Prostaglandins, Leukotrienes and Essential Fatty Acids 91 (2014) 221–225

Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

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

PPARα-L162V polymorphism is not associated with schizophrenia risk in a Croatian population

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ARTICLE INFO

Article history:
Received 28 February 2014
Received in revised form
18 June 2014
Accepted 4 July 2014

Keywords:
L162V polymorphism
Peroxisome proliferator-activated receptor alpha
Positive and Negative Symptom Scale
Schizophrenia

ABSTRACT

Disturbances of lipid and glucose metabolism have been repeatedly reported in schizophrenia. A functional L162V polymorphism in peroxisome proliferator-activated receptor alpha (PPARα) gene has been extensively investigated in etiology of abnormal lipid and glucose metabolism, yet not in schizophrenia. We determined whether the schizophrenia risk was associated with L162V polymorphism and we examined the impact of L162V variant on age of onset, and data of psychopathology scores. We also hypothesized that plasma glucose and lipid concentrations in patients may be influenced by L162V polymorphism. Genotype and allele frequencies between 203 patients and 191 controls did not differ significantly. Females heterozygous for the PPARα genotype (L162V) manifested significantly lower negative symptom scores, tended toward an earlier onset, and had significantly greater triglyceride levels. The PPARα-L162V polymorphism is not associated with schizophrenia risk in Croatian population, but it impacts clinical expression of the illness and plasma lipid concentrations in female patients.

1. Introduction

Peroxisome proliferator-activated receptor alpha (PPARα) is a ligand-activated transcription factor that belongs to the nuclear steroid receptor superfamily [1,2]. Activated by its ligand, PPARα heterodimerizes with retinoid X receptor, and binds to peroxisome proliferator response elements in the promoter region of genes to modulate their expression [2,3]. Due to its role in regulation of the expression of genes involved in fatty acid uptake, transport, β- and ω-oxidation, and ketogenesis, PPARα represents an important mediator of lipid and glucose metabolism [2,3]. Dietary fatty acids, particularly long chain polyunsaturated fatty acids (LC-PUFAs), such as arachidonic acid (20:4$n-6$, ARA), eicosapentaenoic acid (20:5$n-3$, EPA) and docosahexaenoic acid (22:6$n-3$, DHA) are known to be potent natural ligands of PPARα [3,4]. Several experiments in animal models suggest that PPARα may act as an important sensor of LC-PUFA status in organism [5,6]. It has been established that under conditions of essential fatty acid deficiency PPARα can enhance LC-PUFA synthesis from precursor PUFAs, such as linolenic acid (18:2$n-6$, LA) and alpha linolenic acid (18:3$n-3$, ALA), by increasing activity of Δ^6- and Δ^5-desaturases and elongases [6,7].

Patients with schizophrenia have significantly increased risk of developing diabetes, dyslipidemia and obesity, while mortality from coronary artery disease is two to three times greater than in the general population [8,9]. Treatment with antipsychotic medications particularly increases abnormalities in glucose and lipid metabolism in schizophrenia [8,10]. Furthermore, PUFA deficits both in red blood cell (RBC) membranes and postmortem brain tissues have been extensively reported in schizophrenia [11–14]. Decreased RBC membrane PUFA levels in patients with schizophrenia, mainly attributed to lower contents of LA, EPA and DHA, have been previously reported in our study as well [15].

To date, only one study, performed in the Japanese population, has been investigated association between PPARα gene polymorphic variations and etiology of schizophrenia [16]. However, no association between investigated Val227Ala polymorphism of the PPARα gene and risk for schizophrenia has been reported in their study [16]. Furthermore, there are no reports of Val227Ala polymorphism in the European population [17]. The leucine 162 valine (L162V) polymorphism, caused by a C to G transversion in exon 5, is the most studied variant of the PPARα gene [4,18]. While the influence of PPAR-L162V polymorphism has been intensively studied in dyslipidemia, some measures of adiposity, risk for coronary ischemic events, and age of onset in patients with diabetes [3,18–20], the relevance of L162V polymorphic variation on lipid and glucose metabolism in patients with schizophrenia has not been investigated so far. The less common V allele, the

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http://dx.doi.org/10.1016/j.plefa.2014.07.003
0952-3278/

frequency of which varies from from 2–4%, however, was found exclusively in the European population [21]. To date, several studies have reported gender specific differences in L162V genotype effect on lipid metabolism [3,22,23].

Because PPARα gene is a key regulator of glucose and lipid homeostasis, variations of this gene could possibly contribute to the etiology of schizophrenia, or may influence its clinical expression. We aimed to determine whether the risk for schizophrenia was associated with L162V polymorphism of the PPARα gene in the Croatian population, and to examine the possible impact of the L162V polymorphism on mean age of onset, and baseline psychopathology data, measured via Positive and Negative Symptom Scale (PANSS) scores, in the patient group. We further hypothesized that PPARα-L162V polymorphism may influence plasma glucose and lipid concentrations in patients with schizophrenia.

