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# Multiple indications for anti-inflammatory peptides

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## Abstract

Apolipoprotein mimetic peptides have been shown to dramatically reduce atherosclerosis in animal models and may be an excellent mode of therapy to treat a variety of vascular inflammatory conditions, of which atherosclerosis is one example. Published studies of apolipoprotein mimetic peptides in models of inflammatory disorders other than atherosclerosis, including viral influenza, asthma, chronic rejection after heart transplantation, sickle cell disease, scleroderma, diabetes, cognitive dysfunction, and renal inflammation, suggest that apolipoprotein mimetic peptides may have efficacy in a wide variety of inflammatory conditions.

### Keywords

apoA-I; atherosclerosis; inflammation; HDL function; mimetic peptides; oxidized lipids

## Introduction

### Mimetic Peptides as Therapeutic Agents in Atherosclerosis

As early as 1990, Segrest and colleagues observed that the main protein component of high density lipoprotein (HDL), apolipoprotein A-I (apoA-I), and its amphipathic helix peptide analogues had potential as therapeutic agents [1•]. Studies involving the use of apoA-I in animal models [2•], and in gene-expression studies [3•], suggested that apoA-I may be an attractive therapeutic agent in patients with atherosclerosis. Segrest and Anantharamaiah designed peptides that did not have sequence homology with apoA-I but contained class A amphipathic helixes found in apoA-I [4–6]. These apoA-I mimetic peptides have been shown to mimic a number of the properties of apoA-I and associate readily with phospholipids forming complexes [5•,7]. ApoA-I mimetics also promote cholesterol efflux [4,8•] as well as activate lecithin: cholesterol acyltransferase (LCAT), the enzyme responsible for the maturation of plasma HDL [9]. Moreover these peptides have been shown to interact with lipoproteins [10••] and remove hydroperoxy fatty acids from LDL suppressing LDL oxidation *in vitro* [11,12]. Navab *et al* showed that a mimetic peptide synthesized from only D-amino acids (D-4F) when administered orally to LDL receptor-null (LDLR−/−) mice on a Western diet (WD), reduced aortic lesions 79% compared to controls [13•]. Recently it was demonstrated that peptides synthesized from either D- or L-amino

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acids behave similarly. Ou *et al* administered D-4F and found improved arterial vasoreactivity in LDLR−/− mice on a WD similar to results obtained with injected L-4F [14••,15]. Van Lenten *et al* found that rabbits on a 1% cholesterol diet injected daily with either D-4F or L-4F had similar reductions in lipoprotein inflammatory properties and the percent of aorta with atherosclerotic lesions compared to controls [16•].

The efficacy of apolipoprotein mimetic peptides in atherosclerosis has not been limited to apoA-I mimetics. Navab and colleagues [17] have shown that an apolipoprotein J (apoJ) mimetic peptide, D-[113–122]apoJ, reduced atherosclerosis in apoE-null mice, as did tetrapeptides too small to form helical structures [18]. Anantharamaiah and colleagues designed a dual-domain peptide containing the arginine-rich domain of apolipoprotein E (apoE) linked to a class A amphipathic helical peptide 18A [19]. A single administration of this apoE mimetic peptide resulted in a dramatic clearance of very low density and low density lipoproteins (VLDL and LDL, respectively), and restored endothelial function in Watanabe Heritable Hyperlipidemic rabbits.

In human clinical trials, a study from Nissen and colleagues involving a small set of patients provided evidence that administration of weekly intravenous doses of a genetic variant of apoA-I, apoA-I “Milano”, for 5–6 weeks may achieve therapeutic benefit [20]. However, the results from a subsequent larger short-term clinical study using a compound at a similar dose (40–45 mg/kg) that contained wild-type apoA-I rather than a mutant form, and that included patients with a substantially lower plaque burden, showed a reduction in atheroma volume that was not statistically significant vs placebo, but did result in statistically significant improvement in the plaque characterization index and coronary score on quantitative coronary angiography. These results would suggest that longer periods of intravenous administration will likely be required to realize significant cardiovascular improvement.

