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Glial Cell Line-Derived Neurotrophic Factor (GDNF) serum level in women with schizophrenia and depression, correlation with clinical and metabolic parameters

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ABSTRACT

Aim: Neurotrophic factors have been implicated in neuropsychiatric disorders, including schizophrenia and depression. Glial Cell Line-Derived Neurotrophic Factor (GDNF) promotes development, differentiation, and protection of dopaminergic, serotonergic, GABAergic and noradrenergic neurons as well as glial cells in different brain regions. This study examined serum levels of GDNF in schizophrenia and depression and its correlation with metabolic parameters during 8 weeks of treatment.

Methods: Serum GDNF level, fasting serum glucose and lipid profile were measured at baseline and week 8 in 133 women: 55 with schizophrenia, 30 with a first episode depression and 48 healthy controls. The severity of the symptoms was evaluated using Positive and Negative Syndrome Scale (PANSS), 17-item Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI).

Results: There was statistically significant higher GDNF level in schizophrenia at baseline when compared with week 8. Correlations of GDNF with PANSS in schizophrenia and cholesterol level in depression have also been detected.

Conclusions: To our knowledge, this is the first study which correlates GDNF levels with metabolic parameters. Our results show no differences in GDNF serum level between schizophrenia, a first depressive episode, and healthy controls. GDNF serum level did not correlate with metabolic parameters except for total cholesterol in depression.

1. Introduction

Neurotrophic factors, implicated in neuropsychiatric disorders (such as schizophrenia or depression), are crucial modulators in the neurodevelopment and maintenance of central and peripheral nervous systems (Angelucci et al., 2004; Duman et al., 1997; Ibanez and Andressoo, 2017; Shoval and Weizman, 2005). Neurodevelopmental hypothesis of schizophrenia and depression postulates that the changes in the brains of patients are the result of disturbances of developing processes involving neurotrophic factors, different signaling pathways and life events (Lima-Ojeda et al., 2017; Qin et al., 2017).

Glial Cell Line-Derived Neurotrophic Factor (GDNF) is a member of the transforming growth factor-β (TGF- β) superfamily, along with neurturin (NRTN), artemin (ARTN) and persephin (PSPN). GDNF exerts its biological effects through the Ret receptor tyrosine kinase and a multicomponent receptor complex, known as GDNF family receptor alpha 1 (GFRα−1), to activate the PI3K/Akt and MAPK signaling pathways (Lin et al., 1993). GDNF, widely expressed in the brain, is a potent neurotrophic factor for dopaminergic neurons (Ducray et al., 2006; Naumenko et al., 2013; Pozas and Ibanez, 2005), thus its role in Parkinson's disease has been extensively investigated (Ibanez and Andressoo, 2017). GDNF can increase neurite growth in various neuronal types: dopaminergic, serotonergic, noradrenergic and GABAergic as well as glial cells (Ducray et al., 2006; Takaku et al., 2013; Wakeman et al., 2014). Its receptors are detected in many brain regions, including the hippocampus, which is known to be involved in the pathogenesis of psychiatric disorders (Irala et al., 2016). GDNF has been associated with the modulation of synaptic plasticity and the formation of neural

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circuits (Airaksinen and Saarma, 2002); it also protects neurons and glial cells against oxidative stress (Golan et al., 2011). Moreover, it has been reported to be related to cognitive functions, including learning and memory in animals (Gerlai et al., 2001).

Genetic association studies have been conducted for GDNF and its receptor polymorphisms in schizophrenia (Lee et al., 2001; Ma et al., 2013; Michelato et al., 2004) and mood disorders (Kotyuk et al., 2013; Ma et al., 2013; Wang et al., 2014), indicating association of GDNF with individual variability of anxiety (Kotyuk et al., 2013) and depression (Ma et al., 2013). In vitro and animal studies show that antipsychotic, antidepressant and electroconvulsive therapy elevate GDNF expression in different brain regions and in peripheral blood (Ibanez and Andressoo, 2017; Maheu et al., 2015). Post-mortem study revealed increased GDNF level in the parietal cortex and non-significant trend towards an overall increase in cortical regions, the cingulate cortex and the basal ganglia in depression (Michel et al., 2008).

Metabolic dysregulation influences the brain function, therefore the disturbances in peripheral glucose regulation might be associated with cognitive impairment and depressed mood. Depression, as well as schizophrenia, are highly associated with obesity, metabolic syndrome and type-2 diabetes (Lang and Borgwardt, 2013; Malhotra et al., 2013; Rzewuska, 2007). Data from population-based cohort studies show an association of depression (Ohmori et al., 2017) and schizophrenia (Cordes et al., 2016) with metabolic syndrome and impaired glucose metabolism. Studies also indicate GDNF involvement in glucose and lipid metabolism. In rodents, GDNF and its receptors are expressed in the areas of the hypothalamus known to regulate food intake. Animal studies have shown that chronic hypothalamic or nigrostriatal expression of GDNF protects against high-fat diet-induced obesity and might induce weight loss in age-related obesity through promoting lipolysis and energy expenditure (Mwangi et al., 2014). GDNF is a neurotrophic factor that plays a critical role in the development and survival of the enteric nervous system; overexpression of GDNF in pancreatic glia improves glucose tolerance (Mwangi et al., 2008).

