Schizophrenia Research 121 (2010) 213–217

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Polymorphisms of the *LEP*- and *LEPR* genes, metabolic profile after prolonged clozapine administration and response to the antidiabetic metformin

Erika Fernández [a], Edgardo Carrizo [a], Virginia Fernández [a], Lisette Connell [a], Ignacio Sandia [b], Dexy Prieto [c], Johana Mogollón [b], Dennys Valbuena [d], Iliana Fernández [d], Enma Araujo de Baptista [e], Trino Baptista [f,*]

[a] *Institute of Clinical Research "Dr. Américo Negrette", Zulia University Medical School, Maracaibo, Venezuela*
[b] *Department of Psychiatry, Los Andes University Hospital, Mérida, Venezuela*
[c] *Department of Psychiatry, Zulia University Medical School and IVIC Zulia, Maracaibo, Venezuela*
[d] *CATESFAM, Maracaibo, Venezuela*
[e] *Department of Microbiology, Pharmacy School, Los Andes University, Merida, Venezuela*
[f] *Department of Physiology, Los Andes University Medical School, P.O. Box 93, Mérida, 5101-A, Venezuela*

ARTICLE INFO

Article history:
Received 26 March 2010
Received in revised form 26 May 2010
Accepted 1 June 2010
Available online 29 June 2010

Keywords:
Atypical antipsychotics
Antidiabetics
Genotype
Leptin
Metabolic syndrome
Obesity
Receptors

ABSTRACT

Background: The role of leptin in atypical antipsychotic-induced metabolic dysfunction was explored by assessing the anthropometric and metabolic profile and the response to metformin (MET) of clozapine- (CLZ) treated schizophrenia patients according to their single nucleotide polymorphisms (SNPs) in the leptin promoter (*LEP*2548/GA) and leptin receptor (*LEPR* Q223R) genes.
Methods: Phase 1. Body mass index (BMI), waist circumference, serum glucose, HbA1C, lipids, leptin, cortisol, insulin resistance index (HOMA-IR), metabolic syndrome and the frequencies of SNPs were assessed in 56 CLZ-treated patients (78.6% males). *Phase 2.* Fifty two phase 1 subjects were randomly assigned to MET XR (n = 23) (1000 mg/day) or placebo (n = 29) for 14 weeks. Changes in anthropometric and biochemical variables were compared between the SNPs.
Results: Phase 1. The QQ group displayed the lowest triglyceride levels ($p<0.05$). No other significant difference was observed. *Phase 2.* Change in anthropometric variables did not differ between the genotypes in any treatment group. After MET, glucose levels significantly increased in the GG group ($p<0.05$), whereas the HOMA-IR and the low density cholesterol significantly decreased in the QQ- but not in the (QR + RR) group ($p<0.05$). No differences were observed after placebo.
Conclusions: BW response to CLZ was not related to *LEP*- and *LEPR*-SNPs. The GG and (QR + RR) genotypes showed an unexpectedly opposite and blunted response to MET administration respectively.

1. Introduction

Olanzapine and clozapine (CLZ) are the atypical antipsychotics (AAPs) with the highest propensity to induce body weight (BW) gain and metabolic dysfunction. A role for leptin (LEP) was suggested (Melkersson et al., 2000), but it was not confirmed either in cross-sectional (Haupt et al., 2005; Peña et al., 2008) or longitudinal studies (Baptista et al., 2007a).

Recent reports have focused on the association between BW gain and the *LEP* promoter 2548G/A (rs7799039, chromosome 7q31.3) and the leptin receptor (*LEPR*) Q223R (rs1137101, chromosome 1p31) single nucleotide polymorphisms (SNPs).

Regarding *LEP* 2548G/A SNPs, positive associations for BW gain were reported for AA (Zhang et al., 2003), G/A (Kang et al., 2008; Zhang et al., 2007) and GG (Templeman et al., 2005). A significant inverse association was found for the GG genotype (Calarge et al., 2009), and negative results were reported by Ellingrod et al. (2007), Gregoor et al. (2009) and Ryu et al. (2006). Gregoor et al. (2009) reported that the QR

* Corresponding author. Tel.: +58 416 676 0320.
E-mail address: trinbap@yahoo.com (T. Baptista).

0920-9964/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2010.06.001

and RR genotypes were associated with a lower risk of obesity in females but not in males during AAP treatment. These studies point to gender, age, and ethnicity among many other intervening variables.

This study was conducted in subjects who, after prolonged CLZ administration, entered a trial to assess the effects of metformin (MET) (Carrizo et al., 2009a,b). Clinical (Baptista et al., 2007b; Eriksson et al., 2007; Fruehwald-Schultes et al., 2002; Marciniak et al., 2009; Sivitz et al., 2003) and experimental studies (Li et al., 2005, Kim et al., 2006; Klein et al., 2004; Mick et al., 2000; Mueller et al., 2000) suggest that MET decreases leptin synthesis and serum levels and improves leptin and insulin sensitivity.