## Mechanism of action of mimetic peptides of apolipoproteins

Atherosclerosis is a chronic inflammatory process mediated in part by phospholipid oxidation, which in turn induces vascular cells to express various inflammatory molecules [22,23]. The mechanism of action of apolipoprotein mimetic peptides in atherosclerosis appears to relate to the binding of oxidized lipids and their removal from lipoproteins [24–26]. Recent studies using surface plasmon resonance demonstrated that 4F peptides bound oxidized lipids with a much greater affinity than did human apoA-I. However non-oxidized fatty acids that varied in chain length and saturation were bound equally by apoA-I, D-4F, and L-4F [27].

As will be discussed below, apolipoprotein mimetic peptides have been shown to be effective in models of vascular disease other than atherosclerosis, and in inflammatory processes that have an infectious etiology, suggesting that oxidized lipids may be important mediators in a wide variety of inflammatory conditions.

## Apolipoprotein mimetic peptides in models of infection and asthma

Owens *et al* observed in HIV-infected T cells and in recombinant vaccinia-virus-infected CD4+ HeLa cells that apoA-I and its amphipathic helix peptide analogues inhibited the steps of HIV infection involving membrane fusion, thus reducing viral replication [1]. Van Lenten and colleagues, using LDLR−/− mice on a WD nasally infected with influenza A virus, found that intraperitoneal (ip) injections of D-4F into the mice significantly reduced the severity of viral pneumonia [28•]. The levels of IL-6 in both plasma and lung lysates were markedly less after D-4F-treatment compared to controls. HDL taken from control mice post-infection was pro-inflammatory whereas the HDL from mice treated with D-4F was anti-inflammatory. Macrophage trafficking into the innominate artery and aorta was

dramatically increased after viral infection in controls, however peptide-treatment completely prevented macrophage infiltration. Evidence for anti-viral behavior of mimetic peptides was also demonstrated. Lung viral titers in peptide-treated mice were half those seen in controls. In a follow-up study [29] human Type II pneumocytes were infected *in vitro* with influenza A virus. Viral infection caused significant increases in cellular content and release into the media of parent non-oxidized phospholipid, 1-palmitoyl-2-arachidonyl-*sn*-glycero-3-phosphorylcholine, as well as its oxidized products. Treatment of pneumocytes with D-4F prevented viral-induced increases in cellular content and secretion of oxidized phospholipids but not of non-oxidized phospholipids. There was a time-dependent increase in the production of interferon-α and -γ post-infection that was significantly inhibited by D-4F-treatment. Likewise, there was a dramatic time-dependent increase in the activation of a caspase cascade involved in apoptosis post-infection that was significantly prevented by D-4F. Viral infection dramatically increased the release of IL-6 from pneumocytes that was inhibited by D-4F. As was the case *in vivo* [28] *in vitro* viral titers were significantly reduced with D-4F [29].

As the studies above demonstrated, influenza infection in Type II pneumocytes resulted in the formation and release into the media of oxidized phospholipids derived from oxidation of arachidonic acid-containing phospholipids. D-4F-treatment of these cells, however, suppressed the increased formation and release of these oxidized phospholipids [29]. ApoA-I mimetics such as D-4F, by virtue of their ability to avidly bind lipids, may be important in binding and deactivating lipid oxidation products, reducing their cellular and media concentrations, and could therefore play a crucial role in decreasing pulmonary inflammation. Nandedkar and colleagues [30] sensitized C57BL/6J mice with ovalbumin, and mice were either intranasally-treated with D-4F once a day for 4 weeks, or received no treatment for 4 weeks. At the time of sacrifice samples were collected for eosinophil peroxidase activity (EPO) in the bronchioalveolar lavage fluid (BAL), lung histology, 15-lipoxygenase (LOX) expression, and pro-inflammatory HDL (p-HDL) levels. D-4F-treatment decreased EPO in BAL, and reduced histological lung inflammation, 15-LOX expression, and p-HDL levels. The authors concluded that D-4F significantly decreased p-HDL and other indices of airway lung inflammation in a murine model of asthma suggesting that apoA-I mimetic peptides may provide a safe and effective alternative to inhaled steroids in treating inflammation in asthma.