1.1. Aims of the study

In this study, we compared serum levels of GDNF (at baseline and after 8 weeks of treatment) between women diagnosed either with schizophrenia or the first depressive episode and healthy controls. We studied the correlation of GDNF serum level with demographical, clinical and metabolic parameters.

To the best of our knowledge, this is the first study to examine the correlations of GDNF levels and metabolic parameters in psychiatric disorders.

2. Methods

2.1. Participants

Initially, 183 participants were recruited. 62 patients with schizophrenia (57 females, 5 males), 61 patients with depression episode (42 females and 19 males) and 69 healthy controls (48 females and 21 males). The group with depression episode consisted of 30 drug-free female outpatients and 31 inpatients (12 females and 19 males), diagnosed with bipolar affective disorder (n = 30) or unipolar affective disorder (n = 1). 2 female patients with schizophrenia withdraw their consent for participation in the study. During recruitment, male patients more often refused to take part in the study, resulting in the sex ratio disproportion. Therefore, in the present study, we have decided to include only women to improve the homogeneity of the studied subgroups. Ultimately, the study was performed on a group of 133 women: 55 diagnosed with schizophrenia (mean age 32,36 years, SD = 9.88), 30 diagnosed with a first episode of depression (mean age 38.07 years, SD = 10.21) and 48 healthy controls (mean age 40.18 years, SD = 14.07). A consensus diagnosis of schizophrenia or the first episode of depression was made by two experienced psychiatrists for each patient using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, 1996). All patients were evaluated for lifetime psychiatric symptomatology using the Operational Criteria for Psychotic Illness (OPCRIT) (McGuffin et al., 1991). Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and self-reported Beck Depression Inventory (BDI) (Beck et al., 1961) were used to assess severity of schizophrenia (PANSS) and depression (HDRS, BDI). In the schizophrenia group, there were 19 patients with a first episode. All patients with schizophrenia received atypical antipsychotics, 24 additionally typical antipsychotics (haloperidol (n = 19), zuclopenthixol (n = 5)). All patients (n = 30) with depression were drug-free. Patients with depression were randomly chosen for treatment with sertraline (SSRI - selective serotonin reuptake inhibitor) or venlafaxine (SNRI - serotonin-norepinephrine reuptake inhibitor). Clinical characteristics of the group are presented in Table 1.

Table 1
Clinical description of the studied groups.

	Schizophrenia	Depression	Control
Number (n)	55	30	48
Age, (years ± SD)	32.36 ± 9.88	38.06 ± 10.21	40.18 ± 14.06
Age af onset, (years ± SD)	22.85 ± 4.93	35.16 ± 8.4	
Early age of onset (≥18 years) (n)	9	0	
Drug free (n)	19	30	
Medication			
Typical antipsychotics (n total)	24		
Haloperidol (n)	19		
Zuclopenthixol (n)	5		
Atypical antypsychotics (n total)	55		
Sertraline		15	
Venlafaxine		15	

Participants were recruited from inpatients, treated at the Department of Psychiatry, Poznan University of Medical Sciences (schizophrenia) or from outpatients (the first episode of depression). Patients were recruited in an acute phase of illness. Clinical and biological parameters were evaluated at baseline and after 8 weeks of treatment. The control group consisted of healthy volunteers. Exclusion criteria were: chronic or acute somatic or neurological diseases and increased CRP (C-reactive protein). All subjects were of Caucasian origin, in particular, a native Polish population from Great Poland region. The study was performed in accordance with the ethical standards established in the Declaration of Helsinki and was approved by the medical ethics committee of the Poznan University of Medical Sciences. All participants gave written informed consent before participation in the study.

2.2. GDNF determination

10 ml of venous blood was withdrawn between 7.30 and 9.30 h (after overnight fasting) into anticoagulant-free tubes. After 1 h incubation, serum was separated by centrifugation, aliquoted and stored at −70 °C until further analyses. Enzyme-linked immunosorbent assays were performed using DuoSet (cat. No DY 212) ELISA Development Kit (R & D System, Minneapolis, MN, USA), according to manufacturer's instructions, with minor modifications. Plates were blocked for 3 h in reagent diluent (1% Bovine Serum Albumin (BSA)/ Phosphate Buffered Saline (PBS)) and incubated overnight with 100 µL of samples at 4 °C with shaking. All samples and standards were run in duplicates. To avoid the differences between assays, 16 samples at baseline and week 8, along with 8 control samples, were analysed on the same plate. All plates were run within one week, on the same kit lot#, by the same experienced operator. Standard curves ranged from 1000 to 15.6 pg/