We thus evaluated the frequency of the metabolic syndrome and obesity, anthropometric and biochemical variables before and after randomization to MET or placebo. Baseline values and post-treatment changes were compared between the genotypes.

2. Methods

The study was conducted in CATESFAM, Maracaibo, Venezuela, and was approved by the corresponding ethics committee. All participants signed a voluntary informed consent.

Inclusion criteria were to be under CLZ treatment for 3 or more consecutive months, over 18 years of age, free of hormone replacement therapy and have normal physical and laboratory tests.

2.1. Study design and randomization (Fig. 1)

2.1.1. Phase 1

The following variables were assessed in fasting conditions: BW, height, waist circumference, arterial pressure and blood glucose, insulin, lipids, glycated hemoglobin (HbA1C), cortisol and leptin. Body mass index (BMI) = weight (kg)/height squared and insulin resistance index (HOMA-IR = glucose [mmol/L × dL] × insulin [μU/mL]/22.5) were calculated.

2.1.2. Phase 2

The patients were randomly assigned to either MET (Glucophage XR, Merck, Venezuela, 1000 mg daily) or placebo in a double-blind protocol.

After 14 weeks of treatment, the variables mentioned in phase 1 were assessed.

2.2. Chemical analysis

Glucose and lipids were measured with an enzymatic method from Humans (Germany). Insulin, leptin and cortisol were assessed by duplicate by ELISA (DRG, Germany). HbA1C levels were measured by a latex immunoagglutination inhibition method from DCA (Siemens, Canada).

2.3. Genotyping

Genomic DNA was isolated from peripheral leukocytes according to Miller et al. (1988) and Ausubel et al. (1989). Genotyping was conducted by restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR) (Snoussi et al., 2006).

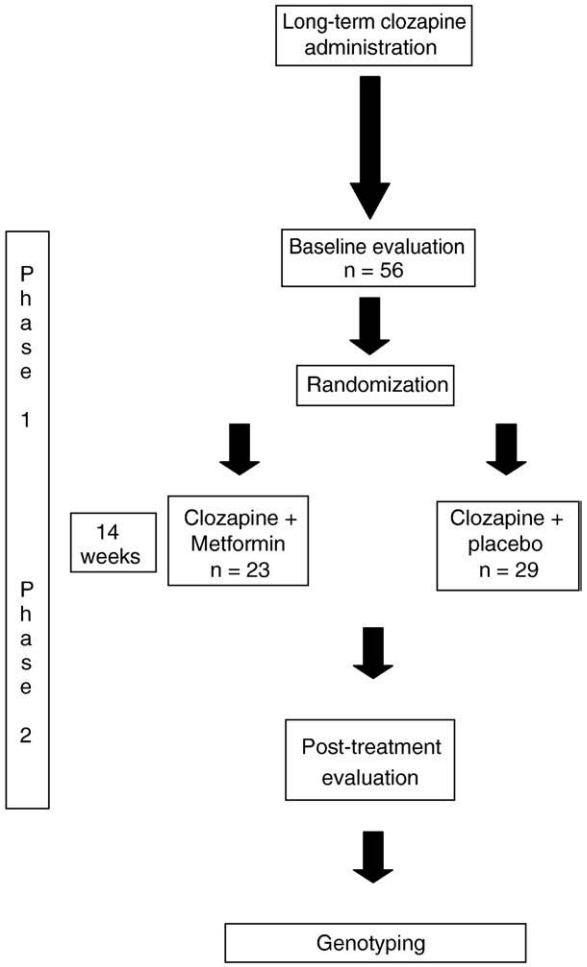

Fig. 1. Study design.

We used the 2548G/A and Q223R nomenclature. The GG and QQ are the "wild type" homozygotic genotypes. The (GA/AA) and (QR/RR) variants are the heterozygotic and homozygotic genotypes.

2.4. Statistical analysis

Separate analyses were conducted for the *LEP* 2548G/A and the *LEPR* Q223R SNPs. Two groups were formed: one comprising the wild-type homozygotic genotype (GG for the *LEP* 2548G/A and QQ for the *LEPR* Q223R), and another, the (GA + AA) and (QR + RR) heterozygotic and homozygotic genotypes.

2.4.1. Phase 1

The frequency of the metabolic syndrome (MS, Third Report of the National Cholesterol Education Program, 2002), obesity (BMI > 30 kg/m^2) and individual variable averages were compared between the two groups using the chi square, the two-tailed *t* test for unrelated samples and the univariate general linear model (for covariance analysis). Pearson bivariate correlation analyses were conducted between CLZ dose/treatment duration and each variable.