## Apolipoprotein mimetic peptides in a model of chronic rejection after heart transplantation

Chronic rejection of transplanted hearts is the leading cause of death among heart transplant recipients. Using a transgenic approach, Araujo *et al* demonstrated that systemic rather than local heme oxygenase-1 (HO-1) overexpression improves cardiac allograft outcomes in a transgenic mouse model [31]. In a murine model of chronic rejection after heart transplantation [32,33], B6.C-H2$^{bm12}$ strain donor hearts were transplanted into wild-type C57BL/6 recipient mice. The transplanted mice were injected ip with saline or saline containing D-4F. The D-4F-treated animals showed a dramatic reduction in cardiac allograft vasculopathy (intimal thickening leading to narrowing or occlusion of the vessels in the transplanted heart). Treatment with D-4F also reduced the number of graft-infiltrating CD4$^+$ and CD8$^+$ lymphocytes and CXCR3$^+$ T-lymphocyte subsets. In addition, HO-1 mRNA was up-regulated in the donor hearts after D-4F treatment, and HO-1 inhibition by a competitive inhibitor, tin protoporphyrin, partially reversed the beneficial effects of D-4F. *In vitro* studies revealed that peptide-treatment reduced allogenic T-lymphocyte proliferation and effector cytokine production by mechanisms independent of HO-1. The authors concluded that this class of peptides with anti-inflammatory and anti-oxidant properties provides a novel strategy for treatment of cardiac allograft vasculopathy.

## Apolipoprotein mimetic peptides in models of sickle cell disease (SCD) and scleroderma

Hypercholesterolemia and SCD impair endothelium-dependent vasodilation by different mechanisms. Hypercholesterolemia impairs vasodilation by an LDL-dependent mechanism. SCD has been characterized as a chronic state of inflammation in which xanthine oxidase (XO) from ischemic tissues increases vascular superoxide anion (O2*-) generation. Pritchard and colleagues tested the effects of the apoA-I mimetic peptide L-4F on hypercholesterolemic mice and on SCD mice [14]. Arterioles were isolated from hypercholesterolemic LDLR−/− mice and from SCD mice that were treated with either saline or L-4F. Both hypercholesterolemia and SCD impaired vasodilation in the mice, which was dramatically improved in both cases by L-4F. L-4F inhibited LDL-induced increases in O2*- in arterial segments, decreased XO bound to pulmonary endothelium, and increased liver XO/XDH (xanthine dehydrogenase) content compared with levels in untreated SCD mice, a sign of decreased ischemic injury. The authors proposed that L-4F restores vascular endothelial function in diverse models of disease and may be applicable to treating a variety of vascular diseases. Pritchard and colleagues also studied tight-skin mice (Tsk(−/+)), a mouse model of systemic sclerosis (scleroderma, SSc) [34]. SSc is an autoimmune, connective tissue disorder that is characterized by impaired vascular function, increased oxidative stress, inflammation of internal organs, and impaired angiogenesis. Tsk(−/+) mice have a defect in fibrillin-1, resulting in replication of many of the myocardial and vascular features seen in patients with SSc. After 6–8 weeks, saline control Tsk(−/+) mice demonstrated impaired endothelial nitric oxide synthase (eNOS)-mediated vasodilation that was significantly improved in mice treated with D-4F. Tsk(−/+) mice also had elevated levels of plasma triglycerides which were normalized with D-4F-treatment. D-4F also improved endothelium-, endothelial nitric oxide synthase-dependent, and flow-mediated vasodilation in Tsk(−/+) mice. The hearts from the Tsk(−/+) mice contained significantly higher levels of angiostatin and autoantibodies against oxidized phospholipids that were reduced by half with D-4F-treatment. These investigators concluded D-4F may be effective at treating vascular complications in patients with SSc.

