

Review Paper

Acetyl Salicylic acid and Omega 3 Fatty Acids in the pro resolving pathway of Cardiovascular Disorders

Abstract

Newer mechanisms of action of Acetyl Salicylic acid have been discovered in the proresolving pathway in various disorders. Omega 3 fatty acids are also involved in the synthesis of resolvins via an aspirin triggered pathway. The present review aims to discuss the newly discovered aspirin triggered lipoxins, resolvins, protectins, maresins in the current understanding of pathophysiology of endothelial dysfunction in various cardiovascular disorders, especially hypertension. The concept of aspirin triggered lipoxins (15-epi-LXA₄ and 15-epi-LX₄) counteracting the action of LTB₄, PGE₂, and TXA₂ is discussed. Aspirin triggered lipoxins also block the expression of IL-8 gene. Aspirin is the only known NSAID to induce NO in a dose dependent manner. In this narrative review, we describe the role of acetyl salicylic acid in the pro-resolution pathways that might prevent or reduce the complications in patients with high blood pressure.

Key Words: Acetyl salicylic acid, Cardiovascular System Disorders, lipoxin, resolvins

Background

Aspirin, a term coined by Bayer Pharmaceuticals, is the acetylated form of salicylic acid. Salicylate is a common constituent of numerous medicinal plants that have been used for thousands of years to treat pain and rheumatic fever in Ayurveda. Ancient Egyptians used the leaves of the Myrtle tree to treat rheumatic pain. Hippocrates treated eye infections with extracts from poplar trees and used extracts from willow bark in treating the pain and fever associated with childbirth. Salicylate was first chemically synthesized in 1859 and was widely used as an anti-inflammatory in 1876. Salicylate is unstable, has an extremely bitter taste and causes gastric irritation so researchers set out to develop analogs with same pharmacological benefits but be easier to tolerate upon ingestion. In 1897 Felix Hoffman, at the Bayer pharmaceuticals, discovered the mechanism to acetylate salicylate and thus the advent of aspirin (acetylsalicylic acid)(1,2).

Aspirin was in use for over 70 years and yet its mode of action remained unknown. In 1960 H.O. Collier and colleagues determined that aspirin worked through the pathways involved in the synthesis of the prostaglandins. In 1971, it was discovered that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) all exerted their effects through the inhibition of PG synthesis by inhibiting of the bifunctional enzyme cyclooxygenase (there are two forms COX-1 and COX-2). However, the ability of aspirin to limit leukocyte migration into sites of inflammation, thereby dampening the recruitment and march of host inflammatory responses could not be explained only later (3). Aspirin and Fish oil is a low cost intervention that can prevent and aid in the resolution of inflammation (4).

Aspirin in the prevention of Cardiovascular Diseases

Cardiovascular Disease is a leading cause of morbidity and mortality worldwide. The pathology is believed to evolve in two stages with endothelial dysfunction and atherosclerosis leading to Hypertension, Myocardial Infarction and Stroke as consequence of systemic inflammation, oxidative stress, and endothelial dysfunction (5,6,7). Endothelial dysfunction is an exaggerated inflammatory response attributed to an unbalanced regulation of innate and adaptive immune responses. In the transition phase endogenous protective pathway resolve the initial inflammation preventing atherosclerosis and leading to a normal vessel wall and Blood pressure (Figure 1). Resolution of inflammation is an ongoing process coordinated by mediators derived from Arachidonic acid, Eicosapentaenoic acid, Docosahexaenoic acid. These include Lipoxins, Resolvins, Protectins and Maresins (8,9). Lipoxins have been shown as an anti-inflammatory mediator in human endothelium in vivo and vitro studies (10). If the initial stage of inflammation could not controlled by immune regulation at the, there is development of oxidative and endoplasmic reticulum stress, release of proinflammatory cytokines, increased anti angiotensin antibodies in the circulation. This leads to endothelial and leukocyte activation in multiple organs. In the cardiovascular system there is hypertension, peripheral edema, pulmonary edema and cardiac failure. In the kidneys there is glomerular endotheliosis resulting in proteinuria and renal failure. In brain there is cerebral vessels there may be ischemia and stroke.

