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Rational design of apolipoprotein E mimetic peptides

Apolipoprotein (apo) A-I and apoE possess multiple tandem lipid-associating amphipathic helical domains. Both apoA-I and apoE possess anti-atherogenic and anti-inflammatory properties. While apoA-I possesses several 11-mer and 22-mer tandem amphipathic helical domains punctuated by a Pro, apoE has two domain structures with a four helix bundle at the N-terminus linked to a long amphipathic helical domain of 57 residues in length. As a first step to support the lipid association function of the amphipathic helix, we first designed an 18 residue peptide DWLKAFYDKVAEKLKEAF (18A), a sequence which has no homology to any of the apolipoproteins but was able to form peptide: Lipid complexes, similar to apo A-I. This and several other analogs were therefore named as apoA-I mimetic peptides. While administration of analogs of this peptide was able to inhibit atherosclerosis in several mouse models, there was no change in plasma cholesterol. Since apoE is known to clear plasma cholesterol via the alternate heparan sulfate proteoglycan (HSPG) pathway, we added the HSPG binding domain of apoE from several species to the lipid associating peptide 18A. Thus the 10 residue pepide 141-150 from human apoE sequence (LRKLRKRLLR) was covalently linked to 18A to obtain Ac-hE18A-NH2. This and analogs with HSPG binding domains from other species were all able to associate with LDL and VLDL to alter electrophoretic mobility. Peptide-containing VLDL and LDL were rapidly taken up and degraded by fibroblasts and HepG2 cells. The uptake and degradation was inhibited by treatment of cells with heparinase/heparitinase. These results suggest that the peptide analogs, analogous to apoE, cleared atherogenic lipoproteins via the HSPG pathway. This marked the beginning of the design of apoE mimetic peptides and recently several more effective peptides have been designed. The abilities of these analogs to reduce plasma cholesterol in several dyslipidemic animal models will be discussed in other two talks.

Biography

G M Anantharamaiah is a Professor in the Department of Medicine since 1982. He received his Post-doctoral training at Ohio State University in Columbus, OH in 1979 and was a research associate in 1982 before coming to UAB as a faculty. His research has focused on structure and function of plasma Apolipoproteins, Apo-A1 Structure and Function, Apo-E Structure and Function, Structure of Apo-A-1 in Alzheimer Disease Research. He initiated studies of peptide mimetics of apolipoproteins A-I and E, both of which are licensed to two different companies for further development as therapies for lipid-mediated inflammatory disorders. He has published more than 200 papers in this field of research.

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