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Apolipoprotein A-I Mimetics

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Abstract

Purpose of Review—To summarize recent publications in the field of apolipoprotein mimetics.

Recent Findings—Apolipoprotein mimetic peptides continue to show efficacy in a number of animal models of disease and demonstrate properties that make them attractive as potential therapeutic agents. A number of new apolipoprotein mimetics have been described recently. A major site of action of apolipoprotein mimetic peptides was found to be in the small intestine where they decrease the levels of pro-inflammatory bioactive lipids. A major problem related to the use of apolipoprotein mimetic peptides is their cost, particularly those that need to be generated by solid phase synthesis with chemical addition of end blocking groups. Novel approaches to apolipoprotein mimetic therapy have emerged recently that show promise in overcoming these barriers.

Summary—Despite the recent failure of therapies designed to raise HDL-cholesterol in humans, an approach to therapy using mimetics of HDL and its components continues to show promise.

Keywords

Apolipoproteins; Apolipoprotein mimetics; HDL; Atherosclerosis; Cancer

Introduction

The failure of recent clinical trials to achieve a positive outcome using therapies that significantly raised HDL-cholesterol levels has brought into question the “HDL Hypothesis” [1**]. However, as recently reviewed, the pursuit of a strategy to use components of HDL or mimics of HDL or mimics of its components is quite different from the strategy to raise

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plasma HDL-cholesterol levels[2**]. In this article we will review recent advances in the field of apolipoprotein mimetics.

Efficacy of Apolipoprotein Mimetics in Models of Disease

Apolipoprotein mimetics have been shown to be efficacious in a large number of models of disease [2**, 3]. Below is a summary of recent publications on the efficacy and mechanism of action of apolipoprotein mimetics in a variety of animal models.

Bacterial lipopolysaccharide (LPS), Endotoxemia, Lung Injury, Asthma, Air Pollution, and Leukocyte Responses

LPS was administered to rats at 10mg/kg via tail vein [4*]. Ten minutes later L-4F (10 mg/kg) was administered intraperitoneally. 4F improved survival in the endotoxemic rats and attenuated histologic damage in lung tissue. The 4F-mediated improvement was accompanied by higher levels of HDL-cholesterol and lower lung myeloperoxidase (MPO) activity compared to LPS alone [4*].

It was previously shown that 4F favors the differentiation of human monocytes to an anti-inflammatory phenotype and that 4F attenuates LPS-induced inflammatory responses. White and colleagues [5*] investigated the effects of LPS on the Toll-like receptor (TLR) signaling pathway in 4F-differentiated monocyte-derived macrophages. Treatment with L-4F downregulated cell-surface TLRs (4,5 and 6) and attenuated the LPS-dependent upregulation of genes encoding TLRs 1, 2, and 6 and genes of the MyD88-dependent pathways. The L-4F-mediated changes were associated with depletion of cellular cholesterol and caveolin, components of membrane lipid rafts. [5*].

The dual (apoE and apoA-I) domain peptide Ac-hE18A-NH_2 peptide with 28 amino acid residues was compared to 4F, an 18 residue apoA-I mimetic peptide for anti-endotoxin activity [6*]. The dual domain peptide inhibited endotoxin activity and disaggregated *Escherichia coli* 055:B5 (wild smooth serotype) better than 4F. In THP-1 cells, isolated primary leukocytes, and whole human blood, the dual domain peptide reduced responses more strongly that 4F [6*].

In a rat model of severe endotoxemia, L-4F (10 mg/kg intravenously) significantly decreased mortality and reduced lung and liver injury, even when administered 1 hour post LPS [7*]. In vitro, L-4F inhibited the activation of isolated human leukocytes and neutrophils by serum taken from patients with acute respiratory distress syndrome (ARDS) [7*].

ApoA-I null and apoE null mice were shown to have enhanced recruitment of neutrophils to the airspace in response to both inhaled LPS and direct airway inoculation with CXCL1. Conversely, treatment with L-4F or an apoE mimetic peptide (COG1410) reduced airway neutrophilia. L-4F was suspected of suppressing chemotaxis through heterologous desensitization [8*]. L-4F was found to induce chemotaxis of human neutrophils and monocytes but failed to induce calcium influx. [8*].

Air pollution is known to contribute to atherosclerosis in humans. Exposure of LDLR null mice to air borne ultrafine particles reduced HDL-cholesterol and antioxidant activity and increased atherosclerosis, which was ameliorated by an apoA-I mimetic peptide, D-4F [9*].

Using a multianalyte microphysiometer, it was demonstrated that L-4F complexed or not complexed with 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) attenuated the macrophage respiratory burst in response to oxidized LDL [10*].

Hypertension induced in mice was accompanied by increased leukocyte and platelet adhesion in cerebral venules and was attenuated by mild hypercholesterolemia [11*]. Using mice with transgenic expression of apoA-I and wild-type mice treated with 4F suggested that the beneficial effect of the mild hypercholesterolemia was HDL-mediated [11*].

