F1000Reports MEDICINE

Published: 03 October 2011

Resolvins and inflammatory pain

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F1000 Medicine Reports 2011, **3**:19 (doi:10.3410/M3-19)

Abstract

Resolvins are a group of molecules derived from omega-3 fatty acids. They are part of a biochemical program that allows inflamed tissues to return to homeostasis once the need for the inflammatory response is over. Resolvins act in very low dose ranges *in vitro* and *in vivo*. New data suggest that they might have the potential to become very potent analgesic drugs in inflammatory pain.

Introduction

Chronic inflammation is a feature of a large number of painful chronic degenerative diseases, such as arthritis, low back pain, and inflammatory bowel disease, among many others. These conditions cause pain and suffering to millions, not to mention the high healthcare and socio-economic costs involved in managing these conditions. Patients with chronic inflammation are currently prescribed cyclooxygenase (COX) inhibitors or opioids to control their pain; however, long-term use of these drugs leads to significant side effects, and the analgesic effect is even lower in chronic pain than in acute pain. Unselective COX inhibitors may cause gastrointestinal bleeding and kidney damage, and selective COX2 inhibitors may increase the risk of cardiovascular disease. Long-term use of opioids leads to tolerance and the need to increase doses, and causes unwanted side effects such as drowsiness, constipation, nausea, sedation, and cognitive disturbances. Thus, an alternative, powerful, and well-tolerated treatment of chronic inflammatory pain would be of great interest to both patients and doctors.

Physiologically, acute inflammation is an important process for successful host defense, and should cease once the stimulus is removed. The process by which inflammation is terminated is not only passive; for example, by elimination of the antigen, it is now understood to be an active process [1]. Important molecular players involved in the active termination of inflammation are the "specialized pro-resolving mediators" [2], which include the essential fatty acid-derived lipoxins, resolvins, protectins, and maresins [1]. If this active process fails, chronic inflammation may ensue. Not only does chronic inflammation underlie disorders like rheumatism, inflammatory bowel disease, and other autoimmune diseases, it has also been implicated in the pathogenesis of diverse neurological disorders like Parkinson's and Alzheimer's disease, cancer, chronic heart failure, and pain. A closer look at the specialized pro-resolving mediators described above that help resolve inflammation may help us find a more effective treatment to combat inflammatory pain.

