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Apolipoprotein E polymorphism affects plasma levels of lipoprotein(a)

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Summary

In a group of 303 healthy Caucasian adults of both sexes we studied the influence of the apolipoprotein E (apo E) polymorphism on plasma levels of Lipoprotein(a) (Lp(a)). The APOE*2 allele was found to decrease the mean plasma Lp(a) level by 24.8%, whereas the APOE*4 allele increased the mean Lp(a) level by 25.7%. These effects were parallel to the effect of apo E polymorphism on plasma cholesterol and low density lipoprotein (LDL)-cholesterol. For the Lp(a) levels, the genetic variance associated with the APOE locus contributed about 4% to the total phenotypic variance. For plasma cholesterol and LDL-cholesterol this contribution was 4.5 and 6.3%, respectively. We also found a significant positive correlation between LDL-cholesterol and Lp(a) levels. Since the apo E polymorphism effects LDL-receptor activity, we conclude that, at least in healthy normolipidemic individuals, plasma levels of Lp(a) are modulated by the LDL-receptor activity.

Key words: Apolipoprotein E; Lipoprotein(a); Genetic polymorphism

Introduction

Apolipoprotein E (apo E) plays a central role in the metabolism of cholesterol and triglycerides. It is one of the major protein constituents of chylomicron and very low density lipoprotein (VLDL) remnants, and serves as a ligand for the receptor-mediated endocytosis of these particles by the liver [1]. ApoE is genetically polymorphic, showing three common isoforms, E2, E3 and E4, on isoelectric focusing and encoded by 3 different alleles, E*4, E*3 and E*2, at a single APOE gene locus on chromosome 19 [2,3]. Population

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studies demonstrated that the apo E polymorphism affects plasma lipid and lipoprotein levels [4–7]. The APOE*2 allele was found to exert a lowering effect on the levels of total cholesterol and low density lipoprotein (LDL)-cholesterol, whereas the APOE*4 allele showed the opposite effect.

Lipoprotein(a) [Lp(a)] was first described in 1963 by Berg as a distinct form of LDL [8]. For detailed information about Lp(a) see reviews in [9,10]. It is now well established that Lp(a) represents an LDL-particle in which the apolipoprotein B (apo B)-100 molecule is covalently linked by a disulphide bridge to apolipoprotein(a) (apo(a)) [11]. Plasma levels of Lp(a) in healthy Caucasian individuals vary between 0.01 and 100 mg/100 ml. Various studies have demonstrated that plasma levels of Lp(a) exceeding 20–30 mg/100 ml are positively associated with the development of premature atherosclerosis [12–14]. Several distinct isoforms of apo(a) can be distinguished [15,16]. These isoforms differ in size and are encoded by different alleles at a single LPA gene locus on chromosome 6 [17]. This size polymorphism is directly correlated with the number of kringle 4 domains in apo(a) and inversely correlated with plasma levels of Lp(a) [18,19]. Although the size polymorphism of Lp(a) was found to explain 42% of the variability in its plasma levels [20], the precise mechanisms responsible for this regulation remain unknown.

There are conflicting reports whether or not Lp(a) is cleared by the LDL-receptor. The involvement of the LDL-receptor in Lp(a) metabolism has been suggested by several groups [21–23,26]. However, other groups have disputed the importance of the LDL-receptor in the catabolism of Lp(a) [24,25–28].

The influence of the apo E polymorphism on plasma lipid and lipoprotein levels is thought to be due to its effect on the LDL-receptor activity in the liver. A possible influence of the apo E polymorphism on plasma Lp(a) levels would therefore support the hypothesis that the LDL-receptor is involved in Lp(a) catabolism. The data presented show that Lp(a) levels are indeed influenced by the apo E polymorphism in parallel to that of LDL-cholesterol levels.

Materials and methods

EDTA blood samples were obtained from 303, randomly selected, healthy Dutch individuals (151 males, mean age 48.2 years, and 152 females, mean age 45.7 years) after overnight fasting. Plasma was immediately separated from the cells and stored either at 4 °C or −20 °C until further use. Cholesterol concentrations were measured enzymatically using a Boehringer test kit (CHOD-PAP). LDL-cholesterol was calculated using the Friedewald formula [29]. Lp(a) levels were measured using a bi-site "sandwich" ELISA, with rabbit anti-human Lp(a) (Behringwerke, Marburg, Germany) as a catching antibody and rabbit anti-human apo B (raised in our institute) conjugated to horse-radish peroxidase (EC 1.11.1.7) as a detecting antibody. The Immuno reference serum (Immuno AG, Vienna, Austria) was used as the standard in this procedure. LDL and plasminogen are not detected with this assay. The working range of the assay is 0.1–3 μg per ml. Intra- and inter-assay variation coefficients are 4.5 and 8.5%, respectively.

