resolving tissues, levels of pro-inflammatory cytokines decrease and the metabolism of polyunsaturated fatty acids (PUFAs) changes, with a class switching in lipid mediator generation that changes from enzymatic conversion of pro-inflammatory mediators (e.g., leukotrienes (LTs) and prostaglandins (PGs)) to pro-resolving mediators (e.g., lipoxins (LXs), resolvins (Rvs) and protectins (PDs)) (20-22). This review will focus on rapidly emerging information on the generation and actions of recently identified resolvins and protectins that are enzymatically derived from the n-3 PUFAs eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3).

2. Resolvins

Resolvins are stereospecific small molecules that are enzymatically derived from EPA and DHA, n-3 PUFAs that are abundant in cold water fish (21,22 and reviewed in 1). These naturally occurring bioactive mediators were first identified by physical methods during lipidomic system-based analyses of spontaneously resolving murine exudates. They were arbitrarily termed resolvins to reflect their identification as resolution phase interaction products. As compounds were isolated, retrograde analysis was carried out using biogenic as well as total organic synthesis to elucidate structures and characterize stereochemistry (21-26). Using these methods, several classes of resolvins were identified. Resolvins are now categorized as either E-series (from EPA) or D-series (from DHA) (Figure 1) and aspirin-triggered epimers of these compounds have also been identified (as reviewed in 3).

2.1 E-series Resolvins

The E-series resolvins currently comprise Resolvin E1 (RvE1) and Resolvin E2 (RvE2). Each of these molecules is enzymatically-derived from EPA and was originally isolated *in vivo* from murine resolving exudates (21). Transcellular formation of RvE1 can occur during inflammation when endothelial cells interact with leukocytes. For example, in the presence of aspirin, EPA can be enzymatically transformed to 18R-hydroxyeicosapentaenoic acid (18R-HEPE) by endothelial cell cyclooxygenase-2 (COX-2). Aspirin acetylates COX-2 and the acetylated enzyme no longer generates prostaglandins, but can still convert EPA to 18R-HEPE, a biosynthetic precursor for RvE1. During cell-cell interactions, 18R-HEPE is released to

neighboring leukocytes for subsequent conversion by 5-lipoxygenase (ALOX5) to RvE1 via a 5(6) epoxide-containing intermediate (21,23). RvE1 is present in human whole blood and can be increased by ingestion of aspirin (23). The structure of RvE1 was elucidated as 5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-EPA and complete stereochemistry confirmed (21,23).

The bioactivity of RvE1 is highly stereoselective both *in vivo* and *in vitro*. Anti-inflammatory actions for RvE1 include potent regulation of PMN trafficking and activation. RvE1 blocks PMN transendothelial migration (21), and PMN functional responses to inflammatory stimuli, such as NF- κ B activation (27) and superoxide anion generation (28). In addition to these anti-PMN actions, RvE1 promotes PMN removal by clearance from the apical surface of mucosal epithelial cells (18) and macrophage-mediated phagocytosis of apoptotic PMNs (5). RvE1 also regulates the levels of pro-inflammatory peptide mediators by inhibiting dendritic cell migration and cytokine release (23,29) and upregulating leukocyte CCR5 expression (30). This complex array of bioactions provides both anti-inflammatory and pro-resolving properties for this compound.

RvE1 displays potent *in vivo* regulation of mucosal inflammation at many levels of the aerodigestive tract. In a rabbit model of periodontitis, RvE1 both dampens inflammation and promotes restoration of periodontal tissues, including bone (31,32). RvE1 also markedly decreases the inflammatory sequelae of 2,4,6-trinitrobenzene sulfonic acid-induced colitis (33) and can facilitate the resolution of allergic airway inflammation (29;Figure 2). In comparison with other agents that are clinically available to decrease inflammation, RvE1 proved log-orders more potent than dexamethasone or aspirin in a murine dorsal air pouch model of dermal wounding and inflammation. In nanogram quantities, RvE1 decreases leukocyte infiltration by 50-70%, whereas the IC₅₀ for dexamethasone and aspirin in this model are in the microgram and milligram range, respectively (21,23). RvE1 also displays important actions on structural cell functional responses, including the facilitation of wound healing by epithelial cells (34). Thus, RvE1 displays characteristics *in vitro* and *in vivo* of a mediator for catabasis.

RvE1 is metabolically inactivated in a rapid and regiospecific manner. The first step in its inactivation is a regiospecific conversion at carbon 18 to generate 18-oxo-RvE1 (35). RvE1 inactivation is complex and shows species-, tissue- and cell-type specific pathways (35). Rapid inactivation of RvE1 in a regulated manner provides local control for cells and tissues in catabasis. In addition, elucidation of these metabolic pathways has informed the design of structural analogs of RvE1 that resist inactivation (35).

