Serum leptin and its relationship with psychopathology in schizophrenia

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Received 29 April 2014; received in revised form 18 August 2014; accepted 25 August 2014

KEYWORDS
Adipokines; Psychosis; Dopamine

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.

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1. Introduction

A complex interplay of physiologically important bioactive molecules has been implicated in the pathophysiology of schizophrenia. More recently, adipokines, in particular...
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 sati-
fety 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 supplemen-
tation. Leptin also plays important roles in the central and
peripheral nervous system (Monti et al., 2006). Its recep-
tors 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 associ-
ation 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 sug-
gested that antipsychotics may alter the neuropeptide Y
(NPY)-leptin relationship through interactions with multiple
receptors and neurotransmitters to modulate the expres-
sion 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 clini-
cal 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 fac-
tors. 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 physi-
ology 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 relation-
ship 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 con-
trols. 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 associ-
ated 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 indi-
viduals, and (ii) assess the relationship between serum leptin
and psychopathology. We hypothesized that serum leptin is
increased in participants with schizophrenia, and is posi-
tively 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 coun-
try. Cases — aged 21—50 years and fulfilling DSM-IV-TR
diagnosis of schizophrenia — were recruited from the outpa-
tient clinics between 2010 and 2011. Controls were healthy
individuals from the community with no history of psychi-
atric 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, cur-
rent 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 health-
care group, Singapore. Information related to the study was
carefully explained to all study participants, and only par-
ticipants 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 inter-
views by a trained investigator. Height and weight were
measured and BMI was computed accordingly. Medical
records were reviewed to collect medical histories of par-
ticipants 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 psy-
chotic 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 equiva-
lents (Woods, 2003) for participants with schizophrenia. For
healthy controls, details of their medical history, medica-
tions 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.
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