Psychiatry Research 209 (2013) 150–154

Contents lists available at ScienceDirect

Psychiatry Research

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

Lifestyle modification and behavior therapy effectively reduce body weight and increase serum level of brain-derived neurotrophic factor in obese non-diabetic patients with schizophrenia

Feng-Chih Kuo [a], Chien-Hsing Lee [a,b], Chang-Hsun Hsieh [a], Philip Kuo [c], Yi-Chyan Chen [b,d], Yi-Jen Hung [a,*]

[a] Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[b] Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan
[c] Department of Biological Sciences, University of Illinois at Chicago, USA
[d] Department of Psychiatry, Buddhist Tzu Chi General Hospital, Taipei Branch, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 3 April 2012
Received in revised form
30 September 2012
Accepted 12 November 2012

Keywords:
Brain-derived neurotrophic factor
Schizophrenia
Obesity
Body weight reduction

ABSTRACT

The goal of the study was to elucidate the relationship between serum circulating brain-derived neurotrophic factor (BDNF) and body weight reduction via lifestyle modification and behavior therapy in obese non-diabetic patients with chronic schizophrenia. Thirty-three obese non-diabetic subjects with schizophrenia treated with stable antipsychotic medication in a day-care unit for at least 3 months were recruited. Thirty age-, body weight-matched subjects without psychiatric disorders were enrolled as controls. All participants underwent a 10-week weight reduction program, including lifestyle modification, psychosocial treatment, behavior therapy and exercise in the day-care unit. Blood biochemistry, serum BDNF, adipokine (adiponectin), inflammatory markers (C-reactive protein, tumor necrosis factor-alpha and interleukin-6) and oral glucose tolerance test were evaluated before and after the program. Serum BDNF concentrations were significantly lower among patients with schizophrenia compared to control subjects. Serum BDNF levels were significantly increased following the weight reduction program. Elevations in serum BDNF levels were positively correlated with body weight and body mass index reduction. Altogether, our results demonstrate that a non-pharmacological weight reduction program effectively reduces body weight with significant elevation of serum BDNF levels in obese non-diabetic patients with schizophrenia.
© 2012 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Schizophrenia is a chronic psychotic mental disorder characterized by abnormalities in the perception or expression of reality affecting approximately 1% of the general population (Freedman, 2003). Symptoms generally start in late adolescence or early adulthood and include both positive and negative symptoms (Crow, 1980; Freedman, 2003). Positive symptoms consist of delusions, hallucinations, disorganized speech, or bizarre behavior. Negative symptoms include affective flattening, alogia, or decline in motivation. Multiple genetic and environmental factors seem to be implicated simultaneously in the etiology of schizophrenia. Further, neuropathological and neuroimaging studies support that schizophrenia may be a neurodevelopmental disorder associated with obstetric complications (prenatal virus infection, hypoxia), brain structural change (reduced brain volume, increased ventricular volume) and neurotrophin imbalance (Mueser and McGurk, 2004; Shoval and Weizman, 2005; Chaldakov et al., 2009).

Neurotrophins are a family of proteins involved in the survival, development and function of neurons in both the central and peripheral nervous system (Skaper, 2008). They also regulate nerve regeneration and synaptic activity, thus maintaining neural plasticity in the brain (Skaper, 2008). Recently, the extraneuronal, particularly metabotrophic, effects of neurotrophins are increasingly evaluated (Chaldakov et al., 2009). Brain-derived neurotrophic factor (BDNF), one of the neurotrophins, is associated with brain regions involved in the pathogenesis of schizophrenia, including the hippocampus, neocortex, thalamus, and cerebellum, and it influences the differentiation of dopaminergic, serotonergic and glutamatergic neurons (Shoval and Weizman, 2005).

Schizophrenic patients have an increased prevalence of obesity, metabolic syndrome and diabetes (Allison et al., 2009). It may attribute to behavioral change, stem from illness-related factors, such as inactivity, higher fat or low fiber diet, and antipsychotic medications (Holt et al., 2004). On the other hand, metabolic syndrome and its components (impaired glucose tolerance,

* Correspondence to: Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, No.325, Sec. 2, Chen-Kung Rd., Nei-Hu, Taipei, Taiwan. Tel.: +886 2 87927182; fax: +886 2 87917183.
E-mail address: metahung@yahoo.com (Y.-J. Hung).

