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Genetics and Pharmacogenomics

3.4 Overexpression of the Cannabinoid CB1 Receptor in Visceral Adipose Tissue of Overweight Patients with Dysmetabolism

R. Sarzani, M. Bordicchia, P. Marcucci, L. Scappini, A. Giovagnoli, F. Salvi, S. Santini, S. Bedetta, P. Dessì-Fulgheri, A. Rappelli

Department of Internal Medicine - University Politecnica delle Marche, Ancona, Italy

Introduction: Overweight patients has an hyper-activation of endocannabinoid system (ECBS) acting through their CB1 receptor. Rimonabant, a CB1 receptor blocker, was able to reduce cardiovascular risk factors and systolic blood pressure in overweight patients. About 50% of rimonabant effects were through by peripheral CB1 such as those in adipose tissue. The aims of this study was to characterised CB1 splice variants and CB1 gene expression in visceral (VAT) and subcutaneous adipose tissues (SAT) and analyse the relationship with anthropometric and metabolic parameters. The messenger levels of the fatty acid amide hydrolase (FAAH) that inactivates the endogenous cannabinoids was also evaluated.

Methods: Samples of VAT were obtained from 36 consecutive patients undergoing nephrectomy (from 12 patients SAT was also sampled). CB1 splicing variants were analysed by PCR, semi-quantitative determination and sequencing; gene expression was studied by RealTime Taq-Man assay and mRNA levels were calculated relative to GAPDH. Clinical data were obtained before surgery.

Results: Adipose tissue is characterised by the presence of CB1E variant and an even higher level of CB1A. CB1 receptor expression in normal-weight (NW) patients (BMI>25) CB1 receptor expression was about 1.5 fold higher in TAV (P=0.05). When CB1 expression was compared between same adipose depots a significant higher expression was found in SAT of NO (P=0.015) tied with an higher expression in TAV of OW (P=0.011). FAAH gene analysis showed an higher expression in TAV than SAT of OW (P=0.012) and the comparison between same depots revealed a lower expression in SAT of OW than in NO (P=0,006). This altered CB1 expression pattern in OW was also associated with higher levels of waist circumference.

Conclusions: In human adipose tissues are presents two of five alternative splice variants characterised by the presence of the main encoding exon 4. OW patients with dysmetabolism showed a gene expression pattern that suggested an hyperactivity of ECBS in visceral adipose tissue and an increased local endocannabinoid production with secondary FAAH overexpression. Such expression pattern in adipose tissue was associated also with features of the metabolic syndrome.