Aspirin Cyclooxygenase Interactions

Aspirin is unique in that it not only has analgesic (pain), antipyretic (fever) and anti-inflammatory effects (exerted at the level of the PG and TX synthesis) but it also exerts beneficial effects on the cardiovascular system via anti-inflammatory pathways distinct from PG and TX inhibition mediated by the salicylate group and the acetyl group (Figure 2). At high doses aspirin functions to block the PG and TX synthesizing activity of COX-1 which results in inhibition of the primary pro-inflammatory, pyretic and pain-inducing action of these eicosanoids (11). At the site of coagulation is a balance between the levels of platelet derived TXA₂ and endothelial cell derived PGI₂. This allows for platelet aggregation and clot formation but prevents excessive accumulation of the clot thereby maintaining blood flow around the site of the clot (12,13,14). Endothelial cells regenerate active COX faster than platelets because mature platelets cannot synthesize the enzyme, requiring new platelets to enter the circulation (platelet half-life is approximately 4 days). Thus, PGI₂ synthesis is greater than that of TXA₂. The effect of aspirin is more in favor of endothelial cell-mediated inhibition of the coagulation cascade (16,17,18,19,20).

Classical and aspirin triggered Synthesis of the lipoxins: Lipoxin synthesis from arachidonic acid occurs through several different trans cellular interactions. An initial stimulus activates Phospholipase A₂ that hydrolyzes arachidonic acid from the membrane-associated phosphoinositide. Three pathways exist for the synthesis of the lipoxins. The "classic" pathway involves 5-lipoxygenase (5-LOX, encoded by the ALOX5 gene) activity in leukocytes followed by 12-lipoxygenase (12-LOX, encoded by the ALOX12 gene) action in platelets. The second pathway is the action of 15-lipoxygenase (15-LOX, encoded by the ALOX15 gene) in epithelial cells followed by the 5-LOX action in leukocytes.

The third pathway is that induced by aspirin-mediated acetylation of COX-2. Aspirin can trigger the synthesis of stereoisomers (epimers) of LXA₄ and LXB₄ identified as 15 epi-LXA₄ and 15 epi-LXB₄ (these compounds are also referred to as aspirin-triggered lipoxins (ATLs). In endothelial and epithelial cells the aspirin-

induced acetylation of COX-2 alters the enzyme such that it now converts arachidonic acid to 15*R* hydroxyeicosatetraenoic acid (15*R*-HETE). This is rapidly metabolized to the epi-LXs in monocytes and leukocytes through the action of 5-lipoxygenase (5-LOX). COX 2-enzyme initiation of leukotriene synthesis is prevented by acetylation (15,16).

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103 **Aspirin Lipoxygenase interaction.**

104 Only at low doses (75mg) aspirin elicits its most important anti-inflammatory
105 benefits. The low dose anti-inflammatory effects of aspirin are due to its ability to
106 trigger the synthesis of the lipoxins (LXs: Epi LXA₄ and Epi LXB₄). Higher doses of
107 aspirin have no significant effect on LX synthesis. A **lipox - in** is an anti-
108 inflammatory eicosanoids synthesized through the **lipoxygenase interactions**.
109 The LXs and Epi LXs also inhibit the actions of the leukotriene (17). Higher doses of
110 aspirin have no effect on lipoxin synthesis.

