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The −250G/A polymorphism in the hepatic lipase gene promoter influences the postprandial lipemic response in healthy men

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Abstract *Background and aim:* The −250G/A promoter polymorphism of the hepatic lipase gene has been associated with changes in the activity of the enzyme. We investigated whether this polymorphism modifies the postprandial response of triacylglycerol-rich lipoproteins (TRL) in young normolipemic males.
Methods and results: Fifty-one healthy apolipoprotein (apo) E3/E3 male volunteers (30 G/G and 21 carriers of the A allele) underwent a vitamin A fat-loading test and blood samples were drawn every hour until the 6th, and every 2 h and 30 min until the 11th. Total plasma cholesterol and triacylglycerols (TG), as well as cholesterol, TG and retinyl palmitate (RP) in TRL, isolated by ultracentrifugation, were determined.

Carriers of the A allele showed a higher response ($P = 0.008$), a higher area under the curve (AUC; $P = 0.022$) and a lower RP peak time ($P = 0.029$) in small TRL during the postprandial response, as well as a lower peak time in total plasma TG levels ($P = 0.034$) and large TRL-TG ($P = 0.033$) than subjects who were homozygous for the G allele.
Conclusion: Our data indicate that the presence of the A allele in the −250G/A promoter polymorphism of the hepatic lipase gene is associated with a higher postprandial lipemic response.

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Introduction

Human hepatic lipase (HL) is a lipolytic enzyme synthesized in the liver [1–3], which is secreted from hepatocytes and bound to the hepatic sinusoidal endothelial surface. It plays an important role in the metabolism of high-density lipoprotein (HDL), and transforms large triacylglycerol-rich HDL_2 into small, dense HDL_3 [4]. HL also acts as a ligand for lipoproteins during the uptake of these by hepatic cell-surface receptors [5–7], and is involved in the reverse transport of cholesterol [8,9]. Furthermore, this enzyme takes part in the formation of small, dense low-density lipoprotein (LDL) particles [10]. Therefore, HL activity may be involved in cardiovascular disease (CVD) because of its essential functions in the metabolism of lipoproteins.

HL activity appears to be associated with several different factors, including intra-abdominal fat [11], ethnic background [12,13], sex-steroid hormones [14], age [15,16] and various hepatic lipase gene promoter polymorphisms [12,17]. The 5′ flanking region of the HL gene contains four polymorphic sites: G-250A, C-514T, T-710C and A-763G [17], and all of them are in almost complete linkage disequilibrium. The frequency of rare alleles varies from 0.15 to 0.29 in white populations, 0.45 to 0.53 in African-Americans, and 0.47 in Japanese-Americans. The presence of these alleles have been associated with low HL activity and with high TG levels [18,19], high HDL cholesterol (HDL-C) levels [13,19,20], buoyant LDL particles [13], and coronary heart disease [20].

Postprandial lipemia is characterized by an increase in triacylglycerol-rich lipoproteins (TRL) (chylomicrons, very low density lipoproteins (VLDL) and their remnants). Several studies have demonstrated that the inhibition of HL activity produces an impairment of the uptake of chylomicron remnants by the liver [21,22]. The −514C/T variant in the HL gene promoter has been found to influence fasting and postprandial lipoprotein containing both apo C-III and apo B (LpC-III:B) levels in the European Atherosclerosis Research Study II (EARSII) population in such a way that carriers of the −514T had higher levels of apo CIII:B [19]. However, our group has demonstrated that the T allele of the −514C/T polymorphism in the promoter region of the hepatic lipase gene is associated with a lower postprandial lipemic response [23] in young normolipemic males. This last results contrasts with the existing knowledge that the T allele is associated with lower levels of hepatic lipase activity [13] and with the effects of this enzyme on TRL metabolism. Although a linkage disequilibrium exists between the −514C/T and −250G/A polymorphisms, in the present study we observed that this linkage is not complete since some subjects with the common −250G allele had the rare −514T haplotype (30 subjects with the −250G/G polymorphism, of which 23 were C/C and seven were carriers of the T allele of the −514C/T polymorphism). For this reason, we wanted to investigate the effect of the −250G/A promoter polymorphism of the hepatic lipase gene on the postprandial response of TRL in the same population used in our previous study [23].

Methods

Population

Fifty-one healthy male students were included in this study. Thirty were homozygous for the most common allele (G/G) and 21 were carriers of the A allele (18 GA and 3 AA). Informed consent was obtained from all participants. Volunteers showed no evidence of any chronic disease (hepatic, renal, thyroid or cardiac dysfunction). All volunteers were selected to have the apo E3/E3 genotype in order to avoid the allele effects of this gene locus on postprandial lipemia [24]. None of the subjects was taking medication or vitamins known to affect plasma lipids. The fasting plasma lipids, lipoproteins, apolipoproteins, age and body mass index (BMI) are shown in Table 1. All studies were carried out in the research unit at the Reina Sofia University Hospital. The experimental protocol was approved by the hospital's Human Investigation Review Committee.

Table 1 Plasma lipids and apolipoproteins according to the −250G/A HL promoter polymorphism

	GG (30)	GA/AA (21)	*P*
Age (years)	22.5 ± 3.3	21.0 ± 1.9	0.060
BMI (kg/m^2)	25.0 ± 2.9	25.6 ± 4.4	0.580
C (mmol/L)	4.0 ± 0.65	3.9 ± 0.6	0.479
LDL-C (mmol/L)	2.5 ± 0.6	2.4 ± 0.6	0.375
HDL-C (mmol/L)	1.20 ± 0.3	1.22 ± 0.3	0.573
TGs (mmol/L)	0.90 ± 0.3	0.99 ± 0.4	0.408
Apo A-I (g/L)	0.97 ± 0.2	0.98 ± 0.2	0.874
Apo B (g/L)	0.69 ± 0.2	0.64 ± 0.1	0.271

Values are given as mean ± SD. BMI, body mass index; C, cholesterol; TGs, triacylglycerols; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol *P*: ANOVA. There were no significant differences between the two groups.