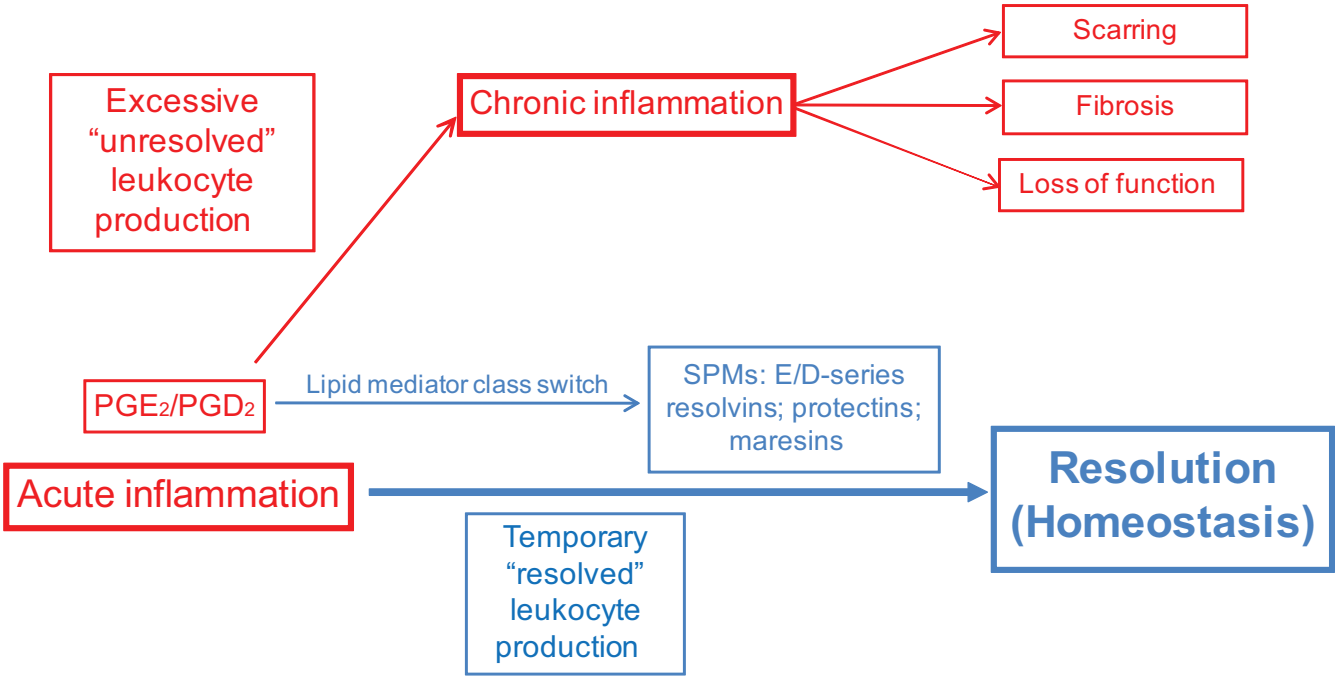
Lipoxins—as all specialized pro-resolving mediators do—stimulate the uptake of apoptotic polymorphnuclear leukocytes and activate antimicrobial defense mechanisms. This action is supported by these mediators shifting to an anti-inflammatory response; lipoxins inhibit the production and action of chemokines and inflammatory cytokines while stimulating anti-inflammatory cytokines [3]. Resolvins block the production of proinflammatory mediators and regulate leukocyte trafficking to inflammatory sites as well as clearance of neutrophils from mucosal surfaces. Specifically, resolvins limit polymorphnuclear leukocyte migration and infiltration across the endothelium. Protectins additionally possess protective actions in neural tissues and systems. Like resolvins, protectins stop polymorphnuclear leukocyte infiltration and they also

limit cytokine expression. Protectins reduce injury and stroke damage, and improve corneal wound healing. Macrophages, which are also essential in inflammation, biosynthesize the fourth specialized pro-resolving mediator on our list, maresins (macrophage mediator in resolving inflammation), from docosahexaenoic acid (DHA), thereby contributing to the anti-inflammatory action of DHA. Maresins also contribute to wound healing and host defense. In summary, each of these specialized pro-resolving mediators is temporally and spatially biosynthesized to actively regulate inflammation resolution by acting on specific receptors initiating anti-inflammatory and pro-resolving signals to terminate inflammation and prevent chronic disease [4] (Figure 1). Among these specialized pro-resolving mediators, the resolvins in particular have recently received attention by researchers and been studied in various disease models, including pain.

The Serhan laboratory at Brigham and Women's Hospital at Harvard Medical School discovered resolvins when they were looking for potential endogenous bioactive compounds derived from omega-3 fatty acids [2,5]. Omega-3 fatty acids such as eicosapentaenoic acid (EPA) and DHA have long been known to have beneficial effects in several diseases, including atherosclerosis, asthma, cardiovascular disorders, and cancer [6]. The American Heart Association even recommends the intake of fish rich in omega-3 fatty acids for cardiovascular disease prevention. However, it was not known exactly how omega-3 fatty acids worked in the diverse clinical trials. Furthermore, in some of the trials, omega-3 fatty acids had been given together with aspirin, which is anti-inflammatory in its own right. The Serhan laboratory therefore set out to analyze the interaction of EPA and DHA with aspirin and to identify molecular components derived from the fatty acids.

