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Serum leptin and its relationship with psychopathology in schizophrenia

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Summary Leptin plays an important role in the modulation of the dopaminergic system and has recently been implicated in schizophrenia. There have been conflicting reports on leptin levels in schizophrenia; as well as on the association between leptin levels and clinical symptoms. Therefore, this study aims to examine (i) leptin levels in schizophrenia relative to control, and (ii) the relationship between leptin and symptoms in schizophrenia. One hundred participants with schizophrenia and 89 healthy controls were recruited from the Institute of Mental Health in Singapore. Demographic information and medical histories were collected. Schizophrenia symptoms were assessed using the positive and negative syndrome scale (PANSS) and serum leptin was measured using a commercially available bioplex leptin assay. Linear regressions were performed to examine the relationship between serum leptin and the positive, negative, general psychopathology subscales and total PANSS scores. Contrary to previously published literature, we did not find any significant difference in leptin level between participants with schizophrenia compared to controls, which might be the result of recruited controls being of comparable body mass index. Serum leptin was found to be positively associated with positive symptoms, general psychopathology and total PANSS score. This study provides evidence to suggest a positive association between serum leptin level and symptomatology in schizophrenia. However, since conflicting results in this area of research exist, it is important to understand better the mechanism behind this relationship and to examine temporal fluctuations in leptin levels in relation with changes in clinical symptomatology.

1. Introduction

A complex interplay of physiologically important bioactive molecules has been implicated in the pathophysiology of schizophrenia. More recently, adipokines, in particular

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leptin, have been of interest in schizophrenia. Leptin is a 16 KD protein hormone encoded by the obese (ob) gene and links nutritional status with neuroendocrine and immune functions (Otero et al., 2005). Leptin functions as a satiety factor, and is involved in obesity and insulin resistance (Faggioni et al., 2001; Otero et al., 2005; Panariello et al., 2012). A reduction in leptin was observed in starvation and malnutrition, and is reversible by caloric supplementation. Leptin also plays important roles in the central and peripheral nervous system (Monti et al., 2006). Its receptors were identified within non-hypothalamic neurons at the hippocampal, cortical, cerebellar and mesencephalon regions. Leptin has been postulated to be involved in brain development and maintenance, and contributes to cognitive and behavioral function. In the adult brain, leptin directs *N*-methyl-D-aspartate (NMDA) receptor dependent synaptic activity responsible for learning and memory, and regulates a variety of signaling pathways and synaptic activity within cortical and cerebellar regions in the brain. In both rodent and human studies, there exists evidence for an association between leptin, cognition and behavioral functions (Morrison, 2009; Warren et al., 2012). Furthermore, leptin has also been reported to modulate activity of mesolimbic dopaminergic neurons in the ventral tegmental area (VTA), which is implicated in schizophrenia (DiLeone, 2009).

There have been conflicting studies in the literature, with reports of reduced (Atmaca et al., 2003; Kraus et al., 2001; Venkatasubramanian et al., 2010) and increased leptin level (Arranz et al., 2004; Wang et al., 2007) in antipsychotic-naive and antipsychotic-free patients with schizophrenia. A systematic review suggests that leptin was increased in individuals with schizophrenia who were treated with antipsychotics, with greater elevation in those treated with atypical antipsychotics (Sentissi et al., 2008). It was suggested that antipsychotics may alter the neuropeptide Y (NPY)-leptin relationship through interactions with multiple receptors and neurotransmitters to modulate the expression of NPY and leptin, resulting in weight gain (Raposo et al., 2011). The reported increase in leptin was observed to be associated with improvement in clinical symptoms and was proposed to be a useful objective predictor of clinical improvement (Kraus et al., 1999; Venkatasubramanian et al., 2010). Although, there are suggestions that leptin is altered in individuals with schizophrenia, it remains unclear whether the altered leptin expression is entirely due to the pathophysiology of schizophrenia or influenced by other factors. In healthy individuals, leptin has been reported to be influenced by age, gender (Al-Harithy, 2004), dietary intake (Jenkins et al., 1997), body mass index (BMI) and cigarette smoking (Jaleel et al., 2007). Older age, females, higher BMI, cigarette smoking and high carbohydrate diet were found to be associated with higher leptin level. In schizophrenia, studies have reported on the association between leptin and age of onset, duration of illness (Herran et al., 2001; Jow et al., 2006) and treatment with atypical antipsychotics (Sentissi et al., 2008).

In spite of extensive research concerning the physiology of leptin, there are conflicting findings about the levels of leptin and its clinical relevance in schizophrenia. There exists a paucity of data that examine the relationship between leptin and psychopathology. Since most reports suggest that antipsychotic treatment increases leptin level and our study population comprises of chronically ill patients with schizophrenia treated with antipsychotics, we would expect leptin levels to be higher compared to healthy controls. In addition, considering leptin's role in upregulation of dopaminergic neurons in the mesolimbic cortex, it would seem plausible to hypothesize that leptin might play a role in the generation of psychotic symptoms. However, two studies reported increased leptin level to be associated with lower psychotic symptoms (Takayanagi et al., 2013; Venkatasubramanian et al., 2010). Therefore, the present study aims to investigate (i) serum leptin in patients diagnosed with schizophrenia in comparison to healthy individuals, and (ii) assess the relationship between serum leptin and psychopathology. We hypothesized that serum leptin is increased in participants with schizophrenia, and is positively associated with symptom severity in our study sample.

2. Methods

2.1. Study participants

This study was conducted at the Institute of Mental Health (IMH), Singapore, the only psychiatric hospital in the country. Cases — aged 21—50 years and fulfilling DSM-IV-TR diagnosis of schizophrenia — were recruited from the outpatient clinics between 2010 and 2011. Controls were healthy individuals from the community with no history of psychiatric disorders, and were recruited through referrals and advertisements. Cases and controls were matched according to age, gender and ethnicity at a group level.

Individuals with a history of neurological disorders, current substance and alcohol use disorders were excluded from the study. Ethics approval for the study was provided by the domain specific review board of the national healthcare group, Singapore. Information related to the study was carefully explained to all study participants, and only participants who were able to provide informed consent were recruited into the study.

2.2. Data collection

Demographic information and current smoking status were obtained from all study participants through clinical interviews by a trained investigator. Height and weight were measured and BMI was computed accordingly. Medical records were reviewed to collect medical histories of participants with schizophrenia. Age of onset (defined as the age at first onset of psychotic symptoms) and duration of illness (defined as the time from the first onset of psychotic symptoms to the date of recruitment) were collected. Current antipsychotic prescriptions were gathered from the medication administration records and daily dosages of antipsychotics were converted into chlorpromazine equivalents (Woods, 2003) for participants with schizophrenia. For healthy controls, details of their medical history, medications or supplements were self-reported during the research interview. If this information was not readily available, a follow-up phone call was made to verify the information obtained.