111

112 The aspirin-triggered lipoxin synthesis pathway is initiated when activated circulating
113 leukocytes (primarily neutrophils) adhere to the vascular endothelium leading to a tilt
114 in balance towards resolution (Figure 3). Activated leukocytes that adhere to
115 epithelial cells as a consequence inflammation. The lipoxins LXA₄ and 15 epi-LXA₄
116 elicit their effects by binding to a specific G protein-coupled receptor (GPCR)
117 originally identified as ALXR. ALXR was originally identified as the formyl peptide
118 receptor-like 1 (FPRL1) protein, a member of the formyl peptide receptor (FPR)
119 family of receptors that bind *N*-formylated peptides derived by the degradation of
120 bacteria or host cells. The ALXR/FPRL1 protein is encoded by the formyl peptide
121 receptor 2 (FPR2) gene (18). The original member of the FPR family (FPR1)
122 recognizes the *N*-formylated bacterial peptide formyl-Met-Leu-Phe. The FPRs are
123 expressed predominantly in phagocytic leukocytes.

124 LXA₄ and LXB₄ promote the relaxation of the vasculature. Lipoxins and epi-LXs
125 inhibit polymorphonuclear leukocyte (PMN) chemo taxis, PMN-mediated increases in
126 vasopermeability, and PMN adhesion and migration through the endothelium. The
127 LXs also stimulate phagocytosis of apoptotic PMNs by monocyte-derived
128 macrophages. PMN phagocytosis represents the resolution phase of inflammatory
129 events, thus aspirin promotes this process and increases the rate of return to the
130 normal tissue state. This transition phase from inflammation to resolution is impaired
131 in metabolic syndrome (19,20,21,22). Lipoxins also lead to a reduction in swelling
132 due to edema by regulating the actions of Histamine (23).

133 The actions of Epi LXA₄ lead to the production of prostacyclin (PGI₂) and Nitric
134 Oxide (NO). The induction of NO by aspirin is correlated, in a dose-dependent
135 manner, with a reduction in leukocyte accumulation at sites of inflammation. No other
136 NSAID has been shown to exert this effect on NO production making aspirin unique
137 among this class of drug (24,25,26). Anti-inflammatory actions of the lipoxins and
138 aspirin-triggered lipoxins include blocking expression of the IL-8 gene (a pro-
139 inflammatory chemokine produced by macrophages and endothelial that stimulates
140 neutrophil migration), inhibition of the release and actions of tumor necrosis factor- α
141 (TNF- α), and stimulation of transforming growth factor- β (TGF- β)(27).

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143 **Aspirin Induced Lipid Mediators from Omega 3 Fatty Acids**

144 Aspirin also induces synthesis of an additional class of anti-inflammatory lipid
145 mediators known as the resolvins (Rvs) and the protectins (PDs)(22). These immune

modulating EPA and DHA derivatives are referred to as Specialized Proresolving Mediators, SPM. Numerous studies have reported the role of omega-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in prevention of cardiovascular diseases (23-30). A combination of aspirin and omega-3 PUFAs is an effective prevention strategy in cardiovascular diseases. The Rv and PD molecules do not inhibit the onset of inflammation but stimulate the resolution response resulting in the shutting off of an inflammatory process. Nine resolvins and two protectins have been characterized.

The resolvins promote the resolution of the inflammatory cycle. The resolvins are divided into two classes with the E-series resolvins (RvE1, RvE2, and RvE3) being synthesized from EPA and the D series resolvins (RvD1–RvD6) being derived from DHA. The resolvins share a 17-hydroxy residue that is introduced into DHA by the lipoxygenase, 15-LOX. Several of the resolvins are synthesized in epimeric form via the effects of aspirin. The levels of RvE1 increase spontaneously in individuals taking aspirin or consuming EPA. RvE1 is produced in a trans cellular manner involving endothelial cells and leukocytes. Within the endothelium EPA is converted to 18R-HEPE (18R-hydroxyeicosapentaenoic acid) by the COX-2 enzyme following its exposure to aspirin (Figure 4). The 18R-HEPE is released by the endothelial cells and taken up by adherent leukocytes where 5-LOX converts it to RvE1. The E series resolvins reduce inflammation, regulate PMN infiltration by blocking trans endothelial migration, regulate interleukin 12 production and lead to resolution of the inflammatory responses. RvE1 stimulates the phagocytosis of apoptotic PMNs by macrophages. RvE1 is also selectively disrupts thromboxane-mediated platelet aggregation.