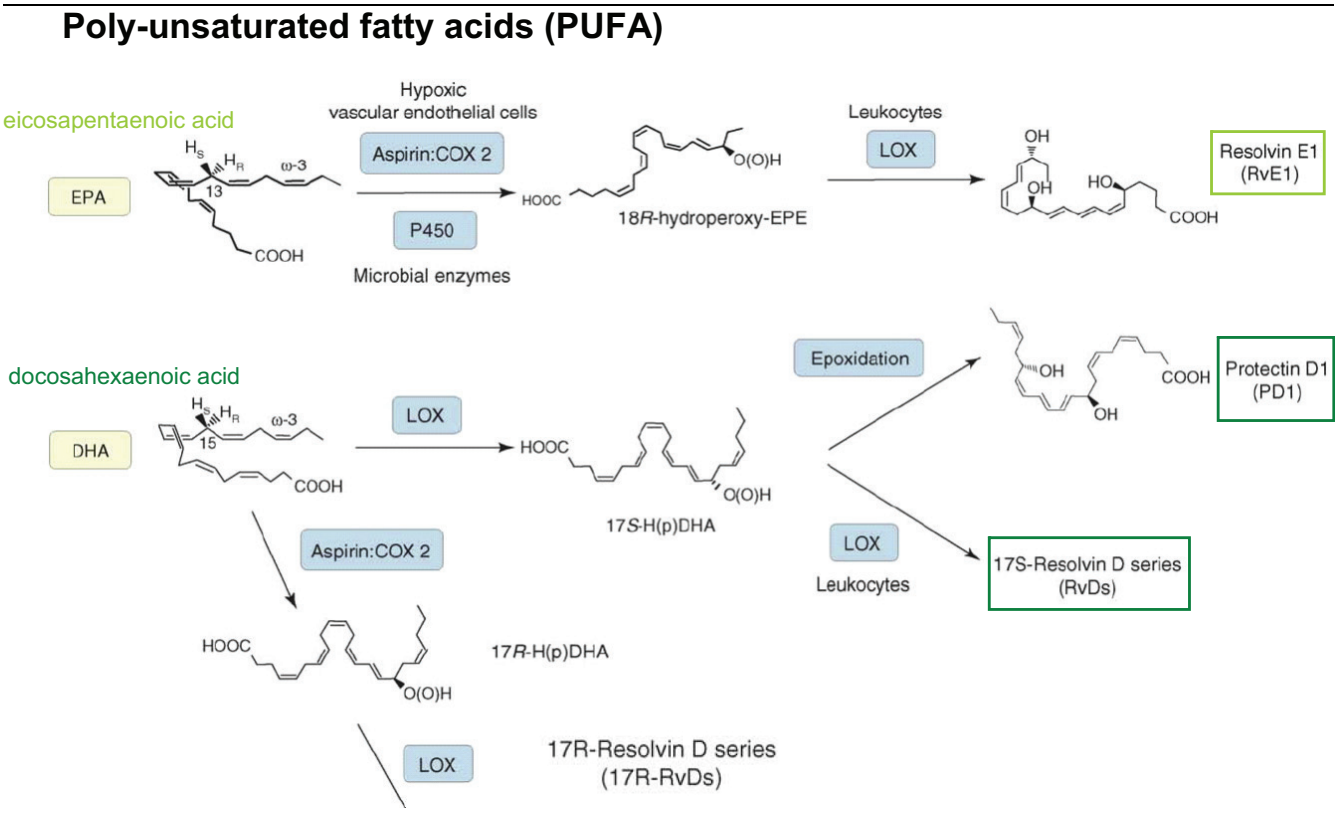
The Serhan group used lipidomic analyses in the model of the mouse air pouch (a subcutaneous pouch induced by injection of air that is frequently used to study inflammation) and described previously unknown biosynthetic circuits leading from omega-3 fatty acids to the novel 17R-hydroxy series of docosanoids [2,5] (Figure 2). They found, in particular, that treatment with aspirin enhanced the production of these compounds. These specialized pro-resolving mediators, when administered in animal models of inflammation such as peritonitis, colitis, or asthma, accelerated the return to homeostasis (for review see [5]). Interestingly, one of the early applications of resolvins to be investigated was in periodontitis [7], and

Figure 1. Resolution of inflammation



Schematic representation showing the processes leading to the resolution of inflammation (blue). If this resolution fails, chronic inflammation, scarring, and loss of function may ensue. PGD2, prostaglandin D2; PGE2, prostaglandin E2; SPM, specialized pro-resolving mediator. Modified from [4].