Endothelial Nitric Oxide Synthase (eNOS), Tight Skin Mice, and Insulin Sensitivity

Acute hyperglycemia is known to decrease the availability of nitric oxide (NO) and impair anesthetic preconditioning (APC)-elicited protection against myocardial infarction. The authors [12*] measured myocardial infarct size in mice in the absence or presence of APC achieved with isoflurane (1.4%) with or without acute hyperglycemia. Myocardial infarct size was significantly decreased by APC in the absence, but not in the presence of acute hyperglycemia. D-4F restored the cardioprotective effect of APC during acute hyperglycemia. In vitro D-4F reduced superoxide generation and enhanced caveolin-1 and eNOS caveolar compartmentalization and posttranslational eNOS modifications restoring NO production when isoflurane was administered under hyperglycemic conditions [12*].

In vitro, reverse D-4F (D-4F sequence read from C-terminal end to the N-terminal end) improved the proliferation, migration, and tube formation of endothelial progenitor cells (EPCs) in a dose dependent manner and activated phosphor-AKT at serine residue 473 and phosphor-eNOS at serine residue 1177 [13*]. The authors concluded that reverse D-4F-mediated improvement of EPC function is dependent on the PI3K/AKT/eNOS pathway [13*].

Having previously shown that treatment with 4F of tight skin ($Tsk^{-/+}$) mice, a model of systemic sclerosis decreases inflammation and restores angiogenic potential in $Tsk^{-/+}$ mice, the authors [14*] hypothesized that 4F differentially modulates interferon regulating factor 5 (IRF5) in myocardium. IRF5 in heart lysates from control and $Tsk^{-/+}$ mice with and without 4F treatment was determined. 4F was shown to bind IRF5. IRF5 activation was increased in $Tsk^{-/+}$ hearts and 4F treatment decreased IRF5 expression and activation in the $Tsk^{-/+}$ hearts by a mechanism related to 4F's ability to bind IRF5 [14*].

Administration of L-4F to obese (B6V-Lep-ob/J) mice restored adipocyte function, increased adiponectin release and decreased levels of IL-1 and IL-6 and was associated with an increase in insulin sensitivity and decreased glucose levels [15*]. The mechanism appeared to be related to an L-4F-mediated increase in heme oxygenase 1 (HO-1) and Wnt10b activity [15*].

ApoA-I mimetic peptides in mouse models of cancer

The first evidence of the utility of apoA-I mimetic peptides in mouse models of cancer was published in 2010 [16]. In 2011 another report appeared [17]. Subsequently, 3 other manuscripts have appeared indicating the mechanism(s) of action [18*, 19*, 20*] and lending support to the possibility that apoA-I mimetic peptides may have therapeutic potential in cancer.

Properties of 4F Peptides and Comparison with ApoE Mimetic Peptides

L-4F complexed to 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) enhanced paraoxonase-1 (PON1) activity and stability compared to controls [21*].

It is known that myeloperoxidase (MPO)-derived hypochlorous acid (HOCl) induces changes in HDL function by causing oxidative modification of apoA-I [22**]. It was found that HOCl caused oxidation of the sole tryptophan (Trp) residue in L-4F. Remarkably, neither L-4F-mediated lipid binding nor ABCA1-dependent cholesterol efflux was altered as result of the oxidation of L-4F by HOCl. It was concluded that L-4F serves as a reactive substrate for HOCl, but the reaction does not influence the lipid binding and cholesterol efflux capacity of the peptide [23*].

An apoE mimetic peptide Ac-hE18A-NH_2 was compared to the apoA-I mimetic peptide L-4F in apoE null mice [24*]. At equal doses, frequency and route of administration plasma cholesterol and triglyceride levels significantly decreased with the apoE mimetic peptide but not with L-4F. Both the apoE mimetic peptide and L-4F significantly decreased lesions by en face analysis, but the decrease with the apoE mimetic peptide was significantly greater than with L-4F [24*].

Other Apolipoprotein-mimetics

A nice summary of molecules that mimic apoA-I properties recently appeared [25**]. These authors developed peptide-lipid nanoparticles using branched, multivalent constructs bearing multiple 23- or 16-amino acid peptides that were combined with phospholipids to produce nanometer-scale discoidal HDL-like particles [26*]. These nanolipid particles promoted efficient cellular cholesterol efflux and were remarkably stable toward enzymatic digestion in vitro and displayed long half-lives and desirable pharmacokinetic profiles in mice and at 50 mg/kg intraperitoneally reduced plasma cholesterol by 50% [26*].

Pegylation of human holo-HDL or reconstituted phospholipid/apoA-I particles (rHDL) led to selective N-terminal monopegylation of apoA-I with full preservation of cholesterol efflux activity [27*]. The plasma clearance of PEG-rHDL was estimated after injection into apoE null mice; the half-life of PEG-rHDL was about 7-fold greater than rHDL. The PEG-rHDL at a dose of 40 mg/kg in apoE null mice led to more pronounced suppression of bone marrow myeloid progenitor cell proliferation and monocytosis. PEG-rHDL compared to rHDL also produced a more stable lesion [27*].

