The Pro12Ala variant of the peroxisome proliferator-activated receptor γ2 gene influences insulin sensitivity in healthy subjects participating in the RISC study

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Introduction

• The thiazolidinediones (TZDs) are insulin-sensitizing agents used in the treatment of type 2 diabetes, and mediate their effects through the nuclear transcription factor, peroxisome proliferator-activated receptor PPARγ.

• This is echoed by the PPARγ gene, which has been found to be a type 2 diabetes susceptibility gene.

• The Pro allele of the Pro12Ala variant was shown to confer an increased risk of type 2 diabetes. 1 The Pro12Ala variant was also shown to influence insulin sensitivity in vitro, with evidence suggesting that this is mediated through altered body composition. 

• Frederiksen et al (2002) studied a cohort of non-diabetic Caucasian subjects and found that subjects homozygous for the Ala allele had decreased levels of serum triglyceride and diastolic blood pressure.2 However, there was no clear association with insulin sensitivity as assessed by HOMA.

Aims

The aims of this study were to investigate the relationship between the Pro12Ala variant and whole body insulin sensitivity determined by the hyperinsulinaemic clamp technique in a cohort of healthy Caucasians.

Subjects and methods

• Healthy subjects aged 30–60 years were recruited at 19 centres in 13 European countries as part of the RISC (Relationship between Insulin Sensitivity and Cardiovascular Disease) study, to investigate the role of insulin resistance in the development of cardiovascular disease. Participating centres are shown in Figure 1.

• A range of data was collected, which included anthropometric, demographic and lifestyle data.

• In addition each subject underwent oral glucose tolerance test (OGTT) and euglycaemic hyperinsulinaemic (40 mU/m2/min) clamp.

• Here we report on 1278 subjects who completed the baseline studies and for whom DNA was extracted and available for genotyping.

Statistical analysis

• Statistical analyses were carried out using Minvite version 12.

• Skewed variables were log transformed to normalise distributions. P values <0.05 were considered significant. The M value, as a measure of insulin sensitivity, was calculated and adjusted for lean body mass and free fat mass.

• The genotype-phenotype association was tested by ANOVA and P values <0.05 were considered significant. The M value, as a variable (Data presented as means [SE])

Table 2

Analysis of Covariance (PPARγ (Pro12Ala) (age, sex, BMI, waist and centre adjusted) (Data presented as means [SE])

Conclusions

We confirm that the Pro12Ala variant PPARγ gene influences insulin sensitivity in the healthy population. Specifically, subjects homozygous for the Pro allele are more insulin sensitive compared to the rest of the population, and this appears in part to be independent of differences in circulating triglyceride levels and medians of adiposity.

References


Further information on the RISC project and participating centres can be found on www.egir.org.