Figure 2. Biochemistry of resolvins



Eicosapentanoic acid (EPA) is converted to resolvin E1 (RvE1) via several steps. The first step requires either aspirin and cyclooxygenase 2 (COX-2) or P450-like enzymes in microbes. In the second step, RvE1 is synthesized from its precursor through a lipoxygenase (LOX)-like mechanism involving leukocytes. Docosahexaenoic acid (DHA) gives rise to the resolvin D series (RvDs) and to protectin D1 (PD1). Again, several intermediate steps are required involving polymorphonuclear leukocytes and aspirin. Adapted from [28] © copyright 2006, with permission from Elsevier.

later in dry eye [8]. For the latter application, a Phase II clinical trial has been completed [9].

Given that the resolvins are derived from omega-3 fatty acids (i.e., from essential nutritional factors) and that they are endogenous anti-inflammatory substances, it seemed a likely hypothesis that they would also have an effect on inflammatory-related pain. In 2010, Xu and colleagues explored this question in an extensive study published in *Nature Medicine* [10] and based on their results they proposed that resolvins could be developed to become potent analgesics. Further models and details of mechanisms of action have become known since then and will be summarized below. Given the increasing awareness of the important role of low-grade chronic inflammation in chronic human pain disorders, the impact of resolvins may go far beyond just a classification as a compound that acts against acute inflammation and inflammatory pain; they might also be developed into potent analgesics that could be used to treat different types of chronic pain.

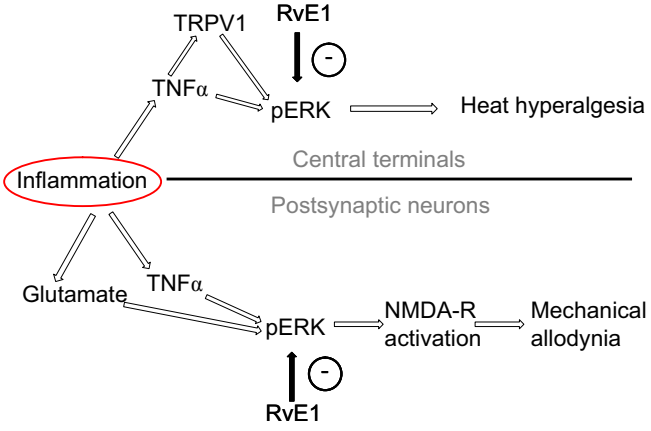
Analgesic actions of resolvins

Xu and colleagues performed a comprehensive study to explore the effects of resolvins in animal models of pain [10]. They tested two different resolvin molecules, RvD1 and RvE1, for their ability to reduce inflammatory pain behavior in mice, and found both molecules to be effective. They reduced pain induced by inflammation caused by intraplantar injection of formalin, Freund's complete adjuvant (CFA), and carrageenan. Interestingly, in the formalin model, only the second phase of pain behavior (which is likely mediated by spinal cord mechanisms) was attenuated, indicating a central action of the molecules via the chemerin receptor 23 (ChemR23; also known as chemokine receptor-like 1), which is a G protein-coupled receptor for resolvin, present on nociceptive neurons in the dorsal horn of the spinal cord.

