Postprandial lipemia is modified by the presence of the polymorphism present in the exon 1 variant at the SR-BI gene locus

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Abstract

It has recently been reported that carriers of the less common allele at the scavenger receptor class B type I (SR-BI) exon 1 polymorphism are more susceptible to the presence of saturated fatty acid in the diet because of a greater increase in LDL cholesterol. Our aim was to determine if this polymorphism could also influence postprandial lipoprotein metabolism, because the SR-BI has been described as a possible mediator in the intestinal absorption of triacylglycerols. Forty-seven normolipidemic volunteers who were homozygous for the E3 allele at the APOE gene were selected [37 homozygous for the common genotype (1/1) at the SR-BI exon 1 polymorphism and 10 heterozygous (1/2)]. They were given a fat-rich meal containing 1 g fat and 7 mg cholesterol per kg body weight and vitamin A 60 000 IU/m² body surface. Fat accounted for 60% of calories, and protein and carbohydrates accounted for 15% and 25% of energy respectively. Blood samples were taken at time 0, every 1 h until 6 h, and every 2·5 h until 11 h. Total cholesterol and triacylglycerols in plasma, and cholesterol, triacylglycerols and retinyl palmitate in triacylglycerol-rich lipoproteins (large and small triacylglycerol-rich lipoproteins) were determined. Postprandial responses for triacylglycerols and retinyl palmitate in small triacylglycerol-rich lipoproteins were higher in 1/1 individuals than in 1/2 individuals. No other significant differences were noted. Our data show that the presence of the genotype 1/2 is associated with a lower postprandial lipemic response.


Introduction

The postprandial state constitutes the normal metabolic situation of human beings throughout the day in developed societies, as the clearance of triacylglycerol (TAG)-rich particles of intestinal or hepatic origin lasts for a period of 6–8 h. This period is characterized by an increase in total TAGs and TAG-rich lipoproteins (TRL) of intestinal and hepatic origin. Previous studies have suggested that postprandial remnant particles may predict the onset of coronary heart disease (CHD) (Patsch et al. 1992, Karpe et al. 1994, Uiterwaal et al. 1994, Kugiyama et al. 1999). Individual variability in the postprandial lipemic response is usually greater than that observed in the fasting state and it appears to be modulated by environmental and genetic factors (Mero et al. 1998). This concept is supported by studies showing that certain polymorphisms at candidate gene loci (the APOA1–APOC3–APOA4 gene complex, APOB, APOE, LIPC, CETP, FABP2 and LPL) are associated with variability in postprandial clearance of lipoprotein (Knuelsen et al. 1997, Zhang et al. 1997, Agren et al. 1998, Ostos et al. 1998, Fisher et al. 1999, Hockey et al. 2001, Ordovas 2001).

The characterization of new cell surface lipoprotein receptors constitutes an important advancement in the study of lipid metabolism (Van Berkel et al. 2000). The scavenger receptor class B type I
(SR-BI) is the first HDL receptor to be reported and it mediates selective uptake of HDL cholesterol (HDL-C) without degradation of entire HDL particles (Acton et al. 1996). Data from experimental animal models clearly demonstrate that SR-BI has a major role in the regulation of HDL metabolism (Krieger 2001). Moreover, SR-BI has been shown to be a multilipoprotein receptor, regulating the concentrations of LDL cholesterol (LDL-C) and VLDL cholesterol (VLDL-C) (Arai et al. 1999, Rigotti et al. 2000).

Associations between \textit{SR-BI} gene polymorphisms and variations in the concentrations of plasma cholesterol have recently been described in humans (Acton et al. 1999). Male carriers of the 2 allele (1/2) in the exon 1 of the \textit{SR-BI} gene showed increased HDL-C and reduced LDL-C concentrations and basal concentrations of triglycerides (Acton et al. 1999). Furthermore, we have demonstrated in a dietary intervention study that carriers of this allele appear to be more responsive to changes in dietary saturated fat intake, as they exhibit a greater increase in LDL-C compared with 1/1 individuals (Pérez-Martínez et al. 2003). Moreover, others have shown that the SR-BI appears to be involved in the intestinal absorption of TAGs, giving support to the hypothesis that SR-BI could modulate postprandial lipemia (Hauser et al. 1998). The main goal of the present research was to test this hypothesis using the \textit{SR-BI} polymorphism in exon 1 as a marker.

### Materials and methods

#### Study volunteers

Forty-seven healthy men were recruited from among 97 students at the University of Cordoba. They had a mean (± s.d.) age of 23 ± 4.12 years. Of these, 37 were homozygous for the most common 1 allele (1/1) and 10 were carriers of the 2 allele (1/2). There were no homozygotes for the 2 allele (2/2). This distribution of genotypes was expected from the Hardy-Weinberg equilibrium ($\chi^2=0.6660$). These individuals had participated in a previous study (Pérez-Martínez et al. 2003) and the allele frequencies were similar to those previously reported. Informed consent was obtained from all participants, none of whom had diabetes or liver, renal or thyroid disease. All were selected to have the \textit{APOE} 3/3 genotype, to avoid the potential confounding effect on postprandial lipemia that is associated with the presence of the other common \textit{APOE} alleles (Boerwinkle et al. 1994). None of the participants was taking medication or vitamins known to affect plasma lipids. The fasting plasma lipids, lipoproteins, apolipoproteins (Apo), 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, and the experimental procedure was approved by the hospital’s Human Investigation Review Committee.
Vitamin A fat-loading test

After a 12-h fast, study participants were given a fatty meal enriched with vitamin A 60 000 units/m² body surface area. The fatty meal consisted of two cups of whole milk, eggs, bread, bacon, cream, walnuts and butter. The amount of fats given were 1 g fat and 7 mg cholesterol per kg body weight. The meal contained 60% of energy as fat, 15% as protein and 25% as carbohydrates and was eaten in 20 min. After the meal, the individual ingested no energy-providing food for 11 h, but was allowed to drink water. Blood samples were drawn before the meal, every 1 h until 6 h and every 2.5 h until 11 h.

Lipoprotein separations

Blood was collected in tubes containing EDTA to give a final concentration of 0.1% EDTA. Plasma was separated from red cells by centrifugation at 1500 g for 15 min at 4 °C. The chylomicron fraction of TRL (large TRL, Sf > 400) was isolated from 4 ml plasma overlaid with 0.15 mol/l NaCl and 1 mmol/l EDTA (pH 7.4, density <1.006 kg/l) by a single ultracentrifugal spin (20 000 r.p.m., 30 min, 4 °C) in a type 50 rotor (Beckman Instruments, Fullerton, CA, USA). Chylomicrons, contained in the top layer, were removed by aspiration after the tubes had been cut open and the infranatant was centrifuged at a density of 1.019 kg/l for 24 h at 45 000 r.p.m. in the same rotor. The non-chylomicron fraction of TRL (also referred to as small TRL, Sf 12–400) was removed from the top of the tube. All operations were carried out in subdued light. Large and small TRL fractions were stored at −70 °C until required for assay for retinyl palmitate.

Lipid analysis

Cholesterol and TAGs in plasma and lipoprotein fractions were assayed by enzymatic procedures (Bucolo & David 1973, Allain et al. 1974). ApoA-I and ApoB were determined by turbidimetry (Riepponen et al. 1987). HDL-C was measured by analyzing the supernatant obtained after precipitation of a plasma aliquot with dextran sulphate-Mg²⁺, as described by Warnick et al. (1982). LDL-C concentration was obtained as the difference in cholesterol content in the bottom part of the tube after ultracentrifugation at a density of 1.019 kg/l.

Retinyl palmitate assay

The retinyl palmitate content of large and small TRL fractions was assayed using a method described previously (Ruotolo et al. 1992). Briefly, different volumes of the various fractions (100 µl for large TRL and 100–500 µl for small TRL) were placed in 13 × 100 mm glass tubes. The total volume in each tube was adjusted, as necessary, to 500 µl using normal saline. Retinyl acetate (40 ng in 200 µl mobile phase buffer) was added to each tube as internal standard. Five hundred milliliters of methanol was added, followed by 500 µl mobile phase buffer, giving a total volume of 1.7 ml. The mobile phase buffer was freshly prepared on a daily basis by combining 90 ml hexane, 15 ml n-butyl chloride, 5 ml acetonitrile and 0.01 ml acetic acid (82:13:5 by volume with 0.01 ml acetic acid). The contents of the tubes were mixed thoroughly after each step. The final mixture was centrifuged at 350 g for 15 min (room temperature) and the upper layer was carefully removed by aspiration and placed into individual autosampler vials. The autoinjector was programmed to deliver 100 µl per injection and a new sample every 10 min in a custom-prepackaged silica column SupelcoSil LC-SI (5 mm diameter by 250 mm length) provided by Supelco Inc (Bellefonte, Pennsylvania, USA). The flow was maintained at a constant rate of 2 ml/min and the peaks were detected at 330 nm. The peak of retinyl palmitate and retinyl acetate was identified by comparing its retention time with a purified standard (Sigma) and the retinyl palmitate concentration in each sample was expressed as the ratio of the area under the retinyl palmitate peak to the area under the retinyl acetate peak (De Ruyter & De Leeheer 1978). All operations were performed in subdued light.

Determination of ApoB-48 and ApoB-100

ApoB-48 and ApoB-100 were determined by SDS-PAGE as described by Karpe & Hamsten (1994). The coefficients of variation in our assay were 7.3% for ApoB-48 and 5.1% for ApoB-100. In brief, samples containing isolated lipoprotein fractions were delipidated in a methanol–diethyl ether solvent system and the protein pellet was
dissolved in 100–500 µl 0·15 mol/l sodium phosphate, 12·5% glycerol, 2% SDS, 5% mercaptoethanol and 0·001% bromophenol blue (pH 6·8) at room temperature for 30 min, followed by denaturation at 80 °C for 10 min. Electrophoresis was performed with a vertical Hoefer Mighty Small II electrophoresis apparatus connected to an EPS 400/500 (Pharmacia) power supply on 3–20% gradient polyacrylamide gels. The upper and lower electrophoresis buffers contained 25 mmol/l Tris, 192 mmol/l glycine, and 0·2% SDS adjusted to pH 8·5. ApoB-100 derived from LDL was used as a reference protein and for standard curve dilutions. A dilution curve ranging from 0·10 to 2 mg ApoB-100 was applied to four of the gel lanes. Electrophoresis was run at 60 V for the first 20 min and then at 100 V for 2 h. Gels were fixed in 12% trichloroacetic acid for at least 30 min and stained in 0·2% Coomassie G-250:40% methanol:10% acetic acid for at least 4 h. Destaining was in 12% methanol:7% acetic acid with four changes of destaining solution for 24 h. Gels were scanned with a videosdensitometer scanner (TDI, Madrid, Spain) connected to a personal computer for integration of the signals. Background intensity was calculated after an empty lane had been scanned.

**DNA amplification and genotyping**

Genotyping of the SR-BI exon 1 (G→A) single-nucleotide polymorphism was carried out as described previously (Osgood-McWeeney et al. 2000). Each probe consisted of an oligonucleotide with a 5' reporter dye and 3' quencher dye. The reporter dyes used were 6 carboxy-fluorescein (FAM) and VIC; 6 carboxy-tetramethyl-rhodamine (TAMRA) was used as the quencher dye. The primer and probe sequences were as follows: forward primer 5'-GTCCCGGTCTCCTGCGCA 3'; reverse primer 5'-CCCAGCAAGGCGACACA GTA-3'; G-allele probe 5'-FAM-AGACATGGGC TGCTCCGCCA-TAMRA-3'; A-allele probe 5'-VIC-CAGACATGAGCTGCTCGCCA-TAMR A-3'. The bases in bold type represent point mutations. PCR was performed in a 10-µl final volume for each individual single-nucleotide polymorphism. The reaction mixture contained 5 µl TaqMan 2X Universal PCR Master Mix (Applied Biosystems, Foster City, CA, USA), 200 nmol/l FAM-labeled probe, 150 nmol/l VIC-labeled probe, 900 nmol/l reverse primer, 900 nmol/l forward primer (all from Epoch Biosciences, Bothell, WA, USA) and 2–20 ng genomic DNA. The termal cycler program included: one cycle at 50 °C for 2 min to active uracil-N-glycosylase (Trevigen Inc., Gaithersburg, MD, USA), which was added to prevent carryover contamination; one cycle at 95 °C for 10 min to activate the AmpliTaq Gold Polymerase (Applied Biosystems); 40 cycles at 95 °C for 15 s for denaturing and at 62 °C for 60 s for annealing/extending. Allelic discrimination was performed on the post-PCR product. Fluorescence data were collected by 7700 Sequence Detection System (Perkin-Elmer/Applied Biosystems) on the samples for 5 s and analyzed with the use of Sequence Detection System software, version 6·0 (Applied Biosystems), which could be visualized in graph form (Osgood-McWeeney et al. 2000).

**Statistical analysis**

Several variables were calculated to characterize the postprandial responses of plasma TAGs, large TRL and small TRL to the test meal. The area under the curve (AUC) is defined as the area between the plasma concentration versus time curve and a line drawn parallel to the horizontal axis through the 0 h concentration. This area was calculated by a computer program using the trapezoidal rule. Other variables were the normalized peak concentration above baseline and the peak time, which was the average of the time of peak concentration and the time to the second greatest concentration.

Data were tested for statistical significance between genotypes by analysis of variance (ANOVA) and Kruskal–Wallis test, and between genotypes and time by ANOVA for repeated measures. In this analysis, we studied the statistical effects of the genotype alone, independent of the time in the postprandial study, the effect of time alone or change in the variable after ingestion of fatty food over the entire lipemic period, and the effect of the interaction of both factors, genotype time, indicative of the magnitude of the postprandial response in each group of individuals with a different genotype. When statistical significance was found, the Tukey’s post-hoc comparison test was used to identify group differences. A probability value less than 0·05 was considered significant. Stepwise multiple regression analyses were carried out using small TRL TAGs as
dependent variables and exon 1 genotype, total TAG, LDL-C, HDL-C, age and BMI as independent variables. Discrete variables were divided into classes for analysis.

All data presented in text and tables are expressed as means ± s.d The Statistical Package for the Social Sciences (SPSS) 9·0 was used for the statistical comparisons.

**Results**

The basal characteristics by genotype are shown in Table 1. No significant differences for any of the variables examined were observed at baseline between genotype groups.

The postprandial response of plasma TAGs and TAGs in different lipoprotein fractions were analyzed. A significant effect of time on plasma TAG concentrations ($P<0·001$), HDL-C ($P<0·001$), LDL-C ($P<0·001$), total cholesterol ($P=0·009$), ApoA-I ($P=0·001$), ApoB ($P=0·002$), in the small TRL ($P<0·001$), large TRL ($P<0·001$) (Fig. 1a), small TRL cholesterol ($P<0·001$), large TRL cholesterol ($P<0·001$), and in the small TRL retinyl palmitate ($P<0·001$), large TRL retinyl palmitate ($P<0·001$), small TRL ApoB-100 ($P=0·038$) and large TRL ApoB-48 ($P=0·008$) were observed, indicating an increase or decrease in these parameters in the different groups of individuals during the postprandial period. This effect was not observed in the other variables analyzed. Furthermore, 1/1 individuals showed a higher postprandial response of plasma TAGs and small TRL TAGs than did carriers of the 2-allele (1/2) as demonstrated by a significant genotype-by-time interaction ($P=0·029$ and $P=0·032$ respectively). Individuals carrying the 1/1 genotype showed greater postprandial concentrations of small TRL TAGs than did carriers of the 2-allele ($P=0·015$) (Fig. 1b). Moreover, 1/1 individuals presented greater concentrations of small TRL retinyl palmitate at times 1 ($P=0·045$), 2 ($P=0·011$) and 3 ($P=0·018$) than did carriers of the 2-allele (1/2) (Fig. 1c).
The AUC of small TRL TAG was greater in 1/1 individuals than in carriers of the 2 allele \((P=0.05)\). No other statistically significant genotype-related differences in the AUC for other parameters were observed (Table 2).

Multiple regression analysis (Table 3) revealed that the polymorphism present in exon 1 of the \(SR-BI\) \((P<0.01)\) and fasting TAGs plasma concentrations independently \((P<0.045)\) predict postprandial response of small TRL TAGs.

**Discussion**

Our findings show that healthy male carriers of the 2-allele at the \(SR-BI\) exon 1 polymorphism have a lower postprandial response of small TRL TAGs as compared with 1/1 individuals. Smaller, partially catabolized TRLs are thus believed to be more atherogenic or thrombogenic than larger, newly secreted TRLs (Cohn et al. 1999).

The SR-BI has been described as the first functionally active HDL receptor capable of facilitating the selective uptake of HDL-C (Acton et al. 1996). Several recent \textit{in vivo} studies suggest that this cell-surface glycoprotein receptor may also process LDL and other ApoB-containing particles (Swarnakar et al. 1999). A previous epidemiological study has clearly demonstrated an association between BMI and basal concentrations of LDL and HDL cholesterol and TAGs in relation to the \(SR-BI\) gene (Acton et al. 1996). In that study, men who were carriers of the 1/2 in exon 1 had an increase in HDL-cholesterol and a decrease in LDL-cholesterol concentrations. We have recently

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**Table 2 Area under the postprandial curve in study participants, according to the exon 1 variant at the \(SR-BI\) gene locus**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>1/1</th>
<th>1/2</th>
<th>(P) (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l per s)</td>
<td>(0.722 \pm 0.13)</td>
<td>(0.725 \pm 0.09)</td>
<td>(0.939)</td>
</tr>
<tr>
<td>Triacylglycerols (mmol/l per s)</td>
<td>(0.138 \pm 0.09)</td>
<td>(0.171 \pm 0.12)</td>
<td>(0.372)</td>
</tr>
<tr>
<td>LDL-C (mmol/l per s)</td>
<td>(-0.021 \pm 0.03)</td>
<td>(-0.024 \pm 0.02)</td>
<td>(0.814)</td>
</tr>
<tr>
<td>HDL-C (mmol/l per s)</td>
<td>(-0.006 \pm 0.01)</td>
<td>(-0.001 \pm 0.01)</td>
<td>(0.440)</td>
</tr>
<tr>
<td>ApoB (g/l per s)</td>
<td>(-0.002 \pm 0.008)</td>
<td>(-0.005 \pm 0.004)</td>
<td>(0.319)</td>
</tr>
<tr>
<td>ApoA-I (g/l per s)</td>
<td>(-0.004 \pm 0.01)</td>
<td>(-0.006 \pm 0.008)</td>
<td>(0.664)</td>
</tr>
<tr>
<td>Large TRL TAG (mmol/l per s)</td>
<td>(0.088 \pm 0.05)</td>
<td>(0.101 \pm 0.070)</td>
<td>(0.553)</td>
</tr>
<tr>
<td>Small TRL TAG (mmol/l per s)</td>
<td>(0.019 \pm 0.02)</td>
<td>(0.003 \pm 0.021)</td>
<td>(0.050)</td>
</tr>
<tr>
<td>Large TRL RP (ng/ml per s)</td>
<td>(835.5 \pm 807)</td>
<td>(652.8 \pm 615)</td>
<td>(0.511)</td>
</tr>
<tr>
<td>Small TRL RP (ng/ml per s)</td>
<td>(342.0 \pm 276)</td>
<td>(231.6 \pm 199)</td>
<td>(0.245)</td>
</tr>
<tr>
<td>Large TRL ApoB-48 (AU)</td>
<td>(335.7 \pm 357)</td>
<td>(277.5 \pm 407)</td>
<td>(0.731)</td>
</tr>
<tr>
<td>Small TRL ApoB-48 (AU)</td>
<td>(251.4 \pm 356)</td>
<td>(129.5 \pm 178)</td>
<td>(0.427)</td>
</tr>
<tr>
<td>Large TRL ApoB-100 (AU)</td>
<td>(463.0 \pm 560)</td>
<td>(126.6 \pm 206)</td>
<td>(0.164)</td>
</tr>
<tr>
<td>Small TRL ApoB-100 (AU)</td>
<td>(6983.0 \pm 18827)</td>
<td>(9177.0 \pm 9063)</td>
<td>(0.785)</td>
</tr>
</tbody>
</table>

Values are mean±S.D. RP, retinyl palmitate; AU, arbitrary units.

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**Table 3 Multiple stepwise regression analyses**

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variables</th>
<th>Beta coefficient</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small TRL TAG AUC</td>
<td>Exon 1 genotype</td>
<td>(-0.381)</td>
<td>(0.010)</td>
</tr>
<tr>
<td></td>
<td>TAG</td>
<td>(0.372)</td>
<td>(0.045)</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>(-0.054)</td>
<td>0.750</td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>(-0.259)</td>
<td>0.087</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>(0.200)</td>
<td>0.184</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>(0.103)</td>
<td>0.462</td>
</tr>
</tbody>
</table>
observed that the presence of the 1/2 genotype in exon 1 of the \textit{SR-BI} gene enhances the response of LDL cholesterol to the presence of saturated fatty acid in the diet of healthy individuals (Pérez-Martínez \textit{et al.} 2003). These findings are consistent with the fact that the \textit{SR-BI} exon 1 polymorphism may have a role in the metabolism of LDL cholesterol.