A 26-mer α-helical peptide (ATI-5261) was exposed to acrolein and resulted in adducts at positions 5 and 25 and led to a concentration-dependent reduction in cholesterol efflux

activity [28*]. Placement of EXXK in the center of the peptide resulted in site-specific modification of lysine, which was glutamate dependent [28*].

Two tandem repeats of the 4F peptide were fused to the C terminus of the murine IgG Fc fragment [29*]. The resultant peptibody, mFC-2X4F, dose dependently promoted cholesterol efflux in vitro, and the efflux potency was superior to monomeric 4F peptide. When administered to mice, the peptibody increased both pre-β and α-1 HDL subfractions. The peptibody and apoA-I were found to coexist in the HDL particles formed in vivo [29*].

The peptide ELK-2A2K2E (EKLKAKLEELKAKLEELL-P-EKLKAKLEELKAKLEELL) at a dose of 30 mg/kg administered intraperitoneally three times per week enhanced the rate of reverse cholesterol transport in C57BL/6 mice and modestly reduced the size of atherosclerotic plaques in the aortic arch with significant reductions in CD68 positive staining, VCAM-1 positive staining and nitrotyrosine staining in the aortic arch of apoE null mice [30*].

A series of 24 amino acid residue peptides mimicking apoA-I were tested [31*]. The FAMP5 peptide was equally as effective in promoting ABCA1-mediated cholesterol efflux in vitro whether or not its end groups were chemically blocked. In contrast L-4F was no more effective than bovine serum albumin without end groups but was significantly more effective than FAMP5 when its end groups were chemically blocked. In apoE null mice fed a high-fat high-cholesterol diet for 16 weeks administration of FAMP5 at 50 mg/kg given intraperitoneally three times per week significantly reduced aortic lesion area, but a dose of 10 mg/kg was not effective [31*].

FAMP was modified so it could be radiolabeled with gallium-68 for noninvasive positron emission tomography (PET) in a rabbit model of familial hypercholesterolemia that spontaneously develops myocardial infarction (WHHL-MI) [32*]. The radiolabeled FAMP was dramatically taken up by atherosclerotic tissues in the blood vessels and aorta of WHHL-MI rabbits but not in control rabbits [32*].

Site, Mechanism of Action, and Novel Approach to ApoA-I Mimetic Peptides

ApoA-I mimetic peptides 4F, 5F, and 6F derived from the 18A sequence have been studied for their mechanism of action in detail. The small intestine was found to be a major site of action for apoA-I mimetic peptides regardless of their route of administration [33,34*]. The dose of peptide needed for efficacy in the small intestine was determined to be high (40 – 100 mg/kg) and likely explains the divergent results of studies in humans [3**, 33, 34*]. There have been three reports on the use of the 4F peptide in humans [35–37]. Two of these reports showed efficacy [35, 36] and one did not [37]. The third report [37] used doses that were ineffective in the first two studies (i.e. the maximum dose tested in the third study was 1.43 mg/kg).

To overcome the problem of the high cost of production of chemically synthesized peptides such as 4F, which require chemically added end blocking groups, a search was conducted for peptides that did not need end blocking groups for efficacy. The peptide 6F was found to be such a peptide [38**, 39*]. Transgenic tomatoes expressing the 6F peptide (Tg6F) were

generated. When Tg6F was freeze-dried and added to a Western diet at only 2.2% of diet by weight there was a significant reduction in aortic atherosclerosis in LDLR null mice that was significantly correlated with levels of unsaturated lysophosphatidic acid in the small intestine [38**, 39*]. Intact Tg6F was found in the small intestine but not in the plasma indicating that it was indeed working in the small intestine [38**,39*]. Addition of unsaturated (but not saturated) lysophosphatidic acid to low-fat mouse chow produced levels of unsaturated lysophosphatidic acid in the small intestine, dyslipidemia and inflammation similar to those seen on feeding LDLR null mice a high-fat high-cholesterol Western diet; and Tg6F ameliorated the changes [40**, 41*].

Conclusion

Despite the failure of clinical trials to demonstrate the value of raising HDL-cholesterol levels, there continues to be active research on strategies to use HDL, its components, or mimetics of its components as therapeutic agents. The efficacy of apolipoprotein mimetics in such a large number of models of disease suggests that if a practical method of producing and administering these agents can be found, they may still have great therapeutic potential.

Acknowledgments

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Key Points

- Apolipoprotein mimetics have been found to be efficacious in a large number of disease models.
- The dose of apolipoprotein mimetics required for chronic administration makes the cost of treatment prohibitive if the mimetics have to be generated by chemical synthesis.
- At least some apolipoprotein mimetics appear to act primarily in the small intestine and thus oral administration is favored as the route of administration.
- Novel methods for producing apolipoprotein mimetics at a reasonable cost will be required for the strategy to be tested in humans at the doses required to treat chronic conditions.