These neurons also express the transient receptor potential vanilloid 1 (TRPV1), also known as the capsaicin receptor. In the carrageenan model, peripheral actions were also found; specifically, a reduction in local inflammation shown by reduced edema, reduced leukocyte infiltration, and reduced production of proinflammatory cytokines. Intriguingly, RvE1 did not alter responses to painful stimuli in mice that had not undergone inflammation or injury. This means that resolvins affected only pathological pain sensations, not normal sensations evoked by painful stimuli. RvE1 was also effective in reducing pain behavior after direct injection of the irritant capsaicin and the proinflammatory cytokine tumor necrosis factor-alpha (TNF) into the tissue. Also, RvE1 reduced pain behavior in a model of tissue injury and in a model of neuropathic pain (spinal nerve ligation).

To electrophysiologically characterize the mechanism of action of RvE1, Xu and colleagues used patch-clamp recording to record spontaneous excitatory postsynaptic currents (sEPSCs) in lamina II neurons *ex vivo* in isolated spinal cord slices from mice. RvE1 did not alter basal synaptic transmission but blocked the TNF-induced increase in sEPSC frequency. Subsequently, the authors showed that RvE1 inhibited glutamate release by a pathway dependent on the extracellular signal-regulated kinase (ERK). ERK belongs to the mitogen-activated protein kinases (MAPKs), which play critical roles in regulating neural plasticity and inflammatory responses (Figure 3). The ERK pathway is activated in spinal cord dorsal horn neurons by nociceptive activity and plays a critical role in central sensitization [11]. Blocking the ERK pathway is therefore considered a promising therapeutic target for the treatment of pain [12].

Figure 3. Assumed mode of action of RvE1 in inflammatory pain



According to the findings of Xu et al. [10], resolvin E1 (RvE1) reduces thermal hyperalgesia through a TRPV1-, TNFα-, and pERK-dependent mechanism, while mechanical allodynia is reduced via a TNFα-, glutamate-, pERK-, and NMDA-R-dependent pathway.
NMDA-R, *N*-methyl-D-aspartic acid receptor; pERK, phosphorylated extracellular signal-regulated kinase; TNFα, tumor necrosis factor-alpha; TRPV1, transient receptor potential vanilloid 1. Modified from [10].

In a further series of experiments, Xu et al. [10] also showed that RvE1 reduced the potentiation of *N*-methyl-D-aspartic acid (NMDA) glutamate receptor currents by TNF, again via an ERK-mediated pathway. Hyperactivity of spinal NMDA receptors is a well-known mechanism of mechanical allodynia (i.e., hypersensitivity to innocuous mechanical stimuli). After application of RvE1, the NMDA glutamate receptor currents were back to normal, thus the spinal synaptic plasticity implicated in pain hypersensitivity was reverted.

In summary, the resolvins, at very low doses, effectively reduced inflammatory pain symptoms in different mouse models, through both peripheral and central actions, without altering basal pain sensitivity.

Since the publication of the first paper by Xu et al. describing the analgesic effect of resolvins [10], others have followed. These new studies described positive effects in other pain models, and have uncovered additional mechanisms. RvD1 was shown to prevent and to transiently attenuate postoperative pain in a rat model [13]. In this study, tactile allodynia and hyperalgesia, measured 2 weeks after a skin and muscle incision/retraction procedure, was prevented by 40 ng of intrathecal RvD1 given 2 days after the operation. If RvD1 was given on postoperative day 9 or 17, the effect was only transient and incomplete. In a model of adjuvant-induced arthritis in rats, RvD1 had antihyperalgesic effects, which were partially related to decreased TNF and interleukin-1β in the rat hind paw [14]. In this model, systemic administration of the resolvins was effective. Supporting the inhibiting action of resolvins on TRP channels, which are of paramount importance in nociception, RvD1 inhibited further members of this receptor family in cell cultures, namely TRPA1, TRPV3, and TRPV4 [15]. Subsequent *in vivo* experiments then demonstrated that when agonists of these receptors were injected into mouse hind paws, pain behavior was induced, which could be attenuated when the mice were pretreated with local intradermal injection of RvD1.