The apo E phenotype was determined by isoelectric focusing of delipidated plasma samples followed by immunoblotting using a polyclonal goat anti-human apo E antiserum as first antibody [30]. The Hardy-Weinberg value was calculated for the male, female and combined group to test genetic equilibrium with respect to the distribution of apo E phenotypes. Differences in mean lipid concentrations between various groups and influences of the different APOE alleles were estimated using one-way analysis of variance (ANOVA). Linear correlations between the parameters considered were calculated using the Spearman rank correlation test. The contribution of the apo E polymorphism to the total variance of the measured parameters was calculated according to Sing and Davignon [5]. Since Lp(a) levels were highly skewed, we used the logarithmic transformed Lp(a) levels for these statistical comparisons. Findings were regarded to be statistically significant when the probability of these data under the null hypothesis was less than 0.05. All statistical calculations were made by use of either the SPSS program (Northwestern Univer-

TABLE 1

APOLIPOPROTEIN E PHENOTYPE DISTRIBUTION, MEAN LEVELS ± SD OF PLASMA CHOLESTEROL (mmol/l) AND LDL-CHOLESTEROL (mmol/l) AND THE MEAN, MEDIAN AND RANGE (MINIMUM AND MAXIMUM) VALUES OF Lp(a) (mg/100 ml) IN 303 ADULT HEALTHY DUTCH INDIVIDUALS

apo E phenotype	*n*	Plasma-chol	LDL-chol	Lp(a)		
				Mean	Median	Range
E2E2	3	4.60 ± 0.89	2.69 ± 0.71	6.35	1.60	0.50– 17.50
E2E3	45	5.43 ± 0.85	3.53 ± 0.75	11.34	4.40	0.50– 57.00
E3E3	178	5.70 ± 1.07	3.92 ± 0.99	13.04	6.25	0.70–114.00
E4E2	9	5.74 ± 1.10	3.85 ± 1.06	4.72	3.70	1.00– 14.20
E4E3	63	6.03 ± 1.15	4.23 ± 1.11	15.15	8.20	0.80– 65.40
E4E4	5	6.33 ± 1.40	4.54 ± 1.54	34.04	24.00	5.50– 70.50
all phenotypes	303	5.73 ± 1.08	3.92 ± 1.02	13.36	6.20	0.50–114.00
P-value *		0.020	0.002			0.017

The phenotype distribution is in Hardy-Weinberg equilibrium ($\chi^2 = 0.08$; $df = 5$; $P < 0.05$ at $\chi^2 > 11.07$).
**P*-value, indicating the significance level of the difference between the phenotype means (for plasma cholesterol and LDL-cholesterol) or logarithmic transformed means (for Lp(a)) of the measured parameters, calculated by ANOVA.

sity, Chicago, U.S.A.) or NCSS (Dr. J.L. Hintze, Kaysville, U.S.A.).

Results

Since there were no significant differences in the apo E phenotype distribution between the two sexes (data not shown), the two groups were combined into one sample of 303 individuals. The apo E phenotype distribution of this sample was in Hardy-Weinberg equilibrium ($\chi^2 = 0.08$; $df = 5$; $P < 0.05$ at $\chi^2 > 11.07$) and did not differ significantly from that found in other Caucasian populations ([4–7]; Table 1). Mean total cholesterol, LDL-cholesterol and Lp(a) levels were calculated for each apo E phenotype group. By ANOVA, significant differences between the apo E phenotypes were found for each of these parameters. The E*2 allele exhibited a lowering effect on these parameters, while the E*4 allele showed the opposite effect. This influence of apo E polymorphism on plasma lipid levels was independent of age and sex (data not shown). We calculated the average allelic effects of the APOE alleles on total cholesterol, LDL-cholesterol and Lp(a) levels (Table 2). The APOE*2 allele decreases the mean levels of total cholesterol, LDL-cholesterol and Lp(a) by 5.9, 10.9 and 24.8%, respectively, whereas the APOE*4 allele has an increasing influence of 5.4, 8.0 and 25.7%, respectively. The relative contribution of apo E polymorphism to the total variance of these measured parameters was estimated to be 4.5, 6.3 and 4.1%, respectively (Table 3).

Spearman's linear correlation coefficients between these three parameters are presented in Table 4. Besides the widely-reported correlation between LDL-cholesterol and total cholesterol

TABLE 2

AVERAGE EFFECT OF THE DIFFERENT APOE ALLELES (IN % OF THE POPULATION MEANS) ON PLASMA CHOLESTEROL, LDL-CHOLESTEROL AND Lp(a) LEVELS

Lipoprotein parameter	Apo E alleles		
	E*2	E*3	E*4
Plasma cholesterol	−5.9	−0.2	+5.4
LDL-cholesterol	−10.9	+0.1	+8.0
Lp(a)	−24.8	−0.8	+25.7

TABLE 3

RELATIVE CONTRIBUTION (IN %) OF THE GENETIC VARIANCE (σG^2) ASSOCIATED WITH THE APOE LOCUS TO THE TOTAL PHENOTYPIC VARIANCE (σ^2)

