J. Physiol. Biochem., **58** (4), 219-220, 2002

CHO intake alters obesity risk associated with Pro12Ala polymorphism of PPARγ gene

Obesity in humans results from combined effects of genes, environment and lifestyles (3, 9). Therefore, a case-control study (obese vs. lean controls) was conducted to assess the possible association between obesity risk and the Pro12Ala polymorphism of the PPAR gamma gene depending on the dietary intake.

The study population comprised 313 Spanish subjects (66 men), which were gender and age-matched. In total 159 obese patients (BMI 37.7 ± 5.3 Kg/m^2) and 154 normal weight subjects (BMI 22.0 ± 1.8 Kg/ m^2) were selected (20-60 years old). Dietary intake was assessed through a validated food frequency questionnaire for epidemiological studies (8). Plasma insulin was measured by radioimmunoassay (DP Corporation) and plasma leptin by enzymeimmunoassay (EIA-1843). Also, blood samples were taken for the extraction of genomic DNA from leukocytes as previously described (2, 6) in order to identify Pro12Ala gene polymorphism carriers and to assess the allele frequency for the Ala12 gene polymorphism by PCR-RFLP (7). A Student-*t* test was used to assess the differences between the selected variables in case and control groups, while different equations were modelled using unconditional multiple linear or logistic regressions to analyse the relationship between the macronutrient intake and BMI obesity risk.

The Pro12Ala gene polymorphism distribution was similar for case and controls as previously reported in other Caucasian populations (1, 10). Thus, the 12Ala polymorphism was found in 21.4% of the obese and in 19.5% of the controls, with the allelic frequency of 0.11 in cases (obese subjects) and 0.10 in controls (lean individuals). As expected, the phenotype characteristics concerning BMI, insulin and leptin were statistically different between obese and lean individuals from this population, however, no statistical differences were found among subjects when these variables were categorised according to the presence or absence of the polymorphism. The observed marginal shift in insulin levels (R=0.054) between the subjects depending on the polymorphism is in agreement with data from other studies (1, 3, 10). The carbohydrate intake reported by the examined population was not statistically different among groups ($p>0.05$). When the association between the Ala12 polymorphism and obesity risk was analysed by a logistic regression model, obesity incidence was not affected by the Ala12 polymorphism (ORa=1.18; p=0.573; IC95%:0.66-2.09). However, the macronutrient distribution of the intake appeared as an effect modifier, since among those individuals with higher carbohydrate intake (>49% E), an increased obesity risk (ORa=5.12, $p<0.04$; IC95%:1.01-25.80) accompanied the occurrence of the polymorphism. The product-term introduced in the multivariable model to assess effect modifications also revealed a significant interaction ($p<0.02$) between both factors (Fig. 1).

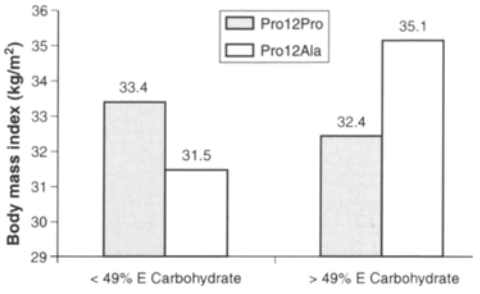

Fig. 1. *Body mass index categorised according to the presence of the Pro12Ala polymorphism and the carbohydrate intake* (p interaction= 0.02).

This gene-nutrient interaction emphasizes the interest of examining the outcome of some polymorphisms depending on lifestyle (diet) and may explain the heterogeneity of findings from previous studies (4). This current analysis revealed that the effect of the 12Ala mutation on obesity risk was modified by the macronutrient composition of the dietary intake when adjusted by age and gender. Our data complement a previous study reporting the influence of the dietary fat intake on the Pro12Ala polymorphism for the PPAR Locus (5) on obesity risk.

However, despite that the studied gene polymorphism had no direct effect on obesity risk, this information suggests that heterogeneous responses to different dietary situations (like macronutrient distribution or weight-reducing approaches) are compatible with the hypothesis that there are individual differences in the susceptibility to dietary intake (5, 9) and supports that gene-diet interactions have a role in obesity onset and prevalence as well as in the dietary management of obesity.

Correspondence to J. Alfredo Martínez (Tel.: +34 948 425 600 ext. 6424; Fax: +34 948 425 649; e-mail: jalfmtz@unav.es).

Key words: Obesity risk, Pro12Ala PPAR gene polymorphism, Diet.

References

1. Clement, K., Hercberg, S., Passinge, B., Galan, P., Varroud-Vial, M., Shuldiner, A. R., Beamer, B. A., Charpentier, G., Guy-Grand, B., Froguel, P. and Vaisse, C. (2000): *Int J. Obes.*, **24**, 391-393.
2. Corbalán, M. S., Marti, A., Forga, L., Martínez-González, M. A. and Martínez, J. A. (2002): *Ann. Nutr. Metab.*, **46**, 152-158.
3. Deeb, S. S., Fajas, L., Nemoto, M., Pihlajamaki, J., Mykkanen, L., Kuusisto, J., Laakso, M., Fujimoto, W. and Auwerx, J. (1998): *Nat. Genet.*, **20**, 284-287.
4. Kadowaki, T., Hara, K., Kubota, N., Tobe, K., Terauchi, Y., Yamauchi, T., Eto, K., Kadowaki, H., Noda, M., Hagura, R. and Akanuma, Y. (2002): *J. Diabetes Complication*, **16**, 41-45.
5. Luan, J., Browne, P., Harding, A. H., Halsall, D. J., O'Rahilly, S., Chatterjee, V. K. and Wareham, N. J. (2001): *Diabetes*, **50**, 686-689.
6. Macho, T., Calabuig, J., Marti, A., Martínez, J A. (2002): *J. Physiol. Biochem.*, **58**, 103-109.
7. Mori, Y., Kim-Motoyama, H., Katamura, T. *et al.* (1998): *Biochem. Biophys. Res. Commun.*, **251**, 195-198.
8. Martín-Moreno, J. M., Boyle, P., Gorgojo, L. Maisonneuve, P., Fernández-Rodríguez, J. C., Salvini, S. and Willet, W. C. (1993): *Int. J. Epidemiol.*, **22**, 512-519.
9. Peruse, L. and Bouchard, C. (2000): *Am. J. Clin. Nutr.*, **72**, 1285-1290.
10. Valve, R., Heikkinen, S., Rissanen, A., Laakso, M. *et al.* (1999): *Clin. Endocrinol. Metabol.*, **83**, 950-957.

A. Marti, M. S. Corbalán, M. A. Martínez-González, L. Forga, and J. A. Martínez

University of Navarra. Department of Physiology and Nutrition, Pamplona (Spain)

(Received on September 17, 2002)