Structure-activity assays for RvE1 and related compounds indicate that the mechanism of action of RvE1 relies on specific receptors (23). Use of [³H]-labeled RvE1 confirmed specific binding and the molecular identification of RvE1 cognate receptors has followed. The first RvE1 receptor identified was a G-protein coupled receptor termed ChemR23, a seven-membrane spanning receptor expressed on dendritic cells and monocytes (23). RvE1 serves as an agonist at this receptor to block cytokine-initiated NF- κ B activation and stimulate specific MAP kinases (23). ChemR23 was initially characterized as a receptor for the peptide chemerin that also transduces anti-inflammatory signals (36). Thus, similar to the lipoxin A₄ receptor ALX 37, ChemR23 can interact with both lipid or peptide ligands. Distinct from dendritic cells and monocytes, RvE1 also displays high affinity specific binding to human PMN membranes with a K_d of 48.3 nM at 4°C. Competitive displacement of [³H]-labeled RvE1 binding to PMN membranes is observed with unlabelled RvE1 (K_i = 34.3 nM), LTB₄ (K_i = 0.08 nM), and the LTB₄ receptor 1 (BLT1) selective antagonist U-75302 (K_i = 1.5 nM). These findings suggest binding sites for RvE1 on human PMNs, including BLT1 (27). RvE1 interactions at BLT1 block LTB₄ signaling and display partial agonist/antagonist effects on PMNs (27). To date,

these two distinct receptor signaling systems have been determined for RvE1, exerting agonist actions as a ligand for ChemR23 and antagonist/partial agonist effects on BLT1.

RvE2 is the trivial name for 5S,18(R/S)-dihydroxy-eicosapentaenoic acid (38). RvE2 is a structurally distinct member of the E-series resolvins (38). RvE2 is synthesized from EPA by human PMNs, and has similar actions as RvE1. When given together, the protective actions of RvE1 and RvE2 are additive at low doses, suggesting distinct receptors for RvE2 and RvE1 (38). A cognate receptor for RvE2 has yet to be identified, but is the subject of ongoing research (38).

2.2 D-series Resolvins

D-series resolvins are enzymatically derived from DHA. Endogenous DHA can serve as a substrate for 15-lipoxygenase (ALOX15) that transforms the PUFA to 17S-hydroperoxy-DHA (17S-H(p)DHA) (Figure 3A). This pivotal biosynthetic intermediate can be converted to several bioactive compounds, including resolvin D1 (RvD1, Figure 1), RvD2, RvD3 and RvD4 (24). There are also aspirin-triggered forms of D series resolvins (AT-Rv) that are also enzymatically derived from DHA via a pathway with sequential oxygenation initiated by aspirin-acetylated COX-2 (Figure 3). For the biosynthesis of AT-RvDs, DHA is initially converted to 17R-hydroxy-DHA. The stereochemistry at carbon 17 is conserved, so AT-RvDs each carry a 17R alcohol group configuration, resulting in a distinct series of compounds. The complete stereochemistry of RvD1 (7S,8R,17S,-trihydroxy-4Z,9E,11E,13Z,15E,9Z-docosahexaenoic acid) and ATRvD1 (7S,8R,17R-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid) was recently confirmed (22, 26). These compounds are collectively termed the D-series resolvins.

In a model of acute peritoneal inflammation, the bioactivity of D-series resolvins was established with structure-function relationships identified (22,26). RvD1 and ATRvD1 display similar dose dependent regulation of PMN infiltration (26). Similar to RvE1, RvD1 is also inactivated by initial conversion to 17-oxo-RvD1 (26).

3. Protectins

In addition to the D-series resolvins, Protectin D1 (PD1) is generated from the biosynthetic intermediate 17S-hydroxy-DHA (25;Figure 3). PD1 biosynthesis proceeds via an ALOX15 catalyzed epoxide intermediate at the 16(17) position (24,25). The complete stereochemistry of PD1, the lead member of the protectin family, has been established and now verified by total organic synthesis and matching studies to show that PD1 (known as neuroprotectin D1 (NPD1) when generated in neural tissues) is 10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid (25). The route of biosynthesis for PD1 via the epoxide intermediate distinguishes it from the formation of the double dioxygenation product 10S,17S-dihydroxy-DHA (Figure 3). PD1 is log orders of magnitude more potent than its parent compound DHA (24,25,39,40). In sharp contrast, PD1 positional isomers, including 4S,17S-diHDHA or 7S, 17S-diHDHA, display less potent and nonselective actions (24).