The protectin identified as (N) PD1 (where the N refers to neuroprotectin) is derived from DHA through the actions of the lipoxygenase, 15-LOX and then enzymatic hydrolysis. Aspirin can trigger the formation of an epimeric PD1 molecule identified as AT-PD1. The protectins (N) PD1 and AT-PD1 have been shown to exert potent inflammation resolving actions by inhibiting T cell and PMN chemotaxis, by promoting T cell apoptosis, by decreasing TNF α and INF- γ secretion, during ischemia-reperfusion injury. Thus an Aspirin and omega 3 fatty acid combinations not only prevents the onset of inflammation but also resolves it.

Maresins, named maresin 1 (MaR1) and maresin 2 (MaR2), are produced from DHA, when the lipoxygenase, 12-LOX acts on DHA. **Ma re sins** are produced by macrophages and so the name “maresin” means macrophage mediator **resolving inflammation**. Maresin 1 has anti-inflammatory, pro-resolving, analgesic and wound healing potencies. Maresin 1 mainly acts on vascular smooth muscle cells and vascular endothelial cells. In vascular smooth muscles and endothelium, Maresin 1 prevents the adhesion of monocytes to the endothelium induced by tumor necrosis factor alpha (TNF α). Maresin 1 also reduces the production of reactive oxygen species (ROS) by vascular smooth muscle cells and endothelial cells. The main pathway, through which Maresin 1 exerts its effects, is through down-regulation of the transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), in the vascular smooth muscles and vascular endothelium.

Maresin 2 has potent efferocytosis properties. It has been shown to reduce neutrophil infiltration and to enhance efferocytosis, the macrophage-mediated phagocytosis of dead and dying cells. The process of efferocytosis plays an important part in clearing of inflammation. In addition, when maresins produced by macrophages are released and acted upon by platelets, two related structures termed the maresin-like mediators

(MaR-L1 and MaR-L2) are produced. The are numerous DHA-derived bioactive lipid mediators in addition to resolvins, protectins, and maresins. Other DHA-derived Bioactive lipids are the electrophilic Oxo-derivatives (EFOX) which exert anti-proliferative and anti-inflammatory effects; the neuroprostanes (NP) which have wound healing and cardio protective effects; the epoxides which have analgesic and antihypertensive effects; the ethanol amines which exhibit neuromodulator, immune modulatory, and metabolic effects; the fatty acid esters of hydroxy fatty acids (FAHFA) which lead to inflammation proresolution and the *N*-acyl amides which have the neuroprotective and metabolic regulatory effects.

Current recommendations of aspirin

The US preventive Task force recommends the use of aspirin for the primary prevention of cardiovascular diseases (CVD). Aspirin is recommended for men age 45-79 to reduce the risk of myocardial infarction when a net benefit is prevent. A net benefit means that the potential benefit from taking the aspirin outweighs the harms, mainly gastrointestinal (GI) bleeding. Aspirin is recommended for women age 55-79 to reduce the risk of ischemic stroke when a net benefit is prevented. The USPTF recommends against the use of aspirin in men<45 and women<55, and also in men and women aged more than 80. Online calculators can be used to predict the 10 year CHD risk in men (<http://hp2010.nlm.nih.gov/atp/iii/calculator.asp>) and women (<http://www.westrenstroke.org>). High Risk Population criteria and Recommendation of aspirin is outlined in Table 1 (Table 1). The recommendation to take aspirin becomes stronger if the individual risk increases above these thresh holds given in the table (31).

Contraindications to aspirin prescription are documented allergy to aspirin, asthma, bleeding disorders and gastritis. G6PD enzyme deficiency is a relative contraindication though long-term low dose aspirin has been found to be safe (32).