## Apolipoprotein mimetic peptides in models of diabetes

Abraham and colleagues examined the effects of daily ip injections of D-4F on O2*-, extracellular superoxide dismutase (EC-SOD), vascular heme oxygenase (HO-1 and HO-2) levels, and circulating endothelial cells in rats made diabetic by administration of streptozotocin [35]. With D-4F-treatment, both the amount of protein and the activity of HO-1 were increased. D-4F-treatment also decreased O2*- levels compared with untreated diabetic rats. The average number of circulating endothelial cells was higher in diabetic rats than controls and was significantly decreased in D-4F-treated rats whereas the impaired relaxation typical of blood vessels in diabetic rats was prevented by D-4F. Western blot analysis showed decreased EC-SOD levels in diabetic rats that were restored by D-4F. The authors concluded that increases in circulating endothelial cell-sloughing, superoxide anion, and vasoconstriction in diabetic rats can be prevented by D-4F. In a subsequent study, Abraham and colleagues [36] investigated whether chronic use of D-4F would lead to up-regulation of HO-1, endothelial cell marker (CD31(+)), and thrombomodulin (TM) expression and increase the number of endothelial progenitor cells (EPCs) in streptozotocin-treated rats. D-4F or vehicle was administered by daily injection for 6 weeks. HO-1 activity was measured in liver, kidney, heart, and aorta. After 6 weeks of D-4F-treatment, HO activity increased in the heart and aorta and caused a significant increase in TM and CD31(+) expression. D-4F-administration increased anti-oxidant capacity (as reflected by a decrease in oxidized protein and oxidized LDL), and enhanced EPC function, as evidenced by an increase in EPC eNOS and prevention of vascular TM and CD31(+) loss. In conclusion, HO-1 and eNOS are relevant targets for D-4F and may contribute to the D-4F-

mediated increase in TM and CD31(+), the anti-oxidant and anti-inflammatory state, and robust vascular protection in this animal model of type1 diabetes.

## Apolipoprotein mimetic peptides in a model of brain arteriole inflammation and dementia

In large arteries such as the aorta, a few sentinel macrophages are always present that "patrol" the subendothelial space removing accumulated cellular debris as part of the innate immune system, even in the human fetus [37–39]. In diseases such as atherosclerosis there is an influx of monocytes into the subendothelial space of these large arteries in response to the production of chemokines such as monocyte chemotactic protein-1, or MCP-1. With time, the monocytes convert into macrophages and become foam cells. Arterioles are the smallest arterial vessels ranging in size from 10 to 100 mm in diameter and without significant subendothelial space. Thus, the sentinel macrophages associated with brain arterioles, the microglia, are found intimately associated with their adventitia. Buga and colleagues found that upon feeding LDLR−/− mice a WD there was a marked increase in microglia associated with brain arterioles [40]. D-4F (but not an inactive scrambled peptide, ScD-4F) reduced the percent of brain arterioles associated with CCL3/macrophage inflammatory protein-1α (MIP-1α) and CCL2/MCP-1. A WD increased brain arteriole wall thickness and smooth muscle α–actin, which was reduced by D-4F but not by ScD-4F. There was no difference in plasma lipid levels, blood pressure, or arteriole lumen diameter with D-4F-treatment. Neuronal cells are known to have surface receptors for MCP-1 and MIP-1α and one might expect that neuronal/brain function might change as a result of the increased association of these chemokines with brain cells. Cognitive performance in the T-maze continuous alternation task and in the Morris Water Maze was impaired by a WD and was significantly improved with D-4F but not ScD-4F. It was concluded that hyperlipidemia can induce brain arteriole inflammation resulting in increased levels of diffusible chemokines that can interact with surrounding brain cells resulting in cognitive impairment. However a significant reduction in the inflammation of brain arterioles could be achieved with apoA-I mimetic peptides commensurate with an improved cognitive function in this model [40].