0165-1781/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psychres.2012.11.020

abdominal or central obesity, hypertension, hypertriglyceridemia and reduced high-density lipoprotein cholesterol) are also linked to the risk of developing cognitive impairment (Frisardi et al., 2010). Previous studies in schizophrenic patients on long-term treatment with antipsychotics found that decreased brain-derived neurotrophic factor (BDNF) levels were associated with weight gain in females and variations in the BDNF gene may be a risk factor for weight gain in male patients (Zhang et al., 2007, 2008). Animal studies have also revealed that central or peripheral administration of BDNF decreases food intake, increases energy expenditure, and ameliorates hyperinsulinemia and hyperglycemia by a central nervous system-mediated mechanism (Nagakawa et al., 2000; Nonomura et al., 2001; Tsuchida et al., 2001; Xu et al., 2003). BDNF is expressed at high levels in the ventromedial hypothalamus, which is responsible for the regulation of food intake and body weight (Rao et al., 2008). Several lines of evidence support the important role of BDNF in eating behavior, weight regulation and the pathophysiology of schizophrenia; thus, pharmaceutical or non-pharmaceutical methods developed to increase central or peripheral BDNF levels may present a novel approach in the treatment of obesity or schizophrenia (Chaldakov et al., 2009; Buckley et al., 2011; Favalli et al., 2012).

In diabetic mice on voluntary wheel running and dietary energy restriction, increased levels of BDNF with enhanced dendritic spine density in the hippocampus were demonstrated (Stranahan et al., 2009). In clinical studies, treadmill walking for 30 min increased BDNF concentrations in panic disorder patients (Ströhle et al., 2010); elevated serum BDNF levels were found after a 3-month reduced-calorie diet in obese subjects (Araya et al., 2008) and after at least a 1-month hypocaloric diet in schizophrenic patients (Guimarães et al., 2008). Since schizophrenic patients are vulnerable to the metabolic syndrome with subsequent morbidity of cardiovascular disease, it is desirable to promote weight reduction in obese schizophrenic patients and evaluate the change of serum BDNF levels. Hence, we conducted a weight reduction program including exercise, lifestyle modification, and psychosocial/behavioral therapy in obese non-diabetic subjects with chronic schizophrenia to determine the possible relationship between BDNF and body weight reduction.

2. Methods

2.1. Subjects

Thirty-three obese non-diabetic outpatients (14 female and 19 male) at the Tri-Service General Hospital, Taipei, Taiwan, with ages ranging from 18 to 50 years and body mass index (BMI) ≥ 27 kg/m^2 were enrolled in this study. Eligibility was determined by a fasting plasma glucose of less than 126 mg/dl and 2-h plasma glucose of less than 200 mg/dl following a 75-g oral glucose tolerance test, diagnosis of schizophrenia, and absence of co-morbid axis-I disorder; subjects were recruited consecutively in our day-care unit. The diagnosis of schizophrenia was evaluated using diagnostic criteria of schizophrenia from the *Diagnostic and Statistical Manual of Mental Disorder, fourth edition* (DSM-IV) in an interview by two psychiatrists. The Brief Psychiatric Rating Scale (BPRS) was adapted to assess the patient's general mental condition. Participants were treated with stable typical or atypical antipsychotic medication (Table 1) for at least 3 months. Prior to intervention with the weight reduction program, patients underwent an oral glucose tolerance test (OGTT). None of the schizophrenic patients had a history of systemic disease or family history of diabetes. The nature and possible adverse events of the study procedure were explained in detail to all participants. Thirty age-, body weight-matched obese subjects without psychiatric disorders were enrolled as controls.

2.2. Weight reduction program

All patients underwent the structured weight reduction program, including lifestyle modification, psychosocial/behavioral therapy, and exercise in the day-care unit for 10 weeks. Psychosocial evaluation was performed individually to help them learn how to deal with personal emotion instead of just eating more foods. Behavior therapy included more vegetables, more monounsaturated fat, and diminished simple sugars in diet with reduced daily caloric intake and weekly group physical activity intervention for 1 h. The dietitian set up the components of food with $<7\%$ saturated fat, 15–20% protein and daily calories were restricted around 2 kcal/kg. We served 20% and 40% of daily calories for breakfast and lunch, respectively. Exercise with mild intensity such as slow walking, housecleaning for 30 min or moderate intensity such as faster walking, cycling for 20 min should be performed at least five times per week. Diary records of diet and exercise components were reviewed and adjusted via individual counseling by physicians weekly. Body weight and blood pressure were measured weekly. Anthropometric measurements including height, waist and hip circumferences were made before and after this program. Bood biochemistry measures [fasting glucose, lipid profiles, homeostasis model assessment-insulin resistance and β cell function (HOMA-IR and -β)], serum levels of BDNF, adipokine (adiponectin), inflammatory markers [C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)], OGTT, and BPRS were assessed before and after this program.