Conclusion

Aspirin is a low cost intervention that can prevent the metabolic syndrome atherosclerotic vessels by its anti-inflammatory, antiplatelet and Proresolving abilities. Recent understanding of the pathophysiology of Hypertension and proresolving pathways can help to understand the rational use of aspirin in prevention and reducing the complications of high blood pressure. A combination of aspirin and omega 3 fatty acids has potential benefits. DHA metabolites have been found to have potent role in the resolution pathway of inflammation. Future endeavours would focus on the identification of subset of high-risk hypertensive patients who will benefit most from aspirin, omega 3 fatty acids and DHA. Different dosage and time of initiation in various high-risk groups needs to be identified. Further research is also required to identify the correct time and the oral doses that will help in minimizing the long-term risk of future cardiovascular diseases.

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349 Figure Legends

350 Figure 1: The Three Phases: Inflammation, Transition and Resolution. Endogenous
 351 protective pathway resolves the initial inflammation leading to prevention of
 352 atherosclerosis In the transition phase endogenous protective pathway resolve the
 353 initial inflammation preventing atherosclerosis and leading to a normal vessel wall and
 354 Blood pressure.

355 Figure 2: Aspirin mechanism of action mediated by the acetyl group and salicylate
 356 group.

357 Figure 3: Aspirin-triggered lipoxin synthesis pathway is initiated when activated
 358 circulating leukocytes (primarily neutrophils) adhere to the vascular endothelium and
 359 balance is tilted towards Resolution.

360 Figure 4: Aspirin and Omega 3 fatty acids prevent the onset of inflammation by the
 361 release of Aspirin triggered Lipoxins, Protectins, Resolvins and Maresins.

362 Table 1: High Risk Population criteria and Recommendation of aspirin (Adapted from
 363 US preventive service task force. Aspirin for the Prevention of Cardiovascular
 364 Disease: Recommendation statement. AHRQ Publication No. 09-05129-EF-2, March
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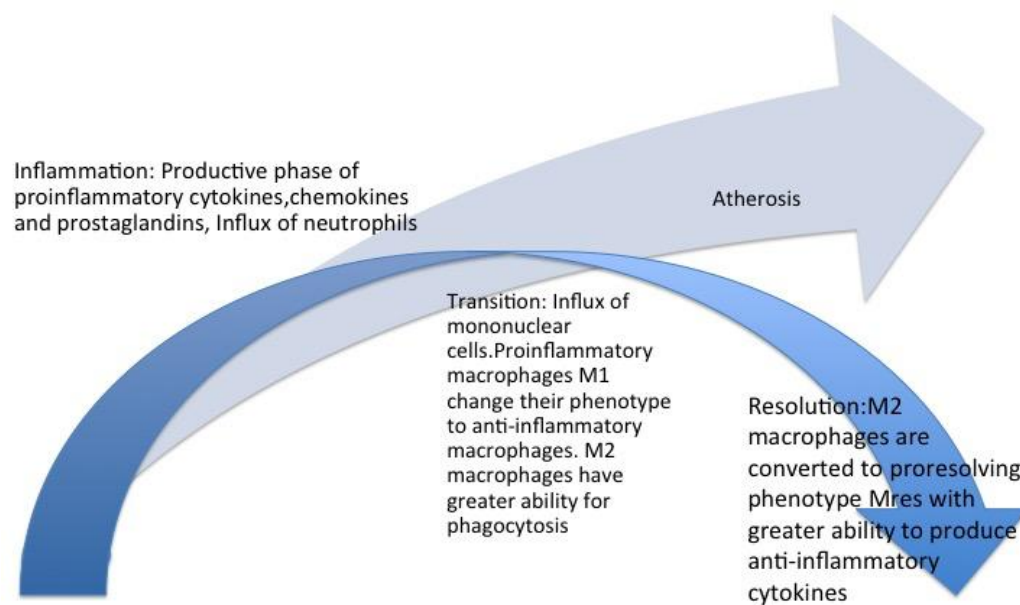
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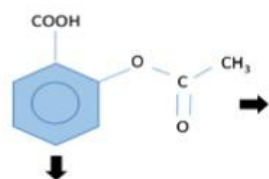
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381 Figure 1:



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383 Figure 2



Salicylate Group

- ✓ Induction of proton transport across the cell membrane leading to uncoupling of oxidative phosphorylation and thus showing a decreased proliferation and cell death in tumor cells
- ✓ Inhibits binding of enhancer binding protein β to its promoter region of COX 2

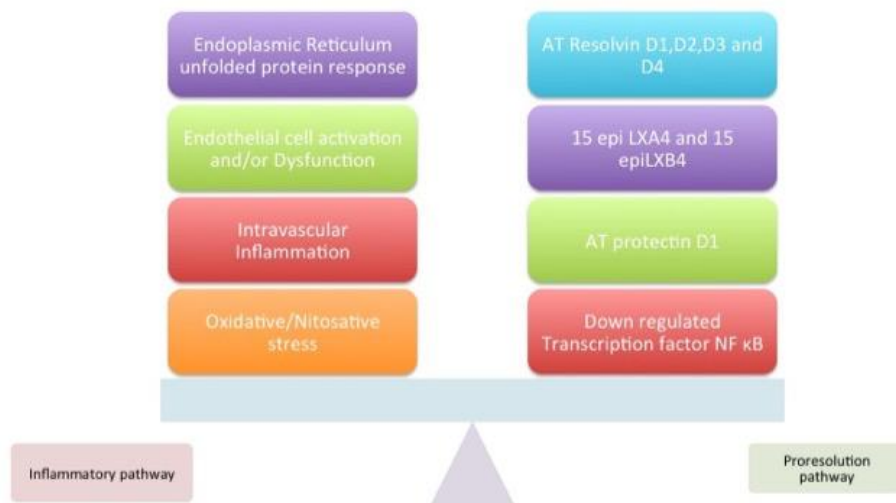
Acetyl Group

- ✓ Acetylation of Platelet COX 1(Serine 529) Leading to inhibition of TXA2
- ✓ Acetylation of COX 2(Serine 516) and inhibiting prostaglandins and redirecting to 15R HETE
- ✓ Acetylation of endothelial NO synthase (eNOS) in a dose dependent manner
- ✓ Induction of Haemoxygenase in endothelial cells and thus reducing the oxidative stress

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385 Figure 3

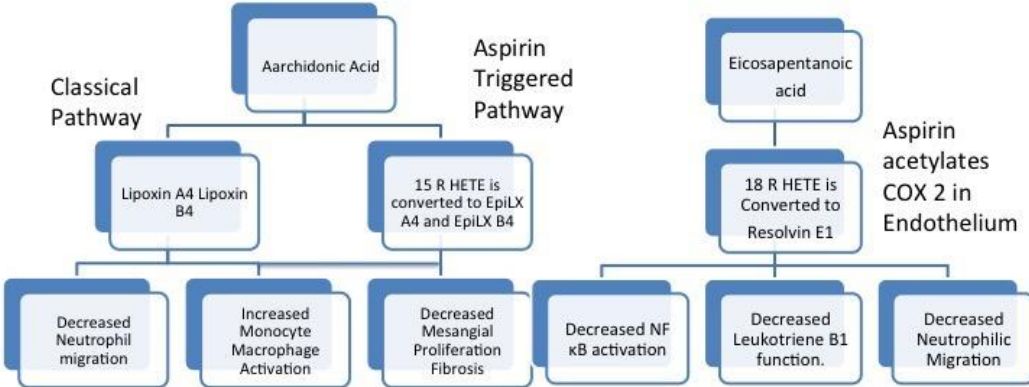
Aspirin and omega 3 fatty acids tilt the balance towards resolution in vascular smooth muscle and endothelium



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388 Figure 4



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390 Table 1:

Risk Thresh hold Assessment (Recommendation to start aspirin if risk thresh hold is crossed)			
Age	10 year MI risk (Men)	Age	10 year stroke risk (Women)
45-59	≥4%	55-59	≥3%
60-69	≥9%	60-69	≥8%
70-79	≥12%	70-79	≥11%

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