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Apolipoprotein E mimetics dramatically reduce plasma cholesterol levels in several animal models

Analogous to apolipoprotein (apo) E, apoE mimetic peptide is a dual domain peptide, containing receptor binding domain from apoE (LRKLRKRLLR, [hE], residues 141-150), linked to 18A the lipid-associating peptide. The resulting peptide, Ac-hE18A-NH_2, reduces plasma cholesterol in several animal models and possess anti-inflammatory properties which are independent of the effect on plasma cholesterol. To enhance the cholesterol-reducing ability, we synthesized several analogs of this peptide with fatty acyl chains of different length to LRRLRRRLLR-18A-NH_2 ([R]hE18A-NH_2) to produce Ac-Aha-[R] hE18A-NH_2, Octanyl-, Oleyl-, Palmityl- and Myristyl-[R]hE18A-NH_2. The modified peptides were much more effective in reducing plasma cholesterol in apoE null mice. Myristyl-peptide analog was the most effective. This analog was also most effective in apoE null mice fed a Western diet, capable of reducing plasma cholesterol from 900mg/dL to almost undetectable amount of plasma cholesterol in 5h. Plasma cholesterol levels in cynomolgus monkeys fed a Western diet was reduced by the Myristyl-analog in a dose-dependent manner. A single dose maintained plasma cholesterol and low-density lipoprotein (LDL) levels below baseline even after one week. However, plasma HDL levels were increased compared to baseline levels. Considering the peptide Ac-hE18A-NH_2 has undergone Phase 1 clinical trials in humans, the new and highly active analogs are expected to exhibit enhanced potency with lower doses in humans.

Biography

GM Anantharamaiah is a Professor in the Department of Medicine. He received his BS degree in 1967 from Bangalore University, India and his MS degree in 1969 from Bangalore University, as well. He completed his PhD degree in 1978. He has published more than 190 research papers and has several patents to his credit.

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