2. Patients and methods

2.1. Study participants

Our study group was comprised of 203 chronically ill schizophrenia patients (111 males and 92 females), recruited from the Department of Psychiatry, Clinical Medical Centre in Rijeka, Croatia ($n=110$), and Psychiatric Hospital in Rab, Croatia ($n=93$), between 2007 and 2010, and 191 non-psychiatric control subjects (87 males and 104 females). Rijeka and the island of Rab belong to the same geographic area. Patients' clinical data are presented in Table 1. Diagnoses were assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria using the structured clinical interview. Age of onset was obtained from medical records and determined as the patient's age at the time at their first hospital admission due to a psychotic episode at which the diagnosis of schizophrenia was used. Evaluation of PANSS psychopathology was performed at the time of last admission, during an acute state of the illness requiring hospitalization. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. After the study's purpose and methods had been described, all participants provided written informed consent to participate in the study, which had been approved by the Ethics Committee of the School of Medicine, University of Rijeka, Croatia.

The control individuals were blood donors who underwent no specific examination for psychiatric status, but declared no psychiatric records. The practice with blood donation in Croatia includes providing a written statement about health status at every session. Therefore, blood donors are representatives of healthy general population, free of chronic diseases or regular medication.

2.2. Methods

2.2.1. Genotyping

Genomic DNA was extracted from whole blood using a Flexi-Gene DNA kit 250 (QIAGEN GmbH, Hilden, Germany) according to the manufacturer's instructions. Genotyping was performed in the Laboratory for Molecular Genetics (Department of Biology and Medical Genetics, School of Medicine, Rijeka) by polymerase chain reaction/restriction fragment length polymorphism analysis using protocol previously described [24].

2.2.2. Biochemical measurements

Venous blood samples were collected from fasting patients. Plasma was separated by centrifugation at 1100*g* for 10 min from blood cells and used immediately for the determinations of glucose, total cholesterol and triglycerides. The analyses were carried out in the Department of Clinical Laboratory Diagnostics of the Clinical Medical Centre Rijeka. Fasting plasma glucose levels ≥ 7.0 mmol/l, total cholesterol levels > 5.0 mmol/l and triglyceride levels > 2.0 mmol/l were considered elevated for the Croatian population [25].

2.2.3. Statistical analysis

Descriptive statistics was used to calculate the mean ages and mean PANSS scores in the patient group. Genotype and allele distributions between patients and controls, as well as observed and expected genotype proportions under Hardy–Weinberg equilibrium, were compared by the χ^2-test. The *t*-test was applied to compare the means of investigated clinical and biochemical measurements in patients with schizophrenia according to PPARα genotypes.

The association between several clinical features (mean age at first hospital admission, and positive, negative, general and total PANSS scores) and PPARα genotypes, as possible predictors, was tested using multiple stepwise regression analysis, adjusted for age at PANSS assessment, and sex, in patients with schizophrenia.

Table 1
Clinical and biochemical features according to PPARα genotypes.

Patients ($n=203$)		**L162L**	**L162V**	***t***	***p***
Age (years)	Males	42.8 ± 12.3	40.1 ± 8.8	−1.20	n. s.
	Females	44.6 ± 11.7	39.1 ± 8.8	−0.60	n. s.
Age at first hospital admission	Males	26.1 ± 7.7	26.5 ± 5.6	0.18	n. s.
	Females	29.0 ± 9.1	22.4 ± 5.0	1.88	n. s.
PANSS positive symptoms score	Males	26.8 ± 5.5	26.2 ± 4.5	−0.28	n. s.
	Females	26.1 ± 5.1	28.8 ± 5.7	−1.22	n. s.
PANSS negative symptoms score	Males	29.3 ± 5.9	31.7 ± 6.7	0.93	n. s.
	Females	30.0 ± 5.8	24.0 ± 7.6	2.34	< 0.05
PANSS general psychopathology score	Males	52.1 ± 6.8	52.8 ± 8.3	0.25	n. s.
	Females	52.9 ± 6.9	53.7 ± 3.6	−0.31	n. s.
PANSS total score	Males	108.2 ± 13.3	110.7 ± 18.0	0.42	n. s.
	Females	109.0 ± 13.1	106.5 ± 9.8	0.46	n. s.
Body mass index (kg/m^2)	Males	26.8 ± 3.8	25.6 ± 4.8	−0.44	n. s.
	Females	26.9 ± 4.5	29.2 ± 5.1	0.99	n. s.
Glucose (mmol/L)	Males	5.7 ± 1.2	5.4 ± 1.1	0.65	n. s.
	Females	5.7 ± 1.0	5.8 ± 0.7	0.24	n. s.
Total cholesterol (mmol/L)	Males	5.4 ± 1.5	4.4 ± 1.4	1.02	n. s.
	Females	5.8 ± 1.0	5.4 ± 1.3	0.53	n. s.
Triglycerides (mmol/L)	Males	2.1 ± 1.2	1.7 ± 1.2	0.53	n. s.
	Females	1.5 ± 0.7	2.4 ± 1.0	2.09	< 0.05