PD1 is present in murine inflammatory exudates, murine lung (Figure 3), peripheral human blood and exhaled breath condensate from asthmatic and healthy humans (22,24,25,40). A wide array of cell types can participate in PD1 biosynthesis, including murine brain cells, human microglial cells (22), human peripheral blood mononuclear cells and Th2 CD4+ T-cells (24,25). When exposed to oxidative stress, retinal pigment epithelium cells generate NPD1 to prevent cell apoptosis (41-43). Similar to resolvins, PD1/NPD1 also possesses stereospecific and potent immunoregulatory actions that are anti-inflammatory and homeostatic *in vitro* and *in vivo* (1). PD1 demonstrates protection of retinal epithelial cells (41,42), experimental stroke-related ischemia-reperfusion injury (44), and animal models of Alzheimer's disease (45). Of

interest, neuroprotection appears to be dysregulated in Alzheimer's disease, as levels of DHA, NPD1 and ALOX15 are selectively decreased in the hippocampus. In addition, after an ischemic stroke, pro-inflammatory gene induction and leukocyte accumulation are blocked by NPD1 (44). PD1 also displays specific actions on T-cells to decrease their migration, cytokine release and cell survival (46).

PD1 is also generated in mucosal inflammation in human airways and murine lung (Figure 3). Airway mucosal tissues contain substantial amounts of DHA, and PD1 can serve as a potent regulator of allergic airway inflammation and responses to provocative challenge (40). In nanogram quantities, PD1 prevents the development of airway hyper-reactivity and markedly inhibits infiltration of the lung eosinophils and T-cells as well as mucus metaplasia (40). Of even more relevance for clinical asthma, when PD1 is given as a treatment after allergic airway inflammation is established, resolution of this experimental model of asthma is accelerated (40). Similar tissue protective actions for PD1 are observed in renal tissues. After ischemia-reperfusion injury, murine kidneys generate PD1 (39) and displays renoprotective actions.

4. Resolvin and protectin mimetics

With the discovery of resolvins and protectins as mediators of anti-inflammation and resolution, potential lead compounds were uncovered for the development of novel therapeutic strategies. While there have been many agents developed to block inflammatory mediator pathways, the resolvins and protectins represent natural agonists for cognate receptors that initiate an array of signaling pathways for catabasis. If successfully developed as new drugs, chemical mimetics as agonists of natural resolution pathways would represent a new genus of therapeutic agents (47). The first stable analog of RvE1 has been prepared by chemical modification at the ω -end of RvE1 in order to block metabolic inactivation (35). This RvE1 analog, 19-(*p*-fluorophenoxy)-RvE1 methyl ester, displays protective actions for acute inflammation in murine experimental model of periodontitis and resists ω -oxidation and rapid dehydrogenation (35). Harnessing the natural resolution signaling pathways with resolvin and protectin mimetics represents an exciting new approach to drug development and, along with the endogenous compounds, provides natural pharmacophores to explore the rapidly emerging field of resolution biology.

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Abbreviations

COX	cyclooxygenase
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
LOX	lipoxygenase
LT	leukotriene
LX	lipoxin
MS	mass spectrometry
PD	protectin
PG	prostaglandin
PMN	polymorphonuclear leukocyte

PUFA polyunsaturated fatty acid
Rv resolvin

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E-Series Resolvins

EPA

Resolvin E1

D-Series Resolvins

DHA

Resolvin D1

Protectins

DHA

Protectin D1

Figure 1. Resolvins and protectins

Resolvins and protectins have been identified in spontaneously resolving exudates. They are enzymatically derived from n-3 fatty acids: E-series resolvins are from EPA, while D-series resolvins and protectins are from DHA. The chemical structure of representative members of these families of natural compounds is shown.

Figure 2. Resolvin E1 accelerates the resolution of experimental asthma exacerbations

(A) Mice were sensitized with allergen and aerosol challenged daily for 4 days. (B) Beginning 24h later, at peak allergic airway inflammation, animals were treated with either RvE1 (100 ng, iv) or vehicle daily for 3 days, prior to determining the lung inflammation resolution interval (R_i). (C) Levels of IL-17A, IL-23 and IL-6 in bronchoalveolar lavage fluids at protocol day 21 (24h after peak inflammation) were markedly decreased by RvE1, pointing to a critical role for Th17 cells in the persistence of allergic airway inflammation.

Figure 3. Protectin D1/neuroprotectin PD1 biosynthesis

(A) DHA is converted by ALOX15 to the pivotal intermediate 17S-H(p)DHA that serves as a substrate for further enzymatic transformation to PD1/NPD1 via a 16(17) epoxide intermediate. This route of synthesis is distinct from the formation of the double dioxygenation product that does not share the same bioactions as PD1/NPD1. (B) Lipid extracts were obtained from inflamed murine lung and taken to LC-MS/MS that uncovered PD1/NPD1. Mass spectra revealing the characteristic fragmentation ions for PD1/NPD1.