Discussion

Pain caused by chronic inflammation, as in arthritis, inflammatory bowel disease, low back pain, and neuropathic pain, causes suffering and high healthcare and socioeconomic costs. Long-term use of the analgesics available today is limited by side effects so there is the need for new, effective, and well-tolerated analgesics.

Extrapolating from the animal data summarized above, the resolvins may be ideal candidates for such novel analgesics. As they are lipid molecules normally produced in the body, resolvins counteract inflammation in a physiological way. Their precursors, the omega-3 fatty acids, have been tested with some success in pain conditions [16], although a recent meta-analysis could not show a definitive effect [17]. However, resolvins appear to work at concentrations about 10,000 times lower than that needed for omega-3 fatty acids, which is advantageous for drug development.

Intriguingly, one of the mechanisms that Xu et al. [10] identified for the analgesic action of the resolvins is that they block various TRP receptors (particularly the TRPV1 receptor), which are mainly expressed on nociceptive neurons and are thus potential targets for very specific analgesic drugs, such as the TRPV1 antagonists. However, the use of those drugs has lead to serious side effects, such as high fever caused by the blocking of thermal afferents. Since resolvins counteract the function of the TRPV1 receptor by blocking TRPV1-dependent release of the excitatory neurotransmitter glutamate rather than by direct antagonism, their mode of action might avoid such life-threatening side effects. Side effects might be even more reduced with the use of TRP receptor-specific resolvins, as recently demonstrated *in vitro* and *in vivo* [18]. This receptor specificity may potentially pave the way to a more specific, tailored treatment for individual pain symptoms such as thermal or mechanical hyperalgesia. A further potential advantage of resolvins is that they may have a dual function as both an analgesic and an inflammatory disease-modifying drug. In fact, a number of molecules with this potential have already been investigated, including: nerve growth factor and its antagonists in the treatment of nerve lesions, neuropathic pain, or osteoarthritis; erythropoietin in diabetic neuropathy; and cytokine inhibitors in rheumatoid arthritis [19]. Unfortunately, of these, currently only the latter have made it to clinical application and other molecules have failed or are still at an early experimental stage [20,21]. Given the potent anti-inflammatory effects of the resolvins, individuals with pain conditions in which chronic inflammation is the key factor of pathophysiology might be the best candidates to test the resolvins in the clinic. For example, acute complex regional pain syndromes, which are characterized by localized exaggerated post-traumatic inflammation and peripheral and central nociceptive sensitization [22], might be good candidate diseases to be treated by resolvins.

The challenge now, as it is for every promising molecule at the preclinical stage of investigation, will be to develop resolvins into a clinically applicable form. Many of the experimental applications have been via the intrathecal route (i.e., into the cerebrospinal fluid), which would very much limit the application in humans. As a drug, these molecules would need to be stable, so that they could be taken orally, for example, and be long-acting. Because they act on the immune system, they might have unexpected unwanted side effects, which will need to be investigated. Furthermore, although the results by Xu et al. [10] and other research groups are impressive and reasonable, the size of the effect on pain behavior in the animals is moderate. Other analgesic drugs, which had even stronger effects than the resolvins in animal models, have failed in clinical human trials because their impact was not sufficiently different that of a placebo [23,24]. The reason might be that human pain still significantly differs even from the best and most elaborated animal pain models. With all these caveats, using the resolvins in clinical trials will be a very elegant way to test the hypothesis of chronic low-grade inflammation as a pathogenic factor, not only in chronic pain [25], but also in many other disorders, with the view to reducing morbidity and mortality in today's societies [26,27]

Abbreviations

COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ERK, extracellular signal-regulated kinase; NMDA, *N*-methyl-D-aspartic acid; sEPSC, spontaneous excitatory postsynaptic current; TNF, tumor necrosis factor-alpha; TRPV1, transient receptor potential vanilloid 1.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

The authors' research is supported by Deutsche Forschungsgemeinschaft (SFB 581, A7) and RTG1253/1 for CS and Graduate School 1044 and Foundation Rheinland-Pfalz (Project 936) for FB.

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