## Apolipoprotein mimetic peptides in a model of hyperlipidemia-induced renal inflammation

In addition to hyperlipidemia, feeding a WD to LDLR−/− mice results in insulin resistance and elevated plasma glucose levels [41–43]. A major problem facing Western societies is an increase in chronic renal disease that appears to be associated with dyslipidemia and diabetes in addition to hypertension [43]. Oxidized phospholipids have been identified as potent mediators of inflammation [22,44]. Buga *et al* [45] asked if feeding a WD to LDLR−/− mice would induce the formation of oxidized phospholipids in the kidney resulting in renal inflammation, and would D-4F-treatment inhibit this inflammation. Based on previous work from Jiang and colleagues [46] and Berliner and colleagues [47,48] Buga *et al* also asked if the Western diet would increase SREBP-1c mRNA levels and if D-4F would repress the increase in renal triglycerides. Indeed, the authors found that feeding a WD to LDLR−/− mice for 7 weeks induced hyperlipidemia with elevated plasma glucose levels associated with increased renal SREBP-1c mRNA levels, increased renal triglyceride levels, increased renal oxidized phospholipid levels, and renal inflammation. D-4F-treatment significantly reduced the formation of oxidized phospholipids and significantly prevented the increase in SREBP-1c mRNA expression elicited by the WD. Moreover, D-4F prevented triglyceride accumulation in the kidneys and significantly reduced renal inflammation without altering plasma lipids, lipoproteins, glucose or blood pressure. It was concluded that D-4F-treatment reduced renal oxidized phospholipids resulting in lower expression of SREBP-1c which in turn resulted in lower triglyceride content and reduced renal inflammation [45].

## Conclusions

In the present review, anti-inflammatory properties of apolipoprotein mimetic peptides have been demonstrated in a number of animal models for disease including atherosclerosis. As a therapeutic agent with the potential for reversing atherosclerosis, apoA-I has been shown in animal models and humans to have promise. However, because of its size, apoA-I must be administered intravenously, making it commercially both difficult and costly. Moreover, from clinical trials data [20,21], it would appear that since the doses of apoA-I compounds used were similar in both studies cited (40–45 mg/kg), coupled with the observation [27] that 4F apolipoprotein mimetic peptides have a much greater binding affinity than native apoA-I for oxidized lipids, which may be important in promoting the atherosclerotic process, the pharmacokinetics would suggest it will likely take a longer period of treatment to effect significant reductions in plaque volume with larger apoA-I compounds, given that higher doses may be toxic [21]. 4F is a small, apoA-I mimetic peptide that in addition to being anti-atherogenic, reduces the effect of pro-inflammatory molecules generated by oxidized lipids. Because it is a small peptide, it can be produced economically.

Why these peptides are so effective in such a wide variety of disease states may be due to a common mechanism of action. In vitro, D-4F caused a dramatic redistribution of apoA-I from α-migrating to β-migrating particles in apoE-null mouse plasma, suggesting that D-4F is acting directly on HDL or some plasma component that in turn remodels HDL. In vivo, in apoE-null mice, despite the small amount of D-4F absorbed 20 minutes after an oral dose, D-4F rapidly caused the formation of cholesterol-containing particles with pre-β mobility that were enriched in apoA-I and paraoxonase activity. As a result, lipid hydroperoxides in lipoproteins were reduced, HDL became anti-inflammatory, and HDL-mediated cholesterol efflux and reverse cholesterol transport from macrophages were stimulated [24]. In addition, we have reported that D-4F was much more anti-inflammatory than human apoA-I in LDL receptor null mice with influenza A viral pneumonia [28]. Since the maximum plasma levels of D-4F achieved in mice after administration are only about ~ 130 nM [24], and plasma levels of apoA-I in mice are ~ 35 μM, it has been difficult to understand how 4F peptides might achieve their beneficial effects in vivo. The dramatic difference in binding affinities for oxidized phospholipids between the mimetic peptides and apoA-I could explain how these apoA-I mimetic peptides exert their potent biological activities, even when surrounded by a “sea” of apoA-I [27]. That oxidative stress may be a common thread running through the disease states discussed in this review, suggests that a strategy seeking to design anti-inflammatory apoA-I mimetic peptides should not focus on the binding properties of the peptides for non-oxidized lipids, but rather should focus on developing peptides that bind oxidized lipids with very high affinity.

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