Table 1
Medications of 33 schizophrenia without diabetes.

Medication	No. of patients (%)	Therapeutic duration (years)	Dosage (mg)
Clozapine (%)	22	3 (0.6–5.6)	200 (100–300)
Olanzapine (%)	15	2.2 (0.5–5.4)	15 (10–25)
Risperdal (%)	18	2.6 (2.7–5.3)	3 (2–4)
Conventional (%)	30	0.9 (0.5–2.4)	–
Others	15	2.7 (0.7–5.6)	–

Data expressed as mean (range).

2.3. Oral glucose tolerance test (OGTT)

After a 10-h overnight fast, the OGTT was performed at 8:30 a.m. using a 75-g load of glucose in 150 ml of de-ionized water. Venous blood samples were drawn for plasma glucose and insulin determination at 0, 30, 60, 90, 120 and 180 min after glucose ingestion. The areas under each curve for glucose and insulin in response to the OGTT were determined. The indices of basal insulin resistance and β-cell function were assessed using the homeostasis model assessment (HOMA-IR and HOMA-β) originally described by Matthews et al. (1985), in which

$$HOMR\text{–}IR\left(\frac{mmol}{L}\times\frac{\mu IU}{mL}\right)=fasting\ glucose\left(\frac{mmol}{L}\right)\times fasting\ insulin\left(\frac{\mu IU}{mL}\right)\div 22.5,$$

$$HOMR\text{–}\beta=fasting\ insulin\left(\frac{\mu IU}{mL}\right)\times\frac{20}{[fasting\ glucose(mml/L)-3.5]}$$

2.4. Laboratory measurements

Following 10 h of fasting, blood samples were obtained between 8.00 a.m. and 10.00 a.m. for determining plasma glucose, insulin, thyroid hormone, cortisol, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lipid profiles. Biochemistry and serum total cholesterol were measured using a dry multi-layer analytic slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film Corporation, Minato-Ku, Tokyo, Japan). The determination of serum triglyceride after enzymatic splitting with lipoprotein lipase was assayed by colorimetric enzymatic test on Hitachi 717 (Biomedilines, San Diego, CA, USA), while the plasma glucose concentration was determined by the glucose oxidase method on a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA, USA).

Plasma insulin was measured with a radioimmunoassay kit (Coat-A-Count Insulin Kit, Diagnostic Products Corporation, Los Angeles, CA, USA). The intra- and inter-assay coefficients of variance (CV) were 3.3% and 2.5%, respectively. Plasma CRP levels were measured using the Tina-quant (Latex) high sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany). Serum adiponectin concentrations were assayed with radioimmunoassay established by Linco Research (St Charles, MO, USA). Total adiponectin, in a range of high- to low-molecular weight multimeric forms, were included. This assay had a sensitivity of 1 ng/ml and intra- and interassay coefficient of variation (CV) of less than 8%. Serum IL-6 concentrations were determined by the method of human high sensitivity Enzyme Linked-Immuno-Sorbent Assay (ELISA) established by Diaclone Research (Besancon Cedex, France). The intra- and inter-assay CVs for IL-6 were 1.4% and 5.5%, respectively. Serum TNF-α was measured with the Biotrak^{TM} high sensitivity human ELISA kit from Amersham Biosciences (Buckinghamshire, UK). The minimal detectable dose of TNF-α was determined to be 0.1 pg/ml, by adding two standard deviations to the optical density value of zero and calculating the corresponding concentration from the standard curve. The intra- and inter-assay CVs for TNF-α were 5.8% and 9.3%, respectively.

BDNF serum concentrations were measured according to the procedure supplied by the manufacturer and using sandwich ELISA kits for BDNF (DuoSet, R&D Systems, Minneapolis, MN, USA).

دریافت فوری ← متن کامل مقاله

ISIArticles
مرجع مقالات تخصصی ایران

✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
✓ امکان دانلود نسخه ترجمه شده مقالات
✓ پذیرش سفارش ترجمه تخصصی
✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
✓ دانلود فوری مقاله پس از پرداخت آنلاین
✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات