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Diet-gene interactions between dietary fat intake and common polymorphisms in determining lipid metabolism

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RESUMEN

Interacciones dieta-genotipo entre el consumo de grasas y polimorfismos comunes determinando el metabolismo lipídico.

Las recomendaciones dietéticas actuales referentes al consumo de grasas en la dieta han sido realizadas sin tener en cuenta las posibles diferencias genéticas de las personas que podrían ser las responsables de las diferentes respuestas interindividuales que frecuentemente se observan ante la misma dieta. La presencia de variabilidad genética ha sido puesta de manifiesto para todos los genes relacionados con el metabolismo lipídico, por lo que existe un ingente número de genes y de variantes genéticas para ser incluidas en los estudios sobre interacciones dieta-genotipo en el ámbito específico del consumo de grasas y aceites. Se revisarán algunos ejemplos sobre interacciones grasa-genotipo. Estas interacciones incluyen: la interacción entre el consumo de grasa total y el polimorfismo −514C/T en el promotor del gen de la lipasa hepática determinando las concentraciones de colesterol ligado a lipoproteínas de alta densidad (c-HDL); la interacción entre el consumo de ácidos grasos poliinsaturados y el polimorfismo −75G/A en el promotor del gen APOA1 en las concentraciones plasmáticas de c-HDL; la interacción entre los ácidos grasos poliinsaturados y el polimorfismo L162V en el gen PPARA determinando las concentraciones plasmáticas de triglicéridos y de apolipoproteína C-III; la interacción entre el polimorfismo −1131T>C en el promotor del gen de la APOA5 determinando el metabolismo de los triglicéridos. Aunque se han publicado cientos de estudios dieta-genotipo en el ámbito del metabolismo lipídico, el nivel de evidencia científica todavía es bajo para realizar recomendaciones nutricionales a la población, por lo que se requiere mucha más investigación nutrigenética.

PALABRAS CLAVE: Dieta – Genes – Interacción – Lípidos – Nutrigenética – Polimorfismos.

SUMMARY

Diet-gene interactions between dietary fat intake and common polymorphisms in determining lipid metabolism.

Current dietary guidelines for fat intake have not taken into consideration the possible genetic differences underlying the individual variability in responsiveness to dietary components. Genetic variability has been identified in humans for all the known lipid metabolim-related genes resulting in a plethora of candidate genes and genetic variants to examine in diet-gene interaction studies focused on fat consumption. Some examples of fat-gene interaction are reviewed. These include: the interaction between total intake and the −514C/T in the hepatic lipase gene promoter in determining high-density lipoprotein cholesterol (HDL-C) metabolism; the interaction between polyunsaturated fatty acids (PUFA) and the −75G/A polymorphism in the APOA1 gene plasma HDL-C concentrations; the interaction between PUFA and the L162V polymorphism in the PPARA gene in determining triglycerides and APOC3 concentrations; and the interaction between PUFA intake and the −1131T>C in the APOA5 gene in determining triglyceride metabolism. Although hundreds of diet-gene interaction studies in lipid metabolism have been published, the level of evidence to make specific nutritional recommendations to the population is still low and more research in nutrigenetics has to be undertaken.

KEY-WORDS: Diet – Genes – Interaction – Lipids – Nutrigenetics – Polymorphisms.

1. INTRODUCTION

Currently, there is a lot of controversy about which is the best diet to prevent or treat disease (Steinberg D, 2005; Getz et al., 2007; Rioux et al., 2007). Cardiovascular diseases are the leading cause of death in the World whether living in rich or in poor countries. The implication of plasma lipids in the atherosclerotic process that determines cardiovascular diseases has been known for many years (Le and Walter, 2007). However, lipid metabolism is a complex process in which different enzymes, receptors, transporters, lipoproteins, etc., are involved. Thus, from food intake to the plasma lipid concentrations detected, a great number of steps take place, than can differ considerably among individuals. It is therefore not surprising that many studies have been carried out with differing results when the relationship between diet and plasma lipids has been investigated (Katan, 2005; Brunner et al., 2007). Arising from this controversy several eating pyramids have been proposed: The healthy eating pyramid, the Mediterranean diet pyramid, the United States Department of Agriculture (USDA) pyramid, the World Health Organization (WHO) pyramid, etc (Chiuve and Willet, 2007). For several decades, the debate on diet and lipid metabolism and cardiovascular diseases has been dominated by the classic “diet-heart” hypothesis centered in the concept of the promotion of a low-fat diet

remnants, intermediate-density lipoproteins (IDL), and HDL. Patients with hepatic lipase deficiency present with hypercholesterolemia or hypertriglyceridemia and accumulate β-very low–density lipoproteins (VLDL), chylomicron remnants, IDL, triglyceride-rich LDL, and HDLs. Hepatic lipase is also an important determinant of HDL concentration, converting the phospholipid-rich HDL2 to HDL3 during reverse cholesterol transport. Four common SNPs (–763A > G; –710T > C; –514C > T and –250G > A) on the promoter of the hepatic lipase gene (LIPC), appear to be in total linkage disequilibrium and define a

identify common polymorphisms for subsequent genetic association studies. Several genetic variants have been identified (Pennacchio et al., 2003; Kluger et al., 2008). However, the most relevant are the –1131T > C, and the a C-to-G nonsynonymous substitution (c. 56C > G) that changes codon 19 from serine to tryptophan (S19W). These polymorphisms are tag SNPs of two independent haplotypes. The minor alleles of these polymorphisms have been associated with higher TG concentrations in several studies (Pennacchio et al., 2003). We analyzed the effect of PUFA consumption on plasma TG concentrations depending on the APOA5 polymorphisms (Lai et al., 2006). After multivariate control for potential confounders, a statistically significant interaction ($P < 0.001$) between SNP –1131T > C and PUFA intake (> 6% or < 6% of energy) on TG concentration was found. The –1131C allele was associated with an increase in fasting TG (21%, $P = 0.002$) only in subjects consuming > 6% of energy from PUFA. However, mean fasting TG concentrations were not statistically higher in carriers of the –1131C allele compared with the TT homozygotes when the PUFA consumption was low (< 6%) ($P = 0.600$). We observed similar and significant interactions between PUFA consumption and SNP –1131T > C on plasma remnant-like particles (RLP)-TG ($P < 0.001$) and RLP-C ($P < 0.001$). As observed for fasting TGs, concentrations of RLP-TG in subjects carrying the –1131C allele were increased ($P = 0.005$) when they consumed more than 6% of energy from PUFAs. When we analyzed the interaction of SNP –1131T > C and PUFA intake in determining LDL and VLDL sizes, we found statistically significant interactions ($P = 0.01$ and $P = 0.008$, respectively). These were consistent with a more atherogenic lipid profile in subjects carrying the –1131C allele and consuming more than 6% of energy from PUFAs. Thus, in carriers of the –1131C allele, a high PUFA intake was associated with smaller LDL particle size and also with larger VLDL size. Using the same statistical models in which fat intake was dichotomized according to its corresponding population mean, we did not uncover any significant interactions between the APOA5 –1131T > C SNP and intake of total fat, SFAs, or MUFAs on concentrations of TG, RLP-TG, or RLP-C or on LDL and VLDL particle size. This gene–diet interaction also showed a clear dose-dependent effect as well as a biologically plausible association consistent with the expected metabolic pathways involved. Moreover, the interaction observed for SNP –1131T > C was not shared by SNP 56C > G, which represents the other common haplotype. Because n-3 and n-6 FAs may differ in their potential preventive effect of hypertriglyceridemia (Le et al., 2007; Harris et al., 2008) we further investigated whether the PUFA-APOA5 interaction applied to the consumption of both families of PUFAs. Our results support the notion that the above-reported interactions are specific to (n-6) PUFA. The potentially negative effects associated with elevated lipoprotein remnant concentrations observed in carriers of the APOA5 –1131C allele who consume high n-6 PUFA were not observed for the consumption of n-3 PUFA.

3. FUTURE DIRECTIONS IN FAT-GENE INTERACTIONS

There are many studies that have shown the existence of common genetic polymorphisms with a great impact on plasma lipid concentrations such as APOE, APOA5, CETP, PPARA, etc. Moreover, there are various studies that have shown statistical significant diet-gene interactions between some of these polymorphism and different types of fat from the diet of (total fat, PUFA, SFA, etc). Although every day more and more studies are undertaken, the level of evidence in nutrigenomics is still too low to make nutritional recommendations to the population. Thus, specifically-designed interventional as well as observational studies are needed. In addition, new bioinformatic tools will be necessary for exploiting and integrating data. Although the current evidence from both experimental and observational nutrigenetics studies is not enough to start making specific personalized nutritional recommendations of fat intake based on genetic information, the accumulated information is enticing now to show proof of concept. Hence, in a few years the "genomic" profile will be an important factor to optimize nutritional recommendations of fat intake in lipid metabolism. An important development comes from the transition of diet-gene interactions from being a purely academic research activity, to become an area of great attraction of food and health-related industries, resulting from the potential of nutrigenetics of fat intake to become one of the greatest developments for the prevention of lipid-related disorders based on a more personalized approach.

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