ORGANIC CHEMISTRY
MC ELVAIN SEMINAR

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Novel Mimetics of Apolipoprotein A-I as Anti-atherosclerosis Agents

Given that cardiovascular disease is the major cause of death in developed countries despite the widespread use of lipid-lowering drugs, there has been a high level of interest in identifying new modes of therapy for atherosclerosis, such as modulating atheroprotective high-density lipoprotein (HDL). Apolipoprotein A-I (apoA-I), a 243-amino-acid protein within HDL, is a key source of the anti-atherosclerotic properties, and numerous efforts have been devoted to mimicking it, especially with linear, alpha-helical, amphiphilic peptides. We have investigated the design, synthesis, and efficacy (in vitro and in vivo) of branched, multivalent apoA-I mimetic molecules with 2–4 copies of an amphiphilic peptide attached to a core scaffold. Multivalent apoA-I mimetics based on 23-mers were better than monomer in effluxing cholesterol from mouse macrophages and in remodeling mature plasma HDL particles into nascent lipid-poor HDLs. These peptide constructs were remarkably stable toward enzymatic digestion in vitro, and displayed long half-lives and desirable pharmacokinetics in mice. Constructs comprised of multiple 16-mers were also explored. Our multivalent apoA-I mimetics, formulated as phospholipids to produce discoidal HDL-like nanoparticles, functioned in vivo in mice to remodel large native HDLs into small, lipid-poor HDLs. Robust atheroprotective activity was observed in 10-week studies with LDL receptor-null mice fed a high-fat diet with intraperitoneal and oral (!!) administration. These promising results led us to investigate cyclic D,L-alpha-peptides, well known to self-assemble into nanotubes, for anti-atherosclerosis activity. Octamers from the Ghadiri Group cyclopeptide library, and newly designed amphiphilic species, were examined for promotion of cellular cholesterol efflux and remodeling of HDL particles. Compound *c*[wLwReQeR] was found to be particularly effective and was then advanced to in vivo studies in LDL receptor-null mice. At 25 mg/kg/day, *ad libitum* in drinking water, *c*[wLwReQeR] reduced plasma total cholesterol 54% in 2 weeks and 30% in 10 weeks. After 10 weeks of oral administration, it reduced aortic lesions by 26% and aortic valve plaque by 50%. The utility of such cyclic peptides as atheroprotective agents (*PCT Int. Appl.* **2014**, WO 2014165563) opens a new avenue for treating cardiovascular disease.

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Room 1315 Chemistry

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