The mechanism by which \textit{SR-BI} delivers cholesteryl esters to cells is not well understood, but it appears to be different from the well-characterized LDL receptor endocytic pathway (Brown & Goldstein 1986). This receptor mediates uptake of lipids from both LDL and HDL, and this uptake is associated with an increase in cholesterol esterification (Stangl \textit{et al.} 1998). The physiological significance of \textit{SR-BI}-mediated metabolism of LDL cholesteryl ester in humans remains to be clarified. It is possible that the receptor contributes to the clearance of the fraction of LDL not removed by the LDL receptor pathway or removes some cholesteryl ester from particles in the VLDL–LDL cascade (Swarnakar \textit{et al.} 1999). This hypothesis may explain, in part, our findings of a lower postprandial response of small TRL TAGs in 1/2 genotype individuals than in those homozygous for the 1 allele (1/1). Hepatic clearance of small TRLs takes place in the space of Disse, where uptake occurs by the LDL-receptor-related protein or, as an alternative pathway, by the LDL receptor (Cooper 1997, Björkegren \textit{et al.} 1998, Mahley & Sheng Ji 1999). The hypothesis has previously been suggested that the \textit{SR-BI} mediated removal of lipoproteins by the liver appears to involve both ApoE and hepatic lipase as ligands or co-receptors (Von Eckardstein \textit{et al.} 2000). It has been demonstrated that hepatocytes secrete large amounts of ApoE, which is recaptured by LDL-receptor-related protein, facilitating the endocytosis of TRL (Fidge 1999). This ApoE could also interact directly with \textit{SR-BI} or with another cellular protein to enhance \textit{SR-BI} activity. The results of our study suggest that the \textit{SR-BI} could participate in one of the stages of this process, in such a way that the carriers of genotype 1/2 with accelerated clearance of small TRL TAG may also have a more rapid hepatic uptake. Furthermore, the findings of previous studies have suggested that the recycling of TRL constituents in hepatocytes might involve \textit{SR-BI} (Mahley & Sheng Ji 1999).

The \textit{SR-BI} gene is located in the region of chromosome 12q24 and the exon 1 polymorphism could interact with other polymorphisms at the \textit{SR-BI} locus or neighboring loci yet to be identified (Acton \textit{et al.} 1999). In addition, the presence of this polymorphism could modify receptor activity. Another factor to consider is the expression of \textit{SR-BI} in relation to the exon 1 polymorphism, as previous studies have clearly demonstrated the effects of overexpression or reduction of the \textit{SR-BI} on HDL concentrations (mediating the reverse cholesterol transport), lipoproteins that contain ApoB (LDL or VLDL-like), or both (Arai \textit{et al.} 1999, Trigatti \textit{et al.} 1999, Huszar \textit{et al.} 2000, Kozarsky \textit{et al.} 2000, Ueda \textit{et al.} 2000).

The influence of \textit{SR-BI} on plasma lipids or lipoproteins is not well known, because of the difficulty in determining \textit{SR-BI} activity and function in humans and the resulting absence of epidemiological studies. Although the physiological mechanism of action of \textit{SR-BI} in the postprandial lipemic response remains to be clarified, our findings suggest that the presence of the 2 allele could be related to an increased hepatic expression of the \textit{SR-BI} gene, with faster clearance of small-TRL. In contrast, the exon 1 polymorphism results in an amino acid change in the protein, but the functional effect of the mutation has not been determined. It seems unlikely that the polymorphism directly impairs selective cholesterol uptake, as this function has been shown to reside primarily in the extracellular domain of the receptor and this amino acid change occurs in its intracellular N-terminus. Although these results are preliminary, the fact that our study was carried out on healthy individuals in a controlled interventional trial could be the key to a better understanding of \textit{SR-BI} activity and its role in lipoprotein metabolism.

In conclusion, allele variability in the \textit{SR-BI} gene could partly explain the interindividual differences in postprandial lipemic response in healthy persons. New studies are needed, however, to elucidate if it is a specific effect of the polymorphism or if, instead, it is a consequence of an association in disequilibrium with other polymorphisms.

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consumption of diets with different fat content in healthy subjects. 

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