Lipoprotein parameter	$\sigma G^2/\sigma^2$ (%)
plasma-cholesterol	4.5
LDL-cholesterol	6.3
Lp(a)	4.1

TABLE 4

CORRELATION MATRIX INDICATING THE SPEARMANS CORRELATION COEFFICIENT AND CORRESPONDING P LEVELS (IN PARENTHESES) FOR LEVELS OF PLASMA CHOLESTEROL, LDL-CHOLESTEROL AND Lp(a)

	Plasma cholesterol	LDL-cholesterol	Lp(a)
plasma cholesterol	+1.0		
LDL-cholesterol	+0.92 ($P < 0.001$)	+1.0	
Lp(a)	+0.20 ($P < 0.001$)	+0.25 ($P < 0.001$)	+1.0

($r_s = 0.92$; $P < 0.001$), we also found small but significant linear correlations between Lp(a) and LDL-cholesterol ($r_s = 0.25$; $P < 0.001$) and between Lp(a) and plasma cholesterol ($r_s = 0.20$; $P < 0.001$).

Discussion

It is generally assumed that the influence of the apo E polymorphism on total cholesterol and LDL-cholesterol levels is the result of its effect on the hepatic LDL-receptor activity [6,7]. The present study, involving 303 healthy males and females, demonstrated also an effect of the apo E polymorphism on plasma Lp(a) levels, parallel to that on plasma total cholesterol and LDL-cholesterol levels. However, such an effect was not observed in a study involving 337 male survivors of myocardial infarction [31].

At present, there is much debate as to whether or not the LDL-receptor plays a key-role in the regulation of plasma Lp(a) levels. Using cultured human fibroblasts, several groups have reported only a minor role of the LDL-receptor in the Lp(a) catabolism [24,25]. Using freshly isolated parenchymal rat-liver cells, Harkes et al. [32] demonstrated that upon increasing the LDL-receptor activity in these cells by treatment of the rats with estrogen, Lp(a) interacts slightly more efficiently when compared to parenchymal cells isolated from untreated rats. These results suggest that the LDL-receptor is not or only to a minor extent involved in Lp(a) metabolism. This is further supported by the observation that in heterozygous FH patients, the plasma Lp(a) levels could not be reduced upon treatment with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, which are known to effectively reduce LDL-cholesterol levels by increasing the LDL-receptor activity [27,28].

In contrast to these findings arguing against the involvement of the LDL-receptor in Lp(a) catabolism, several reports appeared in favour of such an involvement. Several groups showed that cultured human fibroblasts take up and degrade Lp(a) via the LDL-receptor [21–23]. Further support for this was gained from the observation that in FH patients, being partly defective in LDL-receptor activity, plasma Lp(a) levels are 2.5–3 times as high as in healthy individuals, irrespective of their Lp(a) phenotype [26]. In a recent study using transgenic mice with an overexpression of human LDL-receptors, Lp(a) was cleared more rapidly than in the normal mice [33].

The present data show that the apo E polymorphism does influence the plasma Lp(a) levels parallel to that of LDL. A part of the effect of the apo E polymorphism on LDL-cholesterol levels can be explained by its influence on the conversion of VLDL into LDL [34]. However, this can not be the explanation for the effect of apo E polymorphism on Lp(a) levels since Lp(a) has no VLDL precursor [35,36], although it may interact with triglyceride-rich particles [37]. Using primary baboon hepatocytes as an in vitro model, Rainwater and Lanford [38] found only apo(a) bound to the LDL-apo B complex in a lipoprotein with a density of 1.05 g/ml, whereas e.g. apo B was also secreted in VLDL with a density less than 1.05 g/ml [39]. These authors could not detect free apo(a) in the culture medium suggesting that Lp(a) is assembled intracellularly and secreted into the circulation as an intact particle, most probably by the liver. This hypothesis is supported by the virtual absence of free apo(a) in serum of patients with autosomal recessive abetalipoproteinemia [40].

Our data suggest that Lp(a) is cleared from the circulation at least partly by a mechanism involving normal functioning LDL-receptors. These data are in conflict with the results of Sandkamp et al. [31]. This discrepancy might be explained by the differences in the populations studied i.e. a

healthy normolipidemic population (this study) versus a population consisting of myocardial infarction survivors with increased plasma lipid levels. In previous studies, it was shown that in FH patients the apo E polymorphism fails to influence the LDL-cholesterol levels significantly [41,42]. The absence of such an effect might be due to the high LDL-cholesterol levels in these individuals, probably overruling the effect of the apo E polymorphism. Similarly, the high LDL-cholesterol levels could also explain why treatment with simvastatin failed to reduce plasma Lp(a) levels in FH patients [27,28].

In summary, we present evidence that in normolipidemic individuals the Lp(a) level is influenced by the apo E polymorphism similarly to that of the LDL-level. Hence our results sustain the hypothesis that in vivo, the LDL-receptor is involved in Lp(a) catabolism.

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