19
Apolipoprotein E polymorphism and atherosclerosis risk

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INTRODUCTION

Apolipoprotein E (apoE) is a normal constituent of very low density lipoprotein (VLDL) and high density lipoprotein (HDL)\textsuperscript{1}. The primary function of apoE is to serve as the ligand for recognition of lipoproteins by cellular receptors\textsuperscript{2}. In addition, apoE interacts with various proteoglycans and could thus be implicated in the anchoring process of lipoproteins to endothelial lipases\textsuperscript{3}. ApoE is a 299 amino acid protein made of two folded structural domains\textsuperscript{4}. The NH\textsubscript{2}-terminal region (residues 1-191) binds to the LDL receptor. Studies with cyanogen bromide and thrombolytic fragments of apoE, and with anti-apoE monoclonal antibodies, have demonstrated that the LDL-receptor-binding domain is located between residues 130 and 150\textsuperscript{1}. A cluster of basic residues in this region of apoE binds through direct ionic interaction with the negatively charged residues of the ligand-binding domain of the LDL receptor.

The gene locus of apoE is polymorphic\textsuperscript{5}. Three common alleles (e2, e3 and e4) code for three apoE isoforms: E2, E3, E4. ApoE2 and apoE4 differ from apoE3 by a single cysteine or arginine interchange at amino acids 158 and 112\textsuperscript{6}. As a consequence of the cysteine–arginine interchange in position 158, apoE2 isoforms interact poorly with the LDL receptor. This leads to defective clearance of remnants of lipoproteins and their accumulation in type III hyperlipidaemia\textsuperscript{7}. ApoE isoforms associate preferentially with different plasma lipoproteins: apoE4 with VLDL and apoE3 with HDL\textsuperscript{8}. This pattern of distribution is accounted for by structural differences between apoE3 and apoE4. ApoE3 that has a cysteine in position 112 forms a disulphide-linked heterodimer with apoAII of HDL. ApoE4 has a positively charged residue at position 112 (arginine) that leads to preferential association with VLDL.

Although early biological studies suggested that apoE isoforms had different potential to stimulate the atherogenic deposition of cholesterol esters, it was not until epidemiological studies that this association became
noted in humans. This chapter reviews the relationship between apoE polymorphism and plasma lipid levels. The association between apoE polymorphism and atherosclerosis will then be evaluated using data from case-control studies. Finally, the potential impact of apoE isoforms on CHD risk in the general population will be discussed.

ApoE POLYMORPHISMS AND PLASMA LIPID AND LIPOPROTEIN LEVELS

The genetic heterogeneity of apoE is associated with serum lipid and lipoprotein levels that may either directly or indirectly influence susceptibility to atherosclerosis. The association between plasma cholesterol and LDL-cholesterol levels and apoE polymorphism was remarkably consistent among populations and families. More recently, an association between apoE phenotype and plasma triglycerides and HDL-cholesterol levels has also been identified.

Subjects carrying the e2 or e4 alleles have, respectively, lower and higher levels of plasma total and LDL-cholesterol than individuals with the e3/e3 genotype. Compared with individuals with the e3/e3 genotype, triglycerides are higher both in subjects carrying the e2 allele, and in subjects with the e4/e3 genotype. In addition, the concentration of plasma HDL-cholesterol, which depends on the combination of HDL apolipoprotein production, VLDL lipolysis, and plasma lipid transfer protein activity, is significantly lower in apoE 4/3 subjects than those with the E 3/3 phenotype. The relationship is similar among different populations, including samples selected on morbidity criteria (obesity, diabetes, cardiovascular disease and hyperlipidaemia). This indicates that the role of apoE polymorphism in determining relative differences in plasma lipids is homogeneous among different ethnic groups or metabolic situations. The degree to which these relative effects vary within the same population and their mechanisms of control are not known. They probably depend on gene–environment and gene–gene interactions which represent an exciting area of future investigation. Taken together, the available data suggest that subjects carrying the e4 allele are exposed to more atherogenic lipoproteins, and therefore have increased atherogenic risk relative to their e3/e3 counterparts. Inversely, individuals with the e2 allele have less atherogenic risk.

The mechanism whereby apoE polymorphism regulates total and LDL-cholesterol levels is still speculative. ApoE polymorphism has been shown to modulate cholesterol intestinal absorption and delivery to the liver. This in turn regulates liver LDL-receptor activity with subsequent alteration in LDL fractional catabolic rates. In addition, the lipolytic VLDL-to-LDL cascade and the ability of VLDL remnants to compete with plasma LDL for receptor uptake is also influenced by apoE phenotype in vitro. The higher levels of triglycerides observed in subjects carrying the e2 allele can be explained by the slower plasma clearance of chylomicron and VLDL remnants secondary to defective interaction with cellular receptors. Moreover, an alteration with VLDL lipolytic process may also contribute...